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Evaluating the Efficacy of Surgery With Complementary Radiofrequency Ablation in Intermediate-Stage Hepatocellular Carcinoma

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ABSTRACT

Management of intermediate-stage hepatocellular carcinoma (BCLC-B) typically relies on transarterial chemoembolization (TACE), while systemic therapy is used for cases unsuitable for TACE. However, curative outcomes remain limited, prompting investigation into the role of surgical resection (SR), with or without adjunctive radiofrequency ablation (RFA). A retrospective review included 70 BCLC-B HCC patients treated with surgery as the first-line intervention between 2000 and 2022 (median age 67.5 years; 44 patients beyond up-to-7 criteria). Forty-five patients underwent SR alone, and 25 received SR combined with RFA. Outcomes assessed included recurrence-free survival (RFS) and overall survival (OS). Baseline liver function was slightly better in the SR-only group (median ALBI −2.74 vs. −2.52; $p = 0.02$). No statistically significant differences were observed between the groups for median RFS (17.7 vs. 13.1 months) or OS (66.6 vs. 72.0 months). Patients beyond up-to-7 criteria showed comparable outcomes. Five-year survival exceeded 50% in both groups (54% vs. 64%). Surgical resection, with or without complementary RFA, achieves meaningful long-term survival in selected BCLC-B HCC patients. These results support the consideration of SR as a viable curative option, even in patients with extensive tumor burden.

Keywords: Hepatocellular carcinoma, Intermediate stage, BCLC-B, Surgical resection, Radiofrequency ablation, Survival

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Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most frequently diagnosed malignancy worldwide and represents the third leading cause of cancer-related mortality [1]. Among the various staging systems, the Barcelona Clinic Liver Cancer (BCLC) classification is widely utilized for guiding treatment decisions [2]. According to BCLC recommendations, surgical resection (SR) is the preferred option for patients with very early (BCLC-0) or early-stage (BCLC-A) disease, whereas transarterial chemoembolization (TACE) is standard for intermediate-stage (BCLC-B) cases, and systemic therapy is indicated for advanced-stage disease (BCLC-C). The 2022 BCLC update further subdivides BCLC-B patients into three subgroups based on tumor burden and liver function [2]. The first subgroup includes patients with well-demarcated HCC who may be eligible for liver transplantation if extended criteria are met [3]. The second subgroup encompasses individuals with preserved portal flow and localized tumor burden suitable for selective TACE [2]. The third subgroup, consisting of patients with diffuse or infiltrative HCC, is primarily recommended for systemic therapy [2].

Over the past decade, advances in imaging, surgical techniques, and perioperative management have expanded the indications and safety of hepatic resection. Meta-analyses have shown that laparoscopic hepatectomy offers reduced intraoperative blood loss, lower complication rates, and shorter hospital stays compared to open procedures [4]. Major hepatectomy for large, multinodular tumors or those involving major vessels is increasingly feasible [5]. Several studies have reported favorable long-term outcomes even in cases exceeding current guideline

recommendations [6–8]. However, SR alone may not provide sufficient tumor clearance in BCLC-B HCC, and RFA as monotherapy may be inadequate for larger lesions. Prior studies suggest that combining SR with RFA may improve local control and increase curative potential for multifocal disease [9, 10]. Despite these observations, there is still no consensus on the optimal role of SR, alone or combined with RFA, in the management of BCLC-B HCC. This study aims to evaluate the clinical outcomes of SR, with or without adjunctive RFA, as first-line treatment for intermediate-stage HCC.

Materials and Methods

The study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital. Between April 2000 and July 2022, 661 patients with treatment-naïve HCC underwent SR at the institution. After applying exclusion criteria—performance status ≥1, solitary tumor or ≤3 nodules each ≤3 cm, and extrahepatic disease—70 patients with BCLC-B HCC were included (median age 68 years; 54 males; 44 beyond up-to-7 criteria). Patients were categorized into those receiving SR alone (SR group, n = 45) and those undergoing SR combined with RFA (Comb group, n = 25). Clinical data collected included age, sex, HCC etiology, serum tumor markers (alpha-fetoprotein [AFP], des-gamma-carboxy prothrombin [DCP]), tumor number and size, and liver function parameters.

HCC diagnosis relied on dynamic computed tomography (CT) and/or EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI). Tumor diameter was measured on early or late phase images, and staging was determined according to the BCLC classification [11]. Liver function was assessed using Child-Pugh class, albumin–bilirubin (ALBI) grade [12, 13], and modified ALBI (mALBI) grade [14], subdividing ALBI grade 2 into mALBI 2a and 2b using an ALBI score of −2.27 as the threshold.

Patients with multifocal HCC considered unresectable by standard criteria, due to tumor size or location, were counseled regarding all treatment options. Those who consented to combination therapy received SR with adjunctive RFA, while others received guideline-based TACE or systemic therapy **(Figure 1)**. SR was performed via open or laparoscopic approach. RFA was performed under ultrasonographic guidance, either intraoperatively for superficial tumors or pre-/postoperatively for lesions ≤3 cm and ≤3 nodules. Ablation aimed to cover the entire lesion and a safety margin, guided by imaging, and additional sessions were performed if incomplete.

The primary endpoints were recurrence-free survival (RFS), defined as the interval from treatment to documented recurrence, and overall survival (OS), defined as the time from treatment to death from any cause. Treatment-related complications were also recorded and analyzed.

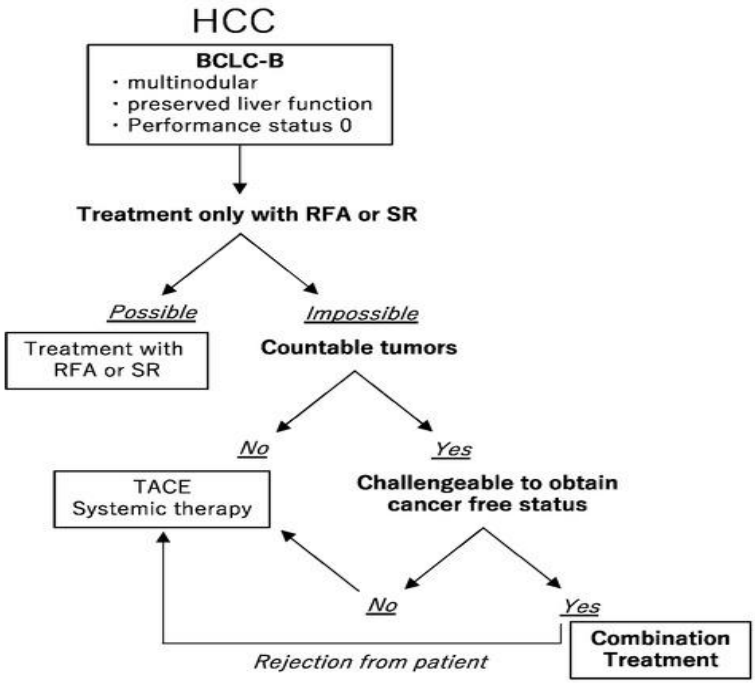


Figure 1. Treatment Selection Flowchart

For patients with intermediate-stage (BCLC-B) hepatocellular carcinoma (HCC), treatment was determined based on the feasibility of surgical resection (SR) and/or radiofrequency ablation (RFA). If either SR or RFA was technically possible, it was selected as the preferred approach. When neither procedure was feasible or the total number of tumors could not be accurately counted, guideline-based therapies such as transarterial chemoembolization (TACE) or systemic therapy were implemented. For patients in whom tumor count was feasible and sufficient liver remnant could be preserved after resection of accessible tumors, RFA was added to target residual lesions, creating a combination approach of SR and RFA. Patients were informed of all available treatment options, including standard guideline-based therapies, and those who opted against the combined SR and RFA approach received TACE or systemic therapy accordingly.

Statistical analysis

All data were extracted from a hospital database and analyzed using standard statistical methods. Continuous variables were compared using Student's t-test or the Mann–Whitney U test as appropriate. Recurrence-free survival (RFS) and overall survival (OS) curves were generated via the Kaplan–Meier method and compared using the log-rank test.

Because patients in the Comb group often had more extensive disease or poorer liver function, selection bias was possible. To adjust for this, inverse probability weighting (IPW) was applied. Propensity scores were calculated using logistic regression based on covariates that could influence RFS and OS. Variables showing $p < 0.05$ between the SR and Comb groups were included in multivariate analysis, with statistical significance set at $p < 0.05$. IPW values were defined as 1/(propensity score) for the Comb group and 1/(1 − propensity score) for the SR group. Survival differences were then assessed using IPW-adjusted log-rank tests.

All statistical analyses were performed using EZR software version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (R Foundation for Statistical Computing, Vienna, Austria), which incorporates frequently used biostatistical functions.

Patient characteristics

In the SR group, the median age was 67 years (interquartile range [IQR]: 64–75) with 33 males (73.3%), while in the Comb group the median age was 68 years (IQR: 62–73) with 21 males (84.0%). Etiology of liver disease did not significantly differ between groups. Laboratory values, including alanine aminotransferase, platelet count, AFP, and des-gamma-carboxy prothrombin (DCP), were comparable. The median ALBI score was significantly better in the SR group than in the Comb group [−2.74 (IQR: −3.02 to −2.57) vs. −2.52 (IQR: −2.90 to −2.26); $p = 0.021$], and the median FIB-4 index was also superior in the SR group [3.28 (IQR: 2.30–3.98) vs. 4.18 (IQR: 3.01–6.92); $p = 0.031$]. Tumor size and number did not differ significantly; however, bilateral lobe involvement was more common in the Comb group (76% vs. 35.6%; $p = 0.002$) **(Table 1)**.

Table 1. Patient characteristics (n = 70).

	All (n = 70)	**SR Group (n = 45)**	**Comb Group (n = 25)**	**p Value**
Age, years *	68 (63–74)	67 (64–75)	68 (62–73)	0.43
Gender, males:females	54:16	33:12	21:4	0.38
Etiology, HBV:HCV:HBV + HCV:alcohol:others	10:37:1:5:17	6:24:1::3:11	4:13:0:2:6	1.0
BMI, kg/m^2 *	23.1 (28.1–25.1)	23.1 (22.1–25.2)	23.0 (21.7–24.0)	0.81
AST, U/L *	45 (30–77)	43 (29–60)	57 (30–86)	0.26
ALT, U/L *	42 (24–64)	41 (26–54)	50 (21–74)	0.43
Platelets, 10^4/μL *	15.5 (11.3–19.1)	16.6 (12.9–19.3)	14.4 (9.7–16.4)	0.1
Total bilirubin, mg/dL *	0.7 (0.5–1.0)	0.7 (0.5–0.8)	0.9 (0.5–1.1)	0.1
Albumin, g/dL *	4.0 (3.7–4.2)	4.0 (3.8–4.3)	3.8 (3.6–4.2)	0.07
Prothrombin time, % *	88.4 (80.7–98.0)	90.7 (86.0–99.3)	84.6 (77.5–90.8)	0.01
ALBI score *	−2.66 (−2.95 to −2.44)	−2.74 (−3.02 to −2.57)	−2.52 (−2.90 to −2.26)	0.02
mALBI, 1:2a:2b:3	41:19:9:1	31:11:3:0	10:8:6:1	0.03

Child-Pugh score, A:B	67:3	45:0	22:3	0.04
FIB4-index *	3.4 (2.5–4.3)	3.3 (2.3–4.0)	4.2 (3.0–6.9)	0.03
AFP, ng/mL *	35.7 (6.9–340.2)	40.9 (7.9–841.1)	32.7 (4.8–68.0)	0.11
DCP, mAU/mL *	739 (150–3462)	673 (166–2737)	1210 (132–3884)	0.73
Tumor location (one:both lobes)	35:35	29:16	6:19	<0.01
Tumor size (maximum), cm *	4.95(4.0–6.0)	5.3 (4.0–7.0)	4.8 (3.7–5.8)	0.1
Number of tumors *	2 (2–3)	2 (2–3)	2 (2–3)	0.3

* Median. Values in parentheses show interquartile range, unless otherwise indicated. SR: surgical resection, Comb: combined SR and radiofrequency ablation, HBV: hepatitis B virus, HCV: hepatitis C virus, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALBI score: albumin–bilirubin score, mALBI grade: modified ALBI grade, AFP: alpha-fetoprotein, DCP: des-gamma-carboxy prothrombin.

Results and Discussion

Tumor distribution and treatment details

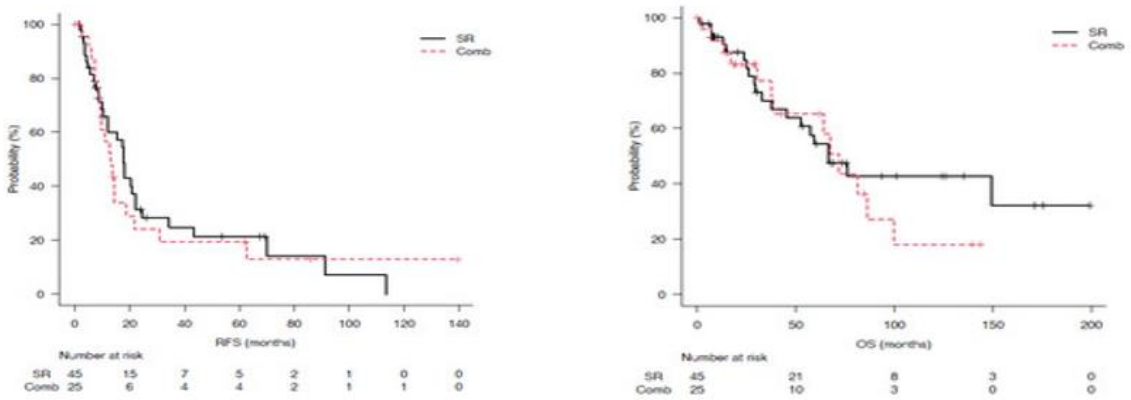
In the surgical resection (SR) group, tumors were localized to a single liver segment in 14 patients and to a single lobe in 15 patients. Bilobar involvement was present in 16 patients, who underwent a variety of surgical approaches: combinations of hemihepatectomy, segmentectomy, subsegmentectomy, or limited resections, tailored according to tumor location and size.

In the combined SR and radiofrequency ablation (RFA) cohort, 19 patients had tumors involving both lobes. All RFA-treated lesions were ≤3 cm. Most patients (n = 21) had a single lesion targeted with RFA, while three had two lesions, and one had three. SR addressed the remaining lesions. Ten patients underwent RFA concurrently with SR, while four received postoperative RFA at a median of 70 days (IQR: 53–75). Eleven patients had preoperative RFA with a median interval of 31 days (IQR: 24–38). Each ablation session was completed in a single attempt. Within two years, local recurrence adjacent to the ablation site occurred in two patients (8%).

Survival outcomes

The median follow-up duration was 41.0 months (IQR: 14.1–80.0) in the SR group and 40.8 months (IQR: 20.2–78.3) in the combined group. Recurrence-free survival (RFS) did not differ significantly, with medians of 17.7 months (95% CI: 10.3–22.1) for SR and 13.1 months (95% CI: 9.0–18.9) for the combined group (p = 0.70). Three- and five-year RFS rates were 21% and 25% for SR, and 19% and 19% for the combined treatment, respectively.

Overall survival (OS) was similarly comparable between groups: median OS was 66.6 months (95% CI: 37.7–NA) in the SR group and 72.0 months (95% CI: 37.5–100.0) in the combined group (p = 0.544). The three-year OS rates were 70% for SR and 77% for the combined cohort, while five-year OS rates were 54% and 65%, respectively.

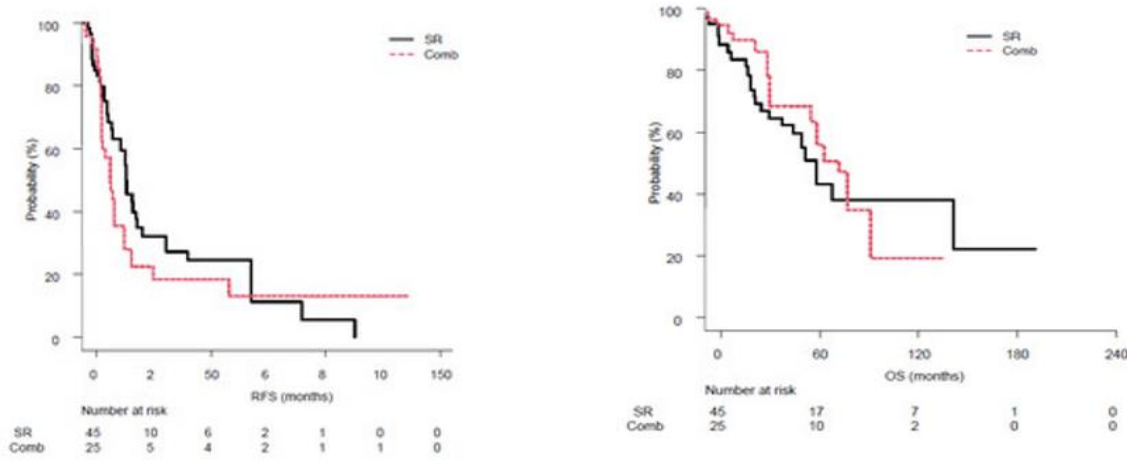


a) b)

Figure 2. Comparative analysis of survival outcomes following surgical intervention in BCLC-B HCC patients.

Panel (a) illustrates recurrence-free survival (RFS), with median values of 17.7 months (95% CI: 10.3–22.1) for patients treated with surgical resection alone (SR) and 13.1 months (95% CI: 9.0–18.9) for those receiving combined surgery and radiofrequency ablation (Comb). No statistically significant difference was detected (p = 0.70). Panel (b) depicts overall survival (OS), with median durations of 66.6 months (95% CI: 37.7–not reached) in the SR cohort and 72.0 months (95% CI: 37.5–100) in the Comb cohort, also showing no significant difference (p = 0.544).

Subsequent multivariate assessment revealed ALBI score, FIB-4 index, and tumor distribution as significant predictors of survival. After correcting for these covariates via inverse probability weighting (IPW), adjusted analyses continued to show no meaningful difference between SR and Comb groups for median RFS (17.7 vs. 12.7 months, p = 0.37) or median OS (66.6 vs. 67.5 months, p = 0.65), as displayed in **Figure 3**.



a) b)

Figure 3. Survival Outcomes After Adjustment.

Following adjustment with inverse probability weighting, the comparison between patients treated with surgical resection (SR) alone and those receiving SR combined with radiofrequency ablation (Comb) revealed no statistically meaningful differences. Median recurrence-free survival was 17.7 months for the SR cohort and 12.7 months for the Comb group (p = 0.37) **(Figure 3a)**. Likewise, median overall survival was comparable, with 66.6 months in the SR group versus 67.5 months in the Comb group (p = 0.65) **(Figure 3b)**.

Postoperative complications

In the SR group, four patients (8.9%) experienced complications that extended hospital stays, including acute respiratory failure related to interstitial pneumonia, severe ascites, pneumonia complicated by sepsis, and prolonged loss of appetite. Within the Comb cohort, three patients (12%) developed adverse events, which included cellulitis, extensive ascites, and acute cholecystitis. Statistical comparison of complication rates indicated no significant difference between the two groups (p = 0.694).

Outcomes for tumors beyond up-to-7 criteria

Among patients with tumors exceeding the up-to-7 criteria, 29 underwent SR alone, and 15 were treated with the combined SR and RFA approach. Demographic characteristics, liver disease etiology, biochemical markers (ALT, platelets, AFP, DCP), and tumor counts were similar across groups. Median tumor diameter was slightly higher in the SR group (6.3 cm, 95% CI: 5.3–8.8) compared with the Comb group (5.5 cm, 95% CI: 4.85–6.35), but this difference was not statistically significant. Median ALBI scores were −2.74 in the SR cohort and −2.52 in the Comb cohort (p = 0.134), indicating comparable liver function. Tumor distribution across both hepatic lobes was significantly more frequent in the Comb group (86.7%) than in the SR group (34.5%) (p = 0.004) **(Table 2)**.

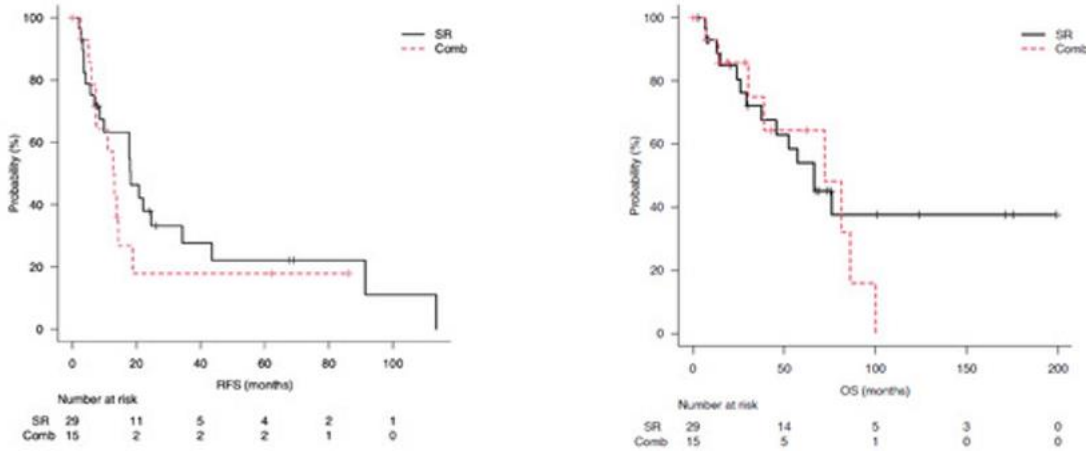
Table 2. Characteristics of patients classified as beyond up-to-7 criteria (n = 44).

	SR Group (n = 29)	Comb Group (n = 15)	p Value
Age, years *	66 (64–75)	64 (61–73)	0.36

Gender, males:females	23:6	13:2	0.70
Etiology, HBV:HCV:alcohol:others	3:13:3:10	2:7:2:4	1.0
BMI, kg/m^2 *	23.1(22.1–25.0)	23.7 (21.2–26.7)	0.78
AST, U/L *	46 (36–62)	54 (30–78)	0.75
ALT, U/L *	42 (27–57)	40 (22–65)	0.94
Platelets, 10^4/μL *	17.1 (14.9–21.5)	15.2 (14.0–17.7)	0.08
Total bilirubin, mg/dL *	0.8 (0.5–0.9)	0.7 (0.4–1.0)	1.0
Albumin, g/dL *	4.1 (3.8–4.4)	3.8 (3.6–4.2)	0.11
Prothrombin time, % *	90.0 (85.0–96.3)	79.0 (75.6–95.5)	0.12
ALBI score *	−2.74 (−3.07 to −2.57)	−2.52 (−2.95 to −2.26)	0.13
mALBI, 1:2a:2b:3	21:6:2:0	6:5:3:1	0.09
Child-Pugh score, A:B	29:0	12:3	0.03
FIB4-index *	3.1 (2.3–3.7)	4.0 (2.6–6.6)	0.13
AFP, ng/mL *	34.8 (6.8–977.2)	37.0 (8.4–88.2)	0.68
DCP, mAU/mL *	831 (169–13,293)	2545 (1246–17,802)	0.32
Tumor location (one:both lobes)	15:4:10	2:0:13	<0.01
Tumor size (maximum), cm *	6.3 (5.3–8.8)	5.5 (4.9–6.4)	0.08
Number of tumors *	2 (2–4)	3 (2.5–4)	0.34

* Median. Values in parentheses show interquartile range, unless otherwise indicated. SR: surgical resection, Comb: combined SR and radiofrequency ablation, HBV: hepatitis B virus, HCV: hepatitis C virus, BMI: body mass index, Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALBI, albumin–bilirubin score; mALBI, modified ALBI grade; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

Among patients whose tumors exceeded the up-to-7 criteria, analysis revealed no significant differences in outcomes between those who underwent surgical resection alone and those who received combined resection with radiofrequency ablation. The median recurrence-free survival was 18.2 months in the SR group (95% CI: 8.5–34.3) and 13.0 months in the Comb group (95% CI: 5.9–18.9; p = 0.36) **(Figure 4a)**. The estimated proportions of patients remaining recurrence-free at three and five years were similar, with 28% versus 18% and 22% versus 18% for SR and Comb groups, respectively. Median overall survival also did not differ significantly, measuring 66.5 months for SR (95% CI: 29.4–NA) and 72.0 months for Comb (95% CI: 30.2–86.2; p = 0.57) **(Figure 4b)**. Three- and five-year overall survival rates were 72% and 54% for SR and 75% and 64% for Comb, respectively, highlighting that long-term survival exceeded 50% irrespective of the addition of RFA. These findings suggest that, even in patients with more extensive tumor burden, surgical resection—with or without adjunctive RFA—can achieve comparable long-term control.



a) b)

Figure 4. Outcomes for patients classified beyond the up-to-7 criteria undergoing surgical resection (SR) or combined surgical resection and radiofrequency ablation (Comb). (a) Median recurrence-free survival

(mRFS) was 18.2 months (95% CI: 8.5–34.3) in the SR group and 13.0 months (95% CI: 5.9–18.9) in the Comb group (p = 0.36). (b) Median overall survival (mOS) reached 66.5 months (95% CI: 29.4–NA) for SR and 72.0 months (95% CI: 30.2–86.2) for Comb (p = 0.57).

Discussion

In this cohort, median RFS and OS for patients receiving SR were 17.7 and 66.6 months, respectively, whereas patients treated with the Comb approach had 13.1 and 72.0 months. Following adjustment with inverse probability weighting (IPW), no significant differences in RFS or OS were observed between the two strategies, indicating comparable therapeutic outcomes.

For BCLC-B patients who are not candidates for liver transplantation but have preserved portal flow and accessible feeding arteries, TACE remains the standard recommendation. The BCLC guidelines suggest an expected median survival of ≥2.5 years for such patients [15]. A review by Prince, covering over 10,000 patients across 101 studies, reported a five-year OS of 32% and median survival of 19.4 months (95% CI: 16.2–22.6) following TACE [16]. By contrast, in this study, both SR and Comb groups achieved median OS of over 66 months, surpassing the typical outcomes associated with TACE.

Kim [17] demonstrated that the prognosis after TACE strongly depends on tumor response, with complete responders after the first session achieving the longest OS (70.2 months), followed by complete responders after two sessions (40.6 months) and patients with partial response (23.0 months; p < 0.01). Bolondi's subclassification [18] and the Kinki criteria [19] indicate that patients beyond the up-to-7 criteria are generally less suitable for TACE. In line with the Kinki criteria, Arizumi [20] reported that the median time to untreatable progression was 25.7 months for substage B1 (within up-to-7) and 16.4 months for B2 (beyond up-to-7) (p = 0.005). Other Japanese cohorts showed median OS of 20.4–27.6 months for beyond up-to-7 patients treated with TACE [21, 22]. By comparison, this study observed median OS of 66.5 months (SR) and 72.0 months (Comb), highlighting the potential benefit of surgical-based approaches in this subgroup.

BCLC-B HCC is defined as multifocal disease with preserved liver function, absence of cancer-related symptoms, and no vascular invasion or extrahepatic spread [2]. However, localization and treatment combinations are not explicitly addressed in the guidelines. Our findings demonstrate that even when tumors involve both lobes, strategic combinations of segmentectomy, limited resection, or adjunctive RFA can preserve sufficient residual liver volume while achieving oncologic control.

Advances in diagnostic imaging, laparoscopic techniques, and perioperative management have improved the safety and feasibility of resection in BCLC-B HCC [23, 24]. Prior studies report that five-year OS after SR for BCLC-B HCC can exceed 55%, comparable to early-stage outcomes [6, 8, 25]. Tsilimigras [26] found that approximately 37.6% of BCLC-B patients achieved complete response after SR, supporting curative potential even in intermediate-stage disease. Furthermore, intraoperative or staged RFA combined with SR has been successfully applied to multifocal HCC [9, 10]. Espinosa [27] reported a propensity-score-matched OS of 60 months for patients receiving SR + RFA versus 39.9 months for TACE-treated patients. Similarly, Tada [28] observed five-year OS rates of 68.2% (SR) and 59.6% (SR + RFA) in patients with ≤5 HCC nodules, without significant differences (p = 0.329).

In line with these reports, the present study shows favorable long-term outcomes for both SR and Comb groups, with five-year survival exceeding 50%, and no statistically significant differences in RFS or OS. These findings suggest that surgical resection, with or without complementary RFA, is an effective therapeutic option for selected BCLC-B HCC patients, including those beyond the up-to-7 criteria.

Recent strategies for intermediate-stage HCC have explored the use of systemic therapy followed by locoregional treatments [29, 30]. Evidence from the TACTICS trial demonstrated that sequential administration of sorafenib and TACE improved outcomes, with median progression-free survival extended by 9.7 months (24.9 months vs. TACE alone) and median overall survival increased by 3.7 months (35.6 months) [31]. Similarly, Kudo *et al.* reported that patients receiving upfront lenvatinib followed by selective TACE had a median OS of 37.9 months, compared with 21.3 months in those treated with TACE alone (hazard ratio 0.48, 95% CI: 0.16–0.79, p < 0.01) [32]. Additionally, the combination of atezolizumab and bevacizumab (Atez/Bev) received approval in 2020 following positive outcomes in the Phase 3 IMbrave150 trial [33], with Finn reporting an overall response rate of 44% in BCLC-B patients treated with this regimen (RECIST ver. 1.1) [34]. These findings suggest that integrating systemic therapies with locoregional approaches may improve survival outcomes in BCLC-B HCC, although achieving a complete cancer-free state remains a challenge.

In our study, select BCLC-B patients were able to undergo aggressive treatment with surgical resection, with or without complementary RFA, achieving prolonged survival and potential cancer-free status under specific conditions. Prospective investigations are necessary to better identify which BCLC-B patients are most likely to benefit from such intensive treatment strategies.

This study has several limitations. The retrospective design may have introduced selection bias, as evolving surgical techniques, including laparoscopic hepatectomy, were not fully considered. The sample size of the Comb group (SR + RFA) was limited. Additionally, outcomes for the SR and Comb groups were not directly compared with patients treated according to conventional BCLC guidelines (TACE or systemic therapy). Future randomized controlled trials with larger cohorts are needed to more conclusively determine the value of SR and combined SR/RFA for BCLC-B HCC.

Conclusion

No significant differences were observed in recurrence-free survival or overall survival between the SR and Comb groups. Even among patients with tumors beyond the up-to-7 criteria, outcomes were similar, with five-year survival exceeding 50% in both cohorts. While current BCLC guidelines primarily recommend surgical resection for BCLC-0/A patients, our results indicate that selected BCLC-B patients may achieve favorable outcomes with aggressive strategies using SR or SR combined with RFA. Clinical decision-making should prioritize flexibility, leveraging the complementary strengths of SR and RFA rather than limiting patients to a single treatment modality.

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Conflict of Interest: Atsushi Hiraoka, received lecture fees from Chugai, Bayer, and Eli Lilly. None of the other authors have potential conflict of interest to declare.

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Ethics Statement: The entire study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 26-11). After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were done in accordance with the declaration of Helsinki. The data were made anonymous before analysis to protect patient privacy.

Informed consent was obtained from all patients before treatment. This study received ethical approval for use of an opt-out methodology based on low risk to the participants.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681–93.
3. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver transplantation for hepatocellular carcinoma: Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020;104(6):1136–42.
4. Cai W, Liu Z, Xiao Y, Zhang W, Tang D, Cheng B, et al. Comparison of clinical outcomes of laparoscopic versus open surgery for recurrent hepatocellular carcinoma: A meta-analysis. Surg Endosc. 2019;33(11):3550–7.
5. Tsilimigras DI, Sahara K, Moris D, Mehta R, Paredes AZ, Ratti F, et al. Assessing textbook outcomes following liver surgery for primary liver cancer over a 12-year time period at major hepatobiliary centers. Ann Surg Oncol. 2020;27(9):3318–27.
6. Wada H, Eguchi H, Noda T, Ogawa H, Yamada D, Tomimaru Y, et al. Selection criteria for hepatic resection in intermediate-stage (BCLC stage B) multiple hepatocellular carcinoma. Surgery. 2016;160(5):1227–35.

7. Bhandare MS, Patkar S, Shetty N, Polnaya A, Kulkarni S, Dusane RR, et al. Liver resection for HCC outside the BCLC criteria. Langenbecks Arch Surg. 2018;403(1):37–44.
8. Hyun MH, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. Hepatology. 2018;68(3):977–93.
9. Elias D, Goharin A, El Otmany A, Taieb J, Duvillard P, Lasser P, et al. Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. Eur J Surg Oncol. 2000;26(8):763–9.
10. Choi D, Lim HK, Joh JW, Kim SJ, Kim MJ, Rhim H, et al. Combined hepatectomy and radiofrequency ablation for multifocal hepatocellular carcinomas: Long-term follow-up results and prognostic factors. Ann Surg Oncol. 2007;14(12):3510–8.
11. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–9.
12. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach—the ALBI grade. J Clin Oncol. 2015;33(6):550–8.
13. Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol. 2016;31(6):1031–6.
14. Hiraoka A, Michitaka K, Kumada T, Izumi N, Kadoya M, Kokudo N, et al. Validation and potential of albumin-bilirubin grade in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan. Liver Cancer. 2017;6(4):325–36.
15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452–8.
16. Prince D, Liu K, Xu W, Chen M, Sun JY, Lu XJ, et al. Management of patients with intermediate-stage hepatocellular carcinoma. Ther Adv Med Oncol. 2020;12:1758835920970840.
17. Kim BK, Kim SU, Kim KA, Chung YE, Kim MJ, Park MS, et al. Complete response at first chemoembolization predicts favorable outcome in hepatocellular carcinoma. J Hepatol. 2015;62(6):1304–10.
18. Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: Proposal for subclassification. Semin Liver Dis. 2012;32(4):348–59.
19. Kudo M, Arizumi T, Ueshima K, Sakurai T, Kitano M, Nishida N. Subclassification of BCLC B stage hepatocellular carcinoma: Modified Bolondi's Kinki criteria. Dig Dis. 2015;33(6):751–8.
20. Arizumi T, Minami T, Chishina H, Kono M, Takita M, Yada N, et al. Time to TACE refractoriness in hepatocellular carcinoma in Kinki criteria stages B1 and B2. Dig Dis. 2017;35(6):589–97.
21. Kimura H, Ohkawa K, Miyazaki M, Sakakibara M, Imanaka K, Tamura T, et al. Subclassification of intermediate-stage hepatocellular carcinoma using up-to-seven criteria and tumor markers. Hepatol Int. 2017;11(1):105–14.
22. Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, et al. Superselective transarterial chemoembolization: Validation of Japanese guidelines. J Hepatol. 2012;56(4):886–92.
23. Zhu F, Chang Q, Duan S, Leng W. Efficacy and safety of radiofrequency ablation vs laparoscopic hepatectomy for small HCC: Randomized trial protocol. Medicine. 2021;100(7):e23678.
24. Kaibori M, Hiraoka A, Matsui K, Matsushima H, Kosaka H, Yamamoto H, et al. Predicting complications after HCC resection using Neo-Glasgow score with ALBI grade. Cancers. 2022;14(6):1402.
25. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. Indications and results of surgery for hepatocellular carcinoma: The HCC East-West study. Ann Surg. 2013;257(5):929–37.
26. Tsilimigras DI, Bagante F, Moris D, Merath K, Paredes AZ, Sahara K, et al. Chance of cure after resection within and beyond BCLC criteria: 1010-patient analysis. Surgery. 2019;166(6):967–74.
27. Espinosa W, Liu YW, Wang CC, Lin CC, Wang JH, Lu SN, et al. Combined resection and RFA vs TACE for intermediate-stage HCC: Propensity-matched study. J Formos Med Assoc. 2018;117(3):197–203.
28. Tada T, Kumada T, Toyoda H, Nakamura S, Endo Y, Kaneoka Y, et al. Validation of combined resection and ablation therapy for multiple HCC. Clin Radiol. 2022;77(2):114–20.

29. Kudo M. Upfront systemic therapy followed by curative conversion for intermediate-stage HCC unsuitable for TACE. Liver Cancer. 2021;10(6):539–44.
30. Kudo M. Atezolizumab plus bevacizumab followed by curative conversion (ABC conversion) in TACE-unsuitable intermediate HCC. Liver Cancer. 2022;11(5):399–406.
31. Kudo M, Ueshima K, Ikeda M, Torimura T, Aikata H, Izumi N, et al. TACTICS: Final OS data from phase II trial of TACE + sorafenib vs TACE alone. J Clin Oncol. 2021;39:270.
32. Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib for intermediate-stage HCC beyond up-to-seven criteria. Cancers. 2019;11(7):1084.
33. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable HCC. N Engl J Med. 2020;382(20):1894–905.
34. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. IMbrave150: Updated OS results from global phase III trial. J Clin Oncol. 2021;39:267.