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Single Hepatocellular Carcinoma approached by curative-intent treatment: A propensity score analysis comparing radiofrequency ablation and liver resection

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ABSTRACT

Introduction: Patients with a single small Hepatocellular Carcinoma (HCC) may be definitively treated by Radiofrequency ablation (RFA) with a very low rate of peri-operative morbidity. However, results are still controversial comparing RFA to Liver Resection (LR).
Methods: All consecutive patients treated by RFA or LR for a single untreated small HCC on liver cirrhosis between January 2006-December 2016 were enrolled. Patients were matched 1:1 basing on: age, MELD-score, platelet count, nodule's diameter, HCV status, α-fetoprotein level, and Albumin-Bilirubin score. First analysis compered LR to RFA. Second analysis compared Laparoscopic LR (LLR) to RFA.
Results: Of 484 patients with single small HCC, 91 patients were selected for each group after a 1:1 propensity score matching (PS-M). The 5-years OS was 70% and 60% respectively for LR and RFA group ($P = 0.666$). The 5-year RFS was 36% and 21% respectively for LR and RFA group ($P < 0.001$). Patients treated by LR had a significantly longer hospital stay and higher complications rate. Comparing 50 cases of LLR and 50 of RFA, the 5-years OS was 79% and 56% respectively for LLR and RFA group ($P = 0.22$). The 5-year RFS was 54% and 19% respectively for LR and RFA group ($P < 0.001$). Post-operative complications were not significantly different.
Conclusions: LLR confers similar peri-operative complications rate compared to RFA. LLR should be considered as a first-line approach for the treatment of a single small HCC as it combines the effectiveness of open LR and the safety profile of RFA.

Introduction

Hepatocellular Carcinoma (HCC) is the most common liver malignancy and, over the past 2 decades, has become one of the leading causes of tumor-related death worldwide [1]. Several studies have already demonstrated the strong curative impact of Liver Transplantation (LT) for HCC [2,3]. However, LT's morbidity along with the severe organs' shortage, force physicians to apply alternative treatment modalities when possible. This is especially true when outcomes are not strongly inferior to LT [4] or when patients are unsuitable for LT [5]. Some randomized controlled trials (RCT), and many retrospective studies, have demonstrated the evident advantages of Radiofrequency Ablation (RFA) for selected cases. Indeed, some patients with HCC may be definitively treated by RFA with a very low rate of procedure-related morbidity and almost zero mortality [5–12]. The alternative treatment for RFA is Liver Resection (LR). LR provides superior outcomes with larger nodules and allows physicians to study tumor pathology including

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crucial information about the radicality of the treatment as well as pathological risk factors. However, LR is associated with a significantly higher rate of peri-operative morbidity and mortality [5–12]. Therefore, patients are generally considered suitable candidates for LR when they are in relatively stable medical condition and have enough liver reserve as well as when tumors are peripherally located and thus easily accessible; otherwise, RFA is preferred for patients with worse general and/or liver conditions and with tumors that are located deeper in the parenchyma [6,13].

Recently, several studies have demonstrated a significantly lower rate of local recurrence in patients treated by LR than RFA, even for very small nodules [6–8]. The balance between risk and benefit for RFA or LR in HCC treatment is therefore mainly evaluated in terms of how extensive of a LR would be needed for what tumor size. In other words, when a major or extended LR is required for a small tumor due to its location, the associated morbidity and mortality might become prohibitive especially in the presence of an alternative therapy such as RFA. Conversely, a planned peripheral resection for a larger tumor would probably justify the peri-operative risks of LR.

Laparoscopy has progressively gained popularity worldwide in liver resection for HCC mainly in cirrhotic patients [14,15]. The minimally invasive approach has been associated with a significant decrease in peri-operative complications [14,15]. Sometimes, the decision to perform a LR rather than RFA may depend on the ability to plan a minimally invasive resection. Indeed, in selected cases with advanced cirrhosis or multiple comorbidities, when laparoscopy is unfeasible, RFA may be preferred to an open resection.

The aim of this study was to evaluate and compare the short and long-term outcomes associated with LR and RFA in the treatment of a single HCC nodule in patients with liver cirrhosis.

Materials and methods

All consecutive patients treated by RFA or LR for a preoperative diagnosis of a single HCC (very early/early stages according to BCLC) [13] on liver cirrhosis from January 2006 until December 2016 were enrolled in the study. The study was conducted on a prospective database. Decision for LR or RFA was made by a multidisciplinary team comprised of surgeons, hepatologists, diagnostic radiologists and interventional radiologists. Patients with peripheral nodules were generally referred for LR, whereas centrally located tumors were first evaluated for RFA. General contraindications for LR were: Child Pugh score C, American Society of Anesthesiologists (ASA) grade $\geq$ III [16], ascites, platelet count <50,000, presence of extrahepatic metastasis, unresectable macrovascular tumor invasion or future remnant liver <40%. General contraindications for RFA were: ascites, peripheral exophytic lesions, macrovascular tumor invasion, nodules >5 cm in diameter or nodules undetectable by ultrasonography (US). Nodules were considered "*superficial*" if they were located at < 1 cm in depth from the liver surface and associated with a liver surface bulge; otherwise they were classified as "*deep*" [17].

Diagnosis of HCC was made according to the EASL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases) guidelines [18,19]. Preoperative biopsy was considered only in cases of suspicious nodules with atypical radiological findings. All HBV patients were treated with antiviral therapy with effective viral control. Starting in 2013, all hepatitis C virus (HCV) patients with positive HCV-RNA received direct-acting antivirals (DAA) [20] after curative treatments for their HCC and with no evidence of tumor recurrence. LT was generally not considered as a first line approach for BCLC 0/A patients. LT was considered for those patients only in case of transplantable recurrence in transplantable patients [21], however their follow-up for the present study was censored at the time of LT.

Liver resection was performed in either open or laparoscopic fashions, tumors located in left lateral or anterior segments were most commonly approached laparoscopically, whereas posterior tumors were usually approached with an open procedure [15]. The liver parenchyma transection was performed using CUSA® Excel/ CUSA® Excel + Cavitron Ultrasonic Surgical Aspirator System (Integra, Ireland) and Ultracision Harmonic scalpel (UHS; Ethicon Endo-Surgery, Cincinnati, OH); hemostasis and biliostasis on the liver cut surface was achieved using metallic clips, Hem-o-lock, non-absorbable sutures, or stapler depending on the vessel diameter and the surgeon's intraoperative judgment. Hilar clamping, when performed, was an intermittent total clamping, with no longer than 15 min of clamping time and at least 5 min of release. All the cases received intra-operative US before LR was performed. In general, non-anatomical resection was chosen for peripheral lesions, however for intra-parenchymal lesions anatomical resection was preferred. For open resections, the patient was placed in supine decubitus position and an inverted L-shaped incision was usually performed. For laparoscopic LR (LLR) the patient was placed with legs spread apart and in supine decubitus when lesions were located in left or anterior segments and in 30° left lateral decubitus in cases of posterior segments lesions. Usually, in LLR five or six 12 mm laparoscopic trocars were inserted and a 30° laparoscope was used [15]. Pneumoperitoneum was maintained at 12 mmHg and sometimes increased to 15 or 19 mmHg in case of necessity. All LLRs were carried by a totally minimally invasive approach [15].

Radiofrequency ablation was applied for the majority of patients suitable for percutaneous ablation. However, selected cases received Microwave Coagulation Therapy. The most common electrode used in our center is the LeVeen Needle Electrode with an insulated 17-gauge outer needle and retractable curved electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA; LeVeen needle electrode, Boston Scientific, Boston, MA); some patients were treated by an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA).

Short-term outcomes were evaluated at 30 days post-operatively. Post-operative complications were classified according to the Clavien-Dindo classification [22]. Biliary fistula and post-hepatectomy liver failure were defined according the International Study Group of Liver Surgery [23,24]. Long-term outcomes evaluated were recurrence-free survival (RFS) and overall survival (OS). Recurrence-free survival was defined as the time from surgery or ablation until the date of any type of HCC recurrence, local or distant. Overall survival was defined as the time from surgery until the date of death, all causes considered. Local recurrence was evaluated based on the EASL guidelines [18]. Patients were followed-up for life and received surveillance for HCC recurrence according to the EASL guidelines [25].

Statistical analysis

Given the differences in the baseline characteristics between patients receiving the two investigated surgical approaches (Table 1), and to control for the nonrandom assignment of patients to RFA or LR, propensity-score matching (PS-M) was used to identify a cohort of patients receiving LR with similar characteristics to the patients receiving RFA.

The PS-M was estimated with the use of a multivariable logistic-regression model, with RFA as the dependent variable and the following baseline characteristics as covariates: age, Model of End Stage Liver Disease (MELD) score, platelet count, diameter of the nodule (mm) at diagnosis, HCV status, α-fetoprotein (AFP) level (categorized by tertiles) and Albumin-Bilirubin (ALBI) score.

Table 1
Comparison between RFA and LR both without PS-M and with PS-M (N = 484).

		Before PS-M			After PS-M		
		LR (N = 341)	RFA (N = 143)	P [a]	LR (N = 91)	RFA (N = 91)	P [a] (D [b])
Variables used in propensity matching							
Age (year), median (IQR)		66 (59, 73)	65 (57, 75)	0.95	65 (62, 72)	65 (56, 76)	0.90 (0.07)
MELD score, median (IQR)		8 (7, 9)	9 (7, 12)	<0.01	8 (7, 10)	8 (7, 11)	0.48 (0.14)
PLT, median (IQR)		160 (105, 215)	102 (70, 147)	<0.01	126 (71, 188)	107 (80, 155)	0.17 (0.13)
Nodule's diameter at DG (mm), median (IQR)		35 (25, 56)	20 (16, 25)	<0.01	20 (19, 28)	20 (17, 26)	0.25 (0.11)
HCV, N (%)	No	173 (50.7)	48 (33.6)	<0.01	33 (36.3)	29 (31.9)	1.00 (0.09)
	Yes	168 (49.3)	95 (66.4)		58 (63.7)	62 (68.1)	
AFP, N (%) [c]	≤5	64 (18.8)	42 (29.4)	<0.01	27 (29.7)	26 (28.6)	0.85 (0.13)
	5–22	69 (20.2)	35 (24.5)		24 (26.4)	26 (28.6)	
	>22	71 (20.8)	33 (23.1)		23 (25.3)	26 (28.6)	
	Missing	137 (40.2)	33 (23.1)		17 (18.7)	13 (14.3)	
ALBI score, N (%)	Grade I	145 (42.5)	50 (35.0)	<0.01	41 (45.1)	37 (40.7)	0.83 (0.09)
	Grade II	187 (54.8)	64 (44.8)		45 (49.5)	49 (53.8)	
	Grade III	6 (1.8)	7 (4.9)		5 (5.5)	5 (5.5)	
	Missing	3 (0.9)	22 (15.4)		0 (0.0)	0 (0.0)	
Variables not used in propensity matching				P [a]			P [a] (D [b])
CHILD score, median (IQR)		5 (5,5)	5 (5, 6)	<0.01	5 (5, 6)	5 (5, 6)	0.46 (0.15)
	Missing	22	20		4	1	
ALT, median (IQR)		43 (26, 74)	42.50 (26, 85)	0.97	49 (28, 90)	47 (29, 91)	0.82 (0.03)
	Missing	4	21		1	2	
AST, median (IQR)		41 (27, 68)	55 (33, 89)	<0.01	48 (28, 88)	60 (34, 100)	0.30 (0.12)
	Missing	118	37		25	13	
INR, median (IQR)		1.10 (1.02, 1.19)	1.15 (1.09, 1.34)	<0.01	1.11 (1.03, 1.23)	1.15 (1.07, 1.27)	0.06 (0.31)
	Missing	3	17		0	0	
Creatinine, median (IQR)		0.84 (0.70, 0.97)	0.80 (0.70, 0.95)	0.49	0.85 (0.72, 0.97)	0.79 (0.70, 0.93)	0.20 (0.12)
	Missing	3	12		0	0	
Sex, N (%)	Men	267 (78.3)	106 (74.1)	0.38	68 (74.7)	66 (72.5)	0.87 (0.05)
	Women	74 (21.7)	37 (25.9)		23 (25.3)	25 (27.5)	
PS, N (%)	0	304 (89.1)	107 (74.8)	<0.01	85 (93.4)	72 (79.1)	0.01 (0.42)
	1	37 (10.9)	35 (24.5)		6 (6.6)	19 (20.9)	
	2	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	
Presence of cirrhosis, N (%)	No	74 (21.7)	6 (4.2)	<0.01	16 (17.6)	2 (2.2)	<0.01 (0.53)
	Yes	267 (78.3)	137 (95.8)		75 (82.4)	89 (97.8)	
Alcol, N (%)	No	285 (83.6)	99 (69.2)	<0.01	76 (83.5)	66 (72.5)	0.11 (0.27)
	Yes	56 (16.4)	44 (30.8)		15 (16.5)	25 (27.5)	
HBV, N (%)	No	258 (75.7)	125 (87.4)	<0.01	76 (83.5)	78 (85.7)	0.84 (0.06)
	Yes	83 (24.3)	18 (12.6)		15 (16.5)	13 (14.3)	
Satellitosis, N (%)	No	265 (77.7)	129 (90.2)	<0.01	81 (89.0)	82 (90.1)	1.00 (0.04)
	Yes	76 (22.3)	14 (9.8)		10 (11.0)	9 (9.9)	
Macrovascular invasion, N (%)	No	327 (96.7)	135 (98.5)	0.44	90 (98.9)	91 (100.0)	1.00 (0.15)
	Yes	11 (3.3)	2 (1.5)		1 (1.1)	0 (0.0)	
	Missing	2	0		0	0	
BCLC, N (%)	0	60 (17.6)	65 (45.5)	<0.01	45 (49.5)	37 (40.7)	0.15 (0.29)
	A	197 (57.8)	77 (53.8)		44 (48.4)	54 (59.3)	
	B	61 (17.9)	0 (0.0)		2 (2.2)	0 (0.0)	
	C	23 (6.7)	1 (0.7)		0 (0.0)	0 (0.0)	
Milano stage, N (%)	In	237 (69.5)	125 (87.4)	<0.01	87 (95.6)	81 (89.0)	0.16 (0.25)
	Out	104 (30.5)	18 (12.6)		4 (4.4)	10 (11.0)	
Sub-capsular nodule, N (%)	Deep	196 (60.9)	51 (52.0)	0.15	34 (37.4)	49 (53.8)	0.04 (0.34)
	Superficial	126 (39.1)	47 (48.0)		57 (62.6)	42 (46.2)	
	Missing	16	14		0	0	
Biopsy pre TRT, N (%)	No	228 (80.6)	120 (85.1)	0.31	64 (78.0)	78 (85.7)	0.26 (0.20)
	Yes	55 (19.4)	21 (14.9)		18 (22.0)	13 (14.3)	
	Missing	58	2		9	0	
Infiltration margin resection (R1), N (%)	No	284 (83.3)	–	–	80 (87.9)	–	–
	Yes	57 (16.7)	–		11 (12.1)[d]	–	

RFA: radiofrequency ablation.
LR: liver resection.
PS-M: propensity-score matching.
PT: patient.
DG: diagnosis.
IQR: interquartile range.
PS: performance status.
TRT: treatment.
[a] Chi-square p-value for categorical variables, Wilcoxon p-value for continuous variables.
[b] Distance D is standardized mean difference.
[c] Categorized by tertiles.
[d] Among 11/91 R1 resections, 3/34 occurred in deep nodules, 8/57 occurred in superficial nodules.

PS-M was performed with the use of a 1:1 matching without replacement (greedy-matching algorithm), with a caliper width equal to 0.15 of the propensity score. Continuous data are reported as median and interquartile ranges (IQR) and categorical data as counts and percentages (%).

Differences in the distribution of patient's characteristics between RFA and LR cohorts were evaluated by using Wilcoxon test for continuous variables and the χ^2 test for categorical ones, both before and after propensity score matching. Furthermore, differences in patient's characteristics included in propensity score were evaluated by standardized mean differences (distance D). A distance D less than 0.1 has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups [26].

For continuous response (i.e. days of hospitalization), the comparison between treatments groups was based on the Wilcoxon test, whereas, for categorical response (i.e. complications graded according to Clavien-Dindo classification), the comparison was based on the χ^2 test.

The RFS and OS functions were estimated using the Kaplan-Meier method. The log-rank test was used to assess differences between groups.

Moreover, to minimize residual confounding, the effect of the surgical approach on RFS and OS was assessed using a multivariable Cox proportional hazards model considering, as adjusting covariates, the propensity score in continuous and the variables not included in PS-M having a distance D greater than 0.1.

Types of recurrence (local, distant intra-hepatic and extra-hepatic relapse) were considered in a competitive risk framework. Patients alive or dead without recurrence were censored.

Cumulative incidence functions (CIF) were estimated according to the method described by Kalbfleisch and Prentice [27]. The Gray's test [28] was used to assess CIF differences between groups. The same approach, based on PS-M, was applied to compare radiofrequency and resection only in laparoscopy. A *P* value < 0.05 was considered statistically significant for all analyses.

All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 734 consecutive patients treated by LR or RFA for HCC between January 2006 and December 2016 were evaluated (Supplementar Material 1). Among these, 484 patients with very early/early stage HCC according to the BCLC staging system were included in the study. Three hundred forty-one patients underwent LR, whereas 143 received RFA as first-line treatment for their single HCC. The baseline patients' and tumor's characteristics were compared before and after the PS-M (Table 1). After the PS-M, 91 patients were selected for each of the LR and RFA groups. Patient median age, median MELD score, median PLT count, median nodule's diameter, HCV status, AFP level, and ALBI score at time of treatment were not statistically different between the two groups after PS-M (Table 1).

The OS at 3- and 5-years was 80% (95% CI = 69–87%) and 70% (95% CI = 57–79%) for the LR group and 82% (95% CI = 70–90%) and 60% (95% CI = 41%–74%) for the RFA group respectively (P = 0.666). The RFS at 3- and 5-year was 41% (95% CI = 30%–52%) and 36% (95% CI = 25–47%) for the LR group and 30% (95% CI = 20–41%) and 21% (95% CI = 11%–33%) for RFA group respectively (P < 0.001) (Fig. 1). After adjusting for residual confounding in a Cox multivariable model, results did not materially change (OS-HR for LR vs RFA = 1.08, P = 0.86; RFS-HR for LR vs RFA = 0.52, P = 0.01).

After a median follow-up of 33 months (IQR: 17–56), the rate of overall deaths was higher for LR patients rather than RFA patients (36.2% vs 21.9%). The rate of recurrence, however, was higher among the RFA patients cohort (69% vs 58%) and the CIF of local recurrence at 5-year was 9% (95% CI = 4%–17%) vs 53% (95% CI = 40%–64%) for the LR and RFS group, respectively (Fig. 1).

Patients treated by LR had a significantly longer hospital stay: the median length of post-procedural hospital stay was 8 days (IQR: 6–11) vs 3 days (IQR: 2–5) (P < 0.01) (Supplementar Material 2). The overall relevant complication rate within 30 days from the procedure was also significantly higher in the LR group (23.6% vs 3.3%, P < 0.01). No mortalities were recorded in the RFA group, whereas 1 patient died due to liver failure after LR (Supplementar Material 2).

Table 2 summarizes a sub-group analysis of patients who underwent pure LLR compared with patients who received RFA. After PS-M, 50 patients were selected in each group (RFA and LLR groups) with no statistical difference in terms of: median age, median MELD score, median PLT count, median diameter of the lesion, HCV status, AFP level and ALBI score. After PS-M, cirrhosis was still more common among RFA patients (84% vs 89%, P = 0.04) whereas tumors were more likely to be *superficial* in LLR patients (86% vs 56%, P < 0.01) (Table 2).

The overall 3- and 5-year survival rates were 84% (95% CI = 68%–93%) and 79% (95% CI = 61%–90%) for the LLR group and 77% (95% CI = 58%–88%) and 56% (95% CI = 31%–75%) for the RFA group respectively (P = 0.22). The RFS rates at 3- and 5-years were respectively 54% (95% CI = 38%–67%) and 54% (95% CI = 38%–67%) for the LLR group and 26% (95% CI = 14%–39%) and 19% (95% CI = 7%–35%) for the RFA group (P < 0.001) (Fig. 2). After adjusting for residual confounding in a Cox multivariable model, results did not materially change (OS-HR for LR vs RFA = 0.78, P = 0.67; RFS-HR for LR vs RFA = 0.30, P < 0.001).

Cumulative tumor recurrence occurred in 42% (21/50) of LLR patients and 76% (38/50) of RFA patients. The type of recurrence was most frequently a “local recurrence” for the RFA group (15% vs 68% respectively for LLR and RFA), whereas “distant recurrence” occurred more frequently among the LLR group (50% vs 12% respectively for LLR and RFA). The CIF of local recurrence at 5-years was significantly higher in the RFA group (9%, 95% CI = 3%–19% vs 60%, 95% CI = 60%–73% respectively for LLR and RFA groups, P < 0.001) (Fig. 2). The length of post-procedural hospital stay was shorter for patients who received RFA (6 vs 3 days respectively for LLR and RFA, P < 0.01), after PS-M of this sub-analysis. Considering complication with Clavien-Dindo score >2, the rate of perioperative morbidity was found to be comparable between the two groups (8% and 4% respectively for LLR and RFA, P = 0.43) (Supplementar Material 3). Type of complications are reported in Supplementar material 4).

Independent factors significantly related to peri-operative complications after LR were: patient's age (at 10 years increase RR = 1.19, 95% CI = 1.01–1.40, P = 0.03), MELD score (RR = 1.03, 95% CI = 1.01–1.07, P = 0.03), BCLC B status vs 0 status (RR = 1.76, 95% = 1.03–2.99, P = 0.04), and BCLC C status vs 0 status (RR = 2.19, 95% CI = 1.20–3.99, P = 0.01) (Supplementar material 5).

Fig. 3 shows the distribution of RFA or LR based on tumor location by liver segment and nodule diameter. Generally, large and anterior nodules were more commonly approached by LR. Whereas for posteriorly located nodules, RFA was usually adopted even for nodules larger than 30 mm. Ninety-nine patients had *superficial* tumors (57 in LR group and 42 in RFA group); whereas 83 had *deep* tumors (34 in LR group and 49 in RFA group). The overall survival was similar among LR and RFA groups irrespective of tumor depth. While patients with *superficial* nodules had a better RFS in the LR vs RFA groups (5-year RFS: 37%, 95% CI = 22%–52% vs 23%, 95% CI = 8%–41% respectively, P < 0.001). Concerning patients with *deep* lesions did not have statistically different RFS between LLR

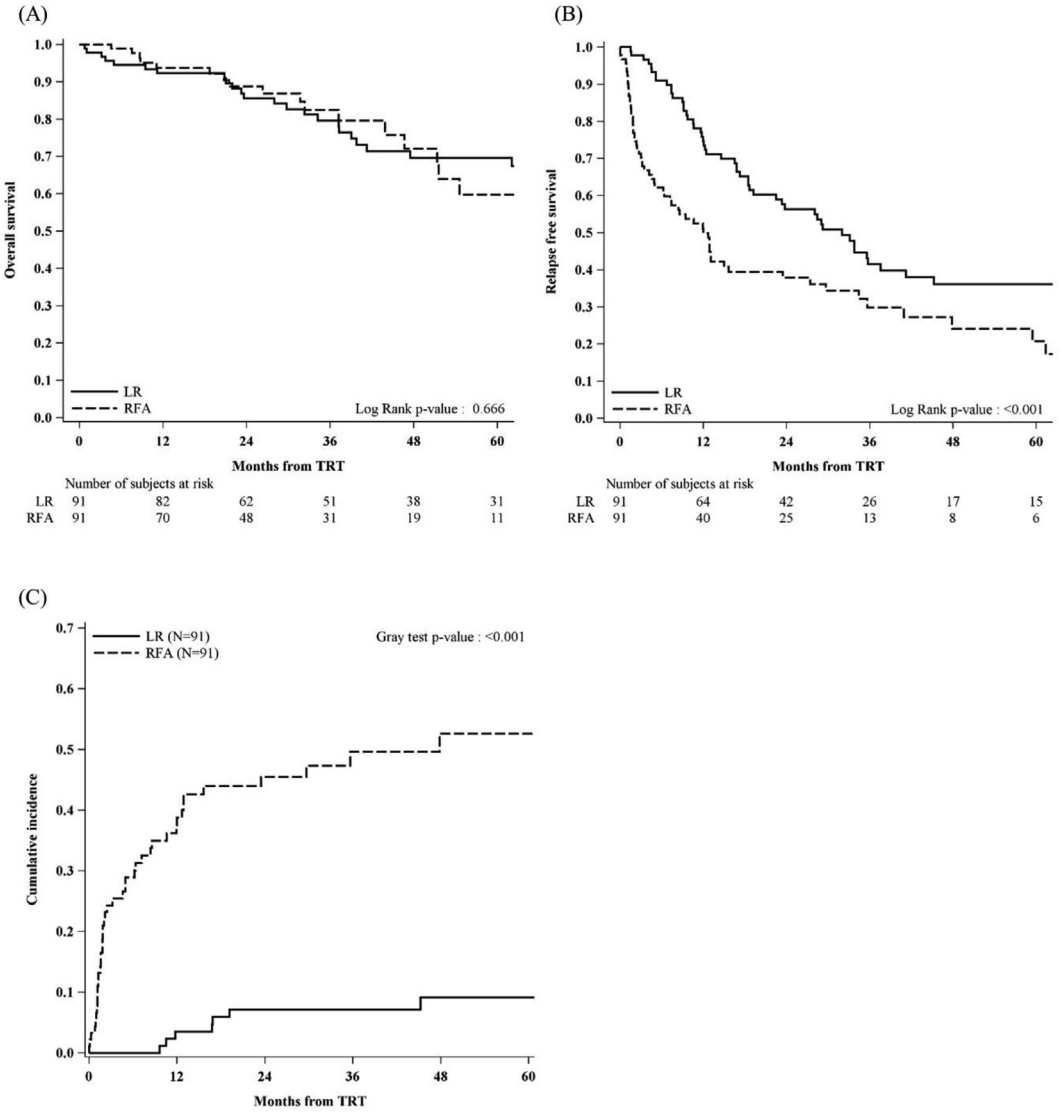

Fig. 1. (A) Overall survival, (B) Relapse free survival and (C) Cumulative incidence curve of local relapse between liver resection, LR (N = 91) and radiofrequency ablation, RFA (N = 91).

and RFA (5-year RFS: 33%, 95% CI = 17%–49% vs 22%, 95% CI = 9%–38%, P = 0.082) (Fig. 4). However, the test of heterogeneity of the surgical approach effect according to the segment localization was not statistically significant (P-value = 0.37).

Discussion

Management of a single small HCC lesion may be challenging for physicians due to the availability of multiple treatment modalities. Liver resection is still considered the gold standard treatment for a single HCC. However, reasons that may favor RFA as a first-line treatment instead include: the significantly lower morbidity and related procedural cost associated with RFA [11]; the possibility to achieve comparable tumor-related outcomes on both the short and long terms for selected small HCCs [5–12].

Several studies have reported better oncological results associated with LR as compared to RFA, even for small (<30 mm) HCC tumors [9]. However, almost all the studies comparing the two approaches have reported worse peri-operative outcomes for patients undergoing LR, namely higher post-procedural morbidity and mortality rates, this is especially true when resections were performed as open surgeries [5–12]. In this scenario, physicians are forced preferring RFA for small HCC (<30 mm), particularly for *deep* nodules. However, RFA presents major limitations such as: 1) Absence of study of pathological tumor features, 2) Inability to check the radicality of the ablation and 3) technical need of detecting the tumor by US for the conduction of the procedure [5].

The present experience demonstrates that after a rigorous PS-M, patients who have received LR for a single and small (<30 mm) HCC, had OS rates comparable to those of patients who underwent RFA. However, the tumor RFS rates were significantly lower in the RFA group from the first treatment, nevertheless this higher tumor recurrence rate was offset by many patients receiving one or more additional interventions for recurrences after the first RFA treatment. Lee HW and co-workers [8] reported results from a prospective trial of a highly selected patient cohort of single small HCCs. The authors showed, similarly to the present study, a significantly better recurrence free survival after LR than RFA (respectively, 44.4% vs 31.2%). The CIF of local tumor recurrence in the present series was particularly higher in the RFA group (53%),

Table 2
Comparison between RFA and LLR both without PS-M and with PS-M (N = 194).

		Before PS-M			After PS-M		
		LLR (N = 51)	RFA (N = 143)	P [a]	LLR (N = 50)	RFA (N = 50)	P [a] (D [b])
Variables used in propensity matching							
Age (year), median (IQR)		68 (62, 76)	65 (57, 75)	0.19	68 (62, 76)	67 (56, 76)	0.75 (0.11)
MELD score, median (IQR)		8 (7, 10)	9 (7, 12)	0.05	8 (7, 10)	7 (7, 9)	0.05 (0.26)
PLT, median (IQR)		139 (98, 208)	102 (70, 147)	<0.01	137 (98, 211)	131 (96, 179)	0.68 (0.07)
Nodule's diameter at DG (mm), median (IQR)		25 (20, 30)	20 (16, 25)	<0.01	25 (20, 30)	22 (18, 30)	0.36 (0.20)
HCV, N (%)	No	19 (37.3)	48 (33.6)	0.76	19 (38.0)	22 (44.0)	0.68 (0.12)
	Yes	32 (62.7)	95 (66.4)		31 (62.0)	28 (56.0)	
AFP, N (%) [c]	≤5	14 (27.5)	42 (29.4)	0.76	14 (28.0)	16 (32.0)	0.94 (0.13)
	5–20	13 (25.5)	35 (24.5)		12 (24.0)	10 (20.0)	
	>20	15 (29.4)	33 (23.1)		15 (30.0)	16 (32.0)	
	Missing	9 (17.6)	33 (23.1)		9 (18.0)	8 (16.0)	
ALBI score, N (%)	Grade I	26 (51.0)	50 (35.0)	0.02	25 (50.0)	29 (58.0)	0.71 (0.17)
	Grade II	23 (45.1)	64 (44.8)		23 (46.0)	19 (38.0)	
	Grade III	2 (3.9)	7 (4.9)		2 (4.0)	2 (4.0)	
	Missing	0 (0.0)	22 (15.4)		0 (0.0)	0 (0.0)	
Variables not used in propensity matching				P [a]			P [a] (D [b])
CHILD score, median (IQR)		5 (5, 6)	5 (5, 6)	0.30	5 (5, 6)	5 (5, 6)	0.64 (0.05)
	Missing	5	20		0	4	
ALT, median (IQR)		47 (30, 70)	42 (26, 85)	0.68	48 (30, 71)	38 (20, 90)	0.62 (0.09)
	Missing	0	21		0	2	
AST, median (IQR)		41 (28, 81)	55 (33, 89)	0.12	41 (28, 82)	38 (26, 86)	0.84 (0.07)
	Missing	12	37		12	6	
INR, median (IQR)		1.11 (1.06, 1.21)	1.15 (1.09, 1.34)	0.03	1.12 (1.06, 1.22)	1.10 (1.04, 1.18)	0.29 (0.11)
	Missing	0	17		0	0	
Creatinine, median (IQR)		0.81 (0.72, 0.95)	0.80 (0.70, 0.95)	0.93	0.81 (0.71, 0.95)	0.80 (0.70, 0.92)	1.00 (0.01)
	Missing	0	12		0	0	
Sex, N (%)	Men	34 (66.7)	106 (74.1)	0.40	33 (66.0)	37 (74.0)	0.51 (0.18)
	Women	17 (33.3)	37 (25.9)		17 (34.0)	13 (26.0)	
PS, N (%)	0	45 (88.2)	107 (74.8)	0.13	44 (88.0)	41 (82.0)	0.57 (0.17)
	1	6 (11.8)	35 (24.5)		6 (12.0)	9 (18.0)	
	2	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	
Presence of cirrhosis, N (%)	No	8 (15.7)	6 (4.2)	0.02	8 (16.0)	1 (2.0)	0.04 (0.50)
	Yes	43 (84.3)	137 (95.8)		42 (84.0)	49 (98.0)	
Alcol, N (%)	No	39 (76.5)	99 (69.2)	0.42	38 (76.0)	33 (66.0)	0.38 (0.22)
	Yes	12 (23.5)	44 (30.8)		12 (24.0)	17 (34.0)	
HBV, N (%)	No	42 (82.4)	125 (87.4)	0.51	41 (82.0)	41 (82.0)	1.00 (0.00)
	Yes	9 (17.6)	18 (12.6)		9 (18.0)	9 (18.0)	
Satellitosis, N (%)	No	40 (78.4)	129 (90.2)	0.06	39 (78.0)	44 (88.0)	0.29 (0.27)
	Yes	11 (21.6)	14 (9.8)		11 (22.0)	6 (12.0)	
Macrovascular invasion, N (%)	No	51 (100.0)	141 (98.6)	0.97	50 (100.0)	50 (100.0)	–
	Yes	0 (0.0)	2 (1.4)		0 (0.0)	0 (0.0)	
BCLC, N (%)	0	18 (35.3)	65 (45.5)	0.07	18 (36.0)	14 (28.0)	0.22 (0.35)
	A	31 (60.8)	77 (53.8)		30 (60.0)	36 (72.0)	
	B	2 (3.9)	0 (0.0)		2 (4.0)	0 (0.0)	
	C	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	
Milano stage, N (%)	In	48 (94.1)	125 (87.4)	0.29	47 (94.0)	43 (86.0)	0.32 (0.27)
	Out	3 (5.9)	18 (12.6)		3 (6.0)	7 (14.0)	
Sub-capsular nodule, N (%)	Deep	7 (14.0)	66 (51.2)	<0.01	7 (14.0)	22 (44.0)	<0.01 (0.70)
	Superficial	43 (86.0)	63 (48.8)		43 (86.0)	28 (56.0)	
	Missing	1	14		0	0	
Biopsy pre TRT, N (%)	No	34 (85.0)	120 (85.1)	1.00	34 (85.0)	41 (82.0)	0.92 (0.08)
	Yes	6 (15.0)	21 (14.9)		6 (15.0)	9 (18.0)	
	Missing	11	2		10	0	

PS-M: propensity-score matching.
LLR: laparoscopic liver resection.
RFA: radiofrequency ablation.
PT: patient.
DG: diagnosis.
IQR: interquartile range.
PS: performance status.
TRT: treatment.
[a] Chi-square p-value for categorical variables, Wilcoxon p-value for continuous variables.
[b] Distance D is standardized mean difference.
[c] Categorized by tertiles.

and it was comparable to other studies [29–31]. However, it should be noted that in most cases re-treatment of a recurrent nodule is easier and more feasible after RFA than LR, this may justify why the overall survival of patients treated by RFA was similar to the LR group despite a higher recurrence rate.

Given the possibility to achieve similar long term survival after RFA or LR for a single HCC, the first-line treatment is sometimes chosen while taking into account the procedure-related morbidity

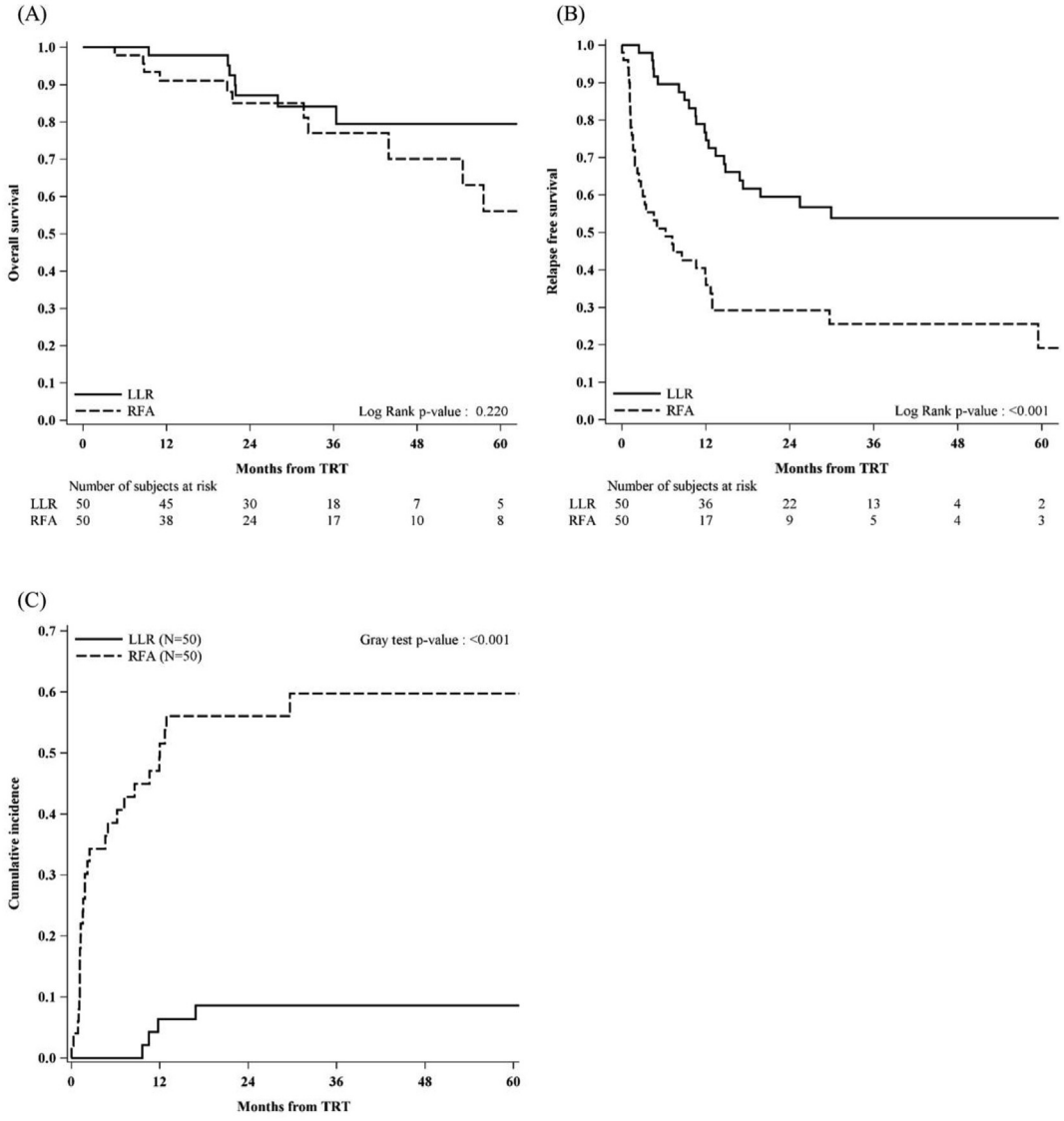

Fig. 2. (A) Overall survival, (B) Relapse free survival and (C) Cumulative incidence curve of local relapse between laparoscopic liver resection, LLR (N = 50) and radiofrequency ablation, RFA (N = 50).

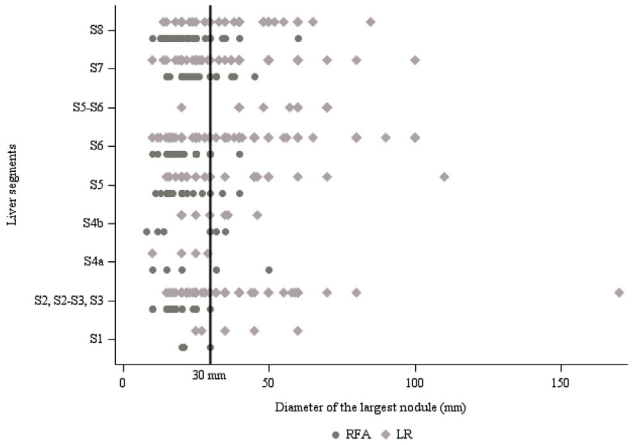

Fig. 3. Nodule diameter distribution (mm) divided according to the treatment before propensity-score matching. LR, liver resection; RFA, radiofrequency ablation.

and mortality risks. In the present series, patients who have received LR experienced a significantly higher risk of peri-operative complication (23.6% vs 3.3% for Clavien-Dindo score ≥ 2 respectively for LR and RFA). Moreover, the hospital stay was much longer for patients treated by LR, considering both the open and laparoscopic technique after PS-M. These results were similar to other series [5–13] and confirm that LR provides a higher potential of cure and tumor-related free survival, but with a significantly higher risk of complications.

Recently the laparoscopic approach for HCC on liver cirrhosis has gained popularity worldwide, particularly in high volume centers [32–35]. Major benefits from LLR are the lower rate of peri-operative complications, particularly in terms of lower post-hepatectomy liver failure and lower bleeding rates, shorter hospital stay and improved esthetic results [14,15]. The oncological and long term patient outcomes after LLR were found to be similar to the open approach [14,15]. In that regard, we have compared the selected cohort of LLR group to the RFA group, after PS-M. The OS was lower in the RFA group, but this was not statistically significant. Otherwise, the RFS was significantly lower for patients who have

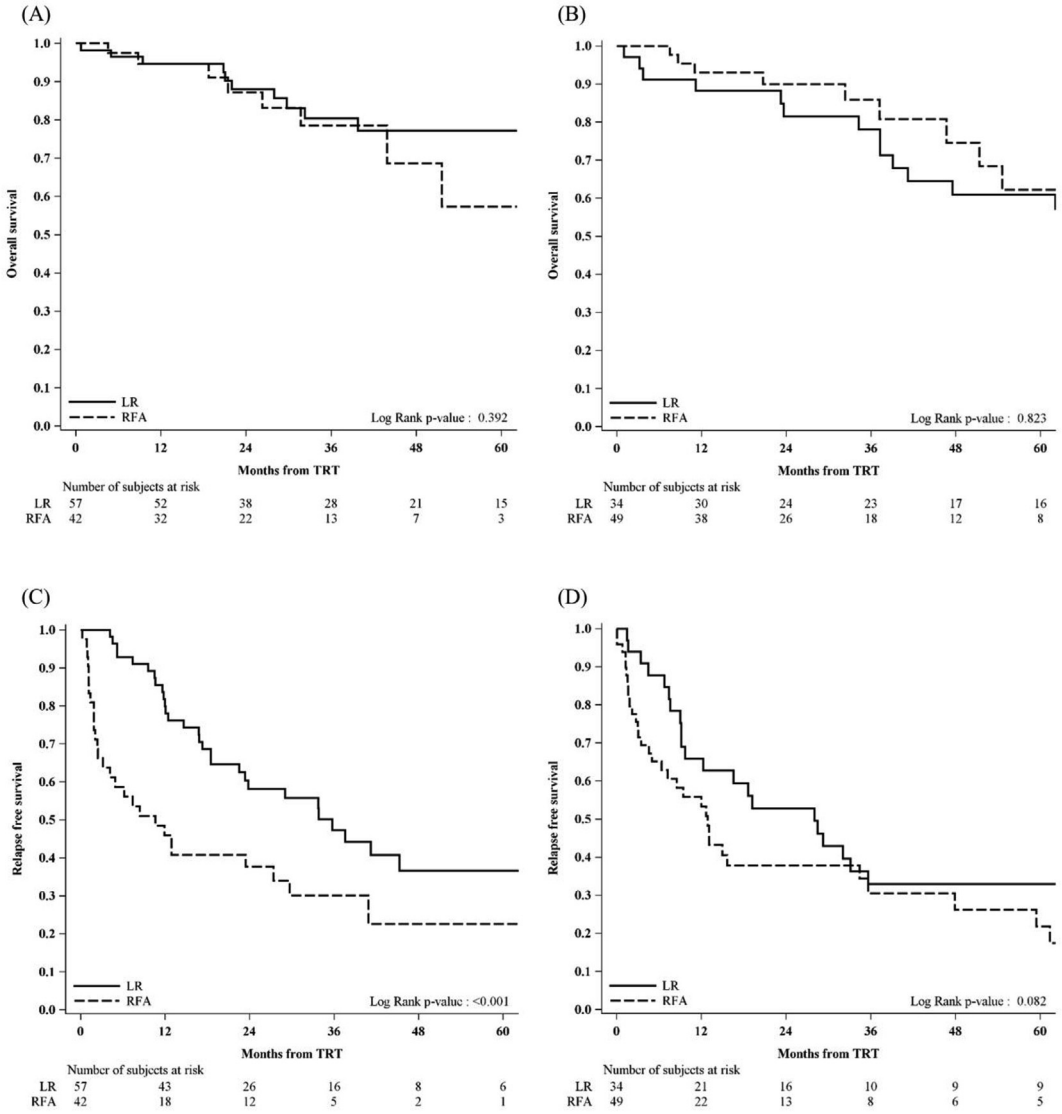

Fig. 4. Overall survival of patients with (A) superficial nodule (N = 99) and (B) deep nodule (N = 83) undergoing liver resection, LR and radiofrequency ablation, RFA after propensity-score matching. Relapse free survival of patients with (C) superficial nodule (N = 99) and (D) deep nodule (N = 83).

received RFA rather than LLR (19% vs 54%, P < 0.0001) as well as the CIF of local recurrence at 5-year was superior in the RFA group (60% vs 9%, P < 0.0001). These results echo those from other experiences, notably the Vitali G. and co-workers' study [8,9]. In contrast to the complete LR group (open and laparoscopic), after selecting only the patients who underwent LLR and comparing them to the RFA group, the peri-operative morbidity and mortality was not found to be significantly different between the two groups (8.0% vs 4.0% for Clavien-Dindo score ≥ 2 respectively for LLR and RFA group, P = 0.43) despite a persistently longer hospital stay for the LLR group. Other experiences reported very similar results [8–12].

The multivariable regression analysis performed on the factors related to peri-operative complications in the LR group showed that older age, higher MELD score, and BCLC B or C are strong predictive factors for *perioperative complications*. Therefore, patients presenting one or more of these risk factors should be considered for LLR or RFA rather than open surgery [14,15].

Although generally RFA is preferred for *deep* lesions and LR for *superficial* ones; sometimes, several other factors may come into play and alter the decision-making process. In fact, in the present series 34 patients received LR for *deep* nodules and 42 patients received RFA for *superficial* nodules. If the OS was similar between RFA or LR, the RFS for *superficial* nodules however was significantly higher for patients who underwent LR. In contrast, the RFS for deep nodules was not statistically different between the two treatment groups. This might be explained by the fact that deeper tumors having a better liver parenchymal surrounding, allow interventional radiologists to reach the nodule center with the RFA needle and more effectively treat it.

The present study is limited by its retrospective nature, the clinical tendency to treat *superficial* nodules by LR and *deep* nodules by RFA which introduces an inherent selection bias as well as the steeper learning curve associated with LLR as compared to open LR which may underestimate some of the advantages associated with LLR.

In conclusion, patient long-term survival is similar when treated by RFA or LR for a single HCC nodule smaller than 3 cm. The RFS however seems to be superior following LR, for all LR as well as for LLR. Laparoscopic liver resection also confers a similar low peri-operative complications rate, comparable to RFA. Therefore, we

believe that LLR should be considered as a first-line approach for the treatment of a single small HCC as it combines the effectiveness of open LR and the safety profile of RFA. Patients with advanced cirrhosis and not suitable for LLR however should still be preferably considered for RFA, especially in cases of *deep* nodules.

Conflict of interest

None of the authors have any conflict of interest.

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Ethical approval

After discussion from our institutional scientific board, the study received the formal ethical approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.023.

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