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ORIGINAL RESEARCH

Liver Transplantation After Radiotherapy-Antiangiogenesis-Immune Checkpoint Blockade Combination Therapy in Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis: A Propensity Score Matching Analysis

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Background: After downstaging, radiotherapy-antiangiogenesis-immune checkpoint blockade (RACIB) combination therapy has shown significant clinical efficacy in hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT), permitting liver transplantation (LT). This study evaluated LT patients' survival outcomes and prognostic factors after RACIB treatment.

Patients and Methods: This retrospective analysis comprised 28 HCC with major PVTT (Vp3/Vp4, portal invasion at the first portal branch or main portal branch according to Japanese Vp classification) patients who were downstaged with RACIB combination therapy between January 2018 and December 2022. 13 patients who achieved successful downstaging underwent LT (RACIB+LT group), while 15 patients who achieved downstaging but did not undergo LT (due to patient choice, lack of donor, or other clinical reasons) formed the non-LT control group (RACIB-only group). Kaplan–Meier analysis and the Log rank test were used for survival analysis. For comparative analysis, one-to-one paired cohorts were derived using propensity-score matching (PSM) analysis.

Results: Over a median follow-up period of 32.1 months (range: 4.1–46.0 months), the median overall survival (OS) and disease-free survival (DFS) were 31.1 and 10.1 months in the LT following RACIB group, and 14.5 months and 7.6 months in the RACIB group, respectively. The LT following RACIB group exhibited significantly better 3-year OS (42% vs 0, p=0.041) and 3-year progression-free survival (15.4% vs 0, p=0.047) than those who only underwent RACIB. In the PSM analysis, the 2-year OS was also superior in the LT following RACIB group (45.7% vs 0, p=0.042). Kaplan–Meier analysis showed that long interval from radiotherapy (RT) to LT, alpha fetoprotein (AFP) levels dropped to normal, AFP was reduced by half and patients with major pathologic response had superior OS (p=0.014, 0.005, 0.019, and 0.023) and DFS (p=0.025, 0.013, 0.011, and 0.014) compared to patients without any of the parameters. In DFS multivariate analysis, the interval from RT to LT and AFP normalization before LT were independent prognostic factors. The RACIB regimen was well tolerated, with no grade ≥3 treatment-related adverse events observed.

Conclusion: Selected HCC patients with major PVTT can be considered viable candidates for LT after downstaging using RACIB combination therapy, with identified prognostic parameters aiding decision-making.

Keywords: hepatocellular carcinoma, portal vein tumor thrombosis, liver transplantation, major pathological response, radiotherapy-antiangiogenesis-immune checkpoint blockade combination therapy

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Introduction

Unlike other cancer types, hepatocellular carcinoma (HCC) is prone to developing portal vein tumor thrombosis (PVTT).[1] The incidence has been reported to be 44–62.2%, and it is widely recognized as a poor prognostic factor for HCC.[2–4] Managing advanced HCC with PVTT is particularly challenging, as it is often multifocal and therefore unresectable Consequently, PVTT remains a contraindication for liver transplantation (LT).[5]

At present, no global consensus or guideline is available for the treatment of HCC patients with PVTT. European and American guidelines, following the Barcelona Clinic Liver Cancer (BCLC) staging system, classify HCC with macroscopic vascular invasion as BCLC Stage C and recommend systemic therapy as the primary treatment strategy.[6–9] In contrast, experts from Asian countries, such as China, advocate for multidisciplinary approaches, including surgery, transcatheter arterial chemoembolization (TACE), radiotherapy (RT), and molecular targeted therapy, which have shown satisfactory outcomes.[10,11] However, the optimal comprehensive treatment remains unclear, and there is an urgent need to address the clinical demands of these patients. In our previous study,[12] we demonstrated that RACIB combination therapy produced a significant response and improved survival, offering promising outcomes.

Recent studies have reported the potential for LT after successful downstaging in patients of HCC with PVTT.[13–15] Accumulating evidence has highlighted the role of immune checkpoint inhibitors as part of pre-transplant downstaging or bridging strategies.[16] However, the evidence from these studies is limited, with most focusing only on non-major PVTT and overlooking the heterogeneity of downstaging therapies.

Given these limitations, which impact the understanding of LT efficacy for HCC with PVTT, our study aimed to evaluate survival outcomes in patients with major PVTT who underwent LT following RACIB. We also explored potential prognostic factors that may influence survival.

Materials and Methods

Eligibility and Patients

This study was designed as a retrospective, non-interventional observational cohort study evaluating patients with HCC and major PVTT who received RACIB therapy in routine clinical practice. The study protocol was reviewed and approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (No.24763-6-01). Because the study involved only anonymized retrospective clinical data and did not include any prospective assignment or controlled intervention, the requirement for written informed consent was waived by the ethics committee. This study adhered to the ethical guidelines of the Declaration of Istanbul. All donor organs were obtained through the national organ donation and allocation system in China, with voluntary donation and written informed consent obtained in accordance with national regulations. Donor identities were anonymized, and no donor-specific information was accessible to the investigators.

Eligible patients had clinically or histologically confirmed HCC with major PVTT and were treated exclusively with RACIB combination therapy as determined by the multidisciplinary clinical team. Additional inclusion criteria included age ≥18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and a life expectancy of ≥3 months. Patients with distant organ metastases were excluded. Patients were considered eligible for liver transplantation only if they achieved radiological downstaging to CR or PR according to mRECIST criteria, confirmed by independent radiologic review, together with a reduction in serum AFP levels, following multidisciplinary team (MDT) discussion.

Systemic Therapy Regimen

All patients received systemic therapy consisting of an antiangiogenic agent combined with immune checkpoint blockade as part of the RACIB strategy. Antiangiogenic therapy consisted of lenvatinib, administered orally at standard doses according to body weight. During radiotherapy, lenvatinib was adjusted or temporarily interrupted when necessary to reduce bleeding risk and potential treatment-related toxicities, and was resumed after completion of RT when clinically appropriate. Immune checkpoint blockade consisted of either sintilimab or tislelizumab, administered intravenously at standard dosing schedules every 3 weeks.

RT Planning and Radiotherapy Technique

All patients underwent four-dimensional computed tomography (4DCT) simulations. The respiratory cycle was divided into 0–90% respiratory phase images based on respiratory signals, and images were reconstructed using the Pinnacle system (Pinnacle[3] version 9.1; Philips Medical System, Madison, WI, USA) for treatment planning. For hepatic lesions, abdominal compression was applied during positioning, followed by simulation using 4DCT and magnetic resonance imaging (MRI). RT was delivered to all metastatic lesions using either intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT). Daily imaging guidance was performed using cone-beam computed tomography (CBCT) to align the target volume.

The gross tumor volume (GTV) of the liver lesion was defined as the visible tumor on fusion CT images with MRI. The internal target volume (ITV) comprised all the GTVs from the 10 respiratory phases. A planning target volume (PTV) was recommended to include a 0.3–0.5 cm expansion of the ITV, depending on the site and motion of the lesion, immobilization, and set-up accuracy. At least 95% of the PTV was covered by the prescribed dose, administered to the periphery of the PTV. The prescription dose varied based on the lesion's site, volume, and proximity to neighboring organs at risk. The patients received doses ranging from 30–60 Gy in 5–20 fractions. Dose comparisons were conducted using the biological equivalent dose (BED) based on a linear-quadratic model (assuming $\alpha/\beta = 10$).

Post-Transplant Management

Post-transplant immunosuppressive therapy typically included a combination of corticosteroids, tacrolimus, and mycophenolate mofetil during the first month after liver transplantation. Corticosteroids were gradually tapered and discontinued within one month. After one month, sirolimus was added, and the tacrolimus dose was correspondingly reduced. All immunosuppressive agents were adjusted individually according to clinical conditions and plasma concentrations.

Evaluation and Follow-Up

Patients were evaluated through medical history and physical examination; blood tests; CT scans of the chest, abdomen, and pelvis; bone scan; and positron emission tomography-computed tomography (PET-CT) when necessary. An additional liver MRI was mandatory for patients with hepatic lesions. Tumor response was assessed using the response evaluation criteria in solid tumors (mRECIST). Successful downstaging is defined as CR or PR. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, with the highest toxicity grade used for the analysis. Following treatment, the patients underwent follow-up at 1 month, then every 3 months for the first 2 years, every 6 months during years 3–5, and annually thereafter.

Endpoints

The primary endpoints were overall survival (OS), defined as the time from the day of surgery to death by any cause or the final follow-up date; disease-free survival (DFS), defined as the time from the date of surgery to disease progression at any site or death; and progression-free survival (PFS), defined as the time from the date of radiation to either disease progression at any site or death.

Statistical Analysis

The χ^2 and Fisher's exact tests were used to compare differences between categorical variables, whereas continuous variables were evaluated using the unpaired *t*-test. OS, DFS, and PFS were calculated using the Kaplan–Meier method and Log rank test. Variables identified as significant in the univariate analysis (defined as a p-value less than 0.1) were included in the multivariate analysis using a backward stepwise Cox regression model. All statistical tests were two-sided, with a p-value < 0.05 considered statistically significant. Propensity score matching (PSM) was also utilized to balance the confounding factors between the two groups (sex, age, ECOG, GTV volume), employing nearest neighbor matching with a matching tolerance set at 0.02, resulting in a 1:1 matching of propensity score values. All statistical analyses were conducted using SPSS 25.0 (IBM SPSS Statistics Inc., Chicago, IL, USA) and R version 4.1.0 (http://www.r-project.org/).

Results

Patient and Treatment Characteristics

Between January 2018 and December 2022, 28 patients diagnosed with HCC with major PVTT (Vp3/Vp4) and successfully downstaged through RACIB combination therapy were enrolled in this study. Among these patients, 13 underwent LT following RACIB downstaging, while the remaining 15 underwent only RACIB. The baseline characteristics of the patients and tumors are summarized in Table 1. The median age of the patients who underwent LT following RACIB was 51 years (range, 42–71 years), with 12 males and one female. The overall median tumor size was 9.0 cm (range: 2.9–18.5 cm) for the LT group and 6.75 cm (range: 2.9–15.8 cm) for the RACIB group. A total RT dose of 30–60 Gy in 3–20 fractions was administered to the PTV, with

Table 1 Patient and Tumor Characteristics Before PSM

Characteristics	RACIB+LT (n=13)	RACIB (n=15)	*p* value
Sex			1.000
Male	12(92.3%)	14(93.3%)	
Female	1(7.7%)	1(6.7%)	
Age, median (range), y	51(42–71)	58(45–73)	0.036
ECOG			0.016
0	8(61.5%)	2(13.3%)	
1/2	5(38.5%)	13(86.7%)	
PVTT level			
Vp3	7(53.8%)	5(33.3%)	0.445
Vp4	6(46.2%)	10(66.7%)	
Tumor size, median (range), cm	9.0(2.9–18.5)	6.75(2.9–15.8)	0.120
≥6.8	9(69.2%)	8(53.3%)	
<6.8	4(30.8%)	7(46.7%)	
GTV volume, median (range), cm^3	420.6 (31.5–1252.3)	192.0 (37.0–811.0)	0.030
≥229.2	10(76.9%)	5(33.3%)	
<229.2	3(23.1%)	10(66.7%)	
Child-Pugh			0.670
Grade A	9(69.2%)	12(80%)	
Grade B	4(30.8%)	3(20%)	
AFP, median (range), ng/mL	330.6 (2.85–52916.6))	94 (2.65–23962)	0.629
<400	7(53.8%)	10(66.7%)	
≥400	6(46.2%)	5(33.3%)	
AFP dropped to normal			0.114
No	6(46.2%)	12(80%)	
Yes	7(53.8%)	3(20%)	
AFP reduced by half			0.718
No	5(38.5%)	7(46.7%)	
Yes	8(61.5%)	8(53.3%)	
Total dose, median (range), Gy	40(20–65)	50(24–60)	0.410
≥34.5	8(61.5%)	12(80%)	
<34.5	5(38.5%)	3(20%)	
BED_{10} median (range), Gy	48(24–88.5)	60(39–78)	0.255
≥50	33(55%)	20(54.1%)	
<50	27(45%)	17(45.9%)	
Response Category by RECIST			0.464
CR	1(7.7%)	0	
PR	12(92.3%)	15(100%)	
Degree of tumor regression by pathology			
MPR	6(46.2%)	NA	
Non-MPR	7(53.8%)	NA	

Abbreviation: NA, not applicable.

median BED of 48 Gy and 60 Gy, respectively. To balance the confounding factors between the two groups, PSM variables included sex, age, ECOG performance status, and GTV. After PSM, 7 patients in each group were comparable (Table 2).

Survival Outcomes

Over a median follow-up period of 32.1 months (range: 4.1–46.0 months), the median OS and the median DFS were 31.1 months and 10.1 months in the LT following RACIB group, respectively, compared with the 14.5 months and 7.6 months, respectively, in the RACIB-only group. Furthermore, patients who underwent LT following RACIB demonstrated significantly better 3-year OS (42% vs 0%, p = 0.041) and 3-year PFS (15.4% vs 0%, p = 0.047) compared with those who received only RACIB. In the PSM analysis, which included 7 patients in each group, the LT following RACIB group showed a significantly better 2-year OS (45.7% vs 0%, p = 0.042). The survival results are summarized in Figures 1 and 2.

Table 2 Patient and Tumor Characteristics After PSM

Characteristics	RACIB+LT (n=7)	RACIB (n=7)	*p* value
Sex			1.000
Male	6(85.7%)	6(86.7%)	
Female	1(14.3%)	1(14.3%)	
Age, median (range), y	51(45–71)	62(45–71)	0.452
ECOG			0.559
0	3(42.9%)	1(14.3%)	
1/2	4(57.1%)	6(85.7%)	
PVTT level			
Vp3	3(42.9%)	1(14.3%)	0.559
Vp4	4(57.1%)	6(85.7%)	
Tumor size, median (range), cm	7.0(2.9–15.0)	6.3(3.4–15.8)	1.000
≥6.8	4(57.1%)	4(57.1%)	
<6.8	3(42.9%)	3(42.9%)	
GTV volume, median (range), cm^3	238.3 (31.5–781.8)	375.0 (85.0–553.0)	0.723
≥229.2	4(57.1%)	3(42.9%)	
<229.2	3(42.9%)	4(57.1%)	
Child-Pugh			1.000
Grade A	5(71.4%)	4(57.1%)	
Grade B	2(28.6%)	3(42.9%)	
AFP, median (range), ng/mL	823.99 (4.38–7563.78)	188.0 (7.14–23962)	0.592
<400	4(57.1%)	2(28.6%)	
≥400	3(42.9%)	5(71.4%)	
AFP dropped to normal			1.000
No	3(42.9%)	2(28.6%)	
Yes	4(57.1%)	5(71.4%)	
AFP reduced by half			0.592
No	4(57.1%)	2(28.6%)	
Yes	3(42.9%)	5(71.4%)	
Total dose, median (range), Gy	30(20–46)	40(30–50)	0.266
≥34.5	3(42.9%)	6(85.7%)	
<34.5	4(57.1%)	1(14.3%)	
BED_{10} median (range), Gy	43.2(24–60)	50.7(39–60)	0.592
≥50	33(55%)	20(54.1%)	
<50	27(45%)	17(45.9%)	
Response Category by RECIST			1.000
CR	0	0	
PR	7(100%)	7(100%)	

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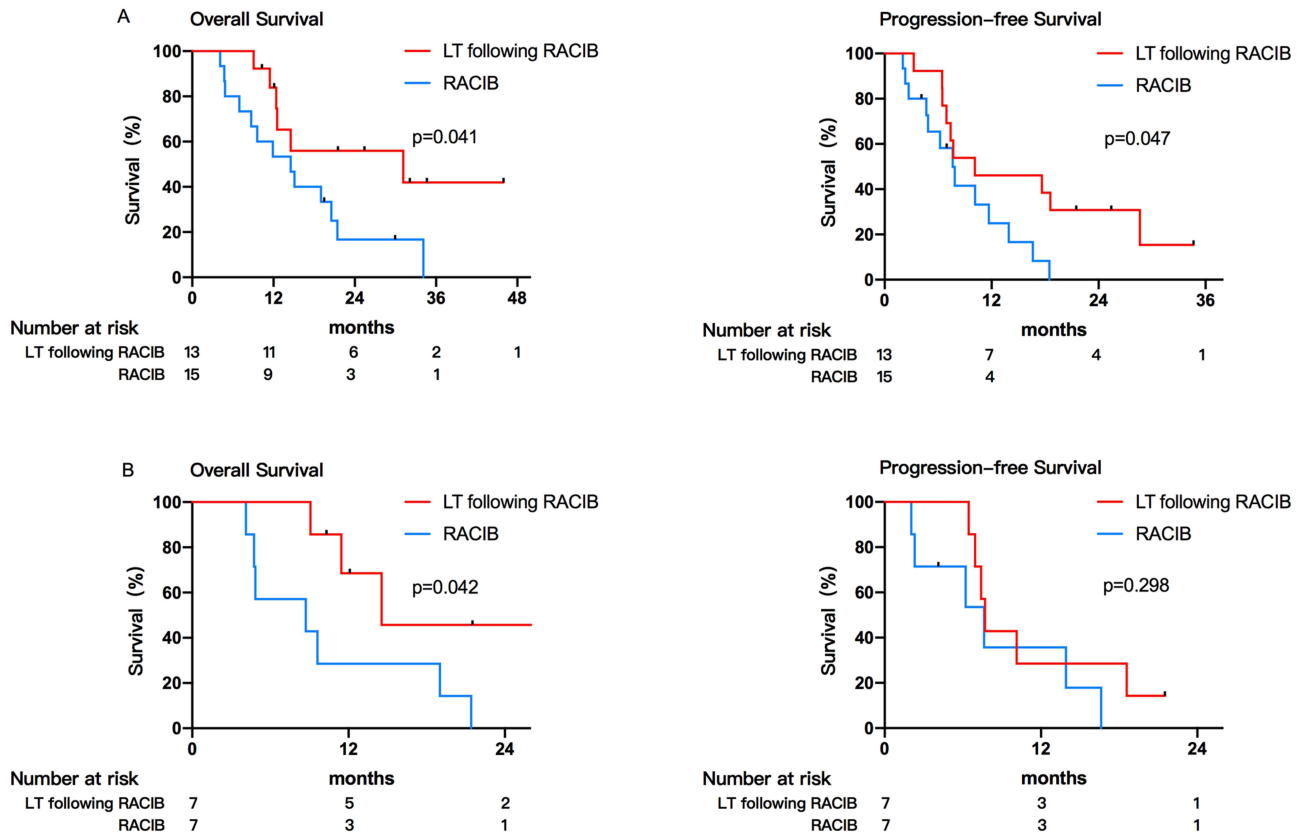

Figure 1 Overall survival and progression-free survival for HCC patients in LT following RACIB group and RACIB-only group before PSM (**A**) and after PSM (**B**) by Kaplan Meier method.

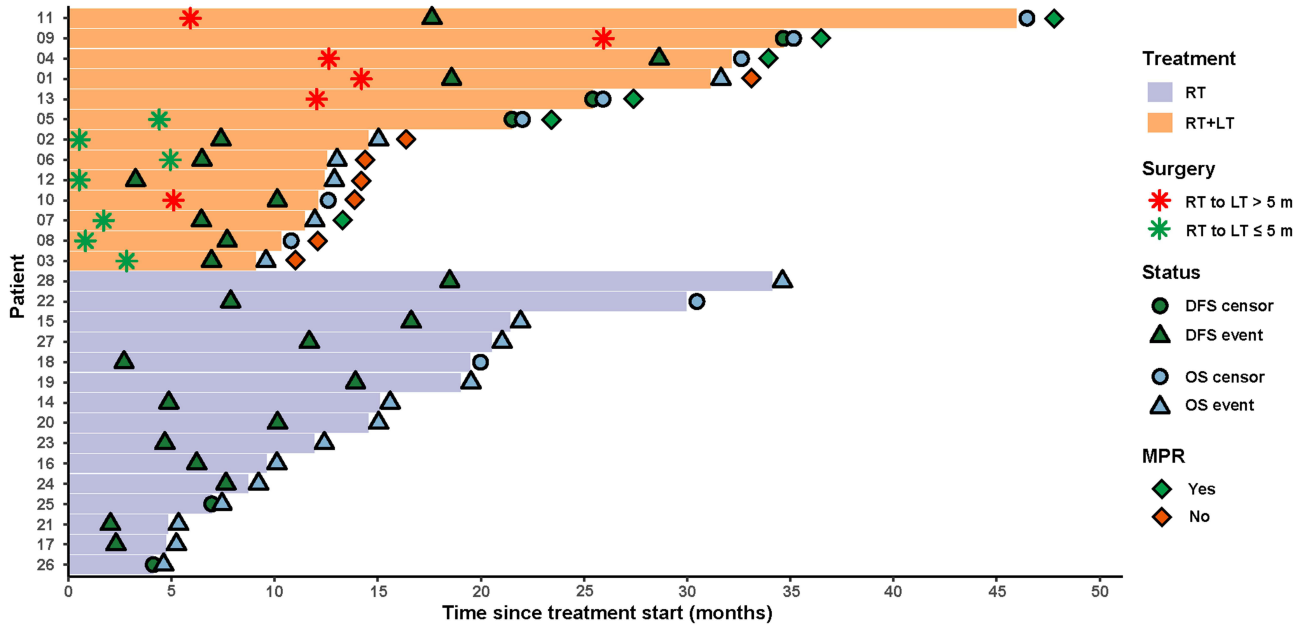

Figure 2 Antitumor activity. The length of each bar represents the duration of treatment for each patient.

Table 3 Prognostic Factors for Overall Survival and Disease-Free Survival

Variable	Overall Survival				Disease-Free Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Interval from RT to LT (m)								
≤5 months	ref		ref		ref		ref	
>5 months	0.124 (0.024–0.645)	0.014	0.010 (0.000–16.192)	0.892	0.213 (0.050–0.913)	0.025	0.065 (0.007–0.627)	0.018
AFP dropped to normal								
No	ref		ref		ref		ref	
Yes	0.078 (0.009–0.701)	0.005	0.109 (0.010–1.203)	0.886	0.195 (0.047–0.804)	0.013	0.065 (0.007–0.581)	0.014
AFP reduced by half								
No	ref		ref		ref		ref	
Yes	0.097 (0.010–0.995)	0.019	0.344 (0.031–3.866)	0.918	0.148(0.028–0.788)	0.011	0.690 (0.079–6.003)	0.737
MPR								
No	ref		ref		ref		ref	
Yes	0.118 (0.013–0.942)	0.023	0.949 (0.018–49.809)	0.925	0.159 (0.031–0.814)	0.014	0.442 (0.049–4.006)	0.468

Abbreviation: ref, reference.

Prognostic Factors Predicting Survival

The uni- and multivariate analyses of survival in patients who underwent LT following RACIB are presented in Table 3. Kaplan-Meier analysis indicated that longer interval from RT to LT (>5months), alpha fetoprotein (AFP) levels dropped to normal and reduced by half, presence of major pathologic response (MPR, ≥90% tumor necrosis) were associated with superior OS (p=0.014, 0.005, 0.019, and 0.023, respectively) and DFS (p=0.025, 0.013, 0.011, and 0.014, respectively) compared with that in patients lacking any of these parameters (Figure 3).

Furthermore, the interval from RT to LT and AFP levels that dropped to normal prior to LT were identified as independent prognostic factors for DFS in the multivariate analysis. No independent prognostic factors for OS were identified in the multivariate analysis, potentially due to the limited sample size.

Toxicity

According to CTCAE version 5.0, none of the patients experienced treatment-related toxicities of grade 3 or higher. Additionally, patients who underwent LT following RACIB did so without any perioperative complications or graft rejection.

Discussion

In our study, for the first time, we examined patients with major PVTT undergoing LT following RACIB treatment for HCC for the first time. We observed a 3-year OS rate of 42% and a median OS of 31.1 months, significantly better than that of patients who only underwent RACIB and historical data for major PVTT (which is often <12 months with systemic therapy alone), highlighting the potential magnitude of survival benefit in carefully selected patients. Consistent results were confirmed through PSM analysis, with no grade 3 or higher toxicity. Additionally, we found that longer intervals from RT to LT, AFP levels dropped to normal, AFP levels reduced by half, and MPR were associated with superior OS. However, multivariate analysis revealed no independent prognostic factors. Therefore, larger-scale studies are needed to identify patients suitable for LT following RACIB.

Multiple studies have confirmed that RT has a modulatory effect on the immune system. Anti-VEGF therapy enhances local intra-tumor oxygenation by improving the status of the vascular endothelium, creating a potential synergistic effect when combined with RT. Based on the findings of our previous study and other literature regarding advanced HCC with PVTT,[12,17] the combination of radiation, antiangiogenesis, and immunotherapy—termed RACIB—demonstrated significant LC and prolonged survival, contributing to promising outcomes. Evidence from previous LT studies on patients with PVTT primarily encompasses mixed types of PVTT. Different sites and extents of PVTT may exhibit distinct biological behaviors and clinical prognostic heterogeneity.[14,15] However, most studies have primarily

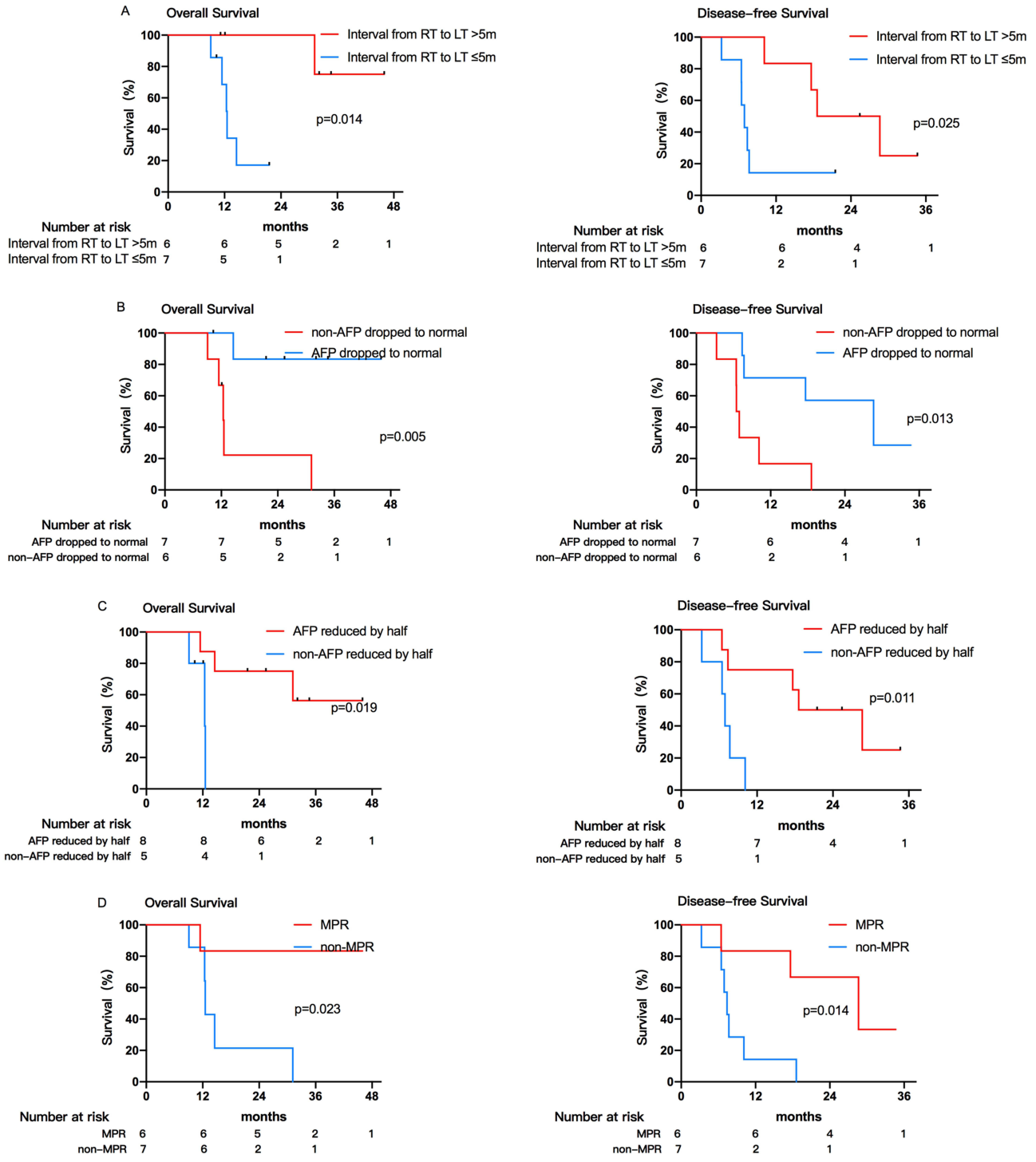

Figure 3 OS and DFS stratified by interval from RT to LT (**A**), AFP dropped to normal (**B**), AFP reduced by half (**C**) and MPR (**D**).

focused on non-major PVTT, overlooking the variations in downstaging therapy. Our results suggest that RACIB therapy followed by LT can still yield favorable outcomes when specifically targeting major PVTT, consistent with findings from other recent reports.[18]

Interestingly, we also found that a longer interval from RT to LT was associated with improved DFS and OS. Although controlled clinical trial data are limited, the OPTN/UNOS and EASL/EORTC guidelines recommend bridging or downstaging therapy for patients with HCC awaiting a donor liver,[7,19,20] acknowledging the importance of disease

stability during the waiting period. Accumulating evidence suggests that the duration of stability following downstaging is not merely a waiting period, but rather a critical observation window that may function as a "test of time" for tumor biology. Soin et al analyzed data from 46 patients with PVTT, drawn from a prospective study of 2348 LT patients between 2006 and 2017.[21] They found that the 5-year OS was better in the successful downstaging group than in the non-downstaging group, although this difference was not statistically significant (57% vs 48%, p=0.79). The researchers suggested that the short median interval of 10 weeks between radiotherapy and LT might have contributed to this unsatisfactory response evaluation. A pilot study by Serenari M indicated that a response to transarterial radioembolization (TARE) at 3 months was a predictive factor for survival, and that an interval of 6 months after downstaging therapy may be more optimal.[22] This aligns with our findings. In our study, the 3-year OS rates for patients with long intervals compared to those in patients with short intervals from RT to LT were 75.0% and 17.1%, respectively (p=0.014). Thus, a prolonged interval after successful downstaging may allow for biological selection of patients with sustained disease control and indolent tumor behavior, while early progression during this period may identify aggressive or treatment-resistant disease. From a clinical perspective, this "test-of-time" strategy may serve as a practical takeaway to optimize candidate selection for LT following RACIB therapy.

Many new transplantation criteria have emerged beyond the Milan criteria, expanding the indications for LT and benefiting more patients, such as those outlined by UCSF and others.[23] A multicenter U.S. study prospectively collected data from 2,645 patients with HCC who underwent LT after downstaging treatment from 2001 to 2015.[24] They compared 10-year post-LT survival between patients with successful downstaging and those whose disease was not downstaged, revealing that OS was significantly better in the successful downstaging group (52.1% vs 43.3%, p<0.001). However, only approximately 20% of the patients in this study had vascular invasion. Previous studies have reported low survival rates in patients with macrovascular invasion in HCC, leading to many of these patients being excluded from LT. However, contrary to these findings, Assalino et al demonstrated that among 30 patients with macrovascular invasion, those who achieved remission of PVTT after downstaging treatment followed by LT were associated with a higher 5-year OS rate of 59.6%.[18] Similarly, Chan et al found that patients exhibiting a major local tumor response (≥60% tumor necrosis) after locoregional therapy had better outcomes post-transplant, with a higher 5-year RFS rate in patients in the major tumor response group than in those who did not achieve major necrosis (91.7% vs 67.5%, p=0.0056).[25] In our study, the 3-year OS rates for patients with MPR and those without MPR were 83.3% and 0% (p=0.023), respectively, indicating a significant difference between the two groups. This finding aligns with the results reported by Grat et al in 127 HCC cases and a multicenter retrospective analysis from the US transplant consortium.[26,27]

Additionally, the AFP level prior to LT has been reported to influence survival outcomes. Choi et al compared 27 patients with non-major PVTT who underwent LT—13 with AFP levels <100 ng/mL and 14 with AFP levels >100 ng/mL. They found that patients with lower AFP levels had significantly better 5-year OS (91.7% vs 32.7%, p=0.044) and DFS (90.9% vs 38.7%, p=0.008).[14] This is consistent with the findings of several other reports.[13,21,28] In the present study, which focused on major PVTT in HCC, we also compared the OS of patients with high and low AFP before LT and found that the 3-year OS in the group with AFP levels dropped to normal was favorable (83.3% vs 0%, p=0.005).

Our study has some limitations. It was a retrospective analysis of data from a single center with inherent and inevitable biases. The small number of included patients limited the ability to confidently identify the prognostic factors. In addition, the reasons for not proceeding to LT in the downstaged RACIB-only group were heterogeneous, which could introduce unmeasured confounding despite the use of propensity score matching. Consequently, further analyses should be conducted in future large-scale studies to validate our findings.

Conclusion

In conclusion, RACIB combination therapy represents an effective and safe downstaging strategy for HCC with major PVTT. Subsequent LT in selected patients, particularly those demonstrating AFP normalization and sustained response over time, can yield significant long-term survival, challenging traditional contraindications.

Reporting Checklist

The authors have completed the STROCSS reporting checklist.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Analysis of patient data for this study was reviewed and approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (No. 24763-6-01).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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