



Radiologic complete response after conversion therapy for hepatocellular carcinoma: is liver transplantation necessary?

Chen-Hao Gao¹, Lin Ping Cao², Shu-Qun Cheng³, Lei Wang³, Ji-Zhou Wang⁴, Mao-Lin Yan⁵, Shu-Sen Zheng^{1,6}, Zhe Yang^{1,6}

¹Department of Hepatobiliary and Pancreatic Surgery, Key Laboratory of Artificial Organs and Computational Medicine in Zhejiang Province, Shulan (Hangzhou) Hospital, Shulan International Medical College, Zhejiang Shuren University, Hangzhou, China; ²Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; ³Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; ⁴Department of Hepatobiliary Surgery, The First Affiliated Hospital of the University of Science and Technology of China, Hefei, China; ⁵Department of Hepatobiliary Surgery, Fujian Provincial Hospital of Fujian Medical University, Fuzhou, China; ⁶Department of Hepatobiliary and Pancreatic Surgery, Shulan (Boao) Hospital, Boao, China

Correspondence to: Zhe Yang, PhD. Department of Hepatobiliary and Pancreatic Surgery, Key Laboratory of Artificial Organs and Computational Medicine in Zhejiang Province, Shulan (Hangzhou) Hospital, Shulan International Medical College, Zhejiang Shuren University, 848 Dongxing Road, Xiacheng District, Hangzhou 310022, China; Department of Hepatobiliary and Pancreatic Surgery, Shulan (Boao) Hospital, Boao, China. Email: yangzhe_0201730@163.com.

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In recent years, significant advances have been achieved in the conversion therapy of hepatocellular carcinoma (HCC). For patients with initially unresectable HCC (uHCC), combining systemic therapy with locoregional treatments as conversion therapy has shown a higher objective response rate (ORR). The promising result raises the question of whether surgical treatments are necessary after attaining radiologic complete response (rCR). In 2024, Li *et al.* revealed that the watch-and-wait (W-W) strategy offered comparable overall survival (OS) but inferior progression-free survival (PFS) to liver resection (LR) in patients with HCC who achieved rCR after conversion therapy (1). However, from the oncologic standpoint, liver transplantation (LT) is the best treatment for HCC since total hepatectomy eliminates unrecognized sites of intrahepatic spread as well as the possibility of *de novo* HCC arising from the diseased parenchyma and further improves patient prognosis. In contrast, the prognosis comparison between LT and LR in patients with HCC who achieved rCR after conversion therapy is still blank and in urgent need of further research. We recently conducted a study on HCC patients who achieved rCR after conversion therapy and compared the prognosis of LR, LT, and non-surgical strategy.

In our multicenter retrospective cohort study, we enrolled patients with uHCC who underwent conversion therapy from January 2018 to December 2021 in five Chinese centers. Patients who met the following criteria were enrolled: (I) age 18–75 years; (II) HCC diagnosed according to imaging studies [contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI)] presenting both early enhancement and delayed decreased enhancement; (III) Child-Pugh class A; (IV) absence of extrahepatic metastases; (V) Eastern Cooperative Oncology Group (ECOG) performance scores of 0 to 1; (VI) Patients who showed rCR to conversion and rCR was identified as complete response (CR) according to the mRECIST criteria. One hundred and twenty-six patients were enrolled in this study, with 90 undergoing LR, 20 undergoing LT, and 16 treated with non-surgical strategy after conversion. Postoperative systemic therapy [immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs)] was started 2–4 weeks after surgery for the LR group, which depends on liver function and patient performance. In the LT group, 8 and 7 patients received chemotherapy and TKIs to control recurrence after LT, respectively, and 5 patients did not undergo subsequent treatment due to achieving pathological CR.

Table 1 Baseline characteristics before downstaging in surgical groups (LR and LT) and non-surgical group

Variables	LR (N=90)	LT (N=20)	Non-surgical (N=16)	P value
Gender				0.58
Female	12 (13.3)	1 (5.0)	2 (12.5)	
Male	78 (86.7)	19 (95.0)	14 (87.5)	
Age (years)	56.4±10	56.0±9	58.9±11	>0.05
Hepatitis B				0.78
No	13 (14.4)	4 (20.0)	2 (12.5)	
Yes	77 (85.6)	16 (80.0)	14 (87.5)	
Hepatitis C				0.05
No	89 (98.9)	18 (90.0)	16 (100.0)	
Yes	1 (1.1)	2 (10.0)	0 (0)	
Alcohol				0.10
No	88 (97.8)	18 (90.0)	14 (87.5)	
Yes	2 (2.2)	2 (10.0)	2 (12.5)	
AFP at diagnosis				0.97
≤400 ng/mL	77 (85.6)	17 (85.0)	14 (87.5)	
>400 ng/mL	13 (14.4)	3 (15.0)	2 (12.5)	
Multiple tumors				0.07
No	68 (75.6)	10 (50.0)	12 (75.0)	
Yes	22 (24.4)	10 (50.0)	4 (25.0)	
Satellites nodules				0.86
No	76 (84.4)	16 (80.0)	13 (81.2)	
Yes	14 (15.6)	4 (20.0)	3 (18.8)	
Max tumor size				0.17
≤5 cm	47 (52.2)	13 (65.0)	12 (75.0)	
>5 cm	43 (47.8)	7 (35.0)	4 (25.0)	

Data are presented as n (%) or mean ± SD. LR, liver resection; LT, liver transplantation; AFP, alpha-fetoprotein; SD, standard deviation.

Among 16 non-surgical patients, 5 patients received transcatheter arterial chemoembolization (TACE) alone or combined systemic therapy, 3 received TKIs combined ICIs, 5 received TKIs, and 3 received ICIs alone to control progression after the diagnosis of rCR.

Of all 126 study populations, 111 were male (88.1%) and an average age at HCC diagnosis of 57 years (range, 30–75 years). Regarding underlying disease, 84.9% (107/126) patients had a history of hepatitis B. In addition, 28.6% (36/126) patients with multiple tumors at the time of diagnosis, and 42.9% (54/126) patients with maximum tumor diameter exceeding 5 cm. There were no statistical differences between LT, LR, and non-surgical groups in

baseline characteristics (*Table 1*). After comparing survival outcomes for patients who had achieved rCR in the LT, LR, and non-surgical groups. We found that the LT group exhibited the best 1-, 3-, and 5-year disease-free survival (DFS) rates (100.0%, 87.5%, and 64.2%). Contrarily, the non-surgical group had the lowest 1-, 3-, and 5-year DFS rates (60.9%, 13.5%, and 6.8%). In addition, the LR group showed DFS rates of 78.8%, 65.1%, and 65.1% at 1-, 3-, and 5-year ($P<0.05$, *Figure 1A*). Regarding recurrence patients, 20.0% (4/20) of LT patients and 30.0% (7/90) of LR patients experienced recurrence within five years. However, for the non-surgical group, 43.8% (7/16) of patients experienced progression within just 1 year. In terms

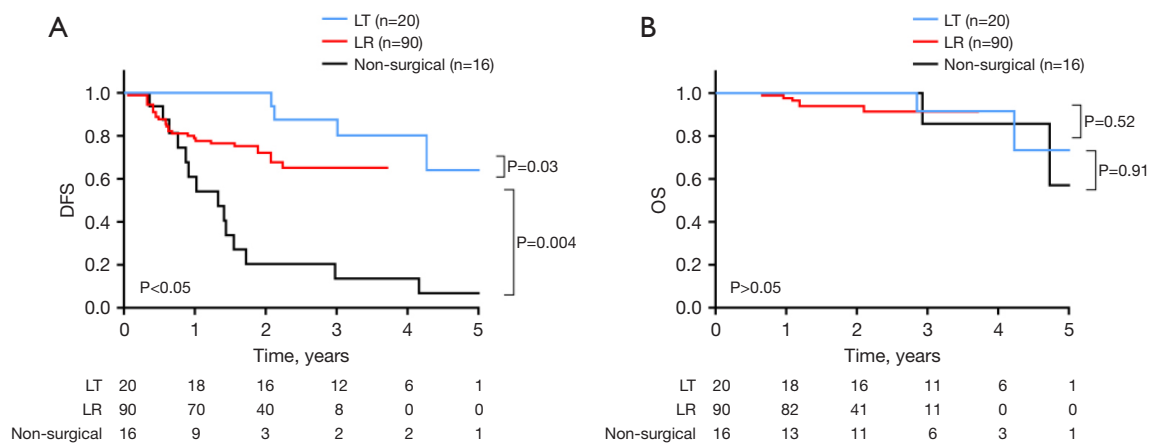


Figure 1 Kaplan-Meier curves of DFS between LT, LR and non-surgical groups (A); Kaplan-Meier curves of OS between LT, LR and non-surgical groups (B). DFS, disease-free survival; OS, overall survival; LT, liver transplantation; LR, liver resection.

of OS, there was no significant difference in 1-, 3-, and 5-year OS between the LT and LR groups (100.0%, 91.7%, 73.3% *vs.* 97.1%, 91.3%, 91.3%, respectively; $P=0.52$). Moreover, compared to the LT group, the non-surgical group also had comparable 1-, 3-, and 5-year OS (100.0%, 91.7%, 73.3% *vs.* 100.0%, 85.7%, 57.1%, respectively; $P=0.91$). While there was no significant statistical difference, the OS of the LT group showed a higher trend compared to the non-surgical group. (*Figure 1B*).

Our study reports that LT is associated with a much better prognosis in DFS for patients who achieved rCR after conversion therapy. This result fills the gap in previous research. Since 2022, to indicate the necessity of radical resection in advance, clinical CR (cCR) has been proposed as a perfect alternative indicator to pathological CR (2). The criteria of cCR include all tumors reaching CR under mRECIST guidelines, positive baseline serum tumor markers returning to normal range, distant metastasis excluded, and the above status remaining stable for 1–6 months. In recent years, there has been research exploring the feasibility of adopting non-surgical treatments in patients with HCC who have subsequently achieved cCR after conversion therapy (3-5). And revealed that for patients who achieved cCR, the W-W group or non-LR group exhibited comparable OS, DFS, and PFS rates compared to the LR group. The above research confirms that for patients who reached cCR after conversion therapy the non-surgical strategy could be offered as an alternative treatment option. Research on the selection of treatments for rCR patients has emerged in

recent years. Starting from 2023, there have been studies exploring that compared with the W-W strategy or TACE, the LR showed significantly higher DFS (1,2). While, our research further confirms that for rCR patients, LT can significantly reduce the recurrence and progression rates of HCC compared to LR.

In our study, different from DFS, the prognosis of LT, LR, and non-surgical groups in terms of OS have no statistical differences. The most possible explanation for this is the different treatments after recurrence and progression. In the LT group, all four recurrent patients received TKIs or chemotherapy only to control tumor progression. As for patients recurrent after LR, 40% of recurrence patients received triple therapy (ICIs and TKIs combined with TACE), and 46.7% of patients received systemic therapies (ICIs and TKIs) only. Moreover, among 14 progression non-surgical patients, 50% (7/14) received triple therapy, 7.1% (1/14) received systemic therapies only, and 21.4% (3/14) received dual therapy (TACE combined TKIs). And 1 of 14 non-surgical patients received salvage LR because of progression and survived until now. Compared with TKIs alone, TACE combined with ICIs and TKIs can lead to tumor vascular normalization and enhance the efficacy of TACE by promoting the accumulation of lipiodol, anticancer agents and gelatin sponges. ICIs and TKIs may stabilize disease progression after each TACE treatment, resulting in prolonged OS. Salvage LR can prevent the further progression of incompletely necrotic tumors and provide pathologic data from the resected tumor specimen, which can help guide subsequent treatments.

Our research confirmed LT can effectively improve DFS compared to LR and non-surgical strategy for HCC patients with rCR after conversion. Moreover, the expansion of medical insurance coverage for LT and the significant advances in adult split LT have greatly diluted the restrictions on LT caused by economic and liver resource limitations. In general, from the perspective of reducing recurrence and progression rates, LT remains a necessary treatment for rCR patients. However, since the inclusion criteria for achieving rCR after conversion therapy are quite stringent, the relatively small sample sizes appear to limit statistical power. This potentially undermines the strength of conclusions about treatment efficacy. Besides, this is a retrospective study, and potential bias also warrants prospective research with larger sample sizes to give robust conclusions, which could be a guideline for treating the HCC with rCR to conversion therapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-2024-702/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committees of the Shulan (Hangzhou)

Hospital (No. KY2024047) and individual consent for this retrospective analysis was waived. Written informed consent was obtained from the patient for publication of this article and accompanying images.

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