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ORIGINAL ARTICLE

Survival according to recurrence patterns after resection for transplantable hepatocellular carcinoma in HBV endemic area: Appraisal of liver transplantation strategy

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KEYWORDS
Hepatocellular carcinoma;
Salvage liver transplantation;
Liver resection;
Milan criteria;

Summary
Background and aims: Since there is a shortage of liver donors, we investigated recurrence patterns and outcomes after liver resection (LR) to determine the feasibility of salvage liver transplantation (SLT).
Methods: We analyzed 468 patients with hepatocellular carcinoma (HCC) within the Milan criteria (MC) who were mainly associated with Hepatitis B virus infection (76.3%) and had undergone curative LR as an initial treatment.

Abbreviations: HCC, hepatocellular carcinoma; LR, liver resection; LT, liver transplantation; SLT, salvage liver transplantation; MC, Milan criteria; CT, computed tomography; MRI, magnetic resonance imaging; AASLD, American Association for the Study of Liver Disease; TACE, transarterial chemoembolization; LRT, locoregional treatment; AFP, α-fetoprotein; PIVKA, prothrombin in vitamin K absence; RFA, radiofrequency ablation; CRR, complete radiologic response; OS, overall survival; SD, standard deviation; HBV, hepatitis B virus; INR, international normalized ratio; RFS, recurrence-free survival; ECOG, Eastern Cooperative Oncology Group.

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Recurrence;
Risk factor

Results: The overall survival (OS) rates were 86.6% and 67.4% at 5 and 10 years after LR, respectively. During a median follow-up of 59 months, 211 patients experienced recurrences including 175 (37.4%) within MC and 36 (7.7%) beyond MC. Survival was lowest in patients with beyond MC-recurrence followed by within MC- and no-recurrence groups (26.5%, 86.6%, and 94.7% at 5 years, respectively, $P < 0.001$). Independent pathologic predictors of recurrence beyond MC were the presence of satellite nodules, microvascular invasion, and unfavorable gross findings (multinodular confluent and infiltrative) (all, $P < 0.05$). Patients with all three risk factors experienced recurrence with the highest cumulative incidence of mortality. Among 173 patients with recurrence within MC, the cumulative incidence of HCC progression beyond MC despite resection and locoregional treatment (LRT) was 29% and 60% at 5 and 10 years after recurrence, respectively, and their 10-year OS rate was 25.8%.
Conclusion: Curative LR achieved a 5-year survival of > 85% in patients with transplantable HCC, but early SLT after recurrence within MC is advocated because of poor survival and high risk of progression thereafter. Further, prophylactic LT could be considered for those with high risk of recurrence.

1. Introduction

Hepatocellular carcinoma (HCC) is a complex, heterogeneous disease. Only 30—40% of HCC patients are eligible for curative treatment at the time of diagnosis [1—3]. At present, liver resection (LR) and liver transplantation (LT) are the conventional curative treatment modalities for patients with operable HCCs [1]. Although LR is considered as a curative treatment, there are theoretical advantages of LT over LR as LT decreases the HCC recurrence risk by removal of the remnant liver and treats the underlying liver disease. On this basis, some studies showed more favorable results for LT than for LR as a first-line treatment in early HCC [4—6].

However, primary LT is usually limited to patients with HCCs within the Milan criteria (MC) because they show a significantly better survival rate than those beyond MC [7,8]. With the implementation of screening programs in high-risk patients, the proportion of HCC patients within MC who are eligible for LT have increased leading to a discrepancy between the demand and availability of organs for transplant [1,2,9]. Many studies were performed to overcome the problem of liver shortage by assessing the outcome of LR in patients with good liver function. Unlike previous studies, improvements in preoperative tumor characterization and operative techniques in experienced centers have increased the survival rates after LR, and it is comparable to that of LT [10—13]. In addition, availability of potent antiviral drugs such as entecavir and tenofovir has attenuated the progression of liver disease especially in Hepatitis B virus (HBV) endemic areas like Asian countries which, in turn, has significantly improved the outcome of LR by decreasing HCC recurrence after resection [14—19].

The challenge lies in the lack of standardized and effective treatment for recurrence after LR as the 5-year recurrence rate is reported to be 70% [20], and LR has a lower recurrence-free survival (RFS) than LT [4,21]. Therefore, salvage LT (SLT) is an alternative treatment strategy. In this study, initial LR is performed in patients within MC, and LT is performed when HCC recurrence pattern adheres to MC. This reserves LT for patients whose liver function deteriorates or HCC recurs in the future, and further, it has the advantage of delaying the need for long-term immunosuppression. One recent meta-analysis revealed that for patients with early HCC and well-compensated cirrhosis, LR achieved 1- and 3-year survival rates similar to that of LT [22]. Since a similar outcome was observed in both treatment modalities, this study provided evidence that LT may be considered in the event of recurrence following resection.

Although SLT seems to be an attractive concept and can be applied to a significant number of patients with preserved liver function at the time of diagnosis, patients with HCC recurrence beyond MC, who initially had HCC within MC, will lose the opportunity of LT [9,21]. The reported actual transplantability after LR is fairly low (< 50%) due to various reasons such as recurrence beyond MC and dropout while on the waiting list due to old age, worsening of cardiovascular comorbidity, and infection even in those who recur within MC [23—25].

In the present study, we aimed to evaluate the performance of curative LR based on strict criteria. Our data are from a homogenous group of HBV-infected patients who are well controlled with antiviral agents, and this may lead to results, which are different from those in Western countries. Further, we attempted to identify patients with a high risk of recurrence beyond MC to propose early prophylactic LT in these patients. In addition, to evaluate the need of SLT, we addressed the efficacy of locoregional treatments (LRT) in prolonging progression beyond MC in patients who recur within MC. Based on these results, we tried to analyze the implication of initial resection followed by SLT.

2. Materials and methods

2.1. Patient selection

From January 2004 to December 2016, 832 consecutive HCC patients who underwent curative liver resection were retrospectively analyzed. The diagnosis of HCC was based on triple-phase computed tomography (CT) and/or gadoxetate

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disodium-enhanced (PrimovistTM, Bayer Healthcare, Berlin, Germany) magnetic resonance imaging (MRI) showing both early hyperenhancement and delayed hypoenhancement (washout) according to the AASLD guideline [9]. We excluded patients with:

- HCC beyond MC at initial image diagnosis;
- residual HCC lesion after resection;
- HCC diagnosis on imaging but not after analysis of resected specimen (dysplastic nodule, intrahepatic cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, and secondary metastatic tumor);
- LRT such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) more than once before resection;
- follow-up less than 6 months, and;
- perioperative death (Fig. 1).

The study was approved by the institutional review board of Korea University, and the need for ''informed consent was waived''. The medical record was reviewed for both clinical and pathological variables.

2.2. MC definition

MC was defined as a single tumor of diameter < 5 cm or up to three tumor foci, each not exceeding 3 cm without extrahepatic involvement or gross vascular invasion [20]. In this study, HCC within or beyond MC was defined according to the pathologic findings from the primary resected specimen.

2.3. Clinical findings

Clinical data included age, gender, ECOG performance status, and laboratory results (complete blood count, liver function, α-fetoprotein (AFP), prothrombin in vitamin K absence (PIVKA), and etiologies of liver disease). Chronic hepatitis B patients were treated with antiviral therapy if indicated.

2.4. Pathologic findings

Pathologic data from resected specimen included tumor size, tumor number, satellite nodules (defined as tumors sized $\leq$ 1 cm and located $\leq$ 2 cm from the main tumor), Edmonson grade (I—IV), presence of microvascular invasion, liver cirrhosis, and gross morphology (vaguely nodular, expanding nodular, nodular with perinodular extension type, multinodular confluent, and infiltrative types) classified according to The General Rules for the Study of Primary Liver Cancer published by Korean Liver Cancer Association [26].

2.5. Treatment and follow-up

Liver resection as primary therapy for HCC within MC was performed in 468 patients. All patients had complete removal of HCC with anatomic resection in 284 (59.2%) patients and wedge resection in 190 (40.8%) patients, according to the severity of liver cirrhosis and location of the tumors. Among the resected HCC patients, 9 patients had TACE as the first modality of treatment before resection without recurrence. After liver resection, routine imaging such as triple-phase CT or gadoxetate disodium-enhanced MRI were performed every 3—4 months in the first 2 years and subsequently, every 6 months in most patients. Patients who were followed-up for at least 6 months were enrolled. Patients who recurred after resection were managed with various treatment modalities including re-resection, RFA, and TACE.

2.6. Outcome definition

Recurrence was defined as the appearance of a new lesion with features of HCC on image findings and/or pathologic findings. The date of recurrence was recorded, and the pattern of recurrence was classified as within or beyond MC. Time to recur was defined as the time from liver resection to recurrence. Complete radiologic response (CRR) was defined as disappearance of recurred HCC for at least 6 months after treatment. Overall survival (OS) was calculated from the date of initial LR until the death of the patient or last follow-up.

2.7. Statistical analysis

Baseline clinical characteristics with continuous variables and categorical data were expressed as mean $\pm$ standard deviation (SD) and median with interquartile range and frequency, respectively. Categorical and continuous variables were compared using the χ^2 test and *t*-test, respectively, among patients without or with HCC recurrence within or beyond MC. Cox proportional hazards model was used to identify predictive factors for survival, HCC recurrence, or recurrence patterns. In multivariate analysis, factors with $P \leq 0.1$ in univariate analysis were included, and finally, factors with $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (SPSS version 20.1; SPSS, Chicago).

3. Results

3.1. Baseline and tumor characteristics

Out of 832 patients, 468 patients were diagnosed with HCC within MC in image study and were included in survival or recurrence pattern analysis (recurrence within MC vs. beyond MC). Baseline clinical characteristics of total patients and recurrence patterns are shown in Table 1. The median age was 58 years (range, 21—95), 76.9% of the patients were male, and 76.3% of patients were infected with HBV without any significant difference in recurrence patterns. Majority of the patients (94%) had a single tumor based on image study, and 463 (99%) patients had good liver function with Child-Pugh grade A while the remaining 5 had Child-Pugh grade B. The median preoperative serum albumin level was 4.2 g/dL (range, 2.8—5.1), bilirubin was 0.66 mg/dL (range, 0.11—4.5), and INR was 1.04 (range, 0.71—1.77). The median AFP was 10.2 ng/mL (range, 0.2—62557) and PIVKA was 36 mAU/mL (range, 2—17066)

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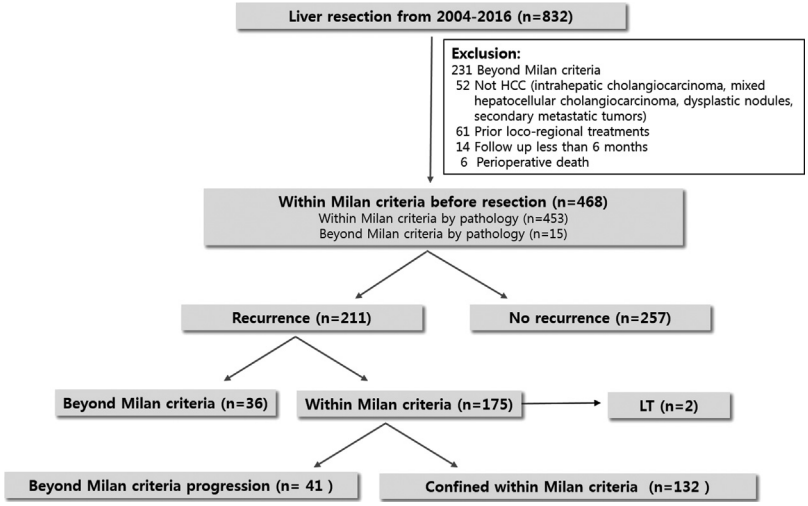

Figure 1 Flow chart of recurrence patterns after hepatic resection.

in 457 and 373 patients, respectively. Low albumin levels, prolonged INR, and increased tumor markers such as AFP (> 100 ng/mL) and PIVKA (> 100 mAU/mL) were more frequent in the recurrence beyond MC group than in the recurrence within MC group.

In the resected HCC specimen, satellite tumors were present in 29 (6.2%) patients. Due to the presence of satellite nodules, 15 (3.2%) patients who were initially within MC, according to image study before resection, were later classified as beyond MC when resected specimens were analyzed, and the number of patients with single tumor decreased to 417 (89.1%). The microvascular invasion was observed in 101 (21.6%), high-grade tumor (ES grade III and IV) in 200 (43.3%), and multinodular confluent and infiltrative gross patterns in 169 (36.1%) patients. These pathologic findings were significantly more predominant in patients with recurrence beyond MC than those with no recurrence or recurrence within MC groups (all, $P < 0.01$).

3.2. Recurrence patterns

The median follow-up duration after liver resection was 59 months (range, 6—177). During this period, HCC recurrence occurred in 211 (45.1%) patients with a cumulative incidence of recurrence of 13.3%, 34.8%, 43.9%, and 52.4% at 1, 3, 5, and 7 years after resection, respectively (Fig. 2). Among 211 recurrences, 175 (82.9%) were within MC while 36 (17.1%) were beyond MC (Fig. 1). The median time to recurrence was 19.1 months (3—126.6), and time to recur in the beyond MC group was significantly shorter than in the within MC group (10.9 versus 21.4 months, $P = 0.003$). In most cases, recurrence beyond MC (77.8%) developed within 2 years. After liver resection, most patients had received regular image follow-up until recurrence, and the last image follow-up interval was not significantly different between within- and beyond-MC recurrences.

Despite the effort for regular image follow-up of 3—6 months, 19 out 36 recurrences beyond MC were detected after 6 months of resection. Early detection was not feasible in these patients due to extrahepatic recurrence, rapid growth after 6 months of resection, and undetectable recurrence with triple-phase CT, and these were eventually detected by multiple lipiodol uptake after TACE. Only 4 patients could have avoided recurrence beyond MC if they had followed the regular image follow-up. Remaining 13 recurrences beyond MC were detected within 6 months after resection.

3.3. Factors associated with recurrence beyond MC

Predictors of recurrence beyond MC in univariate analysis were the presence of satellite nodules, multiple tumors, high tumor grade, presence of microvascular invasion, multinodular confluent, infiltrative gross patterns, low albumin levels, prolonged INR, and high PIVKA levels (Table 2). Using the pathologic data after liver resection, multivariate analysis revealed that the presence of satellite nodules, microvascular invasion, and gross patterns were independent factors associated with recurrence beyond MC. Based on these three independent pathologic factors, the incidence of HCC recurrence beyond MC was stratified. Six patients had all three risk factors, and all of them experienced recurrence after LR including four (66.7%) who experienced recurrence beyond MC (Table 3). On the other hand, among 234 patients without any risk factor, 11 (4.7%) patients recurred beyond MC, and the risk increased to 6.3% and 18.9% for those who had only one and two risk factors, respectively. Two-year cumulative incidence of recurrence beyond MC in patients with all risk factors, two risk factors, and one or no risk factor was 100%, 21.5%, and 4%, respectively (Fig. 3A). Furthermore, patients with three risk factors had the lowest chance of RFS (Fig. 3B).

3.4. Factors associated with any recurrence and OS

Factors associated with any recurrence and OS were analyzed. In the entire study group, the cumulative probability

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Table 1 Baseline clinical characteristics of HCC patients.

Variables	Total	Number of recurrences	Recurrence within MC	Recurrence beyond MC	*P*-value
No of patients	468	257 (54.9)	175 (37.4)	36 (7.7)	
Host data					
Age, years	58 (21–95)	58 (21–95)	58 (37–82)	53 (39–74)	0.058
Age ≥ 60 years	206 (44)	118 (45.9)	76 (42.9)	13 (36.1)	0.32
Male gender	360 (76.9)	185 (72)	145 (82.9)	30 (83.3)	0.386
Etiology					
Viral	403 (86.1)	209 (81.3)	159 (90.9)	34 (94.5)	0.431
HBV	369 (78.8)	195 (75.9)	142 (81.1)	32 (88.9)	
HCV	32 (6.8)	14 (5.4)	16 (9.1)	2 (5.6)	
Alcohol	24 (5.1)	13 (5.1)	10 (5.7)	1 (2.8)	
Cryptogenic	43 (9.2)	35 (13.6)	7 (4)	2 (2.8)	
Image data					
Single tumor	440 (94)	244 (94.9)	162 (92.6)	34 (94.4)	0.91
Tumor size, ≥ 2 cm	292 (62.4)	157 (61.1)	109 (62.3)	26 (72.2)	0.205
Tumor size, ≥ 3 cm	165 (35. 3)	88 (34.2)	63 (36)	14 (38.9)	0.635
Pathologic data					
Tumor size (cm)	2.5 (0.6–5)	2.4 (0.6–5)	2.5 (0.7–5)	2.35 (0.8–5)	0.328
Tumor size, ≥ 2 cm	300 (64.1)	160 (62.3)	113 (64.6)	27 (75)	0.156
Tumor size, ≥ 3 cm	168 (35.9)	89 (34.6)	65 (37.1)	14 (38.9)	0.697
Single tumor	417 (89.1)	236 (91.8)	152 (86.9)	29 (80.6)	0.087
Satellite nodules	29 (6.2)	10 (3.9)	14 (8)	5 (13.9)	0.046
High ES grade (III & IV)	200/462 (43.3)	101/255 (39.6)	76/171 (44.4)	23/36 (63.9)	0.009
Microvascular invasion	101 (21.6)	47 (18.3)	36 (20.6)	18 (50)	< 0.001
Gross (MCN, Infiltrative)	169 (36.1)	85 (33.1)	64 (36.6)	20 (55.6)	0.011
Liver cirrhosis	349 (74.6)	173 (67.3)	147 (84)	29 (80.6)	0.391
Clinical data					
Child-Pugh grade A	463 (99)	254 (98.8)	173 (98.9)	36 (100)	0.516
Albumin ≥ 4.3 g/dL	227 (48.5)	134 (52.1)	82 (46.9)	11 (30.6)	0.036
Bilirubin ≥ 1 mg/dL	79 (16.9)	40 (15.6)	35 (20)	4 (11.4)	0.355
INR ≥ 1	348 (74.4)	179 (69.6)	137 (78.3)	32 (88.9)	0.038
AST > 40 IU/L	160 (34.2)	75 (29.2)	69 (39.4)	16 (44.4)	0.177
ALT > 40 IU/L	154 (32.9)	75 (29.2)	63 (36)	16 (44.4)	0.125
AFP > 100 ng/mL	120 (26.3)[a]	66 (26.2)	40 (23.7)	14 (38.9)	0.073
PIVKA–II > 100 mAU/mL	98/373 (26.3)[b]	51 (24.3)	35 (25.5)	12 (46.2)	0.017
Follow-up data					
Follow-up duration, months	59 (6–177)	58 (6–177)	69 (8–171)	32.5 (6–95)	< 0.001
Time to recur, months	19.1 (3–126.6)		21.4 (3–126.6)	10.9 (3.4–85.3)	0.003
Recur within 2 years	126 (59.7)		98 (56)	28 (77.8)	< 0.001
Last image FU interval, months			4 (0.3–26)	3 (1–28)	0.344
Time to death, months	52.5 (6–153)	52 (20–104)	63.5 (16–153)	26 (6–95)	< 0.001
Mortality	86 (18.4)	15 (5.8)	44 (25.1)	27 (75)	< 0.001

ES: Edmonson Steiner; MC: Milan criteria; MCN: multinodular confluent; FU: follow-up. Categorical variables are shown as the number of cases (percentage); continuous variables as median (interquartile range). *P*-value was analyzed for recurrence beyond MC group vs. recurrence within MC and no recurrence groups.

[a] AFP values were available from 457 patients.

[b] PIVKA levels were available from 373 patients.

of OS at 3, 5, and 10 years after the first resection was 92%, 86.6%, and 67.4%, respectively. Recurrence patterns had a significant impact on survival rates. The 5- and 10-year OS was the lowest in the recurrence beyond MC group (26.5% and 0%, respectively) followed by within MC (86.6% and 62.2%, respectively) and no recurrence groups (94.7% and 85.1%, respectively) ($P < 0.001$) (Fig. 4). In addition, the progression of liver disease represented by low serum albumin levels and liver cirrhosis was associated with survival (Supplementary table* 1). In multivariate analysis, male gender, multiple tumors, presence of microvascular invasion, liver cirrhosis, and prolonged INR were independent factors associated with overall recurrence (Supplementary table* 1).

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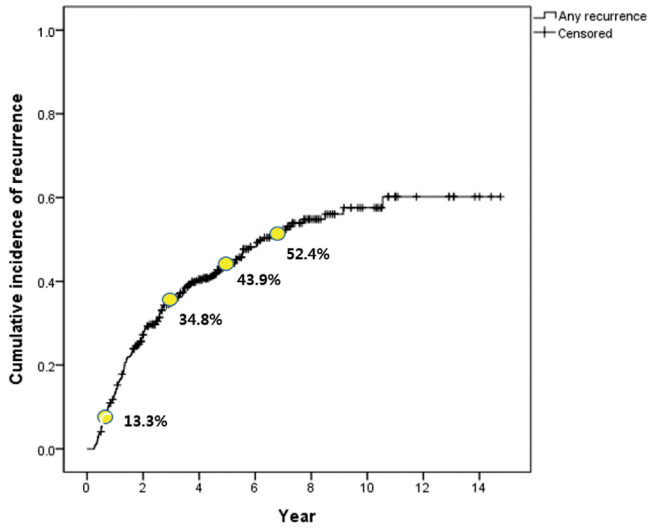

Year after resection	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number at risk	402	321	259	197	139	95	67	43	28	13	10	7	6	2

Figure 2 Kaplan-Meier curve for cumulative incidence of all recurrence after hepatic resection. Cumulative incidence of recurrence at 1-, 3-, 5-, and 7-years are shown in the graph.

Table 2 Factors associated with recurrence beyond Milan criteria.

Variables	HR	95% CI	Univariate *P*-value	Multivariate *P*-value	Multivariate **P*-value
Host data					
Age ≥ 60 years	0.715	0.362—1.412	0.344		
Male gender	1.594	0.663—3.83	0.297		
Etiology					
Viral	—	—	0.325		
Alcohol	0.261	0.036 .907	0.186		
Cryptogenic	0.47	0.064—3.438	0.457		
Image data					
Single tumor			0.899		
Tumor size, ≥ 2 cm	1.588	0.766—3.293	0.214		
Tumor size, ≥ 2.5 cm			0.555		
Pathologic data					
Tumor size (cm)	1.174	0.873—1.578	0.289		
Tumor size ≥ 2 cm	1.733	0.815—3.686	0.153		
Satellite nodules	3.145	1.221—8.101	0.018	0.186	0.023
Single tumor	0.423	0.185—0.967	0.042	0.326	0.581
High ES grade (III & IV)	2.332	1.18—4.609	0.015	0.066	0.173
Microvascular invasion	4.09	2.127—7.865	< 0.001	0.001	< 0.001
Gross (MCN, Infiltrative)	2.351	1.218—4.539	0.011	0.112	0.043
Liver cirrhosis	1.545	0.676—3.528	0.302		
Laboratory data					
Albumin ≥ 4.3 g/dL	0.453	0.223—0.922	0.029	0.125	
Bilirubin ≥ 1 mg/dL	0.633	0.224—1.789	0.388		
INR ≥ 1	2.952	1.044—8.352	0.041	0.058	
AST > 40 IU/L	1.658	0.858—3.204	0.132		
ALT > 40 IU/L	1.695	0.878—3.273	0.116		
AFP > 100 ng/mL	1.825	0.932—3.577	0.08	0.759	
PIVKA—II > 100 mAU/mL	2.618	1.211—5.661	0.014	0.111	

* *P*-value was analyzed based on pathologic data with *P*-values < 0.1 in univariate analysis.

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Table 3 Recurrence patterns according to the number of risk factors.

Number of risk factors (satellite nodules, microvascular invasion, gross patterns)	Number of patients	Number of recurrences *n* (%)	Recurrence within MC *n* (%)	Recurrence beyond MC *n* (%)
0	234	139 (59.4)	84 (35.9)	11 (4.7)
1	175	95 (53.7)	70 (40)	11 (6.3)
2	53	24 (45.3)	19 (35.8)	10 (18.9)
3	6	0	2 (33.3)	4 (66.7)

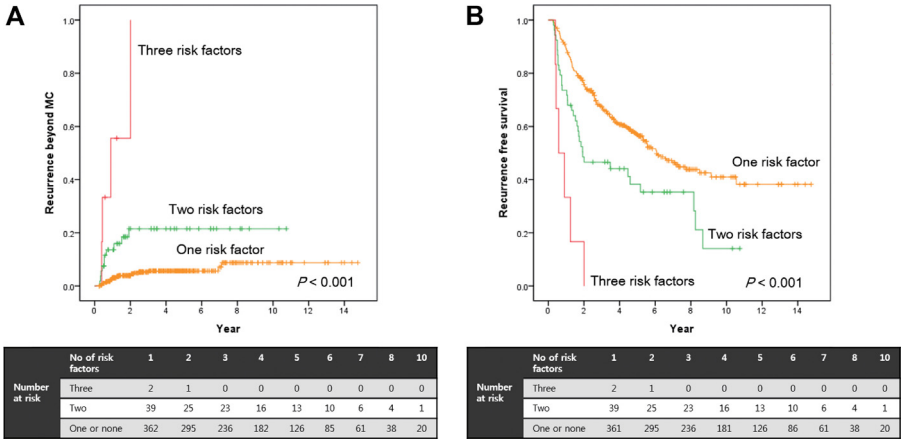

Figure 3 Kaplan-Meier curve for recurrence beyond Milan criteria based on risk factors. Risk factors were the presence of satellite nodules, microvascular invasion, and gross morphology (multinodular confluent and infiltrative). (A) Cumulative incidence of recurrence beyond Milan criteria was the highest in patients with all three risk factors followed by those with two risk factors and one or no risk factor. (B) Cumulative incidence of recurrence-free survival was the lowest for those with all three risk factors.

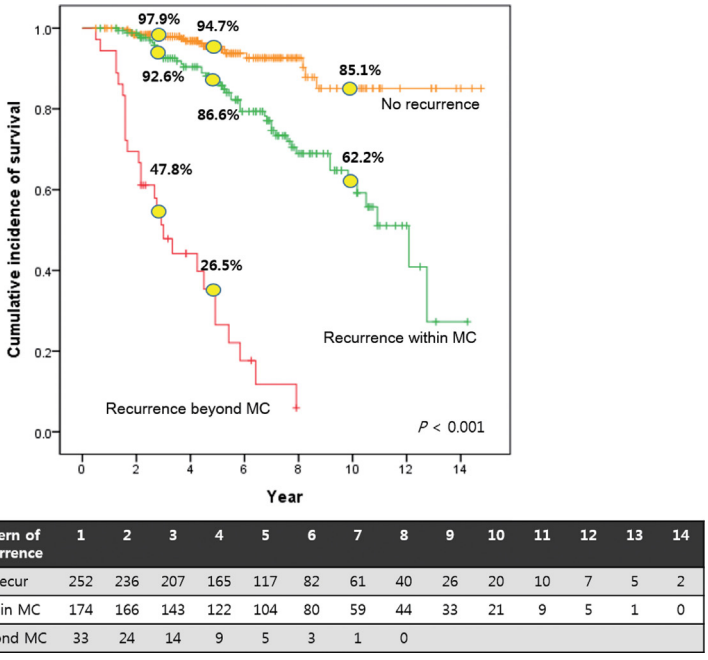

Figure 4 Kaplan-Meier curve for overall survival according to recurrence patterns. Cumulative incidence of overall survival at 3-, 5-, and 10-years are shown in the graph.

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3.5. Progression patterns after the first recurrence within MC

Among 175 patients who experienced recurrence within MC, 2 patients had SLT while 167 patients had treatments such as re-resection ($n = 38$), TACE ($n = 76$), and RFA ($n = 53$). Remaining 6 patients did not receive any treatment due to follow-up loss or patient refusal. Among 173 patients, 41 (23.7%) patients eventually progressed beyond MC with a median time to progression of 2.8 years (range, 0.31—9.19 years) while in the remaining patients, the tumor status reached CRR in 55 (31.8%) with LRTs, or were not cured but still remained within MC in 77 (44.5%) at the time of the last follow-up. At 3, 5, and 10 years after the first recurrence within MC, the cumulative incidence of progression beyond MC was 18%, 29%, and 60%, respectively (Supplementary Fig. 1A) while the OS was 84.4%, 73.8%, and 25.8%, respectively (Supplementary Fig. 1B).

4. Discussion

The best strategy to treat HCC within MC with minimal underlying liver disease is still under debate. Several studies reported better survival after recurrence with primary LT than primary LR followed by SLT [27—29]. However, all these studies are retrospective, without randomization to compare primary LT and SLT, and patients were heterogeneous and included those who do not fulfill MC and had poor liver function [28,29].

Unlike previous studies, we applied strict criteria in selecting patients. All the patients were diagnosed with HCC within MC, and most patients (99%) had good liver function (Child-Pugh class A). In patients with class A cirrhosis and resectable tumor, clinicians should rigorously assess whether primary LT is necessary. As shown in our present study, 257 out of 468 patients had no recurrence after resection, and a liver would have been wasted if LT was performed in these patients indicating that LR should be given priority in patients with good liver function. Majno et al. [21] reported that 29% of organs could be retrenched over 5 years if LR is performed as first-line therapy, and LT is offered as SLT after recurrence.

In our present study, the high incidence of OS when compared to primary LT in other studies justifies primary LR [29—31]. The cumulative incidence of OS at 3, 5, and 10-years was 92%, 86.6%, and 67.4%, respectively for all patients. This finding is comparable to the survival rate of early-stage HCC patients after primary LT according to studies by Bhangui et al. [27] who reported 5- and 10- year OS of 73% and 63%, respectively and Ng KKC et al. [24] who reported 3- and 5- year OS of 91.1% and 86.3%, respectively [24]. There are emerging studies that reveal similar OS between primary LT and SLT both in Asian [24,32] and Western countries [27,33]. In a study by Margarit et al. [12] involving early-stage HCC with single nodule and Child-Pugh class A patients, a similar survival rate was reported between the LR group and primary LT group. In summary, it could be suggested that for patients with early-stage HCC and well-preserved liver function, LR followed by LT could be a more logical modality of initial treatment than primary LT.

Our study reports a much lower overall recurrence rate (45.1%) and recurrence beyond MC (7.7%) than previous studies, which report recurrence beyond MC to be approximately 20% [23,25,30,31]. This result indicates that unnecessary transplantation was avoided in 54.9% of patients with hepatic resection as first-line treatment. The reason for such a low recurrence rate in the present study could be explained by the pathologic findings of resected specimens. Our study reports higher incidence of single tumor (89.1% vs 70.5%), less frequent tumor >3 cm (35.9% vs 53.6%), and lower incidence of microvascular invasion (21.6% vs 43.8%) and satellite nodules (6.2% vs 20.5%) than previous studies, [30] implying that probably, the cases included in this study had very early-stage HCC with less intrahepatic metastasis.

Although the prevalence of recurrence beyond MC was low, the prognosis was dismal in this group of patients when compared to those who recur within MC. Low RFS in patients who recur beyond MC after resection might justify primary LT in these cases if they can be identified in advance [31,34]. In accordance with previous studies, [30,31] pathologic data comprising satellite nodules, microvascular invasion, and gross morphology (multinodular confluent and infiltrative) were important factors that predicted recurrence beyond MC in our study. Of note, gross morphology of HCC has not received much attention in other studies, except those from Asian countries, which demonstrated associations between gross patterns and prognosis [35—38]. Interestingly, HCC gross pattern (multinodular confluent and infiltrative) was an independent predictor of recurrence beyond MC and was more important than size and tumor grade in the present study. These two patterns were associated with higher AFP and PIVKA levels, presence of vessel invasion, and higher tumor grade (all, $P < 0.05$ data not shown). When all three risk factors were present, no patient could avoid recurrence in our study, so prophylactic LT could be suggested in these cases.

However, there are very limited studies showing external validation of the high-risk factors in predicting recurrence beyond MC, and this warrants hasty prophylactic LT ahead of recurrence. However, Ferrer et al. [25] validated the pejorative histological marker developed by Fuks et al. and showed that 5- year OS of the high-risk group (82.4%) which had ab initio LT was similar to that of the low-risk group (81.8%) which had SLT. Additionally, similar result was observed by Tribillon et al. [39] with 5-year OS of 84.6% in de principe LT and 81.3% in SLT. Improved survival rates by performing prophylactic LT based on high-risk factors that predict recurrence beyond MC provides strong evidence for the reliability of the strategy of initial LR followed by prophylactic LT or SLT (Fig. 5).

Although a majority of the patients had liver cirrhosis, it was not a predictive factor of recurrence beyond Milan but a predictor of overall recurrence. Imamura et al. [40] suggested that recurrence should be divided into early (< 2 years) and late recurrence. Tumor factors such as microvascular invasion and satellite nodules are associated with early recurrence, and these factors are not amenable to antiviral treatment. This is in line with our findings where tumor factors were associated with recurrence beyond MC, and all these recurrences occurred within a median interval of 10.9 months, thus corresponding to early recurrence. In contrast,

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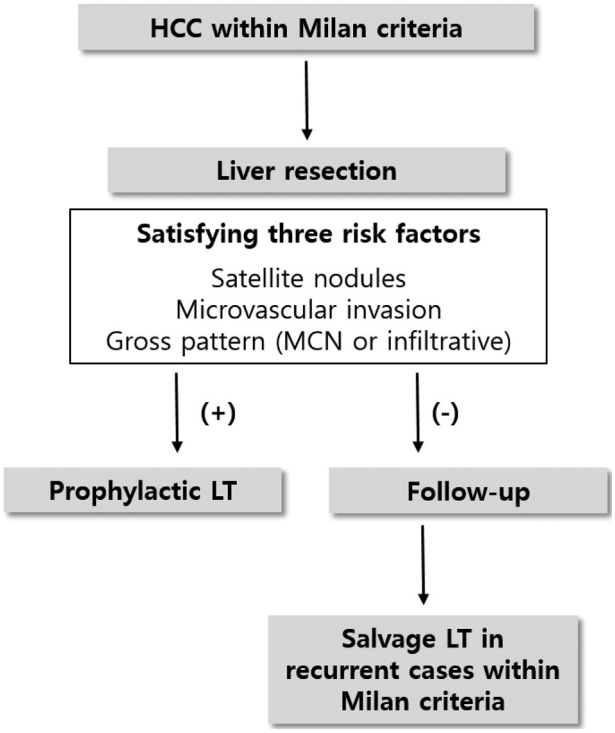

Figure 5 Recommendation for the therapeutic strategy of HCC within Milan criteria at the time of recurrence. LT: liver transplantation; MCN: multinodular confluent.

antiviral treatment had an anti-tumor effect by suppressing viral replication, reducing necro-inflammation, fibrosis, and reversing cirrhosis which could change the microenvironment of hepatocarcinogenesis in LC patients resulting in decreased secondary or primary HCC [16,18,41,42]. Thus, it is highly likely that the use of potent anti-HBV treatment in patients with HBV-related HCCs had contributed to the reduction of overall recurrence of HCC after resection, as shown in the present study.

Another important finding is that patients should adhere to regular follow-up with triple-phase CT or MRI for a longer duration after resection to prevent recurrence beyond MC. Among 36 patients who recurred beyond MC, four recurrences could have been avoided if the patients had been followed-up at close intervals. This indicates that recurrence could have been detected at within MC stage, which could have further lowered the small number of cases of recurrence beyond MC.

In the present study, a detailed analysis was performed to observe the progression of the recurrent HCCs that developed within MC following LR. With the advancement in LRTs such as RFA and TACE, the progression was fairly delayed with a median time to progression of 38 months, which was sufficient to prepare a living donor for SLT, as a living donor is the main source of graft in Asia. However, 60% of the patients who recurred within MC progressed beyond MC eventually over a long period. Furthermore, despite the technological advancement of resection or LRTs, 10-year OS after recurrence had decreased to 25%. This figure is much lower when compared to 10-year OS of those who had SLT after the first recurrence (53-62%) reported in previous studies [23,24,33,43] providing evidence for considering early SLT without delay in the case of recurrence.

5. Conclusion

Our study provides a solid rationale for initial LR in patients with early-stage HCC within LT indication in countries with a high prevalence of HBV infection because curative LR provides a good long-term survival similar to LT, and the rate of recurrence beyond MC is substantially low especially in those with early-stage HCC, well-preserved liver function, and strict follow-up, indicating that most patients are still transplantable at the time of recurrence. However, since those with a recurrence of HCC beyond MC have a dismal prognosis with a loss of the chance of SLT, a prophylactic LT could be proposed before any recurrence occurs, using high-risk predictors on a pathologic basis, although it would be applicable to a minority of patients. For patients with the recurrence of HCC within MC after LR, SLT should be recommended considering their poor survival and high risk of progression after recurrence.

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Author contributions

S.H. Um contributed to the conception and design of the study and critically revised the article for important intellectual content. S.Y. Yim drafted the article and analyzed and interpreted data. C.G. Seo and Y.R. Lee extracted data. Y.J. Lee, T.H. Kim, H.G. Gil, Y.S. Lee, S.J. Suh, and N.Y. Han reviewed the data. All authors have revised the article and approved the authorship list.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2019.11.006.

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