Original Article

Prognostication algorithm for non-cirrhotic non-B non-C hepatocellular carcinoma—a multicenter study under the aegis of the French Association of Hepato-Biliary Surgery and liver Transplantation

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Background: Liver resection and local ablation are the only curative treatment for non-cirrhotic hepatocellular carcinoma (HCC). Few data exist concerning the prognosis of patients resected for non-cirrhotic HCC. The objectives of this study were to determine the prognostic factors of recurrence-free survival (RFS) and overall survival (OS) and to develop a prognostication algorithm for non-cirrhotic HCC.

Methods: French multicenter retrospective study including HCC patients with non-cirrhotic liver without underlying viral hepatitis: F0, F1 or F2 fibrosis.

Results: A total of 467 patients were included in 11 centers from 2010 to 2018. Non-cirrhotic liver had a fibrosis score of F0 (n=237, 50.7%), F1 (n=127, 27.2%) or F2 (n=103, 22.1%). OS and RFS at 5 years were 59.2% and 34.5%, respectively. In multivariate analysis, microvascular invasion and HCC differentiation were prognostic factors of OS and RFS and the number and size were prognostic factors of RFS (P<0.005). Stratification based on RFS provided an algorithm based on size (P=0.013) and number (P<0.001): 2 HCC with the largest nodule ≤10 cm (n=271, Group 1); 2 HCC with a nodule >10 cm (n=176, Group 2); >2 HCC regardless of size (n=20, Group 3). The 5-year RFS rates were 52.7% (Group 1), 30.1% (Group 2) and 5% (Group 3).

Conclusions: We developed a prognostication algorithm based on the number (≤ or >2) and size (≤ or >10 cm), which could be used as a treatment decision support concerning the need for perioperative therapy. In case of bifocal HCC, surgery should not be a contraindication.

Keywords: Hepatocellular carcinoma (HCC); non-cirrhotic liver; prognostic factors; recurrence-free survival (RFS); prognostication algorithm.

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Introduction

Liver cirrhosis is the most common risk factor for hepatocellular carcinoma (HCC). However, non-cirrhotic HCC accounts for 15–20% of HCC, but its incidence widely varies across the world and is higher in Western countries. Only 10% of HCC develop in a non-cirrhotic liver with F0, F1 or F2 in the METAVIR scoring system (1), and the known prognostic factors are hepatopathies such as viral hepatitis, nonalcoholic steatohepatitis (NASH), hemochromatosis and hereditary diseases (2-4). To date, liver resection and local ablation are the only curative treatment for non-cirrhotic HCC. The subgroups of patients treated for non-cirrhotic HCC that are most likely to benefit from liver resection are not clearly defined in the literature.

Moreover, non-cirrhotic HCC studies include small and non-homogeneous cohorts that mix patients with hepatitis, hemochromatosis, or Wilson's disease and patients without these known risk factors. The inhomogeneity of the studies is subsequent to the absence of consensus on the definition of HCC on a "non-pathological liver", which is sometimes defined by a non-cirrhotic liver with a fibrosis score of F0-F1 or F0-F1-F2 in the METAVIR scoring system (1). Consequently, there is very little data in the literature on the prognosis of patients who have undergone liver resection for F0, F1 or F2 non-cirrhotic HCC without underlying chronic disease (2,5-7). The aims of this study were to determine the prognostic factors of recurrence-free survival (RFS) and overall survival (OS) and to develop a prognostication algorithm for patients treated for resectable F0, F1 or F2 non-cirrhotic HCC without underlying viral hepatitis. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-33/rc).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics board of the Toulouse University Hospital (No. RnIPH 2022-67). According to French law on ethics, patients were informed that their codified data would be used for the study.

Population

This is a French retrospective multicenter study, including 11 centers. Between January 2010 and December 2018, patients who underwent hepatectomy for HCC in a non-cirrhotic liver ≤ F2 without underlying hepatitis B virus (HBV) or hepatitis C virus (HCV) were included. We excluded all patients with anti-HBc antibodies. Liver resections were performed using laparoscopy or laparotomy, according to the surgeon's usual practices and with their own parenchymal transection equipment. All types of hepatectomy were included. A non-cirrhotic liver ≤ F2 was defined as the absence or minimal presence of non-tumoral liver fibrosis: F0, F1 or F2 in the "equivalent" METAVIR scoring system (1). The diagnosis of HCC and the extent of non-tumoral liver fibrosis were determined, or confirmed in case of preoperative biopsy, on histological examination of the resected specimen. A non-tumoral liver with fibrosis ≥ F3, iterative hepatectomy, viral hepatitis HBV and/or HCV, metabolic diseases, fibrolamellar HCC and hepatocholangiocarcinoma were excluded. Every patient included in this study had preoperative Magnetic Resonance Imaging (MRI), and when possible, gadoxetic acid enhanced Magnetic Resonance Imaging (EOB-MRI). The eligibility criteria are detailed in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years	Age <18 years
Hepatectomy for HCC	Non-tumoral liver: Fibrosis ≥ F3 in the "equivalent" METAVIR scoring system1
Laparoscopic or open approach	Repeated hepatectomy for HCC recurrence
Non-tumoral liver: Fibrosis F0, F1 or F2 in the "equivalent" METAVIR scoring system1	Viral hepatitis HBV and/or HCV
	Metabolic diseases (hemochromatosis, Wilson's disease)
	Fibrolamellar HCC
	Hepatocholangiocarcinoma

HCC, hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus.

2013). The study was approved by institutional ethics board of Toulouse University Hospital (No. RnIPH 2022-67).

Data collected

For each patient, variables were retrospectively collected and detailed in a supplementary data table (Table S1). The data collected were (I) demographic data, (II) prognostic factors of HCC, (III) HCC diagnosis, (IV) preoperative biopsy, (V) preoperative treatment, (VI) preoperative biological analysis, (VII) surgery, (VIII) postoperative complications, (IX) anatomopathological analysis of the tumor, (X) anatomopathological analysis of the non-tumoral liver and (XI) follow-up. Severe morbidity was defined for a Dindo-Clavien score ≥3 (8). Postoperative liver failure was defined according to "50-50" criteria (prothrombin time <50% and serum bilirubin >50 µml/L) on postoperative day 5 (9). A strictly normal liver was defined as A0-F0 according to the the "equivalent" METAVIR grading score (1).

Statistical methods

Qualitative variables were described as numbers (percentages) and quantitative variables as means ± the standard deviation. RFS and OS were presented with Kaplan-Meir curves. Univariate followed by multivariate Cox regression were performed using either survival or recurrence free survival as the outcome. Variables significantly (P<0.05) associated with survival in the univariate analysis were then introduced in the multivariate analysis. We used multiple imputation to account for missing data in predictors of multivariate Cox models. Multiple imputation was performed using the R Package MICE. To stratify the patient's risk prior to surgery, we introduced preoperative variables significantly associated with RFS in the multivariate analysis in a conditional inference tree. For further stratification in the patients with the best survival rate and who were therefore more likely to benefit from surgery, we drew another conditional inference tree of this population subset and introduced anatomopathological variables significantly associated with recurrence free survival. We used a conditional inference tree using recursive partitioning with a Bonferroni correction for multiple tests. This algorithm finds the variable the most strongly associated with survival and makes the best split in this variable (10,11). We performed this analysis using the partykit package in R. For all analyses, a P value of less than 0.05 was considered statistically significant. All of the statistical analyses were performed using R software.

Results

Population study

Between January 2010 and December 2018, 467 hepatectomies for non-cirrhotic HCC without underlying viral hepatitis, according to the inclusion and exclusion criteria, were performed in the 11 centers, 6 of which included more than 40 patients.

Preoperative characteristics

The preoperative characteristics are listed in *Table 2*. Median age was 69.2 (IQR: 61.8, 75.8 years), with a male/female gender ratio of 3/1. Most (53.3%) the patients in this study had a BMI >25 kg/m^2 and more than a quarter of them had diabetes, hypercholesterolemia, high blood

Table 2 Preoperative characteristics of the total population

Characteristics	Study group (n=467)
Demographic data	
Age (years), median [IQR]	69.2 [61.8, 75.8]
Gender, n (%)	
Female	117 (25.1)
Male	350 (74.9)
BMI, median [IQR]	26 [5.8]
<25	164 (35.1)
25–30	158 (33.8)
≥30	91 (19.5)
Missing data	54 (11.6)
Diabetes, n (%)	132 (28.3)
Dyslipidemia, n (%)	119 (25.5)
High blood pressure, n (%)	258 (55.2)
ASA score, n (%)	
1	80 (17.1)
2	205 (43.9)
3	141 (30.2)
4	2 (0.4)
Missing data	39 (8.4)
Risk factors of HCC, n (%)	
Alcohol consumption	161 (34.5)
Metabolic syndrome	126 (27.0)
Tobacco consumption	158 (33.8)
HCC diagnosis, n (%)	
Symptoms at diagnosis	203 (43.5)
Incidental discovery	227 (48.6)
Screening	23 (4.9)
Preoperative jaundice	6 (1.3)
Alteration in general health status	65 (13.9)
Preoperative biopsy, n (%)	
Tumoral biopsy	255 (54.6)
Non-tumoral biopsy	167 (35.8)
Preoperative treatment, n (%)	
Transarterial chemoembolization	42 (9.0)
Sorafenib	7 (1.5)
Radiotherapy	0
Biliary drainage	2 (0.4)
Portal vein embolization	67 (14.3)
Preoperative biological analysis	
AFP (ng/mL), median [IQR]	9.5 [106.5]
AFP ≥5 ng/mL, n (%)	171 (57.2)
AFP among patients with AFP ≥5 ng/mL (ng/mL), median [IQR]	50.3 [489.6]
Missing data, n (%)	168 (36.0)
MELD, median [IQR]	7 [3]
PR (%), median [IQR]	97 [14]
Platelets (G/L), median [IQR]	250.5 [115.2]
Serum bilirubin level (μmol/L), median [IQR]	8 [5]

IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; PR, prothrombin ratio.

pressure and/or metabolic syndrome. For almost half of them, HCC was discovered incidentally. A total of 10% of the patients had preoperative treatment for HCC [transarterial chemoembolization (TACE) or sorafenib] and 14.3% had preoperative portal vein embolization. Half of the patients (54.6%) had a preoperative tumoral biopsy and one third of the patients (35.8%) had a non-tumoral liver biopsy. A total of 42.8% of the patients had a normal alpha-fetoprotein (AFP) level (AFP <5 ng/mL). For the 57.2% of the patients with abnormal AFP (≥5 ng/mL), the median AFP was 50.3 ng/mL with an IQR of 489.6.

Peroperative and postoperative characteristics

Peroperative and postoperative characteristics are detailed in *Table 3*. The majority of the HCC resections were performed by open approach, with anatomical resection of the HCC. Pedicular clamping was used in more than half of the hepatectomies with a median clamping duration of 30 min (IQR: 26.8). Most resections (52.5%) were major hepatectomies with a median number of resected hepatic segments of 3 (IQR: 2). During surgery, 3.0% of patients

Table 3 Peroperative and postoperative characteristics of the total population

Characteristics	Study group (n=467)
Surgery	
Surgery duration (min), median [IQR]	228 [120]
Surgical technique, n (%)	
Laparoscopic approach	119 (25.5)
Conversion to laparotomy	29 (6.2)
Open approach	348 (74.5)
Anatomic resection, n (%)	315 (67.5)
Capsular effraction, n (%)	14 (3.0)
Number of resected segments, median [IQR]	3 [2]
Major hepatectomy (≥3 resected segments), n (%)	245 (52.5)
Pedicular clamping, n (%)	261 (55.9)
Clamping duration (min), median [IQR]	30 [26.8]
Vascular exclusion of the liver, n (%)	13 (2.8)
Blood loss (mL), median [IQR]	500 [700]
Blood transfusion, n (%)	80 (17.1)
Number of packed red blood cells, median [IQR]	2 [2]
Procedures associated with surgery, n (%)	52 (11.1)
Thermoablation	6 (1.3)
Bilio-enteric anastomosis	5 (1.1)
Vascular resection	16 (3.4)
Digestive resection	4 (0.9)
Diaphragm resection	15 (3.2)
Veinous thrombectomy	6 (1.3)
Postoperative complications	
Surgical complication, n (%)	134 (28.7)
Biliary fistula, n (%)	44 (9.4)
Hemorrhage, n (%)	11 (2.4)
Medical complication, n (%)	299 (64.0)
Liver failure, n (%)	16 (3.4)
Reoperation, n (%)	32 (6.9)
Dindo-Clavien score ≤ POD 90, n (%)	
Dindo-Clavien 1	133 (28.5)
Dindo-Clavien 2	123 (26.3)
Dindo-Clavien 3	46 (9.9)
Dindo-Clavien 4	24 (5.1)
Dindo-Clavien 5	17 (3.6)
Length of hospitalization (days), median [IQR]	10 [7]

IQR, interquartile range; POD, postoperative day.

had capsular effraction. During 90 postoperative days, the overall morbidity was 73.4% (n=343): 64.0% (n=299) of the patients had at least one medical complication and 28.7% (n=134) at least one surgical complication. A total of 9.4% (n=44) had a postoperative biliary fistula. The reoperation rate was 6.9% (n=32). The severe morbidity rate was 18.7% (n=87). Seventeen patients died within 90 post-operative days (3.6%); 4 patients from a biliary fistula, 2 from a cardiac cause, 3 from a respiratory cause, 4 from liver failure and 4 from other miscellaneous causes. The median length of hospitalization was 10 days (IQR: 7).

Pathological characteristics

Pathological characteristics are detailed in *Table 4*. A total of 407 patients (87.2%) had a single lesion and median tumor size was 90 mm (IQR: 90) for the largest nodule. The non-tumoral liver analysis identified mainly F0 (n=237, 50.7%), F1 (n=127, 27.2%) and F2 (n=103, 22.1%) fibrosis according to the "equivalent" METAVIR grading score. A total of 52.2% of the patients had steatosis ≥5%. Among them, the median steatosis rate was 20% (IQR: 20%). More than 80% of the patients had R0 resection (n=391, 83.7%). One quarter of the patients had satellite nodules (n=113, 24.2%) and almost a third had microvascular invasion (n=146, 31.3%). Tumor differentiation was good, moderate and poor in 27.4% (n=128), 45.8% (n=214) and 9.2% (n=43) respectively.

Follow-up

The median patient follow-up was 30.84 months (Q1: 16.08, Q3: 56.16). A total of 209 patients had a recurrence, more than half of whom had a recurrence confined to the

Table 4 Anatomopathological characteristics

Characteristics	Study group (n=467)
Anatomopathological analysis of the tumor	
Number of lesions, n (%)	
1	407 (87.2)
2	40 (8.6)
>2	20 (4.3)
Maximal tumor size (mm), median [IQR]	90 [90]
Tumor differentiation, n (%)	
Poor	43 (9.2)
Moderate	214 (45.8)
Well	128 (27.4)
Missing data	82 (17.6)
R status, n (%)	
R0	391 (83.7)
R1	61 (13.1)
R2	3 (0.6)
Missing data	12 (2.6)
Satellite nodules, n (%)	113 (24.2)
Peritumoral capsule, n (%)	187 (40.0)
Microvascular invasion, n (%)	146 (31.3)
Macrovascular invasion, n (%)	27 (5.8)
Perineural invasion, n (%)	6 (1.3)
Anatomopathological analysis of the non-tumoral liver	
Normal (A0, F0), n (%)	146 (31.3)
Fibrosis, n (%)	
F0	237 (50.7)
F1	127 (27.2)
F2	103 (22.1)
Steatosis, n (%)	244 (52.2)
Steatosis ≥5% (%), median [IQR]	20 [20]
Steatohepatitis	29 (6.2)

IQR, interquartile range.

liver (51.2%, n=107). A total of 86.6% (n=181/209) of the patients with a recurrence received treatment for their recurrence of which 32.6% (n=59/181) received curative treatment for their recurrence.

Independent prognostic factors of OS (multivariate analysis)

The OS of this study population was 91.8% at one year, 73.9 % at 3 years and of 59.2% at 5 years, with a median OS of 88 months (*Figure 1*). The prognostic factors of OS included in the multivariate model based on the results of the univariate analysis (Table S2) were two statistically significant pathological prognostic factors: the presence of microvascular invasion (P=0.003) and tumor differentiation (P=0.011) (*Table 5*).

Independent prognostic factors of RFS (multivariate analysis)

The RFS of this study population was: 68.7% at one year, 41.5 % at 3 years and of 34.5% at 5 years, with a median RFS of 28 months (*Figure 2*). The prognostic factors of disease recurrence included in the multivariate model based on the results of the univariate analysis (Table S3) were 4 statistically significant prognostic factors: two preoperative criteria: >2 lesions (P=0.003) and maximal tumor size >10 cm (P<0.001); and two pathological criteria: the presence of microvascular invasion (P=0.004) and tumor differentiation (P=0.008) (*Table 6*).

Prognostication algorithm based on RFS

Based on the prognostic criteria for RFS noted in the multivariate analysis (*Table 6*), the population was stratified, which provided a prognostication algorithm to help in the therapeutic decision. The population was stratified according to the two statistically significant preoperative prognostic factors of RFS identified in the multivariate analysis: the number of HCC and the size of the largest nodule. Three groups were defined by this algorithm based on preoperative criteria: (I) Group 1 (n=271) included patients with 1 or 2 nodules of less than 10 cm; (II) Group 2 (n=176) included patients with 1 or 2 nodules, the largest of which was greater than 10 cm; (III) Group 3 (n=20) included patients with 3 or more nodules. Group 3 could not be stratified according to the size of the largest nodule because of the small size of this group.

Group 1 had the best prognosis by far, with a 5-year RFS of 52.7% and a median RFS of 46 months. Conversely, in Group 2, when the largest nodule was >10 cm, the RFS was 30.1% at 5 years and the median RFS was 14 months. In Group 3 (≥3 nodules) the RFS at 5 years was 5% and the median RFS was 10 months (*Figure 3*).

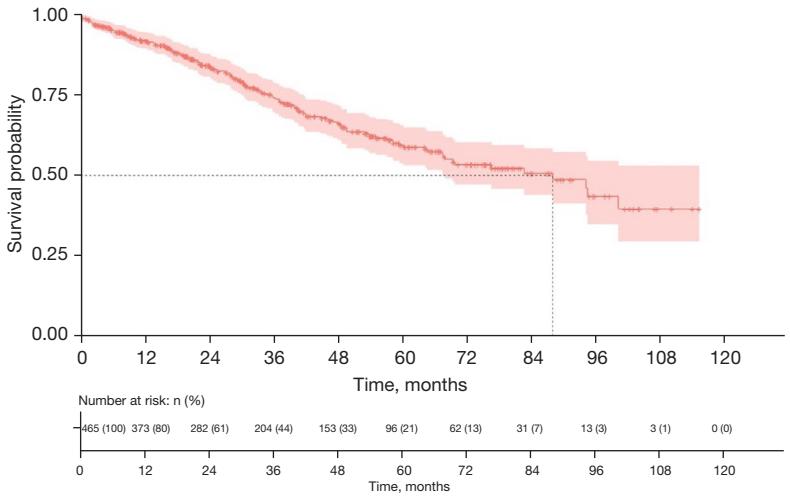

Figure 1 Overall survival.

Table 5 Prognostic factors of overall survival (multivariate analysis)

	Hazard ratios	95% CI	P
Number of HCC >2	1.23	0.75–2.02	0.416
Maximal HCC size >10 mm	1.47	0.96–2.26	0.079
Metabolic syndrome	0.91	0.58–1.41	0.662
Preoperative AFP	1	1–1	0.101
Steatosis of the non-tumoral liver	0.83	0.56–1.24	0.365
Perineural invasion	1.36	0.33–5.61	0.675
Satellite nodules	1.05	0.92–1.2	0.442
Microvascular invasion	1.9	1.26–2.85	0.003*
HCC differentiation	1.89	1.17–3.05	0.011*

*, P<0.05. CI, confidence interval; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

In Group 1 with the best survival (n=271, 1 or 2 nodules ≤10 cm), we performed a new stratification using the two statistically significant pathological prognostic factors of RFS identified in the multivariate analysis: the presence of microvascular invasion and the HCC differentiation. Through this stratification, 3 subgroups of patients (*Figure 4*) were defined. In the subgroup of patients with 1 or 2 well-differentiated nodules of less than 10 cm and without vascular emboli, in group 1a, the RFS was 62.6% at 5 years with a median RFS of 88.8 months. In the absence of invasion with one or two poorly or moderately differentiated nodules, in group 1b, The RFS was 40.0% at 5 years with a median RFS of 33.6 months. Finally, in the presence of microvascular invasion on the specimen, in group 1c, the RFS was 37.8% at 5 years with a median RFS of 25.5 months (*Figure 4*). The prognostication algorithm is detailed in *Figure 5*.

Discussion

The aims of our study were to develop a prognostication algorithm and to highlight the prognostic factors of RFS and OS for patients treated for strictly non-cirrhotic resectable HCC without underlying viral hepatitis. We excluded patients with advanced fibrosis beyond F2 to exclude the influence of liver disease. Although the prognosis for patients after HCC surgery is known to be partly correlated with the underlying liver disease, only few authors have

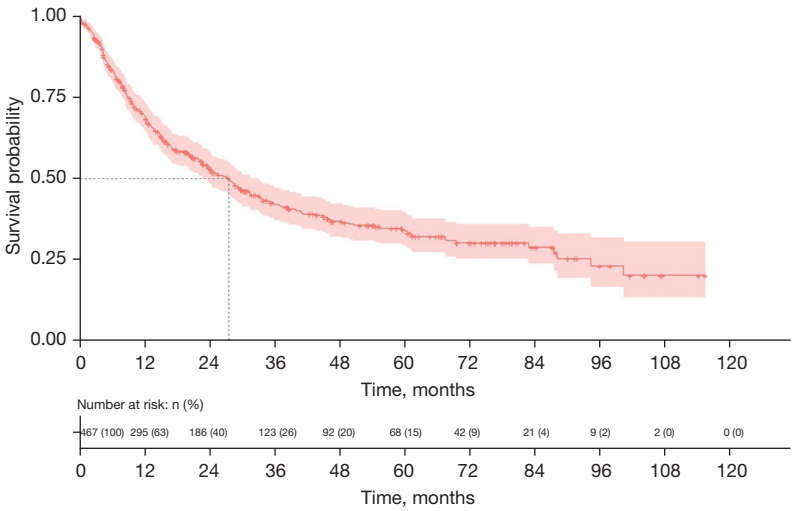

Figure 2 Recurrence-free survival.

Table 6 Prognostic factors of disease recurrence (multivariate analysis)

	Hazard ratios	95% CI	P
Number of HCC >2	1.71	1.21–2.42	0.003*
Maximal size of HCC >10 cm	1.99	1.46–2.72	<0.001*
Metabolic syndrome	0.84	0.61–1.15	0.271
Preoperative AFP	1	1–1	0.083
Steatosis of the non-tumoral liver	0.88	0.66–1.17	0.377
Perineural invasion	1.14	0.33–4.01	0.836
Satellite nodules	1.07	0.97–1.17	0.169
Microvascular invasion	1.64	1.18–2.28	0.004*
HCC differentiation	1.58	1.13–2.2	0.008*

*, P<0.05. CI, confidence interval; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

studied liver resection for HCC in non-cirrhotic liver. These studies were unicentric and included few patients (less than 40 patients) (2,5,6). Therefore, most of the series in the literature on non-cirrhotic HCC were heterogeneous, including patients with underlying liver diseases, such as viral hepatitis (5,7,12-16). The largest cohort included thousands of patients but the study was only conducted on epidemiological criteria, based on the Surveillance, Epidemiology, and End Results (SEER) database, and included patients with underlying liver disease (17). To our knowledge, our study is the largest multicenter cohort of resected non-cirrhotic HCC patients without underlying viral hepatitis.

All the centers in this study were expert liver surgery centers that practice all types of hepatectomy by laparoscopy or laparotomy, including complex liver surgery. The rates of postoperative morbidity and mortality in this study were similar to those in the literature (3). The 5-year RFS and OS of the population were respectively 34.5% and 59.2%, which is similar to the surgical series in the literature (2,7,16-21).

The multivariate analysis identified two anatomopathological prognostic factors of OS and RFS previously described in HCC: tumor differentiation and the presence of microvascular invasion (3,5,21,22). Steatosis in the non-tumoral liver, although present in more than half of patients and

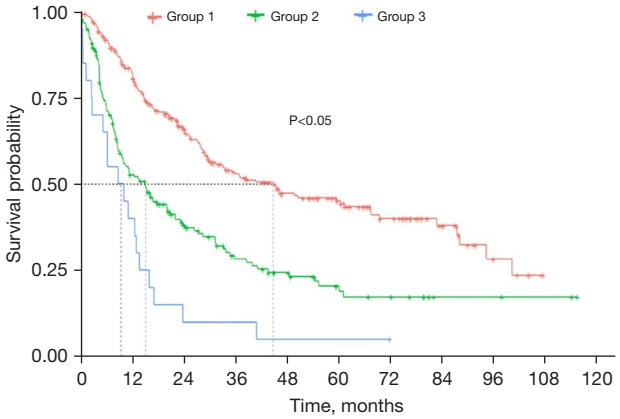

Figure 3 Recurrence-free survival according to two preoperative criteria: the number of nodules and the size of the largest hepatocellular carcinoma nodule. Group 1 (n=271) included patients with 1 or 2 nodules of less than 10 cm, Group 2 (n=176) included patients with 1 or 2 nodules, the largest of which was greater than 10 cm and Group 3 (n=20) included patients with 3 or more nodules.

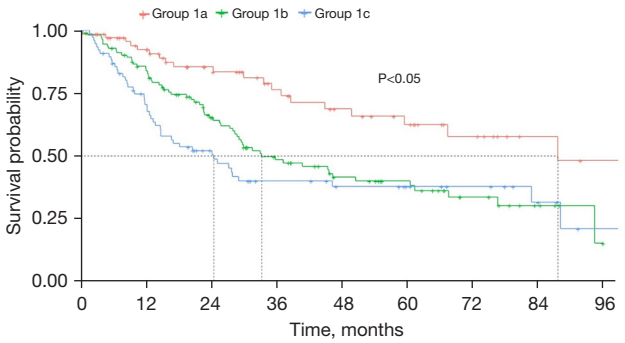

Figure 4 Recurrence-free survival in the subgroups of patients with 1 or 2 nodules of less than 10 cm: Group 1a (n=72) included patients without microvascular invasion with one or two well differentiated nodules, Group 1b (n=115) included patients without microvascular invasion with one or two poorly or moderately differentiated nodules and Group 1c (n=77) included patients with microvascular invasion on the specimen.

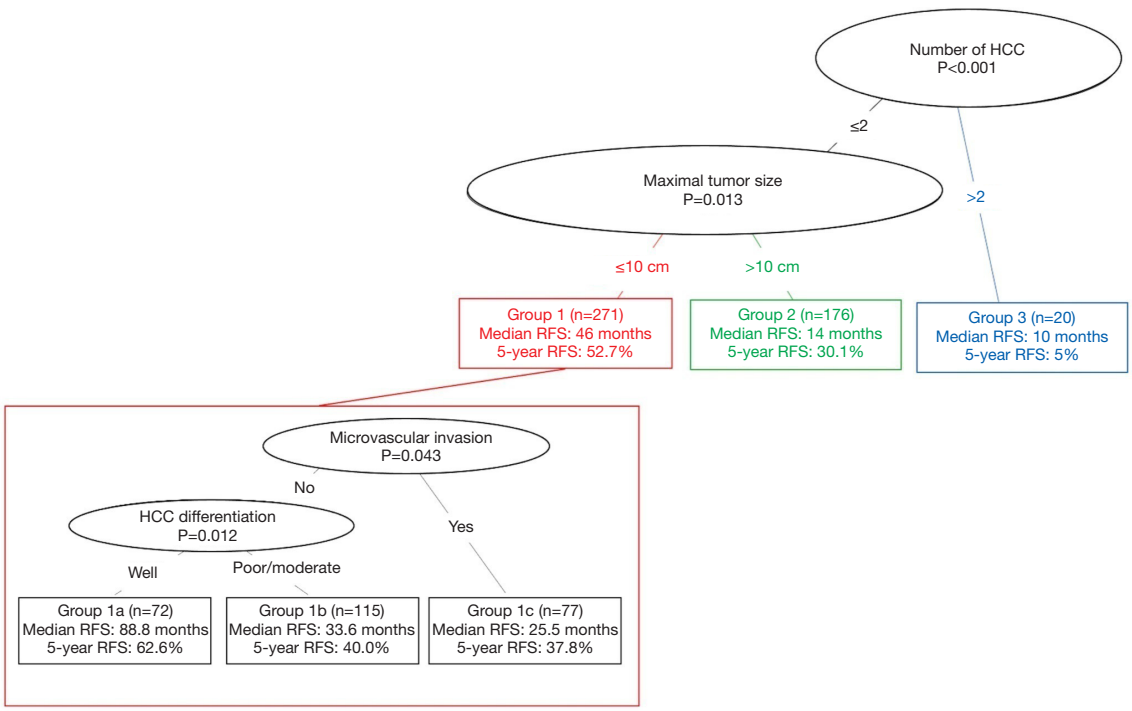

Figure 5 Prognostication algorithm. HCC, hepatocellular carcinoma; RFS, recurrence-free survival.

metabolic syndrome, present in more than a quarter of patients, did not emerge as a prognostic factor of OS or RFS in the multivariate analysis. In addition, AFP did not emerge as a prognostic factor in this study. AFP is a widely used biomarker in the surveillance of patients at risk for developing HCC and in the surveillance of patients treated for HCC (17,23). AFP rates are correlated to vascular invasion and tumor size. However, 30% to 40% of HCC do not secrete AFP and several authors highlight the lack of consistency as a prognostic factor, reporting limited correlation of AFP rates with disease progression or tumor stage (12,17,24-26). In our study, we could not draw a conclusion on the role of AFP as a prognostic factor for patients with non-cirrhotic HCC without underlying viral hepatitis due to the large quantity of missing AFP data, which is a bias in a retrospective study.

Two preoperative criteria were found to be regular prognostic factors of RFS in the multivariate analysis: the number of HCC and the size of the largest nodule. The number of nodules strictly superior to 2 and the size of the largest nodule strictly superior to 10 cm were prognostic factors of RFS. In the literature, large HCCs have a worse prognosis as they are often correlated to the presence of satellite nodules and microvascular invasion, positive resection margins and differentiation grade (17,27). In patients with non-cirrhotic HCC, median tumor diameter is usually greater than in patients with chronic liver disease and is often a factor of poor prognosis (3,12). The large diameter of non-cirrhotic HCC could be explained by the absence of screening in these patients without a known underlying liver disease (7).

The prognostic factors identified in this study are well known in the literature, but the originality of this study is based on the prognostication algorithm developed from the results. In fact, through the stratification of the population based on prognostic factors of RFS, 3 groups of patients with different prognoses were identified. The two preoperative prognostic factors used for this stratification (number and size of nodules) are known at diagnosis, making it possible to classify non-cirrhotic HCC patients in one of these three different prognostic groups before surgery. Moreover, the prognosis of these patients can be estimated in the preoperative period and therefore be considered in the treatment decision-making.

Through the algorithm built in this study a group of patients with good prognosis were identified, for which the benefit of surgery seems to be the very significant. Indeed, in the presence of one or two non-cirrhotic HCC nodules with the largest nodule diameter ≤10 cm (Group 1), the prognosis is favorable, with a median RFS multiplied by almost 4 compared to the other groups of patients (Groups 2 and 3). Thus, surgery should not be a contraindication in case of case of bifocal HCC on non-cirrhotic liver. Furthermore, in this good prognosis group, the RFS is further improved (up to 7 years) if the HCC is well differentiated and without vascular emboli (Group 1a). These anatomopathological criteria of poor prognosis are currently difficult to obtain preoperatively because only half of the patients in this study had a routine preoperative biopsy. Moreover, when a preoperative biopsy is performed, it is often inefficacious for microvascular invasion and sometimes even for differentiation, which is why some authors do not recommend preoperative biopsy, especially for large resectable HCC (28).

The current trend is increasingly towards neoadjuvant treatment for patients with other solid-organ cancer in order to downstage the malignancy and obtain improved rates of survival. However, the role of (neo)adjuvant therapies in the management of resected HCC is not currently defined (29). Moreover, in case of HCC in patients with NASH, immunotherapy is reported to be ineffective (30). Due to the lack of literature on (neo)adjuvant therapies in HCC patients, current guidelines do not have a clear stance on the use of (neo)adjuvant strategies in resected HCC patients (31,32). However, in the subgroups of patients with moderate prognosis (1 or 2 HCC with or without tumor vascular emboli, poor or moderate differentiation, with the largest nodule diameter ≤10, Groups 1b and 1c), the use of adjuvant therapy could help to decrease the incidence of HCC recurrence after resection. In fact, at a time when more and more systemic treatments are being developed for HCC, particularly immunotherapy treatments, the value of combining surgery with systemic treatment is increasingly interesting, especially in patients with a moderate or poor prognosis, and should be studied in prospective cohorts (33).

Furthermore, based on the results of the algorithm, in case of non-cirrhotic bifocal HCC, contrary to the practice in some centers surgery should not be a contraindication, even if extensive resection is required and especially in the presence of nodules ≤10 cm.

In HCC patients with the poorest prognosis (3 or more nodules or one or two HCC nodule >10 cm, Groups 2 and 3), a perioperative treatment should be explored, combining neoadjuvant and adjuvant liver resection treatments. The two criteria used to define these two groups or patients are two simple preoperative criteria (the number and size of

the nodules), which enables multidisciplinary discussion of the use of neoadjuvant therapy prior surgery. In addition, in these groups of patients, the combination of resection and systemic treatment, radioembolization or TACE as perioperative treatment could improve survival outcomes, especially in these patients with non-cirrhotic liver who can tolerate both regional and systemic treatments associated with surgery. This prognostic model requires validation in a prospective cohort to confirm the reproducibility of the results.

Conclusions

In this multicenter retrospective study, RFS analysis enabled the development of a simple algorithm based on two preoperative criteria: the number (≤2 or >2) and size of nodules (≤10 or >10 cm, if less than 2 nodules). This algorithm highlighted distinctive groups of non-cirrhotic HCC patients with different prognoses. It could be used as a treatment decision support for multidisciplinary discussion before surgery concerning the need for perioperative therapy, based on each patient's estimated prognosis. In case of bifocal HCC, surgery should not be a contraindication. This prognostication algorithm could be the basis of a prospective clinical trial.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-33/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-33/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-33/coif). LB receives grant to the institution from the national transplant agency (agence de la biomédecine) for a separate project, and payment for legal expertise in liability cases. LB participates on national RCT on antibiotics in appendicitis (ABAP study) without payment. LB is a past board member of the French association for the study of liver diseases (AFEF), past board member of the French Surgical Association (association francaise de chirurgie), and a past board member of the French Association of HPB Surgery and Transplantation (ACHBT) with no payment. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of the Toulouse University Hospital (No. RnIPH 2022-67). According to French law on ethics, patients were informed that their codified data would be used for the study.

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Supplementary

Table S1 Data collected

Demographic data
Gender
ASA score
Diabetes
History of hepatectomy
Age
BMI
HBP
Hypercholesterolemia
Prognostic factors of HCC
Alcohol consumption
Metabolic syndrome
Tobacco consumption
HCC diagnosis
Symptoms at diagnosis
Fortuitus discovery
Discovery by screening
Preoperative jaundice
Alteration in general health status
Preoperative biopsy
Tumoral biopsy
Non-tumoral biopsy
Preoperative treatment
Transarterial chemoembolization
Sorafenib
Radiotherapy
Biliary drainage
Portal embolization
Preoperative biological analysis
AFP
Creatininemia
INR
PR
Platelets
MELD
Serum bilirubin level
Surgery
Surgery duration
Laparoscopic approach
Laparotomic approach
Conversion to laparotomy
Anatomic resection
Tumoral effraction
Number of resected segments
Pedicular clamping
Clamping duration
Vascular exclusion of the liver
Blood loss
Blood transfusion
Number of packed red blood cells
Procedures associated with surgery
Postoperative complications
Surgical complication
Biliary fistula
Hemorrhage
Medical complication
Liver failure
Dindo-Clavien score
Length of hospitalization
Treatment for complication
Anatomopathological analysis of the tumor
Number of HCCs
Maximal size of HCC
HCC differentiation
R status
Satellite nodules
Peritumoral capsule
Microvascular invasion
Macrovascular invasion
Perineural invasion
Anatomopathological analysis of the non-tumoral liver
Normal (A0, F0: “equivalent” METAVIR grading score)
Fibrosis (“equivalent” METAVIR grading score)
Steatosis
Steatohepatitis
Follow-up
Recurrence
Localization of recurrence
Treatment of recurrence
Death

ASA, American Society of Anesthesiologists; BMI, body mass index; HBP, high blood pressure; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; INR, international normalized ratio; PR, prothrombin ratio; MELD, model for end-stage liver disease.

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Table S2 Prognostic factors of overall survival (univariate analysis)

	Hazard ratio (95% CI)	P
Demographic data		
Gender female	1.105 (0.759, 0.759)	0.606
BMI	0.981 (0.946, 0.946)	0.295
Diabetes	0.812 (0.555, 0.555)	0.276
Dyslipidemia	0.89 (0.584, 0.584)	0.584
High blood pressure	1.05 (0.755, 0.755)	0.771
ASA score		
2	1.064 (0.662, 0.662)	0.798
3	1.084 (0.653, 0.653)	0.755
4	1.811 (0.244, 0.244)	0.561
Risk factors of HCC		
Alcohol consumption	1.113 (0.791, 0.791)	0.542
Metabolic syndrome	0.792 (0.532, 0.532)	0.240
Tobacco consumption	1.615 (1.131, 1.131)	0.008*
HCC diagnosis		
Symptoms at diagnosis	1.336 (0.955, 0.955)	0.090
Incidental discovery	0.927 (0.662, 0.662)	0.659
Screening	0.469 (0.149, 0.149)	0.142
Preoperative jaundice	2.062 (0.656, 0.656)	0.267
Alteration in general health status	1.319 (0.842, 0.842)	0.241
Preoperative biopsy		
Tumoral biopsy	0.713 (0.495, 0.495)	0.073
Non-tumoral biopsy	0.902 (0.601, 0.601)	0.618
Preoperative treatment		
Transarterial chemoembolization	0.95 (0.556, 0.556)	0.849
Sorafenib	0.778 (0.192, 0.192)	0.713
Biliary drainage	0 (0, 0)	0.279
Portal vein embolization	0.998 (0.628, 0.628)	0.993
Preoperative biological analysis		
AFP	1 (1, 1)	0.028*
MELD	1.016 (0.943, 0.943)	0.686
PR	0.992 (0.98, 0.98)	0.196
Platelets	1.002 (1, 1)	0.037*
Serum bilirubin level	1.002 (0.993, 0.993)	0.663
Surgery		
Surgery duration	1.002 (1, 1)	0.019*
Surgical technique		
Laparoscopic approach	0.624 (0.408, 0.408)	0.022*
Conversion to laparotomy	0.844 (0.395, 0.395)	0.655
Open approach	1.62 (1.037, 1.037)	0.025*
Anatomic resection	1.232 (0.832, 0.832)	0.288
Capsular effraction	1.409 (0.572, 0.572)	0.478
Number of resected segments	1.131 (0.996, 0.996)	0.057
Pedicular clamping	1.5 (1.059, 1.059)	0.021*
Clamping duravtion	1.009 (0.998, 0.998)	0.108
Vascular exclusion of the liver	3.34 (1.556, 1.556)	0.009*
Blood loss	1 (1, 1)	0.306
Blood transfusion	2.222 (1.483, 1.483)	<0.001*
Number of packed red blood cells	1.257 (1.125, 1.125)	<0.001*
Procedures associated with surgery	1.396 (0.861, 0.861)	0.256
Thermoablation	0.731 (0.181, 0.181)	0.644
Bilio-enteric anastomosis	0.504 (0.07, 0.07)	0.441
Vascular resection	4.045 (1.874, 1.874)	0.003*
Digestive resection	2.013 (0.496, 0.496)	0.379
Diaphragm resection	1.508 (0.553, 0.553)	0.450
Veinous thrombectomy	2.109 (0.52, 0.52)	0.351
Postoperative complications		
Surgical complication	1.571 (1.102, 1.102)	0.016
Biliary fistula	2.315 (1.467, 1.467)	0.001*
Hemorrhage	2.241 (0.912, 0.912)	0.117
Medical complication	1.977 (1.391, 1.391)	<0.001*
Liver failure	3.218 (1.634, 1.634)	0.004
Reoperation	3.54 (2.122, 2.122)	<0.001*
Dindo-Clavien score ≤ POD 90		
Dindo-Clavien 1	1.044 (0.638, 0.638)	0.864
Dindo-Clavien 2	2.282 (1.44, 1.44)	<0.001*
Dindo-Clavien 3	1.203 (0.288, 0.288)	0.8
Dindo-Clavien 4	2.307 (0.706, 0.706)	0.167
Dindo-Clavien 5	31.521 (16, 16)	<0.001*
Length of hospitalization	1.033 (1.021, 1.021)	<0.001*

*, P<0.05. CI, confidence interval; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; BMI, body mass index; ASA, American Society of Anesthesiologists; PR, prothrombin ratio; MELD, model for end-stage liver disease; POD, postoperative day.

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Table S3 Prognostic factors of disease recurrence (univariate analysis)

	Hazard ratio (95% CI)	P
Demographic data		
Gender female	1.156 (0.877, 0.877)	0.309
BMI	0.987 (0.961, 0.961)	0.322
Diabetes	0.823 (0.628, 0.628)	0.154
Dyslipidemia	0.893 (0.666, 0.666)	0.443
High blood pressure	1.18 (0.923, 0.923)	0.184
ASA score		
2	0.948 (0.673, 0.673)	0.759
3	0.933 (0.648, 0.648)	0.709
4	0.786 (0.108, 0.108)	0.812
Risk factors of HCC		
Alcohol consumption	1.026 (0.799, 0.799)	0.838
Metabolic syndrome	0.723 (0.544, 0.544)	0.022*
Tobacco consumption	0.962 (0.74, 0.74)	0.774
HCC diagnosis		
Symptoms at diagnosis	1.367 (1.07, 1.07)	0.012*
Incidental discovery	0.886 (0.694, 0.694)	0.332
Screening	0.721 (0.393, 0.393)	0.266
Preoperative jaundice	1.843 (0.686, 0.686)	0.270
Alteration in general health status	1.265 (0.909, 0.909)	0.175
Preoperative biopsy		
Tumoral biopsy	0.82 (0.627, 0.627)	0.152
Non-tumoral biopsy	0.854 (0.643, 0.643)	0.274
Preoperative treatment		
Transarterial chemoembolization	0.855 (0.562, 0.562)	0.456
Sorafenib	0.844 (0.314, 0.314)	0.730
Biliary drainage	5.302 (1.296, 1.296)	0.066
Portal vein embolization	1.133 (0.812, 0.812)	0.470
Preoperative biological analysis		
AFP	1 (1, 1)	0.003*
MELD	1.057 (1.003, 1.003)	0.051
PR	0.986 (0.977, 0.977)	0.002*
Platelets	1.003 (1.002, 1.002)	<0.001*
Serum bilirubin level	1.003 (0.997, 0.997)	0.335
Surgery		
Surgery duration	1.002 (1, 1)	0.039*
Surgical technique		
Laparoscopic approach	0.636 (0.473, 0.473)	0.002*
Conversion to laparotomy	0.919 (0.554, 0.554)	0.741
Open approach	1.51 (1.111, 1.111)	0.006*
Anatomic resection	1.103 (0.833, 0.833)	0.490
Capsular effraction	2.455 (1.332, 1.332)	0.011
Number of resected segments	1.221 (1.11, 1.11)	<0.001*
Pedicular clamping	1.283 (0.997, 0.997)	0.051
Clamping duration	1.005 (0.998, 0.998)	0.188
Vascular exclusion of the liver	3.416 (1.809, 1.809)	0.001*
Blood loss	1 (1, 1)	0.016*
Blood transfusion	2.056 (1.52, 1.52)	<0.001*
Number of packed red blood cells	1.216 (1.119, 1.119)	<0.001*
Procedures associated with surgery	1.239 (0.864, 0.864)	0.256
Thermoablation	0.348 (0.086, 0.086)	0.073
Bilio-enteric anastomosis	0.598 (0.149, 0.149)	0.429
Vascular resection	3.389 (1.89, 1.89)	<0.001*
Digestive resection	3.476 (1.289, 1.289)	0.04*
Diaphragm resection	1.977 (1.077, 1.077)	0.046*
Veinous thrombectomy	1.352 (0.432, 0.432)	0.621
Postoperative complications		
Surgical complication	1.498 (1.154, 1.154)	0.003*
Biliary fistula	1.831 (1.256, 1.256)	0.004*
Hemorrhage	1.441 (0.678, 0.678)	0.369
Medical complication	1.576 (1.225, 1.225)	<0.001*
Liver failure	2.393 (1.394, 1.394)	0.005
Reoperation	2.447 (1.63, 1.63)	<0.001*
Dindo-Clavien score ≤ POD 90		
Dindo-Clavien 1	1.205 (0.863, 0.863)	0.273
Dindo-Clavien 2	1.548 (1.099, 1.099)	0.012
Dindo-Clavien 3	1.158 (0.422, 0.422)	0.776
Dindo-Clavien 4	1.626 (0.653, 0.653)	0.297
Dindo-Clavien 5	8.914 (5.03, 5.03)	<0.001*
Length of hospitalization	1.022 (1.014, 1.014)	<0.001*
Anatomopathological analysis of the tumor		
Number of lesions	1.235 (1.141, 1.141)	<0.001*
Maximal tumor size	1.001 (1.001, 1.001)	0.003*
Tumor differentiation		
Moderate	1.033 (0.68, 0.68)	0.879
Well	0.628 (0.396, 0.396)	0.048*
R status		
R1	2.322 (1.68, 1.68)	<0.001*
R2	2.217 (0.55, 0.55)	0.263
Satellite nodules	2.42 (1.869, 1.869)	<0.001*
Peritumoral capsule	0.905 (0.691, 0.691)	0.467
Microvascular invasion	2.267 (1.741, 1.741)	<0.001*
Macrovascular invasion	1.598 (0.977, 0.977)	0.081
Perineural invasion	4.574 (1.655, 1.655)	0.017*
Anatomopathological analysis of the non-tumoral liver		
Normal (A0, F0)	1.116 (0.853, 0.853)	0.426
Fibrosis		
F1	0.863 (0.646, 0.646)	0.318
F2	0.949 (0.701, 0.701)	0.733
Steatosis	0.733 (0.573, 0.573)	0.014*
Steatohepatitis	0.719 (0.433, 0.433)	0.184

*, P<0.05. CI, confidence interval; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; BMI, body mass index; ASA, American Society of Anesthesiologists; PR, prothrombin ratio; MELD, model for end-stage liver disease; POD, postoperative day.

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