**Review Article**

**Neoadjuvant therapy and immunotherapy strategies for hepatocellular carcinoma**

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**Abstract:** Hepatocellular carcinoma (HCC) is one of the most common cancers with high mortality rate worldwide. Due to aggressive and invasive characteristics of HCC, poor prognosis is often displayed at advanced stages while therapeutic options are limited. Liver resection is still an essential curative-intent treatment in HCC management, while locoregional and systematic therapies made promising advances that may improve the proportion and outcomes of patients who are surgical candidates. In this review, we discussed status of currently available neoadjuvant treatments aimed at improving resectability and reducing recurrence rates. More than ever, in order to implement this therapeutic concepts and exploit the full potential of neoadjuvant treatment strategies, it is of utmost importance to use more high-level evidence to guide treatment decision making. Unfortunately, the use of preoperative treatments is not sponsored by tough evidence and consensus guidelines are absent.

**Keywords:** Preoperative/downstage/neoadjuvant therapy, locoregional therapy, systematic therapy, immunotherapy, hepatocellular carcinoma

**Introduction**

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the foremost cause of cancer related death worldwide [1]. The incidence of HCC is increasing most rapidly among all cancers, by 2% to 3% annually around 2010s in the United States [2]. Most HCCs arise in conjunction with liver cirrhosis, which is mainly related to acknowledge risk factors, including chronic hepatitis B and C virus infection, excessive alcohol consumption, nonalcoholic fatty liver disease, obesity, and smoking [3-5]. Current curative treatments mainly included liver transplantation (LT), surgical resection and percutaneous ablation, and plenty of systemic and locoregional therapies had also been developed. However, the 5-year recurrence rates of patients with HCC undergoing radical resection had reached about 80% [6]. Twenty percent of LT recipients on the waiting list will drop out because of tumor progression [7].

The definition of neoadjuvant therapy was made by the American Joint Committee on Cancer, which was consisted of radiation therapy and systemic therapy, such as chemotherapy, immunotherapy and hormone therapy. It was administration before definitive surgery in order to decrease the tumor burden to allow operation and/or to decrease postoperative recurrence rates. The feasibility of neoadjuvant therapies has been demonstrated in other solid-organ malignancies, such as non-small cell lung cancer, melanoma, colorectal cancer, breast cancer and urothelial bladder cancer [8-12]. The use of neoadjuvant therapies in the treatment of HCC has been liberalized and applied to downstage disease to enable surgical resection and limit tumor progression to prevent exceeding transplant criteria. Although preoperative therapy of HCC is lack of enough researches to support and is not recommended in current guidelines, based on the aggressive and invasive characteristics of HCC at advanced stage, it is clear that strategies are needed to rise and maintain patient suitability for curative treatments. In this review, we provided an overview of investigational neoadjuvant strategies for HCC treatment and dis-
Neoadjuvant therapy for hepatocellular carcinoma

cussed its implications for the design of future clinical trials.

**Transarterial chemoembolization**

Transarterial chemoembolization (TACE) is based on the embolization of the arterial blood supply of the target neoplastic lesion, combined with the injection of chemotherapeutic drugs. According to the treatment guidelines for HCC, TACE is widely used as first line treatment for intermediate HCC (BCLC-B) and advanced unresectable HCC [13, 14]. The function of TACE for patients undergoing resection disease has been explored, but the conclusions of these studies are controversial [15-21]. Zhang et al. reported a retrospective review of 1457 patients who had hepatectomy for HCC. Of these, 120 patients who received preoperative TACE had significantly longer 5-year disease free survival (DFS). Moreover, the mean disease-free survival times of over two times TACE group was significantly higher than that of one time TACE group [15]. However, Sasaki A et al. performed a comparative analysis in 235 patients with HCC, including 109 patients underwent preoperative TACE, and found no difference in mortality or disease-free survival. Instead, the 5-year overall survival (OS) rate after hepatectomy was significantly worse in patients treated with TACE group (28.6% vs. 50.6%, P < 0.01) [16]. As for the efficacy and negative effect of preoperative TACE, a TACE-specific model based on routinely available clinical features was developed, including albumin, bilirubin, α-fetoprotein, tumor size, tumor number, vascular invasion and etiology of the underlying liver disease. Comparing to existing hepatoma arterial embolization prognostic (HAP) score, the proposed model showed superior predictive accuracy that may improve the survival of TACE treatment [17].

The use of neoadjuvant TACE for increasing the resectability rate of HCCs by down-staging unresectable tumors had also shown promise. Li et al. showed that 88 patients received preoperative TACE among the 377 enrolled patients, had favorable median OS (32.8 mo vs. 22.3 mo, P = 0.035) and recurrence-free survival (RFS) (12.9 mo vs. 6.4 mo, P = 0.016). Plus, patients in the TACE group had fewer incidences of death and recurrence [18]. A systematic review of 1284 patients underwent major liver resection, represented that the resection rate of patients with preoperative TACE + portal vein embolization (PVE) was 14% higher [risk difference = -0.143; 95% CI (-0.206, -0.08); P < 0.001] than that of patients with PVE alone. On the other hand, neoadjuvant TACE + PVE group was associated with better OS at mean follow-up and low rate of major complications [19]. Overall, the role of neoadjuvant TACE still stays unclear and it is not regularly recommended in clinical practice. However preoperative TACE was more generally used as a bridging therapy before LT [22, 23], its continued evolvement required further validation by large randomized controlled trails (RCTs) to ensure the selection of indications and preoperative treatment times.

**Transarterial radioembolization**

Transarterial radioembolization (TARE) with yttrium-90 microspheres (Y90) blocks the blood supply by injecting radioactive particles into the hepatic artery and performs internal radiotherapy on the tumor. It is safer in impaired portal flow and toxicity than TACE because of lower risk of liver ischemia [24]. TARE is increasingly being utilized to downstage/downsize HCC as a bridge to surgery and to prolong time-to-progression [25, 26]. Labgaa et al. reviewed 349 patients with unresectable HCC who were treated with TARE, underwent radical surgery after successful downstage, including orthotopic liver transplantation (n = 22) and liver resection (n = 10). OS was extended for 47 months and 1-, 3- and 5-years OS reached 97%, 86% and 86% respectively, supporting the feasibility of surgery after TARE [27]. In addition, the use of TARE in patients with small future liver remnant (FLR) could induce a significant volumetric change of the contralateral hepatic lobe comparable to PVE [28, 29]. In a retrospective study, the investigators revealed 10 patients with HCC undergoing preoperative Y90 radiation lobectomy (RL) were achieved tumor control and hypertrophy of small FLR with significantly increased median FLR (pre: 33%; post: 43%, P < 0.01). Moreover, this study also demonstrated RL facilitated R0 resection and brought over 50% necrosis in 92% of resected tumors [30].

In addition, there are increasing evidences that TARE is preferred in suitable HCC patients with portal vein tumor thrombosis (PVTT) [29-32].
Neoadjuvant therapy for hepatocellular carcinoma

2014, She WH et al. conducted a retrospective study with 32 patients to compare the survival benefit of TARE and TACE. The subgroup analysis of the results suggested that patients with major vascular invasion in TARE have prolonged survival (OS: 12 mo vs. 8 mo, 3-year survival rate 20.3% vs. 9.7%) [33]. However, two large multicentric trials failed to demonstrate a significant superiority of TARE group compared to sorafenib group in advanced HCC patients [34, 35]. Therefore, more RCTs should be conducted. With an increasing number of patients enrolled in the control arm, TARE with Y90 would obtain a better definition of the resectable criteria and a better evaluation of its role in neoadjuvant treatment.

Radiotherapy

The role and efficacy of radiotherapy (RT) is increasingly important in the management of HCC while several studies have demonstrated RT was be beneficial for the tumour control, overall survival and disease-free survival [36-38]. The universal application of RT mainly consists of three-dimensional conformal radiotherapy (3-DCRT), stereotactic body radiotherapy (SBRT) and intensity modulated radiotherapy (IMRT) with improvements in technology and awareness of dose-volume effects. Preoperative RT was evaluated to be applied to advanced HCC patients as a bridging therapy prior to LT [39, 40], while its function in neoadjuvant treatment for potentially resectable tumors had been developed. In 2018, Lin H et al. conducted a retrospective review of 244 HCC patients from the Surveillance, Epidemiology and End Results (SEER) database, including 93 patients who received radiotherapy before surgery. Compared with patients who underwent postoperative RT resection, patients who underwent neoadjuvant RT had a clear advantage in unadjusted OS and cancer-specific survival (P < 0.001 for log-rank test). Additionally, all-cause mortality risk (HR: 0.31; 95% CI: 0.16-0.60, P < 0.001) and cancer-specific mortality risk (HR: 0.30; 95% CI: 0.15-0.59, P = 0.001) showed a significant decrease in preoperative RT group versus postoperative RT group [41].

Another favorable application of RT in patients with PVTT has also accomplished a high resection rate and low toxicity [42, 43]. Wei X et al. conducted a multicenter randomized controlled study, which included 164 patients (82 treated with neoadjuvant RT followed by hepatectomy and 82 controls with hepatectomy alone). The results presented a significant extend in OS and DFS (P < 0.001, respectively) and decrease in HCC-related mortality and recurrence rates (HR, 0.35 [95% CI, 0.23 to 0.54; P < .001] and 0.45 [95% CI, 0.31 to 0.64; P < .001]) [44]. More well-designed clinical investigations are necessary to verify the ideal dosage of neoadjuvant radiotherapy and time interval between RT.

Hepatic arterial infusion chemotherapy

Hepatic arterial infusion chemotherapy (HAIC), in which high concentrations of anticancer agents are directly injected into the hepatic artery, was more effective than intravenous chemotherapy by localizing their application and minimizing systemic adverse effects. While HAIC has showed favorable response rate (RR) and survival benefits in advanced HCC patients [45-47], the role of neoadjuvant HAIC remains limited. From 2003 to 2015, the recent retrospective study revealed 12 patients who underwent hepatectomy after preoperative HAIC had better OS compared to patients treated with HAIC alone (median survival time 37±6.6 mo vs. 13±1.4 mo, P = 0.002) [48]. Neoadjuvant HAIC is also used in HCC with PVTT to downstage prior to liver resection [49, 50]. However, more solid statistics of HAIC efficacy are needed to promote clinical application.

Systematic therapy

Current systemic therapy for patients with HCC consists of tyrosine kinase inhibitor (TKI) and immunotherapy. Following the positive SHARP trial in 2008, TKI sorafenib was accepted for use in patients with Child-Pugh class A cirrhosis and intermediate to advanced HCC stage, creating a new era in the management of HCC [51-53]. Sorafenib remained the sole available option for frontline therapy until the non-inferiority of lenvatinib opened another first-line drug in 2018 [54]. In the second line, regorafenib [55], cabozantinib [56] and ramucirumab [57] have all demonstrated efficacy against patients with AFP ≥ 400 ng/mL. Meanwhile, nivolumab [58] and pembrolizumab [59] are granted approval for second-line alternatives in the US in 2017 and 2018, respectively. And
most recently, IMbrave150, the positive immunotherapy phase-III study has published the convincing data for the combination of atezolizumab and bevacizumab, which is superior to the current standard.

Systematic therapy was originally developed for advanced unresectable HCC patients as a palliative treatment, and now the preoperative application has also been partially explored. Some studies had reported safety and efficacy of preoperative administration of sorafenib was observed after hepatectomy for unresectable HCC [60-62]. Preoperative sorafenib has also been investigated in the management of HCC patients with PVTT and underwent LT [63-66]. However, they have all been reported in small series (2-40 patients) to successfully downstage, and larger clinical experience is still lacking. In addition, the use of sorafenib may raise concerns regarding the potential adverse effects and be limited by negative datum [67, 68].

Immune checkpoint inhibitors (ICIs), mostly represented by the programmed cell death 1 (PD-1) inhibitor and cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitor, have made exciting progress. Nivolumab [69], pembrolizumab [70], durvalumab [71], atezolizumab [72], tremelimumab [73] and ipilimumab [74] already showed clinical significant improvements in certain outcomes. Over the past several years, immunotherapy in the neoadjuvant setting is evolving. Recently, Kaseb A et al. conducted a randomized, phase II pilot trial to evaluate the role of perioperative immunotherapy for potential resectable HCC. Eight patients in Arm A were underwent with PD-1 targeted monoclonal antibody nivolumab while nine patients in Arm B were treated concurrently with CTLA-4 targeted antibody ipilimumab. In its interim analysis, the trial reached the primary objective that treatment was safe and surgical resection was not delayed. Additionally, the study was ongoing and reported pathologic complete response of 29% [74]. They also provided an illustrative case report that complete pathologic response was correlated with highly cytotoxic effector CD8+ T cells infiltrating the tumor after perioperative immunotherapy [75].

The use of neoadjuvant immunotherapy for LT has also presented in the first case, showing the patient successfully downstaged with nivolumab according to Milan criteria [76]. Although ICIs could be fatal when used in the immediate pre-transplant setting or after LT [77], a prospective national database present how and when to use ICIs in LT recipients [78]. Further investigation is needed to identify reliable biomarkers to predict therapeutic response and to better stratify patients with high risk of tumor progression.

**Combination therapy**

Past and ongoing combinations studies for advanced HCC have presented encouraging results with notable objective responses and are being investigated further with the goal of demonstrating improvement of OS. ICIs in combination with TKIs [79-82] and systemic plus local-regional treatment [83, 84] have already been investigated or are being investigated, while combination therapies as downstage treatment to hepatectomy are also currently evaluated (NCT03510871, NCT03222076) [74]. A case report demonstrated by Chen X et al. that the combination treatment of lenvatinib and nivolumab showed great efficacy and safety to make the patient with massive HCC undergoing extended right hepatectomy [85]. Overall, most current data supports the use of adjuvant treatment for HCC and combination neoadjuvant therapy may still have a long way to go.

**Conclusion**

Surgery is still the core treatment for patients with resectable disease and normal liver function. Meanwhile, multimodality therapy is increasingly explored to reduce disease recurrence rates and increase the proportion of patients undergoing surgery. Unfortunately, the use of neoadjuvant strategies in HCC resection is still at the stage of exploration with paucity of conclusive literature. Therefore, future neoadjuvant researches should pay more attention to standardization of endpoints and trial design and be investigated to identify biomarkers of response and mechanisms of resistance to acquire enough data. With exciting advances in locoregional and systemic therapies, including development of immunotherapy, large RCTs will be required to ensure the optimal components and sequence of multimodality therapy.

**Disclosure of conflict of interest**

None.
Neoadjuvant therapy for hepatocellular carcinoma

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References


Neoadjuvant therapy for hepatocellular carcinoma


Neoadjuvant therapy for hepatocellular carcinoma


Neoadjuvant therapy for hepatocellular carcinoma


Neoadjuvant therapy for hepatocellular carcinoma


