

# World Journal of *Clinical Cases*

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## Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis

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### Abstract

Extrahepatic metastasis (EHM) of hepatocellular carcinoma (HCC) has increasingly been seen due to improved survival with effective management of intrahepatic lesions. The presence of EHM indicates an advanced stage of HCC, for which systemic therapy serves as the standard treatment modality. Since the approval of Sorafenib as the first systemic agent in 2007, it took almost a decade to show its efficacy in both first and further lines of setting until the landscape of systemic drugs was finally expanded. Moreover, with inspiring results from immunotherapy trials in HCC, it appears that the introduction of immunotherapy may lead to an evolution in the portfolio of HCC treatment. Although the locoregional approach in the management of EHM is not recommended for advanced-stage HCC, efforts have been made to demonstrate its efficacy in symptom relief and potential benefit for overall survival. This review provides a summary of recent updates of the systemic agents in the treatment of advanced HCC, with an emphasis on aggressive locoregional management of EHM by various treatment modalities.

**Key Words:** Hepatocellular carcinoma; Extrahepatic metastasis; Systemic therapy; Targeted therapy; Immunotherapy; Locoregional therapy

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**Core Tip:** The presence of extrahepatic metastasis (EHM) indicates an advanced stage

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked as the sixth most common neoplasm and the fourth leading cause of cancer death worldwide[1]. Extrahepatic metastasis (EHM) of HCC is relatively rare at the time of initial diagnosis, even in those with advanced intrahepatic lesions. However, EHM is of growing significance as the overall survival (OS) of patients has been improved due to advances in the management of intrahepatic lesions[2]. According to the Barcelona Clinic Liver Cancer (BCLC) staging, the presence of EHM indicates an advanced stage, with a poor prognosis pertaining to an expected median survival time of 6 mo to 8 mo or a quartered survival rate at one year [3].

Most patients in advanced stage would die of liver failure due to the progression of intrahepatic lesions rather than extrahepatic metastatic dissemination[4]. Even in patients with EHM, therapeutic approaches to control intrahepatic tumors are still beneficial for improving survival[5,6]. Therefore, current studies are mainly focused on the development and validation of systemic agents in improvement of survival and relief of symptoms. First-line Sorafenib, a tyrosine kinase inhibitor (TKI), has been taken as the standard of care for over a decade[7,8]. With the treatment landscape being expanded, another TKI, Lenvatinib, has shown to have noninferior performance in survival *vs* sorafenib and thus has joined Sorafenib as a preferred agent for first-line treatment[9]. Other TKIs, including Regorafenib and Cabozantinib, have shown significant improvement in OS after the failure of Sorafenib, which subsequently led to regulatory approval in a second-line setting[10,11]. In addition, anti-angiogenic agent Ramucirumab is a potential second-line option for patients with high  $\alpha$ -feto-protein (AFP) levels (400 ng/mL or greater)[12,13]. More recently, immune checkpoint blockade (ICB) therapy targeting programmed death 1/programmed death ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) has marked a new era in immune-oncological treatment of advanced HCC.

It remains controversial whether patients in advanced stage HCC would benefit from aggressive locoregional control of EHM, including surgical resection, thermal ablation, radiotherapy, and transcatheter arterial chemoembolization (TACE). Previous studies have demonstrated that palliative locoregional treatment is beneficial for symptom relief and might improve survival.

Herein, we review the recent updates in the systemic agents for treatment of advanced stage HCC. In addition, emphasis is laid upon aggressive locoregional control of EHM by various treatment modalities.

## SYSTEMIC THERAPY

Systemic therapy is the main treatment modality for the majority of patients with advanced HCC, broadly categorized as cytotoxic chemotherapy, targeted therapy, and immunotherapy. In this section, we focus on the recent updates in targeted therapy and immunotherapy. While the prospective data for systemic therapies is expanding, there is limited data for sub-group analysis in patients with EHM and thus the efficacy of systemic agents in extrahepatic lesions is still unknown.

### Targeted therapy

**Sorafenib:** No effective treatment modalities for patients who were diagnosed as having advanced HCC or those who progressed into advanced stage after failure in initial therapies were available until 2007 when a randomized, controlled phase III SHARP trial (Sorafenib HCC Assessment Randomized Protocol trial) revealed the efficacy of Sorafenib[7]. Sorafenib, a small molecule inhibitor in advanced HCC, is an oral multi-targeted TKI against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and RAF kinase, with anti-proliferative and anti-angiogenic effects. In the SHARP trial, 602 patients with advanced HCC who had not received previous systemic therapy were randomized to receive Sorafenib or placebo, with OS and time to symptomatic progression used as primary outcomes. Median OS in the Sorafenib group was 10.7 mo *vs* 7.9 mo in the placebo group [hazard ratio (HR) = 0.69; 95% confidence interval (CI): 0.55-0.87;  $P < 0.001$ ]. Although only seven patients in the sorafenib arm (2%) had a partial response (PR) and none had a complete response (CR) by RECIST, the median time to radiologic progression was 5.5 mo in the Sorafenib arm, which was longer than that in the placebo arm (HR = 0.58, 95%CI: 0.45-0.74,  $P < 0.001$ ). Similar results were demonstrated in another parallel phase III trial in the Asia-Pacific region[8]. Based on the positive results from the two multi-center phase III trials, Sorafenib was approved as the first systemic standard of care for advanced HCC.

**Lenvatinib:** Sorafenib has dominated the treatment of advanced HCC for a decade, until Lenvatinib, another oral multi-TKI with anti-angiogenic activity against VEGFR1-3, PDGFR alpha, fibroblast growth factor receptor 1-4 (FGFR1-4), RET, and KIT[14]. In 2017, an open-label phase III REFLECT trial involving mainly Asian patients demonstrated that Lenvatinib was non-inferior to Sorafenib in OS in untreated advanced HCC[9]. Median OS in the Lenvatinib arm was 13.6 mo *vs* 12.3 mo in the Sorafenib arm (HR 0.92, 95%CI: 0.79-1.06). Significant improvements in secondary endpoints were identified, including progression-free survival (PFS, 7.4 mo *vs* 3.7 mo; HR = 0.66, 95%CI: 0.57-0.77) and time to progression (TTP, 8.9 mo *vs* 3.7 mo; HR = 0.63, 95%CI: 0.53-0.73). Interestingly, objective response rate by mRECIST was significantly higher in the Lenvatinib arm [24.1% *vs* 9.2%; odd ratio (OR) = 3.1; 95%CI: 2.2-4.6], which was subsequently confirmed as an independent predictor of OS in a multivariate Cox regression analysis[15]. Notably, the REFLECT trial excluded patients with adverse prognostic tumor characteristics, such as main branch portal vein thrombosis or greater than 50% tumor occupation of the liver, which are commonly seen in advanced stage and nearly unavoidable in routine clinical decision making. Recent studies have found that Lenvatinib also offered a survival benefit in patients with highly advanced HCC and may lead to more favorable outcomes compared with Sorafenib[16-18]. Approval for Lenvatinib was granted by the Food and Drug Administration (FDA) as the first-line agent, and it was included in the latest BCLC and EASL guidelines[1,3].

**Regorafenib:** For those who have failed Sorafenib treatment, the OS is about 8 mo[19-21]. There is an urgent need to develop an effective second line agent to improve prognosis after the failure of Sorafenib. In 2017, a randomized controlled phase III RESORCE trial proved the efficacy of Regorafenib in OS in patients with HCC progressing during Sorafenib treatment[10]. As an oral fluorinated analog of Sorafenib, Regorafenib shares a similar spectrum of molecular targets and significantly inhibits neo-angiogenesis and tumor proliferation. Median OS in the Regorafenib arm was 10.6 mo *vs* 7.8 mo in the placebo arm (HR = 0.63, 95%CI: 0.50-0.79,  $P < 0.001$ ), with a consistent benefit across all subgroups (region, portal vein thrombosis, AFP levels, and presence of EHM). Regorafenib was also noted to provide a significant improvement in median TTP (3.2 mo *vs* 1.5 mo, HR = 0.44, 95%CI: 0.36-0.55,  $P < 0.001$ ) and objective response rates (10.6% *vs* 4.1%,  $P = 0.005$ ). An exploratory analysis based on data from RESORCE showed that Regorafenib conferred a clinical benefit regardless of the last Sorafenib dose or TTP on prior Sorafenib[22]. Subsequently, Regorafenib was approved by the FDA as a second line agent for patients with advanced HCC who failed Sorafenib. Recent cohort studies have verified the efficacy and safety of Regorafenib, which were consistent with those of the previous RESORCE trial[23,24]. Notably, Regorafenib was not recommended as a treatment agent for patients with impaired liver function (Child-Pugh grade B population), due to the poor clinical outcomes and increased frequency of severe adverse event[25]. As the first systemic agent demonstrating a significant improvement in OS in second-line setting, it is currently approved for patients with advanced HCC who tolerated Sorafenib but experienced radiological progression.

**Cabozantinib:** Cabozantinib, an TKI targeting VEGF receptors, MET, and AXL, has showed clinical activity in patients with advanced HCC, regardless of previous treatment, in a randomized phase II trial[26]. In the phase III CESETIAL trial, Cabozantinib was compared with placebo in second- and third-line settings for advanced HCC with preserved liver function (Child-Pugh grade A) and good performance status (Eastern Cooperative Oncology Group Performance Status 0-1). Median OS in the Cabozantinib arm was 10.2 mo *vs* 8.0 mo in the placebo arm (HR 0.76, 95%CI: 0.63-0.92). Also, there was an improvement in secondary endpoints, including PFS (5.2 mo *vs* 1.9 mo, HR = 0.44, 95%CI: 0.36-0.52,  $P < 0.001$ ) and objective response rates (4% *vs* 0.4%,  $P = 0.001$ ) by RECIST 1.1[27]. Subgroup analysis showed that among those who had received Sorafenib, Cabozantinib continued to provide benefit in OS compared to placebo (11.3 mo *vs* 7.2 mo, HR = 0.70, 95%CI: 0.55-0.88). The results above confirmed the role of Cabozantinib as a second- or third-line therapeutic agent of advanced HCC regardless previous systemic therapies. Recently, a matching-adjusted indirect comparison analysis showed that Cabozantinib may achieve a similar OS and prolonged PFS compared with Regorafenib in patients with progressive advanced HCC after Sorafenib[28]. Currently Cabozantinib is approved for patients with advanced HCC who are either intolerant, or experience radiological progression on Sorafenib.

**Ramucirumab:** Different from TKI agents, Ramucirumab is an anti-VEGF recombinant monoclonal IgG antibody that specifically binds to the VEGF2 domain and thus blocks the ligand-receptor interaction. Although promising results were demonstrated initially in the phase II study for advanced HCC, Ramucirumab failed to achieve the expected improvement in OS in the randomized controlled phase III REACH trial, with a median OS of 9.2 mo compared to 7.6 mo with placebo (HR = 0.87, 95%CI: 0.72-1.05,  $P = 0.14$ )[12]. However, a sub-group analysis of patients with baseline serum AFP higher than 400 mg/mL revealed a potential survival benefit[29]. Thereafter, the REACH-2 trial was launched to investigate the efficacy of Ramucirumab in patients with serum AFP concentrations at 400 ng/mL or greater[13]. Mean OS was improved from 7.3 mo in the placebo group to 8.5 mo in the Ramucirumab group (HR = 0.71, 95%CI: 0.53-0.95,  $P = 0.019$ ), and RFS was improved from 1.6 mo to 2.8 mo (HR = 0.45, 95%CI: 0.40-0.60,  $P < 0.0001$ ). In a combined analysis pooling results from REACH and REACH-II trials, a significant improvement in OS was confirmed in patients with serum AFP concentrations at 400 ng/mL or higher (8.1 mo *vs* 5.0 mo, HR = 0.69, 95%CI: 0.57-0.84,  $P = 0.0002$ )[30]. Ramucirumab is an important second-line option specifically for those with high AFP levels who were either intolerant or progressed on Sorafenib.

### Immunotherapy

In recent years, immunotherapy represented by immune checkpoint inhibitors (ICIs) including anti-PD-1/PD-L1 and anti-CTLA-4 antibodies has exhibited potential therapeutic effects for advanced HCC. Inspired by the promising outcomes in phase II trials, more phase III trials have been launched to investigate the potency of immunological agents in advanced HCC.

### AtezoBev

Atezolizumab is a monoclonal antibody that selectively targets PD-L1 to prevent receptor-ligand interaction with receptors PD-1 and B7-1, thus reversing T-cell suppression[31]. Bevacizumab is a monoclonal antibody that targets VEGF and thus inhibits angiogenesis and tumor growth[32]. Despite the modest activity of Bevacizumab alone in advanced HCC in some small phase II studies[33,34], the combination of Atezolizumab and Bevacizumab (AtezoBev) demonstrated a promising antitumor activity in untreated and unresectable HCC in a phase Ib trial, with an objective response rate of 36% including 12 patients with CR. Median OS and PFS were 17.2 and 7.0 mo, respectively[35]. Subsequently, a multicenter, open-label, randomized phase III trial, IMbrave150, was conducted to determine the safety and efficacy of AtezoBev compared with Sorafenib in patients with unresectable HCC[36]. Although median OS was out of reach for AtezoBev, the HR for death with the AtezoBev arm as compared with the Sorafenib arm was 0.58 (95%CI: 0.42-0.79,  $P < 0.0001$ ). The 6-mo and 12-mo survival rates were 84.8% and 67.2% in the AtezoBev arm *vs* 72.2% and 54.6% in the Sorafenib arm, respectively. Median PFS was significantly improved from 4.3 mo to 6.8 mo compared with Sorafenib (HR = 0.59, 95%CI: 0.47-0.76,  $P < 0.0001$ ). The 6-mo PFS rates were 54.5% *vs* 37.2% in AtezoBev arm and Sorafenib arm, respectively. HR for disease progression or death was 0.59 (95%CI:

0.47-0.76,  $P < 0.0001$ ). The overall response rates were 27% in the AtezoBev arm *vs* 12% in the Sorafenib arm according to RECIST 1.1 criteria ( $P < 0.001$ ), which was still of significance when HCC-specific mRECIST was applied (33.2% *vs* 13.3%,  $P < 0.001$ ). It was the first phase III trial with positive results showing a significant improvement in both OS and PFS compared to Sorafenib. Consequently, approval for Atezolizumab plus Bevacizumab in the treatment of adult patients with unresectable locally advanced or metastatic HCC without prior systemic treatment was granted by the FDA on May 29, 2020[37].

**Nivolumab:** Nivolumab was the first immunotherapeutic agent applied in clinical trial of HCC. The phase I/II, open-label, non-comparative dose escalation and expansion trial CheckMate 040 unprecedentedly demonstrated the manageable safety profile and potential efficacy of anti-PD-1 antibody in advanced HCC, with high objective response rates and disease control rates at 20% and 64% in the dose-expansion phase, and 15% and 58% in the dose-escalation phase, respectively[38]. Based on the exciting findings, accelerated approval was granted to Nivolumab by the FDA as a second-line treatment for advanced HCC. Thereafter, a randomized, multi-center phase III study of Nivolumab *vs* sorafenib as first-line treatment for advanced HCC was launched [39]. Nivolumab did improve OS compared to Sorafenib but failed to reach the specified criteria of statistical significance (HR = 0.84,  $P = 0.0419$ ). Median OS was 16.4 mo in the Nivolumab arm and 14.7 mo in the Sorafenib arm (HR = 0.85, 95%CI: 0.72-1.02,  $P = 0.0752$ ). Similar median PFS was identified in both arms, 3.7 mo and 3.8 mo for Nivolumab and Sorafenib, respectively. Although Nivolumab failed to show satisfying results as being expected in this CheckMate 459 trial, relatively long median OS, high objective response rate, and significantly lower treatment-related adverse event by Nivolumab were still inspiring as it was the first clinical trial to demonstrate the potential of immunotherapy in advanced HCC.

**Pembrolizumab:** Another PD-1 monoclonal antibody, Pembrolizumab, was approved by FDA as a second-line agent for HCC in 2018 based on the phase II KEYNOTE-224 trial[40]. Different from Nivolumab, Pembrolizumab was primarily set as a second-line agent, for the KEYNOTE 224 trial was carried out in patients who were previously treated with Sorafenib but experienced either intolerance or radiographic progression. Subsequently, the KEYNOTE-240 was launched as a randomized, placebo controlled, phase III study in patients with prior administration of Sorafenib[41]. Prolonged median OS and PFS were observed in the Pembrolizumab arm compared with the placebo arm (OS: 13.9 mo *vs* 10.6 mo, HR = 0.781, 95%CI: 0.611-0.998,  $P = 0.0238$ ; PFS: 3.0 mo *vs* 2.8 mo, HR = 0.718, 95%CI: 0.570-0.904,  $P = 0.0238$ ). However, both of OS and PFS did not reach statistical significance *per* predefined threshold, although the objective response rate was significantly higher at 16.9% and duration of response was relatively long with a median of 13.8 mo. Another phase III trial, KEYNOTE-394, is ongoing to continue the investigation of Pembrolizumab in a second-line setting after failure of Sorafenib in Asia area. Strong evidence of Pembrolizumab in survival improvement makes it necessary to support its feasibility as a second-line treatment.

To conclude, systemic treatment options for advanced HCC have substantially increased over the past years (Table 1). A question to be answered is the sequence of clinical application of the systemic agents. According to the ASCO guideline (Edition 2020)[42], Sorafenib and Lenvatinib are set as the first-line therapy. Second-line therapy options for appropriate candidates include Cabozantinib, Regorafenib, and Ramucirumab. Combination of Atezolizumab and Bevacizumab is also an option as first-line therapy while patients do not have access to Sorafenib or Lenvatinib. Potential second-line setting Pembrolizumab and Nivolumab are also reasonable options for appropriate patients following Sorafenib or Lenvatinib treatment. In a latest systematic review and network meta-analysis of 14 phase III trials[43], combination of Atezolizumab and Bevacizumab is considered the standard of care in the first-line setting. Regorafenib and Cabozantinib remain preferred options in refractory patients, with Ramucirumab as an additional option in those with AFP at 400 ng/mL or higher.

Another issue that we concern about is the efficacy of systemic agent in the local control of EHM lesions. Unfortunately, data was not available on these phase II/III trials, though the presence of EHM was identified as a prognostic factor related to poor survival of advanced HCC after systemic therapy[44-46]. Sporadic case reports were available to describe the complete remission of extrahepatic metastatic lesions after administration of systemic agents[47-53]. Further investigation remains in need to demonstrate the effect of systemic agents in the local control of EHM.

**Table 1** Data from phase III trials for first-line and second-line therapy of hepatocellular carcinoma

Drugs	Level of evidence	Absolute OS (mo)	Comparison between OS	ORR	ClinicalTrials.gov Number	
<b>First-line setting</b>						
SHARP[7] ( <i>n</i> = 602)	Sorafenib <i>vs</i> placebo	Phase III	10.7 <i>vs</i> 7.9	HR 0.69 (95%CI: 0.55-0.78)	RECIST, 2% <i>vs</i> 1%	NCT00105443
Asia-Pacific[8] ( <i>n</i> = 271)	Sorafenib <i>vs</i> placebo	Phase III	6.5 <i>vs</i> 4.2	HR 0.68 (95%CI: 0.50-0.93)	RECIST, 3.3% <i>vs</i> 1.3%	NCT00492752
REFLECT[9] ( <i>n</i> = 954)	Lenvatinib <i>vs</i> Sorafenib	Phase III	13.6 <i>vs</i> 12.3	HR 0.92 (95%CI: 0.79-1.06)	mRECIST, 24.1% <i>vs</i> 9.2%	NCT01761266
IMbrave150[36] ( <i>n</i> = 501)	Atezolizumab + Bevacizumab <i>vs</i> Sorafenib	Phase III	NE <i>vs</i> 13.2	HR 0.58 (95%CI: 0.42-0.79)	RECIST 1.1, 27% <i>vs</i> 12%; mRECIST, 33.2% <i>vs</i> 13.3%	NCT03434379
<b>Second-line setting</b>						
RESORCE[10] ( <i>n</i> = 573)	Regorafenib <i>vs</i> placebo	Phase III	10.6 <i>vs</i> 7.8	HR 0.63 (95%CI: 0.50-0.79)	mRECIST, 10.6% <i>vs</i> 4.1%	NCT01774344
CESETIAL[11] ( <i>n</i> = 707)	Cabozantinib <i>vs</i> placebo	Phase III	10.2 <i>vs</i> 8.0	HR 0.76 (95%CI: 0.63-0.92)	RECIST 1.1, 4% <i>vs</i> 0.4%	NCT01908426
REACH-2[13] ( <i>n</i> = 292)	Ramucirumab <i>vs</i> placebo	Phase III	8.5 <i>vs</i> 7.3	HR 0.71 (95%CI: 0.53-0.95)	RECIST 1.1, 4.6% <i>vs</i> 1.1%	NCT02435433
CheckMate 459 [39] ( <i>n</i> = 743)	Nivolumab <i>vs</i> Sorafenib	Phase III	16.4 <i>vs</i> 14.7	HR 0.85 (95%CI: 0.72-1.02)	RECIST, 15% <i>vs</i> 7%	NCT02576509
KEYNOTE-240 [41] ( <i>n</i> = 413)	Pembrolizumab <i>vs</i> placebo	Phase III	13.9 <i>vs</i> 13.6 <i>vs</i> 10.9	HR 0.78, 95% CI: 0.61-0.99)	RECIST 1.1, 18.3% <i>vs</i> 4.4%	NCT02702401

OS: Overall survival; ORR: Objective response rate; HR: Hazard ratio; 95%CI: 95% Confidence interval; RECIST: Response evaluation criteria in solid tumors; mRECIST: Modified RECIST for hepatocellular carcinoma; NE: Could not be evaluated.

## LOCOREGIONAL THERAPY

The presence of EHM indicates an advanced stage when locoregional management of extrahepatic lesions is no longer considered a proper option, according to the mainstream HCC guidelines. Systemic therapy, somehow, cannot completely eradicate the lesions and the prolongation in survival is still unsatisfactory. Attempts to manage extrahepatic lesions by locoregional modalities have been made in the clinical practice, in order to facilitate systemic therapy or relieve the symptoms. Given the fact that most patients with advanced HCC die of liver failure or of the progression of intrahepatic lesions, proper management of intrahepatic lesions is the key for better outcomes. However, previous studies have shown that even for patients in advanced stage HCC, locoregional control of extrahepatic lesions is still beneficial for survival in the premise of proper management of intrahepatic lesions and preserved hepatic reserve[54-57]. In this section, we focus on the locoregional treatment modalities for EHM, including surgical resection, ablation, TACE, and radiotherapy.

### Surgical resection

There is no consensus on whether surgical resection of extrahepatic lesions should be performed in patients with advanced HCC. A prospective study including 64 patients with resectable extrahepatic recurrent HCC at various sites have demonstrated that surgical resection could benefit patients with an improved survival under the condition of properly controlled intrahepatic recurrent lesions by locoregional therapies[55]. The median OS was 5.3 (95%CI: 2.5-8.8) *vs* 1.1 (95%CI: 0.8-2.3) years in the surgical and non-surgical groups, respectively ( $P < 0.001$ ). The 5-year survival rates were 55.9% and 9.1% in the surgical and non-surgical groups, respectively. Similar results were found in a retrospective study, of which the patients who had metastatic HCC and underwent extrahepatic metastasectomy had a superior median OS compared to those who were treated with Sorafenib without metastasectomy during the study period (27.2 mo *vs* 7.4 mo,  $P < 0.001$ )[57].

The lung is the most common site of extrahepatic spread from HCC. Several studies have reported the safety and efficacy of pulmonary metastasectomy of HCC following liver transplantation or liver resection, with a 5-year OS rate ranging from 27.5% to

48% [58-66]. Significant prognostic factors for pulmonary metastasectomy were identified, including remission status of intrahepatic lesions, disease-free interval, and serum level of AFP [63,67,68]. Surgical resection of metastasis to other sites including the lymph nodes, adrenal gland, and rarely spinal cord and pancreas has been reported in previous studies [69-73]. To conclude, most surgical resection of EHM was reported in pulmonary metastasis with safety, effectiveness, and survival benefit under the condition of eradication or proper control of intrahepatic lesions.

### **Ablation**

Ablation induces tumor necrosis by temperature modification (radiofrequency, microwave, laser, or cryoablation) or injection of chemical agents (most frequently ethanol). Radiofrequency ablation (RFA) is the first-line ablation for primary HCC, and the application of RFA in treatment of extrahepatic metastatic HCC to the lung, bone, adrenal glands, and other sites has been reported in previous studies [74,75]. Other ablative modalities, including percutaneous ethanol injection, microwave ablation, laser ablation, and cryoablation, have also been reported being applied in EHM [76-79].

Computed tomography-guided RFA has been demonstrated as a safe and effective therapeutic option for unresectable metastatic HCC to the lung, with reported 1- and 3-year OS rates ranging from 73.4% to 88.5%, and from 30% to 69.8%, respectively [80-82]. For lymph node metastases, especially to retroperitoneal space which is considered unresectable, minimally-invasive ablation would be an optimal option [83, 84]. For bone metastases from HCC, pain relief could be achieved by RFA in most patients, regardless of a poor 3-year OS rate at 10.0% [85,86]. Moreover, according to experience from our center, management of metastasis to the adrenal gland by RFA could achieve a high technical success rate and low complication rate of 86.4% and 4.5%, respectively [87].

To conclude, RFA has demonstrated several advantages, including high technical success rate, obvious relief of symptoms, minimal invasiveness, and safety, which makes it an option of alternative treatment in patients who are not potential candidates to surgery.

### **Radiotherapy**

Radiation therapy has been shown to be adaptable for various stages of HCC [88]. For those with extrahepatic lesions spreading to sites where invasive modalities such as surgical resection and ablation are not available, the non-invasive radiotherapy has shown its safety and efficacy with palliative intention. A study enrolling 12 patients with pulmonary metastatic HCC has shown that significant symptom relief (completely or partially) in most patients with an objective response of 76.9% after external beam radiotherapy was achieved, although another study has demonstrated that symptomatic radiation pneumonitis is a common complication with a morbidity of 65.2% [89,90]. For lymph node metastasis, radiotherapy could palliate symptoms with a pooled response rate of 73.1% [91]. Delivered by intensity-modulated radiotherapy (IMRT), excellent local control of metastatic lymph nodes was achieved with minimal toxicity, with 1-year local progression-free rate, 1-year PFS rate, and 1-year OS rate of 100%, 46.7% ± 12.9%, and 73.3% ± 11.4%, respectively [92]. Compared with non-imaging-guided IMRT, image-guided IMRT resulted in a slightly higher delivery dose and showed a superior short-term survival and local control of lymph node metastasis [93]. A maximal dose prescription of 50 Gy was recommended for palliative purposes to relieve symptoms and minimize radiotherapy-induced morbidity [94-96]. For adrenal gland metastasis, Yuan *et al* [97] and Jung *et al* [98] reported an objective response of 55.6% and 38.3%, and 1-year OS rates of 59.9% and 53.1%, respectively, while Zhou *et al* [99] reported a 100% pain relief after completion of radiotherapy with reasonable safety. For bone metastasis, the pain relief rate ranging from 77% to 96.7% has been reported, although treatment-related lymphopenia associated with a poor survival in patients receiving radiotherapy for bone metastasis from HCC needed to be attended [100-103]. For brain metastasis which is rare with an extremely poor prognosis (median OS around 3 mo), palliative treatments using whole-brain radiotherapy stereotactic radiosurgery might improve survival by controlling intracranial tumor and preventing intracranial hemorrhage [104-107].

To conclude, radiotherapy has attracted increasing attention in recent years as a treatment modality for HCC. For extrahepatic lesions, the application of radiotherapy was for palliative purposes such as local tumor control and pain relief. Therefore, dose prescription should be limited to avoid adverse treatment-related events.

## TACE

The application of TACE in extrahepatic lesions of HCC was, less reported in previous studies, involving metastatic sites of the lung, lymph nodes, and adrenal gland[108-110]. We assume that the reason why TACE was less investigated in extrahepatic lesions is that TACE procedure is technically difficult, since the feeding arteries might be too thin to be accessed.

Since most patients with advanced HCC would die of liver failure due to intrahepatic progression, locoregional management of EHM is adopted for the palliative purpose in most cases. Although some studies have demonstrated the potential survival benefit by locoregional control of EHM, patients from such studies were carefully selected with strict inclusion criteria of preserved liver function (*e.g.*, Child-Pugh grade A), oligometastatic lesion to a single organ, and absence or remission of intrahepatic lesions. Moreover, most studies were in small sample size and retrospective with unavoidable bias. Therefore, the efficacy of locoregional therapy in prolonging survival of advanced HCC is still pending.

## MULTIDISCIPLINARY THERAPY

Whether patients with advanced HCC would benefit from combination of systemic therapy and locoregional management of EHM is still under debate. Compared with Sorafenib monotherapy, Sorafenib in combination with radiotherapy targeting EHM achieved better outcomes including median PFS of EHM or macrovascular invasion (13.5 mo *vs* 3.3 mo,  $P < 0.01$ ), PFS of whole lesions (10.6 mo *vs* 3.5 mo,  $P < 0.01$ ), and OS (31.2 mo *vs* 12.1 mo,  $P < 0.01$ )[111]. A study including HCC patients with pulmonary oligometastases showed that Sorafenib combined with regional therapies may be associated with a prolonged OS (18.37 mo *vs* 7.13 mo,  $P = 0.002$ ) and TTP (2.93 mo *vs* 2.23 mo,  $P = 0.004$ ), compared with Sorafenib monotherapy[112]. Another study showed that stereotactic body radiotherapy (SBRT) was associated with encouraging outcomes for patients with macrovascular invasion especially in those patients who received Sorafenib after radiotherapy, with a median OS of 37.9 mo[113]. A large, multicenter, open-label, randomized controlled trial prospective clinic trial (Chinese Clinical Trial Registration No. ChiCTR1900027102) is ongoing, with the aim of evaluating the efficacy and safety of SBRT combined with Camrelizumab (a PD-1 inhibitor) and Apatinib (a VEGFR inhibitor) in HCC patients with portal vein tumor thrombosis[114]. The feasibility and efficacy of combining systemic and locoregional therapy targeting EHM need to be verified with strong evidence supported by large clinical trials, although primary results from previous studies seem to be promising.

## CONCLUSION

Systemic therapy remains the standard treatment modality for patients with EHM of HCC. A rapid expansion of therapeutic options for advanced HCC has been witnessed in recent years. Nowadays, there are two approved agents (Sorafenib and Lenvatinib) as the first-line options and several agents (Regorafenib, Cabozantinib, Ramucirumab, Nivolumab, and Pembrolizumab) as the second-line options. Promising results from clinical trial of immunotherapy combining Atezolizumab and Bevacizumab may reshape the treatment landscape. Aggressive locoregional management of EHM and multidisciplinary therapy combining systemic and locoregional management of EHM have demonstrated the safety and efficacy in symptom relief and potential benefit in survival. Large, multicenter clinical trials are warranted to further verify such findings.

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