79728_Auto_Edited.docx

Salvage Locoregional Therapies for Recurrent Hepatocellular Carcinoma

Salvage Locoregional Therapies

Cody R Criss, Mina S Makary

Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide. Despite the advent of screening efforts and algorithms to stratify patients into appropriate treatments strategies, recurrence rates remain high. In contrast to first-line treatment for HCC, which relies on several factors, including clinical staging, tumor burden, and liver function, there is no consensus or general treatment recommendations for recurrent hepatocellular carcinoma (R-HCC). Locoregional therapies include a spectrum of minimally invasive liver-directed treatments which can be used as either curative or neoadjuvant therapy for HCC. Herein, we provide a comprehensive review of recent evidence using salvage loco-regional therapies for recurrent hepatocellular (R-HCC) after failed curative-intent.

Criss CR, Makary MS. Salvage Locoregional Therapies for Recurrent Hepatocellular Carcinoma. *World J Gastroenterol* 2022; In press

Core Tip: Management of recurrent hepatocellular carcinoma (R-HCC) includes surgical resection, systemic treatment, or locoregional therapies including ablation, transarterial chemoembolization (TACE), or radioembolization (TARE), and stereotactic body radiation therapy (SBRT). In the setting of recurrence, locoregional therapies offer unique advantages over surgery for select patients. Recent investigations have also highlighted the potential of combining locoregional therapies or adding systemic retreatments for R-HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 75-90% of liver malignancies and is the second most common cause of cancer death worldwide [1–3]. While advancements in surveillance efforts have improved prevention and screening, incidence and mortality of HCC in recent decades has gradually increased in the United States [4,5]. Prevalence is increased in East Asia and Africa, and at-risk populations include those with cirrhosis and hepatitis B or C [4,5].

Treatment strategies for patients with HCC are tailored to tumor burden, invasiveness, and liver function, stratified using the Barcelona Clinic Liver Cancer staging (BCLC) [6]. First-line and curative treatment for HCC includes surgical resection or orthotopic liver transplantation with eligibility determined *via* the Milan criteria [5,7]. In patients with early-stage HCC who are not eligible for liver transplantation, surgical resection may be performed [6]. In patients who do not qualify as surgical candidates, the use of locoregional therapies (LRT) using image-guided techniques has grown in popularity over the last several decades, providing a minimally invasive treatment approach to HCC [8,9]. Locoregional therapy is comprised of radiofrequency / thermal microwave ablation (RFA/TA), trans-arterial chemoembolization (TACE), or radioembolization (TARE), which have been commonly used neo-adjunctively to bridge or downstage patients with HCC in order to meet surgical eligibility (Figure 1) [10]. Ablation, in particular, offers a curative-intent option for nonsurgical candidates with early stage HCC (BCLC 0/A) with a corresponding 5-year survival rate of 50-80% [11]. Locoregional therapies provide an alternative strategy with the benefit of reduced comorbidity[12], and avoidance of complications that may worsen clinical outcomes associated with traditional surgery [13,14].

Long-term prognosis for the treatment of HCC remains poor, with a recurrence rate of 41-70% within 5 years following resection[15–18]. Depending on tumor size, severity, liver function, and clinical indices, repeat hepatectomy may not be suitable for some patients. Therefore, alternative treatment options should be explored after initial curative attempts. No definitive consensus on standard salvage treatment approaches exist for recurrent HCC, but common therapies include repeat resection, liver

transplantation, tyrosine kinase inhibitors, locoregional therapies, or a combination of multiple modalities[19]. This manuscript provides a comprehensive review of the current state of the literature for the use of salvage loco-regional therapies for recurrent hepatocellular (R-HCC).

Risk Factors for Recurrent Hepatocellular Carcinoma

Prognostic factors associated with the increased risk of recurrence can vary from morphologic and surgical factors to molecular factors [20,21]. Larger tumors, or nodules with diameters ≥ 5cm, are associated with increased rates of recurrence. Other morphological risk factors include the presence of multiple tumor nodules and satellite lesions [21–23]. The association between tumor size and recurrence is due to its correlation with invasiveness and propensity for portal vein mediated intrahepatic metastasis and vascular invasion[21,24–26]. Microvascular invasion is a poor prognostic factor for R-HCC[27-29], defined as the histopathological observance of malignant cells within hepatic tissue and vascular cavities of the surrounding portal or hepatic vessels [30]. Other tumor-related factors associated with risk of recurrence after resection or liver transplantation, such as AFP levels > 400 ug/L [31,32]. Overexpression of other histological and circulating biomarkers are also associated with negative prognostic factors related to recurrence [33].

SALVAGE LOCOREGIONAL THERAPY FOR RECURRENT HEPATOCELLULAR CARCINOMA

Salvage locoregional therapy for R-HCC is frequently used after resection or in the setting of advanced, unresectable disease [8,9,33]. Compared to locoregional therapy or resection, liver transplantation carries a superior survival benefit for R-HCC [34–37]. However, utility of transplantation is limited due to strict inclusion criteria, donor availability, high treatment costs, and surgical candidacy [9]. In patients who do not meet Milan criteria or not eligible for transplantation, the decision between locoregional therapies such as ablation, or repeated resection remains controversial. While resection

is recognized as a primary treatment for HCC [6], portal hypertension, poor functional reserve from the future liver remnant, and technical difficulties (e.g. adhesions, anatomy modifications) can make repeat resection challenging and risky [38,39]. Therefore, the efficacy of alternative methods may be uniquely promising for R-HCC. The following section includes an overview of specific locoregional therapy modalities, and their efficacy for R-HCC.

Transarterial chemoembolization

The liver parenchyma utilizes dual blood supply with approximately two-thirds of originating from the portal vein and the remaining third from the hepatic artery. Transarterial embolization (TAE) involves selective angiographic occlusion of tumor supplying vessels from the hepatic artery resulting in tumor ischemia and necrosis[9,40]. Similarly, transarterial chemoembolization (TACE) involves the use of embolizing microparticles combined with regional chemotherapy [9]. Several variations of TACE exist, but embolization is commonly completed using gelatin sponge particles, polyvinyl alcohol particles, or spherical embolic agents [41]. Of note, conventional TACE (c-TACE) utilizes a chemotherapeutic agent emulsed with lipiodol, whereas the use of drug-eluding beads (DEB-TACE) carry the added benefit of increased concentration to the target [9,42,43]. Damage to healthy liver parenchyma is spared *via* arterial supply from the unobstructed portal vein [9,44].

TACE can be used as a bridge to transplantation and is currently a first-line multinodular HCC and intermediate-stage disease (BCLC B) [6,9]. It is also reserved for early-stage disease (BCLC A) who do not meet surgical criteria[9]. TACE after resection is particularly beneficial to patients with poor prognostic factors such as microvascular invasion[45–48]. Similar to primary HCC, TACE for R-HCC is tolerable and an optimal therapeutic modality for patients with poor liver function or multifocal HCC [49–51]. Two recent meta-analysis found adjuvant TACE improved overall survival (hazard ratio: 0.64-0.71) [46,52] and disease free survival (hazard ratio: 0.73) [52]. Overall 1 and 3 year survival rates for TACE for R-HCC are reportedly 28-82% and 32-43.9%,

respectively[50,53]. Meta-analysis have reported 5-year survival rates for TACE to be 15.5%[54]. Poorer outcomes and prognosis in patients treated with TACE for R-HCC are multiple sessions, tumor size >5cm and ≥2 Lesions[50]. TACE offers a unique benefit in the presence of microvascular invasion or multifocal disease but studies to date have been largely retrospective and a need for randomized control trials is required before clinical considerations are definitive. A prospective investigation of 629 patients found worse outcomes in patients treated with TACE (*n* = 339), compared to radiofrequency ablation (*n* = 162), and re-hepatectomy (*n* = 128)[49]. Yet, a meta-analysis of seven studies including patients with R-HCC reported no overall survival differences between TACE (*n* = 807) and repeated resection (*n* = 267). Therefore, TACE appears to be an effective treatment option for R-HCC, with preferential advantage to patients with morphological factors such as multiple tumors or disease complicated by microvascular invasion [33].

Transarterial Radioembolization

Transarterial Radioembolization (TARE) is a local radiation therapy also referred to as selective internal radiotherapy (SIRT), whereby Yttrium-90 Labeled microspheres are delivered through the hepatic arteries to the tumor [55,56]. Yttrium-90 is a β-emitter, and has a tumoricidal effect at a sufficient dosage of 400Gy or greater [11]. Similar to TACE, radioembolization is used as a neoadjuvant treatment for downstaging and bridging patients for transplantation or resection[57] and considered a curative approach for early-HCC or BCLC 0/A [58]. TARE has become increasingly popular over the last decade as a safe and tolerable procedure for HCC[59], with shorter hospital length of stay and decreased risk of post-embolization syndrome when compared to TACE [60–62]. Additionally, TARE carries less risk for portal vein tumor thrombosis[63]. Recently, TARE has been adopted within the BCLC algorithm as a second-line treatment for early-stage HCC [11,64]. This change is primarily driven by the LEGACY (Local radioembolization using Glass Microspheres for the Assessment of Tumor

Control with Y-90) study, which found radioembolization >400Gy to be safe and an effective curative approach for patients with nodules less than 8 cm [65].

For R-HCC, there is a scarcity of investigations determining the utility of TARE after failed curative-intent. Meta-analyses have shown similar outcomes between TACE and TARE for unresectable HCC [66]. It is also important to note that a randomized control trial by Salem *et al* found better tumor control outcomes in patients with HCC BCLC stages A/B treated with TARE as opposed to TACE (time to progression: >26 mo; 6.8 mo, respectively) Sangro *et al* reported no differences in adverse events in patients receiving TARE with prior failed curative-intent treatments (surgical or non-surgical) compared treatment naïve patients receiving TARE[67]. A retrospective investigation of 41 patients reported time to progression of 11.3 mo and overall survival of 22.1 mo patients receiving TARE after prior resection.[68]. Due to the advantages of TARE listed above, it has been advocated for advanced, unresectable disease [33,69]. More data is needed to determine efficacy and optimal patient-selection strategies of radioembolization in the context of R-HCC.

Ablation

Ablation involves using a probe placed percutaneously under image guidance into the tumor to induce necrosis *via* thermal energy[11,70]. Ablation consists of either radiofrequency ablation (RFA) or microwave ablation (MVA). RFA is moderated by the "heat sink effect" which can negatively impact tumor response. Blood flow from nearby tissue can dissipate heat transfer and result in a cooling effect [71]. MVA is less impacted by heat sink due to the use of higher temperatures and larger, homogenous ablation zone, but at a cost of increased risk of injury to adjacent structures [72–75]. For both types of ablation, tumor location efficacy can be impacted by location, where tumors abutting nearby structures like the gallbladder, bowel, and diaphragm can be injured or result in insufficient safety margins that leave residual tumor [76]. Ablation is considered a curative treatment for early-stage HCC (BCLC 0/A) [6,11]. A major advantage of

ablation is it can be performed quicker and may be more feasible than surgery with the added benefit of fewer complications and faster recovery [77].

A retrospective review of 211 patients with R-HCC found the 1-year survival rate for locoregional therapy (RFA, TAE, and/or percutaneous ethanol injection; n = 170, 91.6%) to be greater than salvage liver transplantation (n = 41, 90.2%) [37]. However, survival rates became superior in salvage liver transplantations at 3- and 5-years (80.4, and 80.4%, respectively) relative to the locoregional therapy group (71.7, and 51.1%, respectively) [37]. A meta-analysis of retrospective investigations by Chen *et al* found improved clinical outcomes for 3- and 5-year survival rates in repeated hepatectomy compared to RFA for R-HCC[78]. Therefore, repeated hepatectomy carries improved long-term efficacy, although the authors acknowledge selection bias may confound these results since a higher proportion of patients with improved liver function and limited tumor spread may be candidates for surgery. A meta-analysis of randomized control trials and observational studies by Yuan *et al* found similar survival rates between ablation (MVI or RFA) compared to re-resection, but lower perioperative morbidity rates were observed in patients undergoing ablation (3.3%) relative to re-resection (17%) [79]. The majority of these studies included tumors ≦ 3 cm, and therefore the decision to utilize ablation over surgery for R-HCC may be appropriate for smaller tumors [80]. In tumors ≦ 3 cm, disease free survival rates are similar to resection, but hospital length of stay and perioperative morbidity is lower in RFA (5 days, 7%, respectively) compared to repeated resection (13 days, 16%, respectively)[81]. Yang *et al* echoed these findings, illustrating repeat resection for R-HCC has superior overall survival rates, but sub-group analyses of outcomes for smaller tumors diminish survival differences between these two methods [82]. Larger, more homogenous ablation volumes associated with MVA may broaden ablation applicability to larger tumors[83]; however, studies to date evaluating MVA for R-HCC are limited.

Stereotactic body radiotherapy

Stereotactic body radiotherapy (SBRT) is a localized therapy whereby fractionated high-dose radiation is used to ablate liver parenchymal tumors (Figure 1)[84]. Conventionally, SBRT is dedicated to salvage therapy for R-HCC or advanced disease when ablation or embolization has failed or is contraindicated [85]. SBRT is currently not included in the BCLC, but is included in the National Comprehensive Cancer Guidelines[84]. Kimura et al reviewed patients with HCC who either failed or were not eligible for resection or other locoregional therapies, reporting safe and satisfactory overall survival rates for first and second SBRT (n = 81, 60.4% and 61%, respectively)[86]. In patients receiving salvage SBRT after TACE, overall survival rates at 3 years were 72.7% (n = 302), with 95.4% tumors reaching complete response[87]. Therefore, in patients who fail TACE and curative modalities are not suitable, salvage SBRT could be offered as a potential subsequent treatment option.

Multimodal Locoregional Therapy Approaches

Approaches that combine locoregional therapies (e.g., TACE and RFA/MVA) have been proposed. Several mechanisms have been suggested to explain the synergistic or additive effects of combining modalities. Multimodality therapies may overcome individual limitations of monotherapy, such as providing adequate control for intermediate to larger tumors[72,88-90]. TACE is suggested to mitigate the heat sink effect and therefore, positively impact the efficacy of RFA [71]. Chemoembolization may also reduce tumor burden, which can aid RFA by extending safety margin and the resultant coagulation zone [90,91]. A meta-analysis of 8 randomized control trials using RFA-TACE for primary HCC found improved overall survival (HR = 0.58 CI 0.41-.80) and recurrence free survival (HR = 0.65 CI =0.47-0.76) compared to RFA alone.

To date, few investigations have sought to determine the efficacy of multimodal therapy as a salvage treatment approach in unresectable disease or in instances of R-HCC. For the treatment of larger R-HCC tumors ($\leqq$ 7cm), TACE followed by RFA can reveal additional satellite lesions and have a greater 1-, 3-, 4- year survival rates (92.6%, 66.6%, 61.8%) than RFA alone (85.3%, 59%, 45%) [92,93]. Studies comparing the efficacy of

TACE-RFA have indicated comparable 1-, 3-, and 5-year survival outcomes between the two salvage treatment approaches for both smaller tumors (≦ 5 cm) [94,95] and larger ones (> 5 cm)[96]. Interestingly, TACE-RFA achieved satisfactory outcomes with a lower rate of complications (e.g. bleeding, liver failure) and shorter hospital stays [94–96]. Yang *et al* published a retrospective investigation of 103 patients with R-HCC treated with either RFA, TACE, or combination therapy of RFA and TACE. Intrahepatic rates of recurrence were lower in the combination group (20.7%) compared to TACE (57.1%) and the RFA group (43.2%). 1-, 3- and 5-year survival rates were also greater in the combination group (88.5%, 64.6%, 44.3%) compared to the TACE alone group(65.8%, 38.9%, 19.5%)[97]. Other multimodal regimens for R-HCC have been explored, including TACE and MVA, of which when combined, improve tumor response and prolong progression-free survival compared to TACE monotherapy for small R-HCC tumors (≦3cm) [98]. Although prospective investigations are required prior to establishing recommendations, in general, current evidence indicates a potential survival benefit to multimodality approaches with some investigators advocating for the adoption of multimodal therapy in future BCLC treatment guidelines[99].

Combining Locoregional Therapy and Systemic Therapy

Sorafenib, an oral tyrosine kinase inhibitor, reserved for advanced-stage disease (BCLC class C) based on results of the SHARP trial [6]. Overall, Sorafenib can offer survival benefit for unresectable HCC, but worse tumor response and greater adverse events when compared to locoregional therapies[100,101]. Challenges of using sorafenib are further compounded by heterogenous response rates and acquired resistance [102–104]. However, investigations have explored the utility of combining oral systemic agents with locoregional therapy (Table 2). A retrospective study reviewed 1126 patients with R-HCC in patients who received sorafenib and concurrent TACE or TACE monotherapy. The addition of sorafenib to TACE offered significantly improved survival time compared to TACE alone (20.23 *vs* 13.87 mo, respectively) [105]. Peng *et al* retrospectively reviewed patients with advanced R-HCC receiving either sorafenib

monotherapy (n = 101), or a combination of sorafenib and TACE-RFA (n = 106)[106]. While the toxicity profile was similar between both groups, median overall survival and time to progression in TACE-RFA+sorefanib (14 mo; 7 mo, respectively) was superior to sorafenib monotherapy (9 mo; 4 mo, respectively) [106]. A randomized, multicenter control trial comparing TACE (n = 76 and TACE with sorefanib (n = 80) for unresectable HCC, resection, found median progress-free survival to be greater in the combined treatment group (25.2 vs 13 mo)[107]. Although this trial included treatment naiive patients, a large portion of patients received prior locoregional therapy treatments Multicenter phase III randomized control trials comparing TACE alone and TACE with sorefanib for recurrent, unresectable HCC are currently underway.

FUTURE DIRECTIONS

Immuno-locoregional combination therapy

Immunological properties associated with HCC have driven a growing use of immune checkpoint modulators such as anti-PD-1 antibodies (e.g. nivolumab, pembrolizumab, camrelizumab) or CTL-A-4 inhibitors (e.g. ipilimumab, tremelimumab) [108–111] over the last decade. Thus far, phase 2 and 3 trials have found promising tumor response rates and safety profiles compared to previous standard systemic therapies[112]. In addition to tumor necrosis, there has been some evidence that locoregional therapy can activate T-cell responses and augment the expression of multiple immune-mediated processes within the tumor microenvironment[113]. Development of treatment strategies for HCC that combine locoregional therapies and immunomodulators have thus emerged. Despite this rise in utilization, Guo et al found no difference in clinical outcomes or tumor response for combined TACE and camrelizumab compared to TACE monotherapy [109]. Studies determining the efficacy of immunotherapy combined with locoregional therapy are scarce, but multiple trials combining immunomodulators and locoregional therapies are currently underway[114]. It should be noted, adverse events with immuno-checkpoint blockers, such as hyperprogressive disease, have been reported and pose a unique challenge influencing
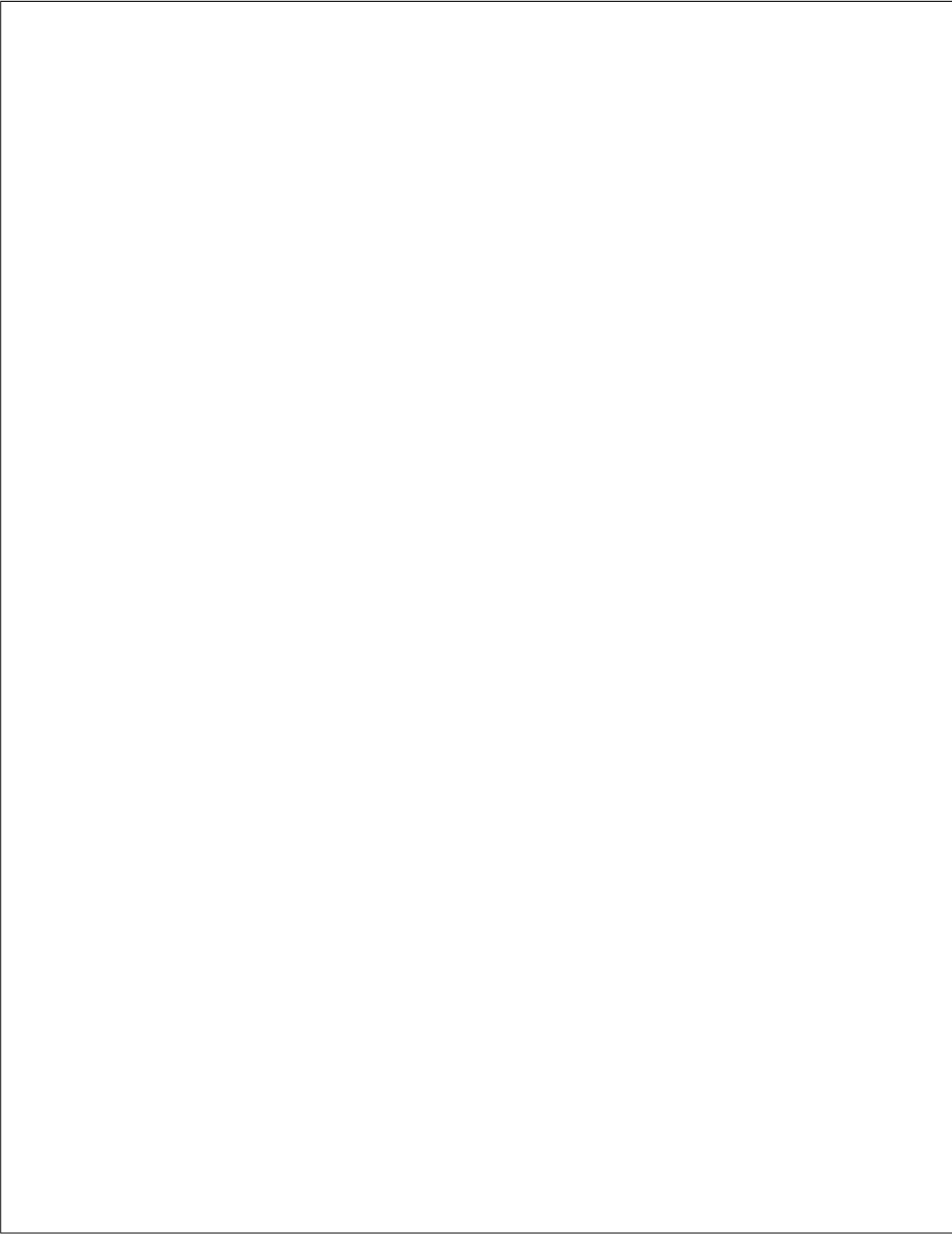
clinical judgment to utilize these agents. Hyperprogressive disease is characterized by a rapid increase in tumor burden and subsequent clinical deterioration in patients treated with immunotherapy agents. Other immunotherapies benefit (e.g. vaccines, oncolytic viruses and adoptive cellular therapies) have also been speculated to provide therapeutic but remain under clinical investigation[111].

Determining treatment algorithms for recurrent hepatocellular carcinoma

After failure of curative-intent or tumor recurrence, the use of locoregional therapies is warranted, especially in patients no longer eligible for surgery. Ablation, however, should be considered as an comparable alternative to repeat-resection in patients with recurrent small solitary tumors, notably ≦ 3cm. Similar to prior reviews, in patients with early recurrence (<1 year), multifocal disease (>2-3 nodules) or in the presence of microvascular invasion, TACE should be considered[33]. Moreover, due to lower toxicity and longer time-to-progression for advanced disease[62], the use of radioembolization offers a favorable alternative to TACE. Evidence supports that multimodal therapy provides superior clinical benefit to monotherapy as well as repeat-resection for smaller tumors (Table 1) for R-HCC. To date, it is unclear which additional patient populations (e.g., those not currently suitable for locoregional monotherapy) may benefit from multimodal or strategies that combine locoregional and systemic therapy (Table 2).

CONCLUSION

Treatment strategies for R-HCC remain a challenge, and there is no consensus for how to manage patients who fail curative-intent therapies. The use of targeted locoregional therapies can improve clinical outcomes after recurrence in patients not eligible for or awaiting transplantation, or in cases of advanced disease. The emerging use of multimodal and additive systemic agents exhibit promise as a novel treatment approach in the setting of recurrence; however, prospective studies are necessary before definitive recommendations can be made.

79728_Auto_Edited.docx

8   Wei Yang. "Combination therapy of radiofrequency ablation and transarterial chemoembolization in recurrent hepatocellular carcinoma after hepatectomy compared with single treatment", Hepatology Research, 03/2009
Crossref

13 words — < 1%

9   test.dovepress.com
Internet

13 words — < 1%

10   Ming Fang Hsu, Yen Sheng Tyan, Yu Chen Chien, Ming Wei Lee. "Hyaluronic acid-based nano-sized drug carrier-containing Gellan gum microspheres as potential multifunctional embolic agent", Scientific Reports, 2018
Crossref

12 words — < 1%

11   pro.uptodatefree.ir
Internet

9 words — < 1%

12   "Essential Interventional Radiology Review", Springer Science and Business Media LLC, 2022
Crossref

8 words — < 1%

13   "Liver Diseases", Springer Science and Business Media LLC, 2020
Crossref

8 words — < 1%

14   Xuying Wan, Xiaofeng Zhai, Zhenlin Yan, Pinghua Yang, Jun Li, Dong Wu, Kui Wang, Yong Xia, Feng Shen. "Retrospective analysis of transarterial chemoembolization and sorafenib in Chinese patients with unresectable and recurrent hepatocellular carcinoma", Oncotarget, 2016
Crossref

8 words — < 1%

15   oaepublishstorage.blob.core.windows.net
Internet

8 words — < 1%

16	wrap.warwick.ac.uk Internet	8 words — < 1%
17	www.ncbi.nlm.nih.gov Internet	8 words — < 1%
18	Angiolo Gadducci, Stefania Cosio, Andrea Riccardo Genazzani. "Ovarian function and childbearing issues in breast cancer survivors", Gynecological Endocrinology, 2009 Crossref	7 words — < 1%
19	Luigi Bolondi, Andrew Burroughs, Jean-François Dufour, Peter Galle et al. "Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions", Seminars in Liver Disease, 2013 Crossref	7 words — < 1%
20	W Helton. "Treatment Strategies for Hepatocellular Carcinoma in Cirrhosis", Journal of Gastrointestinal Surgery, 2003 Crossref	7 words — < 1%
21	"16 Management of Locally Advanced Hepatocellular Carcinoma", Georg Thieme Verlag KG, 2018 Crossref	6 words — < 1%
22	Jordi Bruix, Morris Sherman. "Management of hepatocellular carcinoma", Hepatology, 2005 Crossref	6 words — < 1%