**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 64632

**Manuscript Type:** REVIEW

**Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis**

Long HY *et al*. Extrahepatic metastasis of HCC

Hai-Yi Long, Tong-Yi Huang, Xiao-Yan Xie, Jian-Ting Long, Bao-Xian Liu

**Hai-Yi Long, Tong-Yi Huang, Xiao-Yan Xie, Bao-Xian Liu,** Department of Medical Ultrasonics, Institute of Diagnostic and Interventional Ultrasound, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

**Jian-Ting Long,** Department of Medical Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

**Author contributions:** Long HY and Huang TY were involved in review design and drafting of the manuscript; Xie XY and Long JT were involved in the critical revision of the manuscript; Liu BX was involved in review design and critical revision of the manuscript.

**Supported by** Natural Science Foundation of Guangdong Province of China, No. 2018A0303130165; and Science and Technology Program of Guangzhou, No. 201904010046.

**Corresponding author: Bao-Xian Liu, MD, PhD, Assistant Professor,** Department of Medical Ultrasonics, Institute of Diagnostic and Interventional Ultrasound, the First Affiliated Hospital of Sun Yat-Sen University, No. 58 Zhongshan Road 2, Guangzhou 510080, Guangdong Province, China. liubxian@mail.sysu.edu.cn

**Received:** February 21, 2021

**Revised:** April 20, 2021

**Accepted:** May 25, 2021

**Published online:**

**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

Long HY, Huang TY, Xie XY, Long JT, Liu BX. Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis. *World J Clin Cases* 2021; In press

**Core Tip:** The presence of extrahepatic metastasis (EHM) indicates an advanced stage of hepatocellular carcinoma (HCC), for which systemic therapy serves as the standard treatment modality. Efforts have been made to demonstrate the efficacy of locoregional management of EHM in symptom relief and potential benefit for overall survival. This review provides a summary of recent updates of the systemic agents for advanced HCC, with an emphasis on aggressive locoregional management of EHM by various treatment modalities.

**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-angiogenetic agent Ramucirumab is a potential second-line option for patients with high α-fetoprotein (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 trail, 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: 0.55-088). 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 trail 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 immune-oncological 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.

**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.

**REFERENCES**

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71**: 209–249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Kanda M**, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, Imamura J, Goto T, Yoshida H, Hamamura K, Obi S, Kanai F, Shiina S, Omata M. Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors. *Liver Int* 2008; **28**: 1256-1263 [PMID: 18710423 DOI: 10.1111/j.1478-3231.2008.01864.x]

3 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

4 **Uchino K**, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M, Yoshida H, Koike K. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer* 2011; **117**: 4475-4483 [PMID: 21437884 DOI: 10.1002/cncr.25960]

5 **Lee JI**, Kim JK, Kim DY, Ahn SH, Park JY, Kim SU, Kim BK, Han KH, Lee KS. Prognosis of hepatocellular carcinoma patients with extrahepatic metastasis and the controllability of intrahepatic lesions. *Clin Exp Metastasis* 2014; **31**: 475-482 [PMID: 24496959 DOI: 10.1007/s10585-014-9641-x]

6 **Jung SM**, Jang JW, You CR, Yoo SH, Kwon JH, Bae SH, Choi JY, Yoon SK, Chung KW, Kay CS, Jung HS. Role of intrahepatic tumor control in the prognosis of patients with hepatocellular carcinoma and extrahepatic metastases. *J Gastroenterol Hepatol* 2012; **27**: 684-689 [PMID: 21916984 DOI: 10.1111/j.1440-1746.2011.06917.x]

7 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

8 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

9 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib *vs* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

10 **Bruix J**, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/S0140-6736(16)32453-9]

11 **Abou-Alfa GK**, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klümpen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018; **379**: 54-63 [PMID: 29972759 DOI: 10.1056/NEJMoa1717002]

12 **Zhu AX**, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chung HC, Baron AD, Pfiffer TE, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Schwartz JD, Kudo M; REACH Trial Investigators. Ramucirumab *vs* placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015; **16**: 859-870 [PMID: 26095784 DOI: 10.1016/S1470-2045(15)00050-9]

13 **Zhu AX**, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, Rau KM, Motomura K, Ohno I, Merle P, Daniele B, Shin DB, Gerken G, Borg C, Hiriart JB, Okusaka T, Morimoto M, Hsu Y, Abada PB, Kudo M; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20**: 282-296 [PMID: 30665869 DOI: 10.1016/S1470-2045(18)30937-9]

14 **Ikeda K**, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, Tamai T, Suzuki T, Hisai T, Hayato S, Okita K, Kumada H. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol* 2017; **52**: 512-519 [PMID: 27704266 DOI: 10.1007/s00535-016-1263-4]

15 **Kudo M**, Finn RS, Qin SK, Han KH, Ikeda K, Cheng AL, Piscaglia F, Ueshima K, Aikata H, Vogel A, Lopez C, Pracht M, Meng ZQ, Daniele B, Park JW, Palmer DH, Dutcus CE, Tamai T, Saito K, Lencioni R. Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT). *J Clin Oncol* 2019; **37**: 2 [DOI: 10.1200/JCO.2019.37.4\_suppl.186]

16 **Kuzuya T**, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T, Fujishiro M. Sorafenib *vs*. Lenvatinib as First-line Therapy for Advanced Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis. *Anticancer Res* 2020; **40**: 2283-2290 [PMID: 32234927 DOI: 10.21873/anticanres.14193]

17 **Maruta S**, Ogasawara S, Ooka Y, Obu M, Inoue M, Itokawa N, Haga Y, Seki A, Okabe S, Azemoto R, Itobayashi E, Atsukawa M, Sugiura N, Mizumoto H, Koroki K, Kanayama K, Kanzaki H, Kobayashi K, Kiyono S, Nakamura M, Kanogawa N, Saito T, Kondo T, Suzuki E, Nakamoto S, Tawada A, Chiba T, Arai M, Kanda T, Maruyama H, Kato N. Potential of Lenvatinib for an Expanded Indication from the REFLECT Trial in Patients with Advanced Hepatocellular Carcinoma. *Liver Cancer* 2020; **9**: 382-396 [PMID: 32999866 DOI: 10.1159/000507022]

18 **Chuma M**, Uojima H, Hiraoka A, Kobayashi S, Toyoda H, Tada T, Hidaka H, Iwabuchi S, Numata K, Itobayashi E, Itokawa N, Kariyama K, Ohama H, Hattori N, Hirose S, Shibata H, Tani J, Imai M, Tajiri K, Moriya S, Wada N, Iwasaki S, Fukushima T, Ueno M, Yasuda S, Atsukawa M, Nouso K, Fukunishi S, Watanabe T, Ishikawa T, Nakamura S, Morimoto M, Kagawa T, Sakamoto M, Kumada T, Maeda S. Analysis of efficacy of lenvatinib treatment in highly advanced hepatocellular carcinoma with tumor thrombus in the main trunk of the portal vein or tumor with more than 50% liver occupation: A multicenter analysis. *Hepatol Res* 2021; **51**: 201-215 [PMID: 33270323 DOI: 10.1111/hepr.13592]

19 **Llovet JM**, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; **31**: 3509-3516 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]

20 **Zhu AX**, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, Poon RT, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 2014; **312**: 57-67 [PMID: 25058218 DOI: 10.1001/jama.2014.7189]

21 **Abou-Alfa GK**, Qin S, Ryoo BY, Lu SN, Yen CJ, Feng YH, Lim HY, Izzo F, Colombo M, Sarker D, Bolondi L, Vaccaro G, Harris WP, Chen Z, Hubner RA, Meyer T, Sun W, Harding JJ, Hollywood EM, Ma J, Wan PJ, Ly M, Bomalaski J, Johnston A, Lin CC, Chao Y, Chen LT. Phase III randomized study of second line ADI-PEG 20 plus best supportive care *vs* placebo plus best supportive care in patients with advanced hepatocellular carcinoma. *Ann Oncol* 2018; **29**: 1402-1408 [PMID: 29659672 DOI: 10.1093/annonc/mdy101]

22 **Finn RS**, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Gerolami R, Caparello C, Cabrera R, Chang C, Sun W, LeBerre MA, Baumhauer A, Meinhardt G, Bruix J. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J Hepatol* 2018; **69**: 353-358 [PMID: 29704513 DOI: 10.1016/j.jhep.2018.04.010]

23 **Ogasawara S**, Ooka Y, Itokawa N, Inoue M, Okabe S, Seki A, Haga Y, Obu M, Atsukawa M, Itobayashi E, Mizumoto H, Sugiura N, Azemoto R, Kanayama K, Kanzaki H, Maruta S, Maeda T, Kusakabe Y, Yokoyama M, Kobayashi K, Kiyono S, Nakamura M, Saito T, Suzuki E, Nakamoto S, Yasui S, Tawada A, Chiba T, Arai M, Kanda T, Maruyama H, Kato N. Sequential therapy with sorafenib and regorafenib for advanced hepatocellular carcinoma: a multicenter retrospective study in Japan. *Invest New Drugs* 2020; **38**: 172-180 [PMID: 31172442 DOI: 10.1007/s10637-019-00801-8]

24 **Yoo C**, Park JW, Kim YJ, Kim DY, Yu SJ, Lim TS, Lee SJ, Ryoo BY, Lim HY. Multicenter retrospective analysis of the safety and efficacy of regorafenib after progression on sorafenib in Korean patients with hepatocellular carcinoma. *Invest New Drugs* 2019; **37**: 567-572 [PMID: 30523474 DOI: 10.1007/s10637-018-0707-5]

25 **Kim HD**, Bang Y, Lee MA, Kim JW, Kim JH, Chon HJ, Kang B, Kang MJ, Kim I, Cheon J, Hwang JE, Kang JH, Byeon S, Hong JY, Ryoo BY, Lim HY, Yoo C. Regorafenib in patients with advanced Child-Pugh B hepatocellular carcinoma: A multicentre retrospective study. *Liver Int* 2020; **40**: 2544-2552 [PMID: 32563213 DOI: 10.1111/liv.14573]

26 **Kelley RK**, Verslype C, Cohn AL, Yang TS, Su WC, Burris H, Braiteh F, Vogelzang N, Spira A, Foster P, Lee Y, Van Cutsem E. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol* 2017; **28**: 528-534 [PMID: 28426123 DOI: 10.1093/annonc/mdw651]

27 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

28 **Kelley RK**, Mollon P, Blanc JF, Daniele B, Yau T, Cheng AL, Valcheva V, Marteau F, Guerra I, Abou-Alfa GK. Comparative Efficacy of Cabozantinib and Regorafenib for Advanced Hepatocellular Carcinoma. *Adv Ther* 2020; **37**: 2678-2695 [PMID: 32424805 DOI: 10.1007/s12325-020-01378-y]

29 **Gilabert M**, Raoul JL. Potential of ramucirumab in treating hepatocellular carcinoma patients with elevated baseline alpha-fetoprotein. *J Hepatocell Carcinoma* 2018; **5**: 91-98 [PMID: 30464931 DOI: 10.2147/JHC.S157413]

30 **Kudo M**, Okusaka T, Motomura K, Ohno I, Morimoto M, Seo S, Wada Y, Sato S, Yamashita T, Furukawa M, Aramaki T, Nadano S, Ohkawa K, Fujii H, Kudo T, Furuse J, Takai H, Homma G, Yoshikawa R, Zhu AX. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP) following first-line sorafenib: Pooled efficacy and safety in Japanese patients across two global randomized phase III studies (REACH-2 and REACH). *J Clin Oncol* 2019; **37**: 320-320 [DOI: 10.1200/JCO.2019.37.4\_suppl.320]

31 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]

32 **Finn RS**, Bentley G, Britten CD, Amado R, Busuttil RW. Targeting vascular endothelial growth factor with the monoclonal antibody bevacizumab inhibits human hepatocellular carcinoma cells growing in an orthotopic mouse model. *Liver Int* 2009; **29**: 284-290 [PMID: 18482274 DOI: 10.1111/j.1478-3231.2008.01762.x]

33 **Siegel AB**, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, Chen H, Clark-Garvey S, Weinberg A, Mandeli J, Christos P, Mazumdar M, Popa E, Brown RS Jr, Rafii S, Schwartz JD. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008; **26**: 2992-2998 [PMID: 18565886 DOI: 10.1200/JCO.2007.15.9947]

34 **Boige V**, Malka D, Bourredjem A, Dromain C, Baey C, Jacques N, Pignon JP, Vimond N, Bouvet-Forteau N, De Baere T, Ducreux M, Farace F. Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. *Oncologist* 2012; **17**: 1063-1072 [PMID: 22707516 DOI: 10.1634/theoncologist.2011-0465]

35 **Lee M**, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, Hack S, Spahn J, Liu B, Abdullah H, He R, Lee KH. Randomised efficacy and safety results for atezolizumab (Atezo) plus bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). *Ann Oncol* 2019: 875

36 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]

37 **Casak SJ**, Donoghue M, Fashoyin-Aje L, Jiang X, Rodriguez L, Shen YL, Xu Y, Jiang X, Liu J, Zhao H, Pierce WF, Mehta S, Goldberg KB, Theoret MR, Kluetz PG, Pazdur R, Lemery SJ. FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma. *Clin Cancer Res* 2021; **27**: 1836-1841 [PMID: 33139264 DOI: 10.1158/1078-0432.CCR-20-3407]

38 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

39 **Yau T**, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, Kudo M, Han KH, Harding JJ, Merle P, Rosmorduc O, Wyrwicz L, Schott E, Choo SP, Kelley RK, Begic D, Chen G, Neely J, Anderson J, Sangro B. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) *vs* sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol* 2019: 874

40 **Zhu AX**, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

41 **Finn RS**, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, Breder V, Edeline J, Chao Y, Ogasawara S, Yau T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Siegel AB, Zhu AX, Cheng AL; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2020; **38**: 193-202 [PMID: 31790344 DOI: 10.1200/JCO.19.01307]

42 **Gordan JD**, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, Goff L, Gupta S, Guy J, Harris WP, Iyer R, Jaiyesimi I, Jhawer M, Karippot A, Kaseb AO, Kelley RK, Knox JJ, Kortmansky J, Leaf A, Remak WM, Shroff RT, Sohal DPS, Taddei TH, Venepalli NK, Wilson A, Zhu AX, Rose MG. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. *J Clin Oncol* 2020; **38**: 4317-4345 [PMID: 33197225 DOI: 10.1200/JCO.20.02672]

43 **Sonbol MB**, Riaz IB, Naqvi SAA, Almquist DR, Mina S, Almasri J, Shah S, Almader-Douglas D, Uson Junior PLS, Mahipal A, Ma WW, Jin Z, Mody K, Starr J, Borad MJ, Ahn DH, Murad MH, Bekaii-Saab T. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. *JAMA Oncol* 2020; **6**: e204930 [PMID: 33090186 DOI: 10.1001/jamaoncol.2020.4930]

44 **Yau T**, Chan P, Ng KK, Chok SH, Cheung TT, Fan ST, Poon RT. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. *Cancer* 2009; **115**: 428-436 [PMID: 19107763 DOI: 10.1002/cncr.24029]

45 **Bruix J**, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. *J Hepatol* 2017; **67**: 999-1008 [PMID: 28687477 DOI: 10.1016/j.jhep.2017.06.026]

46 **Berhane S**, Fox R, García-Fiñana M, Cucchetti A, Johnson P. Using prognostic and predictive clinical features to make personalised survival prediction in advanced hepatocellular carcinoma patients undergoing sorafenib treatment. *Br J Cancer* 2019; **121**: 117-124 [PMID: 31182766 DOI: 10.1038/s41416-019-0488-4]

47 **Kudo M**, Ueshima K. Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma and implication of many complete remission cases in Japan. *Oncology* 2010; **78 Suppl 1**: 154-166 [PMID: 20616599 DOI: 10.1159/000315245]

48 **Park JG**. Long-term outcomes of patients with advanced hepatocellular carcinoma who achieved complete remission after sorafenib therapy. *Clin Mol Hepatol* 2015; **21**: 287-294 [PMID: 26527250 DOI: 10.3350/cmh.2015.21.3.287]

49 **Inuzuka T**, Nishikawa H, Sekikawa A, Takeda H, Henmi S, Sakamoto A, Saito S, Kita R, Kimura T, Osaki Y, Kudo M. Complete response of advanced hepatocellular carcinoma with multiple lung metastases treated with sorafenib: a case report. *Oncology* 2011; **81 Suppl 1**: 152-157 [PMID: 22212950 DOI: 10.1159/000333279]

50 **Mizukami H**, Kagawa T, Arase Y, Nakahara F, Tsuruya K, Anzai K, Hirose S, Shiraishi K, Shomura M, Koizumi J, Tobita K, Mine T. Complete response after short-term sorafenib treatment in a patient with lymph node metastasis of hepatocellular carcinoma. *Case Rep Oncol* 2012; **5**: 380-384 [PMID: 23525021 DOI: 10.1159/000341259]

51 **Hagihara A**, Teranishi Y, Kawamura E, Fujii H, Iwai S, Morikawa H, Enomoto M, Tamori A, Kawada N. A complete response induced by 21-day sorafenib therapy in a patient with advanced hepatocellular carcinoma. *Intern Med* 2013; **52**: 1589-1592 [PMID: 23857091 DOI: 10.2169/internalmedicine.52.9340]

52 **Katafuchi E**, Takami Y, Wada Y, Tateishi M, Ryu T, Mikagi K, Saitsu H. Long-Term Maintenance of Complete Response after Sorafenib Treatment for Multiple Lung Metastases from Hepatocellular Carcinoma. *Case Rep Gastroenterol* 2015; **9**: 285-290 [PMID: 26351418 DOI: 10.1159/000438746]

53 **Zhu SG**, Li HB, Yuan ZN, Liu W, Yang Q, Cheng Y, Wang WJ, Wang GY, Li H. Achievement of complete response to nivolumab in a patient with advanced sarcomatoid hepatocellular carcinoma: A case report. *World J Gastrointest Oncol* 2020; **12**: 1209-1215 [PMID: 33133387 DOI: 10.4251/wjgo.v12.i10.1209]

54 **Nakagawa T**, Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Matsushita M, Todo S. Pulmonary resection for metastases from hepatocellular carcinoma: factors influencing prognosis. *J Thorac Cardiovasc Surg* 2006; **131**: 1248-1254 [PMID: 16733153 DOI: 10.1016/j.jtcvs.2006.02.009]

55 **Midorikawa Y**, Takayama T, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Teramoto K, Yoshida N, Kobayashi N, Tsuji S, Higaki T. Favorable outcomes of surgical resection for extrahepatic recurrent hepatocellular carcinoma. *Hepatol Res* 2020; **50**: 978-984 [PMID: 32573905 DOI: 10.1111/hepr.13526]

56 **Hirokawa F**, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, Inoue Y, Uchiyama K. Surgical treatment of extrahepatic recurrence of hepatocellular carcinoma. *Langenbecks Arch Surg* 2014; **399**: 1057-1064 [PMID: 25030500 DOI: 10.1007/s00423-014-1230-6]

57 **Berger Y**, Spivack JH, Heskel M, Aycart SN, Labow DM, Sarpel U. Extrahepatic metastasectomy for hepatocellular carcinoma: Predictors of long-term survival. *J Surg Oncol* 2017; **115**: 505-506 [PMID: 28334437 DOI: 10.1002/jso.24555]

58 **Kitano K**, Murayama T, Sakamoto M, Nagayama K, Ueno K, Murakawa T, Nakajima J. Outcome and survival analysis of pulmonary metastasectomy for hepatocellular carcinoma. *Eur J Cardiothorac Surg* 2012; **41**: 376-382 [PMID: 21727012 DOI: 10.1016/j.ejcts.2011.05.052]

59 **Yoon YS**, Kim HK, Kim J, Choi YS, Shim YM, Paik SW, Kim K. Long-term survival and prognostic factors after pulmonary metastasectomy in hepatocellular carcinoma. *Ann Surg Oncol* 2010; **17**: 2795-2801 [PMID: 20517683 DOI: 10.1245/s10434-010-1073-5]

60 **Wang L**, Ye G, Zhan C, Sun F, Lin Z, Jiang W, Wang Q. Clinical Factors Predictive of a Better Prognosis of Pulmonary Metastasectomy for Hepatocellular Carcinoma. *Ann Thorac Surg* 2019; **108**: 1685-1691 [PMID: 31445050 DOI: 10.1016/j.athoracsur.2019.06.086]

61 **Mizuguchi S**, Nishiyama N, Izumi N, Tsukioka T, Komatsu H, Iwata T, Tanaka S, Takemura S, Kubo S. Clinical Significance of Multiple Pulmonary Metastasectomy for Hepatocellular Carcinoma. *World J Surg* 2016; **40**: 380-387 [PMID: 26306890 DOI: 10.1007/s00268-015-3213-3]

62 **Invenizzi F**, Iavarone M, Donato MF, Mazzucco A, Torre M, Conforti S, Rimessi A, Zavaglia C, Schiavon M, Comacchio G, Rea F, Boetto R, Cillo U, Dondossola D, De Carlis L, Lampertico P, Nosotti M, Mendogni P. Pulmonary Resection for Metastasis of Hepatocellular Carcinoma Recurring After Liver Transplant: An Italian Multicenter Experience. *Front Oncol* 2020; **10**: 381 [PMID: 32351877 DOI: 10.3389/fonc.2020.00381]

63 **Ohba T**, Yano T, Yoshida T, Kawano D, Tsukamoto S, Shoji F, Taketomi A, Saitsu H, Takeo S, Maehara Y. Results of a surgical resection of pulmonary metastasis from hepatocellular carcinoma: prognostic impact of the preoperative serum alpha-fetoprotein level. *Surg Today* 2012; **42**: 526-531 [PMID: 22173647 DOI: 10.1007/s00595-011-0090-8]

64 **Hwang S**, Kim YH, Kim DK, Ahn CS, Moon DB, Kim KH, Ha TY, Song GW, Jung DH, Kim HR, Park GC, Namgoong JM, Yoon SY, Jung SW, Park SI, Lee SG. Resection of pulmonary metastases from hepatocellular carcinoma following liver transplantation. *World J Surg* 2012; **36**: 1592-1602 [PMID: 22411088 DOI: 10.1007/s00268-012-1533-0]

65 **Kuo SW**, Chang YL, Huang PM, Hsu HH, Chen JS, Lee JM, Lee PH, Lee YC. Prognostic factors for pulmonary metastasectomy in hepatocellular carcinoma. *Ann Surg Oncol* 2007; **14**: 992-997 [PMID: 17151787 DOI: 10.1245/s10434-006-9217-3]

66 **Wang C**, Yang L, Liang Z, Liu Y, Liu S. Long-Term Survival and Prognostic Factors of Pulmonary Metastasectomy in Liver Cancer: A Systematic Review and Meta-Analysis. *World J Surg* 2018; **42**: 2153-2163 [PMID: 29435629 DOI: 10.1007/s00268-017-4431-7]

67 **Kuo TM**, Chang KM, Cheng TI, Kao KJ. Clinical Factors Predicting Better Survival Outcome for Pulmonary Metastasectomy of Hepatocellular Carcinoma. *Liver Cancer* 2017; **6**: 297-306 [PMID: 29234633 DOI: 10.1159/000477134]

68 **Takahashi Y**, Ikeda N, Nakajima J, Sawabata N, Chida M, Horio H, Okumura S, Kawamura M; Metastatic Lung Tumor Study Group of Japan. Prognostic Analysis of Surgical Resection for Pulmonary Metastasis from Hepatocellular Carcinoma. *World J Surg* 2016; **40**: 2178-2185 [PMID: 27255943 DOI: 10.1007/s00268-016-3580-4]

69 **Hornstein I**, Schwarz C, Ebbing S, Hoppe-Lotichius M, Otto G, Lang H, Musholt TJ. Surgical resection of metastases to the adrenal gland: a single center experience. *Langenbecks Arch Surg* 2015; **400**: 333-339 [PMID: 25726026 DOI: 10.1007/s00423-015-1293-z]

70 **Ikegami T**, Yoshizumi T, Kawasaki J, Nagatsu A, Uchiyama H, Harada N, Harimoto N, Itoh S, Motomura T, Soejima Y, Maehara Y. Surgical Resection for Lymph Node Metastasis After Liver Transplantation for Hepatocellular Carcinoma. *Anticancer Res* 2017; **37**: 891-895 [PMID: 28179348 DOI: 10.21873/anticanres.11395]

71 **Kim CH**, Chung CK, Jahng TA, Kim HJ. Surgical outcome of spinal hepatocellular carcinoma metastases. *Neurosurgery* 2011; **68**: 888-896 [PMID: 21221023 DOI: 10.1227/NEU.0b013e3182098c18]

72 **Staubitz JI**, Hoppe-Lotichius M, Baumgart J, Mittler J, Lang H, Musholt TJ. Survival After Adrenalectomy for Metastatic Hepatocellular Carcinoma: A 25-year Institutional Experience. *World J Surg* 2021; **45**: 1118-1125 [PMID: 33354731 DOI: 10.1007/s00268-020-05909-0]

73 **Woo SM**, Park JW, Han SS, Choi JI, Lee WJ, Park SJ, Hong EK, Kim CM. Isolated pancreatic metastasis of hepatocellular carcinoma after curative resection. *World J Gastrointest Oncol* 2010; **2**: 209-212 [PMID: 21160600 DOI: 10.4251/wjgo.v2.i4.209]

74 **Doreille A**, N'Kontchou G, Halimi A, Bouhafs F, Coderc E, Sellier N, Seror O. Percutaneous treatment of extrahepatic recurrence of hepatocellular carcinoma. *Diagn Interv Imaging* 2016; **97**: 1117-1123 [PMID: 27138073 DOI: 10.1016/j.diii.2015.11.020]

75 **Mu L**, Sun L, Pan T, Lyu N, Li S, Li X, Wang J, Xie Q, Deng H, Zheng L, Peng J, Shen L, Fan W, Wu P, Zhao M. Percutaneous CT-guided radiofrequency ablation for patients with extrahepatic oligometastases of hepatocellular carcinoma: long-term results. *Int J Hyperthermia* 2018; **34**: 59-67 [PMID: 28540809 DOI: 10.1080/02656736.2017.1318332]

76 **Giovannini M**. Percutaneous alcohol ablation for liver metastasis. *Semin Oncol* 2002; **29**: 192-195 [PMID: 11951217 DOI: 10.1053/sonc.2002.31677]

77 **Gao Y**, Zheng L, Liang P, Cheng Z, Han Z, Tan SL, Yu X. Evaluating the efficacy and safety of ultrasound-guided percutaneous microwave ablation for the treatment of adrenal metastasis. *J Cancer Res Ther* 2020; **16**: 1088-1092 [PMID: 33004752 DOI: 10.4103/jcrt.JCRT\_1119\_19]

78 **Long H**, Zhuang B, Huang G, Li X, Lin M, Long J, Xie X, Liu B. Safety and Local Efficacy of Laser Ablation for the Extrahepatic Metastasis of Hepatocellular Carcinoma: An Available Treatment Strategy. *Coatings* 2020; **10**: 951 [DOI:10.3390/coatings10100951]

79 **Ma J**, Wang F, Zhang W, Wang L, Yang X, Qian Y, Huang J, Wang J, Yang J. Percutaneous cryoablation for the treatment of liver cancer at special sites: an assessment of efficacy and safety. *Quant Imaging Med Surg* 2019; **9**: 1948-1957 [PMID: 31929967 DOI: 10.21037/qims.2019.11.12]

80 **Lassandro G**, Picchi SG, Bianco A, Di Costanzo G, Coppola A, Ierardi AM, Lassandro F. Effectiveness and safety in radiofrequency ablation of pulmonary metastases from HCC: a five years study. *Med Oncol* 2020; **37**: 25 [PMID: 32166529 DOI: 10.1007/s12032-020-01352-2]

81 **Hiraki T**, Yamakado K, Ikeda O, Matsuoka T, Kaminou T, Yamagami T, Gobara H, Mimura H, Kawanaka K, Takeda K, Yamashita Y, Inoue Y, Ogawa T, Nishimura T, Kanazawa S. Percutaneous radiofrequency ablation for pulmonary metastases from hepatocellular carcinoma: results of a multicenter study in Japan. *J Vasc Interv Radiol* 2011; **22**: 741-748 [PMID: 21531575 DOI: 10.1016/j.jvir.2011.02.030]

82 **Li X**, Wang J, Li W, Huang Z, Fan W, Chen Y, Shen L, Pan T, Wu P, Zhao M. Percutaneous CT-guided radiofrequency ablation for unresectable hepatocellular carcinoma pulmonary metastases. *Int J Hyperthermia* 2012; **28**: 721-728 [PMID: 23153217 DOI: 10.3109/02656736.2012.736669]

83 **Gao F**, Gu Y, Huang J, Zhao M, Wu P. Radiofrequency ablation of retroperitoneal metastatic lymph nodes from hepatocellular carcinoma. *Acad Radiol* 2012; **19**: 1035-1040 [PMID: 22591723 DOI: 10.1016/j.acra.2012.04.003]

84 **Mou Y**, Zhao Q, Zhong L, Chen F, Jiang T. Preliminary results of ultrasound-guided laser ablation for unresectable metastases to retroperitoneal and hepatic portal lymph nodes. *World J Surg Oncol* 2016; **14**: 165 [PMID: 27338093 DOI: 10.1186/s12957-016-0917-2]

85 **Kashima M**, Yamakado K, Takaki H, Kaminou T, Tanigawa N, Nakatsuka A, Takeda K. Radiofrequency ablation for the treatment of bone metastases from hepatocellular carcinoma. *AJR Am J Roentgenol* 2010; **194**: 536-541 [PMID: 20093621 DOI: 10.2214/AJR.09.2975]

86 **Carrafiello G**, Laganà D, Ianniello A, Nicotera P, Fontana F, Dizonno M, Cuffari S, Fugazzola C. Radiofrequency thermal ablation for pain control in patients with single painful bone metastasis from hepatocellular carcinoma. *Eur J Radiol* 2009; **71**: 363-368 [PMID: 18514456 DOI: 10.1016/j.ejrad.2008.04.019]

87 **Huang J**, Xie X, Lin J, Wang W, Zhang X, Liu M, Li X, Huang G, Liu B, Xie X. Percutaneous radiofrequency ablation of adrenal metastases from hepatocellular carcinoma: a single-center experience. *Cancer Imaging* 2019; **19**: 44 [PMID: 31242934 DOI: 10.1186/s40644-019-0231-7]

88 **Kondo Y**, Kimura O, Shimosegawa T. Radiation therapy has been shown to be adaptable for various stages of hepatocellular carcinoma. *World J Gastroenterol* 2015; **21**: 94-101 [PMID: 25574082 DOI: 10.3748/wjg.v21.i1.94]

89 **Jiang W**, Zeng ZC, Zhang JY, Fan J, Zeng MS, Zhou J. Palliative radiation therapy for pulmonary metastases from hepatocellular carcinoma. *Clin Exp Metastasis* 2012; **29**: 197-205 [PMID: 22173728 DOI: 10.1007/s10585-011-9442-4]

90 **Lin G**, Xiao H, Zeng Z, Xu Z, He J, Sun T, Liu J, Guo G, Ji W, Hu Y. Constraints for symptomatic radiation pneumonitis of helical tomotherapy hypofractionated simultaneous multitarget radiotherapy for pulmonary metastasis from hepatocellular carcinoma. *Radiother Oncol* 2017; **123**: 246-250 [PMID: 28314468 DOI: 10.1016/j.radonc.2017.02.015]

91 **Rim CH**, Kim CY, Yang DS, Yoon WS. The role of external beam radiotherapy for hepatocellular carcinoma patients with lymph node metastasis: a meta-analysis of observational studies. *Cancer Manag Res* 2018; **10**: 3305-3315 [PMID: 30233246 DOI: 10.2147/CMAR.S175703]

92 **Matoba M**, Tsuchiya H, Kondo T, Ota K. Stereotactic body radiotherapy delivered with IMRT for oligometastatic regional lymph node metastases in hepatocellular carcinoma: a single-institutional study. *J Radiat Res* 2020; **61**: 776-783 [PMID: 32845298 DOI: 10.1093/jrr/rraa067]

93 **Zhang H**, Chen Y, Hu Y, Yang P, Wang B, Zhang J, Sun J, Zeng Z. Image-guided intensity-modulated radiotherapy improves short-term survival for abdominal lymph node metastases from hepatocellular carcinoma. *Ann Palliat Med* 2019; **8**: 717-727 [PMID: 31865732 DOI: 10.21037/apm.2019.11.17]

94 **Park YJ**, Lim DH, Paik SW, Koh KC, Lee JH, Choi MS, Yoo BC, Nam HR, Oh DR, Park W, Ahn YC, Huh SJ. Radiation therapy for abdominal lymph node metastasis from hepatocellular carcinoma. *J Gastroenterol* 2006; **41**: 1099-1106 [PMID: 17160521 DOI: 10.1007/s00535-006-1895-x]

95 **Yamashita H**, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Siina S, Omata M, Ohtomo K. Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: retrospective study. *J Gastroenterol Hepatol* 2007; **22**: 523-527 [PMID: 17376045 DOI: 10.1111/j.1440-1746.2006.04450.x]

96 **Zeng ZC**, Tang ZY, Fan J, Qin LX, Ye SL, Zhou J, Sun HC, Wang BL, Wang JH. Consideration of role of radiotherapy for lymph node metastases in patients with HCC: retrospective analysis for prognostic factors from 125 patients. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1067-1076 [PMID: 15913915 DOI: 10.1016/j.ijrobp.2005.03.058]

97 **Yuan BY**, Hu Y, Zhang L, Chen YH, Dong YY, Zeng ZC. Radiotherapy for adrenal gland metastases from hepatocellular carcinoma. *Clin Transl Oncol* 2017; **19**: 1154-1160 [PMID: 28357632 DOI: 10.1007/s12094-017-1654-x]

98 **Jung J**, Yoon SM, Park HC, Nam TK, Seong J, Chie EK, Kim TH, Kim MS, Kim CY, Jang HS, Kim JH. Radiotherapy for Adrenal Metastasis from Hepatocellular Carcinoma: A Multi-Institutional Retrospective Study (KROG 13-05). *PLoS One* 2016; **11**: e0152642 [PMID: 27022932 DOI: 10.1371/journal.pone.0152642]

99 **Zhou LY**, Zeng ZC, Fan J, Chen B, Rao SX, He J, Yang P, Hou JZ, Wu ZF, Zhang JY, Hu Y. Radiotherapy treatment of adrenal gland metastases from hepatocellular carcinoma: clinical features and prognostic factors. *BMC Cancer* 2014; **14**: 878 [PMID: 25421498 DOI: 10.1186/1471-2407-14-878]

100 **Habermehl D**, Haase K, Rieken S, Debus J, Combs SE. Defining the role of palliative radiotherapy in bone metastasis from primary liver cancer: an analysis of survival and treatment efficacy. *Tumori* 2011; **97**: 609-613 [PMID: 22158492 DOI: 10.1700/989.10720]

101 **Jung IH**, Yoon SM, Kwak J, Park JH, Song SY, Lee SW, Ahn SD, Choi EK, Kim JH. High-dose radiotherapy is associated with better local control of bone metastasis from hepatocellular carcinoma. *Oncotarget* 2017; **8**: 15182-15192 [PMID: 28146433 DOI: 10.18632/oncotarget.14858]

102 **He J**, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, Wang JH, Sun J, Chen B, Yang P, Pan BS. Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. *Cancer* 2009; **115**: 2710-2720 [PMID: 19382203 DOI: 10.1002/cncr.24300]

103 **Park S**, Byun HK, Seong J. Irradiation-Related Lymphopenia for Bone Metastasis from Hepatocellular Carcinoma. *Liver Cancer* 2019; **8**: 468-479 [PMID: 31799204 DOI: 10.1159/000500461]

104 **Yamakawa Y**, Moriguchi M, Aramaki T, Mitsuya K, Asakura K, Sawada A, Endo M, Nakasu Y. Brain metastasis from hepatocellular carcinoma: The impact of radiotherapy on control of intracranial hemorrhage. *Hepatol Res* 2015; **45**: 1071-1075 [PMID: 25470452 DOI: 10.1111/hepr.12457]

105 **Park Y**, Kim KS, Kim K, Chie EK, Kim JH, Kim JS, Kim TH, Kim DY, Jang WI, Kim MS, Koo TR, Chang AR. Nomogram prediction of survival in patients with brain metastases from hepatocellular carcinoma treated with whole-brain radiotherapy: a multicenter retrospective study. *J Neurooncol* 2015; **125**: 377-383 [PMID: 26342711 DOI: 10.1007/s11060-015-1926-7]

106 **Jiang XB**, Ke C, Zhang GH, Zhang XH, Sai K, Chen ZP, Mou YG. Brain metastases from hepatocellular carcinoma: clinical features and prognostic factors. *BMC Cancer* 2012; **12**: 49 [PMID: 22292912 DOI: 10.1186/1471-2407-12-49]

107 **Nam HC**, Sung PS, Song DS, Kwon JH, Nam SW, Yoon DJ, Jang JW, Choi JY, Yoon SK, Moon SW, Jang HS, Park JS, Jeun SS, Hong YK, Bae SH. Control of intracranial disease is associated with improved survival in patients with brain metastasis from hepatocellular carcinoma. *Int J Clin Oncol* 2019; **24**: 666-676 [PMID: 30788672 DOI: 10.1007/s10147-019-01407-z]

108 **Momoi H**, Shimahara Y, Terajima H, Iimuro Y, Yamamoto N, Yamamoto Y, Ikai I, Yamaoka Y. Management of adrenal metastasis from hepatocellular carcinoma. *Surg Today* 2002; **32**: 1035-1041 [PMID: 12541019 DOI: 10.1007/s005950200210]

109 **Wu H**, Liu S, Zheng J, Ji G, Han J, Xie Y. Transcatheter arterial chemoembolization (TACE) for lymph node metastases in patients with hepatocellular carcinoma. *J Surg Oncol* 2015; **112**: 372-376 [PMID: 26368066 DOI: 10.1002/jso.23994]

110 **Hori A**, Ohira R, Nakamura T, Kimura Y, Ueda S, Torii M, Kennoki N, Hori S. Transarterial chemoembolization for pulmonary or mediastinal metastases from hepatocellular carcinoma. *Br J Radiol* 2020; **93**: 20190407 [PMID: 32142364 DOI: 10.1259/bjr.20190407]

111 **Wada Y**, Takami Y, Matsushima H, Tateishi M, Ryu T, Yoshitomi M, Matsumura T, Saitsu H. The Safety and Efficacy of Combination Therapy of Sorafenib and Radiotherapy for Advanced Hepatocellular Carcinoma: A Retrospective Study. *Intern Med* 2018; **57**: 1345-1353 [PMID: 29279513 DOI: 10.2169/internalmedicine.9826-17]

112 **Chen J**, Lu S, Zhang Y, Xu L, Chen J, Wang J, Chen M, Zhang R, Zhou Z. Sorafenib Monotherapy Versus Sorafenib Combined with Regional Therapies for Hepatocellular Carcinoma Patients with Pulmonary Oligometastases: A Propensity Score-matched Analysis. *J Cancer* 2018; **9**: 1745-1753 [PMID: 29805700 DOI: 10.7150/jca.24568]

113 **Munoz-Schuffenegger P**, Barry A, Atenafu EG, Kim J, Brierley J, Ringash J, Brade A, Dinniwell R, Wong RKS, Cho C, Kim TK, Sapisochin G, Dawson LA. Stereotactic body radiation therapy for hepatocellular carcinoma with Macrovascular invasion. *Radiother Oncol* 2021; **156**: 120-126 [PMID: 33285195 DOI: 10.1016/j.radonc.2020.11.033]

114 **Hu Y**, Qin T, Li S, Zhang T, Xue J. Efficacy and Safety of SBRT Combined With Camrelizumab and Apatinib in HCC Patients With PVTT: Study Protocol of a Randomized Controlled Trial. *Front Oncol* 2020; **10**: 1589 [PMID: 32984021 DOI: 10.3389/fonc.2020.01589]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** February 21, 2021

**First decision:** April 19, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Zheng S **S-Editor:** Gao CC **L-Editor:** Wang TQ **P-Editor:**

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

HCC: Hepatocellular carcinoma; 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.