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Clinical Outcomes of Complete Response to Immunotherapy in Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Analysis

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ABSTRACT

The advent of immune checkpoint inhibitors (ICIs) has fundamentally altered the treatment landscape for advanced hepatocellular carcinoma (HCC). Nevertheless, complete responses (CRs) are rarely observed, and their long-term outcomes remain incompletely delineated. This investigation explores the clinical consequences, pathologic associations, and most effective management protocols for HCC patients who achieve CR with ICI-based therapy. We performed a retrospective evaluation of 160 individuals with advanced HCC who achieved CR (70 by mRECIST; 90 by RECIST v1.1) following ICI treatment at 4 tertiary referral centers. Assessed endpoints included recurrence-free survival (RFS), overall survival (OS), and pathological verification of imaging-based CR. Multivariable Cox regression was used to determine factors associated with RFS. CR was documented in 4.8% of the total treated population. This group displayed remarkably favorable survival, with 3-year OS and RFS rates reaching 86% and 55%, respectively. Among 8 subjects who underwent operative resection or hepatic transplantation, 6 (75%) exhibited a pathological complete response—2 within the CR-RECIST v1.1 group and 4 in the CR-mRECIST-only category—thereby affirming the fidelity of imaging. Multivariable assessment disclosed macrovascular invasion (aHR 2.47, P = 0.003) and the presence of extrahepatic metastases (aHR 2.00, P = 0.011) as independent predictors of autonomous recurrence, whereas attaining CR per RECIST v1.1 was associated with improved RFS (aHR 0.62, P = 0.015). Individuals who persisted with ICI administration for ≥ 6 months beyond CR had superior 3-year RFS (81% versus 55%, P = 0.002). Of the 11 subjects who proceeded to curative conversion interventions (resection/transplantation/ablation), 92% remained alive at 3 years with a 75% RFS rate. Although infrequent, CR after ICI therapy corresponds with exceptional survival durations in advanced HCC, even among subsets with high-risk features. CR determined by mRECIST demonstrates sound pathological agreement, allaying concerns regarding anti-angiogenic confounding factors. Maintaining ICI treatment for an extended period after CR, combined with judicious use of conversion therapy, may maximize outcomes. These insights reshape prognostic models and stress the imperative for biomarker-informed approaches to preserve disease remission.

Keywords: Complete response, Hepatocellular carcinoma, Immune checkpoint inhibitors, mRECIST, Survival outcomes

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Introduction

Hepatocellular carcinoma (HCC) stands as one of the most widespread and fatal malignancies worldwide. The disease is commonly identified at a locally advanced or disseminated stage, in which systemic therapy is recommended, provided hepatic function is preserved [1]. Immune checkpoint inhibitors (ICIs) have emerged as a pivotal element of frontline systemic management for advanced HCC, serving as the current benchmark of care [2]. While not inherently curative, ICIs can generate deep-seated and enduring responses in some patients. This phenomenon may permit sequential stage migration, potentially unlocking curative conversion options—such as

resection or liver transplantation—for carefully chosen patients originally presenting with advanced HCC. A minority of subjects may even achieve a complete response (CR) with ICI-based combination regimens [3].

Notwithstanding the growing adoption of immunotherapy in HCC, there is scant knowledge about the long-term outcomes of patients who achieve CR after ICI administration [4]. Currently, no standardized clinical directives exist to steer the care of these individuals after CR, which perpetuates several unresolved issues of substantial importance. Chief uncertainties surround the safety of halting immunotherapy upon achieving CR—and the timing of this decision—as well as whether patients should be advanced to curative-intent conversion strategies (resection or transplantation) or monitored closely for signs of recurrence.

A further point of contention concerns the most appropriate method of defining CR within the immunotherapy context. Although mRECIST is widely used in HCC, its reliability in accurately assessing total tumor necrosis after ICI exposure remains questionable [5]. Certain experts maintain that genuine CR should be classified exclusively using RECIST v1.1 criteria, which require complete resolution of every target lesion [6-8]. Elucidating these questions holds considerable significance, given that achieving CR might translate into extraordinary long-term survival, and that fine-tuning post-CR management could further amplify outcomes.

To remedy these informational deficits, we executed a large-scale, retrospective, multicenter study. The primary intent was to appraise the clinical implications and optimal management strategies for this distinctive group of HCC patients—those who achieved CR following ICI-based systemic treatment.

Materials and Methods

Ethical approval

This research was sanctioned by the Dalian Medical University Institutional Research Committee, and documented informed consent for scientific investigation was obtained from all participants before therapy commencement—every procedure adhered to pertinent guidelines and statutory regulations.

Patient selection

We undertook a retrospective, multicenter review of advanced HCC patients who accomplished radiographic CR upon receiving ICI-based systemic therapy. The study encompassed 160 patients (143 males [89%] and 17 females [11%]) managed between 2015 and 2025 at four tertiary care facilities in China (Henan Cancer Center, Southern University of Science and Technology Hospital, The First Affiliated Hospital of Dalian Medical University, and Shenzhen Qianhai Shekou Free Trade Zone Hospital). Suitable candidates were required to have imaging- or biopsy-confirmed HCC, have received ICI therapy under non-curative intent as decided by a multidisciplinary tumor panel, and have subsequently demonstrated radiographic CR according to either mRECIST or RECIST v1.1 standards. All incorporated patients needed to harbor viable neoplastic tissue at the point of ICI initiation. We omitted those who were administered ICI therapy in the (neo)adjuvant context (before or after surgical removal or ablation) or individuals who received simultaneous locoregional interventions during systemic ICI delivery.

Variable definition

‘Therapeutic conversion therapy’ was characterized as any treatment modality applied to patients who obtained CR, intending to foster durable remission. Pathological complete response (pCR) was meticulously delineated as the total absence of viable malignant cells upon exhaustive histological scrutiny of the entire surgically excised or transplanted hepatic specimen. Two dedicated hepatobiliary pathologists independently examined each specimen. Histologic sections were analyzed by hematoxylin and eosin (H&E) staining to detect residual tumor cells, characterized by nuclear hyperchromasia, prominent nucleoli, and an elevated nuclear-to-cytoplasmic ratio. Specimens underwent thorough sampling, with heightened attention paid to regions corresponding to the pre-treatment tumor location on imaging. The dominant histologic picture in pCR instances comprised widespread necrosis and/or fibrotic cicatrix formation. When imaging and pathologic interpretations were discordant, supplementary immunohistochemical labeling for CD8+ T lymphocytes and PD-L1 was performed to characterize the tumor’s immune microenvironment. Designation as pCR required concordant agreement between the two pathologists. Any operative procedure undertaken after tumor relapse was categorized as management of recurrent disease.

Imaging assessment and follow-up

Structured imaging surveillance was mandated at fixed intervals for every participant across all enrolling sites. Baseline contrast-enhanced CT or MRI was obtained, with repeat scanning scheduled every 6–9 weeks throughout the first treatment year and every 12 weeks thereafter until disease advancement or therapy withdrawal. The identical imaging datasets were evaluated at matching time points using both RECIST v1.1 and mRECIST frameworks for each patient. Central review employing this synchronized, dual-criteria methodology furnished consistent and equitable comparisons of radiographic responses across the entire observation window.

Statistical analysis

We compiled baseline characteristics via standard descriptive approaches. The median observation period was estimated using the reverse Kaplan-Meier estimator to account for censored records. Therapy length spanned from the initiation of immunotherapy to the last delivered dose; individuals still on treatment at the close of data collection were treated as right-censored.

Response assessment time origins were assigned separately per criterion. For the aggregate cohort and the CR-mRECIST subset, the reference date was the earliest scan that met mRECIST complete response criteria (obliteration of all intratumoral arterial enhancement); for the CR-RECISTv1.1 subset, RECIST v1.1 criteria (total clearance of every target lesion) were applied. Three central endpoints anchored the survival analyses: (1) Recurrence-free survival (RFS), timed from initial radiological CR to the earlier of tumor relapse or death, with recurrence-free living subjects censored at their last assessment; (2) Response duration, extending from first CR to relapse, where subjects dying before recurrence were censored at death and relapse-free subjects at last contact; and (3) Overall survival (OS), measured from ICI commencement to death, with survivors censored at their final follow-up.

Kaplan-Meier estimates generated survival plots, with intergroup contrasts evaluated by the log-rank test. Both univariate and multivariate Cox proportional-hazards models were deployed. The multivariate model was refined through stepwise backward elimination of noncontributory covariates (retention criterion $P < 0.05$).

A landmark analysis was incorporated to mitigate immortal-time bias when examining the effect of treatment persistence beyond CR. The landmark anchor was placed 6 months after initial CR documentation. Eligibility for this analysis required being alive and relapse-free at that 6-month juncture. Participants were subsequently dichotomized by their treatment state at the landmark: those who had sustained ICI therapy for ≥ 6 months post-CR (typically still receiving treatment) versus those who had withdrawn from ICI before accruing 6 months of post-CR treatment. RFS was compared across these strata from the 6-month landmark point onward, using the Kaplan-Meier method and the log-rank test.

Statistical analyses were performed using IBM SPSS Statistics (v26.0, SPSS Inc., Chicago, IL), R (v4.3.1, R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (v10.2.1, GraphPad Software, San Diego, CA) for graphical rendering. Two-sided P-values falling below 0.05 were interpreted as statistically meaningful throughout.

Results and Discussion

Patient characteristics and treatment patterns

Spanning September 2015 to November 2023, 3,333 individuals received non-curative ICI therapy for advanced HCC. Of these, 160 (4.8%) attained a complete response and constituted the analytic cohort, comprising 70 with a CR per mRECIST and 90 with a CR per RECIST v1.1. The cohort averaged 65 ± 10 years of age, was heavily male-predominant (n = 143, 89%), and largely exhibited Child-Pugh A hepatic reserve (n = 147, 92%). Disease distribution placed 70.6% of participants (n = 113) at Barcelona Clinic Liver Cancer (BCLC) stage C, while 25.6% (n = 41) were BCLC stage B. Four BCLC stage A patients (2.5%) received ICIs owing to: patient preference (chiefly for recurrent tumors after repeated localized treatments), anatomically challenging tumor sites precluding local therapy, or adverse tumor biology marked by elevated alpha-fetoprotein and paraneoplastic erythrocytosis.

Viral hepatitis represented the predominant underlying hepatic pathology, afflicting 56.3% (n = 90) with HBV- or HCV-related disease (HBV: n = 56; HCV: n = 34). Among HBV carriers, 86.2% (n = 50) were receiving antiviral agents before ICI initiation, 6.9% (n = 4) commenced antivirals concurrently with or following ICI, and the remaining 6.9% (n = 4) had undetectable HBV DNA at baseline. In the HCV subgroup, 22.2% (n = 8) had

detectable HCV RNA at baseline; 8.3% (n = 3) were treated with antivirals during or after ICI, whereas 13.9% (n = 5) were never treated.

Eighty percent (n = 128) had undergone prior surgical or locoregional treatments (TACE: n = 87; resection: n = 64; ablation: n = 42) before systemic therapy, with a median lag of 4.8 months separating the most recent localized intervention from ICI start. Combination ICI regimens (atezolizumab+bevacizumab) were administered to the majority (63.8%, n = 102) **(Table 1).**

Table 1. Baseline data of the 160 patients.

Clinical variable	CR by mRECIST only (n = 70)	CR by RECIST v1.1 (n = 90)	Total (n = 160)
Study center			
The First Affiliated Hospital of Dalian Medical University	34	46	80
Henan Cancer Center	20	23	43
Southern University of Science and Technology Hospital	10	11	21
Shenzhen Qianhai Shekou Free Trade Zone Hospital	6	10	16
Age (years, mean ± SD)	67 ± 10	64 ± 10	65 ± 10
Sex			
Male	63	80	143
Female	7	10	17
Underlying etiology			
Viral	34	56	90
MASLD	18	12	30
ALD	12	10	22
Others	6	12	18
Cirrhosis	56	70	126
Child–Pugh class			
A	63	84	147
B	7	5	12
C	0	1	1
Presence of varices			
Small	45	57	102
Medium/large	25	33	58
History of variceal bleeding	0	3	3
Variceal bleeding prophylaxis			
NSBB	11	8	19
Endoscopic	2	5	7
NSBB + endoscopic	1	5	6
ECOG performance status			
0	42	59	101
1	28	31	59
Macrovascular invasion	27	23	50
Extrahepatic metastases	25	33	58
BCLC stage			
A	1	3	4
B	16	25	41
C	53	60	113
D	0	2	2
Prior treatments			
TACE	30	57	87
Resection	19	45	64
Ablation	21	21	42
Systemic therapy	14	28	42

Radiotherapy	9	13	22
TARE	3	4	7
Previous lines of therapy			
None	25	9	34
One	20	24	44
Two	21	37	58
Three or more	13	22	35
Line of ICI treatment			
First line	55	67	122
Second line	10	18	28
Beyond the second line	5	5	10
ICI regimen type			
Atezolizumab + bevacizumab	52	50	102
Other regimens	18	40	58
CRP ≥ 1 mg/L	25	12	37
AFP (median)	27.0	48.6	40.3

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; BCLC, Barcelona-Clinic Liver Cancer; CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; CRP, C-reactive protein; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; MASLD, metabolic dysfunction–associated steatotic liver disease; NSBB, nonselective beta-blocker; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Treatment discontinuation and clinical outcomes

During observation, 74% of individuals (n = 118/160) permanently stopped ICI therapy for varied reasons: recurrent disease (n = 19, 12%), untoward effects (n = 21, 13%), sustained complete response (n = 43, 33%), curative conversion procedures (n = 8, 5%), or miscellaneous causes (n = 27, 16.9%). Within the adverse-event-driven discontinuation subset, prominent grade 3–4 toxicities prompting definitive cessation included immune-mediated hepatitis (n = 7), colitis (n = 4), pneumonitis (n = 3), and cutaneous reactions (n = 2): remaining events involved other immune-related phenomena or persistent lower-grade toxicities, diminishing quality of life. Every patient—regardless of whether therapy was maintained—underwent protocolized follow-up with contrast-enhanced CT or MRI at routine intervals: every 6–9 weeks in year one and every 12 weeks later, continuing until progression, death, or study termination. This schema ensured standardized monitoring of recurrence and survival throughout the cohort.

Biomarker profiling revealed elevated baseline alpha-fetoprotein (AFP) (≥ 10 ng/mL) in 63.4% of subjects (n = 101). AFP concentrations dropped markedly on therapy, from a median of 39.8 ng/mL (IQR: 4.7–1767.0) at baseline to a nadir of 2.2 ng/mL (IQR: 1.5–3.9). Normalization of AFP (< 10 ng/mL) was reached by 84% of those with initially elevated levels (n = 85/101).

Favorable RFS was observed, with 1-, 2-, and 3-year estimates of 76%, 70%, and 55%. Relapse was recorded in 32% of patients (n = 51), and 11.3% (n = 18) died. OS outcomes were extraordinary, with 1-, 2-, and 3-year rates of 98%, 94%, and 86%, respectively **(Figure 1).** Curative conversion therapy—encompassing resection (n = 4), liver transplantation (n = 4), and ablation (n = 3)—was undertaken in 11 patients (6.9%), with pathological complete response documented in 6 (3.8%). The median time to CR stood at 7 months overall; the CR-mRECIST-only subgroup achieved CR more rapidly (6.9 months) than the CR-RECISTv1.1 subgroup (8.2 months). Extended durability was evident, with 5-year OS approximating 70%. These data attest to the robustness of responses across both CR strata, and subgroup analyses upheld concordant findings even after correcting for possible mRECIST limitations within anti-angiogenic contexts **(Table 2).**

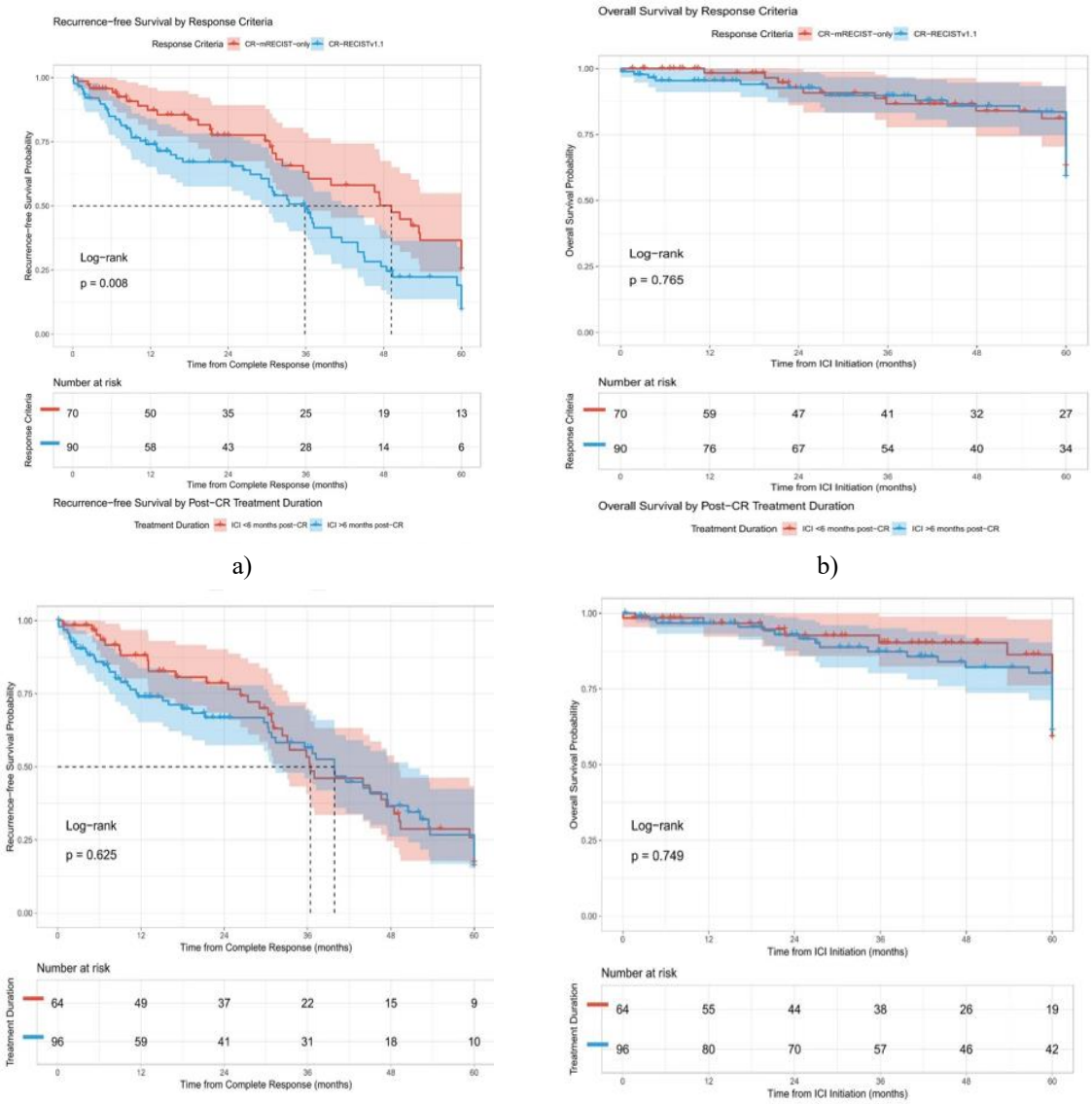


Figure 1. Recurrence-free survival and overall survival stratified by radiographic response criteria and treatment duration.

Table 2. Main outcome results

Outcome	CR by mRECIST only (n = 70)	CR by RECIST v1.1 (n = 90)	Total (n = 160)
Best overall response (RECIST v1.1)			
Complete response	—	90	90
Partial response	62	—	62
Stable disease	8	—	—
Curative conversion therapy			
Resection	4	—	4
Liver transplantation	2	2	4
Ablation	3	—	3
Pathologic complete response	4	2	6
Deaths during follow-up	8	10	18
Time to complete response (median)	6.9	8.2	7
Overall survival			
1-year	99	96	98
2-year	94	94	94

3-year	85	87	86
4-year	78	83	81
5-year	71	70	70
Recurrence-free survival during follow-up			
1-year	79	75	76
2-year	76	67	70
3-year	66	50	55
4-year	51	28	41
5-year	25	11	18

CR-mRECIST, complete response according to modified Response Evaluation Criteria in Solid Tumors; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; FU, follow-up; OS, overall survival; RECISTv1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RFS, recurrence-free survival.

A multivariable model identified several factors that independently shape RFS. The presence of macrovascular invasion was associated with a considerably greater recurrence hazard (adjusted hazard ratio [aHR] 2.47, 95% CI: 1.12–9.46; P = 0.003), and the documentation of extrahepatic metastases likewise increased risk (aHR 2.00, 95% CI: 1.43–6.38; P = 0.011). On the protective side, achieving a CR as defined by RECIST v1.1 was associated with better RFS (aHR 0.62, 95% CI: 0.25–0.94; P = 0.015). Interestingly, the emergence of any treatment-related adverse event (TRAE) appeared to shield against recurrence, with any TRAE tied to lowered risk (aHR 0.67, 95% CI: 0.36–0.99; P = 0.014), and immunosuppressive therapy for TRAEs adding further benefit to RFS (aHR 0.70, 95% CI: 0.35–0.96; P = 0.016). Analysis by underlying liver disease showed that individuals with 'other' etiologies (ruling out viral, alcohol-related, and MASLD) had roughly triple the recurrence risk (aHR 2.89, 95% CI: 1.27–6.36; P = 0.009) compared with those with viral causes. Examining exclusively the 107 patients whose ICI discontinuation was not prompted by tumor relapse, those who extended therapy for at least 6 months beyond CR (n = 56) had notably longer RFS than their counterparts who discontinued earlier (n = 51) (P = 0.008), with 3-year RFS of 66% versus 58%. This separation widened further within the subset who stopped solely owing to a durable CR (n = 57): here, extended (≥ 6 months) post-CR treatment (n = 40) was linked to a 3-year RFS of 81%, whereas early interruption (n = 17) yielded 55% (P = 0.002). Taken as a whole, these findings highlight the powerful roles of intrinsic tumor features and deliberate post-CR management decisions in dictating long-term prognosis following immunotherapy-facilitated CR **(Table 3).**

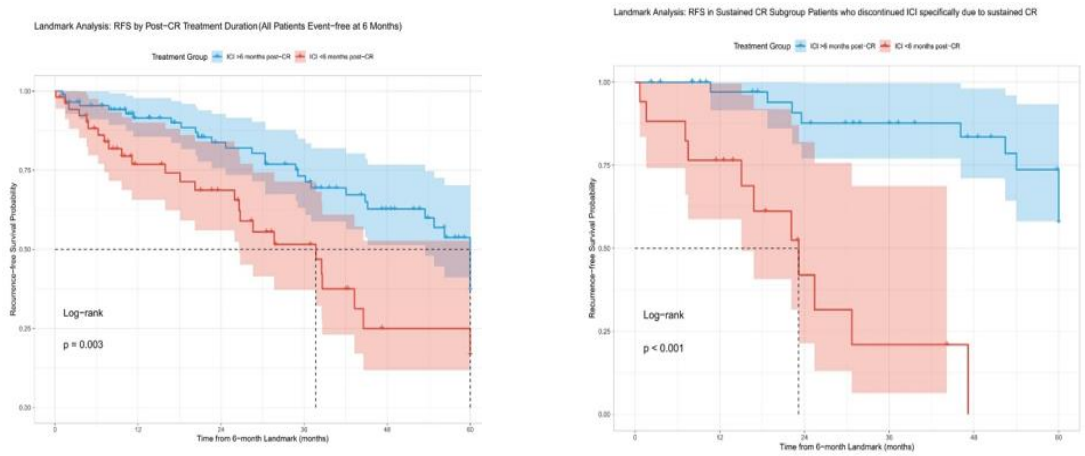
Table 3. Univariate and multivariable analyses of factors associated with recurrence-free survival.

Variable	P-value	Multivariable HR [95% CI]	P-value	Univariate HR [95% CI]
Etiology				
Viral	—	Reference	—	Reference
Alcohol-related	0.234	1.51 [0.65–4.35]	0.087	1.75 [0.94–6.88]
MASLD	0.386	1.57 [0.66–4.67]	0.128	1.45 [0.67–3.08]
Others	0.009	2.89 [1.27–6.36]	0.033	2.43 [1.25–4.52]
ECOG performance status				
0	—	Reference	—	Reference
1	0.774	1.34 [0.35–3.86]	0.634	1.26 [0.56–4.26]
Macrovascular invasion				
Absent	—	Reference	—	Reference
Present	0.003	2.47 [1.12–9.46]	0.005	2.32 [1.25–7.43]
Extrahepatic metastases				
Absent	—	Reference	—	Reference
Present	0.011	2.00 [1.43–6.38]	0.012	1.97 [1.05–5.43]
Alpha-fetoprotein (ng/mL)				
<1000	—	Reference	—	Reference
≥1000	0.672	1.84 [0.54–5.05]	0.437	1.76 [0.63–4.37]
Prior locoregional therapy				
No	—	Reference	—	Reference
Yes	0.752	1.09 [0.64–1.87]	0.541	1.18 [0.69–2.01]
Any TRAE	0.014	0.67 [0.36–0.99]	0.095	0.56 [0.24–1.28]
Immunosuppression for TRAE	0.016	0.70 [0.35–0.96]	0.032	0.67 [0.43–0.95]

CR-RECIST v1.1	0.015	0.62 [0.25–0.94]	0.008	0.58 [0.19–0.87]

aHR, adjusted hazard ratio; CR-RECISTv1.1, complete response according to Response Evaluation Criteria in Solid Tumors version 1.1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MASLD, metabolic dysfunction-associated steatotic liver disease; TRAE, treatment-related adverse event.

To more thoroughly isolate the impact of lengthened ICI exposure, a 6-month post-CR landmark analysis was designed to counteract immortal time bias. Of 142 individuals alive and relapse-free when the 6-month landmark was reached, the group that persisted on ICIs for ≥ 6 months beyond CR (n = 89) experienced markedly better ensuing RFS than the group that halted treatment sooner (n = 53) (3-year post-landmark RFS: 74% vs 52%; P = 0.003). The magnitude of this advantage was further heightened upon restricting the lens to patients whose ultimate motive for stopping therapy was specifically a sustained CR (3-year post-landmark RFS: 91% with prolonged therapy vs 22% with early cessation; P < 0.001) **(Figure 2).**



a) b)

Figure 2. Landmark analysis of RFS by Post-CR treatment duration.

Treatment duration and survival outcomes by response criteria

The length of ICI administration varied by response designation: it spanned 20.1–24.4 months (median 22.2 months) among patients with CR-RECISTv1.1, compared with 22.8 months (95% CI: 2.6–25.1) for the CR-mRECIST-only group. The time gap from ICI initiation to first complete response also showed divergence, with CR-RECISTv1.1 patients (n = 90) achieving CR at a median of 8.2 months (95% CI: 6.2–10.5), while the CR-mRECIST-only group (n = 70) did so at 6.9 months (95% CI: 5.1–8.8); **(Table 2).**

Turning to recurrence events, 38% of patients in the CR-RECISTv1.1 arm (n = 34) and 24% in the CR-mRECIST-only arm (n = 17) went on to develop tumor progression after initially achieving CR. Deaths recorded during the observation period amounted to 11% (n = 10) and 11% (n = 8) in each respective group **(Table 2).**

Survival estimates placed the median RFS from first CR at 28.3 months (95% CI: 18.1–38.5) for CR-RECISTv1.1 patients, with 1-, 2-, and 3-year RFS rates of 75%, 67%, and 50%, respectively. The CR-mRECIST-only arm exhibited a longer median RFS, with corresponding rates of 79%, 76%, and 66% **(Table 2)**. OS was outstanding in both arms. Median OS, computed from the start of immunotherapy, was not reached among CR-RECISTv1.1 patients, who had 1-, 2-, and 3-year OS rates of 100%, 98%, and 87%, respectively. The CR-mRECIST-only group mirrored this excellent survival picture with rates of 96%, 91%, and 85% across the same benchmarks.

Median time to recurrence

Among the 51 patients who experienced disease relapse following CR, the median latency from initial CR documentation to recurrence was 17.8 months (95% CI: 13.4–22.2). Segregating by response definition unveiled that those with RECIST v1.1-defined CR relapsed after a median of 15.6 months (95% CI: 10.8–20.4), whereas those with mRECIST-only CR relapsed after a median of 22.3 months (95% CI: 16.1–28.5). The time distribution of these events showed that 68% of recurrences occurred within the first 18 months after CR, while 19% occurred beyond 36 months, underscoring that most recurrences surface early, yet a fraction occur late, beyond the 3-year mark.

Curative conversion therapy outcomes

Eleven patients (7%) underwent procedures with curative intent once CR was confirmed, split among liver transplantation (n=4), surgical resection (n = 4), and ablation (n = 3) **(Table 2).** These patients had earlier been exposed to various ICI-based regimens.

Microscopic examination of resected or explanted liver specimens (n = 8) verified the absence of viable tumor in 6 instances (75%)—encompassing both CR-RECISTv1.1 patients and 4 of the 6 CR-mRECIST-only patients. Remarkably, in the strata that had received anti-angiogenic combination therapy and fulfilled CR-mRECIST criteria, 4 out of 6 patients (67%) who eventually underwent resection or transplantation exhibited complete pathological clearance.

Over the course of observation, tumor recurrence surfaced in 2 recipients of conversion therapy (15%), with 1 death (8%) documented. This subset achieved durable outcomes, as demonstrated by 1-year and 3-year RFS rates of 75% and OS rates of 92% at both intervals.

Patterns and management of disease recurrence

Through the follow-up period, 51 patients experienced a return of the disease. The most prevalent radiological presentations consisted of new hypervascular hepatic nodules (n = 36, 67%), freshly detected extrahepatic deposits (n = 5, 9%), reemergence of previously hypovascular lesions now displaying hypervascular enhancement (n = 4, 7%), new hypovascular liver lesions (n = 3, 6%), and worsening of pre-existing hypovascular lesions (n = 3, 6%). The remaining cases showed mixed phenotypes of recurrence. At the point of recurrence detection, the median AFP level was 4.8 ng/mL (range: 1.0–3884.0), and the majority of patients (n = 44, 81%) preserved Child-Pugh A hepatic function.

Treatment strategies for recurrent disease

Of the 50 patients who were actively managed for recurrent disease, the most frequently applied first-line modalities included: local-regional interventions, offered as monotherapy or alongside systemic agents (n = 16, 32%); ablation (n = 13, 26%); a switch to distinct systemic regimens (n = 13, 26%); reinitiation of the originally administered ICI protocol (n = 5, 9%); and combinations of local plus systemic treatments (n = 3, 6%).

Rechallenge with immune checkpoint inhibitors

Eight patients whose tumors relapsed after ICI cessation were rechallenged using the same regimen. One further patient, maintained on durvalumab beyond CR, received add-on tremelimumab at relapse while staying on durvalumab; an additional patient was restarted on this combination upon recurrence. Rechallenge or continuation of the original regimen was instituted as first-line (n = 6), second-line (n = 3), or third-line (n = 1) therapy post-recurrence. Among these rechallenged patients, the objective response rate (ORR) was 20%, and the disease control rate (DCR) was 70% per RECIST v1.1; one patient (10%) had progressive disease, and the status of two patients (20%) remained unevaluable.

This multicenter analysis establishes that CR following ICI-based regimens, while attained in fewer than 5% of advanced HCC cases—a proportion mirroring phase III trial outputs of 1.5%–5.5% across ICI backbones [9, 10]—translates into remarkably prolonged survival. Individuals who reached CR achieved extraordinary metrics, with 1- and 3-year OS rates of 98% and 86%, respectively, and corresponding RFS rates of 76% and 55%, respectively. Crucially, these survival gains persisted within subgroups typically deemed high-risk, including those with macrovascular invasion or extrahepatic disease, raising the possibility that CR may single out a biologically privileged population capable of mounting especially potent anti-tumor immunity. The firm correspondence between mRECIST-defined CR and pCR bolsters the practical validity of this response standard in the contemporary immunotherapy era and helps allay concerns regarding its interpretation when anti-angiogenic agents are co-administered. Viewed holistically, these insights underscore the game-changing potential of sustained, immune-driven remissions in a disease once defined by meager therapeutic success.

A particularly striking finding was that patients burdened with macrovascular invasion or extrahepatic metastases [11, 12]—features that independently forecasted greater recurrence likelihood (aHR 2.47 and 2.00, respectively)—could still secure CR and go on to experience durable benefit. This apparent contradiction suggests that the small fraction of the most advanced tumors that nevertheless undergo complete regression may represent a molecularly unique niche characterized by exceptionally vigorous immune engagement [13]. Our study cohort

was enriched with individuals who had previously received locoregional treatments, reflecting the typical real-world trajectory of advanced HCC, in which sequential therapeutic lines are the norm. We recognize that such prior interventions might confound interpretation, potentially enriching for tumors of indolent biology or remodeling the tumor microenvironment in ways that influence subsequent ICI sensitivity. To confront this directly, the history of prior locoregional therapy was incorporated as a covariate in the multivariable model. That analysis revealed it was not an independent determinant of RFS (aHR 1.09, 95% CI: 0.64–1.87; P = 0.752), implying that while antecedent treatments are ubiquitous in this setting, durable CR achievement and downstream outcomes are more decisively governed by factors captured in our final model—namely, freedom from macrovascular invasion, freedom from extrahepatic metastases, and depth of radiographic regression (CR-RECISTv1.1). Whether prior procedures might nonetheless function as an immunologic primer remains an open avenue of inquiry.

Where RECIST v1.1 demands clearance of all target and non-target deposits, mRECIST centers solely on the abolition of intratumoral arterial enhancement. Tellingly, of six patients adjudicated as CR by mRECIST who subsequently came to resection or transplantation, four (67%) harbored no viable tumor on pathology. This tight pathological linkage, together with reassuring recurrence rates and survival trajectories in the mRECIST CR subset, supports the notion that ICI-induced mRECIST responses often denote genuine tumor necrosis rather than simply pharmacologic modulation of vascular perfusion—a differentiation rendered clinically salient by the controversy surrounding mRECIST reliability during anti-angiogenic treatment. Though sample-size constraints apply, these findings merit replication in larger cohorts undergoing tissue-based confirmation after immunotherapy.

Maintaining ICI exposure for an extended period after CR achievement may be associated with better outcomes. This observation dovetails with a broader oncologic literature indicating that suspending anti-PD (L)1 agents within 12 months amplifies relapse risk [14-16]. For metastatic melanoma, the current European Society for Medical Oncology guidance recommends continuing immunotherapy for at least 6 months beyond a confirmed complete response, based on improved disease-free survival among patients meeting that threshold [17]; by contrast, rates of recurrence climb among those receiving shorter post-response treatment intervals. In our HCC dataset, patients who continued ICI for ≥6 months after CR had significantly better RFS than earlier stoppers, an advantage most apparent in the subgroup who halted treatment solely because of a durable complete response. A landmark analysis, undertaken to reduce confounding, corroborated that extending ICI at least 6 months beyond CR was independently associated with superior subsequent RFS (3-year post-landmark RFS: 85% vs 62%). These findings suggest that a post-CR ICI continuation period of at least 6 months may be advisable in HCC practice.

Although the existing evidence favors prolonged immunotherapy delivery, more sophisticated biomarkers are urgently needed to individualize cessation decisions. Circulating tumor DNA (ctDNA) profiling represents an appealing tool: ctDNA clearance might identify individuals suitable for safe discontinuation, whereas a persistent ctDNA signal could flag residual tumor, warranting continued pressure [18]. Nevertheless, in HCC, ctDNA-based monitoring is still exploratory and awaits rigorous trial validation before integration into routine clinical algorithms [19].

In contradistinction to the colorectal cancer liver metastasis paradigm—where consolidation local treatment after systemic response is standard of care [20, 21]—this approach remains in the investigational realm for HCC. In the present report, only a small sliver of patients proceeded to curative-intent conversion procedures, despite exceptionally strong long-term results among that minority. The overriding therapeutic ambition should be the attainment of treatment-free, enduring remission, a goal that may become reachable through wider uptake of conversion therapy in optimally selected candidates. A recent multicenter evaluation of atezolizumab/bevacizumab followed by conversion therapy documented that 23% of patients reached treatment-free status without relapse [22]. However, that analysis specifically excluded individuals with vascular invasion or extrahepatic metastases. Refining the criteria for optimal candidate selection stands as a priority for future research.

From a clinical oncology vantage point, ceasing ICI after CR demands a careful trade-off: the RFS dividend of protracted treatment must be weighed against the accumulating toll of toxicities and economic strain. Our observations, complemented by strong pathological concordance with mRECIST-defined CR, affirm imaging-based CR as a clinically meaningful endpoint in HCC immunotherapy, substantiating mRECIST as a dependable surrogate for true tumor necrosis, distinct from the vascular footprint of anti-angiogenic agents. Trials moving

forward should embed quality-of-life instruments and standardized histological correlatives to better inform both post-CR management and patient selection for conversion strategies.

Although this work sheds meaningful light on the management of HCC patients who reach complete remission with immunotherapy, certain limitations must be acknowledged. The retrospective architecture opens the door to selection bias and therapeutic heterogeneity across enrolling sites. The relatively small number of patients attaining CR—especially those undergoing curative conversion—constrains statistical power to dissect subgroups. Employing a range of ICI combinations and regimens may also obfuscate outcome attribution. Moreover, the extent of follow-up, while substantial, may still fall short of capturing very late relapses or late-emerging toxicities. Finally, the lack of uniform rules for discontinuing immunotherapy or proceeding to conversion therapy underscores the necessity for prospective corroboration of these findings. To mitigate the influence of these limitations on our central conclusions, we implemented centralized imaging review to standardize response determination, adhered to strict, uniform entry criteria, and adjusted for the enrolling center in multivariable modeling, which did not emerge as an independent, significant factor. Nonetheless, the specters of residual confounding and selection bias cannot be completely exorcised.

Conclusion

To summarise, this national, multicenter effort documents that, while rare, a complete response to ICI-based therapy is associated with exceptional survival in advanced HCC. Our data reinforce the clinical meaningfulness of mRECIST-defined responses, which align tightly with pathologic complete remission. The apparent advantage of continuing immunotherapy for at least 6 months beyond CR, alongside the promising results of selective conversion therapy, suggests viable strategies to optimize outcomes in this population. Yet the observation that some patients whose tumors harbor adverse features—macrovascular invasion or extrahepatic metastases—nonetheless achieve durable CRs despite heightened baseline recurrence vulnerability argues for deeper mechanistic exploration of the biologic underpinnings. Future studies should prospectively test ctDNA-informed surveillance and uniform conversion protocols to achieve sustained treatment-free remission. These findings collectively highlight the transformative power of immunotherapy in HCC while underscoring the knowledge gaps that demand urgent attention.

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