

Clinical Utility of the Novel Oncological Criteria of Resectability for Advanced Hepatocellular Carcinoma

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Keywords

Consensus statement · Hepatocellular carcinoma · Resectability · Surgery · Systemic therapy

Abstract

Introduction: Introduction of new systemic therapies for hepatocellular carcinoma (HCC) has led to the development of new oncological criteria of resectability for the resectability of HCC. This study was aimed at validating the prognosticating ability and clinical utility of the resectability classification based on the novel criteria in real-world clinical practice. **Methods:** This study was conducted in 1,822 patients who had undergone curative resection for HCC (population 1) and 107 patients with unresectable disease who had received lenvatinib therapy (population 2). Patients were classified into three groups according to the novel oncological criteria for resectability (R, resectable; BR1, borderline resectable 1; and BR2, borderline resectable 2), and the prognosticating ability and clinical utility of this classification based on the novel

criteria were examined. **Results:** Multivariate analysis confirmed that classification of the patients according to the oncological resectability criteria was significantly correlated with the overall survival (OS) (BR1: hazard ratio [HR], 1.88; 95% CI, 1.38–2.55; BR2: HR, 4.12; 95% CI, 3.01–5.65) and recurrence-free survival (BR1: HR, 1.86; 95% CI, 1.44–2.41; BR2: HR, 3.62; 95% CI, 2.71–4.82) in population 1. In population 2, the resectability classification was correlated with the rates of successful additional intervention (surgery, transarterial chemoembolization, or radiotherapy) (BR1 65.7% vs. BR2 42.3%, $p = 0.023$) and curative-intent conversion surgery (BR1 17.1% vs. BR2 4.2%, $p = 0.056$) after lenvatinib therapy, and was also predictive of the OS (HR, 1.96; 95% CI, 1.13–3.38 for BR2 [vs. BR1]) and time-to-treatment failure (HR, 1.81; 95% CI, 1.04–3.17 for BR2 [vs. BR1]). **Conclusion:** The resectability classification based on the novel oncological criteria for resectability showed acceptable prognosticating ability in both surgically and medically treated populations with advanced HCC.

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Introduction

Recent introduction of new systemic therapies has dramatically changed the landscape of clinical management of hepatocellular carcinoma (HCC). This field is currently drawing a lot of attention, and a large number of papers have been published regarding the efficacy of combination therapies or even curative-intent conversion surgery for patients with advanced HCC [1–7]. However, the lack of a consensus on the resectability criteria for cases with advanced disease has precluded a constructive discussion on who could be suitable candidates for preoperative therapy and what might be the best timing and situation for conversion surgery. HCC is a very unique tumor, in that its origin is associated with liver injury and patients usually suffer from both HCC and the underlying liver disease. This fact makes it difficult to clearly define the resectability criteria for advanced HCC because the efficacy and safety of surgery are highly influenced not only by technical difficulties in achieving R0 resection but also by the oncological features of the HCC and the hepatic functional reserve.

Previously, our group reported our own criteria for resectability of HCC to demonstrate the efficacy of conversion surgery for advanced disease after systemic therapies [1]. However, these criteria were based on our experience in daily clinical practice, and no external validation was performed. Because patients with advanced disease categorized as BCLC stage B or C are not considered as being suitable candidates for surgery in Western countries, and only limited evidence is available with regard to the efficacy of surgical resection for advanced HCC in the literature [8–13], it is difficult to construct new evidence for surgical management of advanced HCC using the existing data. Therefore, the Japan Liver Cancer Association (JLCA) and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) launched a working group to discuss new criteria for oncological resectability of HCC, and an expert consensus statement has just proposed a novel definition of oncological resectability of HCC in 2023 [14].

However, given that clinical data on surgical resection for advanced disease are only available from a limited number of institutions where aggressive surgical resection is performed, a validation study based on an existing public database is expected to be difficult. As such, as the first step before proceeding to a multicenter study, we conducted this study to investigate the prognosticating ability of the novel oncological criteria for resectability of HCC using a database from a tertiary referral center specialized in the treatment of hepatic malignancies.

Methods

Study Population

The study population consisted of 1,822 consecutive patients who had undergone curative resection for HCC between January 1995 and August 2023 at the Department of Gastroenterological Surgery, Toranomon Hospital (population 1), and 107 patients with advanced HCC who had received treatment with lenvatinib for advanced HCC between October 2010 and September 2020 at the Department of Hepatology, Toranomon Hospital (population 2). Population 1 was used for testing the prognosticating ability of the resectability classification based on the recently proposed oncological criteria for resectability [14] in HCC patients undergoing surgery, and population 2 was used for validating the clinical utility of this classification for the management of advanced HCC through a review of updated data of a prospective cohort that was used in our previous study [1, 7]. This study was carried out in accordance with the principles of the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan, with the approval of our institutional review board (No. 1919 and No. 1438-H/B).

Indications for Surgery and Follow-Up

Our broad treatment strategy and surgical indications for patients with HCC have been reported elsewhere [7, 15]. Indications for surgery are based on the Clinical Practice Guidelines for Hepatocellular Carcinoma proposed by the Japan Society of Hepatology [16]. The clinical management of patients with advanced HCC, including the decision to proceed to conversion surgery, was determined at a multidisciplinary team meeting, considering oncological stability and technical feasibility of complete removal of the disease as a part of multidisciplinary treatment approach. Surgical procedures are determined according to the location, extension, and distribution of the disease considering the balance between the extent of surgery and hepatic functional reserve.

Resectability Criteria for HCC

The study populations were classified according to both the oncological criteria for resectability and technical criteria for resectability of HCC. The oncological classification was based on the criteria proposed in the JLCA and JSHBPS Expert Consensus Statement 2023 and the patients were classified into three groups: R (resectable), BR1 (borderline resectable 1), and BR2 (borderline resectable 2) (online suppl. Table 1; for all online suppl. material, see <https://doi.org/10.1159/000539381>) [14].

The technical classification was based on the criteria reported in our previous study (online suppl. Table 2) [1], and the patients were classified into three categories: R (resectable), MR (marginally resectable), and UR (unresectable). Briefly, technical R is defined when margin-negative resection is expected to be feasible with sufficient hepatic functional reserve, while technical MR refers the status that portal flow modulation procedures and/or management of portal hypertension are required to secure the safety of surgery. Technical UR is the status where margin-negative resection is impossible and/or Child-Pugh A/B with uncontrollable ascites or Child-Pugh class C patients.

Statistical Analysis and Interpretation of Data

Statistical analysis was performed using the IBM SPSS software (ver. 26.0; SPSS Inc., IL, USA) and JMP software (ver. 14.0; SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as the median values (range) and compared using the Wilcoxon

Table 1. Baseline characteristics of the population 1 (*n* = 1,822)

Age ^a	67 (28–90)
Male	1,374 (75.4%)
Body mass index	22.9 (20.8–25.0)
HBsAg positive	504 (27.7%)
HCV-Ab positive	940 (51.6%)
Prior history of curative treatment for HCC	364 (20.0%)
Preoperative systemic therapy	15 (0.8%)
Albumin, g/mL	3.8 (3.5–4.1)
Bilirubin, mg/mL	0.9 (0.7–1.1)
Prothrombin, %	90.1 (81.6–98.2)
Platelet, 10 ⁴ /mm ³	14.3 (10.4–18.8)
Child-Pugh A/B	1,687 (92.6)/135 (7.4%)
Presence of intrahepatic lesion	1,801 (98.8%)
Maximum size, mm ^a	22 (2–250)
Number ^a	1 (1–16)
Portal invasion (vp0/vp1/vp2/vp3/vp4) ^b	1,309 (71.8%)/462 (25.4%)/33 (1.8%)/12 (0.7%)/6 (0.3%)
Venous invasion (vv0/vv1/vv2/vv3) ^b	1,716 (94.2%)/97 (5.3%)/4 (0.2%)/5 (0.3%)
Biliary invasion (b0/b1/b2/b3/b4) ^b	1,780 (97.7%)/34 (1.9%)/3 (0.2%)/3 (0.2%)/2 (0.1%)
Presence of extrahepatic lesion	35 (1.9%)
BCLC stage (stage 0/stage A/stage B/stage C)	593 (32.6%)/1,077 (59.1%)/82 (4.5%)/70 (3.8%)
Technical resectability (R/MR/UR) ^c	1,355 (74.4%)/467 (25.6%)/0 (0%)
Oncological resectability (R/BR1/BR2) ^d	1,674 (91.9%)/83 (4.6%)/65 (3.6%)
AFP, ng/mL	10.0 (4.0–54.9)
DCP, mAu/mL	31.0 (17.0–120.0)
Cirrhosis	896 (49.2%)
Differentiation (well/moderate/poor/unknown)	191 (10.5%)/1,204 (66.1%)/385 (21.1%)/42 (2.3%)
Margin status (R0/R1/unknown)	1587 (87.1%)/209 (11.5%)/26 (1.4%)
Year (1995–2008/2009–2017/2018–2023)	663 (36.4%)/673 (36.9%)/486 (26.7%)

Figures represent median (interquartile range) or number (percentage) unless indicated. HBsAg, hepatitis B antigen; HCV-Ab, anti-hepatitis C antibody; AFP, alpha fetoprotein; DCP, des-gamma-carboxy prothrombin. ^aMedian (range). ^bHistopathological diagnosis. ^cBased on the criteria reported by Shindoh et al. [1]. ^dBased on the JLCA and JSHBPS Expert Consensus Statement 2023 [14].

rank-sum test. Categorical data were expressed in numbers (%) and compared using the χ^2 test or Fisher's exact test, as appropriate. The prognostic indicators used in this study were as follows: overall survival (OS), calculated as the time period from the date of resection or initiation of lenvatinib therapy to death from any cause, recurrence-free survival (RFS), calculated as the time period from the date of surgery to initial recurrence or death, and time-to-treatment failure (TTF), calculated as the time from the date of initiation of lenvatinib therapy to diagnosis of untreatable disease progression

(i.e., a disease status for which only best supportive care is suitable) or death. Survival curves were generated using the Kaplan-Meier method and compared by the log-rank test. To identify independent factors associated with these prognostic indicators, multivariate analysis was performed using a Cox proportional hazards model with backward elimination. *p* < 0.05 was considered as denoting statistical significance. Data interpretation was discussed including external reviewers (K.A., M.T., and N.K.) from the expert panel for the JLCA and JSHBPS Consensus Statement 2023.

Table 2. Predictive factors for OS in population 1

	<i>p</i> value ^a	Coefficient ^b	SE	Wald χ^2	HR	95% CI
Age	<0.001	0.026	0.004	35.55	1.03	1.02–1.04
Hepatitis C	0.001	0.273	0.083	10.88	1.31	1.12–1.55
Prior history of curative treatment	<0.001	0.622	0.109	32.63	1.86	1.51–2.31
Child-Pugh score +1	<0.001	0.354	0.052	45.80	1.43	1.29–1.58
Technical resectability (vs. R) MR	0.091	0.158	0.094	2.85	1.17	0.98–1.41
Oncological resectability (vs. R) BR1	<0.001	0.631	0.151	16.32	1.88	1.38–2.55
BR2	<0.001	1.417	0.161	77.29	4.12	3.01–5.65
AFP (+1 log ng/mL)	<0.001	0.186	0.038	23.93	1.20	1.12–1.30
DCP (+1 log mAu/mL)	<0.001	0.249	0.048	26.99	1.28	1.17–1.41
Era (vs. 1995–2008) 2009–2017	<0.001	−0.307	0.088	12.28	0.74	0.62–0.87
2018–2023	<0.001	−0.554	0.145	14.65	0.58	0.43–0.76

Multivariate Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($p > 0.1$) with survival adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 12 tested variables were as follows: age, gender, history of curative treatment for HCC, hepatitis B (y/n), hepatitis C (y/n), Child-Pugh score, technical resectability, oncological resectability, preoperative systemic therapy (y/n), alpha-fetoprotein (AFP) (logarithm), des-gamma-carboxy prothrombin (DCP) (logarithm), and year of treatment. SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval. ^aBased on likelihood test adjusted for the other factors in the final model. ^bEstimated coefficient for the variable and the associated standard error.

Results

Prognostication Ability of the Oncological Criteria for Resectability

The baseline characteristics of population 1 are summarized in Table 1. The tumor stage distribution according to the BCLC staging system [17] was as follows: stage 0, 593 patients (32.6%); stage A, 1,077 (59.1%) patients; stage B, 82 (4.5%) patients; stage C, 70 (3.8%) patients. In regard to classification according to the oncological criteria for resectability, 1,674 (91.9%) patients were categorized as R (oncological), 83 (4.6%) as BR1, and 65 (3.6%) as BR2. With regard to classification according to the technical criteria for resectability, 1,355 (74.4%) patients were categorized as R (technical), and the remaining 467 (25.6%) patients were classified as MR. There were no patients in the study populations who were classified as UR.

Over a median follow-up period of 97.2 months (range, 1–327 months), the 1-year, 3-year, and 5-year OS rates of Population 1 were 94.0%, 81.3%, and 71.0%, respectively, and the 1-year, 3-year, and 5-year RFS

rates were 73.4%, 48.6%, and 38.1%, respectively. Multivariate analysis confirmed that the classification based on the oncological criteria for resectability was significantly correlated with the OS (BR1: hazard ratio [HR], 1.88; 95% CI, 1.38–2.55; BR2: HR, 4.12; 95% CI, 3.01–5.65), while the classification based on the technical criteria for resectability showed a marginal correlation with the OS (MR: HR, 1.17; 95% CI, 0.98–1.41) (Table 2). A similar analysis for RFS indicated that both the classifications based on the oncological criteria (BR1: HR, 1.86; 95% CI, 1.44–2.41; BR2: HR, 3.62; 95% CI, 2.71–4.82) and technical criteria (MR: HR, 1.25; 95% CI, 1.08–1.46) were significantly correlated with the RFS (Table 3). Adjusted curves for the OS and RFS clarified that the oncological criteria for resectability allowed reliable stratification of the prognosis of patients who underwent surgery for HCC (Fig. 1). Each item constituting the oncological criteria for resectability of HCC (i.e., size/number, extent of vascular invasion, and presence of extrahepatic spread) showed independent correlation with the OS in a similar way (online suppl. Fig. 1).

Table 3. Predictive factors for RFS in population 1

	<i>p</i> value ^a	Coefficient ^b	SE	Wald χ^2	HR	95% CI
Age	<0.001	0.012	0.003	12.98	1.01	1.01–1.02
Male	0.003	0.221	0.075	8.66	1.25	1.08–1.44
Hepatitis C	0.001	0.213	0.066	10.41	1.24	1.09–1.41
Prior history of curative treatment	<0.001	0.602	0.085	49.79	1.83	1.54–2.16
Child-Pugh score +1	<0.001	0.235	0.044	28.28	1.27	1.16–1.38
Technical resectability (vs. R)						
MR	0.004	0.224	0.077	8.45	1.25	1.08–1.46
Oncological resectability (vs. R)						
BR1	<0.001	0.621	0.131	22.62	1.86	1.44–2.41
BR2	<0.001	1.285	0.147	76.53	3.62	2.71–4.82
AFP (+1 log ng/mL)	<0.001	0.196	0.032	38.05	1.22	1.14–1.29
DCP (+1 log mAu/mL)	<0.001	0.176	0.040	18.95	1.19	1.10–1.29
Era (vs. 1995–2008)						
2009–2017	0.004	−0.202	0.070	8.34	0.82	0.71–0.94
2018–2023	<0.001	−0.684	0.102	45.19	0.51	0.41–0.62

Multivariate Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($p > 0.1$) with survival adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 12 tested variables were as follows: age, gender, history of curative treatment for HCC, hepatitis B (y/n), hepatitis C (y/n), Child-Pugh score, technical resectability, oncological resectability, preoperative systemic therapy (y/n), alpha-fetoprotein (AFP) (logarithm), des-gamma-carboxy prothrombin (DCP) (logarithm), and year of treatment. SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval. ^aBased on likelihood test adjusted for the other factors in the final model. ^bEstimated coefficient for the variable and the associated standard error.

Clinical Utility of the Novel Oncological Criteria for Resectability in the Management of Advanced Disease

Then, clinical utility of the novel oncological criteria for resectability was tested using the 107 patients who had received lenvatinib for the treatment advanced HCC that was determined at diagnosis as being unsuitable for surgery. The baseline characteristics of this population are presented in online supplementary Table 3. Based on the technical criteria for resectability, this population was classified at the baseline as follows: R (technical), 10 (9.3%) patients; MR, 13 (12.2%) patients; UR, 84 (78.5%) patients. Similarly, they were classified according to the oncological criteria for resectability as follows: R (oncological), 1 (0.9%) patient; BR1, 35 (32.7%) patients; BR2, 71 (66.4%) patients. Given that most patients were classified as BR1 or BR2 before the start of lenvatinib therapy, further analyses were performed focusing on the 106 patients who were initially categorized as BR1 or BR2.

Over a median duration of lenvatinib therapy of 5.6 months (range, 1–34.9 months), the objective re-

sponse rates in the patients with BR1 disease versus BR2 disease were 45.7% (16/35) versus 33.8% (24/71) ($p = 0.234$) according to the RECIST 1.1, and 65.7% (23/35) versus 64.8% (46/71) ($p = 0.925$) according to the modified RECIST. Additional interventions could be employed in 23 (65.7%) patients of the BR1 group (surgery, 7; transarterial chemoembolization [TACE], 20; and TACE + radiotherapy, 1) and 30 (42.3%) patients of the BR2 group (surgery, 9; TACE, 13; hepatic arterial infusion chemotherapy, 1; bronchial arterial infusion chemotherapy, 6; and radiotherapy, 6), respectively ($p = 0.023$). R0 resection (i.e., conversion surgery) was achieved in 6 (17.1%) patients of the BR1 group and 3 (4.2%) patients of the BR2 group ($p = 0.056$).

Multivariate analysis confirmed a significant correlation between BR2 (classification according to the oncological criteria for resectability) and the OS (HR, 1.96; 95% CI, 1.13–3.38 [vs. BR1]) and TTF (HR, 1.81; 95% CI, 1.04–3.17 [vs. BR1]) (Table 4). Adjusted survival curves confirmed that classification according to the oncological criteria for resectability was useful to predict both the OS

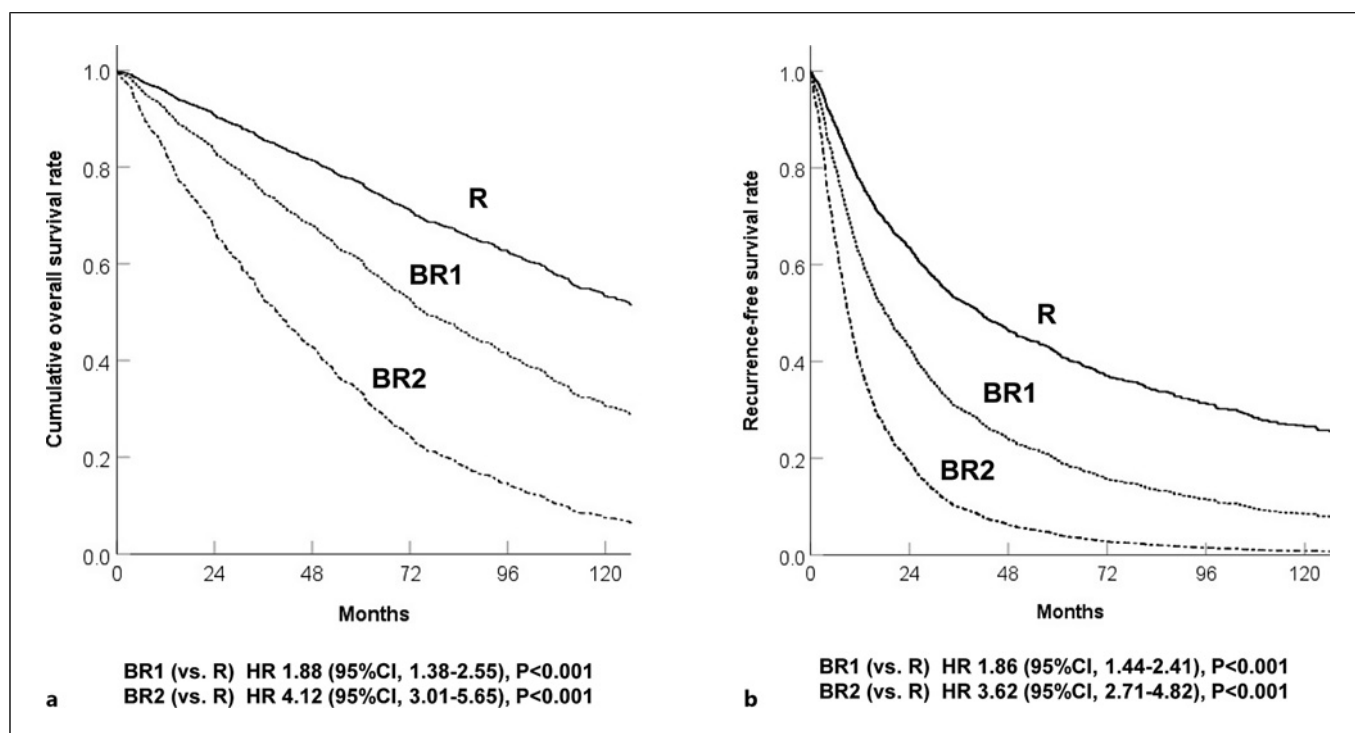


Fig. 1. Adjust Kaplan-Meier curves stratified by the oncological criteria for resectability of HCC in population 1. **a** OS. **b** RFS.

and TTF in patients receiving lenvatinib treatment for advanced HCC found to be unsuitable for surgery at diagnosis (Fig. 2).

Discussion

This study was conducted in surgical and medical populations with HCC to investigate the prognosticating ability of the novel oncological criteria for resectability of HCC proposed by the JLCA and JSHPBS in 2023. After adjustments for potential confounders, the resectability classification based on the oncological resectability criteria was significantly correlated with the OS and RFS in the surgical population in which curative resection for HCC had been achieved; furthermore, it was also predictive of the OS and TTF in the medical population with unresectable disease that had initially received treatment with lenvatinib. The rate of successful additional intervention was significantly higher in patients with BR1 disease as compared with that in cases with BR2 disease, and that of curative-intent conversion surgery was also higher in cases with BR1 disease.

Conventionally, in Western countries, surgical resection is contraindicated for cases with macroscopic vascular

invasion or extrahepatic spread of HCC, while aggressive surgical approaches for such cases have been used exclusively in Asian countries, including Japan. Although the survival outcomes of patients with advanced HCC are generally inferior to those of patients with early-stage HCC, according to data from a nationwide follow-up survey of patients with primary liver cancer in Japan, there is actually a “gradation” in the clinical outcomes according to the maximum size of the tumors, number of tumors [10, 18], and the extent of vascular invasion [8, 9, 18]. Furthermore, it is empirically known that selected patients with extrahepatic disease may enjoy survival benefit from surgery [11–13]. A recent study that examined the efficacy of surgery for HCC patients with multiple tumors reported that surgical resection may offer greater survival benefit as compared with other treatment modalities in selected populations [10]. As such, it is incorrect to regard every patient with advanced HCC as having systemic disease and conclude that surgery would not be effective for cases with advanced disease. Meanwhile, it is also difficult to define criteria for surgical resection based on the existing data, because the available evidence is limited. Therefore, the JLCA and JSHPBS proposed the present novel oncological criteria for resectability of HCC in 2023 based on a consensus of expert hepatobiliary surgeons.

Table 4. Predictive factors for OS in population 2

	<i>p</i> value ^a	Coefficient ^b	SE	Wald χ^2	HR	95% CI
OS						
Child-Pugh score +1	<0.001	0.796	0.140	32.53	2.22	1.69–2.92
Technical resectability (vs. R)						
MR	0.829	−0.113	0.526	0.05	0.89	0.32–2.50
UR	0.057	0.859	0.451	3.63	2.36	0.98–5.71
Oncological resectability (vs. BR1)						
BR2	0.016	0.671	0.279	5.80	1.96	1.13–3.38
mRECIST (vs. PD)						
SD	<0.001	−1.828	0.388	22.20	0.16	0.08–0.34
PR or CR	<0.001	−1.300	0.295	19.38	0.27	0.15–0.49
Successful additional intervention	0.036	−0.478	0.228	4.38	0.62	0.40–0.97
TTF						
Child-Pugh score +1	<0.001	0.791	0.132	36.15	2.21	1.70–2.85
Technical resectability (vs. R)						
MR	0.871	0.091	0.558	0.03	1.10	0.37–3.27
UR	0.013	1.199	0.485	6.11	3.32	1.28–8.59
Oncological resectability (vs. BR1)						
BR2	0.038	0.594	0.286	4.32	1.81	1.04–3.17
mRECIST (vs. PD)						
SD	<0.001	−1.973	0.398	24.56	0.14	0.06–0.30
PR or CR	<0.001	−1.482	0.300	24.48	0.23	0.13–0.41
Successful additional intervention	0.079	−0.405	0.231	3.08	0.67	0.42–1.05

Multivariate Cox regression was applied with a stepwise backward selection. Initially, all the potential confounders that showed marginal statistical correlation ($p < 0.2$) in univariate analysis were included in the model. Then factors that showed no or limited statistically significant association ($p > 0.1$) with each prognostic indicator adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 8 factors tested were as follows: Child-Pugh score, CONUT undernutrition grade, technical resectability (R vs. MR vs. UR), oncological resectability (BR1 vs. BR2), serum AFP level, plasma DCP level, best response (mRECIST) (CR/PR vs. SD vs. PD), and additional intervention after treatment with lenvatinib. SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval; AFP, alpha fetoprotein; DCP, des-gamma carboxy prothrombin. ^aBased on likelihood test adjusted for the other factors in the final model. ^bEstimated coefficient for the variable and the associated standard error.

As shown by our results, the novel oncological criteria for resectability show acceptable prognosticating ability in both surgical and medical populations of patients with HCC. It is noteworthy that they could also predict the probability for successful additional interventions after lenvatinib therapy, which is one of the independent predictors of survival (Table 4). Given that the tumor load and extent of cancer spread are higher in BR2 cases than in BR1 cases, it is easy to conceive that the potential choice of other treatments and the prognosis can differ between BR1 and BR2 cases. However, one of the noteworthy results of this study was that there is actually a gradation of the oncological features among patients with “so-called” advanced disease in the BCLC staging system which is considered as a contraindication for surgery.

In fact, our analysis of the surgical population confirmed that the estimated 5-year OS was as high as 60% in patients with BR1 (Fig. 1a), even though the estimated tumor recurrence rate at 5 years was nearly 80% (Fig. 1b).

From a practical standpoint, it should be acknowledged that the RFS is not linearly correlated with the OS in patients with HCC because additional treatments for recurrent disease can prolong the survival, and the time-to-interventional failure could be a surrogate measure of the OS [15]. Indeed, the concept of cure is difficult to expect in patients with HCC because the carcinogenic potential of the underlying liver disease persists even after curative treatment by surgery or ablation. Since the prognosis after tumor recurrence is more strongly influenced by both the

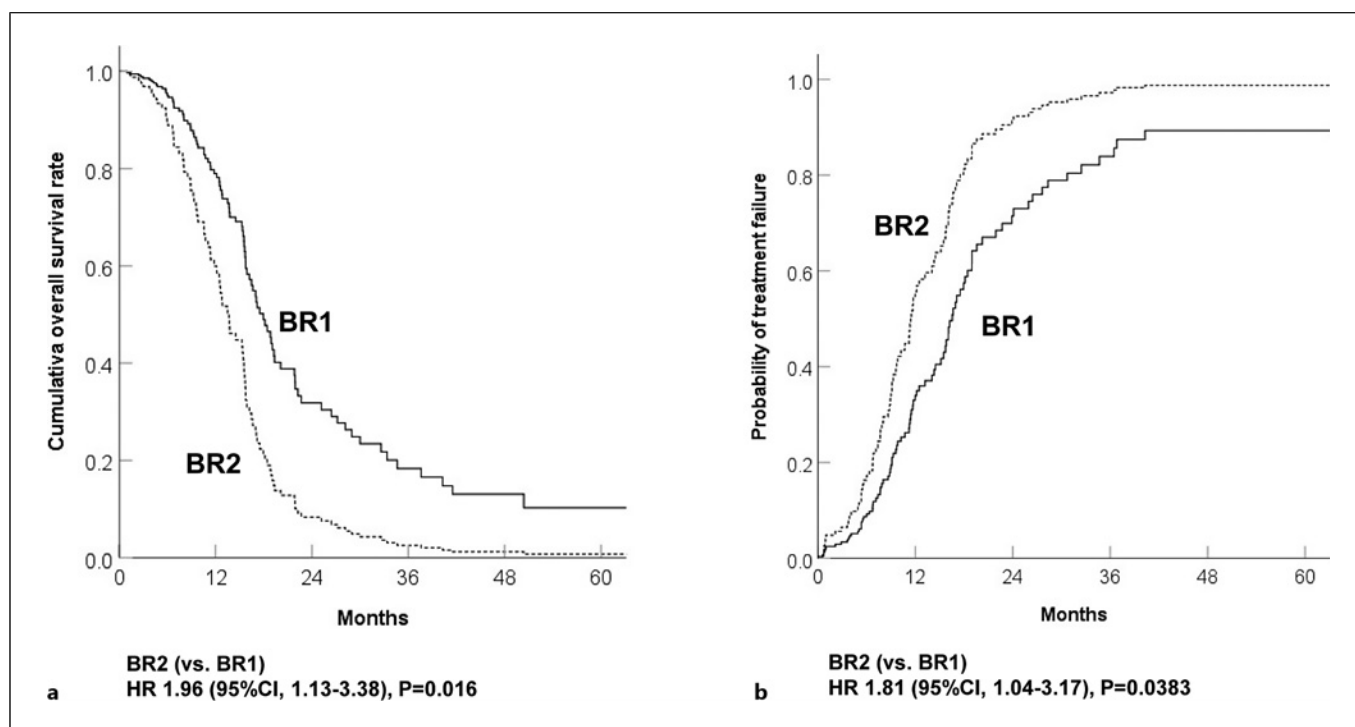


Fig. 2. Adjust Kaplan-Meier curves stratified by the oncological criteria for resectability of HCC in population 2. **a** OS. **b** TTF.

pattern of recurrence and the disease-free interval from the previous surgery than by the tumor stage at the previous surgery [19], the efficacy of surgery for advanced HCC should be discussed in the context of multidisciplinary treatment, and it may not be reasonable to determine the efficacy of surgery by the RFS alone. In fact, a multivariate analysis considering time-dependent factors clarified that individual subsequent interventions for disease relapse have positive impact on the OS even in patients with advanced HCC [7]. Accordingly, the potential efficacy of surgical intervention for HCC should be sought based on the OS, and the present results may shed light on the possibility of expansion of the surgical indications as part of a multidisciplinary approach for the treatment of advanced HCC in the era of effective systemic therapies.

The limitations of the present study were that it was a retrospective study based on data from a single institution. However, given that aggressive surgical approaches for advanced HCC have been attempted in only a limited number of institutions so far and only limited evidence is available on this subject, and that treatment policies for advanced HCC differ considerably among institutions according to individual expertise, it would be difficult to conduct a detailed analysis in multicenter settings. It is noteworthy that the present analysis confirmed the

clinical relevance of the novel oncological criteria for resectability as follows: (1) the oncological resectability classification was correlated with the survival outcomes in both surgical and medical populations of patients with HCC, independent of the technical criteria for resectability, and (2) the classification could also predict the potential for additional interventions, including conversion surgery for patients with advanced disease. These results suggest that the present criteria can be used as universal criteria for discussing novel treatment strategies for patients with advanced HCC and for clinical trials.

In conclusion, the novel oncological criteria for resectability of HCC show acceptable clinical relevance in real-world practice in the setting of aggressive treatment for HCC. The present results warrant a future multicenter study and a study using a population-based dataset to confirm the generalizability of the new criteria in order to expand curative-intent approaches for patients with advanced HCC.

Statement of Ethics

This study was carried out in accordance with the principles of the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan, with the approval of the Institutional Review Board

at Toranomon Hospital (No. 1919 and No. 1438-H/B). Written consent was exempted by the Institutional Review Board at Toranomon Hospital due to retrospective nature of chart review.

Conflict of Interest Statement

Junichi Shindoh and Yusuke Kawamura receive honoraria from Eisai Pharmaceutical Co., Ltd.

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Author Contributions

Study conception and data analysis: J.S. Acquisition of data: J.S., Y.K., M.M., S.O., N.A., Y.S., and M.H. Interpretation of data: J.S., K.A., M.T., and N.K. Drafting manuscript: all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available without approval of the Institutional Review Board. Further inquiries can be directed to the corresponding author.

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