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Review Article

Neoadjuvant therapy and immunotherapy strategies for hepatocellular carcinoma

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

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

Introduction

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

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

cussed its implications for the design of future clinical trials.

Transarterial chemoembolization

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

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

Transarterial radioembolization

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

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

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

Radiotherapy

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

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

Hepatic arterial infusion chemotherapy

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

Systematic therapy

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

most recently, IMbrave150, the positive immunotherapy phase-III study has published the convincing data for the combination of atezolizumab and bevacizumab, which is superior to the current standard.

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

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

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

Combination therapy

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

Conclusion

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

Disclosure of conflict of interest

None.

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References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-E386.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.

[3] Maucort-Boulch D, de Martel C, Franceschi S and Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer 2018; 142: 2471-2477.

[4] Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, Eguchi Y, Wong VW, Negro F, Yilmaz Y, Romero-Gomez M, George J, Ahmed A, Wong R, Younossi I, Ziayee M and Afendy A; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2019; 17: 748755, e3.

[5] Tapper EB and Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018; 362: k2817.

[6] Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G and Llovet JM; STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015; 16: 1344-1354.

[7] Kulik L, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, Murad MH and Mohammed K. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: a systematic review and meta-analysis. Hepatology 2018; 67: 381-400.

[8] Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, Alonso G, Borro JM, González-Larriba JL, Torres A, Camps C, Guijarro R, Isla D, Aguiló R, Alberola V, Padilla J, Sánchez-Palencia A, Sánchez JJ, Hermosilla E and Massuti B; Spanish Lung Cancer Group. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010; 28: 3138-3145.

[9] Rozeman EA, Menzies AM, van Akkooi ACJ, Adhikari C, Bierman C, van de Wiel BA, Scolyer RA, Krijgsman O, Sikorska K, Eriksson H, Broeks A, van Thienen JV, Guminski AD, Acosta AT, Ter Meulen S, Koenen AM, Bosch LJW, Shannon K, Pronk LM, Gonzalez M, Ch'ng S, Grijpink-Ongering LG, Stretch J, Heijmink S, van Tinteren H, Haanen JBAG, Nieweg OE, Klop WMC, Zuur CL, Saw RPM, van Houdt WJ, Peeper DS, Spillane AJ, Hansson J, Schumacher TN, Long GV and Blank CU. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol 2019; 20: 948-960.

[10] Chalabi M, Fanchi LF, Van den Berg JG, Aalbers AG, Sikorska K, Lopez-Yurda M, Grootscholten C, Beets GL, Snaebjornsson P, Maas M, Mertz M, Veninga V, Bounova G, Broeks A, Beets-Tan RG, de Wijkerslooth TR, van Lent AU, Marsman HA, Nuijten E, Kok NF, Kuiper M, Verbeek WH, Kok M, Van Leerdam ME, Schumacher TN, Voest EE and Haanen JB. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med 2020; 26: 566-576.

[11] Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, Chien AJ, Forero-Torres A, Ellis E, Han H, Clark A, Albain K, Boughey JC, Jaskowiak NT, Elias A, Isaacs C, Kemmer K, Helsten T, Majure M, Stringer-Reasor E, Parker C, Lee MC, Haddad T, Cohen RN, Asare S, Wilson A, Hirst GL, Singhrao R, Steeg K, Asare A, Matthews JB, Berry S, Sanil A, Schwab R, Symmans WF, van 't Veer L, Yee D, DeMichele A, Hylton NM, Melisko M, Perlmutter J, Rugo HS, Berry DA and Esserman LJ. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol 2020; 6: 1-9.

[12] Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, Szabados B, Pous AF, Gravis G, Herranz UA, Protheroe A, Ravaud A, Maillet D, Mendez MJ, Suarez C, Linch M, Prendergast A, van Dam PJ, Stanoeva D, Daelemans S, Mariathasan S, Tea JS, Mousa K, Banchereau R and Castellano D. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019; 25: 1706-1714.

[13] European Association For The Study Of The Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.
[14] Galle PR, Tovoli F, Foerster F, Wörns MA, Cucchetti A and Bolondi L. The treatment of intermediate stage tumours beyond TACE: from surgery to systemic therapy. J Hepatol 2017; 67: 173-183.
[15] Zhang Z, Liu Q, He J, Yang J, Yang G and Wu M. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. Cancer 2000; 89: 2606-2612.
[16] Sasaki A, Iwashita Y, Shibata K, Ohta M, Kitano S and Mori M. Preoperative transcatheter arterial chemoembolization reduces long-term survival rate after hepatic resection for resectable hepatocellular carcinoma. Eur J Surg Oncol 2006; 32: 773-779.
[17] Han G, Berhane S, Toyoda H, Bettinger D, Elshaarawy O, Chan AWH, Kirstein M, Mosconi C, Hucke F, Palmer D, Pinato DJ, Sharma R, Ottaviani D, Jang JW, Labeur TA, van Delden OM, Pirisi M, Stern N, Sangro B, Meyer T, Fateen W, García-Fiñana M, Gomaa A, Waked I, Rewisha E, Aithal GP, Travis S, Kudo M, Cucchetti A, Peck-Radosavljevic M, Takkenberg RB, Chan SL, Vogel A and Johnson PJ. Prediction of survival among patients receiving transarterial chemoembolization for hepatocellular carcinoma: a response-based approach. Hepatology 2019; [Epub ahead of print].
[18] Li C, Wang MD, Lu L, Wu H, Yu JJ, Zhang WG, Pawlik TM, Zhang YM, Zhou YH, Gu WM, Wang H, Chen TH, Han J, Xing H, Li ZL, Lau WY, Wu MC, Shen F and Yang T. Preoperative transcatheter arterial chemoembolization for surgical resection of huge hepatocellular carcinoma (≥ 10 cm): a multicenter propensity matching analysis. Hepatol Int 2019; 13: 736-747.
[19] Tustumi F, Ernani L, Coelho FF, Bernardo WM, Junior SS, Kruger JAP, Fonseca GM, Jeismann VB, Cecconello I and Herman P. Preoperative strategies to improve resectability for hepatocellular carcinoma: a systematic review and meta-analysis. HPB (Oxford) 2018; 20: 1109-1118.
[20] Gao ZH, Bai DS, Jiang GQ and Jin SJ. Review of preoperative transarterial chemoembolization for resectable hepatocellular carcinoma. World J Hepatol 2015; 7: 40-43.
[21] Cheng X, Sun P, Hu QG, Song ZF, Xiong J and Zheng QC. Transarterial (chemo) embolization for curative resection of hepatocellular carcinoma: a systematic review and meta-analyses. J Cancer Res Clin Oncol 2014; 140: 1159-1170.
[22] Affonso BB, Galastri FL, da Motta Leal Filho JM, Nasser F, Falsarella PM, Cavalcante RN, de Almeida MD, Felga GEG, Valle LGM and Wolosker N. Long-term outcomes of hepatocellular carcinoma that underwent chemoembolization for bridging or downstaging. World J Gastroenterol 2019; 25: 5687-5701.
[23] Galastri FL, Nasser F, Affonso BB, Valle LGM, Odísio BC, Motta-Leal Filho JM, Salvalaggio PR, Garcia RG, de Almeida MD, Baroni RH and Wolosker N. Imaging response predictors following drug eluting beads chemoembolization in the neoadjuvant liver transplant treatment of hepatocellular carcinoma. World J Hepatol 2020; 12: 21-33.
[24] Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A 3rd, Nemcek AA Jr, Gates VL, Abecassis M, Omary RA and Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008; 47: 71-81.
[25] Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L and Lewandowski RJ. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016; 151: 1155-1163, e2.
[26] Tabone M, Calvo A, Russolillo N, Langella S, Carbonatto P, Lo Tesoriere R, Richetta E, Pellerito R and Ferrero A. Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience. J Gastrointest Oncol 2020; 11: 84-90.
[27] Labgaa I, Tabrizian P, Titano J, Kim E, Thung SN, Florman S, Schwartz M and Melloul E. Feasibility and safety of liver transplantation or resection after transarterial radioembolization with Yttrium-90 for unresectable hepatocellular carcinoma. HPB (Oxford) 2019; 21: 1497-1504.
[28] Edeline J, Lenoir L, Boudjema K, Rolland Y, Boulic A, Le Du F, Pracht M, Raoul JL, Clément B, Garin E and Boucher E. Volumetric changes after (90)Y radioembolization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? Ann Surg Oncol 2013; 20: 2518-2525.
[29] Lau WY, Sangro B, Chen PJ, Cheng SQ, Chow P, Lee RC, Leung T, Han KH and Poon RT. Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. Oncology 2013; 84: 311-318.

[30] Lewandowski RJ, Donahue L, Chokechanachaisakul A, Kulik L, Mouli S, Caicedo J, Abecassis M, Fryer J, Salem R and Baker T. (90) Y radiation lobectomy: outcomes following surgical resection in patients with hepatic tumors and small future liver remnant volumes. J Surg Oncol 2016; 114: 99-105.

[31] Spreafico C, Sposito C, Vaiani M, Cascella T, Bhoori S, Morosi C, Lanocita R, Romito R, Chiesa C, Maccauro M, Marchianò A and Mazzaferro V. Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. J Hepatol 2018; 68: 724-732.

[32] Cheng S, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY and Wu M. Chinese expert consensus on multidisciplinary diagnosis and treatment of hepatocellular carcinoma with portal vein tumor thrombus (2018 edition). Liver Cancer 2020; 9: 28-40.

[33] She WH, Cheung TT, Yau TC, Chan AC, Chok KS, Chu FS, Liu RK, Poon RT, Chan SC, Fan ST and Lo CM. Survival analysis of transarterial radioembolization with yttrium-90 for hepatocellular carcinoma patients with HBV infection. Hepatobiliary Surg Nutr 2014; 3: 185-193.

[34] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, Sibert A, Bouattour M, Lebtahi R, Allaham W, Barraud H, Laurent V, Mathias E, Bronowicki JP, Tasu JP, Perdrisot R, Silvain C, Gerolami R, Mundler O, Seitz JF, Vidal V, Aubé C, Oberti F, Couturier O, Brenot-Rossi I, Raoul JL, Sarran A, Costentin C, Itti E, Luciani A, Adam R, Lewin M, Samuel D, Ronot M, Dinut A, Castera L and Chatellier G; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017; 18: 1624-1636.

[35] Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, Choo SP, Cheow PC, Chotipanich C, Lim K, Lesmana LA, Manuaba TW, Yoong BK, Raj A, Law CS, Cua IHY, Lobo RR, Teh CSC, Kim YH, Jong YW, Han HS, Bae SH, Yoon HK, Lee RC, Hung CF, Peng CY, Liang PC, Bartlett A, Kok KYY, Thng CH, Low AS, Goh ASW, Tay KH, Lo RHG, Goh BKP, Ng DCE, Lekurwale G, Liew WM, Gebski V, Mak KSW and Soo KC; Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: selective internal radiation therapy versus sorafenib in asiapacific patients with hepatocellular carcinoma. J Clin Oncol 2018; 36: 1913-1921.

[36] Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M and Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008; 26: 657-664.

[37] Yoon SM, Lim YS, Park MJ, Kim SY, Cho B, Shim JH, Kim KM, Lee HC, Chung YH, Lee YS, Lee SG, Lee YS, Park JH and Kim JH. Stereotactic body radiation therapy as an alternative treatment for small hepatocellular carcinoma. PLoS One 2013; 8: e79854.

[38] Wang WH, Wang Z, Wu JX, Zhang T, Rong WQ, Wang LM, Jin J, Wang SL, Song YW, Liu YP, Ren H, Fang H, Wang WQ, Liu XF, Yu ZH and Li YX. Survival benefit with IMRT following narrow-margin hepatectomy in patients with hepatocellular carcinoma close to major vessels. Liver Int 2015; 35: 2603-2610.

[39] Hasan S, Thai N, Uemura T, Kudithipudi V, Renz P, Abel S and Kirichenko AV. Hepatocellular carcinoma with child Pugh-A Cirrhosis treated with stereotactic body radiotherapy. World J Gastrointest Surg 2017; 9: 256-263.

[40] Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT and Hezel AF. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. Int J Radiat Oncol Biol Phys 2012; 83: 895-900.

[41] Lin H, Li X, Liu Y and Hu Y. Neoadjuvant radiotherapy provided survival benefit compared to adjuvant radiotherapy for hepatocellular carcinoma. ANZ J Surg 2018; 88: E718-E724.

[42] Kamiyama T, Nakanishi K, Yokoo H, Tahara M, Nakagawa T, Kamachi H, Taguchi H, Shirato H, Matsushita M and Todo S. Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma. Int J Clin Oncol 2007; 12: 363-368.

[43] Wada H, Sasaki Y, Yamada T, Ohigashi H, Miyashiro I, Murata K, Doki Y, Ishikawa O, Nishiyama K and Imaoka S. Successful preoperative treatment for hepatocellular carcinoma with tumor thrombus in the major portal branch by three-dimensional conformal radiation therapy-two case reports. Hepatogastroenterology 2005; 52: 343-347.

[44] Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, Xing H, Xu Y, Shi J, Guo W, Zhou D, Zhang H, Sun H, Huang C, Lu C, Zheng Y, Meng Y, Huang B, Cong W, Lau WY and Cheng S. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. J Clin Oncol 2019; 37: 2141-2151.

[45] Song MJ. Hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma. World J Gastroenterol 2015; 21: 3843-3849.

[46] Miyaki D, Aikata H, Honda Y, Naeshiro N, Nakahara T, Tanaka M, Nagaoki Y, Kawaoka T, Takaki S, Waki K, Hiramatsu A, Takahashi S, Ishikawa M, Kakizawa H, Awai K and Chayama K. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma according to Child-Pugh classification. J Gastroenterol Hepatol 2012; 27: 1850-1857.

[47] Park JY, Ahn SH, Yoon YJ, Kim JK, Lee HW, Lee DY, Chon CY, Moon YM and Han KH. Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. Cancer 2007; 110: 129-137.

[48] Lee BH, Lee DS, Cho CW and Yun SS. Role and limitation of neoadjuvant hepatic arterial infusion chemotherapy in advanced hepatocelluar carcinoma patients with Child-Pugh class A. World J Surg Oncol 2019; 17: 143.

[49] Hamaoka M, Kobayashi T, Kuroda S, Iwako H, Okimoto S, Kimura T, Aikata H, Nagata Y, Chayama K and Ohdan H. Hepatectomy after down-staging of hepatocellular carcinoma with portal vein tumor thrombus using chemoradiotherapy: a retrospective cohort study. Int J Surg 2017; 44: 223-228.

[50] Chong JU, Choi GH, Han DH, Kim KS, Seong J, Han KH and Choi JS. Downstaging with localized concurrent chemoradiotherapy can identify optimal surgical candidates in hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2018; 25: 3308-3315.

[51] 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 and Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

[52] Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JH, de Guevara LL, Papandreou C, Takayama T, Sanyal AJ, Yoon SK, Nakajima K, Lehr R, Heldner S and Lencioni R. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol 2016; 65: 1140-1147.

[53] Berhane S, Fox R, Garcia-Finana M, Cucchetti A and 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.

[54] 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 and Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163-1173.

[55] 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 and 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.

[56] 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 and Kelley RK. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018; 379: 54-63.

[57] Zhu AX, Baron AD, Malfertheiner P, Kudo M, Kawazoe S, Pezet D, Weissinger F, Brandi G, Barone CA, Okusaka T, Wada Y, Park JO, Ryoo BY, Cho JY, Chung HC, Li CP, Yen CJ, Lee KD, Chang SC, Yang L, Abada PB and Chau I. Ramucirumab as Second-Line treatment in patients with advanced hepatocellular carcinoma: analysis of REACH trial results by child-pugh score. JAMA Oncol 2017; 3: 235-243.

[58] Yau T, Park JW, Finn RS, Cheng AL, Mathurin P and Edeline J. LBA38_PR 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; 30.

[59] 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 and 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.

[60] Irtan S, Chopin-Laly X, Ronot M, Faivre S, Paradis V and Belghiti J. Complete regression of locally advanced hepatocellular carcinoma induced by sorafenib allowing curative resection. Liver Int 2011; 31: 740-743.

[61] Barbier L, Fuks D, Pessaux P, Muscari F, Le Treut YP, Faivre S and Belghiti J. Safety of liver resection for hepatocellular carcinoma after

sorafenib therapy: a multicenter case-matched study. Ann Surg Oncol 2013; 20: 3603-3609.
[62] Bouattour M, Fartoux L, Rosmorduc O and Scatton O. BIOSHARE multicenter neoadjuvant phase 2 study: results of preoperative sorafenib in patients with resectable hepatocellular carcinoma (HCC)-From GERCOR IRC. J Clin Oncol 2016; 34: 252-252.
[63] Golse N, Radenne S, Rode A, Ducerf C, Mabrut JY and Merle P. Liver transplantation after neoadjuvant sorafenib therapy: preliminary experience and literature review. Exp Clin Transplant 2018; 16: 227-236.
[64] Eilard MS, Andersson M, Naredi P, Geronymakis C, Lindnér P, Cahlin C, Bennet W and Rizell M. A prospective clinical trial on sorafenib treatment of hepatocellular carcinoma before liver transplantation. BMC Cancer 2019; 19: 568.
[65] Kermiche-Rahali S, Di Fiore A, Drieux F, Di Fiore F, François A and Scotté M. Complete pathological regression of hepatocellular carcinoma with portal vein thrombosis treated with sorafenib. World J Surg Oncol 2013; 11: 171.
[66] Ye SL, Chen X, Yang J, Bie P, Zhang S, Liu F, Liu L, Zhou J, Dou K, Yip CS and Yang X. Evaluation of sorafenib in Chinese unresectable hepatocellular carcinoma patients with prior surgery and portal vein tumor thrombosis: a subset analysis of GIDEON study data. Tumour Biol 2017; 39: 1010428317695030.
[67] Truesdale AE, Caldwell SH, Shah NL, Argo CK, Al-Osaimi AM, Schmitt TM and Northup PG. Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant. Transpl Int 2011; 24: 991-998.
[68] Hoffmann K, Ganten T, Gotthardtp D, Radeleff B, Settmacher U, Kollmar O, Nadalin S, Karapanagiotou-Schenkel I, von Kalle C, Jäger D, Büchler MW and Schemmer P. Impact of neoadjuvant Sorafenib treatment on liver transplantation in HCC patients - a prospective, randomized, double-blind, phase III trial. BMC Cancer 2015; 15: 392.
[69] 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 and 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.
[70] 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 and 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.
[71] Kelley RK, Abou-Alfa GK, Bendell JC and Kim TY. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): phase I safety and efficacy analyses. J Clin Oncol 2017; 35: 4073.
[72] Stein S, Pishvaian MJ, Lee MS, Lee KH, Hernandez S, Kwan A, Liu B, Grossman W, Iizuka K and Ryoo BY. Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). J Clin Oncol 2018; 36: 4074.
[73] Sangro B, Gomez-Martin C, De La Mata M, Iñarrairaegui M, Garralda E, Barrera P, Riezu-Boj JI, Larrea E, Alfaro C, Sarobe P, Lasarte JJ, Pérez-Gracia JL, Melero I and Prieto J. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013; 59: 81-88.
[74] Kaseb A, Vence L, Blando J and Yadav S. Open-label, perioperative phase II study evaluating nivolumab alone versus nivolumab plus ipilimumab in patients with resectable HCC. Ann Oncol 2019; 37: abstr 4098.
[75] Kaseb A, Vence L, Blando J, Yadav S, Ikoma N, Pestana RC, Vauthey JN, Allison JP and Sharma P. Immunologic correlates of pathologic complete response to preoperative immunotherapy in hepatocellular carcinoma. Cancer Immunol Res 2019; 7: 1390-1395.
[76] Schwacha-Eipper B, Minciuna I, Banz V and Dufour JF. Immunotherapy as a downstaging therapy for liver transplantation. Hepatology 2020; [Epub ahead of print].
[77] Gassmann D, Weiler S, Mertens JC, Reiner CS, Vrugt B, Nägeli M, Mangana J, Müllhaupt B, Jenni F and Misselwitz B. Liver allograft failure after nivolumab treatment-a case report with systematic literature research. Transplant Direct 2018; 4: e376.
[78] Ho CM, Chen HL, Hu RH and Lee PH. Harnessing immunotherapy for liver recipients with hepatocellular carcinoma: a review from a transplant oncology perspective. Ther Adv Med Oncol 2019; 11: 1758835919843463.
[79] Stein S, Pishvaian MJ and Lee MS. Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). J Clin Oncol 2018; 36: 4074.
[80] Pishvaian M, Lee M and Ryoo B. LBA26 updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC). Ann Oncol 2018; 29: mdy424.

[81] Ikeda M, Sung MW and Kudo M. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). J Clin Oncol 2018; 36: 4076.

[82] Liu Z, Li X, He X, Xu Y and Wang X. Complete response to the combination of Lenvatinib and Pembrolizumab in an advanced hepatocellular carcinoma patient: a case report. BMC Cancer 2019; 19: 1062.

[83] Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, Davis JL, Hughes MS, Heller T, ElGindi M, Uppala A, Korangy F, Kleiner DE, Figg WD, Venzon D, Steinberg SM, Venkatesan AM, Krishnasamy V, Abi-Jaoudeh N, Levy E, Wood BJ and Greten TF. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol 2017; 66: 545-551.

[84] Harding JJ, Erinjeri JP and Tan BR. A multicenter pilot study of nivolumab (NIVO) with drug eluting bead transarterial chemoembolization (deb-TACE) in patients (pts) with liver limited hepatocellular carcinoma (HCC). J Clin Oncol 2018; 36: TPS4146.

[85] Chen X, Zhang Y, Zhang N, Ge Y and Jia W. Lenvatinib combined nivolumab injection followed by extended right hepatectomy is a feasible treatment for patients with massive hepatocellular carcinoma: a case report. Onco Targets Ther 2019; 12: 7355-7359.