Ann Surg Oncol (2025) 32:6312–6323
https://doi.org/10.1245/s10434-025-17673-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Patterns of Site and Timing of Recurrence After Curative Resection in Single and Multiple Large Hepatocellular Carcinoma: A Multicenter International Comprehensive Analysis

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ABSTRACT

Background. Curative options for large hepatocellular carcinoma (LHCC) are limited because of the high risk of early and extrahepatic recurrence. However, only a few studies report data on long-term outcomes in large cohorts of resected LHCC. We therefore investigated timing and site of recurrence of LHCC and assessed factors strictly associated with adverse patterns.

Patients and Methods. This was a retrospective, international, multicenter study of patients undergoing anatomic resection of HCC ≥ 5 cm at 12 hepatobiliary high-volume centers. Extrahepatic recurrence was defined as any distant site of metastasis, while recurrence within 2 years after surgery was classified as early recurrence.

First Received: 4 December 2024
Accepted: 29 May 2025
Published online: 19 June 2025

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Results. A total of 869 patients were included. Recurrence was observed in 487 (56%) cases. Patterns associated with reduced overall survival were early ($p < 0.001$) and simultaneous intrahepatic and extrahepatic recurrence ($p = 0.038$). Variables independently associated with early recurrence were age ($p = 0.037$), major hepatectomy ($p = 0.023$), microvascular invasion ($p = 0.011$), satellites nodules ($p = 0.005$), and open approach ($p = 0.025$). Variables correlated with simultaneous intra- and extrahepatic relapse were age ($p < 0.001$), preoperative transarterial chemoembolization (TACE) ($p < 0.001$), microvascular invasion ($p < 0.001$), and satellite nodules ($p = 0.026$).

Conclusions. Surgery for LHCC is associated with a high risk of early recurrence. Apart from pathological variables, factors independently associated with adverse patterns were open approach and age for the early recurrence and preoperative TACE and age for simultaneous intra-extrahepatic relapse. BCLC stage was not associated with timing nor with site of recurrence.

Keywords Hepatocellular carcinoma · Surgical resection · BCLC score · Patterns of recurrence · Outcomes

Hepatocellular carcinoma (HCC), the most prevalent primary hepatic malignancy,[1] currently represents an important socioeconomic problem, due to its well-known risk factors as virus, alcohol, and metabolic dysfunction-associated fatty liver disease.[2,3] Different therapeutic options are available according to liver function, patient performance status, and disease staging, features that are mixed together in the Barcelona Clinical Liver Cancer (BCLC) model to propose a treatment flow chart and predict long-term outcomes.[4] Curative options are essentially represented by liver transplantation, thermal ablation, and surgical resection (SR), to which strict criteria are normally applied. In any case, in the presence of a correct liver function, tumor size and number of nodules are the first filter to select the best treatment. As in other liver tumours,[5] thermal ablation is, for instance, the treatment of choice in small (< 2–3 cm), single lesions,[6,7] while Milan criteria (or the "extended criteria" in particular cases),[8,9] guide indications for liver transplantation. Some patients, however, present larger lesions at diagnosis, which modifies treatment flow chart and limits curative possibilities. Large HCC (LHCC), lesions with a largest diameter ≥ 5 cm, show worse outcomes compared with smaller lesions.[10] In case of solitary LHCC, classified as early stage (BCLC-A), SR often remains the only possible curative treatment, on condition of a minor degree of portal hypertension and a resectable disease.[4] When multiple localizations are evident at imaging evaluation in LHCC, tumor shifts to the intermediate stage (BCLC-B) and surgery is no more indicated. Nevertheless, some patients in this category could benefit from SR. Indeed, surgical series reported how the distinction between BLCL-A and B in LHCC does not represent an independent prognostic predictor after curative resection.[11,12] The main issue in these patients and the reason why criteria for SR are so strict remains, however, the higher risk of developing an early or an extrahepatic recurrence. These patterns are in fact known to be associated with impaired overall survival (OS) and disease-free survival (DFS) rates in all types of HCC.[11,13] Although dimensional criteria are important in the BCLC staging system, only a few studies report in literature data on outcomes in large cohort of resected LHCC and assess factors associated with the risk of early or extrahepatic recurrence.

We therefore investigated patterns of timing and site of recurrence after curative resection of LHCC in a large, multicenter database. Furthermore, we aimed to assess factors strictly associated with those types of recurrence associated with impaired long-term outcomes.

PATIENTS AND METHODS

Study Design

This is a retrospective study conducted on a multicentric international database. Data were prospectively collected and provided by 12 hepatobiliary high-volume centers across Italy, France, and South Korea. The study was aligned to the ethical standards of the Declaration of Helsinki[14] and no specific informed consent was obtained given the retrospective and observational nature of the analysis. Cases presenting histopathologically confirmed HCC, with a tumor diameter ≥ 5 cm at preoperative imaging [contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI)], considered resectable at diagnosis and undergoing an anatomical SR with a curative intent between January 2014 and December 2021, were included. Patients resected for recurrent LHCC, undergoing preoperative systemic therapies or adjuvant treatments, invading the main portal trunk or the portal bifurcation, or with a history of extrahepatic disease were excluded. Patients with less than 4 months of follow-up (FU) were not considered for the analysis as well. Cases were included and reported according to the principles of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] Data collection was performed by completing a common database sent to all the participating centers. Data submitted were then evaluated by the local investigators of the promoting center and inclusion/exclusion criteria were manually checked before starting the analysis.

The primary endpoint was the analysis of survival rates according to timing of recurrence (early, late) and site (intrahepatic, extrahepatic, or both). Secondary endpoints were

perioperative factors independently associated with patterns of recurrence (according to timing and site).

Perioperative Variables and Follow-Up

Demographic and clinical data were collected for each patient, including age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) score, Charlson comorbidity index (CCI) score, comorbidities, and history of hepatitis (hepatitis B or hepatitis C virus infection). In case of known underlying cirrhosis, liver function was assessed according to the Child–Pugh classification. Preoperative blood tests included alpha-fetoprotein (AFP) level, liver and renal function tests, and platelet and coagulation tests. As regards tumoral information and management, number and maximum diameter of the LHCC (assessed on preoperative radiologic imaging), performance of preoperative transarterial chemoembolization (TACE), preoperative portal vein embolization (PVE), or ligation (PVL) were reported. Surgical and pathological variables were assessed including type of approach [open versus minimally invasive (MI)], extension of hepatectomy according to the Brisbane terminology and its recent updates (major ≥ 3 segments),[16] intraoperative blood transfusion, operative time, postoperative complications according to Clavien–Dindo classification,[17] maximum tumor size on pathologic assessment, satellite nodules (defined as tumors < 2 cm in size located < 2 cm from the main tumor),[18] microvascular infiltration, capsular invasion, surgical margin (R1 considered as ≤ 1 mm) and tumor grading [according to the World Health Organization (WHO) classification].[19] Preoperative strategy, as choice of performing PVE or TACE, and intraoperative planning, including type of approach or extension of the hepatectomy, were dependent on surgeon preferences and multidisciplinary board recommendations, but always with the aim of obtaining a curative resection.

After patient discharge, a follow-up (FU) was planned according to the EASL recommendations. Patients were seen by a surgeon or a hepatologist every 3 months for the first 2 years after surgery and subsequently every 3–6 months until 5 years. Visits consisted of physical examination, serum AFP determination and liver function tests, and at least one imaging examination (contrast-enhanced CT or MRI). HCC recurrence was suggested by an elevation of serum AFP or by new hepatic or extrahepatic lesions at CT or MRI imaging. Any doubtful lesion during FU was discussed in a dedicated HPB multidisciplinary team meeting to confirm HCC recurrence or whether further investigations were needed [biopsy, positron emission tomography (PET), and so on]. If proved, the best therapy according to patient's status and disease extent was validated. Site of recurrence during FU, type of treatment administrated, and following FU were recorded. Extrahepatic recurrence was defined as the appearance of any distant site of metastasis, regardless of the presence of an intrahepatic relapse. Recurrence within 2 years after surgical resection was classified as early recurrence, while late recurrence was defined as a disease relapse at least 2 years after liver resection.[20–23]

Statistical Analysis

Categorical data were reported as absolute number with relative proportions (%) and compared by the χ^2 test with Yates correction if necessary, or Fischer's exact test if indicated. Continuous data were expressed as median and range and compared using Student's *t* test or Mann–Whitney *U* test in case of normal distribution. Kaplan–Meier analyses were performed and survival outcomes compared using log-rank test for categorical variables and through Cox test in case of continuous data. Hazard ratios and the relative 95% CI were always reported. A logistic model was built to identify independent factors associated with those patterns showing reduced OS and DFS rates. Only variables with *p*-value less than 0.25 in simple regression model were included in the final model.[24] All statistical analyses were performed using SPSS software (version 29.0, IBM Corp., Armonk, NY, USA) and R (R Project for statistical computing, version 4.2.2, R Core Team) while forest plots for binary logistic regression made with Excel (Microsoft 365, Microsoft Corporation). Two-sided p-value < 0.05 was considered as statistically significant.

RESULTS

Data from 1043 patients were gathered from the participating centers according to the applied criteria. After screening, 179 cases were excluded from the cohort because of missing FU (n = 51), incomplete data ($n = 103$), or tumor size inferior to 5 cm at preoperative imaging ($n = 25$). A total of 869 patients were finally considered for the analysis. Of these, 479 had no underlying cirrhosis (55.1%) and 399 (45.9%) had a history of viral infection. Regarding surgical variables, a major hepatectomy was needed in 446 cases (51.3%), and in 315 patients (36.2%) MI approach was used. Histological assessment confirmed multinodular disease (BCLC-B) in 208 cases (23.9%), with a total of 869 (74.2%) LHCC including 224 (25.8%) huge HCC (≥ 10 cm). A summary of all clinicopathological features of the cohort is included in Table 1.

Timing of Recurrence

Median FU in the whole cohort was 28 months (IQR 15.7–56.2 months). Recurrence was observed in 487 (56%) of the cases. Of those, 402 (82.5%) patients experienced recurrence within 2 years of the resection while late recurrence was documented in 85 cases (17.5%). Table 1 presents

TABLE 1 Patient characteristics in the whole cohort according to timing of recurrence

Variable	No recurrence $n = 382$ *n (%)*	Early recurrence $n = 402$	p^*	Late recurrence $n = 85$ *n (%)*	p^{**}	p^{***}
Age (years), SD	68 (12)	65 (12)	***<0.001***	68 (12)	0.273	0.302
Sex						
Male	300 (78.5)	324 (80.6)	0.474	70 (82.4)	0.432	0.708
Female	82 (21.5)	78 (19.4)		15 (17.6)		
BMI (kg/m^2), SD	25.2 (4.4)	24.6 (4.2)	0.102	25 (4.8)	0.468	0.107
ASA						
I	35 (9.2)	33 (8.2)	0.881	2 (2.4)	0.120	0.206
II	205 (53.7)	209 (52)		46 (54.1)		
III	136 (35.6)	153 (38.1)		34 (40)		
IV	6 (1.6)	7 (1.7)		3 (3.5)		
Charlson comorbidity index ≤ 5 > 5	234 (61.3) 148 (38.7)	258 (64.2) 144 (35.8)	0.398	55 (64.7) 30 (35.3)	0.554	0.927
Underlying cirrhosis (Child–Pugh) No A B	214 (56) 163 (42.7) 5 (1.3)	216 (53.7) 172 (42.8) 14 (3.5)	0.135	49 (57.6) 34 (40) 2 (2.4)	0.720	0.741
Normal platelets count, (≥ 150 × 10^9/L) No Yes	77 (20.2) 305 (79.8)	96 (23.9) 306 (76.1)	0.209	19 (22.4) 66 (77.6)	0.650	0.763
History of viral infection (HBV/HCV) No Yes	217 (56.8) 165 (43.2)	201 (50) 201 (50)	0.056	52 (61.2) 33 (38.8)	0.461	0.061
AFP level (ng/mL), SD	24 (5753)	29 (7082)	0.060	14 (1559)	0.066	***0.012***
HCC median size at diagnosis (mm), SD	68 (52)	77 (61)	***<0.001***	66 (66.3)	*0.927*	***0.004***
Preoperative TACE performed No Yes	334 (87.4) 48 (12.6)	324 (80.6) 78 (19.4)	***0.009***	66 (77.6) 19 (22.4)	***0.020***	0.536
PVE/PVL performed No Yes	333 (87.2) 49 (12.8)	328 (81.6) 74 (18.4)	***0.032***	70 (82.4) 15 (17.6)	0.243	0.869
Approach Open Minimally invasive	221 (57.9) 161 (42.1)	282 (70.1) 120 (29.9)	***<0.001***	51 (60) 34 (40)	0.717	0.068
Extension of hepatectomy Minor Major	201 (52.6) 181 (47.4)	171 (42.5) 231 (57.5)	***0.005***	51 (60) 34 (40)	0.217	***0.003***
Operative time (min), SD	269 (103)	274 (109)	0.174	260 (114)	0.919	0.373
Intraoperative blood transfusion No Yes	326 (85.3) 56 (14.7)	313 (77.9) 89 (22.1)	***0.007***	67 (78.8) 18 (21.2)	0.137	0.846
Severe postoperative complications (CD ≥ 3) No Yes	343 (89.8) 39 (10.2)	349 (86.8) 53 (13.2)	0.196	78 (91.8) 7 (8.2)	0.581	0.207
HCC median size on pathology (mm), SD	70 (35)	78 (41)	***<0.001***	67 (63)	0.902	***0.024***
WHO tumor differentiation Well Moderate Poor/undifferentiated	108 (28.3) 220 (57.6) 54 (14.1)	98 (24.4) 244 (60.7) 60 (14.9)	0.465	32 (37.6) 44 (51.8) 9 (10.6)	0.212	***0.039***
Tumor number Solitary Multiple	301 (78.8) 81 (21.2)	293 (72.9) 109 (27.1)	0.054	67 (78.8) 18 (21.2)	0.995	0.257

Table 1 (continued)

Variable	No recurrence $n = 382$ *n (%)*	Early recurrence $n = 402$	p^*	Late recurrence $n = 85$ *n (%)*	p^{**}	p^{***}
Microvascular infiltration No Yes	193 (50.5) 189 (49.5)	156 (38.8) 246 (61.2)	***<0.001***	41 (48.2) 44 (51.8)	0.703	0.108
Capsular invasion (*n = 210 missing*) No Yes	190 (65.1) 102 (34.9)	187 (66.3) 95 (33.7)	0.754	38 (64.4) 21 (35.6)	0.923	0.779
Satellite nodules No Yes	315 (82.5) 67 (17.5)	276 (68.7) 126 (31.3)	***<0.001***	69 (81.2) 16 (18.8)	0.779	***0.021***
Margin status Negative Positive	361 (94.5) 21 (5.5)	360 (89.6) 42 (10.4)	***0.011***	83 (97.6) 2 (2.4)	0.226	***0.018***

Bold values indicate in Reaching statistical significance

*Analysis performed between patients with early recurrence and patients with no recurrence

**Analysis performed between patients with late recurrence and patients with no recurrence

***Analysis performed between patients with late recurrence and patients with early recurrence

SD standard deviation, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha fetoprotein, *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization, *PVE* portal vein embolization, *PVL* portal vein ligation, *CD* Clavien–Dindo, *WHO* World Health Organization

differences among the three groups of patients in terms of baseline, surgical, and pathological variables. Patients with late recurrence and without relapse were similar in all the variables assessed, except from the rate of preoperative TACE performed ($p = 0.020$). When comparing patients with early and late recurrence, the latter had a significantly lower baseline AFP level ($p = 0.012$), a smaller tumor diameter at preoperative imaging and on pathological specimen ($p = 0.004$ and $p = 0.024$, respectively), a higher percentage of well-differentiated tumor ($p = 0.039$), and a lower number of satellite nodules ($p = 0.021$) and positive resection margin ($p = 0.018$). The 1-, 3-, and 5-year OS rates were 97.3%, 90.2%, and 87.9% for the no recurrence group, respectively, and 100%, 90.6%, and 78.2% for those patients experiencing late recurrence, respectively, while the early recurrence group experienced the worst survival rates with 87.1%, 48.9%, and 35.5%, respecitvely ($p < 0.001$, Fig. 1A). Table 2 presents differences in pattern and treatment of disease relapse in the two types of recurrence. Early recurrence had a significantly higher rate of extrahepatic site of disease relapse (148/402 patients, 36.8%) compared with those with late recurrence (21/85 patients, 24.7%; $p = 0.033$). Similarly, patients with a disease relapse within 2 years more often needed systemic treatments or best supportive care compared with patients with late recurrence, who were mostly treated with local therapies ($p = 0.002$).

Site of Recurrence

Intrahepatic recurrence occurred in 318 patients (36.6 %) while extrahepatic localization of the disease was observed in 169 cases (19.4%). Table 3 presents differences among patients with no recurrence, intrahepatic recurrence, and extrahepatic recurrence. Compared with those with no disease relapse, patients with liver-only recurrence had mainly more aggressive histological variables, such as tumor size (preoperatively, $p = 0.019$), tumor number ($p = 0.030$), satellite nodules ($p = 0.010$), and margin status ($p = 0.030$). On the contrary, cases with evidence of extrahepatic disease showed multiple pre-, perioperative, and pathological differences compared with those with intrahepatic recurrence. However, when comparing OS curves of cases with intrahepatic and extrahepatic recurrence, no difference was observed ($p = 0.21$, Fig. 1B). Site of disease relapse was therefore split in intrahepatic recurrence (n =318, 65.3%), extrahepatic-only ($n = 48$, 9.9%), and simultaneous intrahepatic and extrahepatic recurrence, which was observed in 121 patients (24.8%). When assessing survival rates in these groups, the 1-, 3-, and 5-year OS rates were 90%, 56.4%, and 45.8% in case of liver-only recurrence, respectively, and 91.3%, 58.8%, and 51.5% in the extrahepatic recurrence group, respectively, while in simultaneous intrahepatic and extrahepatic relapse they were 90%, 59.6%, and 41.7%, respectively, with a statistically significant difference among the three groups ($p = 0.038$, Fig. 2A). Clinico-pathological

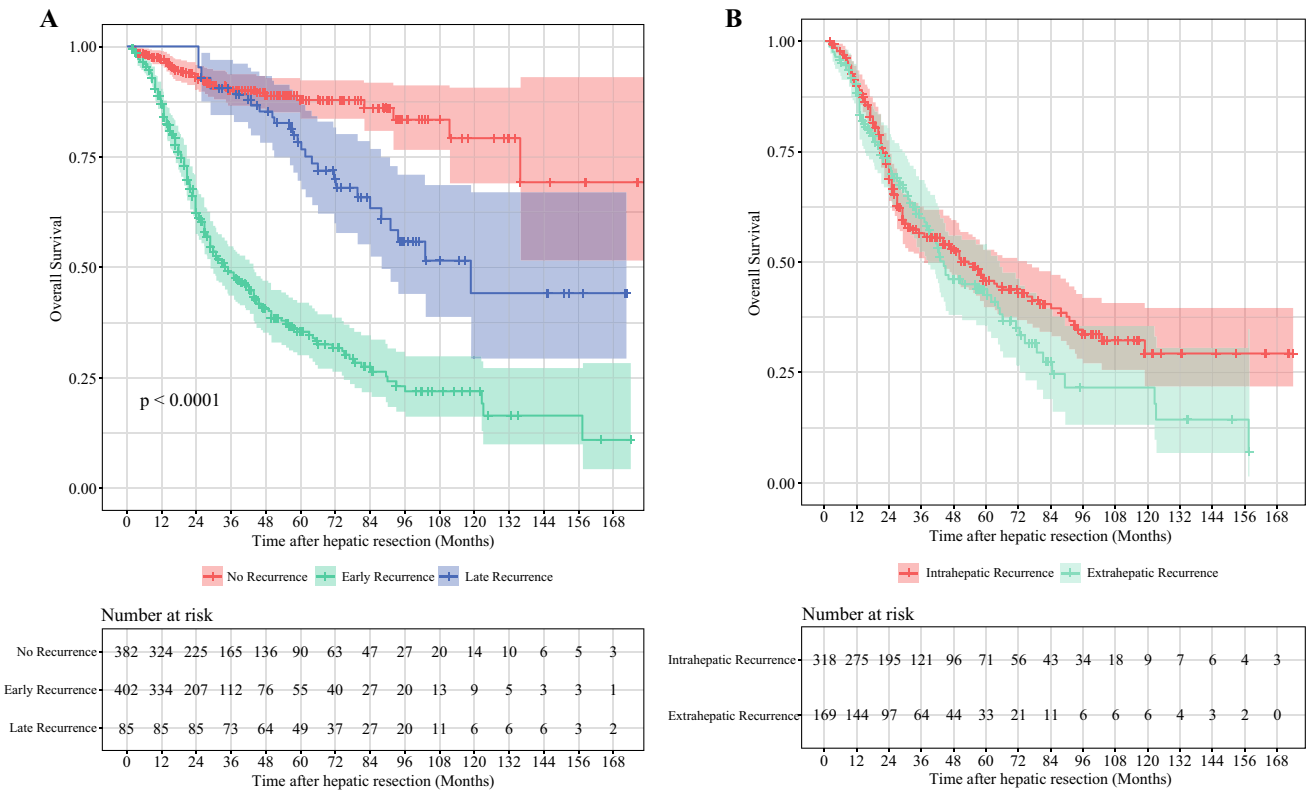

FIG. 1 **A** Kaplan–Meier curves exploring OS according to timing of recurrence and **B** intra- or extrahepatic recurrence after curative resection in large HCC

TABLE 2 Comparisons of long-term outcomes and treatment modalities of recurrence according to time of recurrence

Variable	Total *n* = 487 *n (%)*	Early recurrence *n* = 402	Late recurrence *n* = 85	*p*
Follow-up, median (range)	27 (3–174)	24 (3–174)	66 (25–173)	
Site of recurrence	318 (65.3)	254 (63.2)	64 (75.3)	***0.033***
Intrahepatic	169 (34.7)	148 (36.8)	21 (24.7)	
Extrahepatic				
Organ of recurrence	318 (65.3)	254 (63.2)	64 (75.3)	0.117
Liver	10 (2.1)	10 (2.5)	–	
Lungs	6 (1.2)	6 (1.5)	–	
Bone	18 (3.7)	17 (4.2)	1 (1.2)	
Other intra-abdominal	135 (27.7)	115 (28.6)	20 (23.5)	
Multi-metastatic				
Treatment of recurrence	137 (28.1)	100 (24.9)	37 (43.5)	***0.002***
Curative	157 (32.2)	134 (33.3)	23 (27.1)	
Palliative local	193 (39.6)	168 (41.8)	25 (29.4)	
Palliative systemic/BSC				
Disease-free survival, median (months, 95% CI)	10 (8.7–11.3)	7 (6.3–7.7)	39 (33.8–44.1)	***<0.001***
1-year DFS rate (%)	42.5	32.1	100	
3-year DFS rate (%)	9.9	–	56.5	
5-year DFS rate (%)	3.3	–	18.8	
Overall survival, median (months, 95% CI)	50 (40.5–59.5)	35 (28.3–41.6)	119 (79–159)	***<0.001***
1-year OS rate (%)	89.4	87.1	100	
2-year OS rate (%)	57.5	48.9	90.6	
5-year OS rate (%)	45.1	35.5	78.2	

Bold values indicate in Reaching statistical significance

BSC best supportive care, *DFS* disease-free survival, *CI* confidence interval, *OS* overall survival

TABLE 3 Patient characteristics in the whole cohort according to site of recurrence

Variable	No recurrence $n = 382$	Intrahepatic recurrence $n = 318$	p^*	Extrahepatic recurrence $n = 169$	p^{**}	p^{***}
	n (%)			*n (%)*		
Age (years), SD	68 (11)	68 (11)	0.324	63 (13)	***<0.001***	***<0.001***
Sex Male Female	300 (78.5) 82 (21.5)	247 (77.7) 71 (22.3)	0.784	147 (87) 22 (13)	***0.019***	***0.013***
BMI (kg/m^2), SD	25 (4.2)	25 (4.4)	0.703	24.5 (3.9)	0.051	0.159
ASA I II III IV	35 (9.2) 205 (53.7) 136 (35.6) 6 (1.6)	17 (5.3) 160 (50.3) 135 (42.5) 6 (1.9)	0.113	18 (10.7) 95 (56.2) 52 (30.8) 4 (2.4)	0.655	***0.028***
Charlson comorbidity index ≤ 5 > 5	234 (61.3) 148 (38.7)	196 (61.6) 122 (38.4)	0.918	117 (69.2) 52 (30.8)	0.073	0.096
Underlying Cirrhosis (Child-Pugh) No A B	214 (56) 163 (42.7) 5 (1.3)	167 (52.5) 141 (44.3) 10 (3.1)	0.199	98 (58) 65 (38.5) 6 (3.6)	0.171	0.457
Normal platelets count, (≥ 150 × 10^9/L) No Yes	77 (20.2) 305 (79.8)	82 (25.8) 236 (74.2)	0.077	33 (19.5) 136 (80.5)	0.864	0.122
History of viral infection (HBV/HCV) No Yes	217 (56.8) 165 (43.2)	172 (54.1) 146 (45.9)	0.471	81 (47.9) 88 (52.1)	0.054	0.195
AFP level (ng/mL), SD	24.5 (5753)	27 (5220)	0.689	27 (8305)	0.100	0.173
HCC median size at diagnosis (mm), SD	68.5 (52.6)	71 (70)	***0.019***	80 (42)	***<0.001***	***0.017***
Preoperative TACE performed No Yes	334 (87.4) 48 (12.6)	272 (85.5) 46 (14.5)	0.463	118 (69.8) 51 (30.2)	***<0.001***	***<0.001***
PVE/PVL performed No Yes	333 (87.2) 49 (12.8)	271 (85.2) 47 (14.8)	0.455	127 (75.1) 42 (24.9)	***<0.001***	***0.006***
Approach Open Minimally invasive	221 (57.9) 161 (42.1)	218 (68.6) 100 (31.4)	***0.004***	115 (68) 54 (32)	***0.024***	0.909
Extension of hepatectomy Minor Major	201 (52.6) 181 (47.4)	155 (48.7) 163 (51.3)	0.307	67 (39.6) 102 (60.4)	***0.005***	0.055
Operative time (min), SD	269 (103)	275 (106)	0.182	270 (116)	0.707	0.497
Intraoperative blood transfusion No Yes	326 (85.3) 56 (14.7)	257 (80.8) 61 (19.2)	0.110	123 (72.8) 46 (27.2)	***<0.001***	***0.041***
Severe postoperative complications (CD ≥ 3) No Yes	343 (89.8) 39 (10.2)	281 (88.4) 37 (11.6)	0.546	146 (86.4) 23 (13.6)	0.244	0.528
HCC median size on pathology (mm), SD	70 (35)	73 (47)	0.056	82 (43)	***<0.001***	***0.015***
WHO tumor differentiation Well Moderate Poor/undifferentiated	108 (28.3) 220 (57.6) 54 (14.1)	94 (29.6) 189 (59.4) 35 (11)	0.464	36 (21.3) 99 (58.6) 34 (20.1)	0.090	***0.010***
Tumor number Solitary Multiple	301 (78.8) 81 (21.2)	228 (71.7) 90 (28.3)	***0.030***	132 (78.1) 37 (21.9)	0.856	0.125

Table 3 (continued)

Variable	No recurrence $n = 382$ *n (%)*	Intrahepatic recurrence $n = 318$	p*	Extrahepatic recurrence $n = 169$ *n (%)*	p**	p***
Microvascular infiltration No Yes	193 (50.5) 189 (49.5)	145 (45.6) 173 (54.4)	0.194	52 (30.8) 117 (69.2)	***<0.001***	***0.002***
Capsular invasion (*n = 210 missing*) No Yes	190 (65.1) 102 (34.9)	175 (69.2) 78 (30.8)	0.310	50 (56.8) 38 (43.2)	0.160	***0.035***
Satellite nodules No Yes	315 (82.5) 67 (17.5)	237 (74.5) 81 (25.5)	***0.010***	108 (63.9) 61 (36.1)	***<0.001***	***0.014***
Margin status Negative Positive	361 (94.5) 21 (5.5)	287 (90.3) 31 (9.7)	***0.033***	156 (92.3) 13 (7.7)	0.323	0.451

Bold values indicate in Reaching statistical significance

*Analysis performed between patients with intrahepatic and no recurrence

**Analysis performed between patients with extrahepatic and no recurrence

***Analysis performed between patients with intrahepatic and extrahepatic recurrence

SD standard deviation, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha fetoprotein, *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization, *PVE* portal vein embolization, *PVL* portal vein ligation, *CD* Clavien–Dindo, *WHO* World Health Organization

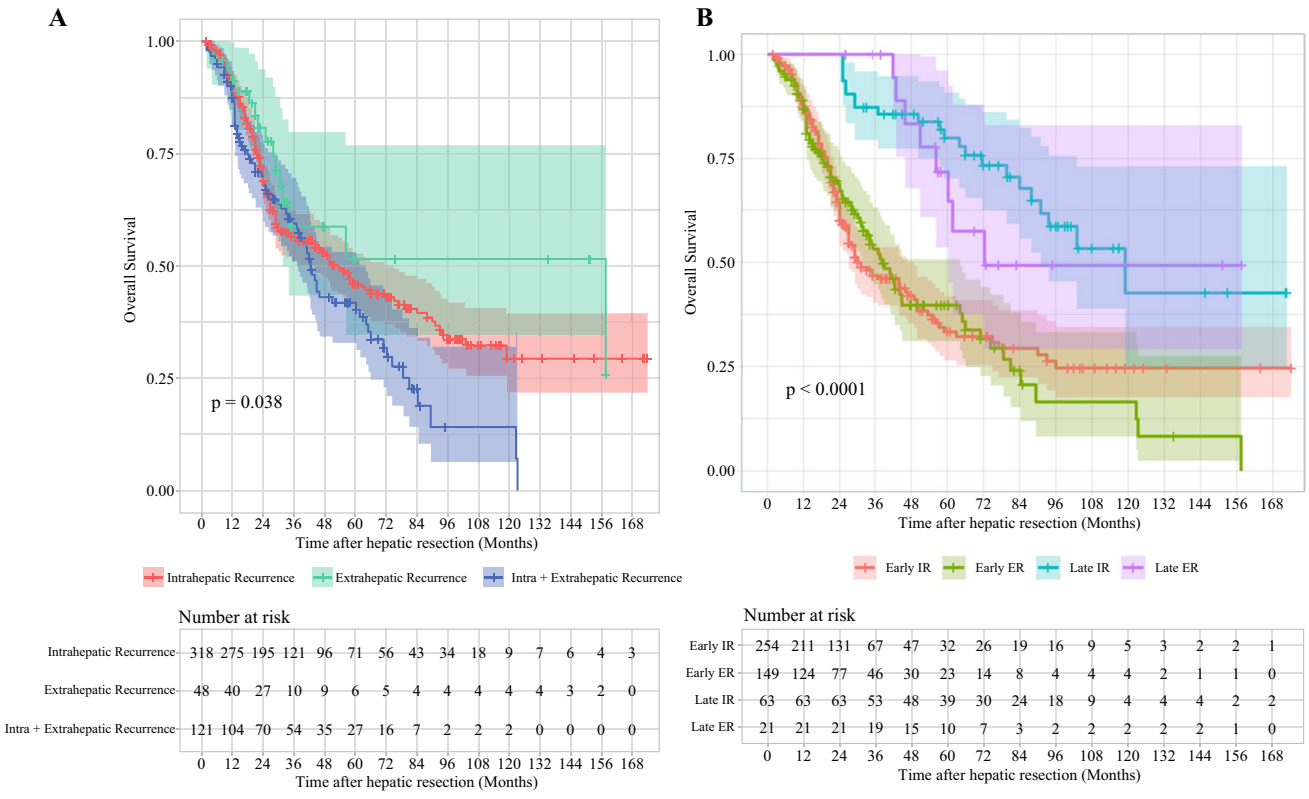

FIG. 2 **A** Kaplan–Meier curves exploring OS according to site of recurrence and **B** Kaplan–Meier curves exploring OS according to site and timing of disease recurrence; *IR* intrahepatic recurrence, *ER* extrahepatic recurrence

features of those patients with both intra- and extrahepatic recurrence and differences with the rest of the cohort are presented in Table S1. When combining site (intrahepatic versus extrahepatic) and timing of recurrence (early and late) in four groups (EIR: early intrahepatic recurrence, EER: early extrahepatic recurrence, LIR: late intrahepatic recurrence, and LER: late extrahepatic recurrence) an overall significance was reached ($p < 0.001$, Fig. 2B). However, worse OS rates were observed in EIR and EER cases (EIR versus EER, $p = 0.864$) compared with the two groups with late recurrence (LIR versus LER, $p = 0.455$).

Factors Associated with Worst Patterns of Recurrence

Due to the similarity between patients with late and no recurrence, as well as the worst prognosis observed in cases with early relapse, a binary logistic regression was performed to find predictors of recurrence within 2 years after surgery. The result of the univariate analysis is presented in Table S2. Results of this multivariate model were depicted as a forest plot in Fig. 3A. Variables independently associated with early recurrence were age (OR 0.987, 95% CI 0.975–0.999; $p = 0.037$), major hepatectomy (OR 1.415, 95% CI 1.049–1.91; $p = 0.023$), MVI (OR 1.469, 95% CI 1.092–1.976; $p = 0.011$), and presence of satellite nodules (OR 1.66, 95% CI 1.166–2.363; $p = 0.005$). The model also showed that MI approach was a protecting factor, as it was associated with a lower risk of early recurrence (OR 0.705, 95% CI 0.519–0.956; $p = 0.025$). The same analysis was repeated to assess independent predictors of cases that will develop simultaneous intrahepatic and extrahepatic recurrence during FU, that is, those patients who experienced the worst OS rates (see Table S1 and Fig. 3B). At multivariate analysis, variables found to be strongly correlated with multisite of relapse were age (OR 0.961, 95% CI 0.947–0.976; $p < 0.001$), performance of preoperative TACE (OR 2.919, 95% CI 1.805–4.722; $p < 0.001$), microvascular invasion (OR 2.161, 95% CI 1.379–3.387; $p < 0.001$), and satellite nodules (OR 1.657, 95% CI 1.064–2.582; $p = 0.026$).

DISCUSSION

In this large multicentric study we found that after curative surgical resection, overall risk of recurrence was not significantly higher if compared with smaller lesions described in other large series,[10,13,25–27] with less than a half of the patients in the cohort not developing disease relapse. However, what seems to differ in these patients is the risk of early recurrence, which is probably higher compared with tumors < 5 cm.[13,20,25,27] Early and simultaneous intra- and extrahepatic recurrence were patterns that experienced impaired OS rates. Furthermore, size and number of lesions in our cohort, and therefore the distinction between early and intermediate BCLC stage, did not influence directly the risk of early or

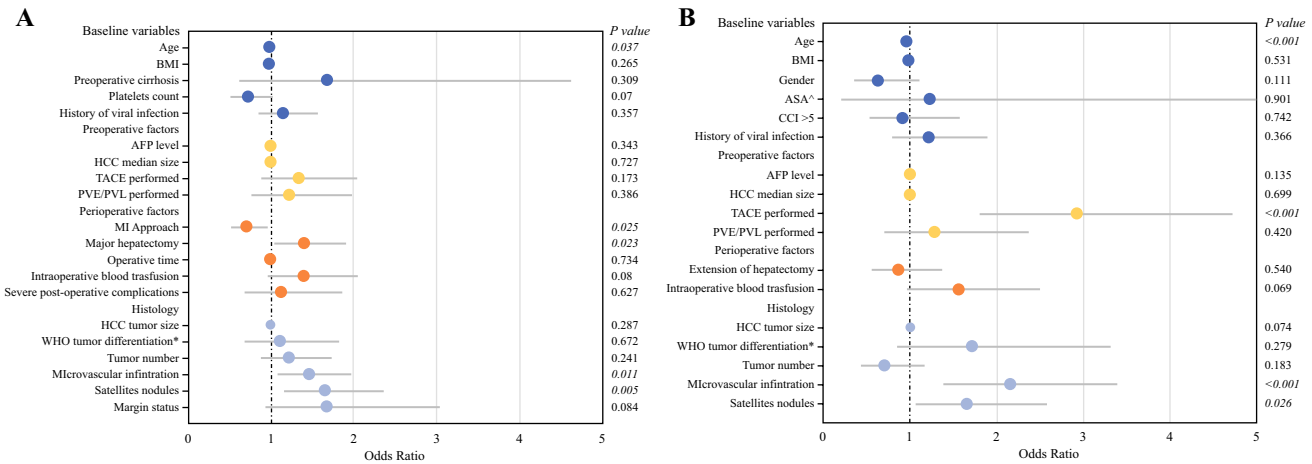

FIG. 3 Forest plots showing the association between different variables (with $p < 0.250$ at univariate analysis) and specific pattern of recurrence in the multivariable logistic regression model; *x*-axis represents odds ratio (OR) obtained in the analysis with the relative 95% CI, identified by the horizontal line of each dot; **A** first image shows results of the multivariate analysis for the assessment of independent predictors of early recurrence; OR > 1 identifies a higher risk of developing early recurrence, while OR lower than 1 is associated with a higher probability of no or late recurrence; **B** results of the multivariate logistic regression analysis for the prediction of patients experiencing simultaneous intra- and extrahepatic recurrence during follow-up; for variables consisting of more than two categories (WHO tumor differentiation and ASA score), overall *p*-value was noted, while OR and its relative CI are referred to: * the risk between G3 and G1 tumors for WHO tumor differentiation and ^ the risk between ASA 4 and ASA 1 patients for the ASA score variable; *BMI* body mass index, *AFP* alpha fetoprotein, *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization, *PVE* portal vein embolization, *PVL* portal vein ligation, *MI* minimally invasive, *WHO* World Health Organization, *ASA* American Society of Anesthesiologists, *CCI* Charlson comorbidity index

multisite recurrence, which are those patterns showing an impaired prognosis.

Early recurrence in HCC has always been considered one of the worst prognostic indicators after curative resection, with many authors trying to create valid predictive models to select the best candidates for surgery.[23,28,29] Rates of early recurrence after liver resection for single HCC ranges between 30 and 41% in literature, lower than the 46.3% found in our cohort of HCC ≥ 5 cm.[13,22,23,27] However, our study also included cases with multiple lesions, which are known to have higher rate of early disease relapse.[30] Patients experiencing early recurrence have more aggressive baseline morpho-pathologic features compared with cases with no or late recurrence as well as worse survival rates. This is in line with data reported by other authors, although LHCC studies mostly come from Eastern populations.[11,12] Similarly to other series,[25] patients with early relapse in our cohort carry a higher burden of disease, as demonstrated by their rate of extrahepatic localizations and the need to make more use of palliative treatments. Furthermore, timing of recurrence was more indicative of an aggressive disease than the site of recurrence itself, as demonstrated by our combined survival analysis. Patient and tumor features independently associated with early recurrence have been extensively investigated in literature. Micro- and macrovascular invasion, satellites nodules, tumor margin, and tumor grading are variables that are normally associated with premature disease relapse in the largest series for resected HCC.[12,13,25,27,31] In LHCC, these independent predictors are less explored and to our knowledge our study represents the largest cohort reporting this type of analysis. Apart from the well-known satellite nodules and microvascular invasion, already seen in small HCC and obtained only after pathological sampling, older age, MI approach, and minor hepatectomies have been found as independent protective factors of early recurrence. Age and extension of hepatectomy can be easily correlated with worse survival rates, because of tumors biology and aggressiveness. More difficult to support is the real benefit of the MI approach found significative at multivariate analysis. Although only experienced laparoscopic centers took part in this study and the non-inferiority of laparoscopy was already reported in literature for LHCC,[32] our aim was not focused on this topic, and further investigations are needed to confirm these data. Tumor size and presence of multiple nodules (BCLC-B), already known to be not directly associated with DFS and OS in resected LHCC,[10,11,33] were confirmed not to be even independently related to the risk of early recurrence.

Another aim of the analysis was the assessment of the risk of extrahepatic recurrence in these patients, significantly affecting treatment possibilities.[34,35] However, as reported in other studies, extrahepatic spread itself is not always associated with worse outcomes compared with those with intrahepatic recurrence, and other factors have to be considered before drawing precise conclusions.[13,36] Firstly, patients with EER show worse survival rates compared with cases experiencing LER, as timing of recurrence represents a stronger predictor than site of recurrence alone.[13,37,38] Our results corroborate these findings, with EER cases presenting significantly shorter OS compared with extrahepatic spread after 2 years. As EER and EIR had similar outcomes, no specific analysis was done to assess the risk of a premature extrahepatic relapse. Secondly, extrahepatic recurrence includes a heterogeneous spectrum of disease presentation, as multi-metastatic cases or patients with a unique pulmonary or adrenal localization could benefit from ablative local therapy. Analyzing cases with simultaneous extrahepatic and intrahepatic recurrence separately represents a first simple solution to this type of bias. Indeed, patients developing this multi-metastatic relapse in our cohort have significantly worse survival rates compared with cases with intrahepatic-only or extrahepatic-only recurrence. Similar results were already reported for LHCC by Xiang et al.,[11] although this study was based on an Eastern cohort and the group of intra/extrahepatic recurrence was slightly smaller. As for timing of recurrence, independent predictors associated with this adverse pattern were assessed. Different authors reported risk factors for extrahepatic recurrence for both small and large HCC, but no studies to our knowledge reported these results for simultaneous intra- and extrahepatic relapse after curative resection, especially in LHCC.[11,34–37,39] Apart from age, microvascular invasion, and satellite nodules already associated with the risk of early recurrence, we found that preoperatively performing a TACE increases the possibility of developing simultaneous intra- and extrahepatic recurrence. The absence of oncologic benefit of this procedure before hepatic resection for LHCC has already been demonstrated in literature,[40,41] but the few studies assessing similar outcomes in terms of site of recurrence did not confirm this association between TACE and extrahepatic relapse.[42,43] This could be probably related to a loss of time when a preoperative TACE is indicated, delaying surgical resection. Due to the nature of our study, with a multicentric cohort and no homogeneity on the indication for TACE, clear recommendations cannot be made, although these data further discourage the systematic use of this option before SR for LHCC.

Some limitations have to be reported. Data collection was guided by strict criteria to make the cohort as homogenous as possible, but the multicentric and retrospective nature of the study was a source of some potential confounding factors. For instance, data on presence of macrovascular invasion was not always possible to obtain, probably because of tumor dimension. Furthermore, some specific indications, such as the type of approach for hepatic resection or whether to perform preoperative PVE or TACE, are entirely dependent on the preferences and expertise of the surgeon

or the recommendations of each canter's multidisciplinary board. Although cases with main portal vein/portal confluence infiltration were excluded, cases with invasion of portal branches, even if second order, are classified as advanced stage according to the BCLC classification and show worse outcomes. Similarly, indication of specific procedures or approaches, such as TACE or minimal invasiveness, which were found to be significant in the analysis, depend on center and surgeon's attitude. Finally, although 2-year cutoff is generally used to define early recurrence, some authors reported other thresholds, such as 1 year or 8 months,[12,44] which were not investigated in our cohort.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at https://doi.org/10.1245/s10434-025-17673-3.

DATA AVAILABILITY Data available on request from the authors

DISCLOSURE The authors have no related conflicts of interest or fundings to declare.

REFERENCES

1. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol*. 2023;20:864–84.
2. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2021;18:223–38.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol*. 2020;73:202–9.
4. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol*. 2022;76:681–93.
5. Giannone F, Grollemund A, Felli E, Mayer T, Cherkaoui Z, Schuster C, et al. (2023) Combining radiofrequency ablation with hepatic resection for liver-only colorectal metastases: a propensity-score based analysis of long-term outcomes. *Ann Surg Oncol*
6. Takayama T, Hasegawa K, Izumi N, Kudo M, Shimada M, Yamanaka N, et al. Surgery versus radiofrequency ablation for small hepatocellular carcinoma: a randomized controlled trial (SURF Trial). *Liver Cancer*. 2022;11:209–18.
7. Doyle A, Gorgen A, Muaddi H, Aravinthan AD, Issachar A, Mironov O, et al. Outcomes of radiofrequency ablation as first-line therapy for hepatocellular carcinoma less than 3 cm in potentially transplantable patients. *J Hepatol*. 2019;70:866–73.
8. Herrero JI, Sangro B, Pardo F, Quiroga J, Iñarrairaegui M, Rotellar F, et al. Liver transplantation in patients with hepatocellular carcinoma across Milan criteria. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2008;14:272–8.
9. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35–43.
10. Fang Q, Xie Q-S, Chen J-M, Shan S-L, Xie K, Geng X-P, et al. Long-term outcomes after hepatectomy of huge hepatocellular carcinoma: a single-center experience in China. *Hepatobiliary Pancreat Dis Int*. 2019;1(18):532–7.
11. Xiang C, Xiao Y, Ma Z, Peng Y, Li X, Mao X, et al. Liver resection for large and huge hepatocellular carcinoma: predictors of failure, recurrence patterns, and prognoses. *Asia Pac J Clin Oncol*. 2023;19:e60–70.
12. Zhou L, Rui J-A, Wang S-B, Chen S-G, Qu Q. Early recurrence in large hepatocellular carcinoma after curative hepatic resection: prognostic significance and risk factors. *Hepatogastroenterology*. 2014;61:2035–41.
13. Yan W-T, Li C, Yao L-Q, Qiu H-B, Wang M-D, Xu X-F, et al. Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: a large-scale multicenter study. *Hepatobiliary Surg Nutr*. 2023;10(12):155–68.
14. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;27(310):2191–4.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the reporting of observational studies in epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg Lond Engl*. 2014;12:1495–9.
16. Wakabayashi G, Cherqui D, Geller DA, Abu Hilal M, Berardi G, Ciria R, et al. The Tokyo 2020 terminology of liver anatomy and resections: updates of the Brisbane 2000 system. *J Hepato-Biliary-Pancreat Sci*. 2022;29:6–15.
17. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
18. Roayaie S, Blume IN, Thung SN, Guido M, Fiel M-I, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology*. 2009;137:850–5.
19. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182–8.
20. Nevola R, Ruocco R, Criscuolo L, Villani A, Alfano M, Beccia D, et al. Predictors of early and late hepatocellular carcinoma recurrence. *World J Gastroenterol*. 2023;28(29):1243–60.
21. Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GAM, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg*. 2006;243:229–35.
22. Kobayashi A, Miyagawa S, Miwa S, Nakata T. Prognostic impact of anatomical resection on early and late intrahepatic recurrence in patients with hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg*. 2008;15:515–21.
23. Chan AWH, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. *J Hepatol*. 2018;69:1284–93.
24. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;16(3):17.
25. Wei T, Zhang X-F, Bagante F, Ratti F, Marques HP, Silva S, et al. Early versus late recurrence of hepatocellular carcinoma after surgical resection based on post-recurrence survival: an international multi-institutional analysis. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2021;25:125–33.

26. Famularo S, Piardi T, Molfino S, Di Martino M, Ferrari C, Ielpo B, et al. Factors affecting local and intra hepatic distant recurrence after surgery for hcc: an alternative perspective on microvascular invasion and satellitosis - A Western European multicentre study. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2021;25:104–11.
27. Li W-F, Yen Y-H, Liu Y-W, Wang C-C, Yong C-C, Lin C-C, et al. Preoperative predictors of early recurrence after resection for hepatocellular carcinoma. *Am J Surg*. 2022;1(223):945–50.
28. Wang T, Chen H, Chen Z, Li M, Lu Y. Prediction model of early recurrence of multimodal hepatocellular carcinoma with tensor fusion. *Phys Med Biol*. 2024;5:69.
29. Liu L, Qin S, Lin K, Xu Q, Yang Y, Cai J, et al. (2024) Development and comprehensive validation of a predictive prognosis model for very early HCC recurrence within one year after curative resection: a multicenter cohort study. *Int J Surg Lond Engl*. 2024
30. Guo Y, Linn YL, Koh YX, Tan EK, Teo JY, Cheow PC, et al. Preoperative Predictors of early recurrence after liver resection for multifocal hepatocellular carcinoma. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2023;27:1106–12.
31. Zhang Z-H, Jiang C, Qiang Z-Y, Zhou Y-F, Ji J, Zeng Y, et al. Role of microvascular invasion in early recurrence of hepatocellular carcinoma after liver resection: a literature review. *Asian J Surg*. 2024;47:2138–43.
32. Dumronggittigule W, Han H-S, Komoltri C, D'Silva M, Lee B, Cho JY. Laparoscopic versus open hepatectomy for large hepatocellular carcinoma: a single center propensity-score-matching comparative analysis of perioperative outcomes and long-term survival. *Surg Endosc*. 2023;37:2997–3009.
33. Zhang H, Yuan S-X, Dai S-Y, Zhang J-M, Huang X, Lu C-D, et al. Tumor size does not independently affect long-term survival after curative resection of solitary hepatocellular carcinoma without macroscopic vascular invasion. *World J Surg*. 2014;38:947–57.
34. Byeon J, Cho E-H, Kim SB, Choi DW. Extrahepatic recurrence of hepatocellular carcinoma after curative hepatic resection. *Korean J Hepato-Biliary-Pancreat Surg*. 2012;16:93–7.
35. Li J, Huang L, Liu C, Qiu M, Yan J, Yan Y, et al. Risk factors and clinical outcomes of extrahepatic recurrence in patients with post-hepatectomy recurrent hepatocellular carcinoma. *ANZ J Surg*. 2021;91:1174–9.
36. Hashimoto M, Kobayashi T, Ishiyama K, Ide K, Ohira M, Tahara H, et al. Predictive independent factors for extrahepatic metastasis of hepatocellular carcinoma following curative hepatectomy. *Anticancer Res*. 2017;37:2625–31.
37. Yoon JH, Lee WJ, Kim SM, Kim KT, Cho SB, Kim HJ, et al. Simple parameters predicting extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma. *Sci Rep*. 2021;21(11):12984.
38. Yoon JH, Choi SK, Cho SB, Kim HJ, Ko YS, Jun CH. Early extrahepatic recurrence as a pivotal factor for survival after hepatocellular carcinoma resection: a 15-year observational study. *World J Gastroenterol*. 2022;28(28):5351–63.
39. Chen Z-H, Zhang X-P, Feng J-K, Li L-Q, Zhang F, Hu Y-R, et al. Patterns, treatments, and prognosis of tumor recurrence after resection for hepatocellular carcinoma with microvascular invasion: a multicenter study from China. *HPB*. 2022;24:1063–73.
40. Giannone F, Felli E, Cipriani F, Branciforte B, Rhaiem R, Al Taweel B, et al. Prognostic benefit of preoperative transarterial chemoembolization in upfront resectable large hepatocellular carcinoma: a multicentric propensity score based analysis of European high-volume centers. *HPB*. 2024;26:840–50.
41. Qi X, Liu L, Wang D, Li H, Su C, Guo X. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Oncotarget*. 2015;5(6):36838–59.
42. Chan KS, Tay WX, Cheo FY, Shelat VG. Preoperative transarterial chemoembolization (TACE) + liver resection versus upfront liver resection for large hepatocellular carcinoma (≥5 cm): a systematic review and meta-analysis. *Acta Chir Belg*. 2023;123:601–17.
43. Kang JY, Choi MS, Kim SJ, Kil JS, Lee JH, Koh KC, et al. Long-term outcome of preoperative transarterial chemoembolization and hepatic resection in patients with hepatocellular carcinoma. *Korean J Hepatol*. 2010;16:383–8.
44. Xing H, Zhang W-G, Cescon M, Liang L, Li C, Wang M-D, et al. Defining and predicting early recurrence after liver resection of hepatocellular carcinoma: a multi-institutional study. *HPB*. 2020;22:677–89.