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Predictors of non-transplantable recurrence in hepatocellular carcinoma patients treated with frontline liver resection

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) recurrence is common in patients treated with liver resection (LR). In this study, we aimed to evaluate the incidence and preoperative predictors of non-transplantable recurrence in patients with single HCC ≤5 cm treated with frontline LR.

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IQR, interquartile range; ITA.LI.CA, Italian Liver Cancer; LR, liver resection; LT, liver transplantation; MC, Milan criteria; MVI, macrovascular invasion; NTR, non-transplantable recurrence; OS, overall survival; RFS, recurrence-free survival; SVR, sustained virologic response.

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Methods: From the Italian Liver Cancer (ITA.LI.CA) database, 512 patients receiving frontline LR for single HCC ≤5 cm were retrieved. Incidence and predictors of recurrence beyond Milan criteria (MC) and up-to-seven criteria were compared between patients with HCC <4 and ≥4 cm.

Results: During a median follow-up of 4.2 years, the overall recurrence rate was 55.9%. In the ≥4 cm group, a significantly higher proportion of patients recurred beyond MC at first recurrence (28.9% vs. 14.1%; $p < 0.001$) and overall (44.4% vs. 25.2%; $p < 0.001$). Similar results were found considering recurrence beyond up-to-seven criteria. Compared to those with larger tumours, patients with HCC <4 cm had a longer recurrence-free survival and overall survival. HCC size ≥4 cm and high alpha-fetoprotein (AFP) level at the time of LR were independent predictors of recurrence beyond MC (and up-to-seven criteria). In the subgroup of patients with available histologic information ($n = 354$), microvascular invasion and microsatellite lesions were identified as additional independent risk factors for non-transplantable recurrence.

Conclusions: Despite the high recurrence rate, LR for single HCC ≤5 cm offers excellent long-term survival. Non-transplantable recurrence is predicted by HCC size and AFP levels, among pre-operatively available variables. High-risk patients could be considered for frontline LT or listed for transplantation even before recurrence.

KEYWORDS
hepatectomy, liver cancer, liver transplantation, recurrence, tumour size

1 | INTRODUCTION

Among the available treatments for hepatocellular carcinoma (HCC), surgery ranks at the top of the therapeutic hierarchy.[1,2] Liver resection (LR) and liver transplantation (LT) are the first options in patients with early tumours,[3] but the choice between these two alternatives can be challenging. In well-selected candidates LR provides excellent results, with a 5-year survival rate of 60%–80%.[3,4] Nevertheless, it is burdened by a high risk of tumour recurrence, which complicates 50–70% of the cases at 5 years[5–7] and which remains high also for tumours within the Milan criteria (MC) (5-year recurrence-free survival rate 40%–48%).[8–10] By contrast, in early HCC, upfront LT provides excellent survival results with a 5-year recurrence rate of <15%.[11] Drawbacks of this approach are the shortage of donor organs and the risk of progression and drop-out while on the waiting list. Therefore, the strategy of treating patients with LR in first-line, leaving LT as an option in case of HCC recurrence has been advocated.[12,13] Although salvage and upfront LT showed comparable survival results,[14–17] the former approach could be an option provided that a transplantable recurrence has occurred. In this study, we aimed to assess the incidence and preoperative predictors of non-transplantable recurrence (NTR) in patients with single small (≤5 cm) HCC treated with frontline LR, evaluating in particular whether tumour size in these patients could be a relevant prognostic parameter.

Lay summary

HCC recurrence is common after liver resection (LR), and salvage liver transplantation (LT) could be an option provided that a transplantable recurrence has occurred. Among patients with single HCC ≤5 cm treated with frontline LR, we found a greater risk of recurrence beyond Milan criteria and up-to-seven criteria in those with HCC ≥4 cm and higher AFP levels. These patients could be considered for frontline LT or listed for transplantation after LR even before recurrence.

2 | PATIENTS AND METHODS

2.1 | Study design and population

In this retrospective study, data were retrieved from the Italian Liver Cancer (ITA.LI.CA) database, a multicenter registry including data of 9573 HCC patients consecutively managed at the 24 participating Institutions from January 1988 to December 2020. Patients provided written informed consent for every diagnostic and therapeutic procedure, as well as for having their data recorded anonymously in the ITA.LI.CA database. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was

approved by the Institutional Review Board of the participating Institutions.

From the ITA.LI.CA database, 805 patients with single HCC treated with frontline LR after January 2000 were considered. A total of 293 patients were excluded because of HCC size >5 cm ($n=128$), unknown size ($n=59$), presence of macrovascular invasion (MVI) ($n=21$) or extrahepatic spread (EHS) ($n=5$). Additional 80 patients were excluded for having a recurrence registered in the database in the 3 months following LR, thus leaving the possibility that these represent tumour persistence rather than true recurrences. Finally, 512 patients receiving LR as first-line treatment for single HCC ≤5 cm were included in the present study (Supplementary Figure S1). The study cohort was analysed in two groups of patients according to the calculated best cut-off of HCC size at the time of LR. A sensitivity analysis was conducted in the subgroup of patients defined as transplantable at the time of LR ($n=330$). Transplantability was arbitrarily defined as any patient younger than 70 years old, with no comorbidities that would preclude LT (e.g. uncontrolled cardiovascular, renal and pulmonary disorders; BMI >30 kg/m^2; history of extrahepatic malignancy).

HCC was histologically confirmed before LR in 166 patients (32.4%), whereas the others were diagnosed with non-invasive criteria according to international guidelines.[3,4]

Beyond standard demographic and clinicopathological data, the ITA.LI.CA database reports on main macroscopic tumour characteristics (number and size of lesions, presence of MVI and EHS) and treatment. Even though information obtained from the pathological specimen after resection is not systematically reported in the ITA.LI.CA database, in order to account for these parameters in the analyses, histologic information (i.e. microvascular invasion, tumour differentiation, diameter in the resected specimen, microsatellite lesions, R0 margin) was retrospectively collected. Unfortunately, we were not able to collect these data for the entire study cohort (pathological information available in 354/512 patients [69.1%]), and a subgroup analysis was performed in these patients. The HCC histological grade was evaluated on the pathological specimen according to the Edmondson-Steiner system.[18]

For each patient in the database, complete information regarding all HCC recurrence events (defined as the appearance of a new lesion on imaging, radiologically compatible with HCC or confirmed by histology) is recorded. In this study, tumour recurrences were divided into intrahepatic or extrahepatic, and when both were present, recurrence was classified as extrahepatic. Moreover, recurrences were also divided into early or late (≤2 vs. >2 years after LR, respectively). Milan criteria and up-to-seven criteria were considered in this study to define NTR. Recurrence beyond Milan criteria (MC) was defined as a single nodule >5 cm, or up to 3 tumours with at least one >3 cm, or >3 neoplastic lesions, or with MVI or EHS.[11] Recurrence beyond up-to-seven criteria was defined as HCC crossing the threshold of seven as the sum of the size of the largest tumour (in cm) and the number of tumours.[19] Patients were classified as within or beyond MC (or up-to-seven criteria) at the time of the first recurrence after LR. Patients with the first recurrence within MC (or up-to-seven criteria) could have undergone further treatment and NTR could be diagnosed at any time during the follow-up.

2.2 | Statistical analysis

First, the study population was divided into two groups according to the identified best cut-off of tumour diameter (HCC <4 cm vs. HCC ≥4 cm). The detailed statistical analysis for the identification of this cut-off is shown in Supplementary Text 1.

Categorical variables are reported as absolute and relative frequency, while continuous data as median and interquartile range (IQR). Difference between groups were evaluated using the chi-square test and Fischer's exact test for categorical variables, and Mann–Whitney test for continuous variables, as appropriate.

Primary outcomes were time-to-first recurrence beyond MC and time-to-recurrence beyond MC overall, at any time during the follow-up. Time-to-recurrence beyond up-to-seven criteria at first recurrence episode and at any time during follow-up were also evaluated. Other outcomes of interest were recurrence rate beyond MC, recurrence rate beyond up-to-seven criteria, overall HCC recurrence rate, recurrence-free survival (RFS), overall survival (OS). Time-to-recurrence beyond MC (or up-to-seven criteria) was defined as the time elapsed between LR and diagnosis of NTR. RFS was defined as the time between LR and diagnosis of HCC recurrence or death (whichever occurred first). Patients who underwent LT as a treatment for recurrent disease were censored at the date of transplant. The study follow-up ended on 31 December 2020, and patients alive and without recurrence at this date were censored in survival analyses.

Time-to-event curves were estimated with the Kaplan–Meier method and compared with the log-rank test. Univariable and multivariable Cox regression analyses were performed to evaluate predictors of recurrence beyond MC or up-to-seven criteria. In the multivariable model, only variables significantly or borderline ($p \le 0.10$) associated with the outcome at the univariable analysis were included. Alpha-fetoprotein (AFP) was included as a categorical variable in the multivariable models. To adjust for over-fitting HRs estimates of best cut-off categories (HCC size and AFP), univariable and multivariable analyses with a shrinkage procedure with a 95% confidence interval (CI) were calculated with the bootstrap-percentile method.[20] However, beyond this confirmatory analysis and in order to give a more useful clinical message, AFP was included as categorized into three groups (<19, 19–100 and >100 ng/mL) in multivariable models. The detailed statistical procedure used to identify the cut-offs for AFP is shown in Supplementary Text 1. Results of multivariate analyses performed in the subgroup of patients with available histopathologic information on the resected specimen were graphically translated in nomograms for all the endpoints (time-to-recurrence beyond MC and beyond up-to-seven criteria, both at first recurrence and at any time during follow-up).

IBM SPSS Statistics (Version 28.0. Armonk, NY: IBM Corp.), R statistical software (version 4.3.0, R Core Team, Vienna, Austria. https://www.R-project.org/) and GraphPad Prism version 8.3.1 (GraphPad Software) were used for statistical analysis. Statistical significance was set at $p \le 0.05$.

TABLE 1 Baseline patient characteristics.

Variable	Overall $n=512$	HCC <4 cm $n=377$	HCC ≥4 cm $n=135$	p
Males—*n* (%)	375 (73.2)	265 (70.3)	110 (81.5)	0.01
Age—median (IQR)	68 (60–73)	67 (59–73)	70 (63–75)	0.01
Etiology				
HBV	59 (11.5)	40 (10.6)	19 (14.1)	0.03
HCV	285 (55.6)	224 (59.4)	61 (45.2)	
ETOH	51 (10.0)	37 (9.8)	14 (10.4)	
NASH	50 (9.8)	35 (9.3)	15 (11.1)	
Other	67 (13.1)	41 (10.9)	26 (19.2)	
Cirrhosis—*n* (%)	405 (79.1)	307 (81.4)	98 (72.6)	0.04
Surveillance—*n* (%)	352 (68.7)	276 (73.2)	76 (56.3)	<0.001
Biopsy for diagnosis—*n* (%)	166 (32.4)	100 (26.5)	66 (48.9)	<0.001
AFP (ng/mL)—median (IQR)	7.0 (3.1–23.1)	6.5 (3.4–21.9)	7.7 (3.0–28.0)	0.95
MELD—median (IQR)	8 (7–9)	8 (7–9)	8 (7–9)	0.67
Child-Pugh A—*n* (%)	467 (91.2)	346 (91.8)	121 (89.6)	0.48
CSPH[a]—*n* (%)	206 (40.2)	165 (43.8)	41 (30.4)	0.008
ECOG-PS 0—*n* (%)	486 (94.9)	358 (95.0)	128 (94.8)	0.99
Albumin (g/L)—median (IQR)	40 (36–43)	40 (36–43)	39 (36–43)	0.29
Bilirubin (mg/dL)—median (IQR)	0.80 (0.60–1.10)	0.80 (0.60–1.10)	0.89 (0.60–1.10)	0.52
INR—median (IQR)	1.09 (1.01–1.16)	1.09 (1.02–1.16)	1.10 (1.00–1.18)	0.92
Creatinine (mg/dL)—median (IQR)	0.88 (0.75–1.00)	0.88 (0.74–1.00)	0.89 (0.75–1.00)	0.56
Platelets ($\times 10^9$/L)—median (IQR)	150 (106–198)	141 (101–189)	173 (136–208)	<0.001
Hepatitis C with SVR—*n* (%)[b]	19 (6.7)	14 (6.3)	5 (8.2)	0.57
Hepatitis B with suppression—*n* (%)[c]	52 (88.1)	34 (85.0)	18 (94.7)	0.41
Pathological information in the resected specimen[d]				
Microvascular invasion—*n* (%)	123 (34.7)	79 (31.2)	44 (43.6)	0.04
Tumour grade				
I	67 (18.9)	52 (20.6)	15 (14.9)	0.25
II	147 (41.5)	109 (43.1)	38 (37.6)	
III	133 (37.6)	87 (34.4)	46 (45.5)	
IV	7 (2.0)	5 (2.0)	2 (2.0)	
Diameter in the resected specimen (cm)	3.0 (2.0–4.0)	2.5 (1.8–3.1)	4.5 (3.9–5.0)	<0.001
Microsatellite lesions—*n* (%)	36 (10.2)	20 (7.9)	16 (15.8)	0.03
R0 margins—*n* (%)	321 (90.7)	230 (90.9)	91 (90.1)	0.84

Abbreviations: AFP, alpha-fetoprotein; CSPH, clinically significant portal hypertension; ECOG-PS, Eastern Cooperative Oncology Group performance status; ETOH, alcoholic liver disease; HBV, chronic hepatitis B; HCV, chronic hepatitis C; INR, International Normalized Ratio; IQR, interquartile range; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis; SVR, sustained virologic response.

[a]CSPH diagnosis was based on the presence of unequivocal signs (splenomegaly, varices, ascites) and platelet count $<100 \times 10^9$/L.

[b]Among the 285 patients with chronic hepatitis C.

[c]Among the 59 patients with chronic hepatitis B.

[d]Available in 354 patients (69.1%).

3 | RESULTS

3.1 | Timing and pattern of HCC recurrence after liver resection

The characteristics of the study cohort are summarized in Table 1. At the time of LR, 377/512 patients (73.6%) had an HCC <4 cm and 135/512 patients (26.4%) had an HCC ≥4 cm.

During a median follow-up of 4.2 years (IQR 2.1–7.2), HCC recurrence was diagnosed in 286/512 patients (55.9%). In particular, 201/377 patients (53.3%) in the HCC <4 cm group and 85/135 patients (63.0%) in the HCC ≥4 cm group experienced tumour recurrence ($p=0.06$).

The median RFS was 3.2 years (95% CI 2.6–3.7) for the entire cohort. Patients with HCC <4 cm had a significantly longer median RFS (3.4 years, 95% CI 2.7–4.0) compared to patients with HCC ≥4 cm (2.3 years, 95% CI 1.8–2.8; $p=0.003$) (Figure 1). The 1-, 3- and 5-year recurrence rates were 14.9%, 44.9% and 59.4% in the HCC <4 cm group versus 23.9%, 57.8% and 74.0% in the HCC ≥4 cm group.

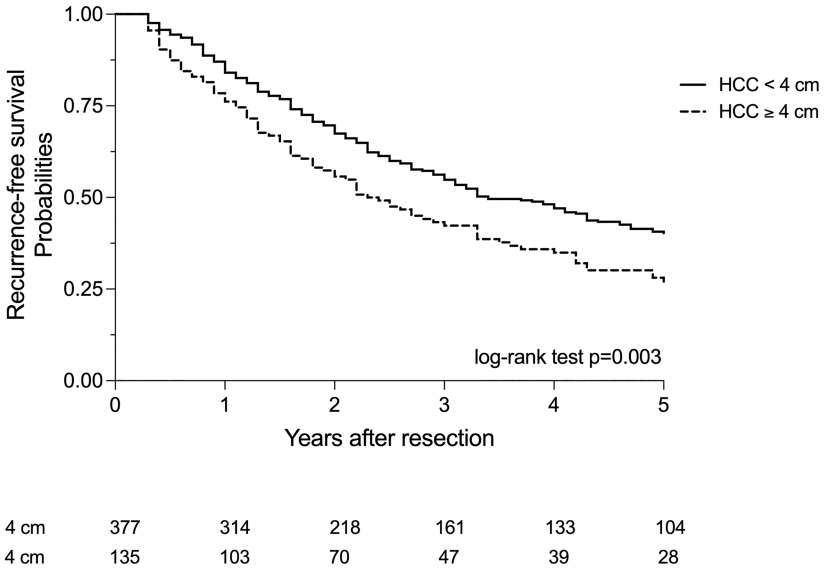

FIGURE 1 Recurrence-free survival probabilities among patients with HCC <4 cm and ≥4 cm treated with first-line liver resection. HCC, hepatocellular carcinoma.

TABLE 2 Patterns of recurrence after liver resection as first-line therapy for patients with HCC ≤5 cm.

Recurrence patterns	Overall *n* = 512	HCC <4 cm *n* = 377	HCC ≥4 cm *n* = 135	*p*
Recurrence—*n* (%)	286 (55.9)	201 (53.3)	85 (63.0)	0.06
First recurrence type—*n* (%)				
Intrahepatic	243 (47.5)	173 (45.9)	70 (51.9)	0.27
Extrahepatic	43 (8.4)	28 (7.4)	15 (11.1)	0.21
Beyond Milan criteria—*n* (%)				
At first recurrence	92 (18.0)	53 (14.1)	39 (28.9)	<0.001
At any time during follow-up	155 (30.3)	95 (25.2)	60 (44.4)	<0.0001
Reason for being classified as beyond Milan criteria—*n* (%)[a]				
Tumour size and/or number	80 (51.6)	44 (46.3)	36 (60.0)	0.10
Macrovascular invasion	37 (23.9)	31 (32.6)	6 (10.0)	0.002
Metastatic disease	38 (24.5)	20 (21.1)	18 (30.0)	0.25
Beyond Up-to-seven criteria—*n* (%)				
At first recurrence	78 (15.2)	46 (12.2)	32 (23.7)	0.002
At any time during follow-up	135 (26.4)	85 (22.5)	50 (37.0)	0.001

[a]Among the 155 patients who had recurrence beyond Milan criteria.

Table 2 reports the pattern of HCC recurrence after LR. The first recurrence was intrahepatic in 243/512 patients (47.5%) and extrahepatic in 43/512 patients (8.4%). The time-to-recurrence was 1.8 years (95% CI 1.5–2.1) in patients with intrahepatic recurrence and 1.7 years (95% CI 0.7–2.6) in those with extrahepatic disease ($p = 0.20$).

Among patients with HCV, 19/285 (6.7%) had achieved sustained virologic response (SVR) at the time of LR. The recurrence rate was 37.5% among patients with SVR and 55.1% for those without SVR ($p = 0.20$). Among the 59 patients with HBV, 52 (88.1%) were suppressed at the time of LR, and the recurrence rate was not significantly different among patients with and without virologic suppression (63.5% and 71.4%, respectively; $p = 0.99$).

After a median time of 2.0 years (IQR 0.9–3.8), a *first* recurrence beyond MC was diagnosed in 92/512 patients (18.0%). Among them, 40/92 patients (43.5%) exceeded the MC for size/number, 24/92 (26.1%) for MVI and 28/92 (30.4%) for EHS. *First* recurrence beyond MC was less frequent in the <4 cm group (54/377, 14.1%) than in the ≥4 cm group (39/135, 28.9%) ($p < 0.001$), and the cumulative hazard of *first* recurrence beyond MC was significantly lower in the former group ($p < 0.001$) (Figure 2A).

During the follow-up, 155/512 patients (30.3%) overall had a recurrence beyond MC, after a median time of 2.4 years (IQR 1.2–4.2) from LR. The cumulative hazard of recurrence beyond MC was significantly higher in patients with tumours ≥4 cm ($p < 0.001$) (Figure 2B). Namely, 95/377 patients (25.2%) in the HCC <4 cm and 60/135 patients (44.4%) in the HCC ≥4 cm group recurred beyond MC ($p < 0.001$). The majority of patients (80/155, 51.6%) exceeded MC for size/number of nodules, while MVI (37/155, 23.9%) and EHS (38/155, 24.5%) occurred less frequently.

As far as up-to-seven criteria were considered, *first* non-transplantable recurrence was diagnosed in 78/512 patients

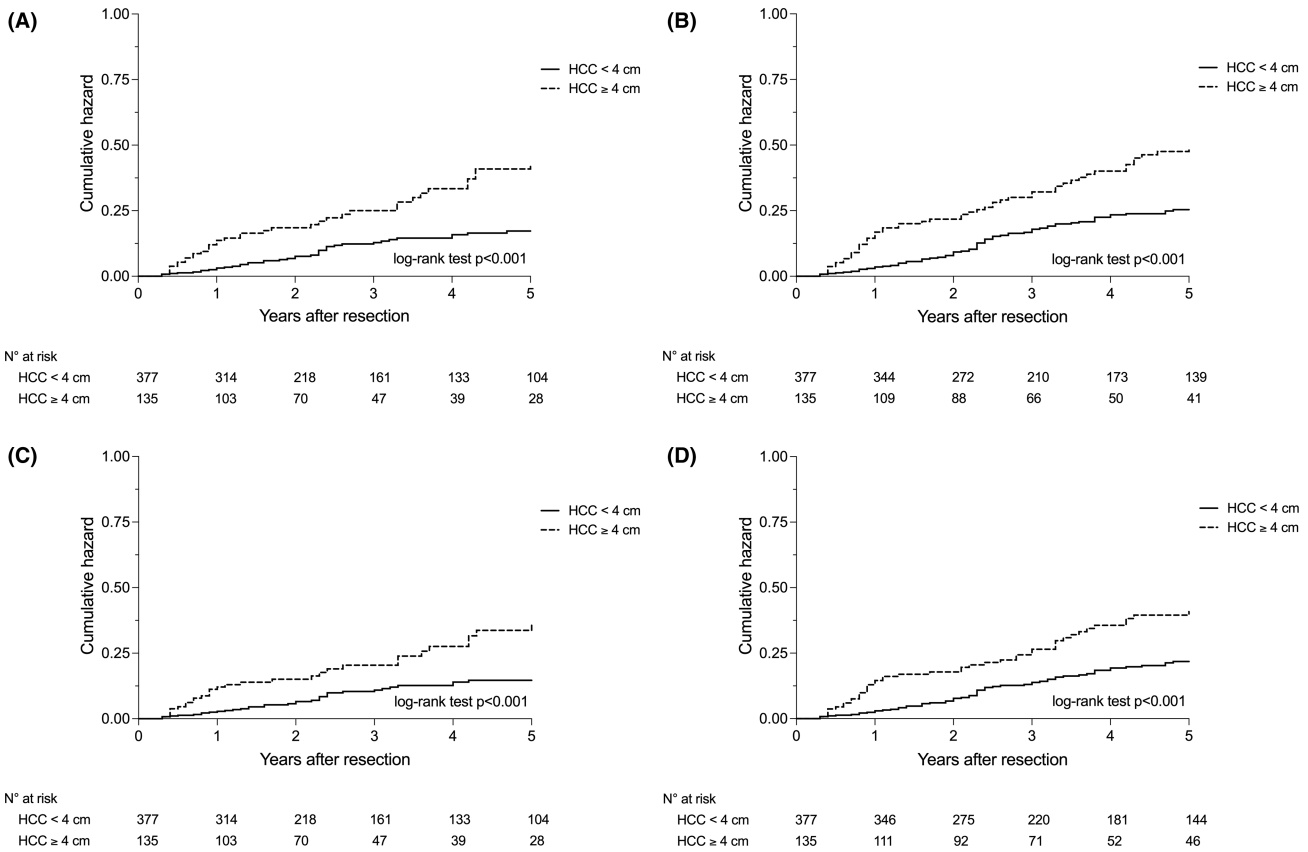

FIGURE 2 Cumulative hazard of recurrence beyond Milan criteria and up-to-seven criteria among patients with HCC <4 cm and ≥4 cm treated with first-line liver resection. (A) Cumulative hazard of *first* recurrence beyond Milan criteria. (B) Cumulative hazard of overall recurrence beyond Milan criteria during follow-up. (C) Cumulative hazard of *first* recurrence beyond up-to-seven criteria. (D) Cumulative hazard of overall recurrence beyond up-to-seven criteria during follow-up. HCC, hepatocellular carcinoma.

(15.2%), with a higher risk in patients with HCC ≥4 cm ($p < 0.001$) (Figure 2C). Indeed, *first* recurrence beyond up-to-seven criteria was registered in 46/377 patients (12.2%) of the HCC <4 cm group and in 32/135 patients (23.7%) of the HCC ≥4 cm group ($p = 0.002$). Among the 135/512 patients (26.4%) with recurrence beyond up-to-seven criteria at any time during the follow-up, 85/377 patients (22.5%) had an HCC <4 cm and 50/135 (37.0%) had an HCC ≥4 cm ($p = 0.001$). The cumulative hazard of recurrence beyond up-to-seven was significantly higher in patients with larger tumours ($p < 0.001$) (Figure 2D).

HCC recurred *early* (≤2 years after LR) in 151/512 patients (29.5%) (Supplementary Table S1) and this type of recurrence was significantly more common in the HCC ≥4 cm group than in the HCC <4 cm group (52/135 [37.8%] vs. 100/377 [26.5%], respectively; $p = 0.02$). Moreover, among the 58/512 patients (11.3%) with an early recurrence beyond MC, this event occurred more frequently in patients with an initial HCC ≥4 cm than in the counterpart (20.7% vs.8.0%, respectively; $p < 0.001$). The majority of patients with an early recurrence beyond MC (45/512, 8.8%) crossed the boundaries of these criteria already at their *first* recurrence episode, and this event was less frequent in the HCC <4 cm group (23/377, 6.1%) than in the HCC ≥4 cm group (22/135, 16.3%) ($p < 0.001$). Early recurrence beyond up-to-seven criteria was demonstrated in 38/512 patients (7.4%) at *first* recurrence and in 48/512 patients (9.4%) at any time during follow-up. Both at *first* recurrence episode and during follow-up, the threshold of up-to-seven criteria was crossed by a statistically significant higher proportion of patients in the HCC ≥4 cm group ($p = 0.004$ and $p < 0.001$, respectively).

3.2 | Treatment of the first recurrence episode

In both groups, the majority of first recurrences were managed with ablation (41.3% in the <4 cm group vs. 31.8% in the ≥4 cm group, $p = 0.14$) or transarterial chemoembolization (25.9% vs. 34.1%; $p = 0.20$) (Supplementary Table S2). LR was repeated in 23/201 patients (11.4%) with initial HCC <4 cm and in 10/85 patients (11.8%) with initial HCC ≥4 cm ($p = 0.99$). Interestingly, only 9/201 patients (4.5%) with initial HCC <4 cm and 4/85 patients (4.7%) with initial HCC ≥4 cm ($p = 0.99$) underwent LT at the time of the first recurrence, and the limited use of LT was confirmed even in those with recurrence within MC. During the entire follow-up, only 23/286 patients (8.0%) were eventually transplanted, without differences between the two groups [17/201 (8.5%) in the <4 cm group and 6/85 (7.1%) in the ≥4 cm group ($p = 0.81$)].

3.3 | Predictors of non-transplantable recurrence after liver resection

Among the preoperatively available variables, only HCC size and AFP were significantly associated with the recurrence beyond MC at the univariable analysis. After the demonstration that these variables categorized according to the identified best cut-offs remained independent prognostic predictors adjusting for over-fitting of HRs estimates with the shrinkage procedure (Supplementary Table S3), the final multivariable models were created (Table 3). Independent predictors of *first* recurrence beyond MC were tumour size ≥4 cm (HR = 2.25, 95% CI 1.46–3.48) and AFP levels (HR = 2.02, 95% CI 1.19–3.44, for AFP 19–100 ng/mL and HR = 3.39, 95% CI 2.00–5.76, for AFP > 100 ng/mL) at the time of LR. The same variables independently predicted overall recurrence beyond MC at any time during the follow-up. As far as the recurrence risk beyond up-to-seven criteria was considered, similar results were obtained, with tumour size and AFP that remained independently associated with the outcome (Supplementary Table S4).

The combination of tumour size and AFP accurately stratified the risk of first and overall recurrence beyond MC and up-to-seven criteria (Figure 3). Patients were divided into three groups according to the presence of 0, 1 and 2 risk factors (HCC ≥4 cm and AFP > 100 ng/mL). The 5-year recurrence rate beyond MC (at *first* recurrence episode) was 15.7% in patients without pre-operative risk factors, 39.9% in those with only one risk factor, and 58.5% in those with both risk factors. Similar results were obtained considering the risk of crossing the MC threshold at any time during follow-up and with time-to-recurrence beyond up-to-seven criteria as an outcome.

TABLE 3 Multivariable regression models to predict recurrence beyond Milan criteria at first recurrence and at any time during the follow-up in single ≤5 cm HCC patients treated with first-line liver resection.

	Beyond MC at first recurrence				Beyond MC at any time during the follow-up			
	Univariable		Mutlivariable		Univariable		Multivariable	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex								
Male	–	–	–	–	–	–	–	–
Female	0.87 (0.56–1.36)	0.55			0.90 (0.64–1.27)	0.55		
Age	1.02 (0.99–1.04)	0.16	–	–	1.01 (0.99–1.03)	0.14	–	–
Surveillance								
No	–	–	–	–	–	–	–	–
Yes	0.79 (0.51–1.23)	0.31			0.90 (0.63–1.27)	0.53		
Etiology								
HBV	–	–	–	–	–	–	–	–
HCV	0.91 (0.49–1.66)	0.75			0.89 (0.56–1.43)	0.64		
ETOH	0.66 (0.27–1.59)	0.35			0.93 (0.50–1.76)	0.83		
NASH	0.97 (0.41–2.26)	0.94			1.01 (0.53–1.93)	0.98		
Other	0.39 (0.14–1.70)	0.18			0.82 (0.43–1.57)	0.55		
CSPH[a]								
No	–	–	-	–	–	–	–	–
Yes	0.72 (0.46–1.13)	0.16			0.92 (0.66–1.28)	0.62		
HCC size								
<4 cm	–	–	–	–	–	–	–	–
≥4 cm	2.41 (1.60–3.65)	<0.001	2.25 (1.46–3.48)	<0.001	2.07 (1.50–2.86)	<0.001	1.92 (1.30–2.84)	<0.001
AFP (ng/mL)								
<19	–	–	–	–	–	–	–	–
19–100	2.04 (1.20–3.46)	0.008	2.02 (1.19–3.44)	0.009	1.96 (1.33–2.90)	<0.001	1.92 (1.30–2.84)	<0.001
≥100	3.29 (1.94–5.59)	<0.001	3.39 (2.00–5.76)	<0.001	2.52 (1.63–3.90)	<0.001	2.52 (1.63–3.90)	<0.001
MELD	1.01 (0.97–1.05)	0.67	–	–	1.01 (0.98–1.04)	0.55	–	–
Child-Pugh								
A	–	–	–	–	–	–	–	–
B	0.99 (0.46–2.16)	0.99			1.27 (0.73–2.21)	0.40		

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CSPH, clinically significant portal hypertension; ETOH, alcoholic liver disease; HBV, chronic hepatitis B; HCC, hepatocellular carcinoma; HCV, chronic hepatitis C; HR, hazard ratio; MC, Milan criteria; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis.

[a]CSPH diagnosis was based on the presence of unequivocal signs (splenomegaly, varices, ascites) and platelet count $<100 \times 10^9$/L.

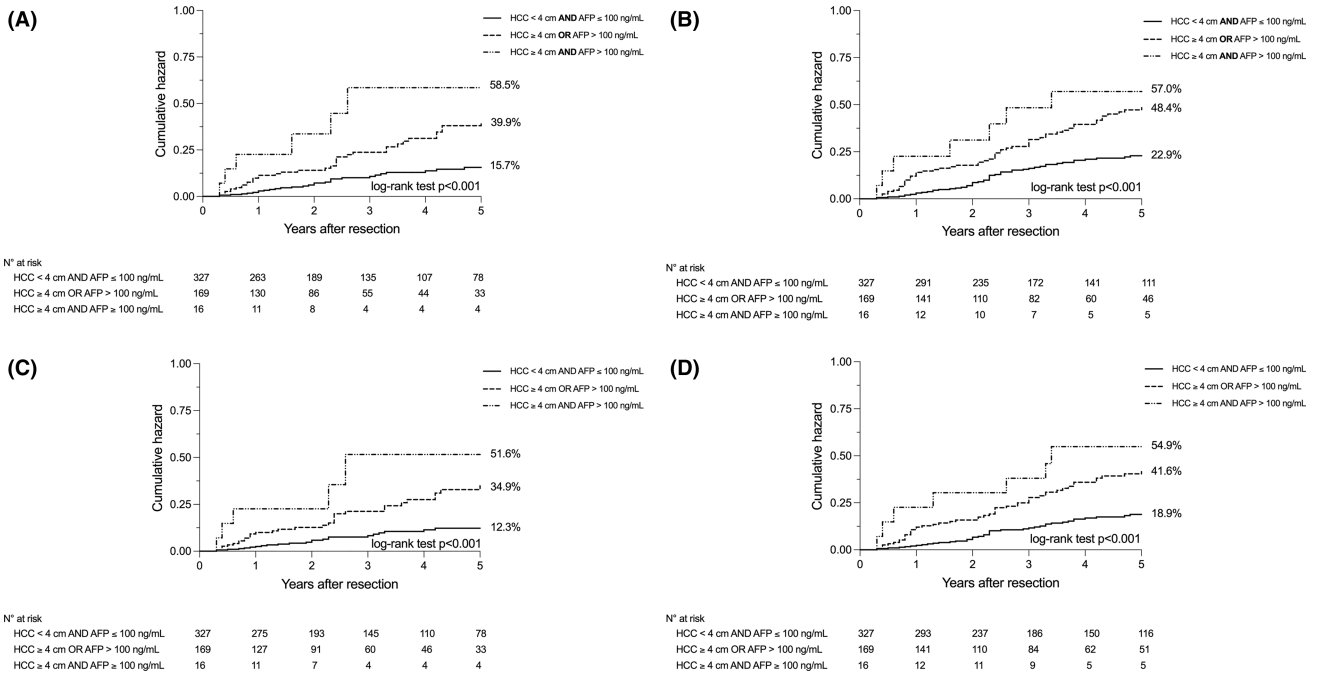

FIGURE 3 Risk of recurrence beyond Milan criteria and up-to-seven criteria according to tumour size and alpha-fetoprotein levels at the time of liver resection. (A) Rates of first recurrence beyond Milan criteria. (B) Rates of recurrence beyond Milan criteria at any time during follow-up. (C) Rates of first recurrence beyond up-to-seven criteria. (D) Rates of recurrence beyond up-to-seven criteria at any time during follow-up. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

Univariable and multivariable analyses in the subgroup of patients with available pathological information after LR are shown in Table 4. In addition to HCC size and AFP levels, that remained independently associated with the outcome in these patients, microvascular invasion (HR = 2.63, 95% CI 1.53–4.51) and microsatellite lesions (HR = 2.23, 95% CI 1.15–4.33) emerged as additional predictors of *first* recurrence beyond MC. When the recurrence beyond MC at any time during follow-up was considered, the same variables were singled out in the multivariable model. Similar results were obtained also considering *first* and overall recurrence beyond up-to-seven criteria (Supplementary Table S5). The variables singled out in multivariate models as independent predictors of NTR (HCC size, AFP levels, microvascular invasion, microsatellite lesions) were combined in nomograms, which provided a risk score that can be used to predict the probability of non-transplantable recurrence-free survival at 1, 3 and 5 years (Figure 4).

3.4 | Overall survival

Median survival after LR for the entire cohort was 8.5 years (95% CI 7.4–10.1). The survival of patients with HCC <4 cm (8.8 years, 95% CI 6.7–10.9) was significantly longer than that of patients with larger tumours (7.0 years, 95% CI 4.2–9.9; $p = 0.01$) (Supplementary Figure S6). The 1-, 3- and 5-years survival rates were 97.0%, 85.7% and 72.6% in the HCC <4 cm group vs. 94.0%, 74.9% and 62.4% in the HCC ≥4 cm group.

3.5 | Sensitivity analysis in the group of 'ab initio' potentially transplantable patients

A sensitivity analysis was performed in the subgroup of patients defined as 'ab initio' potentially transplantable. The results obtained in this subgroup, reported in Supplementary Text 2, confirmed those obtained in the entire study population.

4 | DISCUSSION

Liver resection in the treatment of HCC provides a long survival, but it is burdened by a high incidence of tumour recurrence (50%–70% within 5 years).[5–7,21–23] This study confirmed the high recurrence rate even in patients with single HCC ≤5 cm receiving LR, since more than half of them (55.9%) recurred over a median follow-up of 4.2 years. In these patients, frontline LT may be an alternative to LR. Despite several studies carried out on this subject, the best therapeutic management of patients with early-stage single HCC (LR with salvage LT in case of recurrence vs. frontline LT) is still debated.[16,17,24,25] The strategy of frontline LR followed by salvage LT in case of tumour recurrence has some potential advantages, including: the reduction in the use of liver grafts, as resected patients may survive for a long time without recurrence; the delay of LT in patients requiring it will delay the start of immunosuppression; lastly, frontline LR may be more acceptable than being at risk of tumour progression and dropout while on the waiting list.[26] However, the fundamental premise to support this strategy is to know

TABLE 4 Multivariable regression models to predict recurrence beyond Milan criteria at first recurrence and at any time during the follow-up in the subgroup of patients with available pathological information of the resected specimen.

	Beyond MC at first recurrence				Beyond MC at any time during the follow-up			
	Univariable		Mutlivariable		Univariable		Multivariable	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex								
Male	–	–	–	–	–	–	–	–
Female	0.83 (0.47–1.47)	0.53			0.92 (0.61–1.40)	0.70		
Age	1.02 (0.98–1.05)	0.15	–	–	1.02 (0.98–1.04)	0.11	–	–
Surveillance								
No	–	–	–	–	–	–	–	–
Yes	0.86 (0.50–1.48)	0.58			0.89 (0.59–1.36)	0.60		
Etiology								
HBV	–	–	–	–	–	–	–	–
HCV	0.78 (0.36–1.69)	0.53			0.86 (0.48–1.55)	0.61		
ETOH	0.85 (0.32–2.28)	0.75			1.13 (0.54–2.37)	0.76		
NASH	0.94 (0.36–2.44)	0.90			0.96 (0.46–2.02)	0.92		
Other	0.49 (0.25–1.64)	0.25			1.25 (0.59–2.62)	0.56		
CSPH[a]								
No	–	–	–	–	–	–	–	–
Yes	0.54 (0.30–1.15)	0.14			0.75 (0.50–1.13)	0.16		
HCC size								
<4 cm	–	–	–	–	–	–	–	–
≥4 cm	2.63 (1.62–4.30)	<0.001	1.97 (1.16–3.35)	0.01	2.28 (1.56–3.32)	<0.001	1.93 (1.30–2.87)	0.001
AFP (ng/mL)								
<19	–	–	–	–	–	–	–	–
19–100	1.53 (0.77–3.04)	0.22	1.33 (0.67–2.65)	0.41	1.87 (1.18–2.98)	0.008	1.64 (1.03–2.62)	0.04
≥100	3.34 (1.81–6.18)	<0.001	2.55 (1.32–4.93)	0.005	2.50 (1.51–4.13)	<0.001	2.17 (1.30–3.64)	0.003
MELD	1.01 (0.96–1.05)	0.76	–	–	1.01 (0.97–1.04)	0.79	–	–
Child-Pugh								
A	–	–	–	–	–	–	–	–
B	0.75 (0.27–2.07)	0.57			0.96 (0.48–1.92)	0.92		
Microvascular invasion								
No	–	–	–	–	–	–	–	–
Yes	2.88 (1.76–4.72)	<0.001	2.63 (1.53–4.51)	<0.001	1.94 (1.34–2.81)	<0.001	1.76 (1.19–2.60)	0.005
Tumour differentiation								
G1	–	–	–	–	–	–	–	–
G2	1.11 (0.50–2.48)	0.80			1.25 (0.70–2.24)	0.44		
G3–G4	2.12 (0.91–3.83)	0.11			1.64 (0.89–2.94)	0.12		
Microsatellite lesions								
No	–	–	–	–	–	–	–	–
Yes	3.68 (2.02–6.71)	<0.001	2.23 (1.15–4.33)	0.02	2.61 (1.62–4.21)	<0.001	1.92 (1.16–3.19)	0.01
R0 margins								
No	–	–	–	–	–	–	–	–
Yes	0.61 (0.29–1.29)	0.19			0.65 (0.36–1.16)	0.14		

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CSPH, clinically significant portal hypertension; ETOH, alcoholic liver disease; HBV, chronic hepatitis B; HCV, chronic hepatitis C; HR, hazard ratio; MC, Milan criteria; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis.

[a]CSPH diagnosis was based on the presence of unequivocal signs (splenomegaly, varices, ascites) and platelet count $<100 \times 10^9$/L.

how many HCC recurrences are actually transplantable. In line with previous research,[9,10,27–32] we demonstrated that, in patients with single HCC ≤5 cm receiving LR, recurrence beyond MC occurred in only 18.0% of patients at the first recurrence episode and in 30.3% at any time during the follow-up. In both cases, recurrence was classified beyond MC for HCC size/number in the majority of patients.

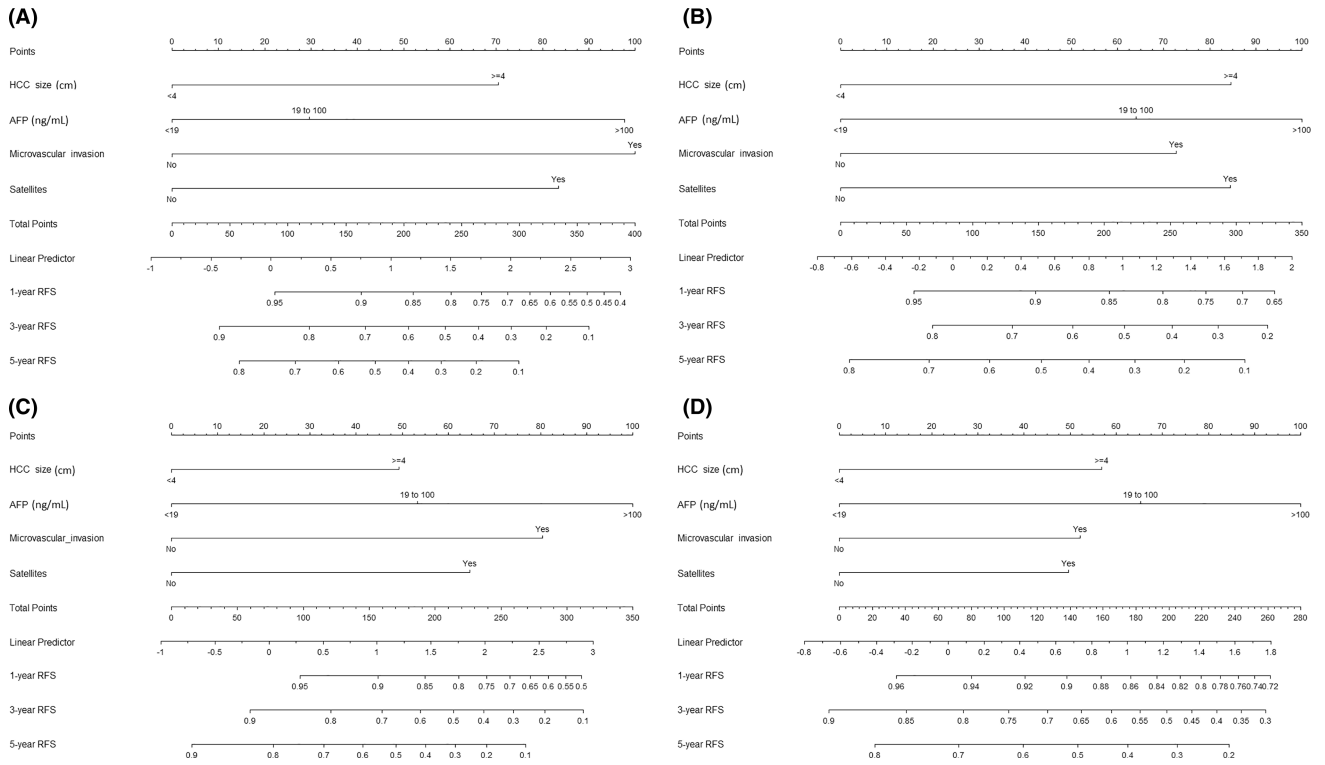

FIGURE 4 Nomograms for prediction of the probability of non-transplantable recurrence-free survival at 1, 3 and 5 years in HCC patients treated with first-line liver resection. These nomograms combine the independent predictors of non-transplantable recurrence (HCC size, AFP levels, microvascular invasion, microsatellite lesions) in the subgroup of patients with available histopathologic information and provide a risk score (i.e. total points) that can be used to predict the non-transplantable recurrence-free survival probability at different time points. (A) Nomogram using as endpoint the time-to-*first* recurrence beyond Milan criteria. (B) Nomogram using as endpoint the time-to-recurrence beyond Milan criteria overall, at any time during follow-up. (C) Nomogram using as endpoint the time-to-*first* recurrence beyond up-to-seven criteria. (D) Nomogram using as endpoint the time-to-recurrence beyond up-to-seven criteria overall, at any time during follow-up. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; RFS, recurrence-free survival.

The distinction of recurrences beyond MC according to the presence of MVI or EHS is meaningful because these two oncologic features represent absolute contraindications for LT even adopting 'extended criteria' or the down-staging strategy. As expected, non-transplantable recurrence occurred in an even lower proportion of patients when the up-to-seven criteria were considered: recurrence beyond the up-to-seven criteria occurred in 15.2% of patients at the time of first recurrence and in 26.4% at any time during the follow-up.

Interestingly, 11.3% of patients recurred beyond MC and 9.4% of patients recurred beyond up-to-seven criteria early after resection (≤2 years). Notably, this particularly aggressive recurrence was significantly more common in patients with HCC ≥4 cm compared to those with smaller tumours, suggesting that these latter may benefit from early referral for LT.

Given the relatively small percentage of patients recurring beyond MC (and up-to-seven criteria) over the 4 years following LR, and considering the shortage of liver grafts, it is very important to identify pre-operative predictors of NTR. Some Authors demonstrated that the presence of cirrhosis, tumour multifocality and AFP levels are predictive of an increased risk of NTR.[29,31] A definite association between tumour size and risk of NTR has not been clearly demonstrated so far. *Fuks* et al. [28]and *Zhang* et al.[31] found that HCC size >3 cm was independently associated with NTR, while this was not confirmed by other researchers.[29] Our study indicates that tumour size is an important determinant of both the type and the time of recurrence in patients with single HCC ≤5 cm treated with frontline LR. In fact, a significantly higher probability of NTR was demonstrated for patients with tumour ≥4 cm, who also had a higher risk that this event occurs early (within 2 years). As a result, these patients had shorter RFS and OS compared to those bearing a smaller tumour. The other independent predictor of NTR was an elevated AFP before LR. The risk of recurrence beyond MC and up-to-seven criteria was significantly increased for AFP values between 19 and 100 ng/mL, while levels exceeding 100 ng/mL heralded a much higher risk. The same two variables (preoperative tumour size and AFP) were singled out as independent predictors of an increased risk of recurrence beyond MC in a recent study carried out in patients with early-stage HCC treated with LR.[32]

The results obtained in the entire cohort were confirmed also in the subgroup of patients who were potentially transplantable 'ab initio'.

Based on the independent risk factors identified in our patients (HCC size ≥4 cm and AFP >100 ng/mL), we showed that the risk of

recurrence beyond MC (and up-to-seven criteria) progressively increased according to the presence of none, one or two risk factors. This easily obtainable information can help clinicians in the identification of patients at higher risk of NTR after LR.

In the prediction of the risk of recurrence, additional information that can be obtained by the histologic examination of resected liver, such as microvascular invasion, tumour grade and satellite nodules are considered as prognostic factors.[30,33] Even though our main objective was the evaluation of preoperative risk factors of NTR, we performed a subgroup analysis in those patients with available histologic information after LR. As reported in the literature,[10,30,34–36] microvascular invasion and microsatellite lesions were confirmed to be high-risk features, independently associated with recurrence beyond MC and up-to-seven criteria. Also considering the information on tumour pathology, which helped to refine the prognostic evaluation, HCC size and AFP levels remained independently associated with a higher risk of NTR in multivariable models. Histologic risk factors are so important that some Authors have proposed early LT following LR, even before HCC recurrence, for patients with high-risk histologic factors such as microvascular invasion and microsatellite nodules.[30,35,36] While this strategy might be debatable,[10] certainly high-risk patients (HCC size ≥4 cm, high AFP levels, high-risk histologic features) deserve close monitoring and salvage LT should be provided in case of transplantable recurrence. Moreover, considered the recently released positive results of the IMbrave050 trial,[37] in the near future adjuvant treatment with atezolizumab + bevacizumab could be an option in high-risk patients treated with LR, but the impact of this regimen on transplantability at recurrence remains to be proven. In order to stratify more precisely the risk of NTR, the variables singled out by multivariate models (HCC size, AFP levels, microvascular invasion, microsatellite lesions) have been combined into nomograms which provide a risk score that can be used to estimate the probability of non-transplantable recurrence-free survival at 1, 3 and 5 years. These tools could be extremely useful in clinical practice in deciding on the timing of follow-up and on the evaluation for salvage LT.

Despite the high recurrence rate observed in this study, we do not advocate LT as upfront treatment in all patients with single HCC ≤5 cm. In fact, we demonstrated that LR in these patients provides long survival and is associated with a relatively low percentage of recurrences beyond MC (and up-to-seven). Therefore, considering the long-term survival similar to that obtainable with LT, these results would support the use of LR as first-line treatment in these patients whenever feasible (preserved liver function, no other surgical contraindications), due to the small transplant benefit.[38] This strategy would spare many organs that can be used for patients with greater transplant benefit (e.g. decompensated cirrhosis, down-staged multinodular HCC). LT should be considered in patients at high-risk of NTR and as a salvage treatment at the time of recurrence because survival rates achievable with salvage LT are higher than those following re-resection or ablation.[17,39]

Surprisingly, despite the first recurrence being theoretically transplantable in a high percentage of patients included in this study (82.0% according to MC and 84.8% according to up-to-seven) and some NTR could have benefitted from downstaging strategy or 'extended criteria', LT was performed only in 4.5% of patients (without significant differences according to tumour size). Unfortunately, in this study, we were not able to evaluate the rate of patients listed for LT at the time of recurrence as well as the drop-out rate for tumour progression, since these data are not available in the ITA.LI.CA database. In the interpretation of this result, the advanced age of patients at the time of LR (median 68 years) and the long time elapsed from LR to recurrence (median RFS of 3.2 years) should be considered. Probably, a large share of patients in this study exceeded the accepted age limit for transplant eligibility at the time of recurrence. Indeed, as demonstrated by *Cucchetti* et al.,[40] being resected at an age 2 or 3 years below the age limit carries a high risk of being too old for salvage LT. In any case, our results raise the suspect of under-referral to transplant centres at recurrence, and underscore the importance of the referral for LT in order to improve the prognosis of these patients. In addition, in those patients at higher risk of recurrence beyond MC and up-to-seven criteria (i.e. initial tumour size ≥4 cm and high AFP levels) the referral should be already considered at the time of HCC diagnosis in order to adopt the best choice between LR and LT according to the individual and population-based transplant benefit.[38]

Among the limitations of this study, its retrospective observational design could have introduced unintentional biases. Nevertheless, nowadays it would be very difficult to perform a prospective randomized trial on different management strategies in patients with small single HCC and no contraindications to LR. Another limitation is the lack of availability in the ITA.LI.CA registry of data regarding a detailed description of surgical procedure (e.g. type of hepatectomy) and the lack of histologic analysis of the resected tumour for all the study cohort. However, our study was primarily aimed at detecting risk factors for recurrence beyond MC (and up-to-seven criteria) among variables available preoperatively, and a subgroup analysis has been provided for patients with available histologic information. Lastly, the lack of a standardized surveillance schedule after LR, being the ITA.LI.CA database an observational registry, might have biased the evaluation of the RFS and the proportion of patients with non-transplantable recurrence.

Besides its limitations, this study also has some strengths including the multicenter design, the prediction of risk based on ordinarily available variables, the statistically robust identification of the thresholds for HCC size and AFP, and the definition of the primary outcome (recurrence beyond MC and up-to-seven criteria) which is relevant for most LT centres worldwide in light of salvage transplantation.

In conclusion, our study suggests that, despite the high incidence of recurrence, LR as a frontline treatment for single HCC ≤5 cm offers excellent long-term survival rates and should be considered the treatment of choice in patients who are surgical candidates. The low percentage of patients crossing the threshold of MC (and up-to-seven criteria) at the time of first recurrence underscores the need of improving the referral for salvage LT. Since HCC size and AFP levels at the time of LR are important preoperative risk factors for NTR,

patients at highest risk (HCC ≥4 cm and high AFP) could be considered for frontline LT. Alternatively, if these patients are resected, they could be listed even before recurrence after LR, considering the local organ availability and the allocation system, in particular, whether high-risk histologic features are present.

AUTHOR CONTRIBUTIONS

Conceptualization: Filippo Pelizzaro, Franco Trevisani, and Fabio Farinati; methodology: Filippo Pelizzaro, Franco Trevisani, Vittorio Simeon, and Fabio Farinati; *Software*: Franco Trevisani; *Formal analysis*: Filippo Pelizzaro, Vittorio Simeon, and Fabio Farinati; *Investigation*: Filippo Pelizzaro, Franco Trevisani, and Fabio Farinati; *Resources*: Franco Trevisani; *Data curation*: Filippo Pelizzaro, Franco Trevisani, Alessandro Vitale, Umberto Cillo, Fabio Piscaglia, Gabriele Missale, Angelo Sangiovanni, Francesco Giuseppe Foschi, Giuseppe Cabibbo, Eugenio Caturelli, Maria Di Marco, Francesco Azzaroli, Maurizia Rossana Brunetto, Giovanni Raimondo, Gianpaolo Vidili, Maria Guarino, Antonio Gasbarrini, Claudia Campani, Gianluca Svegliati-Baroni, Edoardo Giovanni Giannini, Andrea Mega, Alberto Masotto, Gian Ludovico Rapaccini, Donatella Magalotti, Rodolfo Sacco, Gerardo Nardone, and Fabio Farinati; *Writing—original draft preparation*: Filippo Pelizzaro, Franco Trevisani, Vittorio Simeon, and Fabio Farinati; *Writing—review and editing*, Alessandro Vitale, Umberto Cillo, Fabio Piscaglia, Gabriele Missale, Angelo Sangiovanni, Francesco Giuseppe Foschi, Giuseppe Cabibbo, Eugenio Caturelli, Maria Di Marco, Francesco Azzaroli, Maurizia Rossana Brunetto, Giovanni Raimondo, Gianpaolo Vidili, Maria Guarino, Antonio Gasbarrini, Claudia Campani, Gianluca Svegliati-Baroni, Edoardo Giovanni Giannini, Andrea Mega, Alberto Masotto, Gian Ludovico Rapaccini, Donatella Magalotti, Rodolfo Sacco, and Gerardo Nardone; *Visualization*: Fabio Farinati; *Supervision*: Franco Trevisani and Fabio Farinati; *Project administration*: Filippo Pelizzaro and Fabio Farinati; All the authors revised the work critically for important intellectual content and approved the final version of the manuscript to be published.

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CONFLICT OF INTEREST STATEMENT

FPe, VS, AV, UC, FPi, GM, AS, FGF, EC, MDM, FA, MRB, GR, GV, MG, AG, CC, GSB, AMe, AMa, GLR, DM, RS, GN and FF: none. FT: advisory board member and/or consultant for AstraZeneca, Abbvie, Bayer, BMS, Eisai, Gilead, MSD and Roche. GC: served as a consultant or on advisory boards for Bayer, Eisai, Ipsen and AstraZeneca. EGG: advisory committees and/or speaker for AstraZeneca, EISAI, MSD, Roche.

ETHICS APPROVAL STATEMENT

The study was approved by the Institutional Review Board of the ITA.LI.CA coordinating center, Alma Mater Studiorum University of Bologna (approval number 99/2012/O/Oss) and by the Institutional Review Board of each participating Institution. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

The management of the ITA.LI.CA database conforms to the Italian legislation on privacy. Patients provided written informed consent for every diagnostic and therapeutic procedure, as well as for having their clinical data recorded anonymously in the ITA.LI.CA database.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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