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ORIGINAL ARTICLE

Non-transplantable Recurrence After Resection for Transplantable Hepatocellular Carcinoma: Implication for Upfront Treatment Choice

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Abstract

Objectives To identify the preoperative risk factors for prediction of non-transplantable recurrence (NTR) after tumor resection for early-stage hepatocellular carcinoma (HCC) to assist in patient selection relative to upfront liver resection (LR) versus liver transplantation (LT).

Methods Patients who underwent curative resection for transplantable HCC and chronic liver disease were identified from an international multi-institutional database. NTR was defined as recurrence beyond the Milan or UCSF criteria, and the preoperative risk factors of NTR were investigated.

Results Among 293 patients with transplantable HCC within Milan criteria and 320 within UCSF criteria, 113 (38.6%) and 131 (40.9%) patients developed tumor recurrence, respectively. Among patients who recurred, NTR was present in 32 (28.3%) patients within Milan and 35 (26.7%) within UCSF criteria. When either Milan or UCSF criteria was adopted, three preoperative risk factors including liver cirrhosis, tumor size > 3 cm, and multiple lesions were consistently identified as risk factors associated with NTR after curative resection. By summing up the three factors, a scoring model was established and the incidence of NTR among patients with 0, 1 or ≥ 2 risk factors incrementally increased from 4.5%, 13.3% to 20.5% when Milan criteria was used, and from 4.5%, 12.4% to 33.9% when UCSF criteria was adopted. The model demonstrated very good discriminatory power on internal validation ($n = 5{,}000$) (c-index 0.689 for Milan criteria, and 0.715 for UCSF criteria).

Conclusions Whereas surgical resection may be optimal first-line treatment for patients with no or one risk factor, patients with ≥ 2 risk factors should be considered for upfront liver transplantation.

Keywords Hepatocellular carcinoma · Resection · Recurrence · Liver transplantation · Transplantable · Non-transplantable

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Introduction

The management and treatment of hepatocellular carcinoma (HCC) can be challenging as most cases occur in the setting of underlying chronic liver disease. The optimal management of HCC is primarily determined by clinical stage, although staging systems can vary among different regions.[1] For early-stage HCC within Milan or extended University of California, San Francisco (UCSF) criteria, liver resection and transplantation can both serve as potentially curative treatment options. Liver transplantation may be the preferred treatment option over resection as tumor recurrence is lower (10–14%) given that both the cirrhotic liver and HCC are removed.[2–4] However, the shortage of donor organs limits the wide applicability of liver transplantation. In turn, surgical resection is often utilized, as the availability of donor organs is not a concern. However, the incidence of recurrence in the remnant liver can be as high as 50–70% among patients with concomitant chronic liver disease.[5,6] Salvage liver transplantation may be feasible for patients with transplantable recurrence (TR) after initial tumor resection with better long-term outcomes than re-resection or ablation.[7–9] Salvage transplantation is not feasible in all clinical situations, as some patients develop non-transplantable recurrence (NTR) despite strict surveillance after resection.

Prediction of NTR risk prior to the initial hepatic resection among patients with early-stage HCC may help inform initial treatment strategies. To date, previous studies have largely included only clinico-pathologic factors available on pathologic assessment of the specimen following the initial hepatic resection (e.g. microvascular invasion, tumor grade) to estimate NTR.[10,11] While helpful in assessing the likelihood of being eligible for salvage transplantation following initial resection, these data do not inform whether resection versus transplantation may have been the preferred initial operation. A recent single-center study sought to predict NTR before the initial index surgery and proposed an alpha-fetoprotein (*AFP*) score to help identify patients most at risk of a NTR;[12] this scoring system has been applied clinically in France, yet has not experienced widespread adoption.[13,14] As such, the objective of the current study was to characterize recurrence patterns after initial liver resection of early-stage HCC using a large international multi-institutional database. In particular, we sought to develop and validate a preoperative risk model to predict NTR at the time of initial surgical presentation in order to improve upfront treatment selection.

Methods

Study Cohort and Data Collection

Patients who underwent curative liver resection for HCC between 2000 and 2017 were identified from eleven international centers from America, Europe, Australia, and Asia. A standardized datasheet was created for collection of the clinicopathologic and surgical information, as well as the outcomes of patients. Tumor-related factors, such as maximum tumor size, tumor number and location, tumor differentiation/grade, presence of fibrosis/cirrhosis, Scheuer classification of hepatic inflammation and fibrosis,[15] microvascular invasion, lymph node and liver capsule involvement, and width of resection margin, were recorded based on the final histologic report. Pathologic examination of the sections was reviewed by senior pathologists according to the international guidelines for evaluation of nodule number and size, grade of liver fibrosis, tumor grade, and surgical margin. For early-stage HCC, liver resection was considered based on tumor number and size according to the Milan criteria, as well as liver function and remnant liver volume.[16] In particular, patients had to have chronic liver disease scored 2 to 4 according to Scheuer classification to be included in the analytic cohort.[17] Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, enlarged, fibrotic portal tracts; F2, periportal or portal-portal septa but intact architecture; F3, fibrosis with architectural distortion but no obvious cirrhosis; F4, probable or definite cirrhosis.[17] Patients who died within 90 days of surgery ($n = 32$) or had no information of tumor recurrence or overall survival ($n = 16$) were excluded. The study was approved by the Institutional Review Boards of each participating institution.

Primary and Secondary Outcome

Postoperative complications were recorded within 30-days of surgery and graded according to the Clavien-Dindo classification. Patients were regularly followed after surgery with serum *AFP* and liver function tests, as well as ultrasound, abdominal CT, and/or MRI scanning every 3 months in the first two years after surgery and every six months thereafter. The primary outcome was NTR. In particular, two well-accepted transplantation criteria—the Milan[16] and UCSF criteria[18]—were used to define whether patients had an HCC amenable to salvage transplantation. When the Milan Criteria was used, NTR was defined as one or more tumor characteristics at the time of recurrence characterized as single tumor > 5 cm, tumor number > 3, or tumor number 2–3 but maximal size > 3 cm, macroscopic vascular invasion, or extrahepatic recurrence.[16] In addition, when the UCSF criteria was used, NTR was defined as one or more tumor characteristics at recurrence: single tumor > 6.5 cm, tumor number > 3, or tumor number 2–3 but the largest size > 4.5 cm, macroscopic vascular invasion, or extrahepatic recurrence.[18] Secondary outcomes included overall (OS) and recurrence-free survival (RFS).

OS was calculated from the date of surgery and censored at the date of death or last follow-up, whereas RFS was defined as time duration from the date of surgery to tumor recurrence.

Treatment of Recurrence

Treatment of recurrence was based on patient performance status, as well as tumor burden and location. Curative-intent treatment of recurrent disease included re-resection, ablation, and liver transplantation. Palliative non-curative treatment of recurrent disease included intra-arterial treatments (e.g., transarterial chemoembolization, transarterial embolization), target therapies, chemo- and radiotherapy, as well as best supportive care.

Statistical Analysis

Clinicopathological variables were reported using frequencies / percentages for categorical variables, and median and interquartile range (IQR) for continuous covariates. Categorical covariates were compared with Chi-square test or Fisher's exact test, and continuous variables with Mann–Whitney *U* test. The OS, RFS, and non-transplantable recurrence rate were calculated using the Kaplan–Meier method and differences were compared using the log-rank test. Univariate analysis was performed to identify potential risk factors of any recurrence or non-transplantable recurrence; factors with a p value less than 0.05 were included in the multivariate Cox regression model. The performance of the model was measured by concordance index (c-index) and calibration with 5,000 bootstrap samples to decrease the overfit bias. All statistical analyses were conducted using SPSS version 23.0 (IBM SPSS, Chicago, IL, USA) or in R version 3.6.1 (http://www.r-project.org). A 2-tailed p value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Among 1,004 patients who underwent curative-intent resection for HCC, 293 (29.2%) patients had an HCC resected within the Milan criteria in the setting of liver fibrosis with a Scheuer classification F2-4 (Table 1). Median patient age was 59 (IQR 52–67) years and the majority of patients ($n = 244$, 83.3%) was male; most patients ($n = 274$, 93.5%) had a Charlson Comorbidity Score ≤ 9. The etiology of underlying liver disease was largely HBV and/or HCV-related ($n = 203$, 69.3%), whereas a subset of patients had non-alcoholic steatohepatitis (NASH) ($n = 16$, 5.5%) or unknown liver disease ($n = 74$, 25.6%). The majority of patients ($n = 283$, 96.6%) had Child–Pugh Class A liver function; 181 (61.8%) patients had liver cirrhosis and 75 (25.8%) had concomitant portal hypertension. On preoperative radiologic imaging, 271 (90.5%) patients had a solitary tumor, whereas 280 (95.6%) patients had a single lesion on final pathologic analysis. In turn, the correlation of preoperative imaging and final pathologic examination relative to tumor number was strong (90.4%). Median tumor size was also similar on preoperative imaging and final pathologic examination (both 3.0 cm). After curative-intent resection, roughly one in three patients ($n = 103$, 35.2%) developed a postoperative complication; a small subset ($n = 19$, 6.5%) had severe Clavien-Dindo Class III to IV complications.

Long-Term Outcomes

Among 293 patients who underwent hepatic resection for transplantable HCC according to Milan criteria, median, 3- and 5-year OS was 76.0 months, 76.8% and 59.7%, whereas the median, 3- and 5-year RFS was 42.0 months, 54.4% and 39.3% (Fig. 1). A total of 113 (38.6%) patients developed tumor recurrence with a median time-to-recurrence of 14.0 months. Among individuals who experienced a recurrence, most ($n = 86$, 76.1%) patients developed tumor recurrence within 24 months after surgery, whereas 27 (23.9%) patients had a recurrence beyond 24 months after liver resection. Regarding recurrence patterns, most recurrence ($n = 86$, 76.1%) was intrahepatic only; one in three ($n = 35$, 31.0%) patients who recurred had multiple recurrent tumors. The median recurrent tumor size was 20 (IQR 14–31) mm. During the study period, NTR developed in 32 patients for a recurrence rate of 28.3% among the 113 patients who recurred, and 10.9% among all patients included in the cohort. In addition, median time-to-recurrence was similar among patients who developed NTR versus TR (median time to recurrence, 15.0 vs. 14.0 months, $p = 0.897$) (Supplementary Table 1). Patients who underwent curative-intent treatment for recurrence (re-resection, $n = 56$; ablation, $n = 46$, and liver transplantation, $n = 10$) had a much more favorable post-recurrence survival than patients who received non-curative treatments (intra-arterial treatments and/or targeted therapy only, $n = 45$) (5-year OS, 66.5% vs. 23.8%, $p = 0.003$).

Preoperative Model for Prediction of NTR

Preoperative factors such as Scheuer classification F4 (*HR* 1.9, 95% CI 1.2–2.8, $p = 0.004$), portal hypertension (*HR* 1.9, 95% CI 1.3–2.9, $p = 0.002$), tumor size > 3 cm (*HR* 1.6, 95% CI 1.1–2.3, $p = 0.025$), and multiple lesions (*HR* 2.8, 95% CI 1.3–6.0, $p = 0.008$) were each independently

Table 1 Baseline characteristics

Variables	*N* (%) or median (IQR)	
	Milan criteria ($n=293$)	UCSF criteria ($n=320$)
Age, years	59 (52–67)	59 (52–67)
Male sex	244 (83.3%)	267 (83.4%)
BMI, kg/m^2	26.8 (23.6–30.1)	27.4 (24.3–30.5)
Diabetes mellitus	64 (21.8%)	80 (25.0%)
Chronic alcohol intake	48 (16.4%)	55 (17.2%)
Smoking	87 (29.7%)	91 (28.4%)
Charlson Comorbidity Score ≤ 9	274 (93.5%)	302 (94.3%)
Baseline liver disease		
Viral hepatitis	203 (69.3%)	220 (68.8%)
B	152 (51.8%)	161 (50.3%)
C	36 (12.3%)	43 (13.4%)
B + C	15 (5.1%)	16 (5.0%)
NASH	16 (5.5%)	23 (7.2%)
None	74 (25.3%)	77 (24.1%)
Child–Pugh classification A	283 (96.6%)	304 (95.0%)
Liver cirrhosis	180 (61.4%)	208 (65.0%)
Portal hypertension	75 (25.6%)	90 (28.1%)
MELD score		
≤ 8	271 (92.5%)	289 (90.3%)
≥ 9	22 (7.5%)	31 (9.7%)
AFP level, ng/ml	11.2 (4.1–96.0)	13.2 (4.0–144.1)
Radiologic single tumors	271 (92.5%)	290 (90.6%)
Radiologic tumor size, cm	3.0 (2.2–4.0)	3.5 (2.4–4.7)
Anatomic resection	217 (74.1%)	238 (74.3%)
Maximum tumor size, cm	3.0 (2.5–4.0)	3.5 (2.5–4.6)
Single tumor	280 (95.6%)	294 (91.9%)
Microvascular invasion	59 (20.1%)	76 (23.8%)
R0 margin	263 (89.8%)	267 (83.4%)
Postoperative complications	103 (35.2%)	122 (38.1%)
Severe complication (III–IV)	19 (6.5%)	18 (5.6%)
Any recurrence	113 (38.6%)	131 (40.9%)
Non-transplantable recurrence	32 (10.9%)	35 (10.9%)

associated with tumor recurrence on multivariable analysis (Table 2). Similarly, Scheuer classification F4 (*HR* 2.1, 95% CI 1.0–4.3, $p=0.045$), tumor size > 3 cm (*HR* 3.2, 95% CI 1.4–7.2, $p=0.005$), and multiple lesions (*HR* 5.1, 95% CI 1.3–9.6, $p=0.017$) were also independent risk factors for NTR (Table 3). In turn, a model that included these three preoperative risk factors was constructed. The incidence of NTR increased incrementally from 4.5% among patients with no risk factor, 13.3% among patients with one risk factor, and 20.5% among patients with ≥ 2 risk factors (Fig. 2). On multivariable analysis, there was an incremental increase in the hazard of death concomitant with the number of risk factors (referent, no risk factor: 1 risk factor, *HR* 3.2, IQR 1.2–6.4, $p=0.022$; ≥ 2 risk factors, *HR* 6.8, IQR 2.2–12.6, $p=0.001$) even when taking into account postoperative risk factors into the Cox regression model (Supplementary Table 2). The scoring model demonstrated good performance on internal bootstrapping validation ($n=5{,}000$) (c-index 0.689, 95% CI, 0.631–0.728).

Additional analyses were performed to assess NTR relative to the expanded UCSF criteria. Of note, 320 (31.8%) patients who underwent an initial curative-intent resection had a transplantable HCC recurrence (Table 1). Among these individuals, 131 (40.9%) patients developed tumor recurrence with a median time-to-recurrence of 14.0 months. The NTR rate was 26.7% ($n=35$) among patients who recurred and 10.9% among all the patients who underwent curative-intent resection. Among patients who had initial resection of early-stage HCC, NTR relative to UCSF criteria was associated with Scheuer classification F4 liver fibrosis (*HR* 3.1, 95% CI 1.6–6.3, $p=0.001$), tumor size > 3 cm (*HR* 2.6, 95% CI 1.2–5.7, $p=0.018$), and multiple lesions (*HR* 3.8, 95% CI

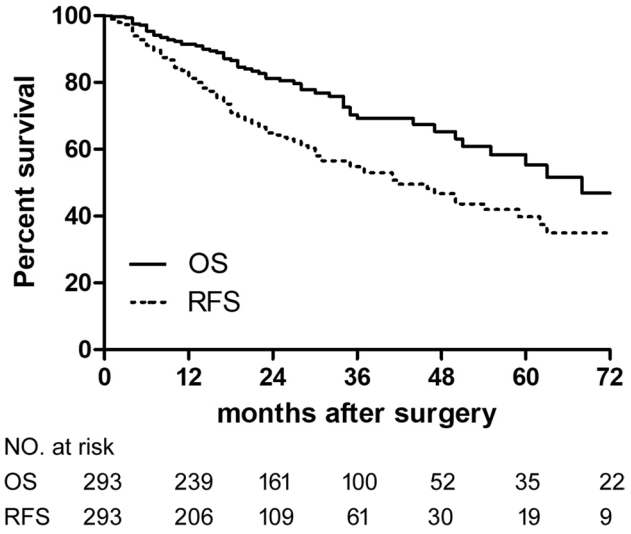

Fig. 1 Overall (OS) and recurrence-free survival (RFS) of patients with transplantable hepatocellular carcinoma (the Milan criteria) and chronic liver disease undergoing liver resection

1.7–8.7, $p = 0.001$) on initial presentation (Table 4). Based on these three risk factors, the incidence of NTR increased stepwise (no risk factor: 4.5% vs. one risk factor: 12.4% vs. ≥ 2 risk factors: 33.9%) (referent no risk factor: 1 risk factor, *HR* 2.9, IQR 1.3–3.2, $p = 0.027$; ≥ 2 risk factors, *HR* 4.7, IQR 2.0–6.7, $p = 0.001$) (Fig. 3) (Supplementary Table 3). The model demonstrated very good discrimination on internal bootstrapping validation ($n = 5{,}000$) (c-index 0.715, 95% CI, 0.654–0.774).

Discussion

Among patients with early-stage HCC with underlying chronic liver disease, both liver resection and transplantation may be curative treatment options. Although liver transplantation may theoretically represent a better option for many patients with early-stage HCC and chronic liver disease, the shortage of donor organs, risk of tumor progression, and drop-out from the waiting list limit the universal application of transplantation. In contrast, liver resection can be safely performed in well-selected patients with good long-term outcomes independent of organ availability, yet some

Table 2 Univariate and multivariable analysis for risk factors associated with tumor recurrence after resection for hepatocellular carcinoma within Milan criteria

Variables	Univariate analysis		Full Multivariable analysis		Multivariable analysis after variable selection	
	HR (95% CI)	*p* value	*HR* (95% CI)	*p* value	*HR* (95% CI)	*p* value
Age ≥ 65	1.2 (0.8–1.8)	0.320	1.0 (0.6–1.7)	0.893		
Male	1.5 (0.9–2.5)	0.144	1.5 (0.8–2.7)	0.233		
Scheuer classification F4	1.5 (1.0–2.3)	0.038	2.2 (1.4–3.4)	0.001	1.9 (1.2–2.8)	0.004
Hepatitis B/C infection	0.9 (0.6–1.4)	0.726	0.8 (0.5–1.3)	0.402		
Portal hypertension	1.6 (1.1–2.3)	0.020	2.0 (1.3–3.2)	0.001	1.9 (1.3–2.9)	0.002
Tumor size > 3 cm	1.4 (0.9–2.0)	0.097	1.7 (1.1–2.7)	0.017	1.6 (1.1–2.3)	0.025
Multiple lesions	1.9 (0.9–3.9)	0.087	2.9 (1.2–6.8)	0.013	2.8 (1.3–6.0)	0.008
MELD ≥ 9	0.7 (0.2–2.3)	0.590	0.7 (0.4–1.6)	0.123		
AFP ≥ 100 ng/ml	1.4 (0.9–2.2)	0.150	1.6 (0.9–2.6)	0.080		

Table 3 Univariate and multivariable analysis of risk factors associated with non-transplantable recurrence after resection for hepatocellular carcinoma within Milan criteria

Variables	Univariate analysis		Full multivariable analysis		Multivariable analysis after variable selection	
	HR (95% CI)	*p* value	*HR* (95% CI)	*p* value	*HR* (95% CI)	*p* value
Age ≥ 65	1.0 (0.4–2.1)	0.920	0.7 (0.3–1.8)	0.518		
Male	2.4 (0.7–7.9)	0.153	1.7 (0.5–5.9)	0.401		
Scheuer classification F4	2.0 (1.0–4.1)	0.047	2.3 (1.0–5.3)	0.047	2.1 (1.0–4.3)	0.045
Hepatitis B/C infection	1.5 (0.6–3.4)	0.367	1.2 (0.5–3.0)	0.709		
Portal hypertension	1.1 (0.5–2.5)	0.751	1.7 (0.7–4.0)	0.212		
Tumor size > 3 cm	2.5 (1.2–5.2)	0.014	3.8 (1.5–9.5)	0.004	3.2 (1.4–7.2)	0.005
Multiple lesions	2.3 (1.2–7.6)	0.021	6.9 (1.6–12.2)	0.009	5.1 (1.3–9.6)	0.017
MELD ≥ 9	1.1 (0.7–2.3)	0.461	0.9 (0.6–1.9)	0.354		
AFP > 100 ng/ml	1.3 (0.5–3.2)	0.549	1.4 (0.5–3.6)	0.493		

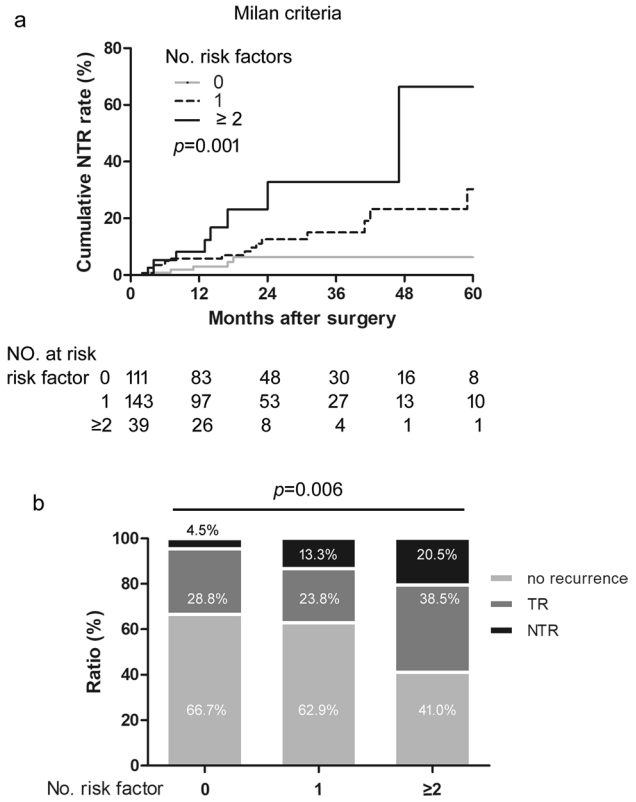

Fig. 2 Cumulative non-transplantable recurrence (NTR) rate (**a**) and recurrence patterns (**b**) stratified by the scores after surgical resection for hepatocellular carcinoma within the Milan criteria

patients developed aggressive and untreatable recurrence during postoperative follow up. As such, selection of patients with early-stage HCC for initial liver resection versus liver transplantation is critical to help optimize long-term outcomes. The current study was therefore important, as we utilized a large international multi-institutional database to establish a preoperative model based on tumor size, number, and severity of liver fibrosis that predicted post-resection NTR among patients with initially transplantable HCC. Of note, roughly 40% of patients developed tumor recurrence after curative resection with almost one in three recurrences being an NTR. Tumor size > 3 cm, multiple lesions, and liver fibrosis of Scheuer classification F4 (cirrhosis) were independent risk factors associated with NTR. Using these three risk factors, a simple scoring system was able to define an incremental increased risk of NTR that ranged from a low of 4.5% among patients with no risk factor to as high as 20–30% among patients with 2 or more risk factors. Taken together, data from the current study suggested that upfront liver transplantation may be preferable among patients with high risk of NTR (≥ 2 risk factors) who are at highest risk of NTR. In contrast, liver resection may be an acceptable initial surgical option among patients with lower risk of NTR.

Decisions about the use of liver resection versus transplantation for early-stage HCC typically include consideration of three major factors: liver function, availability of donor organ, and long-term risk of tumor recurrence in the remnant liver. Among patients with early-stage HCC who are eligible for either liver resection or transplantation, transplantation may generally be preferred as this therapeutic approach removes both the underlying tumor, any occult intrahepatic metastasis/secondary lesions, as well as eliminates the cirrhotic liver that may act as a source of subsequent recurrence. In fact, while recurrence following transplantation for HCC has been reported to be as low as 10–14%, recurrence after liver resection for early-stage HCC can be as high as 50–70%.[2–6] Liver transplantation is not, however, available to many patients due to limited services at certain medical centers, poor access to liver donors, and prolonged wait times.[19,20] In fact, a subset of patients with early-stage HCC and underlying chronic liver disease who are on the waiting list are at risk of tumor progression and drop out from the list.[16,18]

As such, some surgeons have advocated for liver resection over transplantation among patients with early-stage HCC and compensated liver cirrhosis.[21,22] The rationale for liver resection, in part, is that primary resection with salvage

Table 4 Univariate and multivariable analysis of risk factors associated with non-transplantable recurrence after resection for hepatocellular carcinoma within UCSF criteria

Variables	Univariate analysis		Full multivariable analysis		Multivariable analysis after variable selection	
	HR (95% CI)	*p* value	*HR* (95% CI)	*p* value	*HR* (95% CI)	*p* value
Age ≥ 65	1.0 (0.5–2.1)	1.000	0.8 (0.3–1.8)	0.570		
Male	0.9 (0.4–2.1)	0.789	1.1 (0.4–2.6)	0.889		
Scheuer classification F4	2.2 (1.1–4.4)	0.021	3.3 (1.6–7.0)	0.002	3.1 (1.6–6.3)	0.001
Hepatitis B/C infection	0.8 (0.4–1.9)	0.685	1.3 (0.5–3.3)	0.650		
Portal hypertension	1.5 (0.8–2.1)	0.433	1.5 (0.9–2.0)	0.453		
Tumor size > 3 cm	4.9 (1.9–12.7)	0.001	3.0 (1.4–6.6)	0.006	2.6 (1.2–5.7)	0.018
Multiple lesions	4.3 (1.9–9.7)	< 0.001	4.3 (1.8–10.6)	0.001	3.8 (1.7–8.7)	0.001
MELD ≥ 9	1.4 (0.9–2.9)	0.123	1.7 (0.8–3.3)	0.265		
AFP > 100 ng/ml	2.0 (1.0–4.0)	0.061	1.8 (0.9–3.7)	0.101		

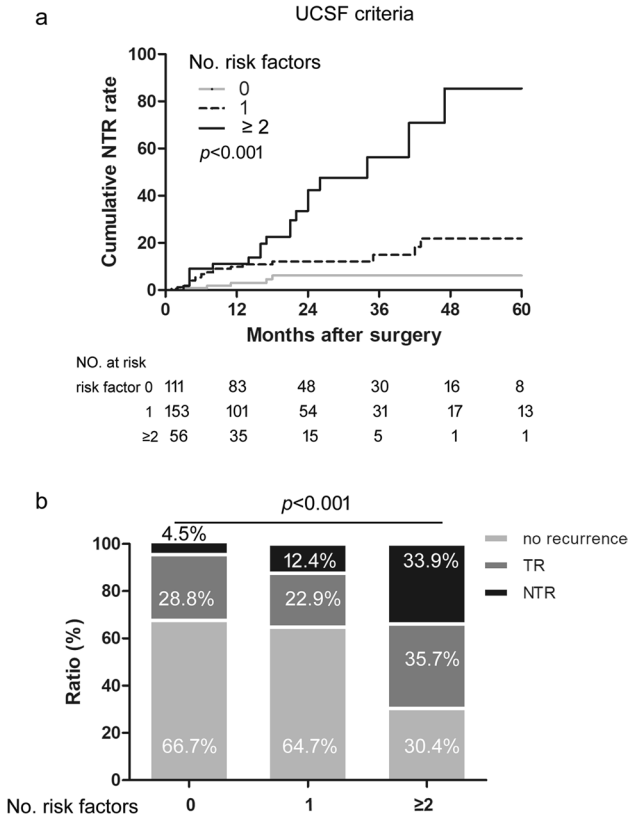

Fig. 3 Cumulative non-transplantable recurrence (NTR) rate (**a**) and recurrence patterns (**b**) stratified by the scores after surgical resection for hepatocellular carcinoma within the University of California, San Francisco (UCSF) criteria

transplantation for HCC may be a reasonable strategy.[23–25] However, data on the use of salvage transplantation have been disparate. While some authors have noted that salvage transplantation was not associated with additional morbidity and comparable long-term outcomes versus up-front transplantations, other investigators have cautioned that a subset of patients who undergo initial resection will recur with NTR and therefore lose the survival benefit that may have enjoyed with initial liver transplantation. [10,11,23–25] In turn, selection of patients for initial liver resection versus transplantation relative to risk of NTR may be important to guide upfront surgical recommendations.

In the current study, among patients who underwent initial hepatic resection for HCC within either Milan ($n=293$) or UCSF ($n=320$) criteria, 1 in 10 eventually developed an NTR. In a study of 148 patients from France that included patients with transplantable HCC, the authors demonstrated that *AFP* > 100 ng/ml, multiple lesions, and cirrhosis were risk factors associated with NTR after initial resection.[12] In contrast, in the current study, preoperative *AFP* was not associated with risk of NTR when evaluated using various cut-off values (100 and 200 ng/ml). The reasons for these disparate results are likely multifactorial and related to the differences in the criteria by which patients were initially considered eligible for resection or transplantation. Rather than using *AFP* levels, we chose to use the Milan and UCSF criteria to define transplantable HCC, as well as NTR, which are the mostly accepted criteria for liver transplantation worldwide.[16,18] Of note, a recent multi-institutional study from five French centers demonstrated higher NTR and worse 3-year overall survival among patients who met *AFP* score criteria but had lesions beyond Milan criteria (22%, 59%, respectively) versus within Milan (12%, 69%, respectively) criteria ($p<0.05$).[26] In the current study, three risk factors (e.g., tumor size > 3 cm, multiple lesions, liver fibrosis/cirrhosis) were used to create a score to predict NTR.

Tumor size and number have been well-recognized risk factors associated with tumor recurrence and long-term survival among patients after curative resection or transplantation for HCC.[27–33] In fact, both tumor size and number are surrogates of tumor aggressiveness, being strongly associated with presence of microvascular invasion, satellite lesions, and vessels that encapsulate tumor cluster.[34,35] Multifocal HCC may represent either intrahepatic metastasis or multiple primary tumors, suggesting aggressive biological behavior at the time of presentation.[21,36] Of note, while tumor size and number were determined based on final pathologic examination, the correlation with preoperative imaging was strong (90.4%). Liver cirrhosis/fibrosis was associated with NTR. Cirrhosis is a strong risk factor of intrahepatic metastasis, as well as de novo recurrence of HCC after surgical resection.[37,38] Given that early-stage HCC may be particularly germane to patients with underlying liver fibrosis, we included patients with liver fibrosis of Scheuer classification F2-4 in the current study.[17] Perhaps as expected, patients with F4 liver cirrhosis had worse RFS (median RFS, F4 24.0 vs. F2-3 46.0 months, $p=0.007$), as well as a higher incidence of NTR versus patients who had non-cirrhotic liver fibrosis (F2-3) (NTR rate, F4 26.9% vs. F2-3 10.8%, $p=0.001$). In turn, preoperative assessment of the severity of liver fibrosis by histologic examination may be important to help predict NTR, especially among patients with chronic hepatitis.[12]

Using these three risk factors, the incidence of NTR among patients with no risk factor, 1 risk factor, and ≥ 2 risk factors increased incrementally from 4.5%, 13.3% to 20.5% for patients with initial HCC tumors that fulfilled the Milan criteria, and from 4.5%, 12.4% to 33.9% for tumors initially meeting UCSF criteria. Interestingly, patients with no risk factor had an extremely low risk of NTR (4.5%), whereas individuals with one risk factor also had an acceptable incidence of NTR (12–13%). In fact, 5-year OS among patients with no risk factor associated with NTR was 67.6%, which was comparable to the ~ 70% reported after liver transplantation.[16,18,39,40] The simple scoring system that utilized only

preoperative factors performed well on internal validation and, therefore, may aid in upfront treatment allocation.

In particular, upfront liver resection may be more appropriate for patients with no or one NTR risk factor, as these patients were more likely to have a recurrence amenable to transplant salvage. In contrast, patients with ≥ 2 risk factors may be more appropriately considered for upfront liver transplantation if donor organs are available, especially in Eastern countries where living-donor liver transplantation is widely performed. Using this approach, the risk of experiencing a NTR would be mitigated and patients may benefit from better long-term outcomes. If resection is performed among patients with high risk of NTR, assessment of postoperative pathological features, such as microvascular invasion, satellite lesions, or cirrhosis, may aid in consideration of early salvage transplantation before recurrence.[10]

Several limitations should be considered when interpreting results of the current study. The multi-institutional nature of the cohort increased patient number and generalizability, yet likely contributed to some variations in surgical selection and procedures, as well as pathologic examination, postoperative surveillance among the hospitals. Only tertiary university hospitals that complied with the international guidelines for HCC diagnosis, treatments, histologic examination, and postoperative surveillance were included. The scoring system to predict NTR was based exclusively on data derived from patients who underwent curative-intent resection for HCC. No parallel comparison group of patients who underwent liver transplantation was available. In addition, not all patients included in the analyses may have been necessarily candidates for liver transplantation based on clinical factors or other components of transplant candidacy including psychosocial history and support. Finally, while the scoring system performed well on internal validation, future external validation studies will be needed.

In conclusion, liver resection is widely performed for patients with HCC within and beyond the Milan or UCSF criteria. Among patients with transplantable HCC and chronic liver disease, tumor recurrence was common (~ 40% of patients). Of particular interest was the finding that, among patients who recurred, almost one in three developed NTR. On multivariable analysis, three preoperative factors including tumor size > 3 cm, multifocality, and Scheuer fibrosis classification were associated with risk of NTR after initial resection. A scoring system based on these factors was able to predict an incremental increased risk of postoperative NTR, which may be helpful to clinicians in informing whether resection or transplantation may be the preferred initial operative approach for patients with early-stage HCC.

Abbreviations HCC: Hepatocellular carcinoma; LR: Liver resection; LT: Liver transplantation; UCSF: University of California, San Francisco; TR: Transplantable recurrence; NTR: Non-transplantable recurrence; *AFP*: Alpha-fetoprotein; OS: Overall survival; RFS: Recurrence-free survival

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Declarations

Conflict of Interest The authors declare no competing interests.

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