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Borderline Resectable Classification Identifies Candidates for Conversion Therapy in Unresectable Hepatocellular Carcinoma Treated With Atezolizumab and Bevacizumab

Yasuto Takeuchi[1] | Masahiko Sue[1] | Nozomi Miyake[1] | Takuya Adachi[1] | Hideki Onishi[1] | Miwa Kawanaka[1] | Akinobu Takaki[1] | Kazuhiro Nouso[2] | Kazuya Kariyama[2] | Shinichiro Nakamura[3] | Emi Tanaka[3] | Toshifumi Tada[4] | Tetsuya Yasunaka[5] | Kenji Kuwaki[6] | Junichi Toshimori[7] | Shota Iwado[8] | Akio Moriya[9] | Hiroaki Hagihara[10] | Hiroyuki Takabatake[11] | Masahiro Sakata[12] | Motoyuki Otsuka[1]

[1]Department of Gastroenterology, Okayama University Hospital, Okayama, Japan | [2]Department of Gastroenterology, Okayama City Hospital, Okayama, Japan | [3]Department of Gastroenterology, Japanese Red Cross Himeji Hospital, Himeji, Japan | [4]Department of Gastroenterology, Kobe University Hospital, Kobe, Japan | [5]Department of Gastroenterology, Fukuyama City Hospital, Fukuyama, Japan | [6]Department of Gastroenterology, Okayama Saiseikai General Hospital, Okayama, Japan | [7]Department of Gastroenterology, Japanese Red Cross Okayama Hospital, Okayama, Japan | [8]Department of Gastroenterology, Hiroshima City Hospital, Hiroshima, Japan | [9]Department of Gastroenterology, Mitoyo General Hospital, Kanonji, Japan | [10]Department of Gastroenterology, Sumitomo Besshi Hospital, Niihama, Japan | [11]Department of Gastroenterology, Kurashiki Central Hospital, Kurashiki, Japan | [12]Department of Gastroenterology, Fukuyama Medical Center, Fukuyama, Japan

Correspondence: Yasuto Takeuchi (pwqs6abz@s.okayama-u.ac.jp)

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ABSTRACT

Background: Conversion therapy, which seeks to achieve curative treatment following systemic therapy, is increasingly acknowledged in the management of unresectable hepatocellular carcinoma (HCC). However, validated criteria for predicting eligibility for conversion remain unclear. We investigated the utility of the recently proposed borderline resectable (BR) classification combined with the barcelona clinic liver cancer (BCLC) staging system to identify patients most likely to benefit from conversion following atezolizumab plus bevacizumab (ATZ/BEV) therapy.

Methods: In this multicenter retrospective study, 532 patients with unresectable HCC treated with ATZ/BEV were categorized using the BR classification and stratified according to the BCLC stage. We evaluated objective response rate (ORR), conversion rate, and overall survival (OS) and carried out multivariate logistic regression analysis to identify predictors of conversion.

Results: Conversion therapy was performed in 5.9% of patients. Among those with BCLC-C HCC, the conversion rate was significantly higher in BR1 HCC than in BR2 HCC (15.2% vs. 2.0% and $p < 0.01$), and BR1 status was independently associated with conversion (odds ratio 7.0). Patients with BCLC-C/BR1 staging showed the highest ORR (45.0%) and favorable OS after conversion ($p = 0.015$). In contrast, the BR classification had limited predictive value in patients with BCLC-B HCC. Notably, downstaging from BR1 to resectable status was more common than from BR2, suggesting higher conversion feasibility.

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin–reactive AFP isoform; ALBI, albumin–bilirubin; ATZ/BEV, atezolizumab plus bevacizumab; BCLC, barcelona clinical liver cancer; BMI, body mass index; BR, borderline resectable; CI, confidence interval; CR, complete response; DCP, des-gamma carboxyprothrombin; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.

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Conclusions: Integrating BR classification with BCLC staging identified BCLC-C/BR1 patients as optimal candidates for conversion therapy after ATZ/BEV treatment. These findings support incorporating anatomical and oncological criteria into systemic strategies to enable curative interventions in advanced HCC.

1 | Introduction

Hepatocellular carcinoma (HCC) frequently presents at an advanced stage, limiting curative treatment options such as surgical resection or ablation. In such cases, systemic therapy remains the mainstay of the treatment. Recently, immune checkpoint inhibitor (ICI)–based regimens, particularly a combination of atezolizumab and bevacizumab (ATZ/BEV), have significantly improved clinical outcomes and have become the standard first-line therapy for unresectable HCC [1–3].

Conversion therapy is an emerging concept in the management of advanced HCC, which aims to achieve curative outcomes in patients who demonstrate a substantial tumor response to systemic therapy. Several studies have reported that ATZ/BEV can induce sufficient tumor shrinkage to allow for surgical or local interventions, leading to improved long-term outcomes [4–8]. However, identifying appropriate candidates for conversion therapy remains a major clinical challenge, and validated predictive criteria are lacking.

In this context, the concept of the borderline resectable (BR) classification, originally developed for pancreatic cancer, was recently adapted for HCC [9, 10]. The BR classification stratifies patients based on tumor burden, vascular invasion, and extent of extrahepatic disease, potentially offering a framework for assessing the feasibility of curative interventions. Although recent studies have suggested the usefulness of the BR criteria in predicting conversion potential, their clinical applicability across different stages of HCC, particularly in relation to the barcelona clinic liver cancer (BCLC) staging system, has not been fully investigated.

Importantly, the BCLC staging system remains the most widely used framework for therapeutic decision-making in HCC, incorporating tumor burden, liver function, and performance status. Integrating the BR classification with BCLC staging may allow for a more refined stratification of patients for whom systemic therapy may serve as a bridge to curative treatment. In particular, it remains unclear whether the predictive value of the BR classification differs between intermediate (BCLC-B) and advanced (BCLC-C) stages, where tumor biology and treatment goals diverge substantially.

Therefore, this multicenter retrospective study aimed to evaluate the clinical utility of the BR classification, alone and in combination with BCLC staging, for predicting the eligibility of patients with unresectable HCC treated with ATZ/BEV. We sought to identify subgroups with the highest likelihood of curative conversion and survival benefits, thereby contributing to individualized treatment strategies for advanced HCC.

2 | Patients and Methods

2.1 | Study Design

This multicenter retrospective study was conducted in Japan. The study was approved by a central ethics' committee (approval code: 2012–017), and local institutional review boards at all participating sites granted approval in accordance with a common protocol.

2.2 | Patients

This study was conducted at 11 hospitals across five prefectures in western Japan. We enrolled patients with histologically or clinically confirmed HCC who received ATZ/BEV therapy between October 2020 and August 2024. The inclusion criteria were as follows: (1) Child–Pugh class A, (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, (3) HCC stage other than D according to the BCLC system, and (4) complete evaluation of clinical data and treatment efficacy (Figure S1).

2.3 | Data Collection

Information about the study was disclosed on each hospital's website, allowing patients the opportunity to refuse participation. Study data were collected from the medical records at each institution and included patient age, sex, PS, body mass index (BMI), clinical characteristics (etiology, complications, HCC staging, BR criteria, liver function, and serum biomarkers), and clinical course (therapeutic effects and prognosis). Missing values were defined as data recorded as blank, not applicable, or outliers. To exclude values likely due to data entry errors, outliers were defined as values falling below the 1st percentile or above the 99th percentile for each variable.

2.4 | Treatment Protocol

The patient received 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab, administered intravenously once every 3 weeks. Treatment was discontinued at the physician's discretion in the following situations: disease progression, deterioration of PS to 2 or higher, unacceptable toxicity, achievement of a complete response (CR), or transfer to best supportive care. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [11].

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2.5 | Treatment Efficacy Assessment and Follow-Up

Initial tumor response was assessed using contrast-enhanced computed tomography or magnetic resonance imaging every 9–12 weeks during the screening period. Responses were evaluated according to RECIST v1.1 [12] and classified as CR, partial response (PR), stable disease (SD), or progressive disease (PD). Tumor markers, such as alpha-fetoprotein (AFP), lens culinaris agglutinin–reactive AFP isoform (AFP-L3), and des-gamma carboxyprothrombin (DCP), were measured at the baseline and every 9–12 weeks after treatment initiation.

2.6 | Conversion Therapy

In this study, we defined conversion therapy as additional therapies after an objective assessment of the tumor response to systemic therapy was graded as PR. Surgical resection and ablation therapy were included. Treatment response was assessed at regular imaging intervals, and conversion was considered when a partial response was first confirmed and maintained or when disease progression was detected after an initial response. The method of conversion therapy for achieving a cancer-free and off-therapy status for each patient was determined through discussions among hepatologists, radiologists, and surgeons, in accordance with the Japanese clinical practice guidelines for HCC [13]. Surgical resection was considered when intrahepatic disease was confined to a lobe or anatomical segment and sufficient future liver remnant volume and liver function were anticipated or when intrahepatic lesions had resolved and curative resection of remaining extrahepatic disease was deemed feasible. Radio frequency ablation was considered when both vascular invasion and extrahepatic spread were absent and when the residual lesion burden met standard ablative criteria ($\leq$ 3 cm and $\leq$ 3 nodules). These criteria were applied uniformly across participating centers. Importantly, cases in which patients achieved a complete response (CR) according to RECIST criteria and subsequently underwent resection for concerns about residual tumor risk were not regarded as conversion therapy and were excluded from the analysis.

2.7 | BR Criteria for HCC

The BR classification was based on the criteria established in the 2023 Expert Consensus Statement of the Japanese Society of Hepatology and the Japanese Society of Hepato-Biliary-Pancreatic Surgery [10]. The classification criteria are as follows: R: (i) solitary lesion (no size limit) or multiple lesions in up to three nodules of $\leq$ 3 cm each, (ii) no macrovascular invasion detected on imaging (Vp0-1, Vv0-1, or B0-1), and (iii) no extrahepatic disease. BR1: (i) multiple lesions exceeding the criteria of R but no more than five nodules with a maximum diameter of 5 cm, (ii) macrovascular invasion (Vp2-3, Vv2, or B2-3), and (iii) localized extrahepatic disease (e.g., solitary nodal involvement at lymph nodes 3, 8, or 12; localized peritoneal dissemination (P1); unilateral adrenal metastasis; or oligometastasis to the lung). BR2: (i) multiple lesions with more than five nodules of > 5 cm in diameter, (ii) major vascular invasion (Vp4, Vv3, or B4), and (iii) extrahepatic disease not meeting the localization criteria of BR1.

2.8 | Statistical Analyses

All eligible patients registered in this study were included in the analysis. The results of the analyses of patient age, sex, BMI, baseline clinical characteristics, and tumor status were reported as aggregate data. Data are expressed as medians with interquartile ranges (25th–75th percentiles). Continuous variables were compared using one-way analysis of variance with Scheffé's post hoc test, and categorical variables were compared between groups using the χ^2 test or Fisher's exact test. Given that conversion therapy was implemented at varying time points during follow-up, we conducted a landmark analysis to reduce potential immortal time and treatment selection bias. Overall survival (OS) was redefined from a landmark time of 90 days after the initiation of systemic chemotherapy, and only patients who were alive at the landmark were included. Patients were classified according to conversion status determined up to the landmark time, and survival outcomes beyond the landmark were compared using Kaplan–Meier methods and the log-rank test. Univariate and multivariate analyses were carried out to identify factors associated with the implementation of conversion therapy. Variables with a p-value < 0.10 in the univariate analysis were entered into the multivariate model. Both categorical (nominal) and continuous variables were included as covariates. Multivariate analysis was conducted using a logistic regression model. Continuous variables were entered into the multivariate logistic regression model after appropriate scaling or transformation to facilitate interpretation. Specifically, age was analyzed per 10-year increase, BMI per 5-unit increase, ALBI score per 0.3-point increase, AFP as log-transformed values per 1-log increase, AFP-L3 per 10% increase, and DCP as log-transformed values per 1-log increase. Statistical analyses were carried out using JMP software (version 18.0; SAS Institute Japan Ltd., Tokyo, Japan). All tests were two-sided, and p-values < 0.05 were considered statistically significant.

3 | Results

3.1 | Patient Characteristics

A total of 532 patients with unresectable HCC who received ATZ/BEV therapy were included in this study. The median patient age was 74 years, and 79.7% of the patients were male. Most patients had preserved liver function (Child–Pugh A in 100%) and good PS (ECOG PS 0 in 78.7%). The BCLC stage distributions were as follows: stage A (8.3%), B (43.0%), and C (48.7%). According to the BR classification, 8.5% of patients were classified as R, 21.7% as BR1, and 69.8% as BR2 (Table 1).

To account for this, patients with BCLC-A or BR R disease who received systemic therapy for clinical reasons other than guideline-based recommendations were excluded from the subsequent sensitivity analyses. A comparison between patients with BCLC-B and BCLC-C HCC revealed that those with

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TABLE 1 | Patient characteristics.

	All patients (n = 532)
Age, years	74 (68–80)
Sex	
Male, n (%)	419 (79.7)
Female, n (%)	107 (20.3)
ECOG PS	
0, n (%)	414 (78.7)
1, n (%)	94 (17.9)
2, n (%)	19 (3.4)
BMI (kg/m^2)	22.9 (20.8–25.5)
Etiology	
HBV, n (%)	84 (16.0)
HCV, n (%)	149 (28.3)
Nonviral, n (%)	293 (55.7)
Child–Pugh score	
5, n (%)	325 (61.8)
6, n (%)	201 (38.2)
ALBI score	−2.19 (−2.47 to −1.88)
Maximal tumor size (cm)	3.5 (2.0–7.0)
Number of nodules	
Single, n (%)	71 (13.5)
2–3, n (%)	120 (22.8)
> 3, n (%)	256 (48.1)
Macrovascular invasion, n (%)	67 (12.7)
Extrahepatic spread, n (%)	158 (30.0)
BCLC stage	
A, n (%)	44 (8.3)
B, n (%)	226 (43.0)
C, n (%)	256 (48.7)
BR classification	
R, n (%)	45 (8.5)
BR1, n (%)	114 (21.7)
BR2, n (%)	367 (69.8)
AFP (ng/mL)	25 (5–439)
AFP-L3 (%)	13.3 (0.5–42.9)
DCP (mAU/mL)	292 (45–2805)
Treatment line	
1st, n (%)	419 (79.7)
Later, n (%)	107 (20.3)
Conversion rate (%)	31 (5.9)

Note: Data are presented as medians (interquartile ranges) or n (%) unless otherwise shown.
Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin–reactive alpha-fetoprotein isoform; ALBI, albumin–bilirubin; BCLC, barcelona clinic liver cancer; BMI, body mass index; BR, borderline resectable; DCP, des-gamma carboxyprothrombin; PS, performance status.

BCLC-C disease showed significantly larger tumors, more frequent macrovascular invasion and extrahepatic spread, and higher levels of tumor markers, including AFP, AFP-L3, and DCP. No significant difference in the overall conversion rate was observed between the two groups (Table 2).

3.2 | Therapeutic Efficacy of ATZ/BEV

The overall objective response rate (ORR) was 33.5%, and the disease control rate (DCR) was 68.3%. When stratified according to the BR classification and the BCLC stage (Supporting Information S2: Table S1), the ORR was higher in patients with BR1 HCC than in those with BR2 HCC in both the BCLC-B (40.0% vs. 35.0%) and BCLC-C (45.0% vs. 27.0%) subgroups. Notably, progressive disease was observed more frequently in patients with BR2 HCC than in those with BR1 disease (30.6% vs. 20.0% in BCLC-C).

3.3 | Conversion Therapy and Predictive Factors

In the BCLC-B and BCLC-C groups, conversion therapy was administered to 28 of 482 patients (5.9%). Resection was performed in 12 cases (42.9%) and ablation therapy in 16 cases (57.1%) (Table 2). Among resection cases, pathological CR was confirmed in 6 cases (50.0%). There was no significant difference in the conversion rates between BR1 and BR2 among patients with BCLC-B HCC (7.3% vs. 6.4% and $p = 0.83$), whereas a markedly higher conversion rate was observed in BR1 HCC than in BR2 HCC within the BCLC-C group (15.2% vs. 2.0% and $p < 0.01$) (Figure 1).

A detailed assessment of posttreatment classification changes in patients with BCLC-C HCC revealed that five of 60 patients with BR1 disease (8.3%) achieved a PR and were reclassified as R. Among them, conversion therapy was performed in nine patients, four after reclassification to R and five while remaining in BR1. In contrast, among the 196 patients initially classified as BR2, only three (1.5%) were downstaged to R and 12 (6.1%) to BR1. Of these, only four patients received conversion therapy: two in each subgroup (Figure 2). These findings suggest that patients with BCLC-C and BR1 HCC more frequently respond to treatment and are more likely to be downstaged to become eligible for curative treatment.

In the BCLC-B group, the recurrence rate after conversion therapy was 7/15 cases (46.7%), whereas in the BCLC-C group, it was 5/13 cases (38.5%). Details regarding recurrence rates by BR criteria and treatment methods are shown in Supporting Information S2: Table S2. Among the five patients with BCLC-C/BR1 disease who underwent surgical resection, three achieved a pathological complete response. Of the two patients without pathological complete response, one developed recurrence during follow-up, whereas no recurrence was observed in the pathological complete response cases (Supporting Information S2: Table S3). Among patients with extrahepatic disease without intrahepatic lesions, four of five patients

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TABLE 2 | Patient characteristics by BCLC stage.

	BCLC-B (n = 226)	BCLC-C (n = 256)	p-value
Age, years	75 (69–80)	74 (68–79)	0.15
Sex			
Male, n (%)	190 (84.1)	201 (78.5)	0.12
Female, n (%)	36 (15.9)	55 (21.5)	
ECOG PS			
0, n (%)	180 (79.7)	196 (76.6)	< 0.01
1, n (%)	46 (20.3)	42 (16.4)	
2, n (%)	0 (0.0)	18 (7.0)	
BMI (kg/m^2)	23.7 (21.5–26.1)	22.7 (20.6–25.0)	< 0.01
Etiology			
HBV, n (%)	31 (13.7)	47 (18.4)	< 0.01
HCV, n (%)	62 (27.4)	70 (27.3)	
Non-viral, n (%)	133 (58.9)	139 (54.3)	
Child–Pugh score			
5, n (%)	143 (63.3)	151 (59.0)	0.33
6, n (%)	83 (36.7)	105 (41.0)	
ALBI score	−2.19 (−2.54 to −1.88)	−2.15 (−2.44 to −1.85)	0.17
Maximal tumor size (cm)	2.9 (1.8–5.2)	5.1 (2.9–8.9)	< 0.01
Number of nodules			
Single, n (%)	0 (0.0)	59 (23.0)	< 0.01
2–3, n (%)	30 (13.3)	58 (22.7)	
4–9, n (%)	102 (45.1)	31 (12.1)	
≥ 10, n (%)	94 (41.6)	40 (15.6)	
Up to 7 criteria			
In, n (%)	40 (17.6)	79 (30.9)	< 0.01
Out, n (%)	186 (82.3)	109 (42.6)	
Macrovascular invasion, n (%)	0 (0.0)	67 (26.2)	< 0.01
Extrahepatic spread, n (%)	0 (0.0)	158 (61.7)	< 0.01
AFP (ng/mL)	18 (5–232)	48 (5–783)	0.026
AFP-L3 (%)	8.5 (0.5–28.7)	20.1 (0.5–60.1)	< 0.01
DCP (mAU/mL)	199 (45–1907)	458 (53–4433)	< 0.01
Treatment line			
1st, n (%)	186 (82.3)	198 (77.3)	0.18
Later, n (%)	40 (17.7)	58 (22.7)	
Conversion rate (%)	15 (6.6)	13 (5.1)	0.47
Conversion therapy			
Resection, n (%)	5 (33.3)	7 (53.8)	0.27
Ablation, n (%)	10 (66.7)	6 (46.2)	

Note: Data are presented as medians (interquartile ranges) or n (%) unless otherwise shown.
Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin–reactive alpha-fetoprotein isoform; ALBI, albumin–bilirubin; BCLC, barcelona clinic liver cancer; BMI, body mass index; BR, borderline resectable; DCP, des-gamma carboxyprothrombin; PS, performance status.

classified as BR1 underwent conversion therapy after achieving an objective response, whereas none of the nine patients classified as BR2 were able to receive conversion therapy despite achieving an objective response ($p < 0.01$).

Multivariate logistic regression identified distinct predictors of conversion therapy according to the BCLC stage. In patients with BCLC-B HCC, better liver function (ALBI scores < −2.26) was the sole independent predictor (odds ratio [OR] 8.4,

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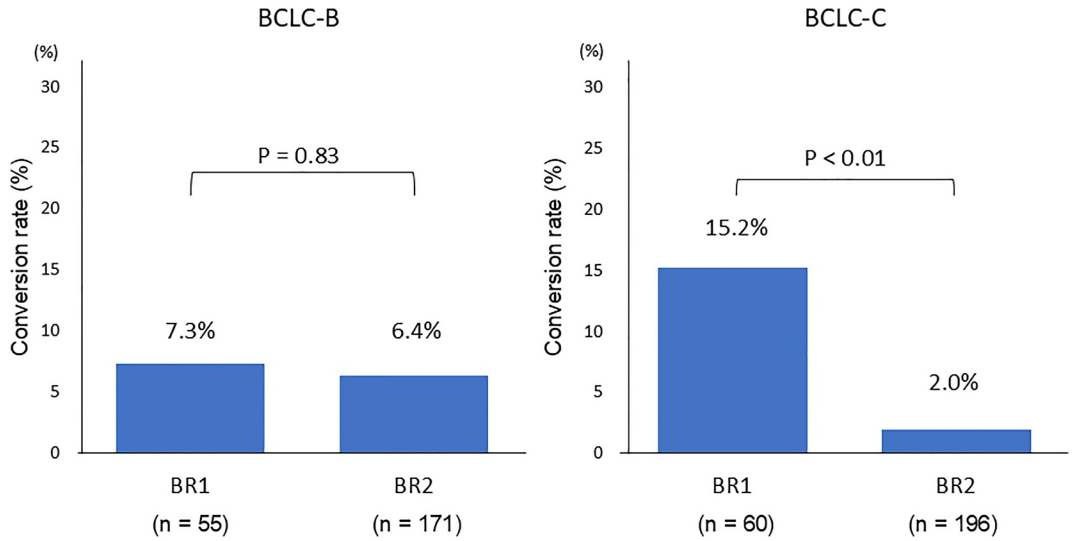


FIGURE 1 | Conversion rate according to BR classification in BCLC stage B and C status. Bar graph comparing conversion rates between patients with BR1 and BR2 HCC within each BCLC stage. In patients with the BCLC-B disease, no significant difference in conversion rates was observed between BR1 and BR2. In contrast, among patients with BCLC-C HCC, the conversion rate was significantly higher in BR1 than in BR2 ($p < 0.01$), showing that the BR classification may help identify candidates for conversion therapy, particularly in advanced-stage disease. BR, borderline resectable; BCLC, barcelona clinical liver cancer; HCC, hepatocellular carcinoma.

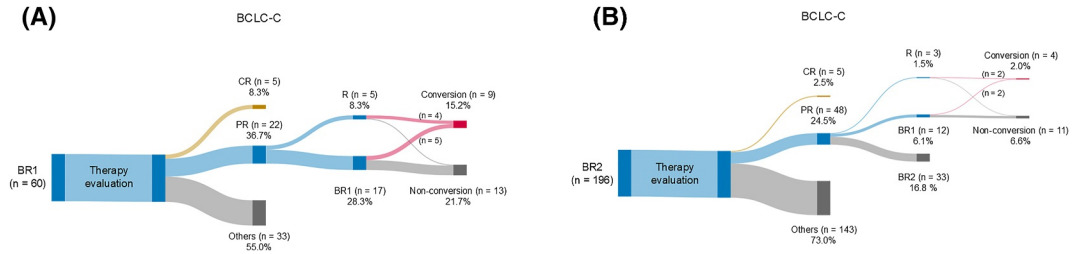


FIGURE 2 | Sankey diagrams illustrating treatment response and conversion therapy in patients with BCLC stage C HCC stratified by baseline BR classification. (A) Among 60 patients initially classified as having BR1 HCC, five (8.3%) were downstaged to resectable (R) following partial responses. Conversion therapy was performed in nine patients: four from the posttreatment R group and five who remained in the BR1 group. (B) Among 196 patients initially classified as having BR2 HCC, three (1.5%) were downstaged to R and 12 (6.1%) shifted to BR1 after treatment. Conversion therapy was performed in four patients: two from the posttreatment R group and two from the BR1 group. BR, borderline resectable; BCLC, barcelona clinical liver cancer; HCC, hepatocellular carcinoma.

$p < 0.01$). In contrast, in patients with BCLC-C HCC, BR1 classifications (OR 7.0 and $p < 0.01$) and lower AFP-L3 levels (< 50%) (OR 6.3 and $p < 0.01$) were independently associated with conversion (Tables 3 and 4). These results underscore the importance of both anatomical status and tumor biology in assessing the curative potential of advanced-stage HCC.

3.4 | Relationship Between Objective Response and the Conversion Rate According to the BCLC Stage and BR Classification

To further evaluate the relationship between tumor response and the feasibility of conversion therapy, we plotted the ORR against the conversion rate for each subgroup defined by the BCLC stage and BR classification (Figure 3). Among the four subgroups (BCLC-B/BR1, BCLC-B/BR2, BCLC-C/BR1, and BCLC-C/BR2), the BCLC-C/BR1 group showed the highest ORR (45.0%) and the conversion rate (15.2%). In contrast, the BCLC-C/BR2 group showed the lowest ORR (27.0%) and the lowest conversion rate (2.0%).

These findings highlight that patients with BCLC-C/BR1 HCC represent an optimal population for conversion therapy, characterized by both high response to systemic treatment and anatomical eligibility for curative intervention. On the contrary, in the BCLC-C BR1 subgroup, 13 patients achieved a partial response but were not converted to local therapy. The reasons included impaired liver function ($n = 1$), medical contraindications ($n = 11$), and patient preference ($n = 1$).

3.5 | Prognostic Impact of Conversion Therapy

Subsequently, we evaluated the prognostic significance of conversion therapy in patients who achieved a partial response to ATZ/BEV. In patients with BCLC-B HCC, no statistically significant differences in OS rates were observed between those

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TABLE 3 | Predictive factors for conversion therapy in BCLC-B hepatocellular carcinoma.

Variables	Category/ unit	Univariate analysis OR (95% CI), *p*-value	Multivariate analysis OR (95% CI), *p*-value
Age (year)	Continuous	1.6 (0.89–2.8), 0.084	1.6 (0.78–3.3), 0.18
Sex	Male	0.82 (0.12–3.1), 0.77	
ECOG PS	0	3.8 (0.71–70), 0.13	
BMI (kg/m^2)	Continuous	0.47 (0.23–0.95), 0.036	0.46 (0.20–1.03), 0.061
Etiology	Nonviral	1.7 (0.61–5.0), 0.33	
ALBI score	Continuous	1.7 (1.2–2.6), < 0.01	1.9 (1.3–2.9), < 0.01
BR category	1	1.1 (0.37–3.5), 0.83	
AFP (ng/mL)	Continuous	0.94 (0.78–1.2), 0.54	
AFP-L3 (%)	Continuous	0.81 (0.69–0.97), 0.025	0.80 (0.66–0.95), 0.015
DCP (mAU/mL)	Continuous	1.2 (0.96–1.6), 0.11	

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin–reactive alpha-fetoprotein isoform; ALBI, albumin–bilirubin; BMI, body mass index; BR, borderline resectable; CI, confidence interval; DCP, des-gamma carboxyprothrombin; OR, odds ratio; PS, performance status.

TABLE 4 | Predictive factors for conversion therapy in BCLC-C hepatocellular carcinoma.

Variables	Category/Unit	Univariate OR (95% CI), *p*-value	Multivariate OR (95% CI), *p*-value
Age (year)	Continuous	1.8 (1.1–3.0), 0.021	1.8 (0.99–3.2), 0.051
Sex	Male	0.7 (0.12–2.5), 0.57	
ECOG PS	0	1.7 (0.46–11), 0.46	
BMI (kg/m^2)	Continuous	0.50 (0.24–1.1), 0.074	0.66 (0.30–1.5), 0.30
Etiology	Nonviral	0.7 (0.2–2.3), 0.59	
ALBI score	Continuous	1.4 (0.91–2.1), 0.14	
BR category	1	8.5 (2.6–32), < 0.01	6.0 (1.7–24), < 0.01
AFP (ng/mL)	Continuous	1.0 (0.86–1.3), 0.83	
AFP-L3 (%)	Continuous	0.89 (0.75–1.1), 0.22	
DCP (mAU/mL)	Continuous	1.3 (1.0–1.7), 0.030	1.2 (0.90–1.6), 0.26

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin–reactive alpha-fetoprotein isoform; ALBI, albumin–bilirubin; BMI, body mass index; BR, borderline resectable; CI, confidence interval; DCP, des-gamma carboxyprothrombin; OR, odds ratio; PS, performance status.

who underwent conversion and those who did not, regardless of the BR classification (Figure 4A). Although longer survival was observed in the conversion groups, the difference was not statistically significant ($p = 0.21$).

In contrast, a pronounced survival benefit was observed among patients with BCLC-C HCC. Specifically, patients with BR1 HCC who underwent conversion therapy demonstrated significantly longer OS than their nonconversion counterparts ($p = 0.015$) (Figure 4B). No such benefit was evident among patients with BR2 HCC, regardless of conversion status.

These results suggest that conversion therapy may improve prognosis in carefully selected patients with BCLC-C/BR1 HCC who respond to systemic treatment, whereas its impact appears to be limited in other subgroups. In additional multivariable analyses, each component of the BR criteria (tumor number, maximum tumor diameter, vascular invasion stage, and extrahepatic spread) was separately included as an independent variable. None of these factors showed a statistically significant association with the feasibility of conversion therapy or overall survival (Supporting Information S2: Table S4).

4 | Discussion

In this multicenter retrospective study, we demonstrated that the BR classification, particularly when combined with BCLC staging, serves as a useful framework for predicting the feasibility of conversion therapy in patients with unresectable HCC treated with ATZ/BEV. Notably, patients with BCLC-C HCC classified as BR1 showed both a higher ORR and a greater likelihood of receiving curative treatment than those classified as BR2, suggesting that this subgroup represents an optimal target population for conversion therapy.

Conversion therapy is increasingly recognized as a strategy to improve long-term outcomes in unresectable HCC; however, appropriate candidate selection remains a major challenge.

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Although the BR classification was recently adapted from pancreatic cancer to stratify patients with HCC based on anatomical and oncological criteria, its integration with the functional stratification of the BCLC stage has not been fully explored. Our findings highlight that the BR classification provides particular value to BCLC-C staging, which is a heterogeneous group encompassing patients with an advanced tumor burden yet variable potential for downstaging.

Among patients with BCLC-C HCC, those classified as BR1 showed a conversion rate of 15.2%, which was significantly higher than the 2.0% observed in the BR2 group. BR1 status, along with an AFP-L3 level of < 50%, was independently associated with conversion in this cohort. These findings suggest that patients with BR1-BCLC-C HCC may retain sufficient oncological control and biological responsiveness to benefit from curative-intent treatment. In contrast, the BR classification had limited discriminatory value among patients with BCLC-B HCC, who typically lack macrovascular invasion or extrahepatic spread, which are the core components of the BR criteria, making further stratification less informative. This may be attributed to the fact that BCLC-B tumors are usually confined to the liver without major vascular involvement or distant metastases, resulting in a narrower anatomical spectrum. Consequently, the utility of the BR classification, which is designed to reflect variations in tumor invasiveness and extent, is reduced in this group. Therefore, the reason why OS tended to be lower in BR2 than BR1 after conversion therapy could not be clearly determined. One contributing factor is thought to be the higher recurrence rate and shorter recurrence-free survival observed in BR2 (results not shown). Conversion therapy is not a randomly assigned intervention and is inherently influenced by tumor response, patient condition, and other time-dependent clinical factors. While a landmark analysis was carried out to reduce immortal time bias, residual confounding due to treatment selection remains possible, and the observed association should not be interpreted as a definitive causal evidence of a survival benefit attributable solely to conversion therapy.

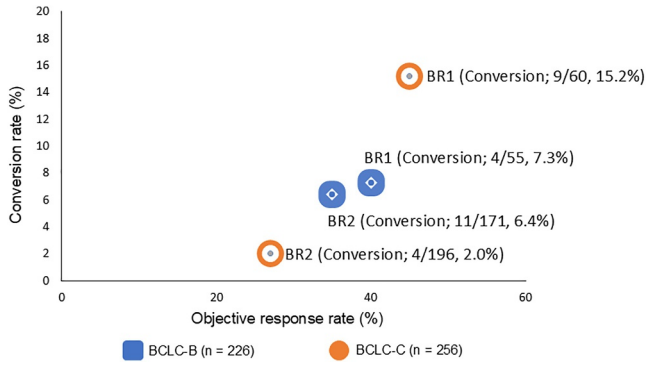


FIGURE 3 | Objective response rate and conversion rate according to the BCLC stage and BR classification. Scatter plot comparing objective response rates (ORRs) and conversion rates across four subgroups: BCLC-B/BR1, BCLC-B/BR2, BCLC-C/BR1, and BCLC-C/BR2. The BCLC-C/BR1 group demonstrated the highest values for both ORRs (45.0%) and conversion rates (15.2%), whereas the BCLC-C/BR2 group showed the lowest values in both metrics. This distribution highlights the differences in treatment responsiveness and curative potential among subgroups defined by both the BCLC and BR classifications. BR, borderline resectable; BCLC, barcelona clinical liver cancer; HCC, hepatocellular carcinoma.

These results align with and extend those of previous studies. Shimose et al. reported that patients with BR1 HCC showed higher rates of conversion after systemic therapy, although they did not stratify their findings according to the BCLC stage [14]. Our study contributes to the literature by demonstrating that the predictive value of the BR classification varies depending on the BCLC context, which could guide future clinical decision-making.

Importantly, the added value of the BR classification should be considered in the context of the internationally validated BCLC staging system. Several factors overlap between the two systems, such as tumor size, number of nodules, macrovascular invasion, and extrahepatic spread. However, the BR classification introduces distinctive criteria, including the "5 nodules or 5 cm" cutoffs, the more detailed grading of vascular invasion (Vp2–4, Vv2–3, and B2–4), and the definition of limited extrahepatic disease. In our cohort, these BR-specific components contributed to the stratification of outcomes, particularly among patients with BCLC-C HCC. Notably, patients with BR1 status, defined by these criteria, demonstrated a substantially higher likelihood of conversion and survival benefit than those with the BR2 disease, despite being within the same BCLC stage. These findings suggest that the BR classification provides additional

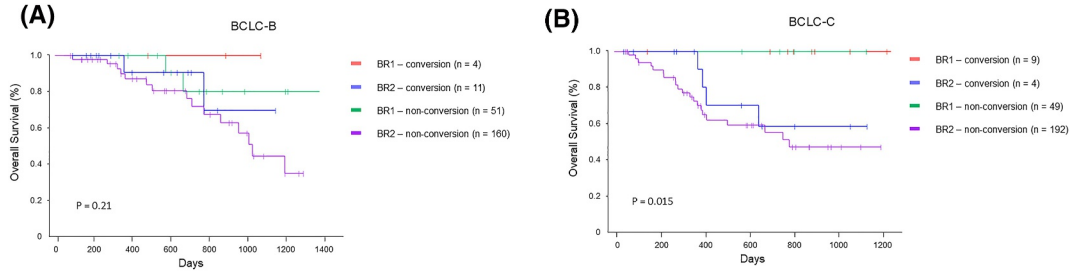


FIGURE 4 | Overall survival according to BR classification and conversion status in patients with BCLC-B and BCLC-C HCC. (A) Kaplan–Meier curves showing overall survival in patients with BCLC-B HCC, stratified into four groups: BR1 with conversion, BR1 without conversion, BR2 with conversion, and BR2 without conversion. No statistically significant differences in survival were observed among the groups ($p = 0.21$). (B) Kaplan–Meier analysis in patients with BCLC-C HCC revealed significantly longer survival in patients with the BR1 disease who underwent conversion therapy than those who did not ($p = 0.015$). No survival difference was observed among patients with the BR2 disease regardless of conversion status. BR, borderline resectable; BCLC, barcelona clinical liver cancer; HCC, hepatocellular carcinoma.

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prognostic granularity beyond BCLC by incorporating anatomical and oncological details that are not fully captured by the conventional staging system. When the individual components of the BR criteria (tumor number, maximum tumor diameter, vascular invasion grade, and extrahepatic spread) were separately included in the multivariate model, none reached statistical significance. This suggests that each factor alone may not sufficiently explain the feasibility of conversion therapy in BCLC-C HCC. Instead, the BR1 classification as a composite criterion appears to better capture the subset of patients in whom conversion therapy is feasible.

In our cohort, the unexpectedly high conversion rate observed in the BCLC-C/BR1 subgroup may be explained by their relatively favorable tumor biology and anatomical characteristics. Patients with the BR1 disease often achieved meaningful tumor shrinkage or improvement in vascular invasion and extrahepatic involvement after ATZ/BEV therapy, creating conditions that permitted curative-intent treatment. This finding suggests that even among patients achieving an objective response, the feasibility of conversion therapy is strongly influenced by baseline resectability and anatomical factors rather than by radiological response alone. This finding also underscores the heterogeneity within the BCLC-C disease, as the clinical implications differ depending on whether the classification is driven by vascular invasion or extrahepatic spread. The BR1 disease, defined by limited and potentially reversible tumor extent, therefore, represents a subset within BCLC-C in which conversion therapy remains feasible when a robust treatment response is achieved.

Clinically, these findings support the use of the BR classification to refine treatment strategies for advanced HCC. For patients with BCLC-C/BR1 status, initiating ATZ/BEV therapy with the intent of curative conversion represents a viable approach. The higher frequency of downstaging from BR1 to R further supports its role as a biologically and anatomically favorable subset. Nevertheless, the overall conversion rate remained modest (5.9%), reflecting real-world challenges. Not all patients with a PR proceeded to conversion therapy, likely owing to technical limitations, comorbidities, or patient preferences. It is considered unlikely that BCLC-B and BCLC-C cases can be cured with radical treatment. Consequently, even when the tumor number or tumor volume reduction is achieved, they frequently fail to meet the criteria for resection or ablation therapy from the perspective of tumor factors. In future studies, it will be essential to systematically capture the reasons for not pursuing conversion to identify potentially modifiable barriers and improve the real-world feasibility of curative strategies.

This study had several limitations. The retrospective design introduces potential selection bias and institutional variability in the indications for conversion therapy. Our analysis was limited to patients receiving ATZ/BEV, and the generalizability of these findings to other treatment regimens remains to be established. Additionally, liver functional reserve, remnant liver volume, and technical resectability have not been formally assessed. Ultimately, we did not examine post-conversion recurrence or quality of life, which are critical factors in evaluating the true value of conversion.

In conclusion, the BR classification provides a practical, anatomy-based complement to BCLC staging for identifying candidates for curative conversion in unresectable HCC. Patients with BCLC-C/BR1 status represent a key subgroup characterized by high treatment responsiveness and conversion feasibility, for whom systemic therapy should be planned with curative intent. Future prospective studies incorporating surgical, biological, and patient-related factors are needed to further optimize the conversion strategies in HCC.

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Ethics Statement

The study adhered to the Declaration of Helsinki and was approved by the ethics committee (approval code: 2012–017).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Due to the nature of this research, the participants could not be contacted regarding whether the findings could be shared publicly, and thus, supporting data, including datasets generated and/or analyzed for the current study, are not publicly available.

References

1. M. G. Rose, E. B. Kennedy, G. K. Abou-Alfa, et al., "Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update Clinical Insights," *JCO Oncology Practice* 20, no. 8 (August 2024): 1035–1039, https://doi.org/10.1200/OP.24.00189.

2. A. Vogel, A. Cervantes, I. Chau, et al., "Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and follow-up," supplement, *Annals of Oncology* 29, no. S4 (October 2018): iv238–iv255, https://doi.org/10.1093/annonc/mdy308.

3. A. L. Cheng, S. Qin, M. Ikeda, et al., "Updated Efficacy and Safety Data From IMbrave150: Atezolizumab Plus Bevacizumab s. Sorafenib for Unresectable Hepatocellular Carcinoma," *Journal of Hepatology* 76, no. 4 (April 2022): 862–873, https://doi.org/10.1016/j.jhep.2021.11.030.

4. M. Kudo, T. Aoki, K. Ueshima, et al., "Achievement of Complete Response and Drug-Free Status by Atezolizumab plus Bevacizumab Combined With or Without Curative Conversion in Patients With Transarterial Chemoembolization-Unsuitable, Intermediate-Stage Hepatocellular Carcinoma: A Multicenter Proof-of-Concept Study," *Liver Cancer* 12, no. 4 (February 2023): 321–338, https://doi.org/10.1159/000529574.

5. T. Kikuchi, Y. Takeuchi, K. Nouso, et al., "Predictive Factors for Transition to Conversion Therapy in Hepatocellular Carcinoma Using Atezolizumab plus Bevacizumab," *Liver International* 44, no. 6 (June 2024): 1456–1463, https://doi.org/10.1111/liv.15907.

6. T. Tomonari, J. Tani, Y. Sato, et al., "Clinical Features and Outcomes of Conversion Therapy in Patients With Unresectable Hepatocellular Carcinoma," *Cancers (Basel)* 15, no. 21 (October 2023): 5221, https://doi.org/10.3390/cancers15215221.

18720344x, 2026, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hepr.70138 by Okayama University, Wiley Online Library on [10/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

7. S. Shimose, H. Iwamoto, T. Shirono, et al., "The Impact of Curative Conversion Therapy Aimed at a Cancer-Free State in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab," *Cancer Medicine* 12, no. 11 (June 2023): 12325–12335, https://doi.org/10.1002/cam4.5931.

8. M. D. Wang, X. J. Xu, K. C. Wang, et al., "Conversion Therapy for Advanced Hepatocellular Carcinoma in the Era of Precision Medicine: Current Status, Challenges and Opportunities," *Cancer Science* 115, no. 7 (May 2024): 2159–2169, https://doi.org/10.1111/cas.16194.

9. J. W. Gilbert, B. Wolpin, T. Clancy, et al., "Borderline Resectable Pancreatic Cancer: Conceptual Evolution and Current Approach to Image-Based Classification," *Annals of Oncology* 28, no. 9 (September 2017): 2067–2076, https://doi.org/10.1093/annonc/mdx180.

10. K. Akahoshi, J. Shindoh, M. Tanabe, et al., "Oncological Resectability Criteria for Hepatocellular Carcinoma in the Era of Novel Systemic Therapies: The Japan Liver Cancer Association and Japanese Society of Hepato-Biliary-Pancreatic Surgery Expert Consensus Statement 2023," *Liver Cancer* 13, no. 6 (March 2024): 0–10, https://doi.org/10.1159/000538627.

11. A. Freites-Martinez, N. Santana, S. Arias-Santiago, and A. Viera, "Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies," *Actas Dermosifiliogr (Engl Ed)* 112, no. 1 (2021): 90–92, https://doi.org/10.1016/j.adengl.2019.05.021.

12. E. A. Eisenhauer, P. Therasse, J. Bogaerts, et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)," *European Journal of Cancer* 45, no. 2 (2009): 228–247, https://doi.org/10.1016/j.ejca.2008.10.026.

13. K. Hasegawa, N. Takemura, T. Yamashita, et al., "Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 Version (5Th JSH-HCC Guidelines)," *Hepatology Research* 53, no. 5 (2023): 383–390, https://doi.org/10.1111/hepr.13892.

14. S. Shimose, I. Saeki, T. Ito, et al., "The Benefit of Conversion Therapy for Patients With Unresectable Hepatocellular Carcinoma Receiving Atezolizumab plus Bevacizumab Using Newly Established Oncological Resectability Criteria in Japan," *Hepatology International* 19, no. 4 (February 2025): 846–855, https://doi.org/10.1007/s12072-025-10781-y.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: hepr70138-sup-0001-suppl-data.docx. **Figure S1:** Trial profile. CONSORT diagram showing patient enrolment, and analysis populations.

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