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*Review Article*

# The past, present and future of conversion therapy for liver cancer

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**Abstract:** Primary liver cancer is one of the world's most common malignant tumors, as well as the malignant tumor with the third highest mortality rate in China. Most Chinese patients with liver cancer already have intermediate or advanced stage disease at initial diagnosis and have lost the opportunity for surgery. Following recent advances in treatments for advanced liver cancer, the associated treatment efficacy and response rates have continuously improved. As a result, the application of preoperative treatments can lead to tumor downstaging in a high proportion of patients and consequently provide initially ineligible patients with opportunities for surgical intervention, representing a breakthrough treatment strategy for liver cancer. Since conversion study is still in its infancy, there remain controversies in terms of patient selection, choice of treatment method, and postoperative management. In this review, we collect and summarize current evidence and clinical experience of conversion therapy, highlight remaining problems and challenges and provide a foundation for further research and development of HCC treatment in clinical practice.

**Keywords:** Liver cancer, conversion therapy, lenvatinib, sorafenib, PD-1 inhibitor, hepatocellular carcinoma, review

## Introduction

Primary liver cancer is one of the most common malignant tumors worldwide [1, 2]. The incidence of primary liver cancer ranked 4th among malignant tumors in 2015 and was the malignant tumor with the third highest mortality rate in China. Around 75-85% of primary liver cancers are hepatocellular carcinomas (HCC) [1]. For patients with early stage HCC (corresponding to China National Liver Cancer [CNLC] stage Ia, Ib and selected patients with stage IIa), radical treatments such as surgical resection, local ablation and liver transplantation are preferred, and the associated median survival time is more than 5 years [2, 3]. Unfortunately, the majority of patients in China with HCC are diagnosed with advanced cancer (CNLC stage IIb, IIIa and IIIB) and are therefore not suitable for surgical treatment. According to the findings of the BRIDGE study, 64% of Chinese HCC patients were diagnosed with CNLC stage II and III disease (equal to Barcelona Clinical Liver Cancer [BCLC] stage B and C) [4], and the majority were therefore not suitable for surgical resection, with an associated median survival time of approximately 2 years [2, 3, 5].

As early as the 1970s, there have been reports of patients with initially unresectable HCC who were able to achieve adequate tumor downstaging to undergo surgical resection [6]. In the 1990s, multiple studies described cases of tumor shrinkage and subsequent radical excision following local treatment of HCC, with a 5-year postoperative survival rate up to 50-60%, equivalent to survival of patients with early stage HCC who undergo resection [7-9]. Following recent advances in systemic treatments for advanced HCC, treatment efficacy and response rates have increased, and utilizing these new potent therapies as part of a conversion therapy treatment strategy has become an area of active research. In this review, we collected and summarized current evidence and clinical experience with conversion therapy in HCC including the definitions, methods and latest progress in conversion therapy as well as highlighting remaining problems and chal-

lenges that need to be solved. We believe this review will provide a foundation for further research and development of HCC treatment in clinical practice.

## Literature search methods

We conducted a literature search on PubMed using the following search terms. Search 1: hepatocellular AND conversion OR surgery OR resection OR salvage OR downstaging. Search 2: "advanced hepatocellular" AND "first-line" OR TACE OR HAIC. Search 3: hepatocellular AND "initially unresectable". No limitation was placed on the date of publication. All results were saved and screened to identify studies reporting first-line treatment of advanced unresectable HCC and including reporting of downstaging and/or surgical intervention rates.

## Definition of conversion therapy

The definition of conversion therapy is any treatment aiming to convert "unresectable" cancer into "resectable" disease. There is some overlap between conversion therapy and neo-adjuvant therapy and the differences require clarification. Neo-adjuvant therapy is used for patients diagnosed with resectable cancer for the purpose of achieving longer post-operative survival or improving the surgical condition of patients. For example, neo-adjuvant therapy in the breast cancer setting can provide patients the opportunity to undergo breast-conserving surgery or for patients with colorectal cancer can reduce the extent of surgical resection and preserve the anus. In contrast, conversion therapy refers to the treatment of patients with initially unresectable cancer with the aim of creating an opportunity for surgical intervention [10, 11]. The population of patients suitable for conversion therapy is therefore a highly selected subgroup of patients who are eligible for palliative treatment.

The definition of "unresectable liver cancer" is at the core of the conversion therapy strategy. At present, patients with unresectable HCC are mainly divided into three categories: patients with physical and liver function intolerance to surgery, patients with insufficient future liver remnant volume, and patients with advanced-stage cancer (BCLC stage B-C) likely to result in resection failure or lower survival compared with palliative treatment. For the first two categories, the general condition of the patient does not permit safe surgery, and for such patients the definition and appropriate treatment methods are relatively clear. For patients in the final category, with late stage HCC likely to result in resection failure or lower survival than palliative treatment, no standard treatments are recommended and the optimal management of such patients is not agreed on. The remainder of this review will focus on the latest progress in conversion therapy for patients with HCC who are ineligible for surgery due to advanced stage disease.

## Common treatments for conversion therapy

For patients with BCLC stage B-C HCC whose Eastern Co-operative Oncology Group performance score is 0-1 and a sufficient remaining liver volume, previous findings showed that the survival rate after resection is not as good as that associated with palliative treatment. Therefore, surgery is not recommended as the first choice for this patient population [12]. Before 2018, the only systemic treatments approved for use in patients with HCC were chemotherapy and sorafenib, with a low objective response rate of 3-10%. Therefore, historically the most common treatments used for conversion therapy have been local treatments such as transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), selective internal radiation therapy (SIRT) and radiotherapy.

### *Transcatheter arterial chemoembolization*

Among patients with resectable HCC, TACE is not associated with a significant survival benefit as a neo-adjuvant therapy and may increase surgical difficulties such as liver inflammation [13-19]. However, for patients with initially unresectable HCC, such as those with multiple tumors, or tumors close to large blood vessels, TACE can lead to tumor shrinkage and a reduction in tumor number, thereby bringing opportunities for surgery. According to previous findings, approximately 6-28% of patients with HCC can be downstaged (BCLC staging) through TACE [20, 21].

### *Hepatic arterial infusion chemotherapy*

In recent years, Chinese research groups have made great progress in the use of HAIC in advanced HCC. According to a multi-center RCT, the objective response rate (ORR) for

HAIC treatment in patients with HCC and portal vein cancer thrombi was significantly higher than that with sorafenib (mRECIST criteria, 27.6% vs. 3.4%, P=0.001) [22]. In addition, a retrospective study published by Lyu et al. also showed that the ORR associated with HAIC treatment in patients with advanced HCC was significantly higher than sorafenib (mRECIST criteria, 47.8% vs. 9.1%, P<0.01), and 26.1% of patients in the HAIC treatment group achieved sufficient downstaging to undergo radical treatment with surgery and radiofrequency ablation [23]. Evidence also suggests that in selected patients with huge HCCs, diffuse HCC and portal vein tumor thrombosis, the downstaging rate following HAIC may be higher than that with TACE [24]. In contrast, a more recent study of HAIC plus sorafenib versus sorafenib alone showed no survival benefit with the combination therapy, with a median OS of 10.0 months (95% CI: 7.0-18.8) versus 15.2 months (95% CI: 8.2-19.7), respectively (P=0.78) [25]. However, this study was underpowered, and the results should be interpreted with caution.

*Selective internal radiation*

SIRT, also known as transcatheter arterial radioembolization (TARE), is currently preferred over external radiotherapy because its main mechanism of action is internal radiotherapy, which appears to be better tolerated by healthy liver tissue. According to a study of 71 patients with unresectable HCC published by the Chinese University of Hong Kong, 26.7% of patients had tumor shrinkage of >50% from baseline after TARE treatment, of whom 4 patients (5.6%) received radical resection and two (2.8%) achieved a pathological complete response [26]. Furthermore, the team also followed up 49 advanced HCC patients who were successfully downstaged for surgical resection after receiving chemotherapy or TARE treatment. The results suggested that the 5-year survival rate of these patients was as high as 57% [20].

### The influence of recent advances in liver cancer drugs on conversion therapy

Since 2018, great progress has been made in the development of drugs for advanced HCC. In particular, combination therapy with a tyrosine kinase inhibitor (TKI) and immune checkpoint inhibitor [27-30], such as bevacizumab combined with atezolizumab, bevacizumab analog combined with sintilimab and apatinib combined with camrelizumab have reported very promising outcomes for the first-line treatment of advanced HCC (**Table 1**). Among the single-agent regimens, lenvatinib is associated with the highest ORR (18.3%; RECIST1.1) [31]. In addition, the ORR of combination regimens is 19.0-54.2% (RECIST1.1), which is higher than single-agent regimens. These high ORRs provide an opportunity for conversion therapy using systemic therapy and this has been evaluated in several retrospective studies. One retrospective study analyzed data from 107 patients with initially unresectable/TACE who received lenvatinib [32]. Among them, 16 patients underwent surgery as a follow-up treatment, and 9 patients achieved R0 excision. The median follow-up period of the study was 27.4 months, and the median OS of patients who underwent R0 excision was 19 months, much higher than that of patients who received other follow-up treatments (P=0.0007) [32]. Lu et al. reported 35 patients with CNLC stage IIIa HCC who received a programmed death-1 (PD-1) inhibitor combined with a TKI, and the conversion resection rate was 42.4% [33]. In a further study, Zhu et al. evaluated 63 patients with initially unresectable HCC treated with PD-1 inhibitors combined with TKIs, and reported a conversion resection rate of 15.9% [34].

The development of systemic therapies for HCC has also provided enhancements to local treatment-based conversion regimens. Multiple reports have explored the conversion rate of TACE/HAIC combined with systemic treatment in unresectable HCC patients. In an RCT of HCC patients with portal vein invasion, HAIC combined with sorafenib was compared with sorafenib monotherapy, and showed that the total effective rate (ORR, progression-free survival and overall survival) of the combined treatment group was significantly better than the sorafenib group. In addition, 12.8% of the patients in the combined treatment group were down-staged after treatment and underwent radical surgical resection, of whom 3 patients achieved a pathological complete response [35]. A further retrospective study also showed that, compared with lenvatinib monotherapy, triple therapy with lenvatinib combined with teriprizumab and HAIC led to a higher ORR and a higher conversion excision rate (0% vs. 12.7%) [36]. In a

**Table 1.** Summary of efficacy of first-line treatments for HCC

| Treatment | Sample size, n | TTR, months | ORR[a], % | PFS[a], months | OS, months | Grade ≥ 3 AE, % | Line of therapy |
|---|---|---|---|---|---|---|---|
| Systemic monotherapy | | | | | | | |
| Lenvatinib [53] | 478 | ---- | 18.3 | 7.4[b] | 13.6 | 57.0 | 1L |
| Sorafenib [54] | 331 | ---- | 2.7 | 3.6 | 10.1 | 49.7 | 1L |
| FOLFOX4 [55] | 184 | ---- | 8.15 | 2.93 | 6.4 | 55.7[c] | 1L |
| Donafenib [54] | 328 | ---- | 4.6 | 3.7 | 12.0 | 37.5 | 1L |
| TKI + IO | | | | | | | |
| Lenvatinib + nivolumab [56] | 30 | ---- | 54.2 | 7.39[b] | - | 60.0[c] | 1L |
| Lenvatinib + pembrolizumab [27] | 100 | 2.8 | 36.0 | 8.6 | 22.0 | 67.0 | 1L |
| Apatinib + camrelizumab [29] | 70 | 1.9 | 34.0 | 5.7 | 20.3 | 77.4[d] | 1L |
| Bevacizumab + teriprizumab [57] | 54 | | 31.8 | - | - | 20.4[c] | 1L |
| Bevacizumab + atezolizumab [58] | 336 | ---- | 30.0 | 6.9 | 19.2 | 43.0 | 1L |
| Regorafenib + pembrolizumab [59] | 35 | ---- | 29.0 | - | - | 86.0[c] | 1L |
| Cabozantinib + nivolumab + ipilimumab [60] | 35 | ---- | 29.0 | 6.8 | NR | 71.0 | 1L/2L |
| Anlotinib + penpulimab [61] | 31 | ---- | 24.0 | - | NE | 12.9 | 1L |
| Bevacizumab[e] + sintilimab [28] | 380 | ----- | 20.5 | 4.6 | NE | 33.7 | 1L |
| Cabozantinib + nivolumab [60] | 36 | ----- | 19.0 | 5.4 | 21.5 | 47.0 | 1L/2L |
| Locoregional therapy | | | | | | | |
| TACE [62] | 76 | ----- | - | 13.5 | NE | - | - |
| HAIC [24] | 156 | ----- | 45.9 | 9.63 | 23.1 | - | - |
| TARE [26] | 71 | ----- | 89[f] | - | 9.4 | - | - |

Note: Only studies with a sample size greater than 30 were included, including published articles and conference reports. Direct comparisons between different clinical trials are inappropriate. AFP, alpha-fetoprotein; HAIC: hepatic arterial infusion chemotherapy: IO: immunotherapy; NE: Not evaluable; NR: Not reached; ORR: Objective response rate; OS: Overall survival; PFS: Progression free survival; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; TEAE: Treatment emergent adverse event; TKI: tyrosine kinase inhibitor; TRAE: Treatment-related adverse event; TTR: Time to response. a: According to RECIST v1.1; b: According to mRECIST; c: TEAE; d: The safety assessment included patients receiving second-line treatment; e: This study used a bevacizumab biosimilar; f: According to changes in AFP levels in 46 patients with elevated pretreatment levels.

recent study of triple therapy with HAIC, lenvatinib and anti-PD-1 antibodies for the treatment of advanced HCC, it was found that even in patients with portal stem cancer thrombi and inferior vena cava cancer thrombi, the conversion rate could reach 40.5% (Data on File).

## Current challenges for conversion therapy

### *Survival benefit for patients achieving successful conversion*

The clinical significance of conversion therapy is to provide a greater proportion of patients with HCC an opportunity for radical treatment, providing longer tumor-free survival and overall survival. The majority of published studies of conversion therapy strategies used short-term endpoints such as surgical resection rate and postoperative recurrence rate and only a minority of studies used long-term survival as the primary endpoint. Some retrospective studies have shown that the survival rates after conversion resection show a greater long-term benefit than palliative treatment such as TACE in selected patient groups. For example, a report by Fan et al. showed that the overall survival rates of patients with unresectable HCC following TACE conversion resection were 80%, 65%, and 56% at 1-, 3- and 5-years, respectively [7]. Similarly, Kulik et al. reported that the overall survival rates 1, 2, and 3 years after TARE conversion resection were 84%, 54%, and 27%, respectively [37]. Lewandowski et al. studied and compared TACE and TARE in 276 patients with unresectable HCC (without portal vein thrombosis or extrahepatic metastases), and the median postoperative tumor-free survival time was 7.1 months and 17.7 months, respectively [38]. According to the findings of Zhu et al., after conversion resection following combined

TKI and immune checkpoint inhibitors, at a median follow-up time of 11 months, 8 patients continued to survive tumor-free, and 4 patients had stopped treatment [34]. It should be noted that retrospective studies may have selection bias, and the definition of unresectable HCC and the criteria for surgical resection in these various studies are not unified, which limits the comparability of survival data. Therefore, whether resection allows patients to obtain long-term survival after successful conversion therapy still requires further evidence from controlled studies (**Table 2**).

*Refinement of the definition of potentially resectable HCC*

At present, the definition of potentially resectable HCC is still relatively broad. It is mainly based on three factors; tumor thrombus, intrahepatic focus and extrahepatic spread, and mainly covers patients with CNLC stage IIb-IIIa disease and some patients with stage IIIb disease. Since the study of HCC conversion therapy is still in its infancy, different studies have included different patient populations, and used different conversion methods. Overall, the reported conversion rates are 8.4-56% [32] (**Table 2**). Therefore, the definition of the potentially resectable patient population still needs to be refined, further differentiating the subgroups of patients that are easy or difficult to convert successfully and recommending personalized treatment regimens. For example, although the conversion rate associated with single-agent therapy is not as good as that of combined therapy, the side effects of single-agent therapy are relatively mild. Thus, targeted single-agent therapy such as lenvatinib may be most suitable for patients with poor hepatitis B virus control who are not suitable for immunotherapy. Combinations of targeted and local therapy may be more suitable for patients who require a liver transplantation. In the present situation, where the efficacy of different regimens are not yet clear, the general principle should be selection of a treatment regimen with the highest ORR to ensure a high probability of tumor downstaging and provide the best opportunity for conversion (**Table 1**).

*Patient selection*

Identifying patients likely to respond well to conversion therapy based on demographics and disease characteristics would have great clinical utility. However, there are currently only limited data to inform patient selection. Zhu et al. reported that presence of extrahepatic disease was the only baseline factor with a significant association with successfully undergoing surgery following treatment with a TKI and an anti-PD-1 antibody in patients with advanced HCC; 0/10 patients who underwent surgery had extrahepatic disease [34]. In the study by Shindoh et al, multivariate analysis found that a decrease in plasma des-gamma-carboxyprothrombin from baseline was correlated with successful R0 resection following lenvatinib treatment in patients with initially unresectable HCC (OR, 22.22; 95% CI: 3.42-144.29; P=0.001) [32]. Huang et al. reported higher response rates and duration of response in macrovascular tumor thrombi than in intrahepatic lesions for patients with initially unresectable HCC treated with lenvatinib combined with an anti-PD-1 antibody [39]. In a study of TACE for the treatment of advanced HCC, age and AFP levels were similar in patients who achieved and did not achieve downstaging [40].

Multiple studies have reported associations between patient factors and response to radiotherapy-based treatments. For example, it has been reported that patients with Child Pugh class A liver function have a higher rate of partial response to SIRT compared to those with Child Pugh class B liver function [41]. Furthermore, a study investigating radioembolization in patients with initially unresectable HCC found that patients who achieved downstaging and subsequently underwent radical treatment were younger and had a higher tumor volume than those who did not undergo radical treatment [42]. However, this study found no association between successful surgical conversion and median AFP level or activity administered per tumor volume. In contrast, a more recent study of radioembolization in patients with unresectable HCC found that tumor absorbed radiation dose and serum AFP levels were significantly higher and lower, respectively, in patients who achieved downstaging compared to those who did not [43]. In summary, there is currently limited and conflicting evidence to support patient selection for conversion therapy based on patient factors and disease characteristics and further studies are required.

**Table 2.** Selected studies of conversion therapy in unresectable HCC patients

| Author | Journal, year | PVTT | Extrahepatic metastasis | Downstaging treatment | Resection criteria | ORR | PFS | Downstaging success rate | OS/OS rate | OS of downstaging pts |
|---|---|---|---|---|---|---|---|---|---|---|
| Llovet, et al. [63] | Lancet, 2002 | N | N | TAE (n=37)<br>TACE (n=40) | / | TAE: 43%<br>TACE: 35% | / | / | TAE, 1-, and 2-year survival rates: 75%, 50%; TACE, 1-, and 2-year survival rates: 82%, 63% | |
| Li, et al. [64] | Annals of Surgery, 2021 | N | N | cTACE (n=42)<br>TACE-HAIC (n=41) | / | RECIST c-TACE: 2.4%; TACE-HAIC: 14.6%<br>ORR (mRECIST) c-TACE: 16.7%; TACE-HAIC=65.9% | TACE-HAIC vs. cTACE: not available vs. 9.2 m | Conversion rate: TACE-HAIC vs. cTACE: 48.8% vs. 9.5% | OS TACE-HAIC vs. cTACE=not available vs. 13.5 m | |
| Byun, et al. [65] | Radiotherapy and Oncology | Y | N | IMRT + CCRT | / | / | / | Surgical conversion rate: 19.8% of the BED ≥ 72 Gy group (20/101) and 11.9% of the BED <72 Gy group (64/536) | OS For ≥ 72 Gy and <72 Gy groups, 21 and 13 months | Surgical conversion OS: 103.8 m; Surgical group: 1-year OS rates for the BED ≥ 72 and <72 Gy groups: 95.0% and 96.9% |
| Orlacchio, et al. [40] | World J Hepatol, 2015 | N | N | DSM-TACE | Reach nMC for liver transplantation | / | / | 75% | / | |
| Kim, et al. [66] | Sugery, 2017 | Y | N | Y90 SIRT and/or TACE | within Milan criteria with an AFP <400 ng/mL | / | / | 26.7% | similar overall survival compared with within Milan criteria | |
| He, et al. [67] | JAMA Oncology, 2019 | Y | Y | Sorafenib; Sorafenib plus HAIC (mFOLFOX) | | The SoraHAIC group: 40.8% sorafenib group 2.46%; P<.001 | Sorafenib + HAIC: 7.03<br>Sorafenib: 2.6 | Sorafenib + HAIC 12.8%<br>Sorafenib 0.8% | Sorafenib + HAIC 13.37<br>Sorafenib: 7.13 | |
| He et al. [68] | Chinese Journal of Cancer, 2017 | N | N | HAIC with the mFOLFOX regimen; TACE | | HAIC with mFOLFOX: 52.6%<br>TACE: 9.8% | | HAIC with mFOLFOX: 26% (10/38)<br>TACE: 9.7% (4/41) | | |
| Fan et al. [7] | Digestive Surgery | UK | UK | TACE | | | | 100% | | 1-, 3- and 5-year survival rates: 80.0%, 65.0% and 56.0% |
| Lau et al. [69] | Clinical Investigation | N | N | TARE | | ORR in terms of AFP: 89% | | 4/71 | Median OS: 9.4 m | |
| Wei et al. [70] | Journal of Clinical Oncology, 2019 | Y | N | Three-dimensional conformal radiotherapy + surgery | | 20.7% (17/82) PR | | 100% | | OS: 6, 12, 18, and 24 months: 89.0%, 75.2%, 43.9%, and 27.4% |
| Kolligs, et al. [71] | Liver International, 2015 | | | SIRT (Y-90); TACE | | TACE vs. SIRT: 13.3% and 30.8% | | TACE: 2/15<br>SIRT: 2/13 | / | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lee et al. [72] | Ann Surg Oncol, 2014 | N | N | Concurrent chemo/radiotherapy followed by HAIC | | | | 6.8% | 9.8% at 5-year survival | Curative resection group: 49.6% at 5-year survival |
| Tang, et al. [73] | Cancer, 1990 | | | 131I + MBV; 131I | | | | 28% | OS 1-year, 2-year: 52.5%, 27.7% | |
| Tang, et al. [74] | World Journal of Surgery, 1995 | N | N | Combination treatment | | | | | | 5-year OS: 62.1% vs. Surgery alone 15.4% |
| Zhang, et al. [52] | The Oncologist, 2016 | Y | N | TACE | | | | 9.9% | 31 m | 49 m |
| Zhu, et al. [75] | Liver Cancer, 2021 | Y | Y | TKI + anti-PD1 | | | | 10 (15.9%) | | |
| Shi, et al. [76] | ESMO, 2020 | N | N | HAIC with FOLFOX (n=159) or TACE (n=156) | | HAIC: 45.9<br>TACE: 17.9%<br>RECIST | HAIC: 9.63<br>TACE: 5.4 | HAIC: 23.8%<br>TACE: 11.5% | HAIC: 23.1<br>TACE: 16.07 | |
| Zhang, et al. [33] | J Chinese Journal of Hepatobiliary Surgery, 2020 | | | Anti-PD-1 + lenvatinib | | 45.5% (15/33) | | 42.4% | | |
| Zeng, et al. [77] | European Journal of Nuclear Medicine, 2002 | Y | N | RIT group: HAL + RIT (n=32);<br>EBRT group: TACE + EBRT (n=35) | | RIT: 72%<br>EBRT: 86% | | RIT: 53%<br>EBRT: 23% | The 1-, 2-, 3- and 4-year survival rates were 50%, 41%, 34% and 31% in the RIT group, and 77%, 39%, 11% and 7% in the EBRT group | |
| Lewandowski, et al. [38] | American Journal of Transplantation, 2009 | N | N | TACE (n=150); TAREY 90 (n=126) | Downstaging to UNOS T2 | TACE: 37%<br>TARE: 61% | TACE: 17.7<br>TARE: 7.1 | TACE: 31%. TARE: 58% | | |
| Inarrairaegui, et al. [42] | the Journal of Cancer Surgery, 2012 | | | TARE | | | | 28.6% | 22.0 months (95% CI 15.0, 30.9) in those who received palliative care | OS was not reached in 6 patients treated radically |
| Lee, et al. [78] | YMJ, 2014 | Y | N | Concurrent chemo/radiotherapy | | | | 6.8% | | |
| Chong, et al. [79] | Ann Surg Oncol, 2018 | Y | N | CCRT followed by HAIC | | | | 26.5% | | |
| Labgaa, et al. [80] | HPB, 2019 | Y | N | TARE followed by OLT or resection | | | | 100% | | 47 m |
| Tabone, et al. [43] | Journal of Gastrointestinal Oncology, 2019 | Y | N | TARE | | | | 20.8% | | |

AFP; alpha fetoprotein; BED; biologically effective dose, CCRT; concurrent chemoradiotherapy, cTACE; conventional trans-arterial chemoembolization, DSM-TACE; degradable starch microspheres trans arterial chemoembolization, EBRT; external beam radiation therapy, HAL; hepatic artery ligation, IMRT; intensity modulation radiotherapy, MBV; mixed bacteria vaccine, mRECIST; modified response evaluation criteria in solid tumors, nMC; new Milan criteria, OLT; orthotopic liver transplantation, ORR; overall response rate, OS; overall survival, PD1; programmed cell death 1, PFS; progression free survival, PVTT; portal vein tumor thrombosis, RECIST; response evaluation criteria in solid tumors, RIT; radioimmunotherapy, TACE; trans-arterial chemoembolization, TACE-HAIC; trans-arterial chemoembolization-hepatic arterial infusion chemotherapy, TAE; trans-arterial embolization, TARE Y90; transarterial radioembolization yttrium-90, TARE; transarterial radioembolization, TKI; tyrosine kinase inhibitor, Y90 SIRT; yttrium-90 selective internal radiation therapy.

*Adverse events and perioperative complications*

Despite recent advances in conversion therapy for HCC, treatment strategies all carry the potential for an increased risk of adverse events and perioperative complications due to the use of combination therapies and the relatively short intervals between conversion therapy and surgery. For example, a network meta-analysis comparing different embolization treatment strategies for unresectable HCC reported that all treatments increased the risk of serious adverse events compared to control and patients receiving two therapies had the greatest risk increase [44]. This analysis reported that the odds ratio for a serious adverse event relative to control in patients receiving TACE plus radiotherapy was 53.1 (95% CI: 4.03-1016) and was 14.6 (95% CI: 4.7-67.7) for those receiving TACE alone [44].

It has also been reported that preoperative TACE can increase intraoperative blood loss and cause liver inflammation, increasing the risk of complications during surgery [45, 46]. However, with a sufficient interval between the last round of TACE and surgery, TACE has minimal impact on surgical outcomes. It is recommended that an interval of at least 4 weeks greatly reduces the effect of TACE on surgical outcomes, perioperative complication rate and the mortality rate [17, 47].

*Adjuvant treatment after successful conversion*

Apart from standard approaches such as conventional liver protection and antiviral treatments (for patients with HBV/HCV infection) following a successful conversion, there is still not enough evidence to determine the benefit of adjuvant treatment. However, for patients achieving a R0 resection after conversion therapy, the lack of surgical indications during initial diagnosis means that patients are often vulnerable for recurrence, including vascular tumor thrombi, larger tumors (diameter >5 cm), residual small foci, and multiple tumor foci. For patients at high risk of recurrence, active intervention measures should be taken to prevent or delay tumor recurrence including antiviral drugs (for patients with HBV/HCV infection), hepatic artery interventional therapy, oxaliplatin-containing systemic chemotherapy, targeted therapies, and traditional Chinese medicine. Either a single regimen or a combined regimen can be used [48, 49]. For patients achieving successful conversion, the preoperative conversion treatment protocol was effective, and it is reasonable for postoperative adjuvant treatment to follow the preoperative regimen. However, the selection of a postoperative treatment regimen should also focus on optimizing safety. If the conversion treatment regimen consisted of combined systemic and local treatment, the adjuvant treatment may only utilize the systemic treatment component. If the original conversion treatment regimen was a multi-drug combination, it is reasonable to select certain drugs from the original regimen according to the patient's physical condition, adverse reactions, liver function and tolerance. However, there is still a lack of sufficient data to inform the optimal dosage and timing of adjuvant treatment following conversion therapy.

## Suggestions for future conversion study design

Most data for conversion therapy come from retrospective studies. As described above, there are still many challenges and questions to be addressed, such as choice of surgical time window, the necessity of surgery after conversion therapy for patients who achieve a pathological complete response, criterion for the failure of conversion therapy and how to choose a second-line regimen. These topics all require further study. In addition, the current conversion rates reported in HCC conversion-related studies vary greatly across different studies (**Table 2**). A key reason for this heterogeneity is that the selection of patient populations and surgical criteria are defined differently in the different studies. Therefore, in order to make findings more accurate and repeatable, the future design of conversion therapy studies needs to be carefully considered. Factors such as inclusion criteria and study endpoints need to be further refined.

*Inclusion criteria*

It is necessary to differentiate the neo-adjuvant therapy population and conversion therapy population and guarantee the surgical safety of successful conversion patients. Therefore, it is recommended that the scope of inclusion criteria for future studies of conversion therapy

should not exceed BCLC stage B-C (CNLC stage IIb-IIIa). Stage IIIb patients with extrahepatic conversion require special consideration. The number of primary tumors, overall tumor burden, and vascular invasion (VP typing) should be limited.

*The definition of successful conversion needs to be clarified*

Outcomes should consider tumor stage, number of tumors, change of overall tumor burden, degree of tumor necrosis, liver function, physical fitness and tumor markers (such as AFP), as well as provisions on drug withdrawal and operation time after successful conversion.

*Selecting study endpoints*

At present, studies of conversion therapy are mostly retrospective. The main indicators analyzed include conversion rate, ORR, recurrence-free survival, and adverse reactions during conversion therapy. These indicators cover the main observations during and after conversion therapy. As well as conversion rate, the surgery rate, defined as the proportion of patients who undergo surgical resection, would also have value as a primary outcome in future trials as not all patients who achieve conversion are able to undergo surgery due to factors including patient refusal and unresolved adverse events [34, 50-52]. It may also be feasible to add changes in serum indicators, as well as the outcome during the operation and postoperative conditions, including intraoperative blood loss and postoperative wound healing time. Since current conversion treatment regimens often include immune therapies such as PD-1/programmed death ligand-1 antibodies, attention should also be paid to the occurrence of postoperative immune-related adverse reactions, including immune-related hepatitis, myocarditis, and pneumonia. According to previous studies, patients with hepatitis B-related HCC may experience reactivation of the hepatitis virus after the application of local therapy or chemotherapy. Therefore, if the conversion regimen includes local therapy or chemotherapy, it is important to include viral load as a secondary endpoint. As for whether overall survival should be used as the primary endpoint, because there are an increasing number of treatments for HCC the effect of later-line treatments on overall survival in current and future studies is greater than for historical studies. Despite representing the gold standard endpoint for oncology trials, overall survival is recommended to be used as a secondary study endpoint in trials of conversion therapy, for cautious interpretation. Recurrence-free survival may have more value as a survival endpoint in these studies.

## Summary & outlook

Advances in systemic and local therapies for advanced HCC have facilitated the application of conversion therapy in selected patients with unresectable HCC, and promising preliminary results have been reported. According to these preliminary data, patients with BCLC stage B-C HCC (equal to CNLC stage IIb-IIIa) can undergo conversion treatment using a number of different treatment strategies. Local treatment combined with systemic treatment is associated with higher conversion success rates and are suitable for patients with BCLC stage B HCC with large tumors as well as patients with portal vein invasion. Because local treatment combined with systemic treatment is also a standard palliative treatment option, patients with unsuccessful conversion can choose a standard second-line regimen with no loss in terms of survival benefit. For patients achieving a successful conversion, whether surgical resection is necessary or provides additional survival benefit remains to be confirmed. In particular, high-quality evidence from prospective trials are required to establish if patients achieving conversion who undergo surgery have longer survival compared with patients who do not undergo surgery.

## Disclosure of conflict of interest

None.

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