Advances in Diagnostic and Interventional Radiology in Hepatocellular Carcinoma

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\textbf{Abstract}

\textbf{Background:} Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths, and radiological imaging and locoregional therapies are essential for the management of patients with HCC. \textbf{Summary:} In cirrhotic patients, a characteristic imaging pattern establishes the non-invasive diagnosis of HCC with acceptable sensitivity and high specificity. In addition to diagnosis, imaging is used in the staging of patients and treatment allocation. Multiparametric MRI with hepatospecific contrast agents improves lesion detection, characterization, and treatment allocation; recently described imaging criteria allow identification of precursor lesions. Radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) have been established in the treatment of patients with HCC at the early and intermediate stages, respectively. Microwave ablation has been described as an alternative to RFA in selected cases. Imaging-guided brachytherapy, a catheter-based radiotherapy technique, offers advantages to overcome some limitations of the aforementioned therapies, including the tumor location and size. Currently, no adjuvant therapy is recommended after RFA or TACE, but several new drugs are under evaluation. Furthermore, although the exact role of selective internal radiation therapy (SIRT) in HCC still needs to be defined, it is an alternative to systemic agents in patients with intolerance, and additional benefit has been shown in selected subgroups. Additionally, SIRT offers an alternate to TACE with higher objective response rates in patients who needs bridging before transplantation. \textbf{Key Messages:} New imaging criteria improved lesion detection in patients at a risk for HCC, and advances in interventional therapies expanded the range of patients eligible for locoregional treatments.

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\textbf{Introduction}

Hepatocellular carcinoma (HCC) comprises about 90% of primary liver cancer; the sixth commonly diagnosed cancer and second leading cause of cancer-related deaths in 2020 [1]. In the Western population, 90% of the cases develop in a cirrhotic liver through the progression from a chronic inflammatory fibrotic stage, through low-
grade and high-grade dysplastic nodules, eventually to neoplasia. Radiology has a crucial role in the management of HCC with surveillance of at-risk patients, diagnosing and allocating patients into therapies, and treating the patients with several locoregional therapies.

**Diagnosis**

**Noninvasive Diagnosis**

Imaging plays an integral role in the diagnosis of HCC, as well as disease staging. Noninvasive diagnosis of HCC based on typical enhancement patterns has been accepted since 2001 [2]. Contrast-enhanced imaging with late arterial, portal venous, and delayed phases are necessary for the diagnosis of HCC. The typical hallmark of HCC is the combination of hypervascularity on the late arterial phase (arterial phase enhancement; washin), and hypointensity compared to the surrounding liver parenchyma on portal venous and/or delayed phases (washout) in a nodule >10 mm, which represents neoangiogenesis during hepatocarcinogenesis resulting in stronger arterial vascularization, and simultaneously, decreased portal vein supply. According to EASL criteria, if the specific enhancement pattern of HCC is observed in a lesion ≥10 mm lesion in the setting of cirrhosis, the diagnosis is established. The optimal strategy for nodules smaller than 1 cm has not been clarified yet, and currently, EASL recommends local multidisciplinary board discussion for these patients. However, the cutoff value for size might change in the future with further evidence in light of higher quality images. Noninvasive diagnosis relies on the high pretest probability of HCC in patients with underlying liver disease and cirrhosis. Imaging appearance of HCC in a noncirrhotic liver is similar to those seen in cirrhotic patients. However, since those patients are not enrolled in surveillance, lesions tend to be larger at diagnosis. Additionally, the specificity of the characteristic enhancement pattern is lower in noncirrhotic patients due to the higher prevalence of alternative diagnoses, like hepatocellular adenoma or hypervascular metastases. Thus, histopathological confirmation is needed in these patients. Similar to noncirrhotic patients, noninvasive diagnosis criteria cannot be applied in patients with cirrhosis secondary to vascular diseases, such as Budd-Chiari syndrome [3, 4]. Chronic impairment of vascular supply to the liver leads to the development of focal liver lesions, mostly benign regenerative lesions, and despite the different underlying mechanisms, benign lesions also have increased arterial perfusion like HCC [3].

Noninvasive diagnosis criteria have very high specificity, close to 100% but the sensitivity is low with 72.3% and 71.6% for 20–30 mm lesions, 70.6% and 67.9% for 10–20 mm lesions for MRI and CT, respectively [5–8]. This results from the absence of hypervascularity or washout in some HCC lesions, especially at earlier stages of hepatocarcinogenesis. However, the tumor number and size play a crucial role in the treatment allocation of patients with HCC, for example, in the BCLC treatment algorithm. An underestimation of the tumor burden is predicted to range from 20 to 30% by using the classical washin/washout criteria. Nevertheless, employment of these criteria with very high specificity is still standard of care in HCC programs focusing on liver transplantation due to the need for avoiding false-positive diagnosis and prioritization of patients to transplant in the context of limited available organs. An additional advantage of this noninvasive criteria is avoiding the necessity of biopsies in these patients, which can be problematic due to higher complications and false negative or positive results in the cirrhotic liver [7, 9].

**Liver Imaging Reporting and Data System**

Liver Imaging Reporting and Data System (LI-RADS) provides standardization for HCC screening and surveillance with a detailed description of image acquisition, interpretation, and terminology [10]. In addition to cirrhotic patients like EASL criteria, LI-RADS can also be applied in patients with chronic viral hepatitis. Lesions in patients with a risk for HCC are classified into a 5-point scale. Lesions with the absence of any major or ancillary features of HCC are assigned as LR-1 (definitely benign) and LR-2 (probably benign); lesions smaller than 2 cm with some perfusion alterations or ≥2 cm but without any major features are assigned as LR-3 (intermediate probability of HCC). Malignant categories include LR-4 (probably HCC), LR-5 (definitely HCC), LR-M (malignant but not specific for HCC), and LR-TIV (tumor in vein). LI-RADS aimed to not interfere with transplant allocation criteria of AASLD, resulting in a comparable sensitivity and specificity of washin/washout criteria. Although LI-RADS incorporates modern imaging features of HCC such as hepatobiliary phase and T2-weighted series, these criteria are not eligible to confirm a definite HCC diagnosis (i.e., LR-5). This results in a high number of HCC cases in LR-4 and also LR-3, necessitating biopsy for confirmation of the disease. Although lesions <1 cm is also interpretable in LI-RADS, unlike EASL recommendations, a definitive HCC diagnosis (LR-5) cannot be made in these lesions.
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Modern Imaging Criteria

However, modern imaging criteria, mainly derived from the multiparametric MRI using hepatobiliary contrast agents, such as Gd-EOB-DTPA, can identify HCC and its precursor lesions with a higher sensitivity with a similar specificity compared to the washin/washout criteria. Renzulli et al. [11] defined the following criteria for HCC lesions with nonclassical appearance:

- Atypical HCC: arterial-phase hypervascularity and hypointensity in the hepatobiliary phase but no washout in the portal venous/delayed phases.

- Early HCC: no arterial-phase hypervascularity and no washout in the portal venous/delayed phases, and no diffusion restriction but the presence of hypointensity in the hepatobiliary phase and diffusion restriction.

- High-grade dysplastic nodule: no arterial-phase hypervascularity, no washout in the portal venous/delayed phases, and no diffusion restriction but the presence of hypointensity hepatobiliary phase.

These criteria achieved a sensitivity of 96% and specificity of 91.8% with all lesions being confirmed by histopathology, and comparison with AASLD criteria showed a superior sensitivity (96% vs. 76.4%) without significant impairment of specificity (91.8% vs. 98.6%). A further analysis from South Korea of hepatobiliary phase hypointense lesions without arterial phase hyperenhancement in patients at a risk for HCC revealed important findings. Centralized histopathological examination showed that only 8% of these lesions were benign with a diagnosis of low-grade dysplastic nodule or regenerative nodule, while 45.4% of the lesions were overt HCCs [12]. Furthermore, 26.2% of progressed and 44% of early HCCs were categorized as an intermediate risk for HCC (LR-3) according to LI-RADS and would end up delayed diagnosis due to the suggestion of follow-up imaging in 3–6 months. These findings are supported by the meta-analysis of 16 studies including 944 patients with 1,819 hypovascular hypointense lesions [13]. Cumulative incidence of transformation into overt HCC with arterial hypervascularity was 18.3% at 1 year, 25.2% at 2, and 30.3% at 3 years, with an initial lesion size associated with an increased malignant transformation risk with a cutoff of 9 mm.

The presence of hepatobiliary phase hypointense lesions without hypervascularity in patients with HCC elsewhere have a significant impact on the outcome after therapy by radiofrequency ablation (RFA) and resection. It was shown that these patients have a significantly higher risk for recurrence and shorter overall survival than patients without such lesions [14–17]. An increased risk of intrahepatic distal recurrence could be the result of enhanced hepatocarcinogenesis of the background liver [17]. Treatment decision process with a higher focus on local therapy of the HCC, the little disadvantage in specificity is accepted, and these criteria are part of the accepted guidelines (Asia-Pacific Association for the Study of the Liver) [18]. For example, a noninvasive diagnosis of HCC according to Asia-Pacific Association for the Study of the Liver is possible if the lesion shows arterial hypervascularization and no washout but hypointensity in the hepatobiliary phase, as well as hypovascular lesions with hepatobiliary phase hypointensity if the contrast-enhanced US confirms the diagnosis. Implementation of hepatobiliary phase in the staging of HCC patients, such as an alternate descriptor for washout in hypervascular lesions or identification of malignancy in hypovascular lesions, results in a significant shift in BCLC classification with a change in up to 14% of the patients [19]. In consequence, the higher sensitivity of implementation of hepatobiliary phase imaging in the assessment of HCC disease has an impact on therapy decision-making. In a sequential analysis of CT only and CT plus gadoxetic acid-enhanced MRI in the second step, Yoo et al. [20] showed a significant change in treatment recommendation. As an example, 45.5% of patients who were initially allocated as suitable for surgery based on CT were identified as not suitable for resection based on CT and gadoxetic acid-enhanced MRI.

The diagnostic arm of the SORAMIC study aimed to analyze the diagnostic accuracy of treatment decision-making of CT and gadoxetic acid-enhanced MRI in patients with HCC [21]. A truth panel served as the gold standard for optimal treatment decisions. Independent review of both modalities was done by 2 reader groups, and HCC diagnosis in gadoxetic acid-enhanced MRI was based on modified HCC criteria according to Renzulli et al. [11] (see above), and in CT, EASL criteria (presence of washin and washout) were used. The accuracy in treatment decision was significantly higher for gadoxetic acid-enhanced MRI in both reader groups (around 80%) as than CT (around 70%), not affected by different baseline characteristics such as the presence of cirrhosis or liver function. Furthermore, a nationwide analysis in South Korea showed that the evaluation of HCC patients with both MRI and CT resulted in longer survival than in patients who underwent only CT [22]. Additionally, in patients with localized disease, gadoxetic acid-enhanced MRI was associated with lower mortality compared with MRI with other contrast agents.
Imaging beyond Diagnosis

In addition to the identification and characterization of lesions, imaging provides information on histopathological features of HCC. Microvascular invasion (mVI) in histopathological analysis has been shown as an independent predictor of recurrence of HCC after surgical resection, locoregional therapies, or liver transplantation [23–25]. Several studies evaluated the potential value of imaging in predicting mVI. The presence of peritumoral arterial enhancement, irregular tumor margin, and peritumoral hypointensity in the hepatobiliary phase on preoperative MRI images were shown to correlate with mVI in resected HCC specimens [26, 27]. Additionally, with the advancement of artificial intelligence in medical imaging, radiomics analyses have been used to predict mVI, recurrence, or overall survival in patients with HCC [28–32].

Interventional Therapies

Imaging-guided liver-directed therapies play an integral role in the management of HCC, with approximately 60% of patients with HCC receiving during the treatment process [33–36]. While local ablation is the cornerstone therapy at early stages and transarterial chemoembolization (TACE) is the standard treatment for intermediate-stage HCC, selective internal radiation therapy (SIRT) offers an additional option to systemic therapies at advanced stages.

Image-Guided Tumor Ablation

Local ablation is the application of chemical substances or sources of energy directly to the tumor to achieve complete or considerable elimination of viable tumor. Several techniques have been developed to induce tumor necrosis by thermal ablation (RFA, microwave ablation [MWA], laser, or cryoablation), radiation (brachytherapy), or injection of chemical agents (i.e., alcohol); however, most of the literature was based on RFA. The main advantages of these methods are percutaneous applicability, low-cost, minimal invasiveness with preserving surrounding healthy parenchyma, shorter hospitalization need, and a low rate of morbidity and mortality. A systematic review of 12,158 patients who underwent RFA, MWA, or ethanol injection showed a major complication rate of 3.29% and a mortality rate of 0.16% [37]. Considering efficacy, several randomized trials have shown the superiority of RFA over alcohol injection in the treatment of small HCCs [38–41], and RFA has been established as the standard ablative therapy for early stages [34–36].

The OS rate has been reported around 60.2–68.0% at 5 years [42, 43] and 27.3% at 10 years after RFA [43]. In addition to the Child–Pugh class and serum AFP level, the tumor size and number were associated with survival. Despite a very high local tumor control rate (96.8% at 10 years), distant recurrence was seen in 80.8% of the patients.

Four randomized controlled trials have compared resection with RFA in patients with HCC at very early or early stages, and except for one study with better survival after resection, there was no significant difference in OS [44–47]. However, the complication rates were significantly lower in the RFA arm. Additionally, cost-effectiveness analysis showed superiority of RFA for very early HCC and 2 or 3 lesions smaller than 3 cm [48]. A recent study comparing resection and RFA in patients with recurrent HCC identified no significant difference in OS; however, subgroup analysis showed survival benefit from hepatectomy in patients with lesions >3 cm or AFP >200 ng/mL [49].

MWA has only been established for a few years, and so far, a comparison of MWA with RFA has only been made for individual scenarios. In general terms, one advantage of MWA is the shorter ablation time and the lower sensitivity to heat sink phenomenon, cooling effects from adjacent larger vessels causing a risk for incomplete ablation or local recurrence. However, at the same time, this also harbors the risk of therapy-associated vascular occlusions. In addition, the size of the ablation zone achieved with MWA is apparently more variable than with RFA and varies greatly between the individual generators/applicators. A recent review of 19 studies with 3,043 patients showed no significant difference in OS and local recurrence of patients with HCC who underwent RFA, MWA, or cryoablation [50].

Despite the lack of consensus on optimal ablative margin, >10 mm margin resulted in significantly better recurrence-free survival than ≥5 mm margin [51]. For both techniques, the best tumor control is achieved in lesions smaller than 3 cm due to technical reasons, whereby lesions up to 5 cm can also be ablated. In addition to size, the position of the lesions (peripheral vs. central) should also be considered in the treatment decision. A peripheral location adjacent to hollow organs can only be carried out with RFA and MWA to a limited extent due to the risk of hollow organ perforation but is usually easily accessible for laparoscopic resection. In a propensity score-based analysis of effects of tumor location on the outcome in patients who received MWA; the peribiliary group had lower PFS and OS at 3 and 5 years after thera-
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Transarterial Chemoembolization

TACE depends on the dual blood supply of the liver, while most of the blood flow to the hepatocytes is from the portal vein, tumor cells receive blood supply almost exclusively from the hepatic artery. Chemoembolization has been shown to improve overall survival compared to best supportive care [62, 63] and is the standard of care for BCLC-B patients [36]. The important point is super-selective catheterization of the tumor feeders to minimize negative effects on the liver function caused by nontarget embolization of the healthy liver parenchyma, as well as identification of parasitic extrahepatic feeders to achieve complete embolization of the tumor.

Different formulations have been described, from the use of bland embolization particles (transarterial embolization), the mixture of an oily contrast medium (lipiodol) with various chemotherapeutic agents (mostly doxorubicin; conventional TACE) to particles loaded with doxorubicin (drug-eluting TACE). Previous studies did not identify the superiority of one technique over others in terms of tumor control or survival [64–66]. However, drug-eluting TACE was associated with lower side effects, probably due to the delayed release of doxorubicin [65, 66].

Contraindications for TACE are acutely decompensated liver function, extensive tumor burden, portal vein thrombosis, biliary obstruction, history of a biliodigestive anastomosis, reduced performance status, Child-Pugh B liver function, and high-risk esophageal varices [67]. Although the initial studies on TACE met their primary end point, they recruited very inhomogeneous patient cohorts with a wide range of liver functions and tumor burden, and due to lack of other effective therapies at that time, TACE was used too widely, including the patients who probably would not benefit from TACE, while the risk of liver decompensation increase. Thus, indications for TACE have been refined, and scoring systems for patient selection have been developed. The hepatoma arterial-embolization prognostic score assigns patients into 4 grades based on the tumor size (>7 cm), AFP (>400 ng/mL), bilirubin (17 μmol/L), and albumin (36 g/dL) and suggests to exclude patients with more than one positive factors [68].

Similar to local ablation, systemic adjuvant therapy after TACE with sorafenib cannot be recommended. Several RCTs showed no benefit in terms of overall response, PFS, and overall survival in the combination arm [69–71]. If new combination therapies are able to overcome this limitation remains to be seen [72, 73]. However, in the era of multiple available systemic therapies for HCC, it is unclear when to switch to systemic therapies after TACE. Similar to the hepatoma arterial-embolization prognostic score, scoring systems have been developed to differentiate patients who would benefit from repeated TACE sessions. The ABCR score, incorporating ≥2 increase in the
Child-Pugh score compared to baseline and absence of radiological response, in addition to baseline BCLC and AFP, has been shown to identify patients with dismal prognosis with evaluation before the repeated TACE sessions [74]. Additionally, increased response rates and prolonged overall survival under checkpoint inhibitor combination therapy have also led to the proposal of substituting TACE by systemic therapy (NCT04712643).

It should be noted that in patients who receive TACE as a bridging procedure for liver transplantation, a more aggressive therapeutic approach should be preferred to achieve higher tumor control and keep the patient within the transplantation criteria, and patient selection criteria concerning liver functions are generally not practicable. The indication should be based on an individual and interdisciplinary decision in these patients.

In summary, TACE is an effective method for locoregional therapy of a subgroup of HCC patients in stage BCLC-B. Patient selection and reevaluation of the therapeutic indication during the following TACEs are crucial for optimal therapeutic benefit. Besides, TACE is an effective bridging procedure in HCC patients listed for liver transplantation and for whom a local ablation/surgical procedure is not possible.

Similar to RFA alone, the combination of TACE and RFA resulted in similar disease control and overall survival rates compared to repeat resection in patients with recurrent HCC lesions ≤5 cm after initial resection [75]. In a propensity-matched analysis, OS rates at 1, 3, and 5 years after the TACE plus RFA were 84.3%, 60.4%, and 46.4%, while after resection were 84.3%, 64.5%, and 49.8%, respectively. However, this approach is not generally recommended due to the limited data, especially considering the possibility of larger liver parenchymal damage [36].

Imaging-Guided Brachytherapy

In addition to local ablation using thermal methods, local ablation using catheter-based radiotherapy (brachytherapy) can also be used. In this technique, image-guided irradiation catheters are introduced into the tumors in sedation, and then high-dose irradiation is carried out using the afterloading technique. Advantages of this ablation technique are the lack of sensitivity to cooling effects of large vessels, the possibility of ablating centrally located tumors which carries an additional risk of bile duct necrosis in thermal ablation, and the lack of size limitation. Additionally, it provides better controllability of the energy application in peripheral herds to avoid toxicities to the adjacent organs (like the stomach, intestines, or heart). Single-center studies confirm a local control rate of around 90% after 12 months for tumors up to 12 cm in size and a median overall survival of 20–29 months with a 3-year survival rate of 46–65% [76, 77]. The patient characteristics in these studies, including the lesion size, indicate that brachytherapy is a local alternative therapy to TACE or thermal ablation, with higher local disease control rates than TACE. A prospective randomized phase II study has shown a significantly longer time to progression and time to untreatable progression after brachytherapy than TACE [78]. The overall survival did not differ but this can be explained by a crossover design with a significant number of patients from the TACE arm who received brachytherapy after disease progression that was not controllable with TACE. Overall, the literature shows promising and comparable to other ablation techniques results, and consequently, brachytherapy was listed as an alternative therapy to RFA in the current ESMO guidelines [79]. Also, brachytherapy could be an alternative to TACE in the context of bridging to liver transplantation. Brachytherapy resulted in significantly higher tumor necrosis in the evaluation of explants than TACE [80]. Although brachytherapy is associated with track seeding similar to thermal ablation, a needle track metastases rate is low with 1.2% within the liver and 0.3% extrahepatic seeding [81].

Yttrium-90 Radioembolization/SIRT

SIRT is a locoregional therapy that relies on the principle of intra-arterial brachytherapy with the infusion of yttrium-90 containing microspheres into the hepatic artery. It can be administered either selectively to individual tumor-bearing segments or nonselectively to the hepatic arteries. A single whole-liver therapy is avoided to avert radiation-induced liver decompensation; if treatment of the entire liver is necessary, this must be done sequentially, separated by lobes, at an interval of 4–6 weeks.

Due to the higher arterial vascular supply of the HCC, a high tumor-to-liver ratio is usually achieved with the accumulation of the yttrium-90 microspheres, which usually results in high effectiveness of the therapy with acceptable side effects. Due to the limitations of the TACE concerning the number and size of the tumors, RE has been proposed as an alternative treatment option for HCC patients with a liver-dominant disease who cannot tolerate systemic therapies, and the SIRT is frequently applied within the framework of individualized therapy concepts.
Many nonrandomized trials have demonstrated the efficacy and safety of SIRT in patients with HCC [82–84]. Although 2 randomized trials, performed in Asian and Western cohorts, failed to show superiority of SIRT over sorafenib, both trials reported significantly lower adverse events in the SIRT arm [85, 86]. Similarly, in the SORAMIC trial [87], the addition of the SIRT did not improve survival, but, in the per protocol analysis, 3 patient subgroups were identified who benefited from the combination therapy: noncirrhotic patients (22.2 vs. 9.9 months, HR 0.46, \(p = 0.015\)), nonalcoholic genesis (15.3 vs. 11.1 months, HR 0.63, \(p = 0.01\)), and patients <65 years (18.6 vs. 11.3 months, HR 0.65, \(p = 0.048\)).

Although there was no clear difference, the statistical power or the sample size of the SARAH and SIRVENIB trials was unfortunately not sufficient to show a noninferiority of the SIRT compared to sorafenib. Also, no subgroups were identified with increased benefit from SIRT or sorafenib. However, both studies showed a significantly better tolerance or fewer toxicities after SIRT than sorafenib therapy and also a higher response rate and a longer time to progression. Furthermore, a meta-analysis of these 3 trials has suggested noninferiority to sorafenib, besides higher tolerability of SIRT [88].

Recently, it has been postulated that the lack of a personalized dosimetry approach in 3 phase III trials of SIRT could be a potential reason for negative results. A propensity-matched post hoc analysis of the SARAH trial has shown that patients who received a tumor dose greater than or equal to 100 Gy have better survival than patients who received sorafenib [89]. Additionally, in a phase II trial using glass particles, personalized dosimetry with a minimum dose of 205 Gy targeted to the index lesion resulted in a significantly higher objective response rate and longer overall survival than standard dosimetry [90]. Similar to other locoregional therapies, concepts combining immune checkpoint inhibitors and radioembolization have been proposed [91]. As with other radiation-based treatment modalities synergistic effects, often referred to as the abscopal effect, have been put forward as a pathophysiological basis for this approach [92, 93]. To date, only experimental data and case reports are available on this matter in HCC, but early clinical trials have already been initiated (NCT03380130) [94, 95].

In summary, based on the current data situation, no general therapy recommendation can be made for SIRT in HCC, whereby the largely comparable survival figures compared to system therapy must be taken into account in the preparation of the individual therapy concept. A positive effect of the SIRT should be considered in the above-mentioned patient groups (SORAMIC study) of noncirrhots, patients with the nonalcoholic origin of HCC, and patients <65 years of age. Regardless of this, it should not be forgotten that with the SIRT and the data now available, there is a therapy option for patients with contraindications for sorafenib, with intolerable toxicities under sorafenib, or with progression under system therapy. Additionally, due to the higher response rate and the better disease control rate after SIRT than TACE, SIRT can be used as a bridging method in transplant candidates [96, 97].

**Future Perspectives**

In addition to many clinical and imaging factors, immune mechanisms and the immune texture of the tumor microenvironment have been shown to play a critical role in the outcome of patients with HCC. Studies evaluated patients who underwent resection, and identified lower recurrence in patients with infiltration by immune effector cells [98, 99]. Locoregional therapies, such as TACE and SIRT, have a potential synergistic effect on immuno-therapy by altering tumor microenvironment and activation of immune cells [100]. A retrospective analysis of resected materials showed an increase in tumor infiltrating lymphocytes, CD4⁺ and CD8⁺ T cells in patients who underwent SIRT compared to patients who underwent TACE or resected without prior locoregional therapies [91]. Combination of locoregional therapies with immune checkpoint inhibitors might improve antitumoral immunity and the patient outcome. There are ongoing trials evaluating combination of immune checkpoint inhibitors with SIRT (NCT03099564) and TACE (NCT04224636).

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