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Complete Response to Locoregional Therapy Plus Immunotherapy for Hepatocellular Carcinoma

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IMPORTANCE Previous studies showed that 42% to 50% of patients with locally advanced hepatocellular carcinoma (HCC) achieved complete remission (CR) after combined locoregional therapy (LRT) plus immunotherapy (IO). However, data on predictors of CR and long-term clinical outcomes without surgery and after discontinuation of IO are lacking.

OBJECTIVE To assess the long-term clinical outcomes among patients with unresectable HCC who achieved CR after LRT-IO and were placed on a watch-and-wait protocol.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included patients with unresectable HCC who achieved CR after LRT-IO in 2 prospective studies between January 2018 and December 2022. The time of data cutoff was June 2023. Radiologic CR was defined per modified Response Evaluation Criteria in Solid Tumors. All patients underwent close surveillance after CR without surgical interventions, and IO was discontinued.

EXPOSURE All patients had received stereotactic body radiotherapy followed by anti–programmed cell death protein 1 or anti–programmed death ligand 1 therapy. Forty-nine patients had received a dose of transarterial chemoembolization before stereotactic body radiotherapy.

MAIN OUTCOMES AND MEASURES The primary outcome was the 3-year overall survival (OS) rate. Secondary outcomes included the 3-year time-to-progression rate, 3-year local control rate, and relapse pattern. Factors associated with CR were analyzed using multivariate analyses.

RESULTS A total of 63 patients were enrolled (58 male [92.1%]; median age, 69 years [range, 18-90 years]); 38 patients (60.3%) had macrovascular invasion, and the median tumor diameter was 10 cm (range, 3.8-31.1 cm). The median follow-up time was 34.7 months (95% CI, 6.5-64.6 months). Twenty-nine patients (46.0%) achieved CR. The patients achieving CR had a significantly better 3-year OS rate than patients not achieving CR (75.5% [95% CI, 58.2%-98.3%] vs 28.1% [95% CI, 7.4%-29.4%]; $P < .001$). Among the 29 patients with CR, the 3-year time-to-progression rate was 58.7% (95% CI, 38.7%-79.1%) and the 3-year local control rate was 90.5% (95% CI, 78.2%-100%). Ten patients (34.5%) developed recurrence; among them, 6 (60.0%) with solitary intrahepatic disease relapse underwent curative surgical treatment. The absence of tumor vascular invasion (odds ratio, 0.30; 95% CI, 0.10-0.89) and the sum of the largest lesion diameters of 8 cm or less (odds ratio, 0.26; 95% CI, 0.07-0.98) were associated with CR.

CONCLUSIONS AND RELEVANCE This cohort study of LRT-IO with long-term follow-up data found a durable response in patients with locally advanced unresectable HCC. Long-term survival was attainable in patients with radiologic CR. Further randomized clinical trials are warranted.

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Supplemental content

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Unresectable hepatocellular carcinoma (HCC) is generally associated with a dismal prognosis.[1] Moreover, complete remission (CR) is a rare event in patients with HCC treated with transarterial chemoembolization (TACE), tyrosine kinase inhibitor, or immunotherapy (IO).[2-4] Interest is growing in combining locoregional therapy (LRT) with IO by using the synergistic activation of the immune system and the complementary antitumor mechanism.[5-7] In a phase 2 clinical trial conducted by our group, 42% of patients with locally advanced HCC attained radiologic CR after receiving a novel combination of sequential TACE and stereotactic body radiotherapy (SBRT) followed by IO (START-FIT).[8]

This promising response presents a new challenge for clinicians regarding the optimal treatment of patients with CR. To our knowledge, no published data report the long-term outcomes of CR in patients with HCC. To address this question, we performed a post hoc analysis to evaluate the oncologic outcomes among all patients who received combined LRT-IO for locally advanced HCC in our institutions.

Key Points

Question What are the long-term oncologic outcomes in patients with locally advanced hepatocellular carcinoma who are placed on a watch-and-wait protocol after achieving radiologic complete remission (CR) with combined locoregional therapy (LRT) and immunotherapy (IO)?

Findings In this cohort study of 63 patients, 46% achieved CR after LRT-IO and 76% of patients with CR were alive at 3 years.

Meaning Watch and wait may be a feasible strategy in patients who have achieved CR after LRT-IO, and further randomized clinical trials are warranted.

Methods

Study Design and Participants

This multicenter cohort study included patients with locally advanced, unresectable HCC who were diagnosed and treated with LRT-IO at Queen Mary Hospital (Hong Kong, China), Tuen Mun Hospital (Hong Kong, China), and the University of Hong Kong–Shenzhen Hospital (Shenzhen, China) between January 2018 and December 2022. Tumors were classified as unresectable after a multidisciplinary team review based on the following criteria: (1) R0 resection was not feasible, (2) remnant liver volume of less than 30% in patients without cirrhosis or less than 40% in patients with cirrhosis and/or indocyanine green clearance greater than 15%, (3) Barcelona Clinic Liver Cancer (BCLC) stage B and exceeding the "up-to-7" criteria (the sum of the number of tumors and the diameter of the largest tumor [in centimeters] is ≤7), or (4) BCLC stage C. This was a post hoc analysis that included patients from the START-FIT phase 2 trial (cohort A)[8] and the LRT-IO prospective cohort (cohort B). All patients provided written informed consent, and the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster approved the study protocol. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Detailed eligibility criteria were previously reported (eTable 1 in Supplement 1).[8] Briefly, eligible patients had a confirmed diagnosis of unresectable HCC, Eastern Cooperative Oncology Group performance status of 0 to 1, Child-Pugh liver function score of A5 to B7, tumor size of 5 cm or greater, and number of tumor lesions of 3 or fewer. Patients with extrahepatic disease were excluded from the study. Eligible patients underwent TACE on day 1 followed by 5 fractions of SBRT on day 28. Anti-programmed death ligand 1 (PD-L1) antibody was administered 14 days after SBRT and every 2 weeks thereafter. Treatment in cohort B was similar except that TACE was omitted in patients with poor kidney function, main portal vein thrombosis, Eastern Cooperative Oncology Group performance status of 2, or on patient refusal and anti-programmed cell death protein 1 (PD-1) antibody was the choice for IO (eMethods in Supplement 1).

Patients who achieved CR were placed on close surveillance without undergoing surgical treatment. Complete remission was defined as the absence of viable tumor components according to modified Response Evaluation Criteria in Solid Tumors assessed through multiphasic imaging (either computed tomography [CT] or magnetic resonance imaging). During close surveillance, CT or magnetic resonance imaging of the abdomen was performed every 3 months. Additionally, CT of the thorax was performed every 4 to 6 months. All patients were followed up every 3 months for physical examination, hepatic function, and α-fetoprotein levels.

Outcomes

Overall survival (OS) was estimated from the start of treatment until death. The time to progression (TTP) was estimated from treatment to the first documented progressive disease (PD). The objective response rate was defined according to modified Response Evaluation Criteria in Solid Tumors. Time to CR was estimated from the start of treatment to the first documented CR. The duration of CR was estimated from the time of the first documented CR until the occurrence of the first documented PD or death. The local control rate was defined as the absence of recurrence within 80% of the isodose volume.

Statistical Analysis

The objective response rate and corresponding 95% CI were estimated using the Clopper-Pearson method. Survival outcomes and local control were analyzed using Kaplan-Meier methods. Cox proportional hazards regression analysis was used to evaluate the association between baseline factors and OS. Logistic regression was used to identify factors associated with CR. Statistical significance was set at 2-sided $P < .05$. All analyses were performed using SPSS, version 27.0 (IBM Corp).

Results

Patients

Between January 2018 and June 2022, 63 patients (5 female [7.9%]; 58 male [92.1%]; median age, 69 years [range, 18-90

Table. Patient and Tumor Characteristics

Characteristic	Patients (N = 63)[a]
Age, median (range) [IQR], y	69 (18-90) [13.5]
Sex	
Female	5 (7.9)
Male	58 (92.1)
ECOG performance status	
0	31 (49.2)
1-2	32 (50.8)
Cause of cirrhosis	
Hepatitis B	44 (69.8)
Hepatitis C	4 (6.3)
Alcohol use	3 (4.8)
Cryptogenic	12 (19.0)
Child-Pugh score	
A5	51 (81.0)
A6	11 (17.5)
B7	1 (1.6)
Albumin bilirubin score	
Grade 1	37 (58.7)
Grade 2	26 (41.3)
INR, median (range)	1.1 (0.9-1.5)
ALT level, median (range), U/L	42 (13-102)
Creatinine level, median (range), mg/dL	0.95 (0.36-2.82)
Platelet count, median (range), $\times 10^3$/μL	191 000 (79 000-778 000)
BCLC stage	
A	14 (22.2)
B	11 (17.5)
C	38 (60.3)
Reason for unresectable tumor	
Inadequate liver remnant volume and/or poor ICG	14 (22.2)
BCLC stage B and "up-to-7" criteria[b]	11 (17.5)
BCLC stage C without extrahepatic spread	38 (60.3)
Tumor vascular invasion	
No	25 (39.7)
Yes	38 (60.3)
Lesions, No.	
1	24 (38.1)
2	35 (55.6)
≥3	4 (6.3)
Size of largest lesion, median (range), cm	8.8 (3.5-18.0)
Sum of largest diameters of lesions, median (range), cm	10.0 (3.8-31.1)
Baseline AFP, ng/mL	
≤400	47 (74.6)
>400	16 (25.4)
Prior treatment	
No	57 (90.5)
Yes	
Any	6 (9.5)
Resection	5 (7.9)
Ablation	1 (1.6)
Locoregional treatment	
SBRT and immunotherapy	14 (22.2)
TACE, SBRT, and immunotherapy	49 (77.8)
SBRT dose, median (range), Gy	35.0 (27.5-450)
Immunotherapy	
Avelumab	33 (52.4)
Nivolumab	27 (42.9)
Pembrolizumab	3 (4.8)

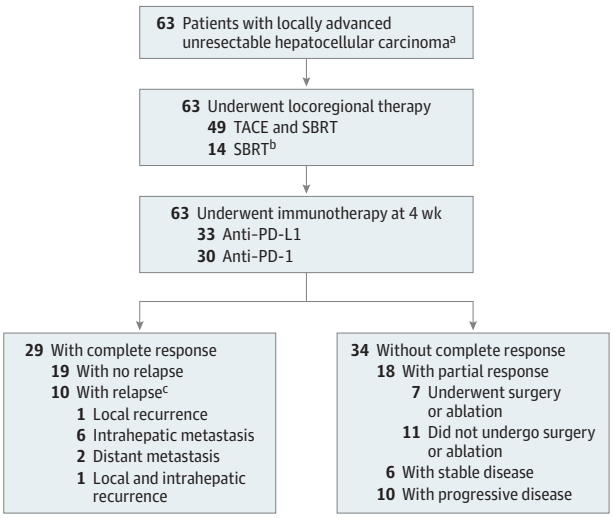
Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ICG, indocyanine green; INR, international normalized ratio; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization.

SI conversion factors: To convert AFP to μg/L, multiply by 1.0; ALT to μkat/L, multiply by 0.0167; creatinine to μmol/L, multiply by 88.4; and platelets to $\times 10^9$/L, multiply by 1.0.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Sum of the number of tumors and the diameter of the largest tumor (in centimeters) is ≤7.

Figure 1. Study Flowchart



PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SBRT, stereotactic body radiotherapy; and TACE, transarterial chemoembolization.

[a] Cohort A included 33 patients, and cohort B included 30 patients.

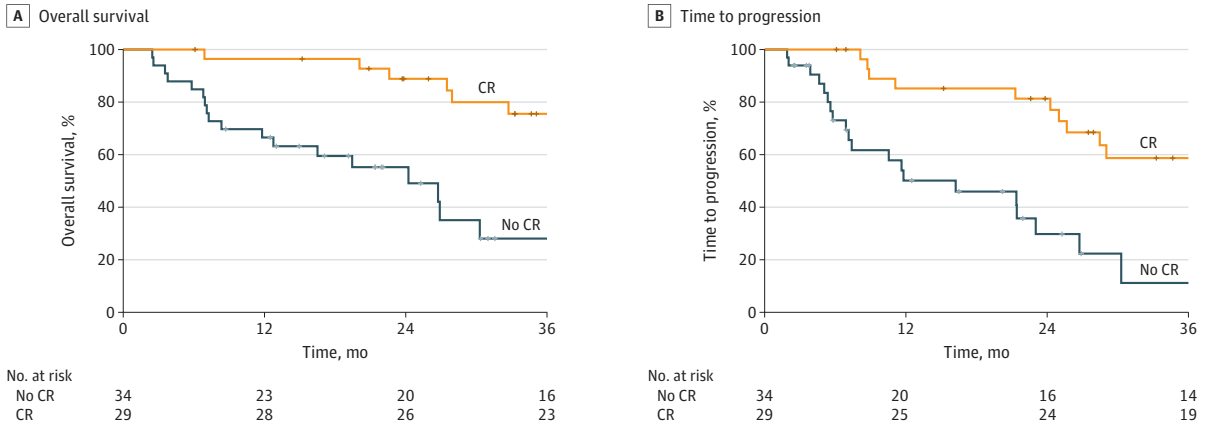
[b] TACE was omitted for the following reasons: poor kidney function (n = 5), Eastern Cooperative Oncology Group performance status of 2 (n = 4), extensive portal vein thrombosis (n = 3), and patient's refusal (n = 2).

[c] The 6 patients who experienced solitary intrahepatic relapse received curative treatment, and the 4 with multifocal recurrence or dissemination received palliative treatment.

(continued)

years]) with locally advanced, unresectable HCC were treated with LRT followed by at least 1 dose of IO. Of the 63 patients enrolled, 38 (60.3%) had macrovascular invasion, and the median tumor diameter was 10 cm (range, 3.8-31.1 cm). Baseline

Figure 2. Comparison of Overall Survival and Time to Progression in Patients With Complete Remission (CR) vs Patients Without CR



characteristics of the study population are presented in the **Table** and eTable 2 in Supplement 1.

At the time of data cutoff (June 30, 2023), the median follow-up time was 34.7 months (95% CI, 6.5-64.6 months). The eligible patients included 33 (52.4%) who received START-FIT in cohort A; 16 (25.4%) who received combined TACE, SBRT, and IO in cohort B; and 14 (22.2%) who received SBRT combined with IO in cohort B. The median SBRT dose was 35.0 Gy in 5 fractions (range, 27.5-45.0 Gy in 5 fractions). Patients received a median of 5.6 months of IO (IQR, 3.5-8.4 months). For IO, 33 patients in cohort A (100%) received avelumab (anti-PD-L1 antibody), whereas 27 patients (90.0%) and 3 patients in cohort B (10.0%) received nivolumab and pembrolizumab (anti-PD-1 antibodies), respectively. Fifteen patients (23.8%) experienced at least 1 grade 3 or higher treatment-related adverse event. The most common grade 3 or higher treatment-related adverse events were transient increases in alanine aminotransferase, aspartate aminotransferase, or bilirubin levels (10 [66.7%]). Eight patients (12.7%) experienced grade 3 or higher immune-related adverse events (IRAEs) (5 [7.9%], hepatitis; 3 [4.8%], dermatitis). Child-Pugh score deterioration of 2 or greater was detected in 5 of 49 patients (10.2%) at 3 months, 4 of 44 (9.1%) at 6 months, and 2 of 32 (6.2%) at 12 months.

Association Between CR and Survival and Potential Factors Associated With CR

Among the 63 patients, 29 (46.0%) achieved CR, 18 (28.6%) achieved partial response, 6 (9.5%) achieved stable disease, and 10 (15.9%) experienced PD (**Figure 1**). Among 29 patients with CR, 10 (34.5%) had BCLC stage A disease and 19 (65.5%) had BCLC stage B or C disease. The patients who achieved CR had significantly better TTP rates than patients who did not achieve CR (3 years: 58.7% [95% CI, 38.7%-79.1%] vs 11.2% [95% CI, 0.0%-24.8%]; $P < .001$) (**Figure 2** and eTable 3 in Supplement 1). Similarly, patients with CR had significantly improved OS rates (3 years: 75.5% [95% CI, 58.2%-98.3%] vs 28.1% [95% CI, 7.4%-29.4%]; $P < .001$) (Figure 2). Treatment response (hazard ratio, 5.10; 95% CI, 1.90-13.64; $P = .001$) was the only independent factor associated with survival (eTable 4 in Supplement 1). The absence of tumor vascular invasion (odds ratio, 0.30; 95% CI, 0.10-0.89) and the sum of the largest lesion diameter of 8 cm or less (odds ratio, 0.26; 95% CI, 0.07-0.98) were independently associated with CR (eTable 5 in Supplement 1). Notably, there was no significant association between the duration of IO, type of locoregional therapy, and the occurrence of grade 3 or higher IRAEs with the chance of CR (eTable 5 in Supplement 1).

Clinical Outcomes Among Patients Who Achieved CR

All patients discontinued IO; of the 29 patients with CR, 25 (86.2%) had IO discontinued once they experienced CR and 4 (13.8%) had IO discontinued after a median of 6.7 months (IQR, 3.8-11.9 months) following CR. The data for individual patients are presented in eTables 6 and 7 and eFigure 1 in Supplement 1.

The median time to CR was 5.4 months (95% CI, 4.7-7.3 months). The median duration of CR was 25.7 months (95% CI, 23.6-36.3 months) (eFigure 2 in Supplement 1). Six of the 29 patients who achieved CR (20.7%) died (HCC progression, 2 [6.9%]; COVID-19, 1 [3.4%]; cardiac arrhythmia, 2 [6.9%]; and cirrhosis, 1 [3.4%]). A total of 10 patients (34.5%) experienced relapse, of whom 6 had solitary intrahepatic disease relapse and received curative surgical treatment and 4 had multifocal or disseminated disease and were treated with palliative intent. Local in-field disease relapse occurred in 2 patients (6.9%), with a 3-year local control rate of 90.5% (95% CI, 78.2%-100%) (eFigure 3 in Supplement 1). Out-of-field intrahepatic disease relapse was the most common mode of initial treatment failure (eTable 8 in Supplement 1). Duration of IO (≤6 vs >6 months) (eFigure 4 in Supplement 1), type of IO (eFigure 5 in Supplement 1), and the occurrence of grade 3 or higher IRAEs (eFigure 6 in Supplement 1) were not significantly associated with 3-year OS and TTP rates in patients.

Discussion

To our knowledge, this is the first in-depth analysis of CR in patients with HCC and the largest prospective series of patients with locally advanced HCC treated with neoadjuvant

LRT-IO. The present analysis reported a CR rate of 46.0% in patients with locally advanced unresectable HCC receiving LRT-IO and further demonstrated that 75.5% of patients with CR remained alive at 3 years. Our results support the premise that LRT could work synergistically with IO to enhance the host response to provide durable tumor control.[9-11]

The watch-and-wait strategy has been extensively studied in patients with other cancers, including rectal and esophageal cancers, who achieved clinical CR after combined chemoradiotherapy.[12,13] Yet, limited data on watch and wait exist in the population with HCC. The main concern remains whether survival and chance of curative treatment are compromised in patients who experience relapse. Our study demonstrated that survival was satisfactory among 29 patients with CR (10 patients [34.5%] with BCLC stage A disease and 19 [65.5%] with BCLC stage B or C), with 3-year OS and TTP rates of 75.5% and 58.7%%, respectively. These results compared favorably with those of other forms of curative treatment.[14,15] With median follow-up of 3 years, 65.5% (19 of 29) of patients with CR were alive without recurrence and did not require additional HCC treatment. Among 10 patients with recurrence, 60.0% were still eligible for surgical treatment, and their 3-year OS rate was not compromised. Our study provides preliminary evidence supporting watch and wait as a reasonable strategy for patients who achieved CR after neoadjuvant LRT-IO.

To our knowledge, no data are available on the long-term outcomes of patients with HCC who achieved a CR and discontinued IO. Among the 29 patients who achieved CR and received a median duration of 6 months of IO, 34.5% experienced relapse at 3 years. Furthermore, no significant association was noted between treatment duration and risk of relapse. Nevertheless, long-term data are required to determine whether discontinuation of treatment after CR is a safe and feasible strategy.

Limitations

This study has several limitations that merit further discussion. First, a significant heterogeneity was present in the choice of LRT and IO. However, our analyses demonstrated that omitting TACE or opting for IO was not associated with survival outcomes. Second, the lack of a control group prevented the formulation of conclusions regarding the feasibility of the watch-and-wait approach. Finally, most patients (69.8%) had hepatitis B–related HCC, which may limit the generalizability of our findings.

Conclusions

Our cohort study demonstrated that LRT-IO was associated with a durable response in patients with locally advanced unresectable HCC. Long-term survival was attainable in patients with radiologic CR. Therefore, further randomized clinical trials are warranted.

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