Comparative Study-retrospective Cohort

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Watch-and-wait strategy vs. resection in patients with radiologic complete response after conversion therapy for initially unresectable hepatocellular carcinoma: a propensity score-matching comparative study

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Background: The optimal subsequent management for patients with initially unresectable hepatocellular carcinoma (uHCC) who have achieved complete response (CR) following conversion therapy remains unclear. This study aims to evaluate the feasibility and outcomes of the watch-and-wait (W-W) strategy versus surgical resection (SR) for these patients.

Materials and methods: This retrospective study reviewed patients with initially uHCC who underwent conversion therapy employing transarterial therapies combined with or without systemic therapies. Radiologic CR (rCR), clinical CR (cCR), and pathologic CR (pCR) were evaluated. Overall survival (OS) and progression-free survival (PFS) were compared between the W-W and SR groups.

Results: Among 1880 patients with uHCC who underwent conversion therapy, 207 (11.0%) achieved rCR. Finally, we enrolled 149 patients meeting the inclusion criteria, including 74 receiving W-W strategy and 75 undergoing SR. Among the 149 patients with rCR, the W-W group demonstrated comparable 3-year OS rates to the SR group (80.9 vs 83.1%, $P=0.77$), but demonstrated inferior PFS rates (14.4 vs 46.5%, $P=0.002$). These results remained consistent after propensity score matching. For the 57 patients who achieved cCR, the W-W group exhibited comparable 3-year OS (88.1 vs 87.9%, $P=0.89$) and PFS rates (27.8 vs 40.8%, $P=0.34$) compared to SR group. Among the 75 patients in the SR group, 31 (41.3%) achieved pCR and 44 (58.7%) reached non-pCR. When compared with patients with pCR, those who achieved rCR in the W-W group showed comparable OS but inferior PFS rates. Moreover, patients who achieved rCR in the W-W group displayed both comparable OS and PFS rates to those with non-pCR.

Conclusion: The W-W strategy offered comparable survival outcomes to SR in patients with initially uHCC who achieved rCR or cCR after conversion therapy. For these patients, the W-W strategy could be offered as an alternative treatment option.

Keywords: complete response, conversion therapy, hepatocellular carcinoma, surgical resection, watch-and-wait strategy

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:2545–2555

Received 19 June 2023; Accepted 26 January 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 8 February 2024

http://dx.doi.org/10.1097/JS9.0000000000001155

Introduction

Hepatocellular carcinoma (HCC) constitutes over 90% of primary liver cancers and ranks as the sixth most prevalent cancer globally, holding the third position in cancer-related mortality rates[1]. Partial hepatectomy remains an effective treatment option for early-stage HCC, boasting a 5-year survival rate of 70–80%[2]. However, amounts of HCC patients lost the opportunity for hepatectomy initially due to factors such as intermediate or advanced tumor stage, liver dysfunction, insufficient residual liver volume, or surgical technique, leading to resection rates below 40%[3]. Conversion therapy has the potential to transform unresectable or borderline HCC tumors into resectable ones, thereby improving survival outcomes for patients with initially unresectable HCC (uHCC)[4].

In recent years, significant advances have been achieved in the noncurative treatment of uHCC. Pharmacological interventions, particularly the synergistic use of antiangiogenic drugs and immune checkpoint inhibitors (ICIs), has shown promise in the treatment of advanced or unresectable HCC, yielding an objective response rate (ORR) of ~30%[5–8]. Furthermore, transarterial chemoembolization (TACE) and hepatic artery infusion chemotherapy (HAIC) has further increased the ORR and tumor regression by administering chemotherapy drugs from systemic

intravenous to locoregional hepatic artery[9]. For patients with initially uHCC, the combination of targeted agents and ICIs with locoregional treatments of TACE or HAIC has shown a higher ORR and a complete response [CR, evaluated based on modified Response Evaluation Criteria in Solid Tumors (mRECIST)] rate of 8–14.1%[9–11]. These promising results raise the question of whether surgical tumor resection remains necessary after attaining radiologic CR (rCR), or even clinical CR (cCR).

While it remains challenging to precisely forecast which patients will attain pathologic CR (pCR) post-treatment, ongoing debate centers on whether surgical resection offers any survival advantage for patients who have achieved either rCR or cCR, and whether the watch-and-wait (W-W) strategy can be used as a potential treatment option. Originally put forth by Habr-Gama for the management of locally advanced rectal cancer[12], the W-W strategy has demonstrated comparable treatment outcomes for patients who attained cCR through neoadjuvant radiotherapy when matched against those achieving pCR via radical surgery. Crucially, this approach circumvents the risk of complications of abdominoperineal resection and the impact of permanent colostomy on quality of life[13]. A systematic review incorporating several follow-up studies supported that there was no significant difference in overall survival (OS) and local recurrence rates between surgically and nonsurgically managed rectal cancer patients who achieved cCR[14].

This is the first study to explore the feasibility of adopting the W-W strategy in patients with initially uHCC who have subsequently achieved rCR or even cCR after conversion therapy. The study aimed to evaluate the survival outcomes of these patients under surgical resection against those managed through the W-W strategy.

HIGHLIGHTS

- In patients with initially unresectable hepatocellular carcinoma who achieved radiologic complete response after conversion therapy, the watch-and-wait (W-W) strategy yielded comparable overall survival (OS) rates to surgical resection, albeit with inferior progression-free survival outcomes.
- For the patients who achieved clinical complete response, the W-W group exhibited OS and progression-free survival rates comparable to those observed in the surgical resection group.
- When compared with the patients with pathologic complete response or those with non-pathologic complete response, the W-W group exhibited comparable OS outcomes.

Materials and methods

Patients

This is a retrospective study on consecutive patients with initially uHCC who underwent conversion therapy from January 2016 to December 2020. The study composed of patients who fulfilled the following inclusion criteria: patients with (a) HCC diagnosed according to clinical practice guidelines[15,16]; (b) absence of extrahepatic metastases; (c) initially ineligibility for R0 resection due to insufficient residual liver volume or inadequate resection margins[3,17]; (d) liver lesions evaluated as achieving rCR after conversion therapy, as per the mRECIST criteria[18], assessed through enhanced computed tomography scan (CT) or MRI; (e) receiving liver resection or with regular follow-up after rCR; (f) Child-Pugh class A or B; (g) Eastern Cooperative Oncology Group (ECOG) performance scores of 0 to 1. The exclusion criteria were patients with (a) a synchronous primary malignancy in another organ; (b) any previous treatment for HCC; (c) severe dysfunction of vital organs; (d) incomplete data on radiologic assessment after treatment.

Tumor response was evaluated using the mRECIST criteria[18]. Briefly, CR is defined as complete disappearance of arterial enhanced areas in all target lesions; partial response (PR) is at least a 30% decrease of the viable (enhancement in the arterial phase) target lesions and progress disease (PD) is at least a 20% increase of viable (enhancing) target lesions; and stable disease (SD) is defined as any cases that do not qualify for either PR or PD. Two independent radiologists evaluated tumor response with blinding to each other, and discussion was made if there was any inconsistency. rCR was identified as CR according to the mRECIST criteria. cCR was defined using the following criteria: (a) achievement of rCR for all tumors, (b) absence of distant metastases, (c) initial elevated alpha-fetoprotein (AFP) levels (>25 ng/ml, one time the upper limit of normal) that subsequently normalized (<25 ng/ml), and (d) maintenance of the aforementioned criteria over two consecutive follow-up assessments. For patients who underwent subsequent surgical resection, surgical specimens were examined for macroscopic features of the tumors. Histological specimens were procured using the standard 7-point baseline sampling method, and if no liver cancer cells were detected, the entire specimen was completely sampled. pCR was defined as the absence of residual viable cancer cells, confirmed through hematoxylin-eosin staining of the surgical tumor specimens[19].

OS was defined as the survival time from the date of achieving rCR after treatments to the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time interval between the date of achieving rCR after treatments and the date of recurrence, progression, death, or the last follow-up. To provide a comprehensive understanding, we performed subgroup analyses to explore the efficacy of the W-W strategy and SR in patient treatment. These analyses included stratifying patients based on Barcelona Clinic Liver Cancer (BCLC) staging, different conversion therapy strategies, and whether they achieved cCR or pCR.

This study is performed in accordance with Declaration of Helsinki of 1975, as revised in 1983. The Institutional Review Board of Sun Yat-Sen University Cancer Center approved this study (Approval Number: B2022-345-01) and the requirement for written informed consent was waived. This study is fully compliant with the strengthening the reporting of cohorting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[20] (Supplemental Digital Content 1, http://links.lww.com/JS9/B836).

Conversion therapy

This study employed a conversion therapy consisting of either TACE/HAIC combined with tyrosine kinase inhibitors (TKIs) and programmed cell death protein-1 (PD-1) antibodies or TACE/HAIC alone. Repeated TACE/HAIC was performed at intervals of 3–4 weeks. The TKIs used in this study included

sorafenib, apatinib, and lenvatinib, while the PD-1 antibodies consisted of camrelizumab, stintilimab, tislelizumab, and pembrolizumab.

Tumor response was evaluated every 3–4 weeks after each hepatic artery intervention and the assessment ceased if tumor progression was detected, if rCR was achieved, or if treatment intolerance was exhibited. For patients who achieved rCR, subsequent treatment options were discussed by the multidisciplinary team (MDT, which included surgeons, physicians, and interventional radiologists). These subsequent treatment options included W-W strategy, systemic therapy, surgical resection, ablation, transarterial therapies, or stereotactic body radiotherapy. Factors affecting the choice of subsequent treatments included tumor burden, the patient's general status, health insurance coverage, and the patient's willingness to accept surgical resection.

Surgical resection and W-W strategy

Surgical resection was carried out after meticulous assessment by two experienced surgeons, ensuring that an estimated residual liver volume of at least 30–40% could be preserved while achieving R0 resection margins[17,21]. The W-W strategy was considered when the managing clinician had comprehensively discussed with the patients the potential benefits and risks of surgical intervention, including its impact on survival outcomes and risks of tumor recurrence. The patient ultimately made the final decision as to whether to receive the W-W strategy.

Patients who underwent surgical resection were routinely followed up once every 3–4 months for the first 2 years, and then once every 6 months thereafter until tumor recurrence or death. Patients in the W-W group were routinely followed up once every 2–3 months for the first 2 years, and then once every 3–6 months thereafter. Routine follow-up procedures included a comprehensive history-taking, physical examination, evaluations of AFP levels, and abdominal enhanced CT or MRI. Tumor progression was defined as the emergence of new lesions at any location, as ascertained by contrast-enhanced CT or MRI[22,23]. For patients experienced tumor progression or recurrence, the further treatment options were determined by the MDT after engaging in discussions with the patients.

Statistical analysis

Continuous variables were compared using the student's *t*-test or Mann–Whitney *U*-test and presented as mean ± SD. Binary and ordinal categorical variables were compared using the χ^2 test or Kruskal-Wallis test and presented as numbers and percentages. OS and PFS curves were constructed using the Kaplan–Meier method and compared by the log-rank test. The prognostic factors for OS and PFS were analyzed using the cox proportional hazards model. Variables with a *P* value less than 0.10 in univariate analysis were included for the multivariate Cox proportional hazard model. All analyses were two-sided, and *P* values less than 0.05 were considered significant. Statistical analyses were performed using the R program (R version 3.5.0; R Foundation for Statistical Computing).

To mitigate potential selection bias and imbalance of potential confounders between the surgical resection and W-W groups, a propensity scores matching (PSM) analysis was used. Propensity scores were estimated by the logistic regression model that included baseline characteristics such as: sex, age, etiology, white blood cell, red blood cell, platelet, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, prothrombin time, alpha-fetoprotein, tumor number, tumor size, vascular invasion, TACE/HAIC sessions, and combined therapy. A one-to-one nearest-neighbor matching algorithm with an optimal calliper of 0.2 without replacement was performed[24].

Results

Patient characteristics

Among the 1880 patients with initially uHCC who underwent conversion therapy, 207 (11.0%) achieved a rCR. Among the 207 patients, the median number of TACE/HAIC sessions was 2 (range, 1–8 sessions). Of these 207 patients, 17, 7, 14, and 20 patients underwent subsequent ablation, transarterial therapies, radiotherapy, and systemic therapy, respectively, and these patients were excluded from this study. Finally, 149 patients who met the inclusion criteria were enrolled in the present study, including 74 patients who were managed with the W-W Strategy and 75 patients who underwent surgical resection (SR) (Fig. 1). Among the 149 eligible patients, 43 (28.9%) patients received combined systemic therapies and transarterial therapies.

When compared with the SR group, patients in the W-W group were older ($P = 0.036$), had lower albumin levels ($P = 0.015$), fewer red blood cell counts ($P = 0.026$), and higher total bilirubin levels ($P = 0.007$) (Table 1). After PSM, 53 patients from the W-W group were matched with 53 patients from the SR group. All baseline characteristics which were significantly different between the two groups became well balanced after PSM.

Survival outcomes for patients who had achieved rCR in the W-W and SR groups

The median follow-up period was 19.23 months (range, 1.27–93.80 months) for the W-W group and 20.97 months (range, 3–84.50 months) for the SR group, respectively ($P = 0.290$). Additionally, the median duration from the date of initial treatment to the date of achieving rCR was longer in the W-W group than that in the SR group (2.85 vs 2.07, months, $P = 0.010$). There were 10 (10/74, 13.5%) patients in the W-W group and 10 (10/75, 13.3%) patients in the SR group who died during the follow-up ($P = 1.000$). The median OS duration for patients who died in the W-W group was 9.68 months (range, 3.4–40.07 months), while in the SR group, it was 15.48 months (range, 5.56–46.56 months) ($P = 0.406$). None of deaths were directly attributed to surgical resection, while vital organ failure and complications related to tumor progression were the causes of death for these patients. In addition, tumor had recurred or progressed in 51 (51/74, 68.9%) patients in the W-W group and 34 (34/75, 45.3%) patients in the SR group, respectively ($P = 0.006$). The median PFS duration for patients who progressed in the W-W group was 7.30 months (range, 1.03–71.10 months), while in the SR group, it was 8.98 months (range, 0.80–65.23 months) ($P = 0.657$). Specifically, among the patients who experienced recurrence or progression, there were 33 patients who achieved cCR, 26 patients who did not achieve cCR, 24 patients who achieved rCR with initially negative levels of AFP, and two patients for whom follow-up AFP data was unavailable. The survival outcomes of these patients are detailed in Table S1 (Supplemental Digital Content 2, http://links.lww.

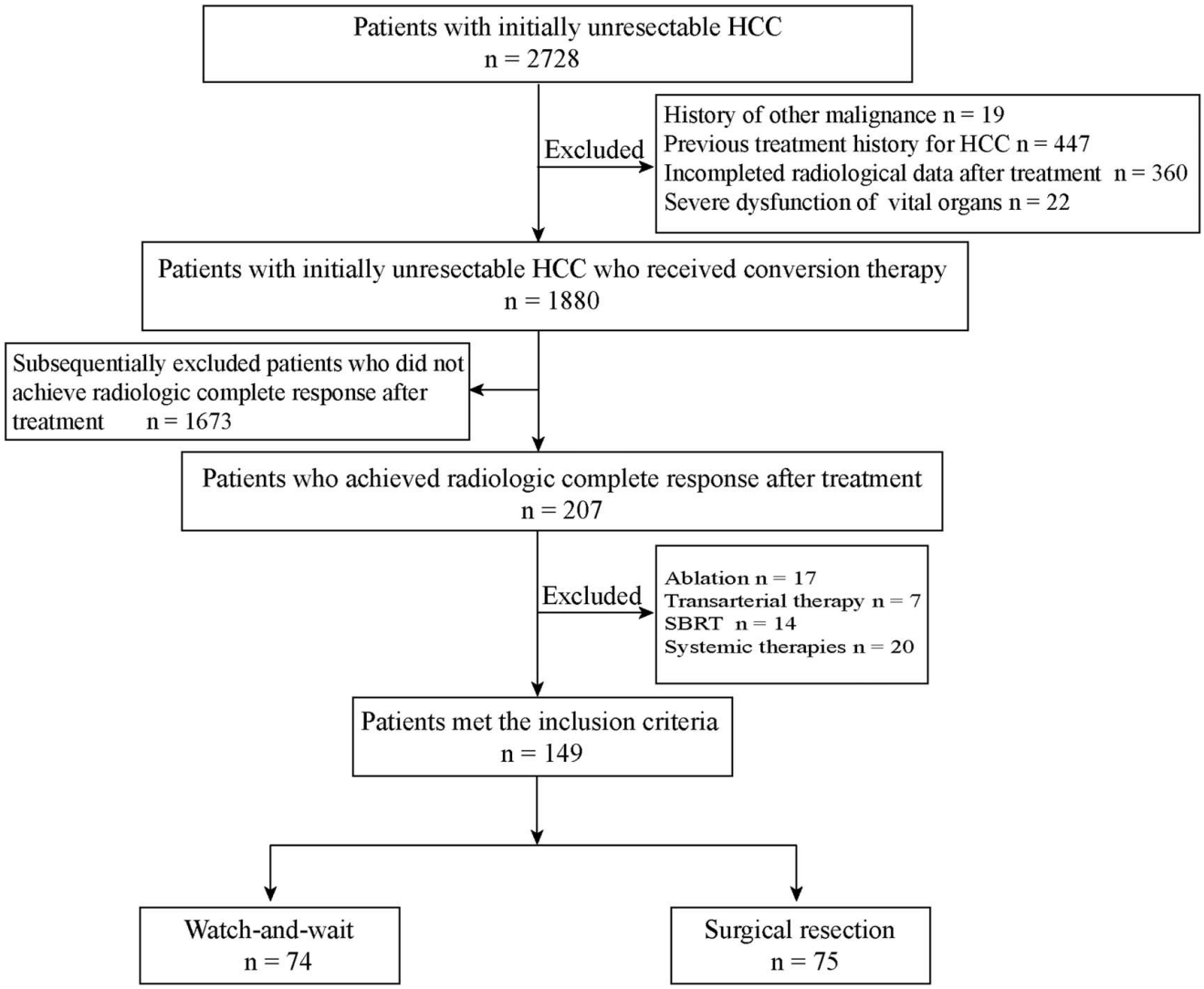

Figure 1. Flow diagram for patient selection. HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; Systemic therapies: Molecular targeted agents, Immune checkpoint inhibitors.

com/JS9/B837). Notably, there were no significant differences observed in the median PFS ($P = 0.256$) and OS ($P = 0.179$) durations among patients who achieved different degrees of CR, including cCR, non-cCR, and rCR with negative AFP. Furthermore, patients who achieved cCR, non-cCR, and rCR with negative AFP demonstrated comparable 1-year, 2-year, and 3-year OS ($P = 0.43$) and PFS ($P = 0.25$) rates (Figure S1A and B, Supplemental Digital Content 2, http://links.lww.com/JS9/B837).

The 1-year, 2-year, and 3-year OS rates in the W-W and SR groups were 92.5, 84.7, 80.9%, and 94.5, 86.3, 83.1%, respectively ($P = 0.77$) (Fig. 2A). The 1-year, 2-year, and 3-year PFS rates in the W-W and SR groups were 51.9, 23.0, 14.4%, and 67.8, 46.5, 46.5%, respectively ($P = 0.002$) (Fig. 2B). These results indicated that, compared to the SR group, the W-W group had comparable OS but inferior PFS rates before PSM.

After PSM, the W-W group still had comparable OS to the SR group. The 1-year, 2-year, and 3-year OS rates in the W-W and SR groups were 92.1, 85.6, 80.9% and 94.2, 89.0, 89.0%, respectively ($P = 0.61$). However, the W-W group still had inferior PFS compared to the SR group. The 1-year, 2-year, and 3-year PFS rates in the W-W and SR groups were 51.1, 25.2, 16.8% and 72.5, 53.1, 53.1%, respectively ($P = 0.003$) (Fig. 2C and D).

Before PSM, among patients with initial uHCC at BCLC A stage, the W-W group had comparable 1-year, 2-year, and 3-year OS rates ($P = 0.46$) but inferior 1-year, 2-year, and 3-year PFS rates ($P = 0.028$) compared to the SR group (Figure S2 A and B, Supplemental Digital Content 2, http://links.lww.com/JS9/B837). In contrast, for patients at BCLC B or C stage, there were no significant differences in 1-year, 2-year, and 3-year OS and PFS rates between the W-W and SR groups (all $P > 0.05$) (Figure S2 C–F, Supplemental Digital Content 2, http://links.lww.com/JS9/B837). Additionally, among patients with initially uHCC who received TACE/HAIC alone as a conversion therapy, the W-W group demonstrated comparable 1-year, 2-year, and 3-year OS rates to the SR group ($P = 0.48$), but experienced worse 1-year, 2-year, and 3-year PFS rates ($P = 0.001$) (Figure S3 A and B, Supplemental Digital Content 2, http://links.lww.com/JS9/B837). Conversely, for patients who received TACE/HAIC combined

Table 1

Patient characteristics.

	Before matching			After matching		
Variables	**W-W (*n* = 74)**	**SR (*n* = 75)**	***P***	**W-W (*n* = 53)**	**SR (*n* = 53)**	***P***
Sex (Female)	8 (10.8)	9 (12.0)	1.000	6 (11.3)	5 (9.4)	1.000
Age (year)	56.00 [49.00–63.75]	53.00 [44.50–61.00]	0.036	55.00 [47.00–64.00]	55.00 [47.00–62.00]	0.519
Etiology			1.000			0.503
No	3 (4.1)	3 (4.0)		1 (1.9)	2 (3.8)	
HBV	70 (94.6)	71 (94.7)		52 (98.1)	50 (94.3)	
HCV	1 (1.4)	1 (1.3)		0 (0.0)	1 (1.9)	
WBC ($\times 10^9$/l)	6.20 [5.37–7.57]	6.98 [5.45–8.02]	0.140	6.29 [5.55–7.57]	7.11 [6.02–8.21]	0.124
RBC ($\times 10^{12}$/l)	4.81 [4.25–5.16]	4.96 [4.66–5.43]	0.026	4.98 [4.44–5.30]	4.96 [4.66–5.39]	0.378
PLT ($\times 10^9$/l)	205.8 [137.0–258.2]	210.0 [162.5–279.5]	0.109	208.0 [159.0–264.0]	205.0 [162.0–265.0]	0.674
ALB (g/l)	41.30 [38.95–44.15]	43.20 [41.45–44.95]	0.015	42.20 [39.80–45.30]	42.60 [40.90–44.60]	0.757
ALT (U/l)	38.80 [26.32–58.42]	39.80 [26.45–56.35]	0.777	39.40 [27.70– 60.40]	45.70 [30.30–63.10]	0.574
AST (U/l)	41.55 [31.92–62.80]	38.10 [27.75–62.35]	0.207	38.50 [31.70–60.10]	40.60 [27.50–63.30]	0.596
TBIL (μmol/l)	16.05 [12.20–20.10]	12.70 [9.90–16.25]	0.007	14.60 [11.50–17.60]	12.70 [10.00–16.40]	0.411
PT (s)	12.30 [11.70– 13.07]	12.10 [11.65–12.80]	0.274	12.10 [11.50– 12.50]	12.10 [11.50–12.80]	0.778
AFP (ng/ml)	121.4 [10.95–2790.2]	219.4 [29.6–9229]	0.237	60.68 [10.02–1526.0]	116.5 [23.27–3449]	0.348
ALBI score (II)	28 (37.8)	9 (12.0)	0.001	14 (26.4)	9 (17.0)	0.346
Tumor location (Bilateral)	24 (32.4)	14 (18.7)	0.082	17 (32.1)	10 (18.9)	0.181
Tumor number (Multiple)	46 (62.2)	41 (54.7)	0.446	32 (60.4)	33 (62.3)	1.000
Tumor size (cm)	5.80 [3.82–9.47]	6.40 [5.05–9.55]	0.077	6.00 [3.90– 10.00]	6.00 [4.90–8.70]	0.544
Vascular invasion (yes)	21 (28.4)	16 (21.3)	0.420	10 (18.9)	13 (24.5)	0.637
BCLC stage			0.144			0.489
A	25 (33.8)	27 (36.0)		19 (35.8)	15 (28.3)	
B	22 (29.7)	31 (41.3)		19 (35.8)	25 (47.2)	
C	27 (36.5)	17 (22.7)		15 (28.3)	13 (24.5)	
TACE/HAIC sessions	2.00 [1.00–3.00]	2.00 [1.00–2.00]	0.396	2.00 [1.00–3.00]	2.00 [1.00–3.00]	0.989
Combined therapy[a] (yes)	18 (24.3)	25 (33.3)	0.302	14 (26.4)	12 (22.6)	0.821

Values are presented as the median (interquartile range) or *n* (%).

[a]molecular targeted agents or immune checkpoint inhibitors.

AFP, alpha-fetoprotein; ALB, albumin; ALBI, Albumin-Bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer stage; HAIC, Hepatic Arterial Infusion; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet; PT, prothrombin time; RBC, red blood cell; SR, surgical resection; TACE, Transarterial chemoembolization; TBIL, total bilirubin; WBC, white blood cell; W-W, watch-and-wait.

with TKIs and ICIs as a conversion therapy, the W-W group showed comparable 1-year, 2-year, and 3-year OS ($P = 0.68$) and PFS ($P = 0.34$) rates to the SR group (Figure S3 C and D, Supplemental Digital Content 2, http://links.lww.com/JS9/B837).

Prognostic factors associated with survival

Univariate and multivariate analyses of predictors for OS and PFS in the overall cohort are shown in Table 2. Multivariate analysis revealed that the only independent predictive factor for OS was high levels of alanine aminotransferase [hazard ratio (HR) = 3.68; 95% CI: 1.03–13.1, $P = 0.044$), and the only prognostic factor for PFS was prolonged prothrombin time (HR = 1.84; 95% CI: 1.02–3.3, $P = 0.041$).

Survival outcomes for patients who had achieved cCR

Among the 149 patients who achieved rCR, 104 (69.8%) patients initially presented with elevated AFP levels (AFP > 25 ng/ml), and 57 (54.8%) out of 104 patients achieved cCR. Within this cCR subgroup, 26 received the W-W strategy, while 31 underwent SR. Furthermore, the W-W group had both comparable OS ($P = 0.89$; and the 1-year, 2-year, and 3-year OS rates: 96.2, 88.1, 88.1% vs. 96.8, 87.9, 87.9%, respectively) and PFS ($P = 0.34$; and the 1-year, 2-year, and 3-year PFS rates: 55.8, 34.8, 27.8% vs. 73.8, 40.8, 40.8%, respectively) to the SR group (Fig. 3A and B).

Four patients lacking follow-up AFP data were excluded. Of the remaining 43 (41.3%) patients who did not achieve cCR, 25 patients underwent SR and 18 patients were still managed by the W-W strategy. The W-W group had both comparable OS ($P = 0.22$; and the 1-year, 2-year, and 3-year OS rates: 93.8, 93.8, 93.8% vs. 87.3, 80.6, 70.5%, respectively) and PFS ($P = 0.23$; and the 1-year and 2-year PFS rates: 51.8, 23.0% vs. 49.0, 44.5%, respectively) to the SR group (Fig. 3C and D). Upon thorough investigation of the 18 patients in the W-W group, 13 patients showed tumor progression during follow-up (median PFS duration: 6.98 months; range, 1.1–31.30). These patients underwent timely salvage treatments including liver resection for one patient, ablation for two patients, TACE or HAIC for four patients, systemic therapies for four patients, and best supportive care for two patients. Finally, there were two patients died during follow-up (median OS duration:17.06 months; range, 2.26–65.40).

Among the 149 patients who achieved rCR, 45 (30.2%) initially had a negative AFP level (AFP < 25 ng/ml). After achieving rCR, 19 patients underwent SR and 26 patients were managed with the W-W strategy. When compared with the SR group, the W-W group had worse PFS ($P < 0.001$). However, the 1-year, 2-year, and 3-year OS rates between the two groups showed no significant difference ($P = 0.31$) (Figure S4A and B, Supplemental Digital Content 2, http://links.lww.com/JS9/B837).

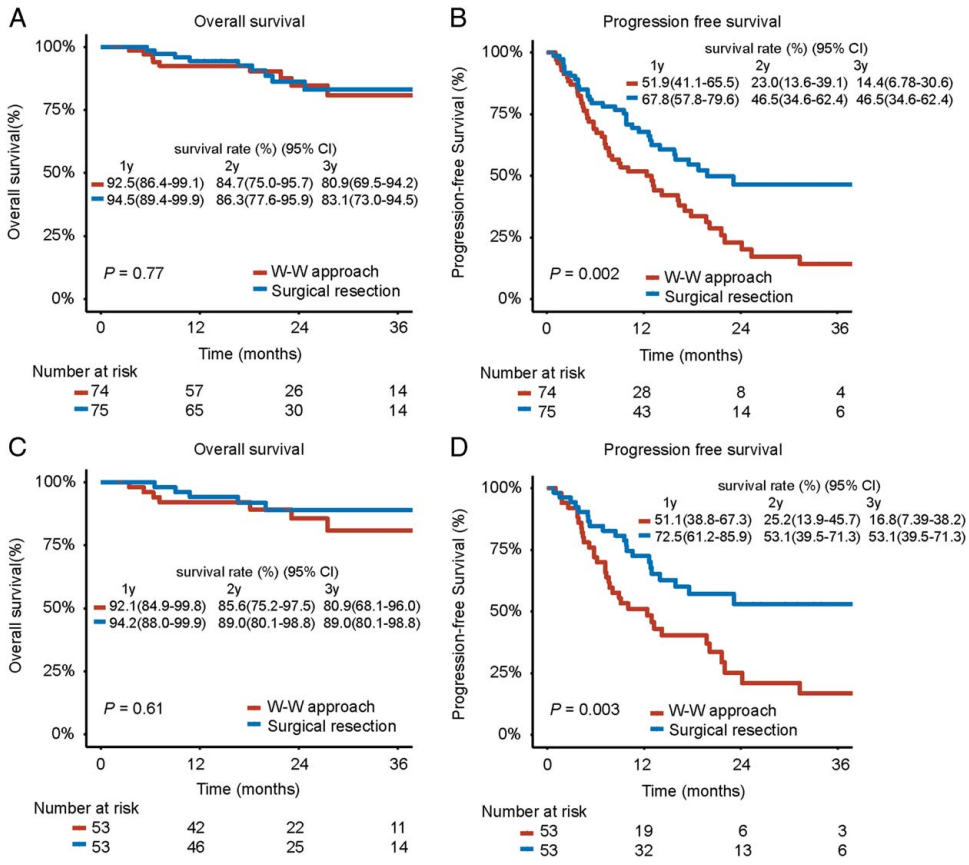

Figure 2. Kaplan–Meier survival analysis for OS and PFS in patients managed by W-W strategy and SR after achieving rCR through conversion therapy. (A) and (B) showed OS and PFS curves before PSM. (C) and (D) showed OS and PFS curves after PSM. OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; rCR, radiologic complete response; SR, surgical resection; W-W, watch-and-wait.

Survival outcomes for patients who had achieved pCR or non-pCR in the SR group

Among the 75 patients in the SR group, 31 (41.3%) achieved pCR and 44 (58.7%) reached non-pCR after resection. Compared to those who achieved pCR, patients with non-pCR exhibited comparable 1-year, 2-year, and 3- year OS rates (92.8, 83.7%, 79.3 vs. 96.8%, 90.3, 90.3%, respectively; $P = 0.23$) but inferior 1-year, 2-year, and 3- year PFS rates (56.6, 38.3%, 38.3% vs. 83.5, 59.3%, 59.3%, respectively; $P = 0.045$) (Figure S5A and B, Supplemental Digital Content 2, http://links.lww.com/JS9/B837).

We also compared the survival outcomes of patients who achieved rCR in the W-W group with those in the pCR or non-pCR subgroups. When compared with the patients in the pCR subgroup, the patients who achieved rCR in the W-W group showed comparable 1-year, 2-year, 3-year OS ($P = 0.30$) but inferior 1-year, 2-year, 3-year PFS rates ($P = 0.001$) (Fig. 4A and B). Moreover, when compared with patients in the non-pCR subgroup, the patients who achieved rCR in the W-W group had both comparable 1-year, 2-year, 3-year OS ($P = 0.77$) and PFS rates ($P = 0.080$) (Fig. 4C and D).

Management of tumor progression in the W-W and SR groups

Fifty-one patients in the W-W group and 34 patients in the SR group developed tumor progression during follow-up ($P = 0.006$). The W-W group had 39 cases of intrahepatic recurrence, four cases of extrahepatic recurrence, and eight cases of both intrahepatic and extrahepatic recurrence, while the SR group had 24, 5, and 5 cases, respectively (Table 3). In the W-W group, 18 patients underwent further curative treatments including liver resection, ablation and radiotherapy, 8 patients underwent TACE or HAIC, 9 patients underwent systemic therapies and 16 patients received best supportive care. In the SR group, 7 patients underwent curative treatments, 8 patients underwent TACE or HAIC, 13 patients underwent systemic therapies, and 6 patients received best supportive care. Moreover, no statistically significant differences were observed in the treatment modalities employed for tumor progression between the W-W and SR groups, encompassing curative treatments, TACE or HAIC, and systemic therapies (Table 3).

Discussion

The W-W strategy is found by this study to be feasible for patients with initially uHCC who subsequently achieve rCR after conversion therapy. The W-W strategy yielded comparable OS rates to SR, albeit with inferior PFS outcomes. Notably, among patients who achieved cCR, the W-W group exhibited OS and PFS rates comparable to those observed in the SR group. Furthermore, the W-W strategy demonstrated equivalent OS outcomes for patients who achieved pCR or non-pCR

Table 2

Univariate and multivariate analysis for predictors of OS and PFS.

	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sex (Male/Female)	1.92 (0.56–6.7)	0.302			1.02 (0.49–2.1)	0.967		
Hepatitis (yes/no)	0.85 (0.11–6.4)	0.874			1.44 (0.45–4.6)	0.539		
Age, year (> 60/ ≤ 60)	0.71 (0.27–1.8)	0.476			0.845 (0.54–1.3)	0.469		
WBC, 109/l (< 4/ ≥ 4)	1.25 (0.29–5.4)	0.763			0.925 (0.4–2.1)	0.856		
RBC, 109/l (< 4.3/ ≥ 4.3)	1.71 (0.62–4.7)	0.301			1.05 (0.61–1.8)	0.85		
PLT,109/l (< 100/ ≥ 100)	1.23 (0.28–5.3)	0.784			1.72 (0.85–3.5)	0.13		
ALT, U/l (> 50/ ≤ 50)	3.01 (0.88–10)	0.079	3.68 (1.03–13.1)	0.044	1.08 (0.68–1.7)	0.746		
PT, sec (> 13.5/ ≤ 13.5)	3.42 (1.2–9.7)	0.020	2.76 (0.92–8.31)	0.069	2.16 (1.2–3.8)	0.007	1.84 (1.02–3.3)	0.041
ALBI (II/I)	2.39 (0.94–6.1)	0.066	2.40 (0.86–6.66)	0.092	1.56 (0.96–2.5)	0.072	1.40 (0.85–2.3)	0.180
AFP, ng/ml (> 200/ ≤ 200)	0.99 (0.41–2.4)	0.998			1.21 (0.79–1.9)	0.389		
Tumor number (multiple/single)	1.01 (0.41–2.5)	0.987	0.800 (0.31–2.04)	0.640	1.35 (0.86–2.1)	0.187	1.28 (0.81–2.0)	0.272
Tumor size, cm (> 3/ ≤ 3)	1.05 (0.42–2.6)	0.924	1.03 (0.39–2.7)	0.937	0.776 (0.5–1.2)	0.253	0.78 (0.50–1.2)	0.295
Vascular invasion (yes/no)	2.77 (1.1–6.9)	0.027	2.15 (0.85–5.43)	0.103	1.48 (0.91–2.4)	0.113	1.37 (0.83–2.3)	0.213

AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; OS, Overall survival; PFS, Progression-free survival; PLT, platelet; PT, prothrombin time; RBC, red blood cell; WBC, white blood cell.

post-surgery. To our knowledge, this is the first study to compare the W-W strategy with surgical resection in patients with initial uHCC who have achieved rCR or cCR after conversion therapy.

In this study, more than half of the patients with initially uHCC received subsequent treatments even when they were informed that the tumor was inactive on radiologic assessment. This is contrary to what has been observed in patients with locally advanced rectal cancer. Rectal cancer patients with cCR preferred to be managed by the nonsurgical W-W strategy, mainly to avoid having a permanent colostomy which affected substantially on

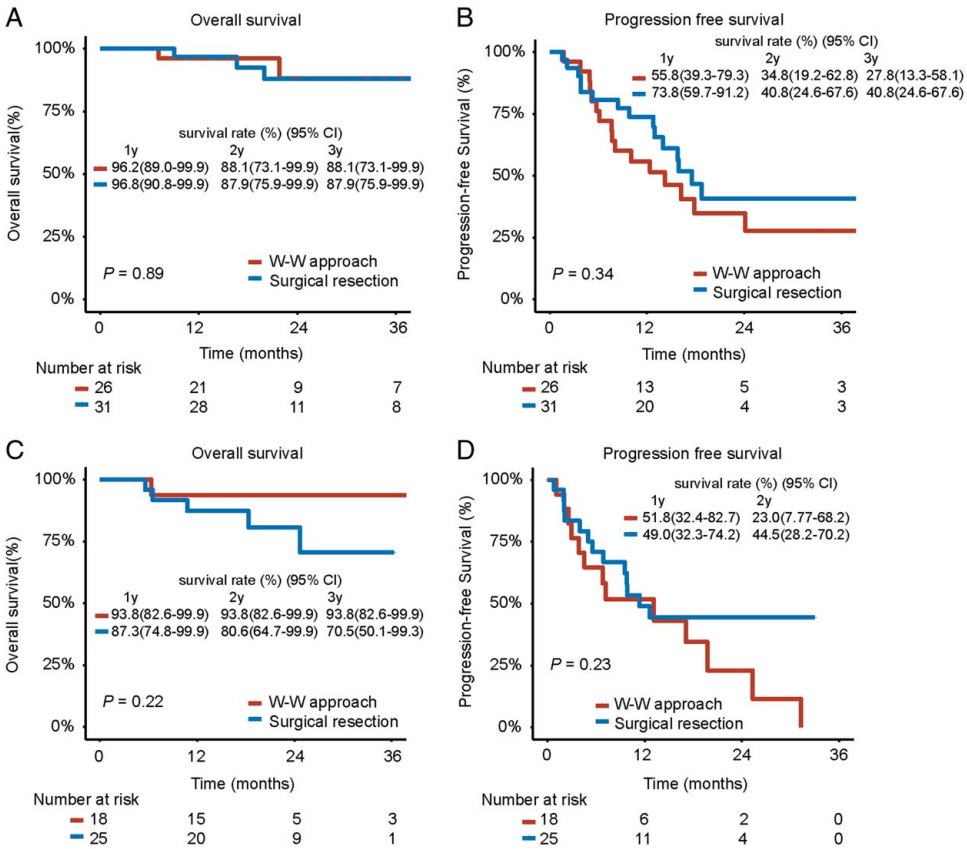

Figure 3. Kaplan–Meier survival plots evaluating OS and PFS in patients employing W-W or SR strategies, stratified by achieving (A and B) or not achieving (C and D) cCR post conversion therapy. cCR, clinical complete response; OS, overall survival; PFS, progression-free survival; SR, surgical resection; W-W, watch-and-wait.

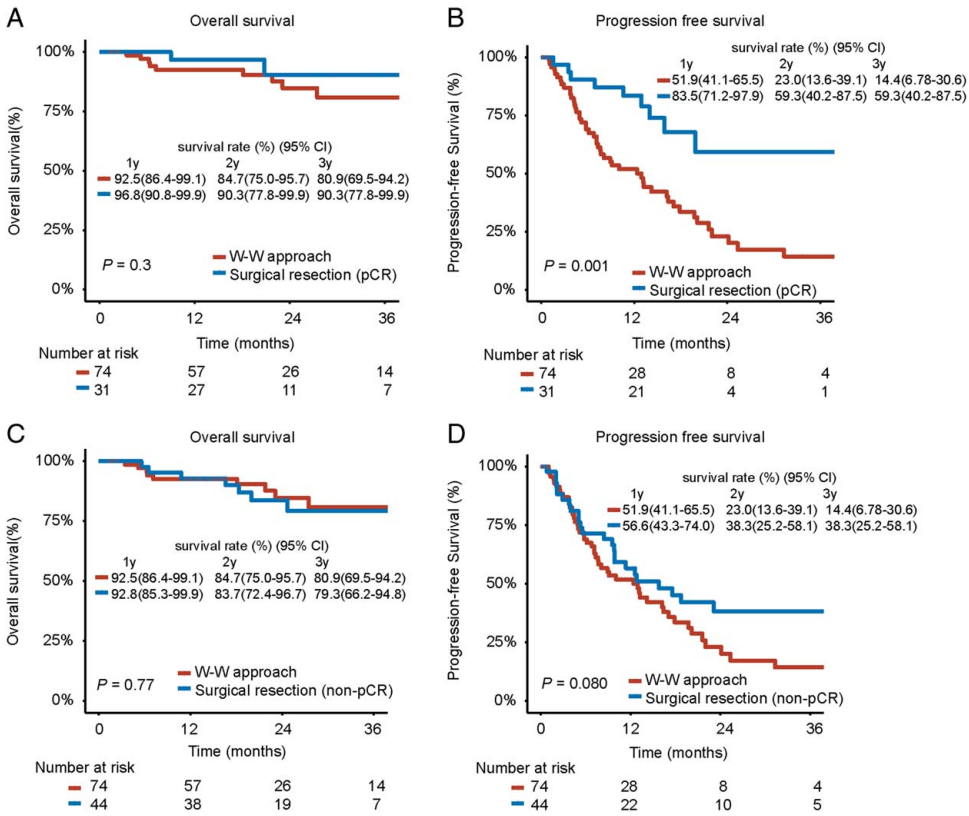

Figure 4. Kaplan–Meier plots for OS and PFS in patients who achieved pCR (A and B) or non-pCR (C and D) in the SR group and patients in the W-W group. non-pCR, no pathologic complete response; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; SR, surgical resection; W-W, watch-and-wait.

quality of life[25]. In fact, a prospective study on rectal cancer demonstrated that the W-W approach for patients with cCR yielded outcomes comparable to, or even better than, those patients achieving a pCR postsurgery[13]. For patients with HCC, liver resection usually does not lead to substantial changes in lifestyle with serious decrease in quality of life. The greatest risks of liver resection in a background of chronic hepatitis/cirrhosis are posthepatectomy liver failure and long-term compromised liver function in a liver remnant which fails to regenerate adequately. Thus, proper preoperative assessment and protection of liver function should be emphasized to reduce the risks of surgery[26]. Another concern is on adverse effects associated with systemic therapy and TACE or HAIC, which can cause deterioration in patient's general and liver functional status, and inevitably increase the risks of surgery. Therefore, hepatic surgeons are tasked with striking an optimal balance, achieving complete eradication of the HCC while safeguarding liver function, minimizing blood loss and trauma, and ensuring comprehensive preoperative evaluation.

The subsequent optimal management for patients with initially uHCC who have achieved rCR after conversion therapy remains unknown. Hepatic surgeons usually recommend surgical resection based on the following reasons: first, achieving either rCR or cCR does not offer unequivocal assurance that a pCR has been attained unless verified through SR. In this study, postoperative pCR accounted for 41.3% of patients with rCR. If the residual active tumor is not removed, the tumor might develop drug-resistant, leading to disease progression; second, rCR does not guarantee that in situ recurrence will not occur. Based on the experience of studies on liver metastases of colorectal cancer, tumor recurrences were observed in 83% of patients who had complete disappearance of liver metastasis (DLM) on medical imaging after preoperative chemotherapy[27]. Our data revealed a 1-year PFS rate of 51.9% for the W-W group, indicating a high probability of short-term tumor relapse or progression. PFS was significantly better in the SR group than in the W-W group. Therefore, patients may still potentially benefit from resection of residual lesions to achieve better long-term survival. In our study, the majority of patients (74.1%, 63/85) experiencing recurrence or progression received timely and effective remedial management. However, a higher proportion of patients who experienced recurrence or progression in the W-W group (35.3%, 18/51) received therapies with curative intent compared to the SR group (20.6%, 7/34). This may offset the relatively shorter PFS resulting from the W-W strategy. Previous studies have reported a significantly improved OS in patients who underwent hepatic resection after initial TACE compared to those who received TACE alone[28]. However, these studies aimed to investigate the survival benefits of hepatic resection following TACE for the treatment of HCC. Our study focused on patients with initially uHCC who achieved CR after conversion therapy, and aimed to assess the feasibility and outcomes of the W-W strategy versus surgical resection for these patients. Based on these results, hepatic resection might be recommended for patients who did not

Table 3

Treatments for tumor progression.

	Before matching			After matching		
	W-W ($n=74$)	SR ($n=75$)	*P*	W-W ($n=53$)	SR ($n=53$)	*P*
Tumor recurrence or progression	51 (68.9)	34 (45.3)	0.006	36 (67.9)	22 (41.5)	0.011
Intrahepatic recurrence	39	24		27	15	
Extrahepatic recurrence	4	5		4	3	
Intrahepatic and extrahepatic recurrence	8	5		5	4	
Treatments for tumor progression						
Support care	16 (31.4)	6 (17.6)	0.245	9 (25.0)	4 (18.2)	0.747
Curative treatment[a]	18 (35.3)	7 (20.6)	0.224	13 (36.2)	4 (18.2)	0.234
TACE or HAIC	8 (15.7)	8 (23.5)	0.533	7 (19.4)	4 (18.2)	1.000
Systemic therapy[b]	9 (17.6)	13 (38.2)	0.061	7 (19.4)	10 (45.4)	0.043

[a]Notes: : resection, ablation, and stereotactic body radiotherapy.

[b]molecular targeted agents, immune-checkpoint inhibitors, or combined molecular targeted agents and immune-checkpoint inhibitors.

HAIC, hepatic arterial infusion; SR, surgical resection; TACE, Transarterial chemoembolization; W-W, watch-and-wait.

achieve CR after neoadjuvant or conversion therapy, while for the patients who achieved CR, the W-W strategy could be considered as an alternative treatment option.

Currently, the W-W strategy has been reported to have clinical value in locally advanced rectal patients who have achieved cCR after radiotherapy. Two prospective studies reported 2-year disease-free survival rates of 89% and 5-year of 92% in the W-W group, respectively[12,13]. In our study, the 1-year PFS rate in the W-W group was only 51.9% for initially unresectable HCC patients who had achieved rCR. This underscores the importance of judicious patient selection for the W-W strategy. Our subgroup analyses shed light on potential beneficiaries of distinct approaches. Specifically, patients at the BCLC A stage, those treated exclusively with TACE or HAIC, and those who were initially AFP-negative, appear to benefit more from SR, resulting in enhanced long-term survival outcomes. Conversely, for patients in BCLC stages B/C, subjected to combined conversion therapy and achieving cCR, the W-W strategy may serve as an efficacious alternative treatment modality. Further prospective study is essential to delve into the effectiveness of treatment strategies for patients who have undergone neoadjuvant or conversion therapy.

The treatment modality prior to achieving CR is another concern that affects the utilization of the W-W strategy in HCC patients. Different treatment modalities, for example, TACE or HAIC when combined with various targeted agents and ICIs, can have impact on treatment outcomes of HCC. A combination of antiangiogenic targeted agents and ICIs have shown superior ORR to monotherapy. Lenvatinib plus pembrolizumab achieved ORR of 46%[29] while the ORR for atezolizumab plus bevacizumab was 33%[5], and pCR of nivolumab in combination with ipilimumab reached 24%[6]. In addition, HAIC have demonstrated significant advantages in therapy of HCC. The ORR for HCC treated with FOLFOX-based HAIC alone reached 47.8%[30]. Another study found HAIC in combination with lenvatinib and ICIs reached a complete clinical remission rate of 21.1% for intrahepatic lesions[11]. These results suggested that HAIC combined with targeted and immunotherapy can achieve higher ORR and pCR rates. As more effective treatment options with high ORRs become available, the W-W strategy is expected to become more practically applicable to HCC patients.

Current methodologies for assessing tumor response have their limitations in accuracy, making it challenging to rely solely on rCR or cCR as indicators of pCR. In the present study, using medical imaging and AFP were not reliable in evaluation of pCR. Despite rCR was obtained for HCC after treatment, minimal residual disease (MRD) still existed in a significant proportion of patients and became a source of recurrence. The concept of MRD has been studied in lung cancer and leukemia[31,32] for a long time. Recent advancements in HCC treatment have led to an increasing number of patients achieving CR. This success has underscored the growing importance of identifying and monitoring MRD. Our previous study found that the gene CpG methylation status could predict recurrence of early HCC after surgery[33]. Also, circulating tumor DNA methylation markers can be used to diagnose and predict prognosis of HCC[34]. In future, medical imaging combined with blood tumor-associated molecular markers can have the potential to improve the predictive accuracy of pCR. For patients who have adopted a W-W strategy, close monitoring of tumor recurrence during follow-up is critical, and timely detection and treatment of early recurrence are important. The current NCCN guidelines still lack the recommendations on follow-up strategies for rCR patients with HCC[35].

This study has several limitations. First, this is a retrospective study with its inherent defects. The underlying factors which led to patients not undergoing surgical treatment can be important in affecting prognosis. We have registered to conduct a related prospective clinical study on this topic with the hope to provide a higher level of medical evidence. Second, the follow-up period of this study is short and the outcomes of long-term survival of these patients need more studies in the future.

Conclusion

In conclusion, the W-W strategy offered comparable survival outcomes to surgical resection in patients with initially uHCC who achieved rCR, or even cCR, after conversion therapy. For these patients, the W-W strategy, if properly carried out, could be an alternative treatment option, especially for those who are unwilling to undergo surgical resection.

Ethical approval

The Institutional Review Board of Sun Yat-Sen University Cancer Center approved this study (Approval Number: B2022-345-01).

Consent

The Institutional Review Board of Sun Yat-Sen University Cancer Center approved this study (Approval Number: B2022-345-01) and the requirement for written informed consent was waived.

Sources of funding

This work was supported by grants from the National Natural Science Foundation of China (No. 82172815).

Author contribution

B.L., C.W., and Y.Y.: contributed to conception and design; W.H., J.Q., Z.L., Y.S., and Y.Y.: contributed to acquisition of data; C.W., Y.Z., R.Z.: contributed to analysis of data; R.Z. and C.Z.: contributed to interpretation of data; B.L., C.W., and W.H.: participated in drafting the article; Y.Y., M.C., and W.Y.L.: participated in revising the article; Y.Y.: gives final approval of the version to be published. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: researchregistry9470.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/64f2d166c8efaa00298e86d3/.

Guarantor

Prof. Yunfei Yuan acts as guarantor for the report and accepts responsibility for the work.

Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

Provenance and peer review

None.

References

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.

[2] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. The Lancet 2018; 391:1301–14.

[3] Luo L, He Y, Zhu G, *et al*. Hepatectomy after conversion therapy for initially unresectable HCC: what is the difference? J Hepatocell Carcinoma 2022;9:1353–68.

[4] Yuan Y, He W, Yang Z, *et al*. TACE-HAIC combined with targeted therapy and immunotherapy versus TACE alone for hepatocellular carcinoma with portal vein tumour thrombus: a propensity score matching study. Int J Surg 2023;109:1222–30.

[5] Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382: 1894–905.

[6] Yau T, Kang YK, Kim TY, *et al*. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol 2020;6:e204564.

[7] Kudo M, Finn RS, Qin S, *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–73.

[8] Xu J, Shen J, Gu S, *et al*. Camrelizumab in Combination with apatinib in patients with advanced hepatocellular carcinoma (RESCUE): a nonrandomized, open-label, phase II trial. Clin Cancer Res 2021;27:1003–11.

[9] He M, Li Q, Zou R, *et al*. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. JAMA Oncol 2019;5:953–60.

[10] Ikeda M, Shimizu S, Sato T, *et al*. Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol 2016;27:2090–6.

[11] He M-K, Liang R-B, Zhao Y, *et al*. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. Ther Adv Med Oncol 2021;13:17588359211002720.

[12] Habr-Gama A, Perez RO, Nadalin W, *et al*. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711–7.

[13] Maas M, Beets-Tan RG, Lambregts DM, *et al*. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–40.

[14] Dossa F, Chesney TR, Acuna SA, *et al*. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:501–13.

[15] Marrero JA, Kulik LM, Sirlin CB, *et al*. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md) 2018;68:723–50.

[16] Galle PR, Forner A, Llovet JM, *et al*. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

[17] Li B, Qiu J, Zheng Y, *et al*. Conversion to resectability using transarterial chemoembolization combined with hepatic arterial infusion chemotherapy for initially unresectable hepatocellular carcinoma. Ann Surg Open 2021;2:e057.

[18] Kim BK, Kim KA, Park JY, *et al*. Prospective comparison of prognostic values of modified response evaluation criteria in solid tumours with European Association for the Study of the Liver criteria in hepatocellular carcinoma following chemoembolisation. Eur J Cancer 2013;49:826–34.

[19] Allard MA, Sebagh M, Ruiz A, *et al*. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? J Hepatol 2015;63:83–92.

[20] Ginimol M, Riaz A. STROCSS 2021. Str STROCSS 2021: strengthening the r engthening the reporting of cohor ting of cohort, crosssectional and case-control studies in surgery. Int J Surg 2021;96:106165.

[21] He W, Li B, Zheng Y, *et al*. Resection vs. ablation for alpha-fetoprotein positive hepatocellular carcinoma within the Milan criteria: a propensity score analysis. Liver Int 2016;36:1677–87.

[22] Fernandez LM, São Julião GP, Figueiredo NL, *et al*. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. Lancet Oncol 2021;22:43–50.

[23] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.

[24] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–61. doi:10.1002/pst.433

[25] Smith JJ, Strombom P, Chow OS, *et al*. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 2019;5:e185896.
[26] Ray S, Mehta NN, Golhar A, *et al*. Post hepatectomy liver failure – a comprehensive review of current concepts and controversies. Ann Med Surg 2018;34:4–10.
[27] Stéphane B, Antoine B, Christophe P, *et al*. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939–45.
[28] Tang YL, Qi XS, Guo XZ. Hepatic resection after initial transarterial chemoembolization versus transarterial chemoembolization alone for the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Asian Pac J Cancer Prev 2015;16: 7871–4.
[29] Richard SF, Masafumi I, Andrew XZ, *et al*. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:2960–70.
[30] Lyu N, Kong Y, Mu L, *et al*. Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma. J Hepatol 2018;69:60–9.
[31] Luskin MR, Murakami MA, Manalis SR, *et al*. Targeting minimal residual disease: a path to cure? Nat Rev Cancer 2018;18:255–63.
[32] Chaudhuri AA, Chabon JJ, Lovejoy AF, *et al*. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. Cancer Discov 2017;7:1394–403.
[33] Qiu J, Peng B, Tang Y, *et al*. CpG methylation signature predicts recurrence in early-stage hepatocellular carcinoma: results from a multicenter study. J Clin Oncol 2017;35:734–42.
[34] Ng CKY, Di Costanzo GG, Tosti N, *et al*. Genetic profiling using plasma-derived cell-free DNA in therapy-naive hepatocellular carcinoma patients: a pilot study. Ann Oncol 2018;29:1286–91.
[35] He W, Zheng Y, Zou R, *et al*. Long- versus short-interval follow-up after resection of hepatocellular carcinoma: a retrospective cohort study. Cancer Commun (Lond) 2018;38:26.