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The Current Status and Future Prospects for Conversion Therapy in the Treatment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. In China, most HCC patients are diagnosed with advanced disease and in these cases surgery is challenging. Conversion therapy can be used to change unresectable HCC into resectable disease and is a potential breakthrough treatment strategy. The resection rate for unresectable advanced HCC has recently improved as a growing number of patients have benefited from conversion therapy. While conversion therapy is at an early stage of development, progress in patient selection, optimum treatment methods, and the timing of surgery have the potential to deliver significant benefits. In this article, we review the current evidence and clinical experience of conversion therapy in HCC. General conversion modalities such as systemic treatments (systemic chemotherapy, targeted therapy, or immunotherapy), locoregional therapy (transarterial chemoembolization, hepatic arterial infusion chemotherapy, or selective internal radiation therapy), and combination therapy were summarized. We also discuss the current challenges of conversion therapy and provide identify areas for future research to improve the development of conversion therapy in advanced HCC.

Keywords

hepatocellular carcinoma, conversion therapy, surgery, review

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. HCC is the third most common cause of cancer-related deaths with an estimated 782 500 new cases each year and an increasing rate of mortality.[1,2] Most HCC patients present with moderate-to-advanced stage disease which accounts for 39.0% to 53.6% of cases.[3] Surgery is the most effective treatment for HCC and involves radical tumor resection. However, HCC is a complex disease that is characterized by vascular invasion and extrahepatic metastasis and so patients often progress after surgery.[4,5]

A potential therapeutic strategy is to convert unresectable disease into a state that is suitable for surgery known as conversion therapy. Interventional treatments, targeted drugs, and immunotherapy have been demonstrated as potential forms of TC in gastric and colon cancer. Liu et al[6] used chemotherapy combined with radiotherapy as a conversion therapy to treat 61 patients with unresectable rectal cancer and reported 51 patients with R0 resection with a conversion rate of 83.6%. Besides, several studies have also demonstrated favorable outcomes to conversion therapy in patients with stage IV gastric cancer.[7–9]

In contrast to gastrointestinal tumors, HCC involves intrahepatic metastasis rather than distant metastasis which provides an opportunity for conversion therapy. In addition to radiotherapy and chemotherapy, systemic targeted immunotherapy, local interventional therapy, and the combination of multiple treatment regimens have been proposed for conversion therapy in patients with HCC. In this review, we provide an overview of the current evidence for conversion therapy in the treatment of HCC. We discuss the latest progress in the field and the

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potential challenges that may limit the success of conversion therapy.

The Definition of Conversion Therapy

Conversion therapy is defined as any treatment that converts unresectable tumors into resectable diseases. Conversion therapy is an important form of treatment for patients with unresectable HCC. Unresectable HCC can be defined as either surgically unresectable or oncologically unresectable disease. The former refers to the inability to perform safe surgical resection and may be due to poor physical status including low liver function and insufficient residual liver volume, while the latter means that the curative effect after resection cannot surpass that of other treatments. The aim of conversion therapy is to eliminate these 2 causes, so as to convert unresectable HCC to a resectable form of the disease.

Conversion therapy and neo-adjuvant therapies can easily be confused in the clinic as they share several characteristics. Both are adjuvant therapies that are given before surgery but have differences in the implementation object and treatment outcomes. Neo-adjuvant therapy is aimed at patients with resectable tumors to improve surgical conditions and survival. In contrast, conversion therapy is used in patients with tumors that are initially unresectable and aims to create favorable conditions for surgery.[10–12] Conversion therapy also differs from down-staging therapy which aims to turn inoperable, advanced tumors into operable cases using systemic or local therapy. Down-staging focuses on down-staging resection while conversion therapy focuses on making unresectable tumors suitable for surgery.

Left-sided HCC involving the main trunk of the portal vein is classified as Barcelona Clinic Liver Cancer (BCLC stage) C disease. These cases are unsuitable for surgical resection initially, but through conversion therapy, it can reduce portal vein thrombus to the left branch of the portal vein to get an operated chance. In cases where the tumor thrombus completely disappears, conversion therapy can turn BCLC stage C cases into BCLC stage B or A disease with further down-staging. Thus, conversion therapy is also considered as a part of down-staging therapy. In the treatment of HCC, hepatectomy is primarily used and so conversion therapy is of practical value.

The target population for modern conversion therapy includes early, middle, and advanced unresectable HCC. However, patients with unresectable disease caused by factors such as poor physical conditions, liver decompensation, and insufficient liver volume are not eligible for surgical treatment as they may be at risk of postoperative liver failure. Thus, the unresectable nature of advanced HCC is the main factor that impacts treatment efficacy and highlights the need for improved forms of conversion therapy.

The classification of advanced liver cancer remains controversial. Cases that involve hepatic vascular invasion or extrahepatic metastasis, such as stage C disease defined by the BCLC or stage III disease defined by the China liver cancer staging (CNLC) system are known as advanced cancers. A recent study[13] showed that evidence-based CNLC and BCLC classification systems have similar value in defining disease stages and informing treatment selection. For instance, BCLC stage C disease is equivalent to CNLC stage III and BCLC stage B is similar to CNLC stage IIb disease. This paper mainly uses the BCLC and CNLC stages to review the conversion strategies of unresectable advanced HCC (Figure 1).

Target Patients and Common Treatments for Conversion Therapy

Patients with unresectable HCC mostly with BCLC stage C-D (CNLC stage III and IV disease) are the target group for conversion therapy.[5] Patients with BCLC stage D (CNLC stage IV) disease have a poor physical function and low tolerance to treatment and so usually require comprehensive medical treatment before conversion therapy. Although patients with BCLC stage C (CNLC stage III) disease can be treated directly in some cases, the therapeutic effect is not significantly better than other treatments and so surgical resection is generally not recommended as the first treatment choice for these patients.[3] The best candidates for conversion therapy are HCC patients with BCLC stage C (CNLC stage IIIa and IIIb) disease.

Conversion therapy in unresectable HCC is divided into systematic and local treatments. Systematic treatments include targeted therapies, immunotherapy, and chemotherapy. Before 2018, chemotherapy and sorafenib were systemic treatments that were approved for HCC but had low objective response rates. Consequently, local treatments are the predominant forms of conversion therapy and include transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), ablation, and selective internal radiation therapy (SIRT).

Systemic Treatments

Systemic Chemotherapy

Chemotherapy is established as the main systemic treatment for HCC[14] using traditional chemotherapy drugs including 5-fluorouracil (5-FU), doxorubicin, and platinum-based agents. General indications for systemic chemotherapy included absolute granulocyte count over 1500/mm^3, platelet count over 100 000/mm^3, A/B Child–Pugh classification, and a performance status score of 2 or less on the Eastern Cooperative Oncology Group (ECOG). A randomized, multicenter phase III study in Asia evaluated the efficacy of FOLFOX4 in advanced HCC and reported a response rate of 8.15% with a median overall survival of 6.4 months.[15] However, conversion therapy using modified cisplatin, interferonα-2b, doxorubicin, and 5-FU performed is effective in unresectable HCC with a 33% conversion rate and a median overall survival of 21.3 months.[16] While systematic chemotherapy is effective in unresectable HCC, it is gradually being replaced by local chemotherapy which has significantly reduced side effects.

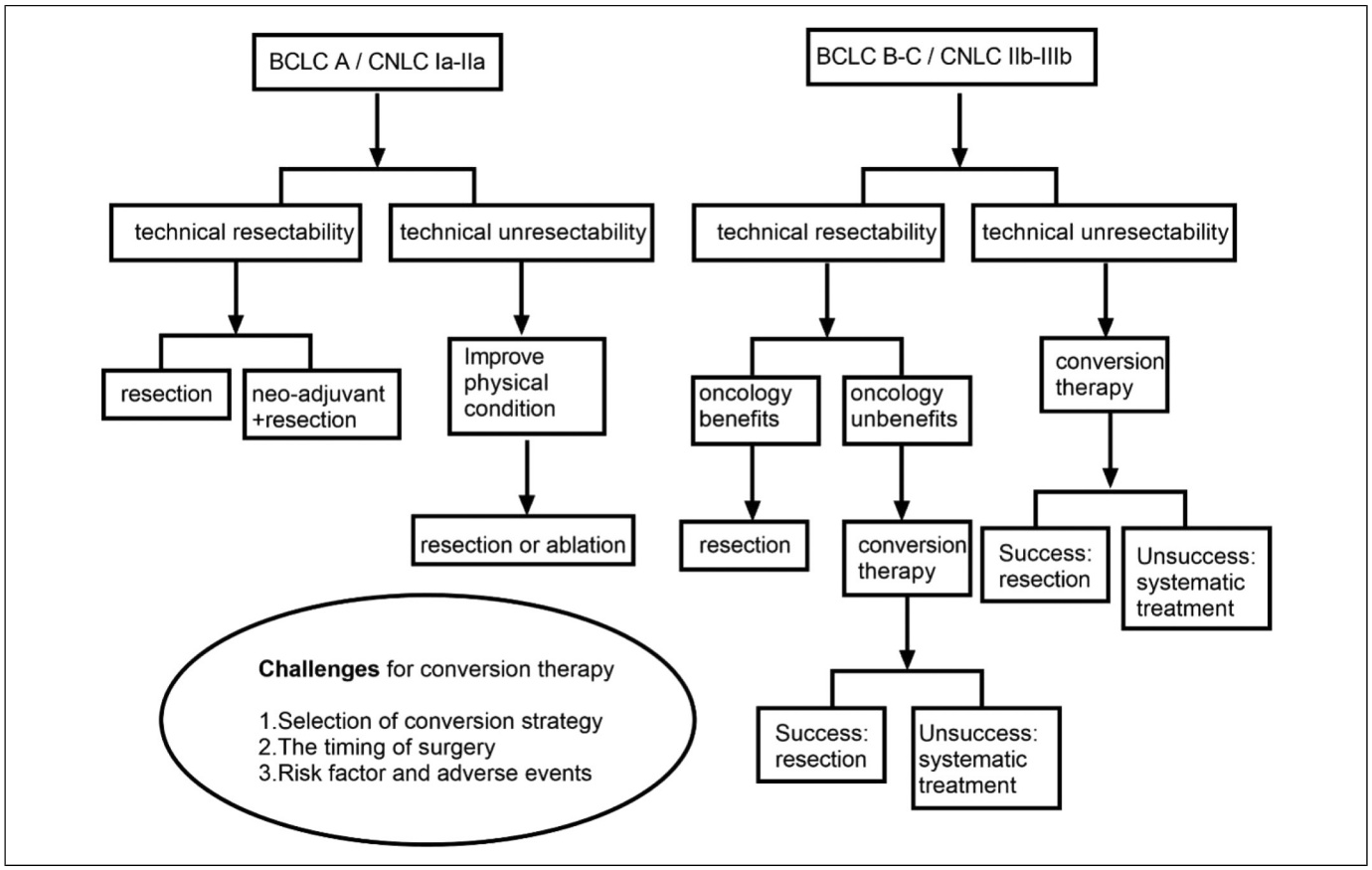

Figure 1. A roadmap for the development of conversion therapy in hepatocellular carcinoma (HCC).

Targeted Therapies

Targeted drugs are mainly divided into small molecular tyrosine kinase inhibitors (TKIs) including sorafenib and lenvatinib, and macromolecular antibodies such as antiangiogenic drugs including bevacizumab and ranibizumab. Sorafenib and lenvatinib were approved in the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2022 Edition) as maintenance therapy.[17]

Targeted drugs have limited efficacy in the treatment of HCC due to a high degree of tumor heterogeneity. And the sufficient liver function is the basis of using targeted therapies. In single-agent regimens, lenvatinib has the highest objective response rate (ORR) (18.3%).[18] Evidence suggests that targeted therapies can be used to create opportunities for surgery and the down-staging of tumors.[19–21] A retrospective study analyzed data from 107 patients that had initially unresectable advanced HCC and received lenvatinib. Of the 107 cases, 16 cases underwent surgery and 9 cases achieved R0 resection.[22] The median OS of patients who underwent R0 resection was 19 months which was significantly higher compared to patients who received other treatments. Also, in a multicenter prospective single-arm trial, Tada et al[23] reported that in 48 patients treated with lenvatinib for 8 weeks, R0, R1, and R2 resections were possible in 27 (56%), 2 (4%), and 4 (8%) cases, respectively. Postoperative 90-day mortality directly related to surgery was not observed, but complications ≥ grade III included abdominal abscess in 3 patients (6%) and bile leakage in 4 patients (8%). This was the first prospective study to evaluate conversion surgery and confirms the safety and feasibility of lenvatinib in conversion therapy.

Despite these findings, there is little evidence to support conversion therapy using only targeted drugs alone and most strategies use combined therapies. Following sorafenib and lenvatinib, many new targeted drugs have been developed for HCC and their potential roles in conversion therapy remain to be fully understood.

Immunotherapy

Immune checkpoint inhibitors are the main research focus for immunotherapy and have been extensively applied in the treatment of HCC. For the included condition, HCC patients with AFP levels < 400 μg/ or Child–Pugh A may achieve a better response rate.[24] A phase I/II clinical trial evaluated the role of navulizumab in patients with advanced HCC showing that it has long-term efficacy and can improve OS in patients with HCC.[25] The Keynote-224 trial showed that pabrizumab is safe and effective in patients with advanced HCC who had previously received sorafenib and had progressed with a PFS of 4.8 months.[26,27] The II phase clinical trial of tisilimazumab in patients with advanced HCC and chronic hepatitis C reported

a disease control rate (DCR) of 76.4% with a time to progression (TTP) of 6.5 months.[28] These data indicate that immunotherapy is not inferior to targeted therapy and could potentially play a critical role in the conversion treatment of HCC. Besides, a phase III, randomized study reported that the ORR using nivolumab as conversion therapy reached 16%, but the progression disease rate was as high as 37%.[29] Response rate is higher in those patients with high expression of PD-L1 and immunotherapy monotherapy may be suitable for conversion therapy if a considerable cutoff data of PD-L1 expression could be developed.

Targeted Therapies Combined With Immunotherapy

The development of drugs for advanced HCC has improved significantly in recent years. Combined treatment with immune checkpoint inhibitors and TKIs have proven to be effective.[30–32] Bevacizumab combined with atezolizumab, and a bevacizumab analog combined with sintilimab have produced promising results as first-line therapies.[17] A previous study in 336 advanced HCC patients treated with atrazumab and lamvatinib reported partial remission in 33.2% of patients and complete remission in 10.2% of patients based on the mRECIST criteria.[33] Combining targeted therapies and immunotherapy, an ECOG performance status score of 0 or 1 and an A/B Child–Pugh classification should be required.

For conversion therapy, Lu et al reported a conversion rate of 42.4% in 35 BCLC stage C (CNLC stage IIIa) patients who received programmed death-1 (PD-1) inhibitor combined with a TKI.[34] Also, Zhu et al[35] reported a conversion resection rate of 15.9% (10 patients) in 63 patients with initial unresectable HCC who received PD-1 inhibitors combined with TKIs. Of the 10 patients who underwent surgery, 5 patients experienced postoperative complications, including 1 (10%) patient with bile leakage, 3 (30%) patients with the subphrenic collection, and 1 (10%) patient who died from immune-related adverse effects. In addition, a prospective study of immune check inhibitors (ICIs) combined with targeted therapy for advanced HCC with intrahepatic macrovascular tumor thrombus reported a conversion rate of 51.0% in 49 patients of which 15 were eligible for surgery who had a 1-year recurrence-free survival rate of 61.1%.[3] These data indicate that immunotherapy combined with targeted therapy is highly effective in advanced HCC and more effective in patients with portal vein tumor thrombus who have BCLC stage C (CNLC ?a stage) disease.

Locoregional Therapy

Transarterial Chemoembolization (TACE)

TACE uses the cytotoxicity of chemotherapy drugs and embolization agents to temporarily restrict tumor blood supply and has been widely applied in the treatment of HCC patients. In patients with early-stage HCC, TACE is not associated with improved survival as a neo-adjuvant therapy and might increase the difficulty of surgery due to liver inflammation.[36] Thus TACE should be applied for HCC patients with relatively adequate liver function. However, for patients with unresectable HCC including those with multiple tumors, lymph node metastasis, or large tumors, TACE can be used as a cytoreductive strategy allowing the potential for surgical resection. A previous study found that 6% to 28% of patients with advanced HCC achieved a tumor down-staging after TACE.[37]

Evidence suggests the benefit of sequential surgery after TACE conversion is more effective compared to TACE alone with respective conversion rates of 11.9% to 24.0%.[38,39] In 831 patients with initial unresectable HCC, Zhang et al reported the successful conversion of 85 patients to resectable disease after TACE and 45 patients underwent sequential resection.[37] Compared to the nonsurgical group, the median OS of the surgical group was longer (49 months vs 31 months), and the survival rates at 2, 4, and 5 years were higher (93% vs 74%, 47% vs 26%, 18% vs 10%). These data indicate that sequential surgery can significantly improve the prognosis of patients after successful conversion therapy. Also, the study found that the median OS of patients in the surgery group was significantly longer compared to the nonsurgical group for patients with partial remission. In HCC patients treated with TACE that have partial remission and are resectable, surgery should be performed as soon as possible. A recent study reported 52 unresectable HCC patients who received conversion surgery after TACE, with a complete response (CR) rate of 9.6% and perioperative mortality of 5.8%.[40] Zhang et al[38] in their research presented a 37% CR rate and 63% tumor residual rate. However, it should be noted that multiple TACE treatments can lead to liver damage to impact the safety of sequential surgery. In the future, the success rate of conversion therapy may be improved by combining TCAE with other therapies.

Hepatic Arterial Infusion Chemotherapy (HAIC)

Substantial progress has been made in the application of HAIC for advanced HCC. Compared to systemic chemotherapy, HAIC can use regional local chemotherapy to kill tumors and remarkably increase the drug concentration within tumors. HAIC is suitable for HCC patients with good liver function (Child–Pugh A/B) and with tumor burden in the liver. In China, FOLFOX4 chemotherapy is mainly used to treat advanced HCC, and its objective remission rate (ORR) can reach 40.8% to 47.8%.[41,42] A multicenter RCT showed that the ORR for conversion therapy based on HAIC treatment in HCC patients with portal vein cancer thrombi was notably higher than that with sorafenib (27.6% vs 3.4%).[43] In research about 103 advanced HCC patients who received HAIC, 12 (11.7%) patients with successful conversion underwent surgical treatment. No one died from the operation and only one patient has a residual tumor.[44] Moreover, compared to TACE, HAIC has higher rates of remission and conversion. A phase II clinical study compared the efficacy of HAIC and TACE in the treatment of unresectable HCC and showed that HAIC had a higher ORR (52.6% vs 9.8%) and a higher conversion rate

Table 1. A Summary of Conversion Therapy.

Modality	Characteristics
Systematic treatment	
Systematic chemotherapy	It may cause major systemic side effects.
Targeted therapy	Lenvatinib has shown the highest objective response rate, and more new targeted drugs are being developed
Immunotherapy	It can effectively control tumor progression
Targeted therapy combined with immunotherapy.	It showed a relatively high conversion rate and excellent performance in advanced HCC
Locoregional therapy	
TACE	Sequential surgery after TACE conversion can significantly improve the prognosis of patients with a successful conversion, but multiple TACE may lead to liver damage.
HAIC	Higher rates of remission and conversion rate with a promising potential for more effective conversion therapy.
SIRT	It causes tumor shrinkage but has limited evidence supporting its role in conversion therapy.
Increase in FLR	
portal vein embolization	It increases the liver volume within a certain period of time, providing the opportunity for surgery

Abbreviations: TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; SIRT, selective internal radiation therapy; HCC, hepatocellular carcinoma; FLR, Future Liver Remnant.

(26.3% vs 7.3%).[45] A further study suggested that the rate of down-staging following HAIC was higher compared to TACE in large HCC and diffuse HCC.[46]

The combination of HAIC with other therapies has the potential to deliver therapeutic benefits in advanced HCC. Chen et al[47] reported an ORR for HAIC combined with sindilimab of 42.9% in HCC patients with localized tumors with portal vein invasion and successful sequential surgery was achieved in 65.4% of the patients. Also, HAIC combined with lenvatinib and teriprizumab leads to a higher ORR (67.6% vs 16.3%) and conversion excision rate (12.7% vs 0%) compared with lenvatinib monotherapy.[48] These findings suggest that HAIC is an effective treatment for unresectable HCC and has the potential as a conversion therapy.

Selective Internal Radiation Therapy (SIRT)

SIRT uses internal radiotherapy to kill tumor cells and is also known as transcatheter arterial radioembolization (TARE). SIRT can reduce tumor volumes and promote the proliferation of contralateral liver tissue which is advantageous in conversion therapy, particularly for advanced HCC patients with vascular tumor thrombus.[49,50] This approach is preferable compared to external beam radiotherapy. The inclusion criteria for receiving SIRT included Karnofsky's performance score of > 70%, good liver function with a total bilirubin < 2.94 mg/dL, and no extrahepatic spread of disease.[51] In a study of 71 patients with unresectable HCC, 26.7% of patients showed marked tumor shrinkage after TARE of which 4 patients underwent radical resection and 2 patients achieved a complete response.[51] However, current the clinical data concerning responses to SIRT in China is limited and more evidence is needed to verify the role of SIRT in HCC (Table 1).

Increase in Future Liver Remnant (FLR)

The safety standards for liver function before hepatectomy proposed by current studies[5,52] include an FLR of at least 20% to 30% for patients without liver cirrhosis and an FLR > 40% for patients with chronic liver disease. HCC patients with insufficient FLRs are classified as having unresectable tumors. For these patients, the goal of conversion therapy is an increase from insufficient to adequate FLR. Portal vein embolization can increase the liver volume within a certain period of time, thus providing the opportunity for surgery. Previous studies have shown that the conversion success rate using this method is 60% to 80%, with a 10% to 20% incidence of complications.[53,54] However, contraindications for portal vein embolization include severe portal hypertension, Vp3-Vp4 tumor thrombus, and the presence of extensive tumor metastasis.[55] Furthermore, this approach should be used with caution in patients with rapid tumor progression or longer expected FLR proliferation. Thus, patients treated with this approach should have Child–Pugh A liver function and good physical condition.

Challenges to the Development of Conversion Therapy

Selection of Conversion Strategies

Currently, patients with BCLC stage B/C (CNLC stage IIb/IIIa) and BCLC stage C (CNLC stage IIIb) diseases are eligible for conversion therapy yet it is important to identify subgroups of patients who are most likely to benefit from personalized treatment. While the rate of single-agent conversion therapy remains lower than for combination therapy, the side effects of single-agent treatment are relatively low. For patients with highly proliferative hepatitis B virus (HBV) who are unfit for immunotherapy or interventional therapy, targeted single-agent

therapy may be the best available option. In contrast, local therapy combined with targeted therapy may be appropriate for patients requiring liver transplantation. In any case, adequate liver function is fundamental for the success of conversion therapy and essential for surgery. For HCC patients with poor liver function, treatments such as liver protection, anti-inflammatory drugs, lowering transaminase levels, and anti-tumor therapies should be considered fully. If patients with HBV-related liver cancer are positive for HBV-DNA before surgery, antiviral and hepatoprotective therapy should be given first, and surgical resection should not be performed until the liver function has improved to increase the safety of the operation and reduce the rate of tumor recurrence.[56] Therefore, it is necessary to monitor both liver function and HBV replication closely during the process of conversion therapy, and antiviral therapy is recommended.

The efficacy of different treatment regimens remains controversial currently but the general aim of treatment is to achieve the highest ORR to maximize potential down-staging and opportunities for surgery. The duration of response (DOR) and depth of response (DPR) are also important parameters for HCC treatment. DOR refers to the duration from the first documented complete response (CR) or partial response (PR) to disease progression or death. DPR is defined as the percentage decrease in tumor volume and both indicators are vital to accurately assess the efficacy of integrated treatments. In a comparative study, Salem et al quantified the DOR and DPR for HCC treatments[57] suggesting that patients with higher DPR may have higher conversion rates.

The Timing of Surgery

The timing of surgery is critical following successful conversion therapy. The duration of conversion therapy ranges from 9 to 12 months and 50% of patients respond within 12 months.[58] For patients with partial remission who are eligible for conversion and do not benefit from other treatments after 2 consecutive evaluations, surgical resection should be carried out as soon as possible. Surgical treatment should also be considered for patients with complete remission. Because imaging examinations did not ensure the complete inactivation of all tumor cells, and surgical resection is an optimal method to maximize the removal of activated tumor cells.[59] What's more, it is recommended to stop using targeted therapeutic drugs according to the half-life of the drug for patients with convertible resection. The current consensus is that targeted drugs such as lamvatinib, apatinib, and sorafenib should be stopped 1 to 2 weeks before surgery and PD-1 inhibitors should be stopped more than 2 weeks before surgery.[34] Eligibility for surgery is an indicator of successful conversion and the degree of remission is related to postoperative recurrence and long-term survival. Based on the risk of recurrence, patients with complete remission should continue treatment with immune checkpoint inhibitors for 6 months, and patients with partial remission should continue treatment with a combined regimen for 6 to 12 months before surgery.[3]

Risk Factors and Adverse Events of Conversion Therapy

Currently, there is no consensus opinion concerning the risk factors associated with conversion therapy. For example, what is the impact on the survival of patients with extrahepatic metastases after conversion therapy? Studies have shown that resection of metastatic lesions is associated with improved survival in HCC patients with lung metastasis.[60,61] But another research presented different conclusions that patients with extrahepatic metastasis treated with TKI and anti-PD-1 antibodies are not eligible for surgery.[35] Also, successful surgical outcomes are not associated with median serum alpha-fetoprotein (AFP) levels or activity per tumor volume.[62] Contrastingly, tumor down-grading has been reported in patients with the unresectable disease treated with radiation embolization who also had lower serum AFP levels compared to patients that did not respond.[63] Further studies are needed to identify the risk factors for patients undergoing conversion therapy as the current evidence is limited and contradictory.

Different treatment strategies may increase the risk of adverse events and perioperative complications during conversion therapy. A meta-analysis comparing different embolization methods for unresectable HCC suggested that all treatments increased the risk of adverse events.[64] TACE can damage liver function and increase the risk of postoperative liver failure. Also, immunotherapy can cause immune-associated hepatitis and targeted therapies may lead to bleeding and incision nonunion. However, these risks have little impact on surgery when the interval between conversion therapy and surgery is adequately controlled. High-quality randomized controlled trials are needed to further evaluate the overall safety of conversion therapy and to identify patients at high risk of adverse effects following treatment.

Problems and Prospects

Conversion therapy is an effective treatment option in advanced unresectable HCC yet significant challenges remain to optimize its clinical value. It is unclear if patients who achieve complete response after conversion therapy require surgery. Also, treatment regimens following conversion therapy failure are not well established and so further studies are needed to optimize the use of conversion therapy.

The data presented in this review provide a broad perspective on the use of conversion therapy in HCC. However, there exist a couple of limitations in this review. First, the majority of reports are retrospective studies and should be validated in prospective studies. The design of randomized controlled trials remains challenging due to patient heterogeneity including factors such as tumor size, the number of lesions, alpha-fetoprotein levels, liver cirrhosis, and metastasis. Second, the conversion rates of advanced HCC vary widely across published studies which may also be due to patient heterogeneity. There are differences in the selection of patient groups and the standards of surgical procedures in different studies, which brings some difficulties to the comprehensive evaluation

and selection of conversion methods. And it is difficult to compare surgical outcomes such as mortality, morbidity, and the degree of residual cancer of different types of conversion therapy due to differences between institutions. Third, this article does not evaluate patients who can benefit from conversion therapy. In the absence of accurate risk stratification criteria, the timing of sequential surgery is difficult to establish and requires biomarkers to more accurately select patients for treatment. Finally, there is currently no consensus on adjuvant therapy and monitoring strategy after conversion therapy.

Advances in systemic and local treatments for advanced HCC have promoted conversion therapy in patients with unresectable liver cancer. This approach has delivered promising preliminary clinical evidence for the treatment of patients with stage BCLC stage B-C (CNLC IIb-IIIb) disease yet further studies are required to realize the full potential of conversion therapy.

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Authors' Contributions

Jinfeng Bai wrote the main manuscript text; Wei Luo and Bohan Song consulted the literature; Rong Ding and Ming Huang designed the subject. All authors reviewed and approved the final manuscript.

Consent for Publication

Not applicable.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

Not applicable. Our study did not require an ethical board approval because it did not contain human or animal trials

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References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Rapisarda V, Loreto C, Malaguarnera M, et al. Hepatocellular carcinoma and the risk of occupational exposure. *World J Hepatol*. 2016;8(13):573-590.
3. Professional Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases of Chinese Preventive Medicine Association; Chinese Society of Liver Cancer; Liver Study Group of Surgery Committee of Beijing Medical Association. Chinese Expert consensus on conversion therapy of immune checkpoint inhibitors combined antiangiogenic targeted drugs for advanced hepatocellular carcinoma (2021 edition). *Chin J Hepatobiliary Surg*. 2021;27(4):241-251.
4. European Association for the Study of the Liver. EASL Clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
5. Zhou J, Sun HC, Wang Z, et al. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 edition). *Liver Cancer*. 2020;9(6):682-720.
6. Liu TY, Chang WJ, Wang J, et al. Efficacy of conversion therapy on initially unresectable locally advanced rectal cancer. *J Cancer*. 2021 May 27;12(14):4418-4423.
7. Morgagni P, Solaini L, Framarini M, et al. Conversion surgery for gastric cancer: a cohort study from a western center. *Int J Surg*. 2018;53:360-365.
8. Solaini L, Ministrini S, Bencivenga M, et al. Conversion gastrectomy for stage IV unresectable gastric cancer: a GIRCG retrospective cohort study. *Gastric Cancer*. 2019;22(6):1285-1293.
9. Choe HJ, Kim JW, Han SH, et al. Conversion surgery in metastatic gastric cancer and cancer dormancy as a prognostic biomarker. *Cancers*. 2019;12(1):86.
10. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. *Gastric Cancer*. 2016;19(2):329-338.
11. Marino D, Leone F, D'Avanzo F, Ribero D, Capussotti L, Aglietta M. Potentially resectable metastatic colorectal cancer: an individualized approach to conversion therapy. *Crit Rev Oncol Hematol*. 2014;92(3):218-226.
12. Zhao M, JM W, Shang CZ, et al. Advances in the techniques and evaluation of conversion therapy for hepatocellular carcinoma. *Chin J Pract Surg*. 2021;41(3):262-268.
13. Vitale A, Farinati F, Finotti M, et al. Overview of prognostic systems for hepatocellular carcinoma and ITA. LI.CA external validation of MESH and CNLC classifications. *Cancers*. 2021;13(7):1673.
14. Wang YJ, Sun H, Xiao ZY, et al. XWL-1-48 exerts antitumor activity via targeting topoisomerase II and enhancing degradation of Mdm2 in human hepatocellular carcinoma. *Sci Rep*. 2017;7(1):9989.
15. Qin SK, Bai YX, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol*. 2013;31(28):3501-3508.
16. Kaseb AO, Shindoh J, Patt YZ, et al. Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. *Cancer*. 2013;119(18):3334-3342.
17. Department of Medical Administration, National Health and Health Commission of the People's Republic of China.

Guidelines for diagnosis and treatment of primary liver cancer in China (2022 edition). *Chin J Pract Surg*. 2022;42(3):241-273.
18. Han Y, Zhi WH, Xu F, Zhang CB, Huang XQ, Luo JF. Selection of first-line systemic therapies for advanced hepatocellular carcinoma: a network meta-analysis of randomized controlled trials. *World J Gastroenterol*. 2021;27(19):2415-2433.
19. Curtit E, Thiery-Vuillemin A, Nguyen T, et al. Complete histologic response induced by sorafenib in advanced hepatocellular carcinoma: a case report. *J Clin Oncol*. 2011;29(12):e330-e332.
20. Barbier L, Muscari F, Le Guellec S, et al. Liver resection after downstaging hepatocellular carcinoma with sorafenib. *Int J Hepatol*. 2011;2011:791013.
21. Irtan S, Chopin-Laly X, Ronot M, et al. Complete regression of locally advanced hepatocellular carcinoma induced by sorafenib allowing curative resection. *Liver Int*. 2011;31(5):740-743.
22. Shindoh J, Kawamura Y, Kobayashi Y, et al. Prognostic impact of surgical intervention after lenvatinib treatment for advanced hepatocellular carcinoma. *Ann Surg Oncol*. 2021;28(12):7663-7672.
23. Tada M, Ichida A, Arita J, et al. Multicenter prospective study to evaluate the efficacy of lenvatinib to achieve conversion surgery for initially unresectable hepatocellular carcinoma: LENS-HCC trial. *J Clin Oncol*. 2022;40(4_suppl):458-458.
24. Spahn S, Roessler D, Pompilia R, et al. Clinical and genetic tumor characteristics of responding and non-responding patients to PD-1 inhibition in hepatocellular carcinoma. *Cancers*. 2020;12(12):3830.
25. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492-2502.
26. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19(7):940-952.
27. Ryoo BY, Merle P, Kulkarni AS, et al. Health-related quality-of-life impact of pembrolizumab versus best supportive care in previously systemically treated patients with advanced hepatocellular carcinoma: KEYNOTE-240. *Cancer*. 2021;127(6):865-874.
28. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66(3):545-551.
29. Yau T, Park J-W, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77-90.
30. Ren Z, Fan J, Xu J, et al. LBA2 Sintilimab plus bevacizumab biosimilar vs sorafenib as first-line treatment for advanced hepatocellular carcinoma (ORIENT-32)2. *Ann Oncol*. 2020;31(S6):S1287.
31. 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(4):1003-1011.
32. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2020;38(26):2960-2970.
33. Finn RS, Qin SK, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905.
34. Zhang W, Hu B, Han J, et al. Preliminary report on the study of conversion therapy of advanced hepatocellular carcinoma combined PD-1 inhibitors with multi-target tyrosine kinase inhibitors. *Chin J Hepatobiliary Surg*. 2020;26:947-948.
35. Zhu XD, Huang C, Shen YH, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. *Liver Cancer*. 2021;10(4):320-329.
36. Lee KT, Lu YW, Wang SN, et al. The effect of preoperative transarterial chemoembolization of resectable epatocellular carcinoma on clinical and economic outcomes. *J Surg Oncol*. 2009;99(6):343-350.
37. Lau WY, Lai EC. Salvage surgery following downstaging of unresectable hepatocellular carcinoma-a strategy to increase resectability. *Ann Surg Oncol*. 2007;14(12):3301-3309.
38. Zhang YQ, Huang GH, Wang Y, et al. Is salvage liver resection necessary for initially unresectable hepatocellular carcinoma patients downstaged by transarterial chemoembolization? Ten years of experience. *Oncologist*. 2016;21(12):1442-1449.
39. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. *Liver Transpl*. 2015;21(9):1142-1152.
40. Shi XJ, Wang MQ, Wei LX, et al. Effect of resection following downstaging of unresectable hepatocellular carcinoma by transcatheter arterial chemoembolization. *Chin Med J Engl*. 2012 Jan;125(2):197-202.
41. Lü N, Lin YE, Kong YN, et al. FOXAI: a phase II trial evaluating the efficacy and safety of hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin for advanced hepatocellular carcinoma. *Gut*. 2018;67(2):395-396.
42. Lü 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(1):60-69.
43. Choi JH, Chung WJ, Bae SH, et al. Randomized, prospective, comparative study on the effects and safety of sorafenib vs. hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Cancer Chemother Pharmacol*. 2018;82(3):469-478.
44. Lee BH, Lee DS, Cho CW, et al. Role and limitation of neoadjuvant hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma patients with Child–Pugh class A. *World J Surg Oncol*. 2019;17(1):143.
45. He MK, Le Y, Li QJ, et al. Hepatic artery infusion chemotherapy using mFOLFOX versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: a prospective non-randomized study. *Chin J Cancer*. 2017;36(1):83-90.
46. Shi M, Li Q, He M, Guo R. 981O Hepatic arterial infusion chemotherapy (HAIC) with oxaliplatin, fluorouracil, and leucovorin (FOLFOX) versus transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC): a randomised phase III trial. *Ann Oncol*. 2020;31(S4):S688.
47. Chen MS, Yuan YF, Guo RP, et al. Application of hepatic arterial infusion chemotherapy in the conversion therapy of hepatocellular

carcinoma–experience of Sun Yat-Sen University Cancer Center. *Chin J Front Med Sci (Electronic Version)*. 2021;13(3):70–76.
48. He MK, Liang RB, 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.
49. Kishore SA, Bajwa R, Madoff DC. Embolotherapeutic strategies for hepatocellular carcinoma: 2020 update. *Cancers*. 2020;12(4):791-811.
50. Gabr A, Abouchaleh N, Ali, et al. Outcomes of surgical resection after radioembolization for hepatocellular carcinoma. *J Vasc Interv Radiol*. 2018;29(11):1502-1510.
51. Lau WY, Ho S, Leung TW, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. *Int J Radiat Oncol Biol Phys*. 1998;40(3):583-592.
52. Oldhafer KJ, Stavrou GA, van Gulik TM, et al. ALPPS—where do we stand, where do we go?: eight recommendations from the first international expert meeting. *Ann Surg*. 2016;263(5):839-841.
53. Aloia TA, Aloia TA. Associating liver partition and portal vein ligation for staged hepatectomy: portal vein embolization should remain the gold standard. *JAMA Surg*. 2015;150(10):927-928.
54. Piron L, Deshayes E, Escal L, et al. Portal vein embolization: present and future. *Bull Cancer*. 2017;104(5):407-416.
55. China Anti-Cancer Association. Expert consensus on standardized diagnosis and treatment of hilar cholangiocarcinoma (2015). *Chin J Hepatobiliary Surg*. 2015;21(8):505-511.
56. Huang G, Li PP, Lau WY, et al. Antiviral therapy reduces hepatocellular carcinoma recurrence in patients with low HBVDNA levels: a randomized controlled trial. *Ann Surg*. 2018;268(6): 943-954.
57. Salem R, Daneng Li DN, Sommer N, et al. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: results from the IMbrave150 trial. *Cancer Med*. 2021;10(16):5437-5447.
58. Sun HC. Conversion surgery for unresectable or advanced hepatocellular carcinoma. *J Abdom Surg*. 2021;34(2):85-87.
59. Han J, Lu SC. Discussion on immune and targeted therapy downgrading conversion for advanced hepatocellular carcinoma. *Chin J Hepatobiliary Surg*. 2020;26(1):67-68.
60. Suga A, Yamada S, Takeichi H, et al. Recurrence in regional pulmonary lymph nodes after surgery for isolated pulmonary metastasis from hepatocellular carcinoma. *Gen Thorac Cardiovasc Surg*. 2016;64(6):351-354.
61. Mizuguchi S, Nishiyama N, Izumi N, et al. Clinical significance of multiple pulmonary metastasectomy for hepatocellular carcinoma. *World J Surg*. 2016;40(2):380-387.
62. Inarrairaegui M, Pardo F, Bilbao JI, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. *Eur J Surg Oncol*. 2012;38(7):594-601.
63. Tabone M, Calvo A, Russolillo N, et al. Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience. *J Gastrointest Oncol*. 2020;11(1):84-90.
64. Katsanos K, Kitrou P, Spiliopoulos S, et al. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: a network meta-analysis of randomized controlled trials. *PLoS One*. 2017;12(9): e0184597.