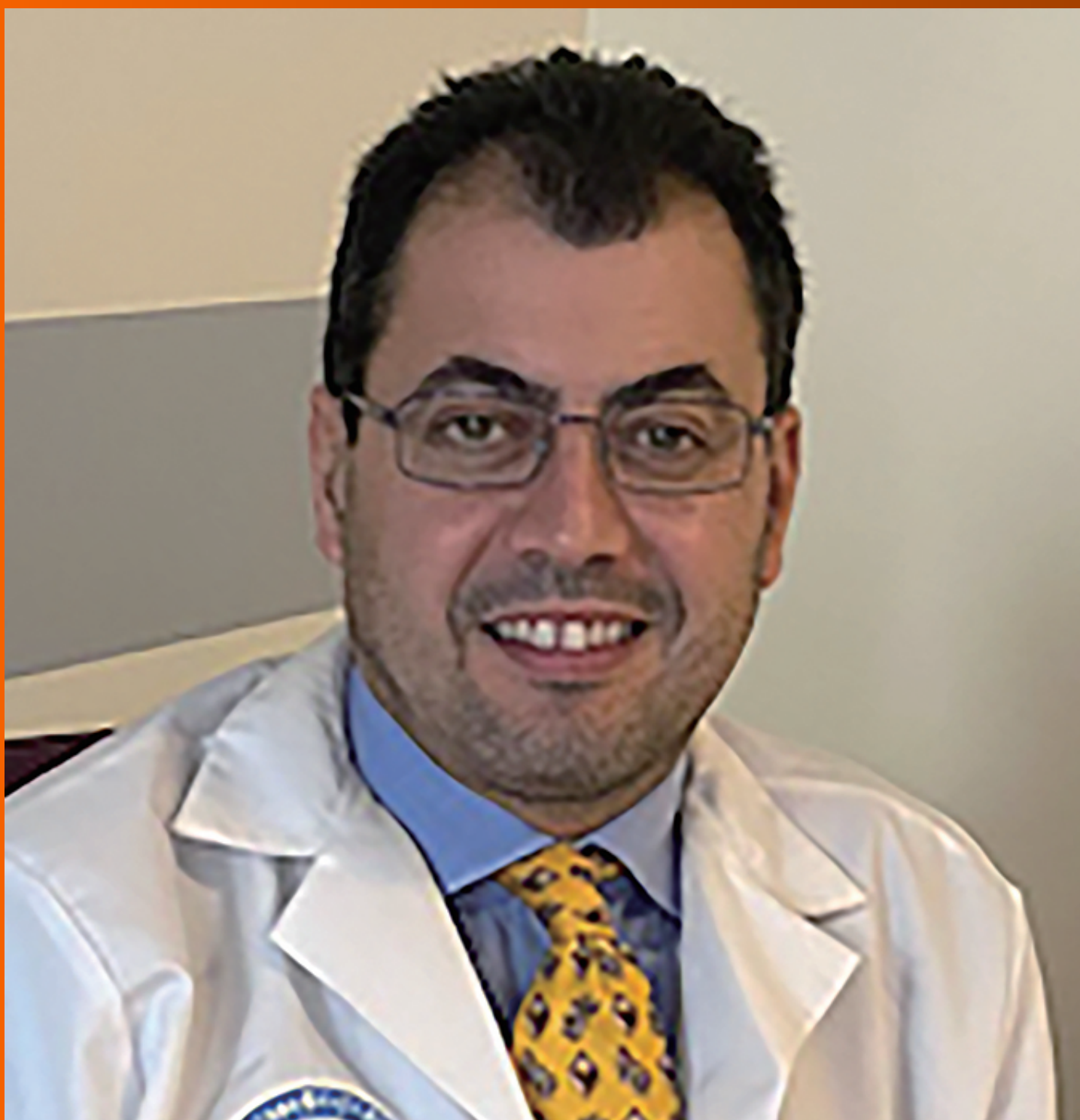


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Neoadjuvant treatment strategies for hepatocellular carcinoma

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Abstract

The incidence of hepatocellular carcinoma (HCC) remains high globally. Surgical treatment is the best treatment for improving the prognosis of patients with HCC. Neoadjuvant therapy plays a key role in preventing tumor progression and even downstaging HCC. The liver transplantation rate and resectability rate have increased for neoadjuvant therapy. Neoadjuvant therapy is effective in different stages of HCC. In this review, we summarized the definition, methods, effects, indications and contraindications of neoadjuvant therapy in HCC, which have significance for guiding treatment.

Key Words: Hepatocellular carcinoma; Neoadjuvant therapy; Prognosis; Indications; Contraindications

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Core Tip: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. A considerable number of patients cannot receive radical therapy due to advanced HCC at the first diagnosis, leading to a poor prognosis. Neoadjuvant treatment enables more patients with HCC inside or outside the Milan criteria to receive surgical treatment, such as partial liver resection and liver transplantation. In this study, we reviewed the current status of neoadjuvant therapy in HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1]. The incidence and mortality of HCC are still increasing in most parts of the world, including China [2]. Viral hepatitis B is the main risk factor for HCC in East Asia and Africa, while nonalcoholic fatty liver disease is becoming an important risk factor in developed countries [1,3,4]. For patients with HCC with surgical indications, surgery [liver resection (LR) and liver transplantation (LT)] is the best treatment for improving their prognosis, with a 5-year survival rate of 60%-80% [5]. However, many patients are beyond the indications for surgery due to advanced tumor stage or severe liver disease at the time of diagnosis, leading to a median overall survival between 3 and 26 mo [6,7].

Neoadjuvant therapy is a new concept of multidisciplinary treatment for malignancies to prevent tumor progression and even downstage solid tumors in recent years [8]. Neoadjuvant therapies for HCC include transcatheter embolization (TACE), radiotherapy, ablation therapy, chemotherapy, targeted therapy and immunotherapy [9]. LT is the optimal treatment for HCC and liver cirrhosis, but many patients with HCC outside the Milan criteria are not suitable candidates for LT [10]. With neoadjuvant therapy, the success rate in downstaging HCC within the Milan criteria can be more than 60% in selected patients [11]. Some clinical studies have confirmed that patients who underwent LT after successful downstaging treatment can achieve prognosis similar to that of patients who received LT without downstaging treatment [12-14]. In the same way, patients with initial unresectable HCC could also receive LR once the lesions were well controlled by neoadjuvant therapy [15]. However, the indications, side effects and effect on the long-term prognosis of neoadjuvant therapy in HCC are still controversial. In this article, we reviewed the clinical application of neoadjuvant therapy in HCC, including clinical indications, evaluation of efficacy, adverse events and effects on prognosis.

WHAT IS NEOADJUVANT THERAPY FOR HCC?

Over the past decade, the overall survival rate of patients who underwent LT has continued to rise. Due to the shortage of livers for transplantation (even patients with HCC within the Milan criteria need to wait for liver donors), the dropout rate during the waiting period remains high [16]. Increasing tumor burden during the waiting period is also detrimental to survival after transplantation. In addition, one of the major factors for the poor prognosis of patients with HCC is the low resectability rate, which is only approximately 20% [17]. How to slow the progression of tumors before surgical treatment and lower the tumor stage to surgical indications is the focus of oncologists and surgeons, and this is the significance of neoadjuvant therapy for HCC.

When defining neoadjuvant therapy, we have to distinguish between bridging, downstaging and conversion therapy and clarify the difference between neoadjuvant therapy and adjuvant therapy. Neoadjuvant therapy refers to local or systemic treatment applied before surgical treatment for malignant tumors, and there are four purposes of neoadjuvant therapy for HCC.

The first point is to prevent patients from dropping out due to tumor progression during the waiting period, ensuring that the patients meet the indications for LT. This is the so-called bridging therapy [18]. In an observational study, up to 8.2% of patients with T1 stage and 13.5% of patients with T2 stage who initially had operable HCC were not candidates for LT due to tumor progression while waiting for the 6th mo without intervention [19]. Alpha fetoprotein ≥ 500 ng/mL on the first diagnosis of T1 stage HCC and rapid tumor progression were risk factors for dropping out during the waiting period for LT [20], which suggests that the bridging effect of neoadjuvant therapy is critical. Bridging therapy can reduce the dropout rate to 0%-10% in candidates for LT with HCC meeting the Milan criteria [21]. One of the focuses of oncology surgery is whether patients with HCC within the Milan criteria should undergo direct radical resection if a long waiting period for a donor liver is required, but no clinical studies have yet confirmed this.

The second point is to shrink or reduce tumors outside the Milan criteria to meet the indications for LT [22]. This is the definition of downstage treatment. The expected 5-year survival rate of patients with HCC within the Milan criteria receiving LT was approximately 65%-80%, which was far higher than those outside the Milan criteria [23]. In all, 25%-70% of patients with HCC outside the Milan criteria achieve tumor downstaging after receiving neoadjuvant therapy; they received LT and achieved

comparable prognosis to those who underwent initial LT[24] (Table 1). A meta-analysis also confirmed this conclusion[25]. Patients with T3 stage HCC who received neoadjuvant therapy before LT had significantly improved prognosis compared with patients who did not. However, patients with T1 and T2 stage HCC showed no difference[26]. Even patients who have failed downstaging can achieve better prognosis than those without neoadjuvant therapy (median overall survival: 10.3 mo *vs* 4.0 mo)[27]. Patients with ruptured advanced HCC may also be candidates for LT after successful downstaging, with a significantly improved prognosis compared with nonsurgical treatment[28]. This confirmed the efficacy and broad applicability of neoadjuvant therapy. Several clinical studies have shown similar outcomes for patients who received neoadjuvant therapy and those who did not[29-31], which was related to the patients enrolled in the studies. Although some studies have suggested that neoadjuvant therapy may increase the risk of recurrence after LT, the prognosis of patients with advanced HCC is encouraging enough[32].

The third point is to increase the LR rate of HCC through neoadjuvant therapy and convert unresectable HCCs into resectable tumors[33]. Conversion therapy can be performed to increase future liver volume and reduce tumor stage[34]. In this case, more patients would have the opportunity to receive salvage LR. A meta-analysis suggested that the prognosis of patients with extensive HCC after hepatectomy was poorer than that of patients with non-extensive HCC, and tumor volume was related to the efficacy of LR[35]. Recent studies have shown that the prognosis of patients receiving hepatectomy after successful conversion is comparable to that of patients receiving initial resection (5-year overall survival: 24.9%-57.0% *vs* 42.0%-64.0%)[15,36,37]. Conversion therapy is necessary and beneficial in resectable or unresectable HCC.

Finally, approximately 40% of patients are eligible for radical treatment with an overall survival rate of 70%[38]. Metastasis and new lesions are common types of recurrence. Neoadjuvant therapy plays a certain role in preventing recurrence after radical treatment. Patients with operable HCC receiving neoadjuvant therapy (5-year disease-free survival: about 50%) tend to achieve superior prognosis compared with those receiving hepatectomy only (5-year disease-free survival: 0%-31%)[39]. The effect of reducing tumor recurrence is related to the tumor response of neoadjuvant therapy [40] (Figure 1). Prognostic comparison of patients with neoadjuvant therapy and those with initial resectable or transplantable hepatocellular carcinoma was summarized in Table 1[14,27,29,30,41-45].

PATIENT SELECTION

Bridging treatment is necessary for patients with HCC within the Milan criteria during a long waiting period. Patients with HCC for tumor downstaging require a high degree of selection. A clinical study showed that neoadjuvant therapy was not beneficial for the prognosis of patients with Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC[46], increasing the recurrence risk after LT instead[38]. Moreover, a meta-analysis demonstrated that neoadjuvant therapy had no efficacy for the overall survival and disease-free survival of patients with HCC within the Milan criteria[27].

The indications for downstaging treatment involve physical condition, liver function and tumor stage as well as tumor biomarkers such as alpha fetoprotein and abnormal prothrombin are often considered one of the protocols[47]. There is no uniform and definite limit on the number and size of HCC in downstaging treatment. One retrospective study limited no other restrictions on the tumor conditions of patients with HCC, except no distant metastasis, and their results showed a success rate of 30% in downstaging treatment and comparable prognosis with patients within the Milan criteria after LT[48].

There are some guidelines for downstaging treatment in HCC. One of the most widely used recommendations is the University of California, San Francisco (UCSF) protocol. The indications for downstaging treatment according to the UCSF criteria were as follows: (1) Single HCC > 5 and ≤ 8 cm; (2) 2-3 lesions, each no more than 5 cm in diameter, with the sum of diameters ≤ 8 cm; and (3) 4-5 lesions, each ≤ 3 cm, with the sum of diameters ≤ 8 cm[29]. The success rate of downstaging treatment was approximately 24%-58% according to UCSF criteria[14,29,48,49]. The criteria adopted by the Bologna Liver Transplant Committee are: (1) Single HCC ≤ 8 cm; (2) Two lesions, each ≤ 5 cm; and (3) Multiple lesions within 5 nodules, with the sum of diameters ≤ 12 cm. The success rate was 68.3% on the basis of the Bologna criteria[32]. The Brazilian selection protocol is a relatively relaxed standard and is as follows: (1) No extrahepatic metastasis or major vascular invasion; and (2) Only TACE was

Table 1 Prognostic comparison of patients with neoadjuvant therapy and those with initial resectable or transplantable hepatocellular carcinoma

Year	Study design	Neoadjuvant group					Resectable or transplantable group				Ref.
		Neoadjuvant therapy	Times of neoadjuvant therapy	Tumor condition	Success rate	Subsequent therapy	Prognosis	Tumor condition	Tumor treatment	Prognosis	
2017	Retrospective study	DEB-TACE	1.38	Within Milan criteria 88%	89.0%	OLT	3-yr OS: 79%; 3-yr DFS: 79%	Within Milan criteria 77%	OLT	3-yr OS: 73.0%; 3-yr DFS: 70.0%	[29]
2015	Retrospective study	TACE	NA	Over 10 cm	28.4%	LR/OLT	1-yr OS: 76.5%	HCC over 10 cm	BSC	1-yr OS: 3.7%	[27]
2019	Retrospective study	TACE, RFA; TACE + RFA	NA	Within Milan criteria 56.7%	25.2%	LT	Downstage: 5-yr DFS: 86%; No downstage: 5-yr DFS: 71.5%	Within Milan criteria 68.4%	LT	5-yr DFS: 83.0%	[30]
2013	Retrospective study	TACE, RFA; HIFU, <i>etc.</i>	1.6 ± 0.4	Outside Milan criteria	NA	LT	5-yr OS: 70.7%	Within Milan criteria	LT	5-yr OS: 74.1%	[14]
2015	Retrospective study	TACE, RFA	NA	Outside UNOS T2 criteria	65.3%	LT	5-yr OS: 77.8%; 5-yr DFS: 90.8%	Within UNOS T2 criteria	LT	5-yr OS: 81.0%; 5-yr DFS: 88.0%	[41]
2019	Retrospective study	TACE, RFA; SIRT, <i>etc.</i>	NA	Outside Milan criteria	45.2%	LT	5-yr OS: 76.0%; 5-yr DFS: 89.0%	Within Milan criteria	LT	5-yr OS: 81.0%; 5-yr DFS: 98.3%	[42]
2017	Retrospective study	TACE, RFA; Sorafenib	NA	Outside Milan criteria	26.7%	OLT	NA, comparable with those within Milan criteria	Within Milan criteria	OLT	NA	[43]
2015	Retrospective study	TACE, RFA	NA	Outside Milan criteria	36.4%	LT	5-yr RFS: 81.8%	Within Milan criteria	LT	5-yr RFS: 94.6%	[44]
2019	Retrospective study	NA	NA	Outside Milan criteria	68.4%	LT	5-yr OS: 63.0%	Within Milan criteria	LT	5-yr OS: 77.0%	[45]

DEB-TACE: Drug-eluting beads transarterial chemoembolization; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; HIFU: High intensity focused ultrasound; OLT: Orthotopic liver transplantation; LT: Liver transplantation; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival; UNOS: United Network for Organ Sharing; NA: Not available; LR: Liver resection; SIRT: Selective internal radiation therapy; HCC: Hepatocellular carcinoma; BSC: Best supportive care.

applied as downstaging treatment[50]. Some studies have also used total tumor volume as a criterion for downstaging treatment in HCC[37]. Even if tumors develop definite progression during downstaging therapy, treatment should be continued as long as tumors are within the indication[51].

There are also contraindications of downstaging treatment for LT. First, the contraindications of the treatment itself cannot be ignored[52]. Second, extrahepatic metastasis and major vascular invasion are also contraindications to downstaging treatment[53]. Finally, downstaging treatment is not recommended for tumors exceeding the criteria. Clinical research has suggested that overall survival is significantly shortened in patients with HCC exceeding the UCSF criteria receiving LT after downstaging treatment[54].

Most patients receiving conversion therapy suffered from HCC that was more advanced than those receiving downstaging therapy. There were more restrictions for patients receiving conversion therapy. The neoplastic features of unresectable HCC include: (1) Insufficient future remnant liver (FLR) volume after hepatectomy; (2) Extensive multiple intrahepatic tumors; (3) Extrahepatic metastasis; and (4) Tumor thrombus in the main portal vein, hepatic vein and inferior vena cava[15]. First,

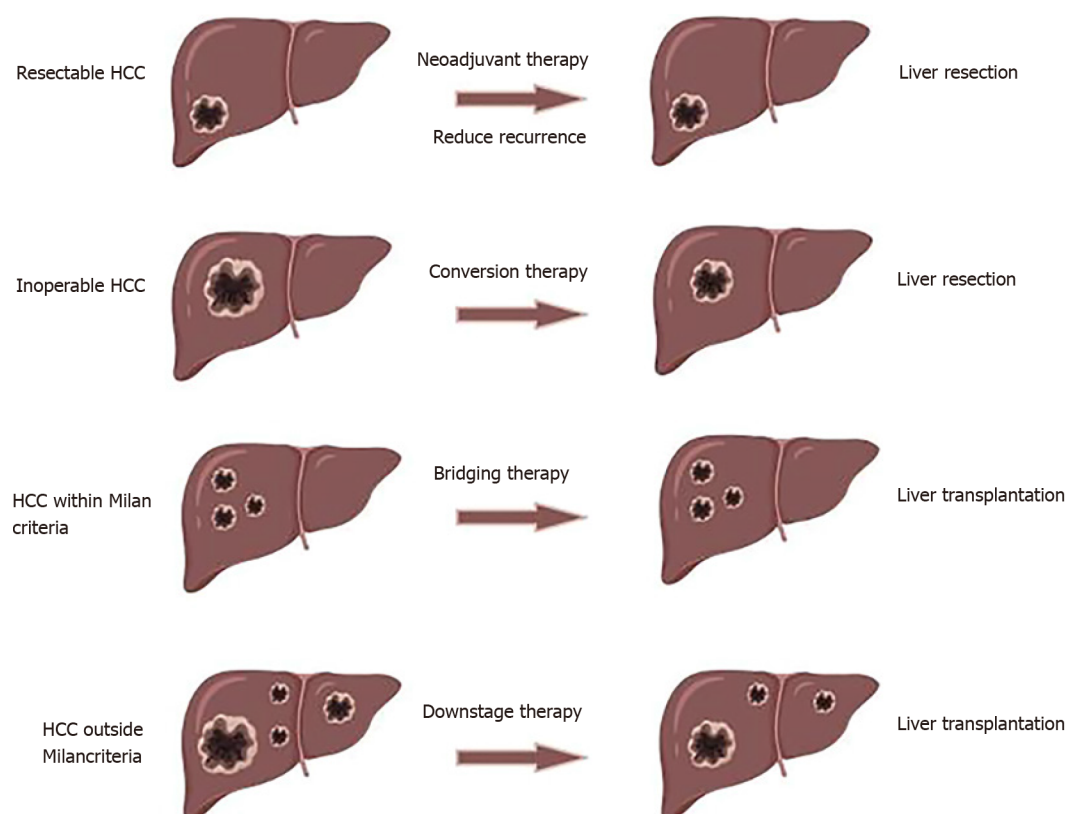


Figure 1 Summary of the goals of neoadjuvant therapy in hepatocellular carcinoma. HCC: Hepatocellular carcinoma.

insufficient residual liver volume after hepatectomy is a contraindication to hepatectomy but not an absolute contraindication. Portal vein embolization (PVE) can be performed to increase the volume of unembolized liver and improve liver function [55]. PVE should be an alternative when the standardized liver volume ratio is no more than 20% in normal liver, 30% in injured liver and 40% in cirrhosis or fibrosis [56]. Second, multiple tumors, major vascular invasion and distant metastasis are not contraindicated in neoadjuvant therapy for patients with normal liver function. A small proportion of patients with advanced HCC after conversion therapy can receive radical therapy, while others also benefit from neoadjuvant therapy[15,57]. Finally, only patients with Child-Pugh grade A and selected patients with Child-Pugh grade B can be candidates for hepatectomy after conversion therapy[58]. A Model of End-Stage Liver Disease score greater than 10 after conversion therapy should be considered a contraindication for hepatectomy[28]. Patients who cannot undergo hepatectomy due to decompensation of liver function are not eligible for conversion therapy.

EFFICACY EVALUATION

Radiological assessment is the main method to evaluate the efficacy of HCC. World Health Organization (WHO) criteria were first performed to evaluate the efficacy of solid tumors based on tumor size[59]. However, WHO criteria lack specific requirements for tumor size measurement and imaging modality was also not clearly specified, leading to incorrect assessment of tumor burden[60]. Response Evaluation Criteria in Solid Tumors (RECIST) criteria made up for many deficiencies in WHO criteria, defining target lesions and non-target lesions, clarifying the method of tumor size measurement and specifying the tumor imaging modality[61]. RECIST 1.1 criteria supplemented the clear definition of lymph nodes and other state lesions on the basis of RECIST criteria, as well as a discussion for fluorodeoxyglucose-positron emission tomography to assess new lesions[62]. The effects of treatment other than tumor reduction were not included in WHO and RECIST/RECIST 1.1 criteria. Given the need to assess efficacy accurately, experts established European Association for the Study of the Liver (EASL) criteria in 2001. The highlight is the measurement of arterially enhanced tumors, taking into account tumor necrosis. EASL criteria also led to a

stricter requirement of tumor response. The modified RECIST criteria simplified the complex steps of EASL criteria, integrates the main advantages of RECIST criteria and puts forward a new suggestion of target lesions, non-target lesions and new lesions [63]. The overall tumor response in modified RECIST criteria is comparable with that in EASL criteria [64]. Due to the delayed treatment of immune checkpoint inhibitors, immune RECIST criteria was also applied in HCC patients receiving immunotherapy [65].

The modified RECIST criteria were performed to evaluate the efficacy of patients receiving neoadjuvant treatment by computed tomography or magnetic resonance imaging in most HCC cases [63]. Efficacy evaluation only considers viable tumors. It takes a period of at least 3 mo of observation for successful downstaging to LT [66]. If the tumor progresses beyond the Milan criteria during this period, LT cannot be performed. If the tumor progresses within downstaging protocols, patients should continue to take downstaging treatment [67], but the Brazilian selection protocol requires no observation period [51]. Most protocols require patients undergoing downstaging treatment to undergo abdominal computed tomography or magnetic resonance imaging every 3 mo.

HOW TO IMPLEMENT NEOADJUVANT THERAPY IN HCC

TACE

TACE combines local embolic ischemia and the cytotoxic effects of chemotherapy, and it has become the recommended first-line treatment for intermediate-stage HCC with preserved liver function [5,68]. Recent research has demonstrated that TACE is the most common first treatment for HCC in China, Korea, North America and Europe. The most common method of TACE is hepatic arterial emulsion with lipiodol plus chemotherapy drugs and embolization with gelatin. TACE can reduce the dropout rate to 3%-13% in patients with early-stage HCC being considered for LT, especially those patients whose waiting time is expected to exceed 6 mo [69,70]. The successful downstaging rate ranged from 23.7% to 63.0% in patients with advanced HCC [71,72]. Patients receiving TACE as downstaging treatment could achieve improved survival (5-year overall survival rate: 77.6%), but TACE cannot improve the long-term prognosis of patients with HCC receiving bridging treatment [73,74]. Clinical studies have shown that the tumor response of pre-transplantation TACE was related to the recurrence rate after transplantation [75].

Drug-eluting beads are non-absorbable embolic microspheres releasing drugs continuously. Compared with conventional TACE, some previous studies indicated that drug-eluting bead TACE (DEB-TACE) not only seemed to be more capable of inducing tumor necrosis but also reduced the systemic blood concentration [76-78]. Other studies have suggested that DEB-TACE led to no advantage in tumor response and survival time compared with conventional TACE [79-82]. There is not enough evidence to support that DEB-TACE is superior to conventional TACE in terms of treatment effect and complications in HCC patients [83]. Approximately 73%-78% of patients within the UCSF criteria achieved successful downstaging, and 40% of them received LT after DEB-TACE [82,84]. The disease control rate was 75%-94% [85-87].

Several studies have demonstrated that appropriate pre-transplant TACE does not increase the risk of LT [88], but others have suggested that the incidence of hepatic artery thrombosis and re-transplantation was significantly higher in patients who received pre-transplant TACE than in those who did not [89]. Tsochatzis *et al* [90] found that the high recurrence rate after LT is associated with the absence of pre-transplant TACE as neoadjuvant therapy (odds ratio 5.395, 95% CI: 1.289-22.577).

Trans-arterial radioembolization

Trans-arterial radioembolization refers to the injection of radioactive substances through the hepatic artery, such as microspheres containing yttrium-90 (Y-90), iodine-131 and iodized oil [91]. HCC is sensitive to radiotherapy [92]. Radioembolization (RE) can achieve different degrees of regression in 25%-50% of HCC patients [93-96]; the success rate of bridging treatment with Y-90 RE can be up to 100% [97,98]. Approximately 20% of patients with an initially unresectable HCC received radical surgery after Y-90 RE [99]. Clinicians have found that Y-90 RE can even be a neoadjuvant treatment for BCLC C stage patients with portal vein tumor thrombosis [100]. However, others also indicated that Y-90 RE can prevent the progression of target lesions but not the generation of new lesions [101]. Complications of radiotherapy embolization mainly stem from the inability to predict precise dosimetry during RE.

Table 2 summarized the outcomes of pre-transplant TACE and trans-arterial radioembolization in downstage treatment for hepatocellular carcinoma[86,89,90,95,96,102-105].

Hepatic arterial infusion chemotherapy

Hepatic arterial infusion chemotherapy (HAIC) can deliver chemotherapeutics to the arterial branches of the HCC at higher concentrations[106]. Compared with traditional systemic chemotherapy, HAIC provides a higher local drug concentration and fewer side effects. The tumor response rate of HAIC is 7%-81%[107,108]. Hepatic artery infusion of FOLFOX (folinic acid, fluorouracil and oxaliplatin), cisplatin plus 5-fluorouracil and cisplatin are common chemotherapy regimens[109-111]. Patients can tolerate HAIC well, and no adverse events above grade 3 have been observed[112]. Recent studies have shown that HAIC is more effective and safer than sorafenib in the treatment of HCC[113]. Preoperative HAIC prolongs the long-term survival of patients[114]. For initially unresectable HCCs, approximately 12% of patients can receive hepatectomy after successful conversion with HAIC[115]. HAIC can prevent the progression of inferior vena cava tumor thrombi, and clinicians have suggested that LR should be performed in patients who initially have no inferior vena cava tumor thrombus and inferior vena cava tumor thrombus controlled by HAIC[116]. Moreover, preoperative HAIC cannot prolong the overall survival of patients with early-stage HCC, but it may be able to prevent intrahepatic distant recurrence[117].

PVE

PVE was originally used to prevent the spread of portal vein thrombi[118] and was found to increase the volume of the unembolized liver. Postoperative liver insufficiency or even liver failure after hepatectomy is closely related to FLR volume. PVE can lead to a significant increase in FLR volume in normal livers or those with chronic disease[119]. There would be functional and volumetric increases in unembolized liver after PVE[120]. The increase in liver volume after PVE is a predictor of postoperative safety. Palavecino *et al*[121] suggested that preoperative PVE was helpful to reduce complications after hepatectomy, and patients with PVE achieved comparable prognosis with those without PVE. However, there were also researchers suggesting that PVE accelerates the growth of tumors in the embolized liver lobe[122].

Repeatedly reversible PVE has achieved satisfactory results in animal experiments, and this new method of PVE requires more evidence[123]. Portal vein ligation can achieve effects similar to PVE, but it is performed less due to its high invasiveness and the risk of treatment-related complications[124]. FLR volume could be insufficient in some patients receiving PVE, and a meta-analysis showed that hepatic and PVE could be an ideal alternative for patients who failed to increase FLR volume with PVE[125].

Radiation therapy

Radiotherapy can be used for more advanced HCC as compared to TACE[126]. Hasan *et al*[127] suggested that radiotherapy is effective in downstaging and bridging therapy for pre-transplant HCC, especially in advanced HCC, which is outside the indications for TACE. Various methods of radiotherapy have been applied in HCC. Clinical studies have demonstrated that stereotactic ablative radiation therapy, selective internal radiation therapy and stereotactic radiotherapy can be effective in the pre-transplant period, with a successful downstaging rate of approximately 60%[128]. For patients with HCC with portal vein tumor thrombosis, radiotherapy before major hepatectomy can achieve a significantly better prognosis. Radiotherapy combined with TACE seemed to be a more effective treatment option, providing a better prognosis[129].

Radiofrequency ablation

Radiofrequency ablation is a radical alternative to surgical resection for BCLC stage 0/A HCC and a palliative treatment for advanced HCC at the same time[5,130]. de Haas *et al*[131] suggested that preoperative radiotherapy had no adverse effects on patient prognosis while providing downstaging and bridging effects. Radiofrequency ablation before LT may indeed cause inflammation and adhesions, increasing the difficulty of operation, but clinical studies have shown that the perioperative mortality and morbidity of the local ablation group are comparable with that of the non-local ablation group[131]. The disease control rate of radiofrequency ablation combined with TACE was significantly higher than that of monotherapy, and the sequence of radiofrequency ablation and TACE appeared to lead no effect on prognosis[132].

Table 2 Summary of pre-transplant transarterial chemoembolization and trans-arterial radioembolization in downstage treatment for hepatocellular carcinoma

Year	Neoadjuvant treatment	Entry criteria	Success downstage rate	Subsequent therapy	Adverse events	Incidence rate	Ref.
2015	Conventional TACE; I ¹³¹ Metuximab TACE	Patients within UCSF criteria	NA	OLT	Hepatic artery thrombosis hepatic aneurysm	1.5%	[89]
2015	DEB-TACE	BCLC 0/A/B stage	26.7%	OLT	Grade 3/4	3.2%	[102]
2017	TACE		NA	OLT	Hepatic artery thrombosis Retransplant	27% 22.7%	[90]
2020	DEB-TACE	AJCC stage ≤ T3a	73.3%	OLT	Grade 3 Grade 4	3.1% 0.0%	[86]
2006	Y-90 RE	UNOS stage T3	66.0%	OLT	NA	NA	[103]
2017	Y-90 RE	BCLC A/B/C stage	78.9%	OLT	NA	NA	[104]
2011	Y-90 RE	UNOS stage T2, T3, T4a	50.0%	OLT	Hyperbilirubinemia (Grade3)	13.0%	[105]
2013	Y-90 RE	UNOS stage T3, T4a	33.0%	OLT	NA	NA	[95]
2021	Y-90 RE	UNOS stage T1, T2, T3, T4	43.0%	OLT	NA	NA	[96]

DEB-TACE: Drug-eluting beads transarterial chemoembolization; TACE: Transarterial chemoembolization; Y-90 RE: Yttrium-90 radioembolization; UCSF: University of California, San Francisco; BCLC: Barcelona Clinic Liver Cancer; AJCC: American Joint Committee on Cancer; UNOS: United Network for Organ Sharing; NA: Not available; I¹³¹: Iodine-131; OLT: Orthotopic liver transplantation.

Systemic therapy

Chemotherapy is effective for the treatment of HCC, but the incidence of adverse events is very high. Up to 44% of patients develop grade 3-4 adverse events[133]. Neoadjuvant therapy rarely uses chemotherapy alone. Localized concurrent chemoradiotherapy could lead to a downstaging rate of 26.5% in advanced HCC so that surgery can be performed[134]. Even in patients with portal vein tumor thrombosis, the operation rate can reach 26.5% after concurrent chemoradiotherapy[134]. The feasibility of chemotherapy combined with targeted drugs requires more clinical research in downstaging and bridging in pre-transplant HCC[135,136].

Sorafenib is a milestone in the systematic treatment of HCC. It was clinically observed that one patient who received sorafenib for downstaging achieved a good prognosis after LT[137]. Sorafenib is also effective in conversion therapy of advanced HCC and even ruptured HCC[138,139]. A decline of more than 20% from baseline in early alpha fetoprotein levels is a predictor of tumor response to sorafenib[140]. However, due to the relatively low response rate of sorafenib in HCC, the application of neoadjuvant therapy is limited[141]. To date, there have been few reports of successful conversion after receiving sorafenib[142-144]. More evidence is required to support the role of sorafenib in neoadjuvant therapy because of the small sample size of clinical studies on sorafenib in neoadjuvant therapy[145]. Compared with other targeted drugs, lenvatinib leads to a higher response rate of approximately 40.6% [146]. Targeted therapy should be an alternative in patients who cannot benefit from TACE. It can be more effective when lenvatinib is administered before TACE in patients with BCLC B stage HCC[147]. Regorafenib and other targeted drugs can also be potential neoadjuvant treatments[148]. Surgery-related complications of molecular targeted drugs must be noted, such as increased bleeding and hindered liver regeneration[149], but clinical research has suggested that the surgical blood loss and complications in the sorafenib group were comparable to those in the control group [150].

Immunotherapy is an emerging systemic treatment for solid tumors[151]. The combination of atezolizumab and bevacizumab showed a strong antitumor effect, with a relatively low rate of grade 3-4 adverse events (15.2%)[152]. Targeted drugs plus immune checkpoint inhibitors can achieve a tumor response rate of 30%, leading to a new emerging treatment[153-155]. Lenvatinib plus pembrolizumab can also be an important treatment option for neoadjuvant therapy. The combination of immuno-

therapy and other treatments, such as chemotherapy and radiotherapy, still requires more evidence to demonstrate efficacy[155,156].

CONCLUSION

To reduce the drop-out rate during the waiting period and downstaging more HCCs outside the Milan criteria, effective neoadjuvant therapy is critical in prolonging patient prognosis. Adverse events of neoadjuvant therapy are manageable under strict indications. The establishment of unified protocols of neoadjuvant therapy requires more clinical studies.

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