

Consensus of Chinese Experts on Neoadjuvant and Conversion Therapies for Hepatocellular Carcinoma: 2023 Update

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Keywords

Hepatocellular carcinoma · Consensus · Conversion therapy · Neoadjuvant therapy

Abstract

Hepatocellular carcinoma (HCC) is a common malignancy in China, with high recurrence rate and low resection rate among patients first diagnosed. Preoperative treatments

including neoadjuvant and conversion therapy have the potential to overcome these challenges. In December 2021, *Chinese expert consensus on neoadjuvant and conversion therapies for hepatocellular carcinoma* was published. With the emergence of new evidence regarding the neoadjuvant and conversion therapies for HCC, the cooperative group brought

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together multidisciplinary researchers and scholars with experience in related fields to update the new edition (2023 Edition) for reference in China, including principle of the treatment strategies, the potential populations selection, treatment methods, multidisciplinary team, and future research for preoperative treatments. The new consensus aims to provide guidance for clinical application. Through the use of neoadjuvant therapy and conversion therapy, we can enhance the resection rate and reduce the recurrence of intermediate-to-advanced HCC patients, thereby improving survival outcomes.

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Overview

Hepatocellular carcinoma (HCC) has a high rate of recurrence, but a low resection rate. The median survival of early stage HCC is around 5 years after radical treatment, while 5-year recurrence rate is as high as 70% [1]. About 64% of patients with HCC first diagnosed with giant tumor, multiple tumor, and tumor thrombus in China are unsuitable or infeasible for surgical resection [2–4]. Neoadjuvant therapy and conversion therapy provide opportunity for reducing the risk of recurrence, converting an unresectable tumor into a resectable tumor and improving the survival of HCC [5, 6].

To provide guidance and suggestions for preoperative treatment of HCC, Chinese experts released *Chinese Expert Consensus on Neoadjuvant and Conversion Therapies for Hepatocellular Carcinoma* in 2021. Researchers around the world have come up with substantial additional clinical data to support neoadjuvant and conversion therapy. In response to these developments, the cooperative group revised the 2021 edition to formulate the 2023 update edition in May 2023. The new consensus purpose is to analyze the new evidence in recent years and the characteristics of diagnosis and therapy of HCC in China, provide guidance for preoperative treatment, and further make more standardized in the practical application. In addition, this consensus adopts the China Liver Cancer (CNLC) staging system (shown in Fig. 1) [7, 8], which is currently the most widely utilized in China due to its alignment with local systems and practices [9].

According to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system [10] and guidelines of Chinese society of clinical oncology (CSCO) for HCC [11], the level of evidence-based medicine in the consensus is classified into level 1, 2, 3 (Table 1). Underlying the GRADE system, economy, medical insurance and accessibility, the recommendation strength of this consensus is categorized into four levels: I–III and not recommended (Table 2).

Concepts and Principle of Neoadjuvant and Conversion Therapies

Preoperative treatments for HCC include neoadjuvant therapy and conversion therapy according to treatment targets (shown in Fig. 2). Neoadjuvant therapy involves application of intervention strategies comprising systematic and locoregional treatments before surgery for HCC patients with high risk of recurrence, who are technically resectable or oncologically suitable for surgery, with the aim of achieving partial or complete pathological remission, eliminating microlesions, increasing surgical margin, reducing recurrence risk, and selecting responders [12]. Conversion therapy involves the application of locoregional therapy, systemic therapy, either individually or in conjunction with locoregional therapy, in patients deemed technically unresectable or oncologically unsuitable for surgery, with the target of eliminating unresectable factors of HCC and meeting the criteria of surgical resection. Patients who are oncologically unsuitable for surgery are technically resectable, but surgical resection does not provide any survival benefit. This includes patients with portal vein tumor thrombus (PVTT) grade 3–4 (Vp3-4), extrahepatic metastasis or extrahepatic lymph node metastasis, as well as other factors that may result in unsatisfactory long-term survival outcomes following direct surgery (shown in Fig. 3a). These two treatment strategies are different in populations, treatment aim and treatment regimen (Table 3). It has been reported that the resectability of HCC can be categorized into three groups: resectable, borderline resectable, and unresectable. Among these, borderline resectable HCC may refer to patients who are initially resectable but have high-risk factors for postoperative recurrence in this consensus [13].

Recommendations

The recommended criteria for technically resectable and oncologically suitable for surgery are as follows: achieving R0 resection, ensuring a sufficient volume of the FLR (FLR/standard liver volume [SLV] >30% for patients with normal liver; FLR/SLV >40% for individuals with chronic liver diseases or liver damages), having Child-Pugh class A/B, absence of PVTT or Vp1-2, and no extrahepatic metastasis (Recommendation I) (shown in Fig. 3b).

Neoadjuvant Treatment Strategies

Potential Populations for Neoadjuvant Therapy

Neoadjuvant therapy is generally not suggested in patients staged at CNLC Ia or Ib and some IIa. However, for patients with initial resectability and high-risk of

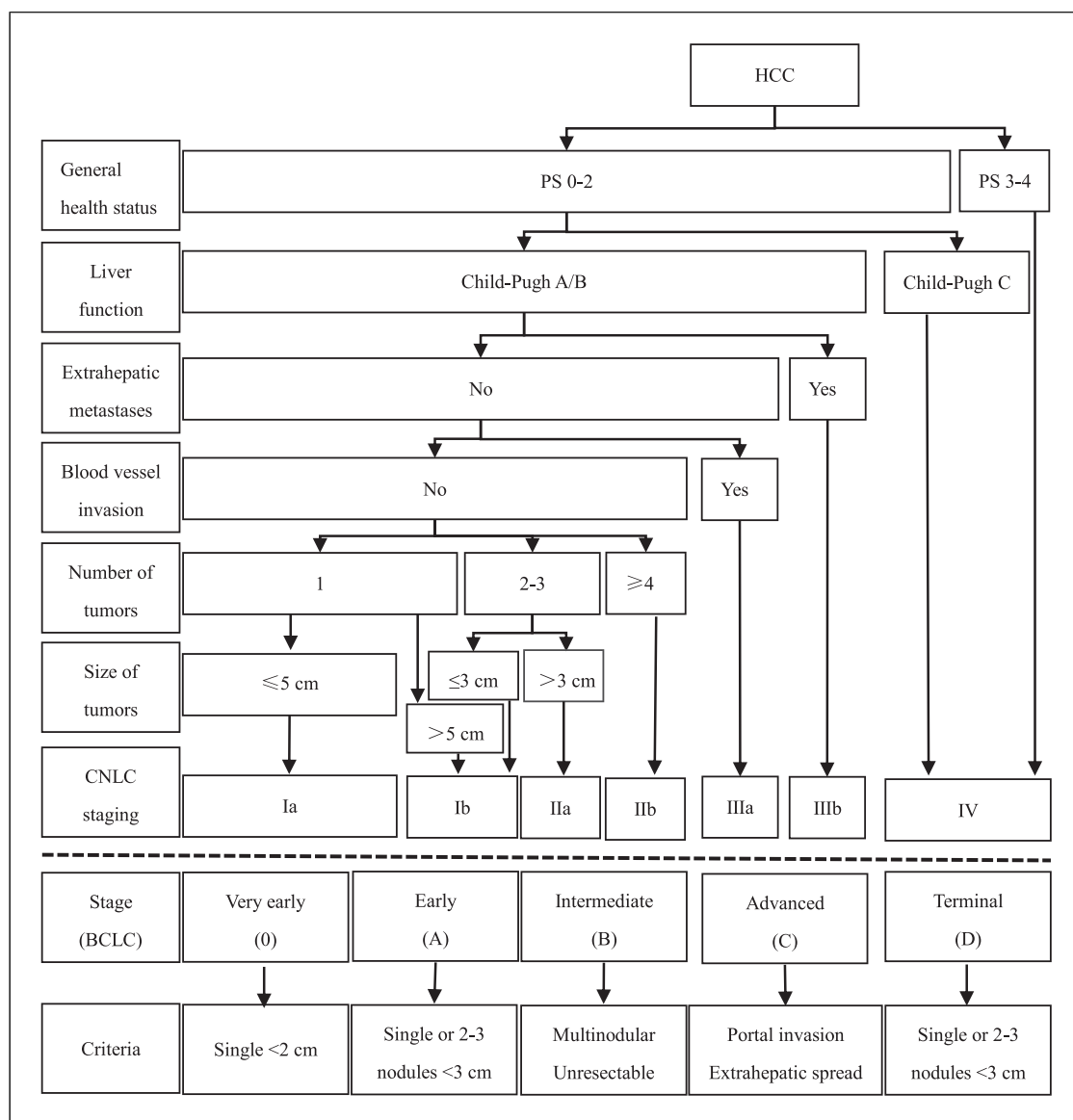


Fig. 1. Comparison between the BCLC staging system and CNLC staging system. CNLC, China Liver Cancer Staging; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PS, performance status.

postoperative recurrence factors, it is recommended to undergo surgery after neoadjuvant therapy under the guidance of a multidisciplinary treatment (MDT) team, aiming to reduce the risk of postoperative recurrence. This intervention is considered to be implemented in clinical trials following the approval of the study protocol by Ethics Committees. Neoadjuvant therapy has the advantage of reducing postoperative recurrence rate in patients with CNLC stage Ia-IIa who are at a high recurrence risk and certain patients at IIb and IIIa stage; patients diagnosed with CNLC IIb stage exhibit tumors located in the same segment or in the same half of the

liver, or the lesions outside the resected area that can be treated by intraoperative radiofrequency ablation (RFA); CNLC stage-IIIa patients include those with tumor confined to the same segment or ipsilateral hemiliver and Vp1-2, or resectable bile duct tumor thrombus, or peripheral hepatic vein tumor thrombus (Vv1) with potential R0 resection.

The documented risk factors for recurrence include: positive microvascular invasion (MVI), ambiguous tumor boundaries or tumor proximity to blood vessels, and suspected residual margin or margin less than 1 cm in CNLC stage Ia-IIa patients; presence of three or more tumors, the

Table 1. Level of evidence in evidence-based medicine

Level of evidence	Description
1	Rigorous meta-analysis, large randomized controlled clinical studies
2	Meta-analyses of general quality, small randomized controlled studies, large and well-designed retrospective studies, case-control studies
3	Noncontrolled single-arm clinical studies, case reports, expert opinions

Table 2. Recommendation strength

Recommendation strength	Description of definition
I	Level 1 evidence In general, level 1 evidence is typically utilized to support grade I recommendation. The grade I recommendation has the following characteristics: universal diagnosis and treatment measures with good accessibility (including clear indications), relatively stable value of tumor treatment, and basically covered by national medical insurance; the grade I recommendation, which will be not changed by commercial insurance, is based primarily on the definite benefit to the patients
II	Level 2 evidence In general, level 2 evidence is typically utilized to support grade II recommendation. The characteristics of a grade II recommendation are as follows: the drugs or treatments that may be inaccessible or not cost-efficient for the public, despite being supported by high-quality evidence from international or national randomized controlled multicenter studies; interventions with significant benefits but high costs can also warrant as grade I recommendation
III	Level 3 evidence The consensus among the experts on diagnosis and treatment methods, which is under investigation and lacking robust evidence-based medical evidence currently, can be considered as grade 3 recommendations for healthcare professionals
Not recommended	It should be written “experts do not recommend” or “oppose” when necessary for drugs or medical technologies that have demonstrated no benefit to patients by sufficient evidence, or even cause harm to patients. It can be any level of evidence

diameter of tumor exceeding 5 cm, macroscopic tumor thrombus, MVI, lymph node metastasis, adjacent organs involvement, preoperative alpha-fetoprotein (AFP) level more than 400 µg/L, and serum HBV-DNA level exceeding 10⁶ copies/mL, etc., in patients with CNLC stage IIb-IIIa [3, 14–17]. The prognosis for Vp3-4 patients is unfavorable, despite some studies suggesting potential benefits associated with surgical resection [18–22]. A report indicates that three-dimensional conformal radiotherapy for type II PVTT (Vp3) yields comparable overall survival (OS) as hepatic resection [23]. Furthermore, there is evidence against liver resection in Vp4 patients [24]. Therefore, surgical resection for patients with Vp3-4 is not recommended in this consensus. In addition, the background of liver disease (such as viral hepatitis and cirrhosis) is also a high-risk factor for HCC recurrence after surgery [3]. The distinct clinicopathologic characteristics of patients with

diverse background liver disease contribute to heterogeneous survival outcomes [15, 25–30]. The microenvironment of HBV-related HCC exhibits more immunosuppressive and exhausted compared to that of nonviral-related HCC microenvironment [31]. The evidence of neoadjuvant therapy is primarily based on HBV-HCC patients. Based on the above information, the decision of whether the patient should undergo surgery directly should be made by MDT, taking into consideration background liver disease.

To achieve the target in a limited time and reduce the “failure rate,” it is crucial to manage the cycle of neoadjuvant therapy, which is generally recommended to last 1.5–3 months (no more than 4 months). Once the pre-planned treatment is completed (regardless of whether the lesions shrink or not), the surgery should be carried out immediately [32, 33]. Importantly, it opposes the excessive pursuit of high treatment intensity to reduce the

“failure rate” and emphasizes that the treatment choices should adhere to the principle of achieving a high disease control rate (DCR), a low progressive disease (PD) rate, and minimizing the risk of missing surgical opportunities.

Recommendations

For patients with initially resectable HCC and high recurrence risk, we recommend neoadjuvant therapy in the setting of the clinical trial. For patients without high recurrence risk, neoadjuvant therapy is not considered (Recommendation III).

Neoadjuvant Therapy Methods
Interventional Therapy

Transarterial chemoembolization: Early randomized controlled trials verified that preoperative transarterial chemoembolization (TACE) did not improve disease-free survival (DFS) or OS of patients with resectable HCC [34, 35]. However, recent meta-analyses revealed that preoperative TACE significantly improved the recurrence-free survival and OS of patients with Barcelona Clinic Liver Cancer (BCLC) stage B [36, 37]. Preoperative TACE combined with sintilimab resulted in an objective response rate (ORR) of 62% in HCC patients with BCLC stage A/B beyond the Milan criteria. Of 51 patients who underwent surgery, 12-month progression-free survival (PFS) rate was 76%, with pathological complete response (pCR) of 14% [38].

Hepatic arterial infusion chemotherapy: In a phase 3 study, FOLFOX – based Hepatic arterial infusion chemotherapy (HAIC) as neoadjuvant treatment for BCLC stage A/B HCC patients beyond the Milan criteria, showed that the 1-, 2-, and 3-year OS rates in HAIC group ($n = 195$) were 97.7%, 86.3%, and 77.1%; 90%, 80.9%, and 70.6% in direct surgery group ($n = 197$). Compared with direct surgery, FOLFOX-HAIC improved median PFS and OS significantly (median PFS: 17.4 months vs. 9.8 months, $p = 0.032$; median OS not reached, $p < 0.001$) [39].

Recommendations

The use of neoadjuvant TACE in resectable HCC remains controversial. TACE alone (Recommendation II) and combined with immunotherapy (Recommendation III) are considered as neoadjuvant treatment for CNLC stage-IIb HCC patients. In addition, neoadjuvant HAIC is applicable for patients with CNLC Ia-IIb (BCLC A/B) beyond the Milan criteria (Recommendation I).

Systemic Treatment

Since the rapid development of immunotherapy and targeted therapy, neoadjuvant systemic therapy for HCC has ushered in a new hope. Numerous explorative studies on targeted therapy and immunotherapy for neoadjuvant therapy have been performed (Table 4) [40–45]. However, the downside is that randomized phase 3 clinical trials need to be further supplemented. In addition, the first-line treatment regimens for advanced patients could be referred. In the future, phase III trials of neoadjuvant systemic therapy are warranted to provide high-quality evidence.

Recommendations

At present, there exists a deficiency of high-level clinical evidence supporting neoadjuvant systematic therapy. Treatment options can be selected based on high-level evidence from the first-line treatment regimens in advanced HCC (Recommendation III). The regimens with low PD rate also are recommended according to the explorative clinical trials results of neoadjuvant therapy (Recommendation III).

Radiotherapy

Thirty-eight patients with central HCC, adjacent to large vessels and expected narrow surgical margins (≤ 1 cm) were treated with preoperative conventional fractionated radiotherapy. The median dose of radiotherapy was 50 Gy. After 1 month of radiotherapy, the ORR was 42.1%, the DCR was 100%. The 3- and 5-year OS rates were 75.4% and 69.1%, and DFS rates were 54.1% and 41.0%, respectively [46], which were better than those of the historical studies.

In the Surveillance, Epidemiology, and End Results (SEER) database, 151 and 93 patients with resectable HCC received postoperative and preoperative radiotherapy from 2004 to 2014, respectively. Compared with postoperative radiotherapy, preoperative radiotherapy significantly reduced the adjusted risk of all-cause mortality and cancer-related mortality risk by 67% (HR: 0.33; 95% CI: 0.19–0.53; <0.001) and 68% (HR: 0.32; 95% CI: 0.19–0.53; $p < 0.001$), respectively [47]. A meta-analysis of radiotherapy, surgery, radiotherapy plus surgery for HCC patients with PVTT and no main portal vein involvement demonstrated that radiotherapy has the similar effects with surgery in OS, while the 1-year and 2-year OS rate with radiotherapy combined with surgery were 77.1% and 45.4%, respectively, which were higher compared with the other two groups [48].

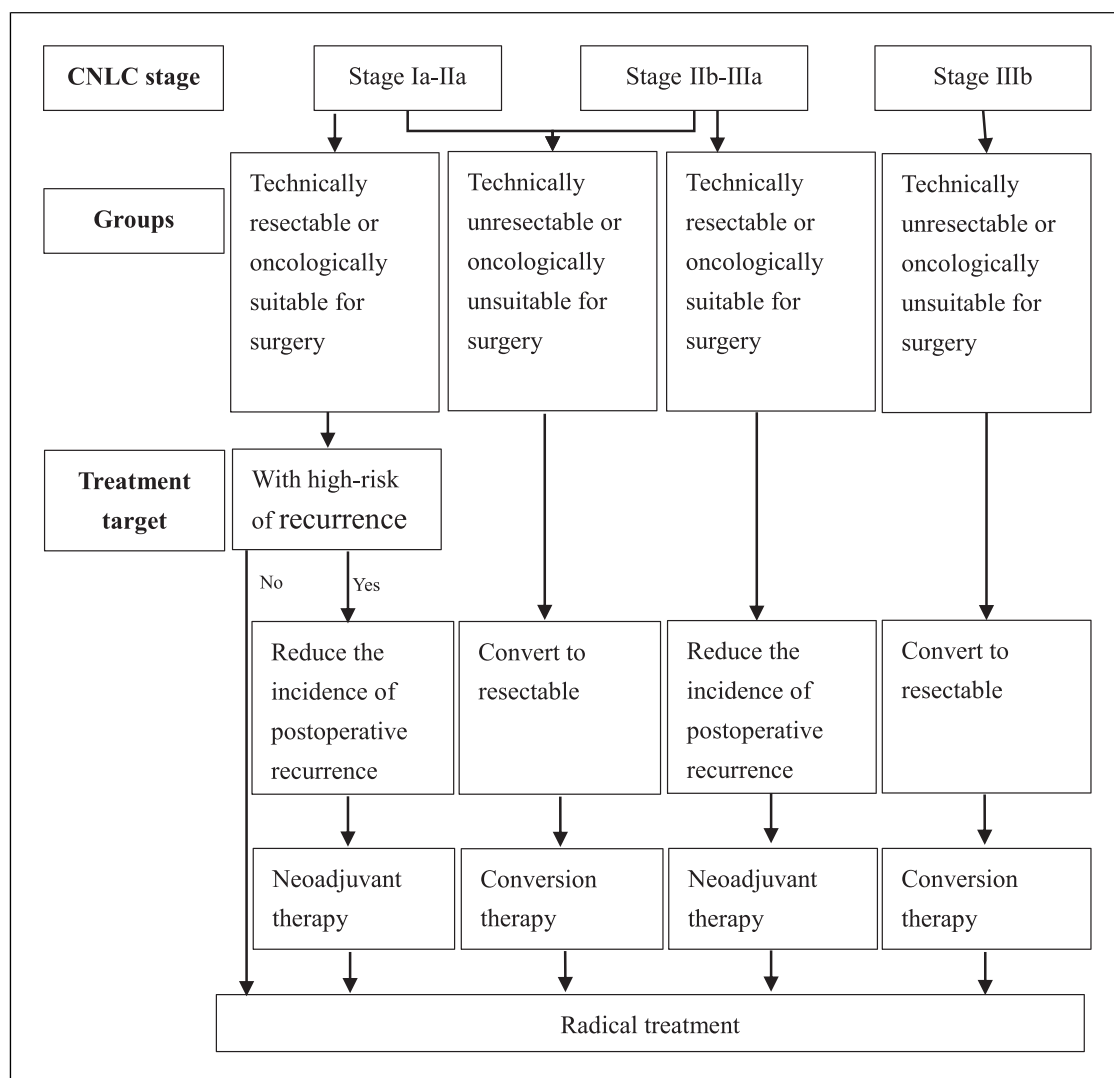
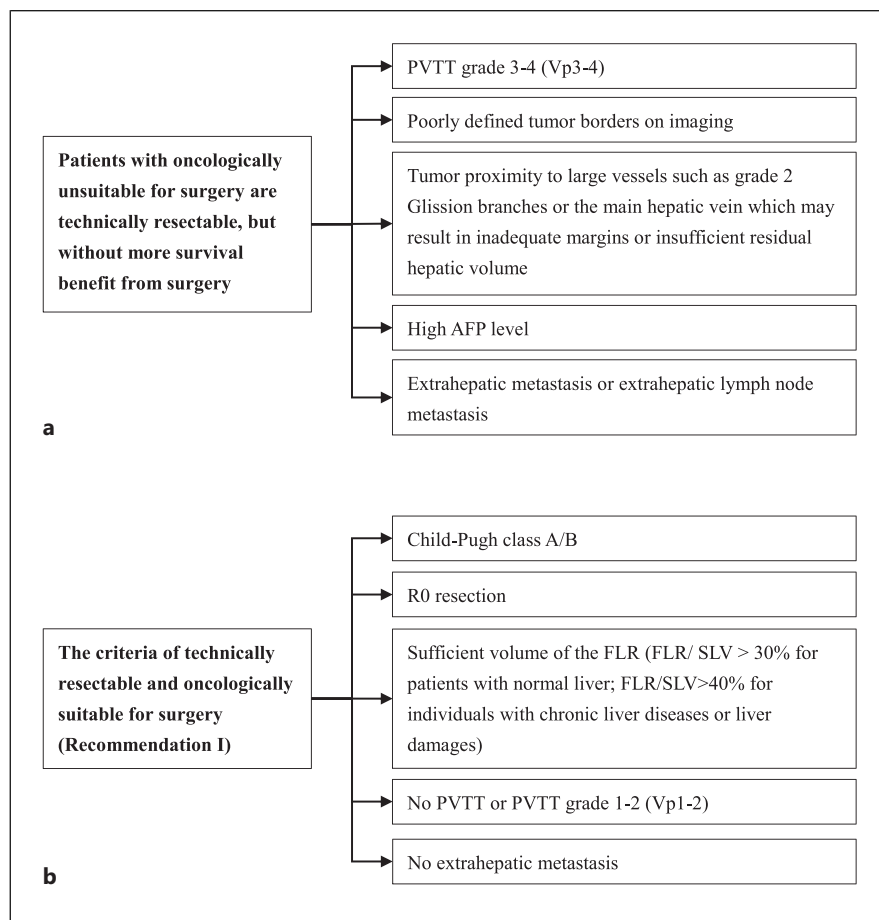


Fig. 2. Pathway of neoadjuvant and conversion therapies for HCC. CNLC, China Liver Cancer Staging.

Recommendations

Neoadjuvant radiotherapy is recommended for high-risk recurrence resectable patients with close proximity of tumor to great vessels and expected narrow surgical margins (Recommendation II), and CNLC stage-IIIa patients with Vp1-2 or Vv1 tumor thrombus (Recommendation II). The aim of neoadjuvant radiotherapy includes shrinking the tumors, decreasing surgical difficulties, ensuring sufficient margin, and reducing the incidence of surgical dissemination in high-risk patients with high AFP, high MVI risk, and unclear margins. To reduce the impact of neoadjuvant radiotherapy on surgery, we recommend concurrent boost radiotherapy techniques with gross tumor volume (GTV) 50–60 Gy/20–25f, planning target volume (PTV) 40–50 Gy/20–25f. The preferred radiotherapy dose should be the upper of the tolerance range of adjacent healthy tissues, with no increase of surgical complications significantly (Recommendation II). At present, evidence for high-dose and hypofractionated radiotherapy is limited. It is recommended that patients undergo surgery 6–12 weeks after neoadjuvant radiotherapy.

Fig. 3. Criteria for technically resectable of HCC. **a** Patients with oncologically unsuitable for surgery. **b** Patients with oncologically suitable for surgery. PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; FLR, future liver remnant; SLV, standard liver volume.



Conversion Therapy Strategies

Conversion therapy aims to eliminate unresectable factors of HCC, completely remove the tumor safely, and improve survival benefits for patients. Therefore, compared to neoadjuvant therapy, the duration of conversion therapy is relatively prolonged, and the treatment period is not strictly constrained. The treatment regimen should prioritize high-efficiency, high-intensity, and multimode therapy based on MDT, while also considering safety and quality of life. Surgical resection should be promptly performed if the patients meet the criteria for R0 resection. If the patients could not tolerate the therapy or cannot be converted to radical resection, the treatment strategy should be adjusted based on comprehensive consideration.

Potential Populations with Insufficient FLR Volume

Conversion therapy is applicable for some patients with insufficient FLR volume. The evaluation criteria of the functional hepatic reserve for safe resection are: normal liver function (Child-Pugh class A, indocyanine

green [ICG] -R15 < 10%) and no liver cirrhosis, the FLR volume/SLV is >20%–30%; patients with chronic liver diseases or parenchymal liver damage (such as liver cirrhosis, severe fatty liver, and chemotherapy-induced liver injury), the FLR/SLV is >40%; for patients with liver dysfunction, a greater FLR volume should be preserved (e.g., for patients with ICG-R15 = 10%–20%, and chronic liver diseases or liver cirrhosis, the FLR/SLV is >50%) [2, 49]. Individuals failing to fulfill the aforementioned criteria are defined as insufficient FLR volume.

Considering the contraindications or complications of insufficient FLR volume treatment, we suggest that the treatment needs to be strictly restricted to the specific patients: less than 65 years of age, normal liver function (Child-Pugh class A, ICG-R15 less than 10%), insufficient FLR volume (e.g., patients with normal liver with FLR/SLV <30%; individuals with chronic liver diseases or liver damages with FLR/SLV <40%). The general condition is good, and the operation is well tolerated, with no evidence of severe liver cirrhosis, fatty liver, and portal hypertension [2].

Table 3. Concepts and principle of neoadjuvant and conversion therapies

	Neoadjuvant therapy	Conversion therapy
Aims	Achieving partial or complete pathological remission, eliminating microlesions, increasing the surgical margin, reducing recurrence risk and selecting responder	Eliminating unresectable factors of HCC, completely removing the tumor safely, improving survival
Potential populations	Patients with initially resectable HCC and a high risk of recurrence	Patients who are technically unresectable or oncologically unsuitable for surgery
Application principles	Implementation in clinical trials	MDT guidance
Treatment options	Minimizing “failure rates” without excessively pursuing high treatment intensity: achieving a high DCR and a low PD rate, as well as avoiding any missed surgical opportunities	High-efficiency, high-intensity, multimode treatment, while considering the safety and quality of life
Duration of treatment	Limited treatment cycles, generally lasting 1.5–3 months (not exceeding 4 months)	No strict constrains
Timing of surgery	The surgery should be performed immediately once the preplanned treatment is completed, regardless of whether the lesions shrink or not	Patients who meet the criteria for R0 resection should undergo surgery promptly

HCC, hepatocellular carcinoma; DCR, disease control rate; PD, progressive disease; MDT, multidisciplinary team.

For patients with insufficient FLR volume, the conversion therapy aims to rapidly increase liver volume and transform tumors that are not suitable for resections into resectable state. The treatment options encompass a two-stage hepatectomy procedure with portal vein embolization (PVE) or portal vein ligation, a two-stage hepatectomy procedure with PVE plus TACE or hepatic vein embolization, and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), depending on different types of tumor, local progression, liver parenchymal pathology report, liver functional reserve status, and patient tolerance assessment for surgery [46].

Recommendations

For patients in CNLC stage Ia-IIIb experiencing insufficient FLR volume following radical surgery, ALPPS and PVE may be the choices for specific cases to enhance FLR volume (Recommendation III).

Potential Populations with Initially Unachieved R0 Resection or Oncologically Unsuitable for Surgery
Conversion therapy also is recommended for patients whose R0 resection cannot be achieved initially or whose tumors are unsuitable for surgery, with the expectation that they will undergo surgical resection after conversion therapy and attain long-term survival. The potential populations include CNLC stage Ia-IIa patients, who could not achieve R0

resection, or guarantee the negative resection margin (≥ 1 cm), CNLC stage-IIb-Ia patients with unachievable R0 resection or oncologically unsuitable for surgery, such as Vp3-4, or main hepatic vein and inferior vena cava tumor thrombus, CNLC stage-IIIb patients with pulmonary oligometastasis (the tumor number ≤ 5 and single lesion maximum diameter < 3 cm) or extrahepatic lymph node metastasis.
After conversion therapy, resectable lesions meet the following criteria: the tumor shrinking or downstaging, great vessels tumor thrombus necrosis, or achieving complete response, partial response, or stable disease lasting for 3–4 months (modified Response Evaluation Criteria in Solid Tumors [mRECIST] criteria) [2]. For details, refer to the following:
Intrahepatic lesions: For unresectable HCC patients whose tumor size exceeding defined limits, a considerable number of lesions (>4), tumors adjacent or invasion to the main intrahepatic vessels, high surgery risk and technically difficulties, the success for conversion therapy includes response according to mRECIST, reduction in the extent of the tumor invasion (including regression/necrosis or decline in primary lesions number), and ensuring negative tumor margin, decreasing surgical difficulty. The patients with stable disease and shrinking lesions for 2–3 months are recommended to undergo surgical resection.
Large vessel tumor thrombus: For patients with large vessel tumor thrombus, such as portal vein or first branch tumor thrombus, inferior vena cava tumor thrombus, the success for conversion therapy includes tumor thrombus

Table 4. Clinical studies of neoadjuvant therapy for HCC

Treatment	Design	n	Cycles	Results	Surgery rate	PD rate
Apatinib + camrelizuma [40]	Phase II	18	6 weeks	MPR: 17.6% pCR: 5.9%	94.4%	5.6%
Cabozantinib + nivolumab [41]	Phase Ib	15	8 weeks	MPR or pCR: 42%	86%	—
Nivolumab versus ipilimumab + nivolumab [42]	Phase II	13: 14	6 weeks	MPR: 33% versus 27% PFS: 9.4 months versus 19.53 months	69.2% versus 78.6%	7.7% versus 0
Lenvatinib +PD-1+TACE [43]	Retrospective	24	3 cycles	ORR (mRECIST): 83.3% ^a , 79.2% ^b DCR: 95.8% MPR: 16.7% pCR: 25%	95.8%	4.2%
SBRT+tislelizumab (neoadjuvant) +tislelizumab (adjuvant) [44]	Phase Ib	20	2 cycles (neoadjuvant) + up to 1 year (adjuvant)	ORR: 42.1% (RECIST 1.1), 63.2% (mRECIST) DCR: 100% pCR: 10.5% MPR: 31.6%	100%	0
TACE+tislelizumab (neoadjuvant) +tislelizumab (adjuvant) [45]	Retrospective	41	1 cycles (neoadjuvant) + at least 6 months or until to disease progression or intolerable toxicity(adjuvant)	ORR: 56.1% (RECIST 1.1), 87.8% (mRECIST) DCR: 100% pCR: 31.7% MPR: 43.9%	100%	0

ORR, objective response rate; MPR, major pathologic response; pCR, pathological complete response; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization. ^aPer investigator assessment; ^bper blinded independent central review assessment.

necrosis or regression, and tumor downstaging (such as CNLC stage-IIIa →IIb).

Extrahepatic metastasis: For patients with extrahepatic (mainly lung and lymph node) metastasis (CNLC stage-IIIb), the success for conversion therapy is disappearance or complete inactivity of the metastases, and downstage to undergo surgical resection of the intrahepatic tumor or combined with extrahepatic metastases.

Recommendations

For patients with initially unachieved R0 resection or oncologically unsuitable for surgery, we recommend conversion therapy in order to undergo surgery. The successful conversion should be judged on the basis of intrahepatic disease, large vessel tumor thrombus, and extrahepatic metastasis (Recommendation I).

Methods of Conversion Therapy

Interventional Therapy

Transarterial chemoembolization: TACE can be classified into conventional TACE (cTACE) and drug-eluting beads-TACE (DEB-TACE). A retrospective study showed receiving salvage surgery following cTACE had longer OS than the only cTACE (median OS: 49 months vs. 31 months, respectively, $p = 0.027$) [50]. Another retrospective study for RFA following cTACE found that OS and PFS were the same as the patients whose condition met the Milan criteria initial and received RFA as first-line treatment ($p = 0.74$ and 0.39 , respectively) [51].

Compared with cTACE, DEB-TACE can maintain local concentration for a longer time, reduce the incidence of adverse reactions, and extend survival of the patients [52]. A retrospective study demonstrated

Table 5. Studies of conversion systemic therapy for HCC patients

Authors	Treatment	n	Results
Zhu et al. [58]	TKI: lenvatinib/apatinib PD-1 inhibitors: pembrolizumab/sintilizumab/camrelizumab/ nivolumab	63	Conversion rate: 19.0%
Zhang et al. [59]	TKI: lenvatinib PD-1 inhibitors: pembrolizumab/sintilizumab/toripalimab/ tislelizumab	56	Conversion rate: 55.4% ORR: 53.6% (mRECIST), 44.6% (RECIST 1.1)
Ichida et al. [60]	Lenvatinib	49	Conversion rate: 68% ORR: 12.5% (RECIST 1.1), 37.5% (mRECIST)
Wang et al. [61]	Lenvatinib + sintilimab	36	Resection rate: 67.3% ORR: 36.1% (RECIST 1.1), 66.7% (mRECIST)
Kudo et al. [62]	Atezolizumab + bevacizumab	110	Conversion rate: 35.5% ORR: 36.4%

ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; PD-1, programmed death-1.

significantly higher ORR ($p = 0.003$) and longer PFS ($p = 0.028$) and OS ($p = 0.037$) in the DEB-TACE group compared with cTACE group ($n = 39$) [53].

Hepatic arterial infusion chemotherapy: Compared with TACE, HAIC is free of embolic agents, and avoids adverse events such as post-embolization syndrome and ectopic embolization. A phase 3 randomized trial showed that FOLFOX-HAIC group had significantly longer median OS (23.1 months vs. 16.1 months, $p < 0.001$), higher ORR (46% vs. 18%, $p < 0.001$) and conversion resection rates (24% vs. 12%, $p = 0.002$), and lower rate of serious adverse events (19% vs. 30%, $p = 0.03$) [54]. In addition, HAIC combined with TACE could further improve the surgical conversion rate [55]. FOHAIC-1 trial demonstrated that FOLFOX-HAIC had significantly superior survival outcomes compared to sorafenib in advanced HCC, with a median OS of 13.9 months and 8.2 months ($p < 0.001$), respectively. Disease downstaging occurred in 16 (12.3%) patients receiving FOLFOX-HAIC, and among them, 93.8% underwent curative surgery or ablation [56].

Transarterial Radioembolization: Transarterial radioembolization (TARE) is also known as selective internal radiation therapy (SIRT). A randomized controlled trial reported that SIRT had a significantly higher ORR than TACE (30.8% vs. 13.3%, $p < 0.05$) [57].

Recommendations

For patients initially unable to take the R0 resection because of tumor burden, we recommend conversion therapy regimens including cTACE and DEB-TACE (Recommendation II), HAIC (Recommendation I), TARE, or SIRT (Recommendation II).

Systemic Therapy

The rapid development of systemic therapy, encompassing targeted therapy and immunotherapy, provides new options for conversion therapy. Several studies have provided evidence for systemic therapies in conversion therapy (Table 5) [58–62]. In consideration of the objective of conversion therapy mentioned above, the treatment with a relatively higher ORR may be a suitable option.

Interventional Therapy Combined with Systemic Therapy

Considering the synergistic effect of Sequential or combination systemic therapy with locoregional therapy [63]. Multiple studies have explored the potential of intervention therapy plus systemic therapy in conversion therapy (Table 6) [64–70]. A stepwise treatment strategy taking into account both the intensity and the safety of therapy may be considered according to current

Table 6. Studies of interventional therapy plus systemic therapy in the conversion therapy for HCC patients

Authors	Treatment	n	Results
Li et al. [64]	TACE + sorafenib	142	Resection rate: 14.8%
He et al. [65]	HAIC + sorafenib	125	Resection rate: 12.8% ORR: 75.2% (RECIST 1.1) 76% (mRECIST)
He et al. [66]	HAIC + sorafenib	35	Resection rate: 14.3% ORR: 40% (RECIST 1.1) 62.8% (mRECIST)
Zhang et al. [67]	HAIC+TKI+PD-1 inhibitor (TKI: sorafenib/apatinib/lenvatinib)	25	Resection rate: 56.0% pCR: 28.0% ORR: 96% (mRECIST)
He et al. [68]	Lenvatinib + toripalimab +HAIC	71	Resection rate: 12.7% ORR: 59.2% (RECIST 1.1) 67.6% (mRECIST)
Gan et al. [69]	Arterially directed therapy + lenvatinib + sintilimab	37	Conversion rate: 40.5% pCR: 8.1% ORR: 67.6% (RECIST 1.1) , 75.7%(mRECIST)
Wu et al. [70]	TACE+ lenvatinib + camrelizumab	55	Conversion rate: 54.5% pCR: 20.7% ORR: 76.4% (mRECIST)

ORR, objective response rate; pCR, pathological complete response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TACE, Transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PD-1, programmed death-1; TKI, tyrosine kinase inhibitor.

treatment standard. For therapeutic methods and surgery timing, the *Chinese Expert Consensus on Conversion Therapy in Hepatocellular Carcinoma (2021 edition)* may be as your reference.

Recommendations

Patients with potentially resectable HCC can benefit from the implementation of multimodal and high-intensity antitumor therapy strategies, with due consideration to the safety and quality of life. The interventional therapy + tyrosine kinase inhibitor + immunotherapy on the basis of MDT is recommended to facilitate the conversion (Recommendation III). Based on comprehensive evaluation of patients' general conditions, tyrosine kinase inhibitor monotherapy (lenvatinib) or combined with immunotherapy can also be considered (Recommendation III).

Radiotherapy

A randomized controlled study showed that the addition of neoadjuvant radiotherapy (18 Gy/3f) based on hepatectomy could greatly improve the OS and DFS, with the 12- and 24-mo OS rate were 75.2% versus 43.1%, 27.4% versus 9.4% ($p < 0.001$), and the

12- and 24-mo DFS rate of 33.0% versus 14.9%, 13.3% versus 3.3% ($p < 0.001$), respectively [71]. In a prospective phase II study on radiotherapy combined with sorafenib [72], the median radiotherapy dose was 54 Gy. The results were ORR of 53.4%, DCR of 76.6%, and median OS of 16.8 months, time to progression of 7.1 months. For patients with Vp4, the median OS and PFS were 14.0 months and 4.2 months, respectively. For the patients with Vp3, the 2-year OS rate of was 66.1%, with the median PFS of 16 months. A meta-analysis revealed that preoperative radiotherapy plus surgery significantly improved OS compared with surgery alone (RR = 2.02; 95% CI: 1.45–2.80; $p < 0.0001$) [73]. A retrospective study reported that the median OS (10.6 months and 4.2 months, $p < 0.001$) and surgical conversion rate (8.5% vs. 1.0%, $p < 0.001$) of the radiotherapy group were both significantly higher than these of the sorafenib group, while G3 toxicity was significantly less (9.2% vs. 16.1%, $p < 0.001$) [74]. A retrospective study for concurrent chemoradiotherapy followed by HAIC showed that 16.9% underwent curative resection, and compared to the concurrent chemoradiotherapy followed by HAIC alone group, the curative resection group showed a higher 5-year OS rate (49.6% vs. 9.8%, $p < 0.01$) [75].

Recommendations

Preoperative conversion radiotherapy is recommended for the following patients: CNLC stage Ia-IIb patients with insufficient liver function reserve (Recommendation III), CNLC stage-IIIa patients with Vp3-Vp4 or Vv2-Vv3 tumor thrombus (Recommendation II), and CNLC stage-IIIb patients with pulmonary oligometastasis or extrahepatic lymph node metastasis, who receive preoperative radiotherapy on primary or metastatic liver lesions (Recommendation III). We recommend preoperative conversion radiotherapy concurrent in combine with targeted therapy, immunotherapy, or target immunotherapy.

The dose of preoperative conversion radiotherapy is recommended as following: patients with sufficient FLR volume are considered to receive simultaneous boost radiotherapy with GTV 50–60 Gy/20–25f and PTV 40–50 Gy/20–25f, with the dose being the upper limit of tolerance range of the adjacent healthy tissues; For patients concurrently treated with targeted therapy, immunotherapy, or targeted immunotherapy, the dose of the peripheral gastrointestinal tract should be more strictly limited to avoid serious complications; preoperative conversion radiotherapy can also be used with hypofractionated or moderately fractionated radiotherapy, but there is no evidence to show that hypofractionated radiotherapy is more effective than conventional radiotherapy. We recommend simultaneous boost radiotherapy with GTV 40–50 Gy/10f, PTV 25–30 Gy/10f (Recommendation III).

Conversion Therapy in Liver Transplantation

Liver transplantation, which can remove tumors and liver lesions simultaneously, has become a viable curative intervention for HCC. Only 6% of patients met the criteria to transplant according to the Milan criteria [76, 77], which is the most widely applied for recipient selection. A series of evidence revealed the excellent OS and PFS of patients beyond the Milan criteria who underwent liver transplantation after successful downstaging to the liver transplantation criteria [78–80].

The 2018 American Association for the Study of Liver Diseases (AASLD) guidelines recommend that patients beyond the Milan criteria should undergo liver transplantation after achieving successful downstaging for at least 3–6 months [81]. In the United States, United Network for Organ Sharing (UNOS) used the University of California, San Francisco (UCSF) downstaging criteria [82]. Different

criteria for successful downstaging have been proposed in other studies, including meeting the Milan criteria with serum AFP no higher than 400 ng/mL [83], a 30%–50% reduction in lesion diameter after treatment [84], or no tumor progression during downstaging treatment in well or moderately differentiated HCC patients [85].

The Strategies of Conversion Therapy

The strategy of conversion therapy in liver transplantation should be individualized, which mainly depends on tumor size, number and site, vascular invasion, liver function reserve, patient's performance status, and the safety and efficacy of treatments. In a prospective study, 33.9% of 64 patients with HCC beyond the Milan criteria underwent successful downstaging and liver transplantation after TACE. The 5-year OS rate was not statistically different between the patients downstaging after TACE and patients within the Milan criteria who received TACE as bridging therapy (73.5% vs. 72.3%, $p = 0.31$) [86]. Patients with HCC beyond the Milan criteria were treated with TACE combined with microwave ablation (TACE-MWA) or TACE alone in another study. The downstaging rate of TACE-MWA group was significantly higher (77.1% vs. 53.8%, $p = 0.039$), and OS was prolonged significantly (1,488 days vs. 700 days, $p = 0.002$) compared with TACE group. No significant difference was observed in PFS between the two groups (380 days vs. 247 days, $p = 0.043$) [87].

The results of a study reported that TARE was superior to TACE in downstaging HCC from UNOS T3 to T2 stage. Partial response rates of TACE group and TARE group were 61% and 37%, respectively. Downstaging was observed in 31% and 58% of patients, respectively. Recurrence-free survival (17.7 vs. 7.1 months, $p = 0.0017$) and OS (41.6 vs. 19.2 months, $p = 0.008$) were significantly longer in TARE group than TACE group [88].

With the progression in systemic treatment of HCC, various new molecular targeted drugs and immune checkpoint inhibitors have been applied to the downstaging of HCC before liver transplantation [89, 90]. Given that immune checkpoint inhibitor may be associated with liver toxicity and fatal graft rejection, close monitoring of adverse reactions during systemic therapy is necessary, and the time interval between drug withdrawal and transplantation should be carefully evaluated according to the half-life of immunotherapy drugs.

Recommendations

The combination of systemic therapy and local therapy is a key strategy for conversion and downstaging of HCC, which increases the possibility of liver transplantation (Recommendation III). For multifocal HCC, the recommended downstaging regimens include TACE (Recommendation II), TACE-MWA (Recommendation II) and TARE (Recommendation II). For tumors with diameter ≤ 3.0 cm, RFA can achieve complete necrosis through thermal energy (Recommendation III). RFA is relatively contraindicated nearby large vessels, whereas MWA is a safer treatment option (Recommendation III).

MDT Is Necessary for Neoadjuvant and Conversion Therapy

Given the diverse advantages and disadvantages among the treatment options, the choice of therapeutic regimen, the most appropriate time to operate posttreatment, and adverse reactions management necessitate regular interdisciplinary communication. Therefore, it is necessary to implement MDT management during neoadjuvant and conversion therapy, which ensure that the treatment strategy can be timely adjusted according to the disease status, so as to provide maximal benefit to patients.

Future Research

At present, high persuasive clinical data of neoadjuvant therapy in HCC is lacking. Therefore, we should carry out more studies to verify a series of clinical problems such as the optimal indication, accurate preoperative diagnosis of high-risk factors, and the preferred treatment regimen. In addition, for both neoadjuvant therapy and conversion therapy, the accurate evaluation criteria for short-term efficacy (such as pCR and major pathological response), the evidence of long-term survival, and the value of short-term efficacy in predicting long-term prognosis [91] still need to be evaluated. Drug

resistance is also a significant impediment to the development of neoadjuvant and conversion therapy in HCC. Despite some studies delving into the mechanism of drug resistance [92–94], their current findings possess limited value, necessitating the development of further research.

Conclusions

Neoadjuvant and conversion therapy are important strategies to reduce the risk of postoperative recurrence and improve the surgical resection rate for patients with intermediate-to-advanced HCC. A national expert consensus on conversion therapy has been published, while the evidence for patient populations and treatment of neoadjuvant therapy needs more research. Based on the update of this consensus, Chinese experts will continue to provide scientific guidance on the concept and methods of preoperative treatment for HCC, which will promote the improvement of prognosis of HCC patients in China.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Jianqiang Cai, Shuqun Cheng, and Minshan Chen: conception, design, and final approval of manuscript. Xinyu Bi, Haitao Zhao, Hong Zhao, Guangming Li, Xiaodong Wang, Bo Chen, Wen Zhang, Xu Che, Zhen Huang, Yue Han, Liming Jiang, Yongkun Sun, Zhengqiang Yang, Jianguo Zhou, Yefan Zhang, and Zhenyu Zhu: supervision, data curation, and writing.

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