Review

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Conversion therapy with an immune checkpoint inhibitor and an antiangiogenic drug for advanced hepatocellular carcinoma: A review

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SUMMARY Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide and is the second most common cause of tumor-related mortality globally. In China, a high proportion of patients with HCC present with an advanced stage of the disease, so HCC is a major challenge to the healthcare system and a substantial socioeconomic burden. The last decade has witnessed an expansion of the treatment landscape for HCC. Various approaches have been explored as potential conversion therapies for advanced HCC. Despite controversies, mounting data have indicated that successful conversion therapy followed by subsequent surgery is achievable in a population of patients with advanced HCC. This conversion therapy is a safe and promising treatment strategy to prolong long-term outcomes. Based on preliminary research, this review has assembled and summarized current clinical experience with and evidence of the efficacy of conversion therapies followed by subsequent surgery for advanced HCC.

Keywords hepatocellular carcinoma, conversion therapy, immune checkpoint inhibitors, antiangiogenic drugs, subsequent surgery

1. Introduction

Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide, with over 500,000 new cases every year, and it represents the second leading cause of tumor-related mortality globally (*1-12*). There is a considerable geographical imbalance in the incidence of HCC. The incidence of HCC has decreased in certain countries or areas where it was high (East Asia and sub-Saharan Africa) but it has increased in some countries or areas where it was low (India, the Americas, Oceania, and southern European countries) (*8*). Data from 2018 have indicated that the estimated global incidence of primary liver cancer (as the principal type of primary liver cancer, HCC represents more than 80% of the total) per 100,000 person-years was 9.3% and its mortality rate was 8.5% (*1,2,7-9*). Due to the prevalence of infection with the hepatitis-B virus, HCC is particularly endemic in China (*13*). Data on Chinese patients with HCC from 2003 to 2015 have indicated that there is substantial room for improvement in long-term outcomes, with a five-year overall survival rate of merely 12.5% (*14*). Liver resection remains the first-line treatment for early-stage HCC, with a five-year overall survival rate of around 40 to 50% (*4,15*). However, around 44-62.2% of the population with HCC in China has cancer of an advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) classification at initial diagnosis. (*14,16*) For patients with such advanced HCC, palliative locoregional or systemic treatments, or even palliative supportive care, are recommended over surgical resection in most HCC guidelines (*4,17*). Outcomes are unsatisfactory, with a median overall survival of around 8-12 months. Even for certain groups of patients with advanced HCC who underwent initial surgical resection, the postoperative prognosis is quite poor. Hence, HCC poses a major challenge to the healthcare system and a substantial socioeconomic burden in China (*16,18*).

The last decade has witnessed profound progress in therapeutic paradigms for advanced HCC (*5,13,16*). A combination of an immune checkpoint inhibitor (ICI) and an anti-angiogenic drug (AAD) has promising use in

cancer treatment. A combination of an ICI and an AAD has yielded inspiring results in the treatment of advanced HCC compared to previous approaches, setting a new benchmark with an objective response rate (ORR) of 33.2-46.0% and a disease control rate (DCR) of 72.3-88% and a complete response (CR) rate of 8.6-11% and median overall survival of 17 months for unresectable HCC (*14,16*). Moreover, the combination of an ICI and an AAD can be utilized as a conversion therapy for advanced HCC, which would change unresectable advanced HCC into resectable tumors and offer patients the possibility to undergo subsequent radical surgery (Figure 1) (*16,19*). As early as 2016, the current authors initiated conversion therapy for unresectable HCC using an ICI and an AAD, and inspiring outcomes were obtained. Based on Chinese practices and discussions among domestic experts, a consensus among Chinese experts has also been reached (*16*). The current review has mainly assembled and summarized current clinical experience with and evidence of the efficacy of conversion therapy (with an ICI and an AAD) followed by subsequent surgery for advanced HCC. This review also discusses several issues with conversion therapy and subsequent surgery for advanced HCC.

2. Necessity of conversion therapy for advanced HCC

Currently, there is little controversy about the definition of advanced HCC in domestic and foreign guidelines. Macrovascular invasion and extrahepatic metastasis are vital elements in the definition of advanced HCC. Table 1 summarizes the relevant information on advanced HCC in three domestic or international guidelines (*8,9,20*). Advanced HCC accounts for 44-62.2% of all patients with HCC at initial diagnosis. The survival rate of such patients is quite low, greatly limiting improvement of the prognosis for HCC. Therefore, there is a pressing need for conversion therapy for advanced HCC. In recent decades, the treatment landscape for advanced HCC has expanded. Local or systemic treatments include transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), stereotactic body radiation therapy (SBRT), localized concurrent chemoradiotherapy (CCRT), ablation, tyrosine kinase inhibitors (TKIs), ICIs, and their combined use. Despite these various approaches, the prognosis for advanced HCC has barely changed (*16*). Data have indicated that the DCR of TAE and TACE mostly ranges from 3.9 to 37.9%, with a median overall survival of 5-15.5 months (*21,22*). Special care should be given to patients with portal vein tumor thrombosis. For such patients with a blocked portal vein, TACE may further aggravate liver ischemia and lead to liver failure (*23*). TARE with yttrium-90 microspheres is a liver-directed therapy for hepatic tumors. Indications for TARE are mainly downsizing tumors, increasing future liver remnant, and bridging to transplantation. For advanced HCC, TARE is used for palliation or delayed progression of disease (*24*). The role of TARE in advanced HCC has been the subject of two randomized trials comparing sorafenib and TARE. No significant difference in median overall survival was evident (8.8 months in the TARE group versus 10

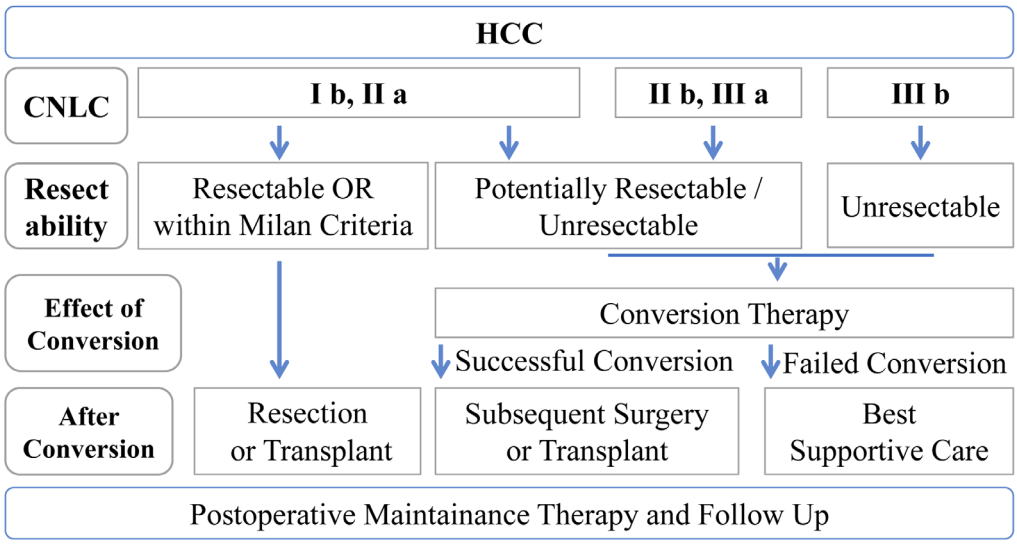

Figure 1. Algorithm for Conversion Therapy for Hepatocellular Carcinoma. CNLC: China Liver Cancer stage; Milan criteria: diameter of a single tumor ≤ 5 cm, the number of tumors ≤ 3, all ≤ 3 cm in diameter, and without angioinvasion or extrahepatic involvement; Resectable: R0 resection, sufficient future liver remnant at initial diagnosis; Potentially Resectable: preoperative predicted functional residual liver volume and liver function reserve at borderline level or with doubtful postoperative oncological benefit; this corresponds to patients with mild to moderate impairment of liver function reserve in the following stages: certain groups of patients with Barcelona Clinic Liver Cancer -B, C, or CNLC-IIIa with intrahepatic portal vein and/or hepatic vein tumor thrombus, or patients with CNLC-IIIb with resectable extrahepatic lesions; Unresectable: one of three situations: insufficient future liver remnant after surgery, tumor thrombus in main portal vein or hepatic vein, or unresectable extrahepatic lesions are present.

Table 1. Definition and recommended treatment for advanced HCC in guidelines

Guideline	Definition/staging	Treatment	Survival
AASLD guidelines	Macrovascular invasion and/or metastatic disease	Local or Systemic therapy*	–
EASL guidelines	Macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) BCLC stage C	Local or Systemic therapy*	Median survival of 6-8 months; 1-year OS 25%
Chinese guidelines	Macrovascular invasion and/or metastatic disease CNLC stage IIIa or IIIb	Local or Systemic therapy*	1-year OS 12-38.3%

HCC: Hepatocellular carcinoma; AASLD guidelines: the American Association for the Study of Liver Diseases Guidelines for the Treatment of Hepatocellular Carcinoma 2018; EASL Guidelines: the European Association for the Study of the Liver Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018; Chinese Guidelines; Chinese Guidelines: Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2022 Edition); OS: Overall survival; BCLC stage: Barcelona Clinic Liver Cancer stage; CNLC stage: China liver cancer stage; *depending on the extent of vascular invasion and/or metastatic disease, the severity of underlying cirrhosis, and the performance status of the patient.

Table 2. Differences between conversion therapy and neoadjuvant therapy for HCC

Items	Subject	Aim	Methods	Observation time	End point
Conversion therapy	Unresectable tumor; #Outside liver transplantation criteria	To make surgery or a transplant feasible and improve overall survival	Local or Systemic therapy (Modalities often overlap)	3-6 months (median of 5 cycles with an ICI + an AAD)	ORR, TTP, OS, RFS Rate of subsequent surgery
Neoadjuvant therapy	Resectable tumor	To simplify surgery and improve long-term results To decrease tumor progression (and dropout) from transplantation waiting list		1.5-3 months (no longer than 4 months)	OS, RFS

HCC: hepatocellular carcinoma; ICI: immune checkpoint inhibitors; AAD: anti-angiogenic drugs; ORR: objective response rate; TTP: time to progression; OS: overall survival; RFS: recurrence-free survival; #mainly referring to the Milan Criteria, diameter of a single tumor ≤ 5 cm, the number of tumors ≤ 3, all ≤ 3 cm in diameter, and without angioinvasion or extrahepatic involvement.

months in the sorafenib group) (*24*). Developments in radiation oncology have facilitated the advancement of SBRT. Studies have suggested that SBRT yielded a high local control rate (2-3 years: 70-100%) and a high overall survival rate (60-70%) in early-stage HCC (*25,26*). Generally, SBRT was regarded as an alternative to other approaches, such as hepatectomy, TACE, and ablation (*8,27*). Controversy still exists about hepatectomy for advanced HCC. The reported median recurrence-free survival after surgery was only 1.5 to 10.0 months, the one-year recurrence rate was 34.0-86.7%, the three-year recurrence rate was high as 85.0-95.4%, and the overall recurrence rate as high as 85.0-97.2%. Median overall survival is 4.8-19.5 months, and the one-year, three-year, and five-year survival rates are 28.6-50.0%, 12.5-22.7%, and 4.0-23.8%, respectively (*16,21,28,29*) . Early recurrence seriously affects the prognosis for advanced HCC. Studies have confirmed that cancer in a late stage is an independent risk factor for a poor prognosis after HCC hepatectomy.

The fundamental reason for a poor prognosis for advanced HCC lies in the limited oncological benefits from the aforementioned local, systemic or surgical treatments. Due to the harmful biological behavior of advanced HCC, none of these treatments can reduce the high recurrence rate and result in a radical cure. Therefore, the current authors propose to focus on the survival benefits for patients and to explore conversion therapy with a combination of an ICI and an AAD for advanced HCC. Conversion therapy for advanced HCC mainly includes the following two connotations: a) conversion to surgical resectability and b) the possibility of an oncological benefit (*16,30,31*).

3. Current status of conversion therapy for advanced HCC

In the treatment of HCC, conversion therapy should be distinguished from neoadjuvant therapy. Both of the two concepts are vital steps in preoperative therapy for intermediate or advanced HCC (*16,18,32-35*). Although there are still debates over the confusing overlap of the two concepts, the differences between conversion therapy and neoadjuvant therapy for HCC are briefly summarized in Table 2.

Unlike neoadjuvant therapy, conversion therapy in

Table 3. Brief summary of conversion approaches for advanced HCC

Treatment	ORR	Conversion rate	Rate of subsequent surgery	Rate of grade 3-4 adverse events	Outcome
ALPPS	–	–	91%	11.1%*	1-year RFS 47.6% 1-year OS 64.2%
TAE, TACE	3.9-37.9%	–	9.8-12%	30%	1-year RFS 36-68%
TARE	–	20.8%	9%#	17.1%	5-year OS 86%
HAIC	28.6%	–	11.7%	19%	–
SBRT	–	–	5.7%	0.6%	1-year OS 36.2-56%
HAIC + CCRT	–	–	16.9%	–	1-year RFS 57.7%
TKI + Local Therapy	5.7-45.0%	–	14.3%	–	1-year OS 46.5-61%
Atezolizumab+ Bevacizumab	29.8%	–	–	56.5%	1-year OS 67.2%
Concurrent chemo/ radiotherapy	–	6.8%	–	–	5-year OS 49.6%
ICI+ TKI		51%	30.6%	6.1%	1-year RFS 61% 1-year OS 74%

HCC: hepatocellular carcinoma; ORR: objective response rate; ALPPS: associated liver partition and portal vein ligation for staged hepatectomy; TAE: transarterial embolization; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; HAIC: hepatic arterial infusion chemotherapy; SBRT: stereotactic body radiation therapy; CRRT: concurrent chemoradiotherapy; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor; RFS: recurrence-free survival; OS: overall survival. #Includes the rate of subsequent liver transplantation and liver resection; *90-day mortality rate; Adverse events are grouped in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Table 4. Targets of tyrosine kinase inhibitors

Tyrosine kinase inhibitors	Bevacizumab	Ramucirumab	Sorafenib	Lenvatinib	Regorafenib	Cabozantinib	Donafenib
Target	VEGFA	VEGFR2	VEGFR1–3 PDGFR RAF KIT	VEGFR1–3 PDGFR FGFR1–4 RET	VEGFR1–3 PDGFR RAF FGFR1–2	VEGFR1–3 MET RET	VEGF PDGF RAF MEK ERK

VEGFA: vascular endothelial growth factor A; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factors; FGFR: fibroblast growth factor receptor.

advanced HCC is not an emerging treatment approach or a new concept (*36-40*). A previous study suggested that 139 of 1,085 patients with unresectable HCC enrolled from 1958 to 2003 were converted and underwent subsequent surgical resection, resulting in a five-year survival rate of 48.7% (*41*). Now, with multiple systemic agents in development, various approaches have been explored as potential conversion therapies for advanced HCC. Specific methods include associating liver partition and portal vein ligation for staged hepatectomy, ablation, TACE, HAIC, SBRT, CCRT, TARE, TKIs, ICIs, and multimodality treatment approaches (*16,18,42,43*). Conversion outcomes of various approaches are cited in Table 3 (*16,18,42,44-46*). Despite controversies, mounting data have indicated that successful conversion treatment followed by subsequent surgery is achievable in the population of patients with advanced HCC (*47*).

4. A combination of an ICI and an AAD offers hope as a conversion therapy for advanced HCC

In recent years, ICIs and AADs have y encouraging outcomes in the treatment of various solid tumors. New drugs including multikinase inhibitors (such as lenvatinib; target of TKIs are summarized in Table 4) and programmed cell death protein 1 (PD-1 as well as programmed cell death ligand 1 and its inhibitors such as pembrolizumab and atezolizumab; combinations of an ICI and an AAD are summarized in Table 5 (*11,48-50*)) have proven effective in the treatment of advanced HCC and have been successively recommended by domestic and international HCC guidelines (*16,46,51,52*). The ORR of an ICI or AAD alone is only 9.2-24.1% (49, 53). Recent studies have confirmed that the combined use of an ICI and an AAD could further improve ORR in advanced HCC, achieving an efficacy of "1+1 > 2" (*16*). For unresectable HCC, a combined regimen was reported to have a DCR rate of 33.2-46.0% (*25*). A combination

Table 5. Combinations of immune checkpoint inhibitors and anti-angiogenic drugs

ICI	Combination	Number of patients	ORR	Survival (month)	Recommended as
anti PD-1	Lenvatinib + Nivolumab	30	54.2	73.9 (PFS)	First line
anti PD-1	Lenvatinib + Pembrolizumab	100	36.0	8.6 (PFS)	First line
				22 (OS)	
anti PD-1	Apatinib + Camrelizumab	70	34.0	5.7 (PFS)	First line
				20.3 (OS)	First line
anti PD-1	Regorafenib + Pembrolizumab	35	29	6.8 (PFS)	First line
anti PD-1	Anlotinib + Penpulimab	31	24	5.4 (PFS)	First line
				21.5 (OS)	/Second line
anti PD-1	Cabozantinib + Nivolumab	36	19	1-year OS 12-38.3%	First line
anti PD-1	*Bevacizumab + Sintilimab	380	21	4.6 (PFS)	First line
anti PD-L1	*Bevacizumab + Atezolizumab	336	30	19.2 (OS)	Second line
anti PD-L1	*Tremelimumab + Durvalumab	74	24	18.7 (OS)	

ICI: immune checkpoint inhibitors; ORR: objective response rate; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; PFS: progression free survival; OS: overall survival. *not a combination of immune checkpoint inhibitors and anti-angiogenic drugs.

of an ICI and an AAD could involve a synergistic mechanism that can not only improve the immune microenvironment but also promote the normalization of immune cell function (*5,13,54*). The degree of tumor infiltration by immune cells can determine the efficacy of immunotherapy. A recent study has indicated that tumors can be categorized into a 'high T cell' group (also called hot tumors) or a 'low T cell group (also called cold tumors) (*55*). Combination therapy (in addition to local therapies) could facilitate immune cell infiltration into 'low T cell' tumors, thus converting 'cold' tumors to 'hot' ones and enhancing the treatment response (*56*). This synergistic mechanism may involve multiple mechanisms, including improved vascular normalization for drug delivery and immune cell infiltration, activation of various antitumor immune cell subsets, and/or inhibition of immune cell types with pro-tumor activity. One example is the vascular endothelial growth factor (VEGF) pathway; inhibition of VEGF signaling also combined with the action of an ICI to enhance the antitumor immune cell response and inhibit key immunosuppressive pathways (*56-58*). This enhanced anti-tumor action has been observed in mouse tumor models using multikinase inhibition with lenvatinib plus anti-PD-1 inhibition. In immunocompetent mice, treatment with a multikinase inhibitor and anti-PD-1 antibodies yielded more significant tumor regression and a greater ORR in comparison to either approach alone (*59,60*). Research results indicated that a multikinase inhibitor could reduce the tumor PD-L1 grades and Treg differentiation to promote anti-PD-1 function (*61,62*). Moreover, a phase Ib study of lenvatinib plus pembrolizumab implied that multikinase inhibition with anti-PD-1 inhibition resulted in a confirmed response rate of 46% according to mRECIST, which gives credence to the improved antitumor activity and increased tumor sensitivity of combined use (*48*). Hence, synergistic action is conducive to improved efficacy.

Moreover, unlike traditional invasive treatments such as HAIC, TACE, and SBRT that require hospitalization, the combination of an ICI and an AAD is simple and convenient. The treatment can be completed in a day ward or at home. The incidence of serious adverse events is relatively low and recovery can be achieved through drug withdrawal or hormone therapy. Research by the current authors has indicated that a combination of an ICI and an TKI resulted in an adverse event incidence of about 46.9%, most of which are below grade three (*63*).The incidence of grade three or four adverse events was 6.1% which is significantly lower than that of other treatment modalities (*18,42,44-46,64-66*). Adverse events are grouped in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (*53*). The high ORR is expected to greatly increase the conversion rate of advanced HCC. The authors & facility has conducted a prospective study of conversion therapy with an ICI and a TKI in 33 patients with advanced HCC and an intrahepatic large blood vessel tumor thrombus (*67*). Preliminary results indicated that the ORR was 45.5% (15/33), the DCR was 81.8% (27/33), and the image-based conversion rate was 42.4% (14/33). Ten patients underwent subsequent hepatectomy and had a six-month recurrence-free survival rate of 60.0% during a median follow-up of 11.5 months.

Conversion therapies also present the unique possibility of expanding the population eligible for liver transplantation. Studies on conversion therapies prior to liver transplantation for patients with HCC outside the Milan criteria are still limited and have mixed outcomes (*68-74*). Despite the concern that an ICI might increase the possibility of acute rejection and graft loss in the early post-transplantation period, transplantation can be performed safely with a sufficient washout period between ICI administration and transplantation (*71*). Tabrizian *et al*. reported nine patients undergoing transplantation for HCC after receiving nivolumab at a single center. Severe post-transplant complications were not observed. During the follow-up period, none of the patients developed severe acute rejection or tumor recurrence (*73*). The current author' team has studied a small cohort of six patients with advanced HCC

undergoing a liver transplantation after bridging therapy with an ICI and an AAD. In the cohort, four patients were found to have BCLC-C or China liver cancer (CNLC) stage IIIa cancer; the other two were found to have BCLC-B or CNLC stage IIb. Patients received an average of 5.5 cycles of an ICI (PD-1 inhibitor) and the washout period was 19.5 days prior to transplantation. All of the patients satisfied the liver transplantation criteria after conversion therapy and successfully underwent an orthotopic liver transplantation. All of the patients recovered well without serious complications. None suffered acute rejection or graft loss. The median tumor-free survival was 10.9 months (range 2.9-27.3 months) after follow-up (*70*). Conversion therapy with an ICI and an AAD displayed promise in transplant recipients under close clinical monitoring. However, further research is needed.

Based on domestic practices and discussion among Chinese experts, an expert consensus has been reached (*16*). Inclusion criteria for conversion therapy with an ICI and a TKI for advanced HCC should be: a) CNLC -III/BCLC-C stage HCC; b) Child-Pugh class A liver function; c) an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1; d) 18-75 years of age; e) expected survival of over three months; f) no gastrointestinal bleeding in the past six months; and g) for patients falling outside the inclusion criteria above, preliminary treatment should be performed step by step depending on the specific situation. At the same time, concomitant local treatment may increase the conversion rate and shorten the overall duration of treatment. For patients with extrahepatic metastasis in particular, appropriate approaches are needed to manage extrahepatic lesions. For bone metastases, radiotherapy represents an approach with definite efficacy; for lung metastatic tumors, image-guided radiofrequency ablation might be the treatment of choice.

5. Assessment of conversion therapy

Regular assessment is especially vital after conversion therapy has started. Assessment of conversion therapy mainly includes a general evaluation, the tumor response to conversion therapy, the change in the residual functional liver volume, and serious adverse events.

A general evaluation includes clinical symptoms, as well as the patient's general condition such as mental state, physical status, appetite, and weight, which can be evaluated based on the ECOG-PS score. Imaging evaluation consists of two aspects: tumor response and residual functional liver volume. Evaluation of tumor treatment response is mainly achieved with enhanced magnetic resonance imaging or computed tomography according to the response evaluation criteria in solid tumors (RECIST) or modified RECIST (mRECIST). After treatment takes effect, tumor necrosis occurs first, and absorption is a relatively slow process. Because of the histological and biological change of a necrotic tumor, mRECIST is more suitable for imaging evaluation of conversion therapy. A reduction in tumor diameter can serve as an index with which to evaluate effective treatment, while the disappearance of or decrease in arterial phase enhancement can serve as an imaging feature with which to evaluate the necrosis of a tumor after conversion therapy (Figure 2). In addition, three-dimensional reconstruction could help to precisely analyze the volume change and structural adjacency of a tumor (Figure 3). Positron emission tomography-CT (PET-CT) can assess the treatment response of a primary tumor and extrahepatic metastases. For patients with extrahepatic metastasis, PET-CT has an irreplaceable role in the evaluation of treatment efficacy. Figure 4 presents a patient who underwent conversion therapy followed by subsequent open left-hepatectomy (*75*). After four cycles of combination therapy with an ICI (sintilimab) and an AAD (lenvatinib) for three months, the standard uptake of the tumor decreased significantly, which substantiates obvious tumor necrosis after conversion therapy. One year after the subsequent left-hepatectomy, PET-CT revealed no signs of recurrence.

Assessment of adverse events is mainly based on the patient's chief complaint, combined with an electrocardiogram, chest X-ray film, thyroid function test, routine blood test, myocardial enzymes, and other biochemical indicators. Common adverse events associated with conversion therapy include: a) Skin: skin rash or mucositis; b) Heart: elevated blood pressure or immune myocarditis; c) Digestive tract: nausea, vomiting, diarrhea, or colitis; d) Endocrine abnormalities: thyroiditis, hypothyroidism, or hyperthyroidism; e) Pulmonary: immune pneumonia; f) Kidney: renal insufficiency; and g) Liver: elevated transaminase or abnormal liver function. Most of the adverse events will spontaneously resolve or only need to be treated symptomatically. Combined treatment is rarely interrupted due to adverse events. The principles for adverse event management can be based on the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities version 2.

When conversion therapy is effective but assessment fails to reveal any further benefit, timely concomitant local therapy or subsequent surgical resection should be performed to eliminate the potential impact of tumor heterogeneity on prognosis. For patients who fail to respond to conversion therapy, second-line approaches need to be taken in accordance with the pattern of tumor progression. Concomitant local therapy or a next-line regimen might be necessary for non-responding or progressive tumors (*11*).

6. Subsequent surgery after conversion therapy

The necessity for subsequent surgery after conversion therapy is mainly determined by: a) A pathological

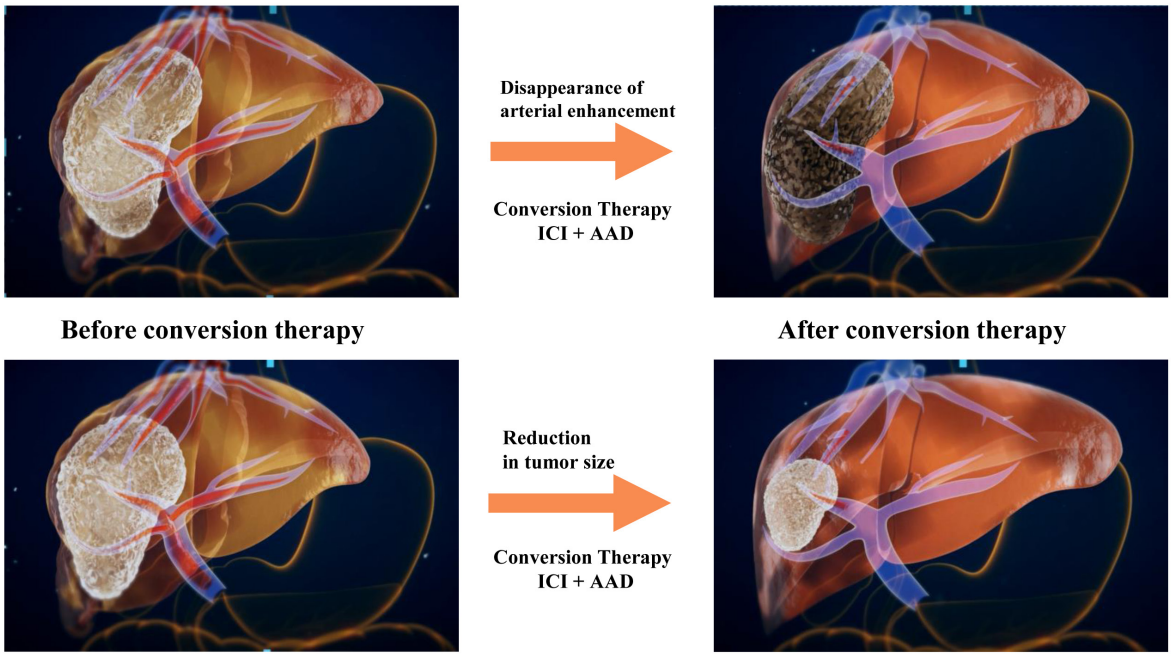

Figure 2. Diagram of Conversion Therapy with an Immune Checkpoint Inhibitor and an Antiangiogenic Drug for Advanced Hepatocellular Carcinoma. The top half of the diagram depicts the disappearance of or decrease in arterial enhancement of the tumor, with shrinkage of a portal or hepatic vein tumor thrombus; the bottom half of the diagram depicts a reduction in tumor size, with shrinkage of the portal or hepatic vein tumor thrombus.

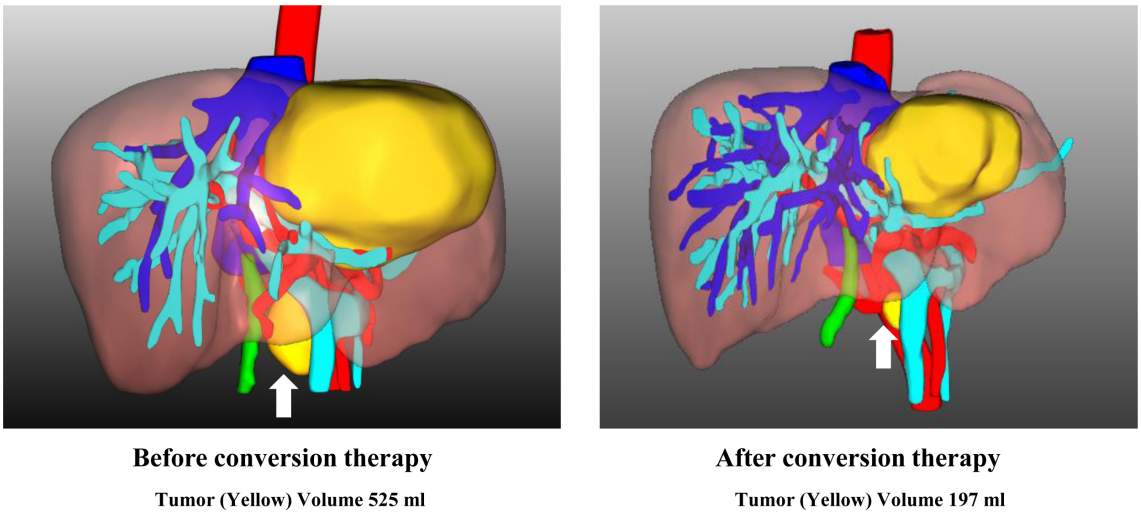

Figure 3. Change in the total tumor volume evident from a 3D reconstruction. A patient in the current conversion cohort. The diagram on the left indicates that the tumor (yellow) volume was 525 mL before combination therapy (a combination of an ICI and an AAD); the diagram on the right indicates that the tumor (yellow) volume was 197 mL after combination therapy (3 cycles of lenvatinib and sintilimab). The white arrow indicates a metastatic lymph node adjacent to the abdominal aorta (lymph node no.16, with increased standard uptake in PET-CT); after combination therapy (3 cycles of lenvatinib and sintilimab), the size and standard uptake according to PET-CT decreased significantly.

examination revealed the efficacy of conversion therapy and guiding postoperative adjuvant treatment, b) Timely surgical intervention to reduce drug resistance and adverse events, c) Complete tumor resection to facilitate radical treatment and ensure a long-term survival benefit. Whether subsequent surgery is indicated in patients in whom a radiological CR has been achieved after conversion therapy is still in question. Studies have indicated that most patients who experienced radiological relief progressed at 12 to 18 months after treatment, even with a continued ICI and AAD (*18,48*). For colorectal liver metastasis, a complete radiological response was achieved in around 60% of resected disappearing liver metastases. If, however, the disappearing lesions remained unresected, then over 50% of the lesions would reappear and recur (*76*). Taken together, most

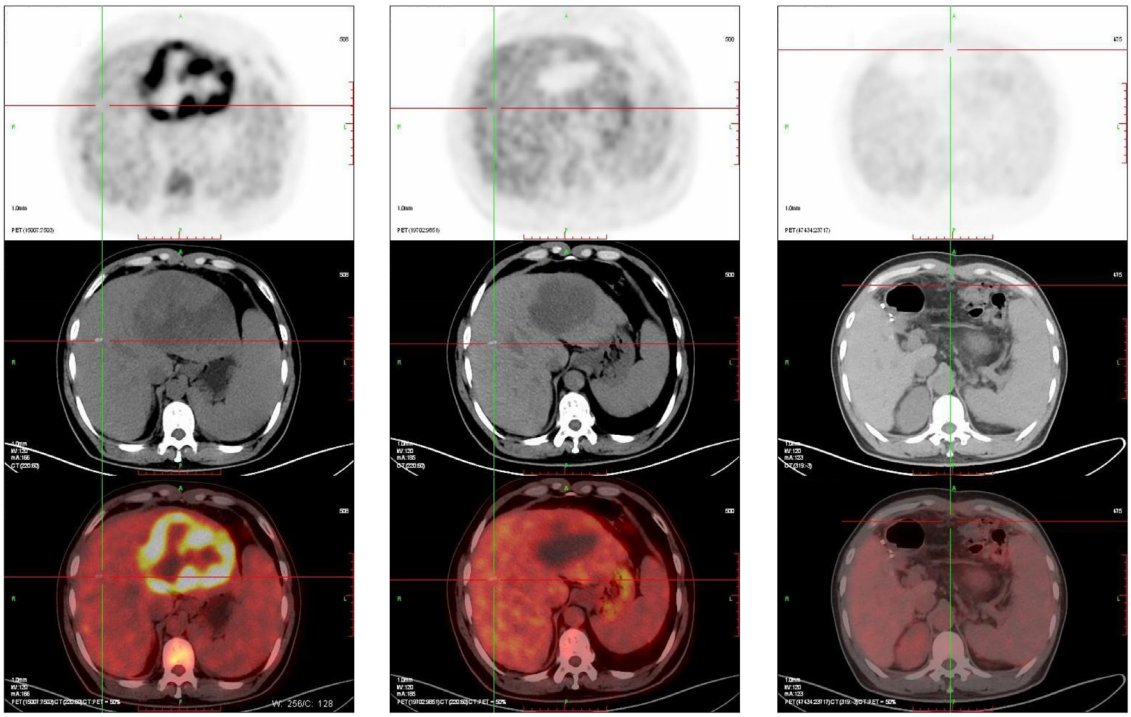

Figure 4. PET-CT assessment of conversion therapy followed by subsequent surgery. A patient in the current cohort who received conversion therapy followed by subsequent open left-hepatectomy. After 4 cycles of combination therapy with an ICI (sintilimab) and an AAD (lenvatinib) for 3 months, the standard uptake of the tumor decreased significantly. One year after subsequent left-hepatectomy, PET-CT revealed no signs of recurrence.

expert consensuses recommend subsequent surgery for patients with a radiological CR after conversion therapy (*16,18*). Nonetheless, more prospective studies need to be conducted to provide more evidence.

Downstaging advanced HCC to CNLC-I stage or BCLC-A stage may be indicated for radical surgery. Technical resectability includes: a) Child-Pugh grade A or B liver function; b) Sufficient residual liver volume, non-cirrhotic patients ≥ 35% standard liver volume, cirrhosis patients ≥ 45% standard liver volume; c) Indocyanine green retention rate at 15 min of < 20%; d) Complete inflow and outflow vasculature; e) Complete biliary structure after surgery; f) ECOG-PS 0~1; g) An American Society of Anesthesiologists Score lower than grade III. Patients who meet the following conditions could also undergo resection or receive local treatment to eliminate tumor heterogeneity: a) Imaging assessment indicates that the tumor has been converted from technically unresectable to technically resectable; b) Extrahepatic metastasis can be resected synchronously; and c) No further tumor response is evident in two consecutive imaging assessments. The timing of surgery remains controversial. Based on the current authors' experience, regular assessment and close management of patients is crucial. In a case series, 41 patients with advanced HCC underwent surgery safely after 3-15 cycles (median five cycle) of conversion therapy; hence, the possibility or timing of subsequent surgery should be assessed after five cycles of an ICI with an AAD (*63*). For patients who are eligible for surgery after conversion, a TKI should be discontinued for seven days and bevacizumab for 28 days before surgery. An ICI can be discontinued at the same time as an AAD (*16*). To prevent tumor progression, the duration of discontinuation should not be too long.

The regimen for postoperative adjuvant therapy remains controversial and mainly requires guidance from a pathological examination of the tumor. Based on discussions among and opinions of domestic experts, preliminary recommendations on post-operative regimens have been formulated. Use of the original conversion therapy regimen for adjuvant therapy after surgery is reasonable, and a consensus recommended that postoperative adjuvant therapy last over six months (*11,18,19*). As a key component in antitumor immunity, memory T-cell recruitment plays a crucial role in long-term maintenance of the antitumor cytotoxic effects of therapy during postoperative immunosurveillance. Continuous postoperative use of an ICI may boost the maintenance of immunosurveillance and immune-clearance against minimal residual disease to reduce the risk of tumor recurrence (*14,77-81*). According to an expert consensus (*11,14,16,82*), if the resected tumor is confirmed to be pathological CR (pCR), preoperative administration of an ICI alone should be continued for six months after surgery. For a tumor confirmed to exhibit a pathological partial response (pPR), the original

conversion regimen should be continued for one year. For pathological progressive disease (pPD), postoperative adjuvant treatment needs to be adjusted depending to the results of a pathological examination and/or genetic testing. The current authors conducted a preliminary study by examining 41 patients with advanced HCC who received conversion therapy and who underwent subsequent surgery from 2018 to 2021 at this facility. These criteria were used to guide post-operative adjuvant therapy. This resulted in a post-operative one-year overall survival rate of 74.7% and a two-year overall survival rate of 60.8%, a one-year recurrence-free survival rate of 56.7% and a two-year recurrence-free survival rate of 48.6%, and a median post-operative recurrence-free survival of 15.9 months (*63*). However, these results are preliminary. Quality evidence and molecular and mechanistic research are still needed to corroborate the recommendations offered here.

Hepatectomy after conversion therapy for advanced HCC is safe and feasible, but more technically demanding (*16,19,63*). An analysis of patients who underwent sequential hepatectomy following conversion therapy indicated that a hepatectomy after conversion therapy resulted in a greater volume of intraoperative blood transfusion, a delayed postoperative recovery, and longer hospitalization than a routine hepatectomy, but the differences were not significant (*16,63,67,75*). A postoperative pathological examination is a crucial indicator of overall survival. Patients with a pathological CR or PR may exhibit significant survival benefits after surgery.

7. Conclusion

The rise of conversion therapy has opened up new avenues for the treatment of advanced HCC. In particular, a combination of an ICI and an AAD has displayed encouraging therapeutic action. Thanks to the combination of an ICI and an AAD or other applicable local treatments, the feasibility of conversion therapy is expected to greatly improve. This will provide more patients with advanced HCC the opportunity to undergo radical surgery and offer them a long-term survival benefit. Moreover, subsequent surgery after conversion therapy with an ICI plus an AAD is a feasible, safe, and promising treatment strategy to prolong long-term outcomes in the population with advanced HCC.

The preliminary results cited herein are encouraging, but certain controversies remain unresolved due to the lack of quality evidence. Hence, more prospective and large-scale studies of conversion therapy and subsequent surgery still need to be conducted.

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