Digestive and Liver Disease 57 (2025) 1673–1682

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Recurrence rate, features, and outcome after hepatocellular carcinoma curative resection or ablation according to the IMbrave050 criteria: a real-world study

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https://doi.org/10.1016/j.dld.2025.05.032

ARTICLE INFO

Article history:
Received 19 February 2025
Accepted 30 May 2025
Available online 26 June 2025

Keywords:
Adjuvant treatment
Overall survival
Recurrence-free survival
Response
Systemic therapy

ABSTRACT

Background/Aims: Adjuvant systemic therapy has been proposed in patients at high-risk of hepatocellular carcinoma (HCC) recurrence. This study assessed the outcomes of a real-world cohort treated with either resection or ablation, stratified according to the IMbrave050 trial criteria.

Methods: We selected, from the Italian Liver Cancer database, 1150 patients with HCC treated with up-front resection (n = 483, 64.2 % high-risk) or ablation (n = 667, 49.6 % high risk), fulfilling the inclusion criteria of the IMbrave050 trial.

Results: Median recurrence-free survival (RFS) was shorter in high-risk resected patients (29.0 vs. 43.0 months; p = 0.024), while no difference was observed after ablation (27.0 vs. 30.0 months; p = 0.098). Recurrence was borderline higher in high-risk resected patients [Hazard Ratio (HR) 1.26, 0.97–1.23; p = 0.052], but not ablated ones (HR 1.13, 0.92–1.38; p = 0.221). Independent predictors of recurrence were cirrhosis (HR 1.52, 1.13–2.05), multinodular HCC (HR 1.31, 1.14–1.52), and microvascular invasion (HR 1.39, 1.05–1.83) in resected, and alpha-fetoprotein (HR 1.15, 1.07–1.23) in ablated patients. Median overall survival was similar in resected risk-groups (147.0 vs. 130.0 months; p = 0.093), shorter in high-risk ablated patients (79.0 vs. 98.0 months; p = 0.021).

Conclusions: The criteria used to assess HCC recurrence risk in the IMbrave050 trial find validation by real-world data in patients treated with resection, while they are inaccurate after ablation.

1. Introduction

In patients with compensated cirrhosis the annual incidence of hepatocellular carcinoma is approximately 2–5 % [1,2]. In these patients, after correction for lead- and length-time biases, surveillance for hepatocellular carcinoma (HCC) improves prognosis mainly due to a higher likelihood of detecting early tumours amenable to potentially curative therapies [3–6]. In these patients, both surgical resection and local ablation represent therapies with curative intent that are associated with improved survival [7,8]. However, both treatments are burdened by HCC recurrence, that may be as high as 50 % at 3-year, and whose incidence depends on both host and tumour characteristics [9–11]. Intrahepatic recurrence of HCC is subdivided in *early* (occurring within 2 years of treatment) and *late* when it occurs thereafter, as they have a different pathogenesis: biological characteristics of the tumour and presence of occult micro-metastases are mainly associated with the occurrence of early recurrence, while the background of enhanced liver necro-inflammatory and regenerative activities are responsible for later recurrence [12]. Aetiological treatment of the underlying liver disease, such as successful antiviral therapy, has been shown to be associated with a decrease in the rate of HCC recurrence after either surgical resection or local ablation, while a prospective, randomised, placebo-controlled study carried out with sorafenib failed to demonstrate an adjuvant effect of this drug on recurrence-free survival (RFS) following curative treatment of HCC [13–15]. Recently, despite preliminary analyses of a study investigating the adjuvant effect of atezolizumab *plus* bevacizumab *vs*. active surveillance in patients with HCC who were deemed at high-risk of recurrence after potentially curative surgical resection or local ablation (IMbrave050) showed improved RFS in the active arm, the updated analyses of this study showed that this effect was not sustained over time and that the adjuvant use of this combination was not supported in a risk-benefit analysis [16,17]. Nonetheless, the adjuvant effect that may be obtained by exploiting the combination of an immune check-point inhibitor and anti-angiogenic drug is being further explored in trials with similar risk-stratification criteria but different drug combination (durvalumab *plus* bevacizumab, EMERALD-2), while other studies using single-therapy with immune check-point inhibitors that failed to demonstrate a survival advantage when used in first-line treatment, such as nivolumab (CA209–9DX) and pembrolizumab (KEYNOTE-937), are also underway in the this setting [18]. Lastly, a recent phase II study reported that the adjuvant use of the immune check-point inhibitor sintilimab was associated with improved RFS as compared to active surveillance following surgical resection of HCC in patients with microvascular invasion [20].

Overall, these apparently contrasting results may be related to some issues related to the definition of high-risk populations, arbitrary and not validated, and to the residual cohort of patients treated with local ablation, when included [16–20]. As a fact, there are no data reporting the outcome of contemporary cohorts of Western patients treated with resection or ablation and segregated according to the risk of HCC recurrence. Such an information may provide a benchmark to assess the effectiveness of potential adjuvant therapies in different categories of patients undergoing curative treatments and inform future approaches to improve patients' outcome. Therefore, this study aimed to compare the main outcomes such as the rate and type of recurrence, the characteristics of patients by recurrence type, and factors influencing this event, and RFS and overall survival (OS) of both resected and ablated patients, stratified according to the baseline risk of tumour recurrence as indicated by the IMbrave050 trial criteria [16,17].

2. Patients and methods

2.1. Patients

In this retrospective study we analysed data of 7659 patients diagnosed with HCC between January 2010 and December 2022 and collected in the Italian Liver Cancer (ITA.LI.CA) database by 25 Italian centres with expertise in the management of this cancer [18–20]. In this database, data are prospectively collected at the time of HCC diagnosis (baseline) and during the follow-up, and are updated every 2 years. The management of the ITA.LI.CA database conforms to the current Italian legislation on privacy. According to Italian law, patient consent is not required for retrospective data analysis, while all patients provided written informed consent to undergo each diagnostic and therapeutic procedure and to have their clinical data recorded anonymously in the ITA.LI.CA database. The use of this database for scientific research was approved by the Institutional Review Board of the ITA.LI.CA Coordinating Centre (approval number 99/2012/O/Oss) and the study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki.

Fig. 1 shows the flow of patients in the study. Among the 7659 patients, we selected 2188 patients (28.6 %) with newly di-

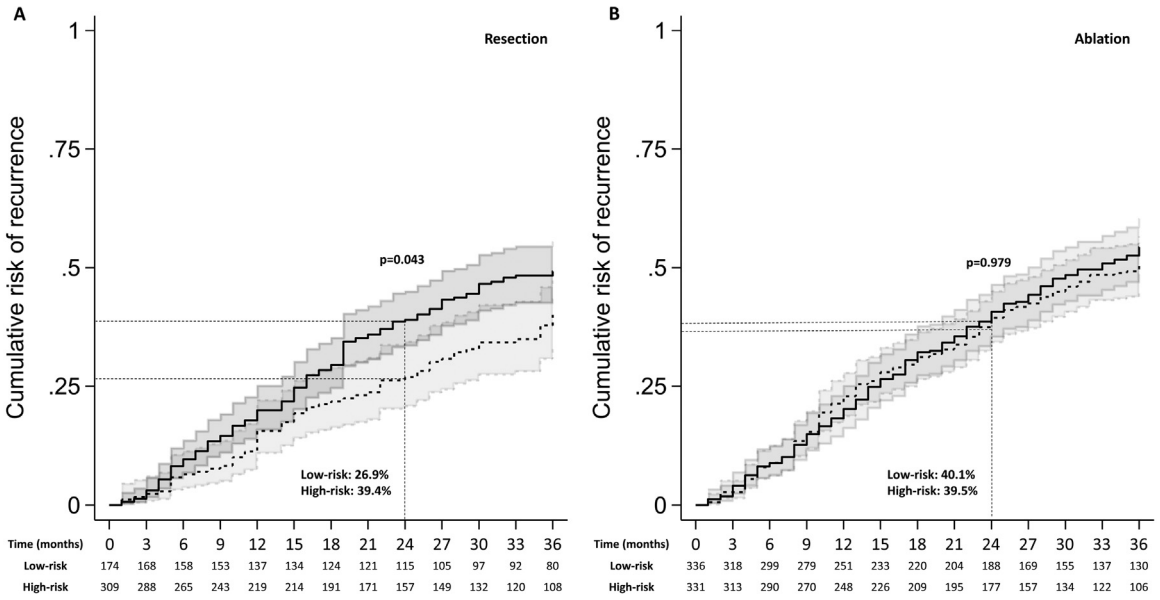

Fig. 1. Recurrence risk analysis comparing patients with low- and high-risk of recurrence according to treatment received (**A**: resection, **B**: ablation).

agnosed HCC who underwent liver resection or ablation with curative intent, and from this group we further selected the patients who fulfilled the inclusion criteria of the IMbrave050 trial (Child-Pugh class A, ECOG-PS $\leq$1, no multi-viral infection) and who had a follow-up of at least 2 years and were not lost to follow-up, regardless of oncological characteristics [17]. After exclusion of 144 patients (11.1 %) with missing data, the final population included 1150 patients: 483 patients (42.0 %) treated with resection and 667 patients (58.0 %) treated with ablation. In each treatment group, patients were considered at high-risk of recurrence according to the criteria set forth in the IMbrave050 trial (Supplementary Table 1), while the remaining patients formed the low-risk group [17].

The following variables were analysed: age, sex, aetiology of liver disease, presence of obesity and diabetes, presence of cirrhosis, platelet count, albumin, INR, creatinine, comorbidities (Charlson Comorbidity Index), Child-Pugh score, albumin-bilirubin (ALBI) grade, Model for End-stage Live Disease (MELD) score, AFP levels, modality of HCC diagnosis (under surveillance, incidental, symptomatic), number and size of HCC nodules, presence of macrovascular invasion and/or extra-hepatic spread, Barcelona Clinic Liver Cancer (BCLC) stage, type of treatment (resection or ablation), recurrence rate, type of recurrence (early $<$2 years, late $\geq$2 years), time-to-recurrence as well as treatments of recurrence, RFS and OS from the index treatment. In resected patients, microvascular invasion and Edmonson grading were also analysed.

Follow-up consisted in trimestral imaging surveillance for both resected and ablated patients, which becomes semi-annual after at least two years of recurrence-free follow-up. A proxy of *curative* resection/ablation was used as indicated: patients who did not receive any downstream treatment in the 6 months following the index resection/ablation were considered *cured* by the first treatment.

2.2. Methods

Among patients potentially eligible to adjuvant treatment according to the IMbrave050 trial inclusion/exclusion criteria, patients were stratified as follows: i) *high-risk group*, potentially eligible for atezolizumab *plus* bevacizumab as adjuvant treatment; ii) *low-risk group*, not eligible for the drug combination treatment [17]. In these subgroups we assessed: a) the rate and type of recurrence b) the characteristics of patients by recurrence type, and factors influencing this event; c) treatment of recurrence; d) RFS and OS since the index treatment.

2.3. Statistical analysis

Continuous data are expressed as mean value $\pm$ standard deviation (SD) or median and interquartile ranges (25th-75th), and discrete variables as absolute and relative frequencies. The normal distribution of the variables was tested using standard procedures such as Levene's test and the Kolmogorov-Smirnov test. Comparisons of continuous variables were made with the Student's *t*-test, and changes over time were assessed using Analysis of the Variance. Discrete variables were compared with the X^2 test. Differences between groups were evaluated using unpaired *t*-tests, Wilcoxon, Mann-Whitney U (for variables not normally distributed), and Fisher's exact tests (when comparing proportions), as appropriate. Relationships among variables were assessed with the Spearman correlation coefficient.

The area under the receiver operating characteristic (ROC) curve was estimated with DeLong's non-parametric method, and the optimal cut-off was identified using Youden's index.

Survival was calculated from the date of the index treatment to that of death, liver transplantation or end of follow up, whichever occurred first. It was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. The 1-, 3-, and 5-year survival rates are also reported. The Cox proportional hazards model was adjusted for death-related risk factors identified by statistical analysis (the probability value for entering the model was $p = 0.10$). In the presence of variables violating the proportionality assumption, multiple multivariate analysis models were constructed. The Hazard Ratio (HR) was also presented as a smoothed HR to represent its variation over time.

A two-tailed p-value $<$0.05 was considered statistically significant. All statistical analyses were performed with SPSS v27.0 (Apache Software Foundation, Chicago, Illinois, USA), R (the R Project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria and EZR: https://github.com/jinkim3/ezr).

Table 1
Main features of the 1150 patients with HCC included in this study, subdivided according to treatment received and stratified in low- and high-risk of recurrence.

	Resection (n = 483)			Ablation (n = 667)		
	Low-risk (n = 174, 35.8)	High-risk (n = 309, 64.2)	p	Low-risk (n = 336, 50.4)	High-risk (n = 331, 49.6)	p
Age, years	70 (63–74)	68 (58–74)	**0.014**	71 (62–76)	71 (64–77)	0.442
Sex, male	126 (72.4)	264 (85.4)	**<0.001**	225 (67.0)	238 (71.9)	0.166
Aetiology, viral	109 (64.5)	188 (64.8)	0.943	248 (75.2)	212 (66.7)	**0.017**
Cirrhosis, presence	140 (80.5)	196 (63.4)	**<0.001**	291 (86.6)	286 (86.4)	0.939
ALBI, grade						
1	89 (51.7)	174 (57.0)	0.263	167 (49.7)	146 (44.2)	0.158
2	83 (48.3)	131 (43.0)		169 (50.3)	184 (55.8)	
Unknown	2 (1.1)	4 (1.3)		0 (0.0)	1 (0.3)	
MELD, score	8 (7–9)	8 (7–9)	0.612	8 (7–9)	8 (7–10)	0.176
Obesity	16 (11.6)	33 (13.6)	0.521	48 (19.5)	45 (19.6)	0.476
Unknown	36 (20.7)	66 (21.4)		90 (26.8)	101 (30.5)	
Diabetes	57 (34.3)	86 (29.9)	0.323	103 (32.5)	115 (37.1)	0.226
Unknown	8 (4.6)	18 (5.8)		13 (3.9)	17 (5.1)	
CCI, score	4 (3 – 6)	4 (3 – 6)	0.207	4 (3 – 5)	5 (4 – 6)	**0.017**
Type of diagnosis						
Surveillance	114 (68.7)	160 (56.3)	**0.006**	250 (79.9)	227 (73.2)	0.147
Incidental	47 (28.3)	96 (33.8)		59 (18.8)	78 (25.2)	
Symptomatic	5 (3.0)	28 (9.9)		4 (1.3)	5 (1.6)	
Unknown	8 (4.6)	25 (8.1)		23 (6.8)	21 (6.3)	
MVI	0 (0.0)	16 (5.2)	**0.002**	0 (0.0)	3 (0.9)	0.122
α-fetoprotein, ng/mL	5.0 (2.9 – 10.5)	7.2 (3.3 – 46.0)	**0.002**	6.0 (3.2 – 16.7)	7.0 (3.5 – 22.9)	0.149
BCLC staging system						
Very early	28 (16.1)	33 (10.7)	**<0.001**	151 (44.9)	0 (0.0)	**<0.001**
Early	131 (75.3)	160 (51.8)		154 (45.8)	281 (84.9)	
Intermediate	10 (5.7)	87 (28.2)		5 (1.5)	14 (4.2)	
Advanced	5 (2.9)	29 (9.4)		26 (7.7)	36 (10.9)	
End stage	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Unknown	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Data are shown as absolute value and percentage or median and interquartile range.
Abbreviations: ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; CCI, Charlson Comorbidity Index; MVI, macro-vascular invasion; BCLC, Barcelona Clinic Liver Cancer.

3. Results

3.1. Demographic and clinical characteristics of patients

According to the IMbrave050 trial inclusion criteria, among the 483 resected patients, the high-risk group included 309 patients (64.2 %) and the low-risk group 174 patients (35.8 %). Among the 667 patients treated with ablation, the high-risk groups included 331 patients (49.6 %) and the low-risk group 366 patients (50.4 %) (Supplementary Figure 1).

The main features of patients, subdivided according to treatment received, are summarized in Table 1. Among resected patients, high-risk patients were younger [68 years (IQR 58–74) *vs.* 70 years (IQR 63–74); $p = 0.014$], more frequently males ($n = 264$, 85.4 % *vs.* $n = 126$, 72.4 %; $p < 0.001$) and less frequently with cirrhosis ($n = 196$, 63.4 % *vs.* $n = 140$, 80.5 %; $p < 0.001$), with a diagnosis of HCC more frequently made outside surveillance ($n = 124$, 40.1 % *vs.* $n = 52$, 29.9 %; $p = 0.006$), higher median AFP [7.2 (3.3–46.0) *vs.* 5.0 ng/mL (2.9–10.5) $p = 0.002$], and more advanced BCLC stage ($p < 0.001$) as compared to low-risk patients. Among patients treated with ablation, those at high-risk had less frequently viral aetiology ($n = 212$, 66.7 % *vs.* $n = 248$, 75.2 %, $p = 0.017$), higher Charlson Comorbidity Index [5 (4–6) *vs.* 4 (3–5); $p = 0.017$], and more advanced BCLC stage ($p < 0.001$) as compared to low-risk patients.

3.2. Rate of recurrence and type of recurrence

Among 1150 patients with HCC, 658 (57.2 %) experienced recurrence. The recurrence rate was significantly lower in those who underwent liver resection ($n = 258$, 53.4 %) compared to those who received ablation ($n = 400$, 59.9 %; $p = 0.027$). Among patients who underwent ablation, recurrence rates were 61.6 % ($n = 204$) in the high-risk group and 58.3 % ($n = 196$) in the low-risk group, while among patients who underwent liver resection and experienced recurrence, 65.5 % ($n = 169$) and 34.5 % ($n = 89$) were classified at high- and low-risk of recurrence, respectively.

Overall, the rate of HCC recurrence after liver resection was 26.0 % higher in high-risk compared to low-risk patients, but this difference was borderline significant (HR 1.26, 95 % CI: 0.97–1.23, $p = 0.052$). Instead, among ablated patients there was no difference in recurrence rate between the high- and low-risk group (HR 1.13, 95 % CI: 0.92–1.38, $p = 0.221$).

High-risk patients who underwent resection experienced a median time-to-recurrence of 37.0 months (95 % CI: 28.4–45.6), that was marginally shorter than that of low-risk patients [51.0 months (95 % CI: 39.8–62.2), $p = 0.052$]. After ablation, the median time to recurrence did not significantly differ between high-risk and low-risk patients [31.0 months (95 % CI: 26.0–36.0) *vs.* 36.0 months (95 % CI: 28.6–43.4); $p = 0.221$].

The incidence of *early* recurrence after liver resection was higher in high-risk patients ($n = 62/157$, 39.4 %) than in low-risk patients ($n = 71/115$, 26.9 %) ($p = 0.043$, Fig. 1A), while it was similar in the two subgroups of patients treated with ablation (high-risk: $n = 66/168$, 39.5 % *vs.* low-risk: $n = 72/180$, 40.1 %; $p = 0.979$, Fig. 1B).

3.3. Characteristics of patients according to recurrence and factors influencing this event

Table 2 presents the results of the comparison of baseline characteristics associated with HCC recurrence, subdivided according to treatment received. Resected patients who experienced recurrence more frequently had cirrhosis ($n = 191$, 74.0 % *vs.* $n = 145$, 64.4 %; $p = 0.022$), multinodular HCC ($n = 51$, 20.4 % *vs.* $n = 24$, 10.6 %; $p = 0.013$), and a higher prevalence of microvascular inva-

Table 2
Baseline characteristics of HCC in patients with and without oncological recurrence, subdivided according to treatment received.

	Resection (n = 485)			Ablation (n = 667)		
	No recurrence (n = 225)	Recurrence (n = 258)	p	No recurrence (n = 267)	Recurrence (n = 400)	p
Age, years	69.5 (61.3 – 75.3)	68.4 (58.5 – 73.1)	0.061	70.3 (61.8 – 77.3)	70.9 (63.2 – 76.3)	0.619
Sex, male	182 (80.9)	208 (80.6)	0.940	189 (70.8)	274 (68.5)	0.530
Aetiology, viral	133 (59.1)	164 (63.5)	0.349	184 (68.9)	276 (69.0)	1
Cirrhosis, presence	145 (64.4)	191 (74.0)	**0.022**	233 (87.3)	344 (86.0)	0.639
ALBI, grade						
1	118 (52.4)	145 (56.2)		130 (48.7)	183 (45.8)	
2	101 (44.8)	113 (43.8)	0.612	136 (50.9)	217 (54.2)	0.429
Unknown	6 (2.7)	0 (0)		1 (0.4)	0 (0)	
MELD, score	8 (7 – 8)	8 (7 – 9)	0.436	8 (7 – 9)	8 (7 – 9)	0.308
CCI, score	4 (3 – 5)	4 (3 – 6)	0.763	4 (3 – 6)	4 (4 – 5)	0.395
Type of diagnosis						
Surveillance	118 (52.4)	156 (60.5)		182 (68.2)	294 (73.5)	
Incidental	70 (31.1)	73 (28.3)	0.133	64 (24.0)	73 (18.3)	0.358
Symptomatic	16 (7.1)	17 (6.7)		4 (1.5)	6 (1.5)	
Unknown	21 (9.3)	12 (4.7)		17 (6.4)	27 (6.8)	
Number of nodules						
one	201 (89.3)	207 (80.2)	**0.013**	230 (86.1)	340 (85.0)	0.076
2–3	20 (8.9)	46 (17.8)		37 (13.8)	53 (13.3)	
>3	4 (1.7)	5 (1.9)		0 (0)	7 (1.8)	
Maximum diameter, cm	3.3 (2.0 – 5.0)	3.5 (2.2 – 5.0)	0.840	2.0 (1.5 – 2.5)	2.0 (1.5 – 2.8)	0.341
α-fetoprotein, ng/mL	5.4 (2.7 – 19.8)	6.6 (3.6 – 28.9)	0.686	5.7 (3.0 – 14.0)	7.1 (3.7 – 21.8)	**<0.0001**
MVI, presence	7 (3.1)	14 (5.4)	0.266	5 (1.9)	9 (2.3)	0.791
EHS, presence	0 (0)	0 (0)	1	0 (0)	0 (0)	1
Milan criteria, in	154 (68.4)	164 (63.6)	0.259	255 (95.5)	380 (95.0)	0.765
BCLC						
Very early	28 (12.4)	33 (12.8)		65 (24.3)	86 (21.5)	
Early	140 (62.2)	151 (58.5)		172 (64.4)	263 (65.8)	
Intermediate	45 (20.0)	52 (20.2)	0.567	6 (2.2)	13 (3.3)	0.747
Advanced	12 (5.3)	22 (8.5)		24 (9.0)	38 (9.5)	
End stage	0 (0)	0 (0)		0 (0)	0 (0)	
Grading, (≥3)	88 (40.9)	106 (42.2)	0.776			
Microvascular invasion, presence	78 (36.6)	123 (45.7)	**0.049**			

Data are shown as absolute value and percentage or median and interquartile range. Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CCI, Charlson Comorbidity Index; EHS, extra-hepatic spread; MELD, model for end-stage liver disease; MVI, macro-vascular invasion.

sion (n = 123, 45.7 % *vs.* n = 78, 36.6 %; p = 0.049). Supplementary Table 2 reports the results of univariate Cox regression analysis for baseline characteristics. The multivariate analysis showed that, among resected patients, presence of cirrhosis (HR 1.52, 95 % CI: 1.13–2.05; p = 0.006), multinodular HCC (HR 1.31, 95 % CI: 1.14–1.52; p < 0.0001), and microvascular invasion [HR 1.39, 95 % CI: 1.05–1.83; p = 0.022] were independently associated with recurrence rate.

Based on the results of the multivariate analysis we incorporated number of nodules, microvascular invasion, and cirrhosis, into a ROC-curve analysis to identify the optimal cut-off to stratify patients according to recurrence risk (Supplementary Figure 2A). Patients presenting higher risk according to this model experienced a significantly shorter median time to recurrence (33.5 months, 95 %CI: 24.7–42.3) compared to those at lower risk (100.4 months, 95 %CI: 86.2–121.1; p < 0.0001; Supplementary Figure 2B).

Among patients treated with ablation, the only parameter significantly associated with HCC recurrence was AFP, that was higher in the group showing recurrence (7.1 ng/mL, IQR 3.7–21.8 vs. 5.7 ng/mL, IQR 3.0–14.0; p < 0.0001; HR 1.15, 95 % CI: 1.07–1.23; p < 0.0001). Hence, we performed a ROC curve analysis to identify the most accurate AFP cut-off able to stratify patients according to risk of recurrence (7 ng/mL, AUC: 0.569, 95CI % 0.523–0.616, sensitivity 0.54, specificity 0.55; Supplementary Figure 3A). Patients with an AFP level above the cut-off showed a significantly shorter median time to recurrence (32.0 months, 95 % CI: 25.6–38.4) compared to those with values below the cut-off (45.3 months, 95 % CI: 34.7–55.8; p = 0.003; Supplementary Figure 3B).

Considering the *type* of recurrence, high serum AFP [8.6 ng/mL (4.0–51.3) *vs.* 5.0 ng/mL (2.9–10.8); p = 0.005] and undifferentiated HCCs [Edmondson grade ≥3: 66 (48.5 %) *vs.* 40 (34.8 %); p = 0.028] were associated with *early* recurrence in resected patients, while no parameters differentiated *early* or *late* recurrence among ablated patients (Supplementary Table 3).

3.4. Recurrence-free survival

Fig. 2 shows the Kaplan-Meier curves of RFS in patients at high- and low-risk of HCC recurrence, subdivided according to treatment. Among resected patients (Fig. 2A), the median RFS was significantly shorter in the high-risk (29.0 months, 95 % CI: 24.2–33.8) than in the low-risk group (43.0 months, 95 % CI: 34.4 – 51.6; p = 0.024). Instead, no statistically significant difference in RFS was observed between the high- (27.0 months, 95 % CI: 23.6–30.4) and low-risk patients (30.0 months, 95 % CI: 24.2–35.8; p = 0.098) after ablation (Fig. 2B).

Among resected patients, the 1-, 2- and 5-year RFS rates, subdivided according to risk of recurrence (high-risk *vs.* low-risk), were: 76.0 % (n = 166/219) *vs.* 82.3 % (n = 113/137, p = 0.147), 55.7 % (n = 88/157) *vs.* 70.7 % (n = 81/114, p = 0.016), and 32.0 % (n = 18/55) *vs.* 38.7 % (n = 15/39, p = 0.662). After ablation, these figures (high-risk *vs.* low-risk) were: 76.6 % (n = 185/242) *vs.* 75.4 % (n = 184/244, p = 0.832), 54.3 % (n = 91/168) *vs.* 57.0 % (n = 103/181, p = 0.666), and 23.2 % (n = 10/45) *vs.* 29.0 % (n = 15/53, p = 0.643).

Supplementary Figure 4 shows the smoothed hazard estimates for RFS in patients at high- and low-risk of recurrence, subdivided according to treatment received. In resected patients, smoothed hazard estimates showed higher initial hazard rates for high-risk, followed by a nonlinear decline (transiently interrupted at 60 months for about 1 year) (Supplementary Figure 4A). Instead, in low-risk resected patients, as well as in patients treated with abla-

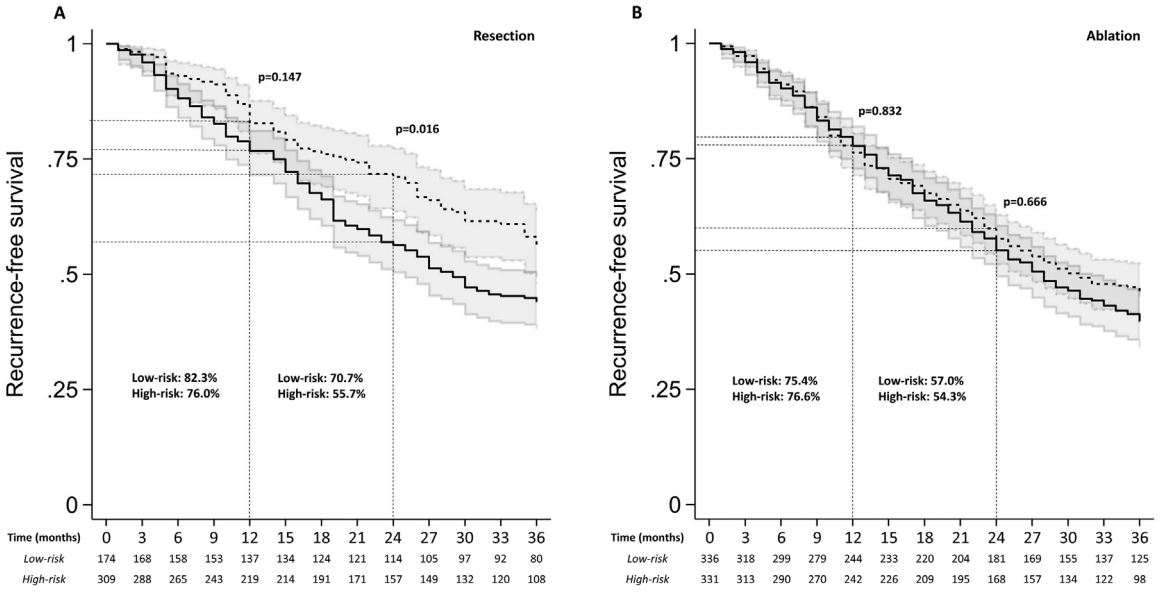

Fig. 2. Recurrence-free survival analysis comparing patients with low- and high-risk of recurrence according to treatment received (**A**: resection, **B**: ablation).

tion regardless of their risk degree, the initial risk zenith was followed by a regular decline (Supplementary Figure 4B).

In the ablation group, we separately evaluated the impact of different high-risk criteria on RFS. Patients with a single tumour >2 cm showed the most favourable prognosis, with a median RFS of 38.0 months (95 % CI: 28.3–47.7), compared to those with multinodular HCC with all nodules ≤2 cm (29.3 months, 95 % CI: 16.1–42.6) and those with at least one nodule >2 cm (32.0 months, 95 % CI: 4.9–59.0), although the difference among groups was not statistically significant ($p = 0.302$, Supplementary Figure 5).

Supplementary Table 4 shows the results of univariate and multivariate Cox regression analysis for baseline characteristics. Among resected patients, presence of cirrhosis (HR 1.50, 95 % CI: 1.12–2.00; $p = 0.006$), multinodular HCC (HR 1.44, 95 % CI: 1.27–1.63; $p < 0.0001$), and microvascular invasion [HR 1.48, 95 % CI: 1.16–1.88; $p = 0.002$] were independently associated with recurrence or death.

Among patients treated with ablation, multinodular HCC [Model 1: 1.23 (1.03–1.45), $p = 0.020$; Model 2: 1.16 (0.97–1.39), $p = 0.098$], log-AFP [Model 1: 1.11 (1.04–1.18), $p = 0.002$; Model 2: 1.12 (1.05–1.19), $p = 0.001$], higher MELD score [Model 1: 1.03 (1.01–1.05), $p = 0.007$] and higher Child-Turcotte-Pugh score [Model 2: 1.31 (1.07–1.60), $p = 0.010$] were independently associated with recurrence or death.

3.5. Oncological characteristics and treatment strategies at HCC recurrence

The oncological characteristics of patients at recurrence for each treatment, sub-divided according to the risk of recurrence at the time of initial treatment, are presented in Table 3.

Among the 258 resected patients who showed HCC recurrence, high-risk patients had higher prevalence of multinodular recurrence (47.9 %, $n = 81$ vs. 38.2 %, $n = 34$; $p = 0.005$), larger maximum diameter of recurrent HCC (1.7 cm, IQR 1.2–2.8 vs. 1.5 cm, IQR 1.0–2.0; $p = 0.017$), higher AFP at the time of recurrence (8.0 ng/mL, IQR 3.8–48.0 vs. 5.6 ng/mL, IQR 3.0–10.6; $p = 0.025$), and higher prevalence of macrovascular invasion (15.5 %, $n = 26$ vs. 5.6 %, $n = 5$; $p = 0.026$) compared to low-risk patients. Conversely, among the 400 patients with HCC recurrence after ablation there were no differences between high- and low-risk patients.

As far as treatment of recurrence is concerned, in the resection group high-risk patients were more likely to undergo liver transplantation with respect to low-risk individuals ($n = 16$, 9.5 % *vs.* $n = 2$, 2.2 %; $p = 0.030$), while in patients treated with ablation liver resection was more commonly used in low-risk patients ($n = 22$, 11.1 % *vs.* $n = 11$, 5.4 %; $p = 0.034$).

3.6. Overall survival

Median OS was marginally longer in high-risk (147.0 months, 95 % CI: 78.1– not reached) than in low-risk patients (130.0 months, 95 % CI: 95.4–164.6, $p = 0.093$) who underwent resection. After ablation, it was significantly shorter in high-risk patients (79.0 months, 95 % CI: 63.8–94.2) compared to low-risk patients (98.0 months, 95 % CI: 75.9–120.1; $p = 0.021$) (Fig. 3).

Among resected patients, the 1-, 2- and 5-year survival rates, sub-divided according to risk of recurrence (high-risk *vs.* low-risk), were: 92.7 % ($n = 249/269$) *vs.* 97.6 % ($n = 158/162$, $p = 0.030$), 84.7 % ($n = 204/241$) *vs.* 96.4 % ($n = 149/155$, $p < 0.0001$), and 65.8 % ($n = 74/112$) *vs.* 73.3 % ($n = 54/74$, $p = 0.337$) (Fig. 3A). After ablation, these figures (high-risk *vs.* low-risk) were: 99.6 % ($n = 306/307$) *vs.* 98.2 % ($n = 312/318$, $p = 0.123$), 88.0 % ($n = 240/273$) *vs.* 92.8 % ($n = 267/288$, $p = 0.062$), and 62.3 % ($n = 75/120$) *vs.* 71.2 % ($n = 93/131$, $p = 0.180$) (Fig. 3B).

OS was significantly affected by the type of recurrence, being remarkably longer in patients with *late* recurrence, both after resection (121.0 months, 95 % CI: 87.4–154.6 vs. 56.0 months, 95 % CI: 40.7–71.3; $p < 0.0001$) and ablation (102.0 months, 95 % CI: 87.4–116.6 vs. 64.0 months, 95 % CI: 56.8–71.2; $p < 0.0001$) (Supplementary Figure 6).

4. Discussion

Adjuvant treatment for patients with HCC currently represents an unmet need, as effective treatments able to improve RFS and OS over active surveillance following potentially curative therapies in patients at high-risk of HCC recurrence have yet to demonstrate a consistent benefit in large populations representative of current cohorts of patients [2,17,21–23]. Patients at high-risk of cancer recurrence should ideally represent the target of adjuvant treatment for HCC. However, validated characteristics of patients who can obtain a benefit from these therapies and dimensioning of the pop-

Table 3
Oncological characteristics and treatment strategies observed at the time of recurrence for each treatment, categorized by the recurrence risk identified at the time of treatment.

	Resection (n = 258)			Ablation (n = 400)		
	Low risk (n = 89, 34.5)	High risk (n = 169, 65.5)	p	Low risk (n = 196, 49.0)	High risk (n = 204, 51.0)	p
Number of nodules			**0.005**			0.415
one	53 (59.6)	84 (49.7)		133 (67.9)	129 (63.2)	
2–3	28 (31.5)	44 (26.0)		51 (26.0)	58 (28.4)	
>3	6 (6.8)	37 (21.9)		9 (4.6)	15 (7.4)	
Maximum diameter, cm	1.5 (1.0 – 2.0)	1.7 (1.2 – 2.8)	**0.017**	1.7 (1.2 – 2.3)	2.0 (1.3 – 2.6)	0.081
α-fetoprotein, ng/mL	5.6 (3.0 – 10.6)	8.0 (3.8 – 48.0)	**0.025**	7.3 (3.9 – 21)	7.0 (3.5 – 24.1)	0.707
MVI, presence	5 (5.6)	26 (15.5)	**0.026**	18 (9.2)	19 (9.3)	1
EHS, presence	5 (5.6)	16 (9.5)	0.344	10 (5.1)	10 (4.9)	1
Milan criteria, in	63 (70.8)	100 (59.2)	0.066	158 (80.6)	155 (76.0)	0.262
BCLC			**0.004**			0.747
Very early	7 (8.9)	18 (11.6)		28 (15.9)	20 (10.3)	
Early	53 (59.6)	61 (36.1)		98 (50.0)	112 (54.9)	
Intermediate	8 (10.1)	17 (11.0)		6 (3.4)	9 (4.4)	
Advanced	11 (13.9)	53 (34.2)		38 (21.6)	48 (23.5)	
End stage	0 (0)	6 (3.9)		6 (3.4)	6 (2.9)	
Unknown	10 (11.2)	15 (8.9)		20 (10.2)	9 (4.4)	
Recurrence site						
Intra-hepatic	84 (94.4)	153 (90.5)		186 (94.9)	194 (95.1)	
Extra-hepatic	2 (2.2)	4 (2.4)	0.470	3 (1.5)	2 (1.0)	0.935
Intra- and extra-hepatic	3 (3.4)	12 (7.1)		7 (3.6)	8 (3.9)	
Surgical therapies						
Liver transplantation	2 (2.2)	16 (9.5)	**0.030**	9 (4.6)	9 (4.4)	0.931
Liver resection	11 (12.4)	22 (13.0)	0.880	22 (11.1)	11 (5.4)	**0.034**
Ablative therapies	39 (43.8)	63 (37.3)	0.307	90 (45.9)	102 (50.0)	0.414
Trans-arterial therapies	28 (31.4)	47 (27.8)	0.566	55 (28.1)	61 (29.9)	0.833
Systemic therapies	6 (6.7)	17 (10.1)	0.374	11 (5.6)	8 (3.9)	0.427

Data are shown as absolute value and percentage or median and interquartile range.
Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; EHS, extra-hepatic spread; MELD, model for end-stage liver disease; MVI, macro-vascular invasion.

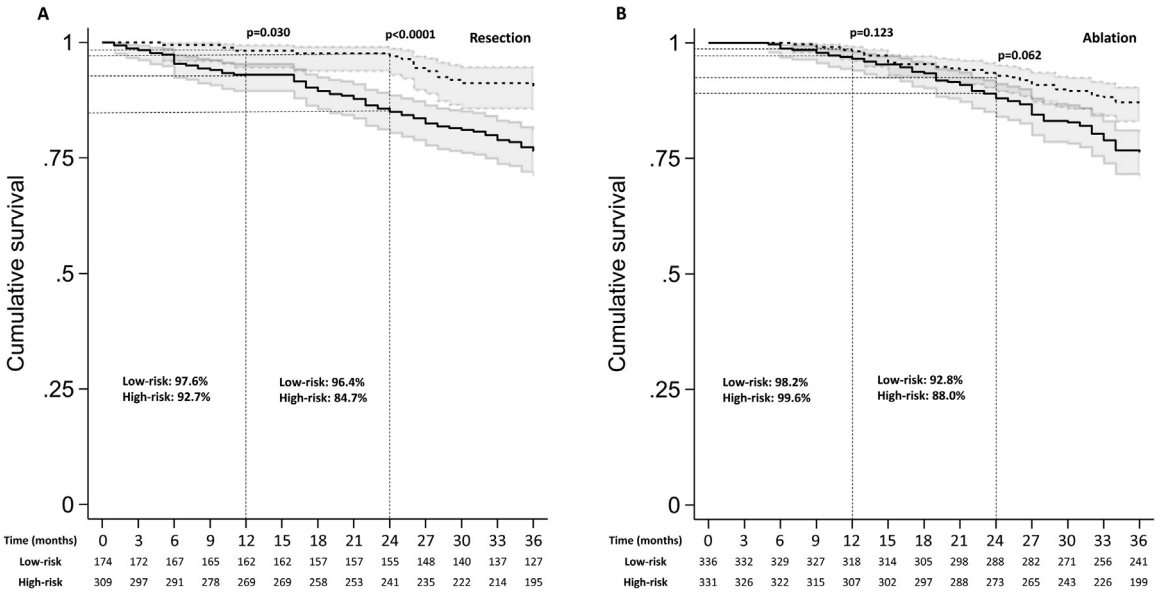

Fig. 3. Kaplan-Meier survival curves for patients undergoing (**A**) resection and (**B**) ablation sub-divided according to risk categories.

ulation of patients with HCC who may be the target of adjuvant therapies are still lacking. To understand the benefit of adjuvant therapies, it is also necessary to know type and timing of recurrence, factors influencing this event, RFS and OS of potential candidates for these treatments with data generated by real-life cohorts. With this aim, we analysed the ITA.LI.CA database applying the inclusion criteria adopted by the Imbrave050 trial that, at the time of our study planning was the only Phase III trial reporting, at the first interim analysis, positive RFS results of adjuvant therapy with atezolizumab *plus* bevacizumab in high-risk patients [17]. Despite the results of the Imbrave050 study were eventually not positive, it must be emphasised that the inclusion criteria for the EMERALD-2 study, which is currently exploring adjuvant treatment with durvalumab *plus* bevacizumab, are overlapping those of the Imbrave050 for patients treated with ablation and quite similar for those treated with resection, and therefore our results may nevertheless provide relevant information also for other settings [18].

Overall, we observed that resected patients at high-risk had a marginally significant increase (HR 1.26, p = 0.052) in the recurrence rate as compared to the counterpart at lower risk; moreover, in the former subgroup, HCC recurred significantly earlier (37 vs. 51 months), and an early recurrence was significantly more fre-

quent. Therefore, in our study, the IMbrave050 high-risk criteria in resected patients were just slightly predictive of recurrence, although were more strongly associated with of early recurrence. This finding supports the concept that adjuvant therapies should primarily aim to prevent early recurrences, as their effectiveness in preventing late recurrences is biologically less plausible and clinically less relevant [7]. Instead, after ablation, we observed no difference between high- and low-risk patients in recurrence rate, timing (31 vs 36 months), and pattern (early *vs.* late). These results cannot be influenced by confounding bias related to potential incomplete ablation, as the RFS we observed even in high-risk patients is better than reports in representative populations of patients with small HCCs treated with ablation and with post-liver transplantation histology considered gold standard [24]. Taken together, these data indicate that the criteria proposed by the IMbrave050 trial for ablative procedures, that are shared by other concomitant studies, do not efficiently predict the risk and time of HCC recurrence and, consequently, the RFS (as discussed below) [17,18].

One of the main endpoints of our study was to compare the RFS in patients deemed at high- and low-risk of HCC recurrence maintained in active surveillance. The main pitfalls in the potential interpretation of our results, in comparison with previous publications, reside in the inclusion of different populations in terms of demography and aetiological factors of liver disease, in the heterogeneity of the criteria adopted to define various degrees of risk, and often in the evaluation of outcome among patients at high-risk alone either treated with adjuvant therapy or undergoing active surveillance. In this regard, a previous phase III randomised trial testing adjuvant sorafenib after surgery or ablation in patients classified at high- and intermediate-risk of recurrence, median RFS figures were approximately 33 months with both adjuvant treatment and active surveillance, while a recent phase II randomised trial, enrolling resected patients considered at high-risk of recurrence (due to the presence of microvascular invasion), reports a RFS of 15 months in patients assigned to active surveillance and 29 months in those on adjuvant sintilimab [15,22]. Our study had the merit of providing RFS figures in patients on active surveillance segregated according initial treatment (*i.e.*, surgery or ablation) and pre-defined criteria of recurrence risk. We observed that high-risk patients treated with resection showed a median RFS significantly shorter than that of low-risk patients (29 vs. 43.0 months), while no difference was observed between high- and low-risk patients after ablation (27.0 vs. 30.0 months). These figures might be used as benchmark for future studies using the same criteria to define the degrees of risk. When we compared the 12-month RFS rates observed in our high-risk groups - about 76 %, independently of the curative treatment - to the IMbrave050 study figures, we observed RFS figures approximately 10 % higher than that of patients on active surveillance (65 %) and very similar to the one observed in patients on adjuvant atezolizumab *plus* bevacizumab (78 %), and since the selection criteria for high-risk patients were the same we feel that this difference may be attributed to unaccounted factors we were unable to identify. However, it is pertinent to note that the IMBrave050 trial reported aggregated data for patients treated with resection and ablation, thus preventing the possibility to segregate the outcome of surgical and non-surgical patients.

As far as parameters predictive of RFS are concerned, we observed that – in patients treated with resection – these aligned with those predictive of recurrence (*i.e.*, presence of cirrhosis, multinodular HCC, and microvascular invasion) suggesting that few patients died before recurrence, while in patients treated with ablation, besides signs of more aggressive tumours (higher AFP, multinodular HCC), presence of liver dysfunction highlighted by higher MELD and Child-Pugh-Turcotte scores was associated with RFS. This last finding may be secondary to the slightly, more advanced liver disease in ablated patients who more frequently had an ALBI grade 2 as compared to resected (53 % *vs* 44 %).

Our data give support to the criteria used in the IMbrave050 study to define the degree of recurrence risk following surgery, which identified sub-populations with statistically significant and clinically meaningful different RFS rates, but not to the criteria chosen for patients treated with ablation to delineate high-risk patients, which failed to provide an adequate discrimination regarding RFS. A possible explanation of this failure relies on the fact that the definition of high-risk in surgical patients included histological parameters undoubtedly heralding a greater tumour aggressiveness, such as the presence of tumour satellites, microvascular invasion and degree of HCC differentiation, while the parameters adopted to define ablated patients at high-risk of recurrence were simply morphological, also missing AFP values. This assumption is supported by the characterization of patients who recurred: in resected patients, the recurrence was independently associated to the biological features of aggressiveness of both the underlying liver disease (presence of cirrhosis) and the tumour (multinodularity and microvascular invasion), and an early recurrence was predicted by undifferentiated tumours and higher AFP levels. Conversely, among ablated patients no baseline parameter, except AFP levels, was able to pinpoint those with early recurrence. Noteworthy, the AFP level cut-off that best predicted recurrence among ablated patients fell within the limit of normal (*i.e.*, 7 ng/mL) and its overall accuracy was not adequate (*i.e.*, 0.569). It is conceivable that the inclusion of a different biological parameter as potential predictor of tumour aggressiveness, such as serological markers (*e.g.*, hepatocyte growth factor, vascular endothelial growth factor, and angiopoietin-2) or functional imaging, might provide a more accurate description of the risk of recurrence in ablated patients [25–27]. Lastly, it may be that patients at high-risk might benefit more from adjuvant therapy than patients at low-risk of recurrence, however since in the IMbrave050 trials patients at low-risk were not treated this hypothesis cannot be confirmed, although our data on recurrence in these patients might provide a theoretical benchmark against which this hypothesis can be tested. However, since high-risk ablated patients represented a heterogeneous population at likely different risk of recurrence even within the same risk-bracket, we tested whether further sub-division of this group (*e.g.*, single tumour >2 cm, multinodular <2 cm, multinodular >2 cm) might have provided different RFS profiles, with no success (Supplementary Figure 5). These findings are not pertinent to the IMbrave050 study alone as also the EMERALD-2 study, that is currently evaluating the adjuvant effect of the combination of durvalumab *plus* bevacizumab after HCC resection or ablation, adopted the same criteria to identify patients at high-risk of recurrence following ablation, and for resected patients number and size of tumours are those proposed by the IMbrave050 study with exclusion of patients with any evidence of macrovascular invasion.

Lastly, we feel that the real-world data of our study regarding the timing of recurrence following HCC cure –particularly after resection – might help plan future studies on adjuvant treatment for HCC. In particular, the bi-phasic incidence of recurrence observed in these patients (Supplementary Figure 3) is likely attributable to a dual cause of recurrence: the “true” oncologic aggressiveness of HCC and the oncogenic “field-effect” of the underlying liver disease. The additional effect of the two oncogenic forces might have contributed to the late disappearance of the benefit on RFS of adjuvant therapy *vs.* active surveillance (HR = 0.90, 95 % CI: 0.72–1.12) recently reported in the updated results of the IMbrave050 trial.

Another peculiarity of our study is the description of patients at the time of the tumour recurrence, sub-divided according to the *a priori* risk of recurrence. Among resected patients, high-risk subjects had an overall worse tumour staging at recurrence, highlighted by more frequent multi-nodularity, larger HCCs, presence

of macro-vascular invasion and higher AFP levels. Multi-nodularity was likely the main factor explaining the more frequent use of liver transplantation to treat post-resection HCC recurrence in high-risk patients. Once again, in ablated patients the definition of high-risk was not able to identify a subset of subjects with characteristics at recurrence different from those of low-risk individuals.

Lastly, despite median OS of resected patients was not significantly affected by the baseline risk of recurrence, at earlier milestones high-risk patients had significantly lower survival figures as compared to low-risk patients, reconciling the OS findings with the greater rate of early recurrence observed in the high-risk group. Conversely, among ablated patients, high-risk subjects had a significantly lower median OS, with survival rates at earlier milestones not significantly different between high- and low-risk patients despite that earlier recurrence negatively affected OS even in ablated patients. Taken together, these results suggest that OS after potentially curative treatments of HCC has several determinants including, besides cancer recurrence, residual hepatic function, treatment of underlying liver disease and downstream cancer treatments.

Limitations of the study. The retrospective nature of our investigation makes it vulnerable to unintended biases and unmeasured confounders. Moreover, in the absence of central adjudication of treatment efficacy and a pre-established follow-up radiologic response to treatments, data may have experienced internal heterogeneity. However, it can be pointed out that all patients were managed in expert centres that adopt a trimestral imaging surveillance for both resected and ablated patients, which becomes semiannual after at least two years of recurrence-free follow-up.

In conclusion, this study provides a seminal comparative assessment of outcomes of patients at high-risk (who likely represent the target population for adjuvant therapy) and low-risk of HCC recurrence after curative treatments, segregated according to the IMbrave050 trial criteria for adjuvant therapy. Its results give support to the criteria proposed for resected patients, while those adopted for patients undergoing ablative procedures are inaccurate to identify the target population, and their use may mask a positive result of adjuvant treatments due to an inherent dilution bias. The inclusion of a biological parameter of aggressiveness could improve the detection of individual at high-risk of HCC recurrence, particularly among ablated patients.

Funding sources

The project was conducted with the unconditional financial support of Roche S.p.a.

Authors' contribution

Edoardo G. Giannini, Andrea Pasta. Laura Bucci, Franco Trevisani: contributed for conceptualization, literature search, figures, study design, data collection, data analysis, writing first draft, and had access and verified data. Giulia Pieri, Maria Corina Plaz Torres, Ciro Celsa, Angelo Sangiovanni, Fabio Piscaglia, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Filippo Pelizzaro, Francesco Giuseppe Foschi, Filomena Morisco, Valentina Santi, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Francesca Romana Ponziani, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Alessandro Vitale: contributed for resources, investigation, data collection, data analyses, writing-review and editing. All Authors approved the final draft submitted.

Declaration of competing interest

Edoardo G. Giannini. AbbVie, AstraZeneca, EISAI, Gilead, Roche: speaking and teaching; Ipsen: advisory board. Franco Trevisani. AbbVie, Astra Zeneca, Gilead, MSD, Roche: research grants; EISAI, Roche: advisory board. Filippo Pelizzaro. MSD advisory board.

Ciro Celsa. AstraZeneca, Ipsen, Eisai, MSD: speaking. Eisai, MSD: advisory board. Roche: travel support.

Andrea Pasta, Laura Bucci, Maria Corina Plaz Torres, Giulia Pieri, Angelo Sangiovanni, Fabio Piscaglia, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Francesco Giuseppe Foschi, Filomena Morisco, Valentina Santi, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Francesca Romana Ponziani, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Alessandro Vitale: nothing to declare.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.05.032.

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