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REVIEW

HCC: Transarterial Therapies—What the Interventional Radiologist Can Offer

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Abstract

With the increasing incidence of hepatocellular carcinoma (HCC) and its high mortality rates, effective treatment options are of urgent need, preferably in a multidisciplinary setting. In the management of those patients, interventional radiologists play a key role. In this article, we reviewed the current literature for regional, intraarterial treatment strategies of advanced-stage HCC including conventional transarterial chemoembolization, transarterial embolization, transarterial embolization with drug-eluting beads, and selective internal radiation therapy.

Keywords Hepatocellular carcinoma (HCC) · Conventional transarterial chemoembolization (cTACE) · Drugeluting bead TACE (DEB-TACE) · Selective internal radiation therapy (SIRT)

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Key Messages

- Intraarterial therapies in patients with intermediate-stage hepatocellular carcinoma (HCC) show improved treatment response and disease control with acceptable safety profiles.
- Conventional transarterial chemoembolization (cTACE), bland transarterial embolization (TAE), transarterial embolization with drug-eluting beads (DEB-TACE), and selective internal radiation therapy (SIRT) are interventional intraarterial therapy options in HCC treatment.
- Patients with HCC should be treated in hospitals with multidisciplinary team with expertise in liver tumors.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide due to its complexity of tumor pathogenesis, disease reccurrence after curative treatment, and metastases [1]. The major risk factor for HCC is liver cirrhosis, usually related to chronic hepatitis B (HBV) or C virus (HCV) infection, or overconsumption of alcohol [2]. Obesity, metabolic syndrome, nonalcoholic steatohepatitis (NASH), and hemochromatosis are also significant risk factors [3–6].

Patients with HCC have a poor prognosis. At the time of first diagnosis, many patients have already an advanced stage of disease that precludes curative options such as liver transplantation, surgical excision, and percutaneous ablation methods including radiofrequency ablation and microwave ablation [7].

Recently developed and improved interventional treatment techniques lead to an increasing importance of interventional radiologists in the management of patients with advanced-stage HCC. In advanced-stage HCC, multiple

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locoregional intraarterial treatment options have been established to slow down disease progression. Those treatment options may improve the outcome of potentially curative therapies of HCC in Barcelona Clinic Liver Cancer (BCLC) A stage as well as a bridging treatment before tumor resection or ablation therapies [7–9].

For each individual patient, the optimum interventional, liver-directed intraarterial treatment option needs to be carefully selected. Treatment options include bland transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), TACE with chemotherapeutically loaded beads (DEB-TACE), or selective internal radiation therapy (SIRT) [7–12]. This article provides an overview of intraarterial therapies in the treatment of HCC based on a review of the current literature.

Conventional Transarterial Chemoembolization (cTACE)

Conventional transarterial chemoembolization (cTACE) is one of the leading treatment options for HCC with nearly half of all HCC patients undergoing this procedure at some point during their clinical history [13, 14].

In accordance with the BCLC guidelines, cTACE is currently the standard of care for patients with HCC in the intermediate stage (BCLC stage B) [15–17]. In patients eligible for curative treatment (BCLC stage A), cTACE can be performed as bridging treatment option.

TACE is also a locoregional catheter-based intraarterial therapy for the treatment of HCC and liver metastases from different primaries including colorectal cancer (CRC), breast cancer (BC), and neuroendocrine tumors (NET) [18–24].

Transarterial chemoembolization (TACE) is based on the effect of simultaneous application of chemotherapeutic drugs and embolic agents such as degradable starch microspheres (DSM), collagen and gelatine sponge (Gelofam), polyvinyl alcohol, or lipiodol. All embolic agents have in common that they increase the time range of the chemotherapeutic effect on tumor lesions. Commonly used chemotherapeutic agents are doxorubicin, epirubicin, mitomycin, cisplatin, and miriplanin. A previous study has shown that HCC cells are highly sensitive to various chemotherapy drugs: irinotecan in 44% of HCC patients, gemcitabine in 36%, mitomycin in 14%, cisplatin in 8%, and 5-fluorouracil oxalate (5-FU) in 4% [25]. While doxorubicin, mitomycin, and cisplatin are commonly used in the USA and Europe, doxorubicin is the most commonly used chemotherapeutic agent in Asia [26]. The selection of chemotherapeutic agents, embolic agents and application method vary from center to center. A further standardization of TACE protocols is needed.

From the technical perspective, chemoembolization should be as selective as possible. Selective or superselective administration of the mixture of chemotherapeutic agent and occluding particles results in a high local concentration of the chemotherapeutic agent within the tumor with low systemic distribution. Due to the occlusion of the vessel by the embolic particles, the chemotherapeutic agent remains in the tumor, and the resulting hypoxia further improves the effect of the chemotherapeutic agent. Most commonly, a mixture of chemotherapeutic and embolic agents is injected first, followed by the injection of embolizing particles until stagnation of blood flow in the tumor branch is observed [27].

Lipiodol as the most commonly used embolic agent in cTACE has an average pharmacological half-life time of 4–12 weeks, while DSM have an average pharmacological half-life time of 90–120 min. The total embolization time of DSM leads to only moderately increased VEGF levels after the embolization compared to cTACE and most likely to less neoangiogenesis [28].

Prerequisite for successful TACE is the presence of a hypervascularized tumor. cTACE is either performed as "on demand" (repeated in case of persistent vascularization) or as "continuous" (repeated every 4–6 weeks until devascularization) schedule.

TACE Procedure

After disinfection, sterile covering of the access point (inguinal region), and local anesthesia, a 5F-sheath is inserted into the femoral common artery using the Seldinger technique. After that, a 5F pigtail catheter is used for the aortography to gain an exploratory view of the abdominal arteries including the celiac trunk and the superior mesenteric artery. In a next step, selective catheterization of the celiac trunk using a 5F sidewinder catheter is performed. The angiography depicts the anatomy of the hepatic artery, tumor blush, feeding arteries, and arteriovenous shunts. In addition to the pre-interventional, contrast-enhanced CT or MRI, an indirect portography should be performed during angiography to ensure a stable flow in the portal vein. During the initial TACE, cone beam CT can be performed to evaluate the tumor-feeding artery and detection of small HCC lesions. A 2.8F coaxial microcatheter system is inserted through the celiac trunk and past the branches of the gastroduodenal artery. The microcatheter for the injection of chemotherapeutic drugs and embolic agents should be placed selectively or superselectively in the segment arteries which feed HCC lesions. After confirming the correct position of the catheter tip, the chemotherapeutic and embolic agents are infused under radiographic guidance. To control the correct administration of drugs and the occlusion of tumor vessels with flow stasis, a final angiography should be performed. After completing

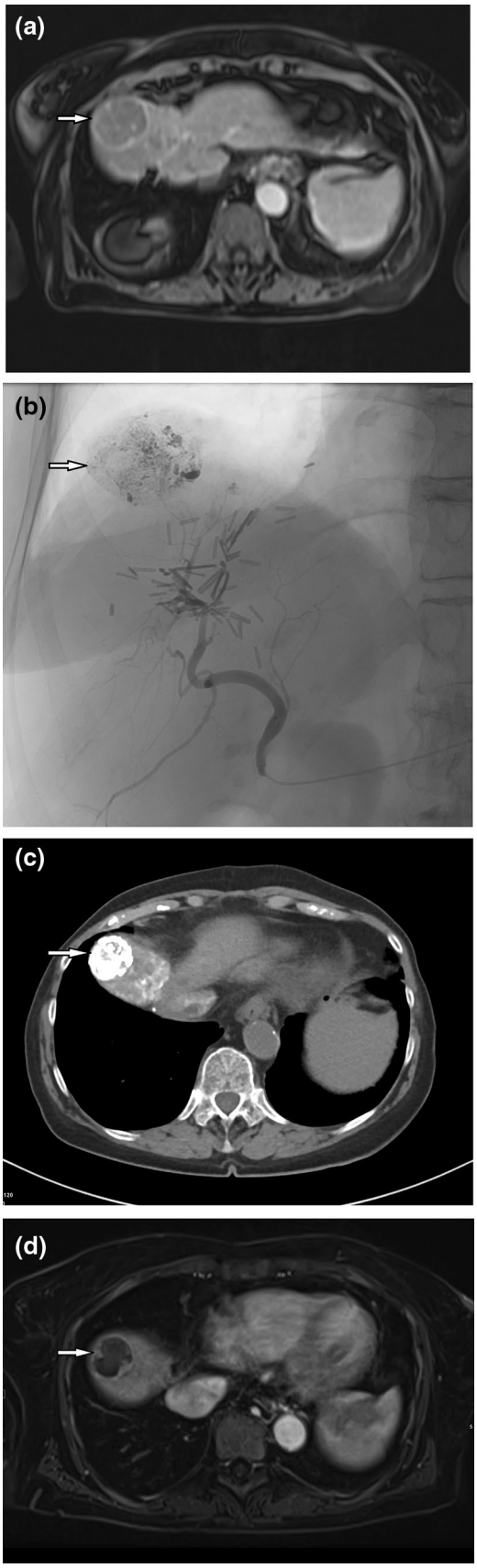

Fig. 1 A 78-year-old female patient with recurrent HCC after first curative atypical resection of HCC in liver segments 7 and 8. Partial response achieved after three sessions of TACE. **a** Pre-treatment transverse contrast-enhanced T1-weighted MR image shows a 3.6×3.9 cm HCC lesion (arrow) in liver segment 4a. **b** Post-embolization DSA image shows the presence of lipiodol deposition in HCC lesion (arrow). A microcatheter was inserted in the right liver artery. **c** CT after 3. TACE. Documentation of lipiodol deposition in HCC lesions in liver segment 4 (arrow). **d** Post-treatment transverse contrast-enhanced T1-weighted MR image after three sessions of TACE shows partial response with devascularization and necrosis of intrahepatic lesion (arrow)

the procedure, the punctured location of the femoral artery must be occluded by using a percutaneous closure device or compression bandage.

After the interventional treatment, patients should be transferred to an interventional ward for subsequent clinical observation. Patients can be discharged on the day of the procedure if no complications occur.

Most patients are either treated as outpatients or stay one night at the hospital; prolonged hospital stay is necessary in case of complications.

Before discharge, patients should be informed about possible post-embolization side effects. Post-embolization syndrome is one of the most common side effects of chemoembolization and includes abdominal pain, slight elevation of temperature, nausea, vomiting, and sometimes fatigue. Intravenous analgesics during and oral analgesics after the procedure provide sufficient pain control. The incidence of major complications after TACE has been reported with 5.6% including necrosis of liver parenchyma, decompensation of liver cirrhosis and abscess, and mortality rates of 0–10% [29].

Benefits and risk of treatment-induced liver failure need to be carefully balanced before TACE. Contraindications of TACE are Child–Pugh class C, uncorrectable coagulopathie, total portal vein thrombosis, poor residual liver function, total bilirubin > 3 mg/dL, extrahepatic metastases, or the presence of high-flow arterioportal or arteriovenous shunts.

TACE treatment usually requires multiple procedures in intervals of 4–6 weeks. MRI and CT are performed to evaluate results of the chemoembolization (Fig. 1).

In conclusion, TACE is a moderately invasive, intraarterial method for the treatment of HCC. Treatment of intermediate-stage HCC aims at a palliative treatment rather than curative. cTACE in patients with BCLC stage B has level I evidence [15, 30–33].

In a meta-analysis including 545 patients, Llovet et al. showed a survival benefit for patients with TACE compared with the best supportive care in well-selected cases. TACE improved the 2-year survival rate with an odds ratio of 0.53 ($p < 0.017$) in comparison with an untreated control group. TACE has been reported to achieve partial response in 15–62% of HCC patients. Patients in TACE group had a

Table 1 Key studies employing transarterial therapies of HCC

Study (years)	Number of patients	Chemotherapeutic agents	Embolic agents	Tumor response	Survival
TACE					
Hatanaka et al. [54]	66	Ciriplatin–lipiodol emulsion	Gelatin-sponge particle	mRECIST: CR 53.0% PR 10.6% SD 19.7% PD 16.7%	Median survival: 902 day
Lo et al. [55]	40	Cisplatin–lipiodol emulsion	Gelatin-sponge particle	Response: 29 SD: 7 PD: 4	Survival rates: 1 year: 57% 2 years: 31% 3 years: 26%
Gruber-Rouh et al. [56]	28	Mitomycin only: 50% Mitomycin with irinotecan: 50% Lipiodol 100	DSM	Mitomycin-irinotecan group: CR: 21.4% PR: 42.9%, SD: 28.6% PD: 7.1% Mitomycin group: PR: 57.2% SD: 21.4% PD: 21.4%	PFS in the mitomycin-irinotecan group: 12 months PFS in mitomycin group: 4 months
Yamakado et al. [57]	1290	Epirubicin: 76.9% epirubicin and mitomycin: 17.8 Others: 5.4%	Lipiodol	NA	The 1-, 3-, 5-, and 7-year overall survival rates: 92.0%, 62.9%, 39.0%, and 26.7%
Takaki et al. [58]	199	Lipiodol and epirubicin or doxorubicin emulsion		NA	Median overall survival: 3.8 years
DEB- TACE					
Varela et al. [36]	27	DEB-TACE		mRECIST: PR: 44.4% SD: 25.9% PD: 18.5%	NA
Malagary et al. [41]	71	DEB-TACE		EASLE: CR: 15.5%	At 30 months survival was 88.2%
Poon et al. [37]	30	DEB-TACE		mRECIST: CR: 6.7% PR: 63.3%	NA
Lammer et al. [40]	212	DEB-TACE: 102 patients cTACE: 110 patients		Disease control rates: DEB-TACE: 63.4% cTACE: 51.9%	NA
Golfieri et al. [59]	177	DEB-TACE: 89 patients cTACE: 88 patients		No differences	DEB-TACE: 1- and 2-year survival rates were 86.2% and 56.8% cTACE: 1- and 2-year survival rates were 83.5% and 55.4%
Facciorussio et al. [60]	1449 (meta-analysis)			No significant difference	No significant difference
SIRT					
Mantry et al. [61]	111			CR: 11.7% PR: 11.7% SD: 9.9% PD: 5.4%	Median survival time: 13.1 months
Kim et al. [62]	40			CR = 11.1% PR = 52.8% SD = 19.4% PD = 16.7%	3-year survival rate = 75%

Table 1 (continued)

Study (years)	Number of patients	Chemotherapeutic agents	Embolic agents	Tumor response	Survival
Kolligs et al. [63]	13			PR 30.8%; disease control rate: 76.9%	1-year survival rate = 46.2%
Golfieri et al. [53]	325			NA	Median overall survival: 14.5 months
Gramenzi et al. [64]	74			CR: 14.3% PR: 53.9% SD: 14.3%	Overall survival: 13.2 months 1-year survival rate = 51.8% 3-year survival rate = 21.6%

CR complete response, *PR* partial response, *SD* stable disease, *PR* progressive disease, *NA* not available, *modified RECIST* modified response evaluation criteria in solid tumors (RECIST) criteria, *PFS* progression-free survival, *EASL* European Association for the Study of the Liver Disease

median survival of 16–20 months [30]. A summary of the previous studies is shown in Table 1.

Transarterial Embolization (TAE)

Bland transarterial embolization (TAE) aims at achieving total arterial occlusion of the tumor vessels in the absence of chemotherapeutic agents. The result of TAE is tumor necrosis [34]. Favorable embolic agents used for tumor vessel occlusion are lipiodol and polyvinyl alcohol particles. Technical methods of TAE are similar to those for conventional chemoembolization.

In combination with ablation therapy, TAE achieves survival rates similar to surgical resection [35]. In addition to the treatment effect of TAE, HCC lesions are well visualized by lipiodol for ablation therapy planning.

TACE with Chemotherapeutically Loaded Beads (DEB-TACE)

In recent years, chemotherapeutically loaded beads (DEB) have been introduced in the clinical practice, including doxorubicin-loaded beads for treatment of HCC. DEB-TACE is defined as the infusion of microspheres which are loaded with chemotherapeutic agents to achieve sustained, in vivo drug release. Indications for DEB-TACE are similar to those for cTACE.

Chemotherapeutically loaded beads are produced from biocompatible polyvinyl alcohol (PVA) hydrogel that has been modified with sulfonate groups for the controlled loading and delivery of chemotherapeutic drugs. The beads are available in different sizes (100–300 µm until 500–700 µm) and can be loaded with doxorubicin or irinotecan. The advantage of DEB-TACE in comparison with cTACE is the favorable pharmacokinetic profile. The use of chemotherapeutically loaded beads results in a lower peak plasma concentration of the chemotherapeutic agents and longer exposure to the tumor compared to other therapeutic agents. Chemoembolization using DEBs results in significantly fewer drug-related side effects compared with cTACE [36, 37]. Doxorubicin is gradually sequestered inside the tumor as the drug dissociates from the beads only under specific ionic circumstances such as those found in tumor cells [36–39].

A randomized phase II study which compared DEB-TACE and cTACE showed that DEB-TACE was associated with a significant reduction in liver toxicity and drug-related adverse effects. Patients with Child–Pugh B, recurrence of HCC, or bilobar HCC disease had a significant increase in objective response [40].

Several trials studying the effect of DEB-TACE with doxorubicin have been performed in patients with HCC and are summarized in Table 1. Overall, these studies reported that DEB-TACE proved to be effective in patients with advanced-stage disease with improved treatment response and disease control while safety profile was described as acceptable. These results may provide a niche for those patients with poor conditions such as patients with Child–Pugh B and ECOG 1 disease.

In comparison with DEBs with smaller diameters, DEBs with larger diameters induced limited necrosis because occlusion of proximal vessel. DEBs with smaller diameters can be delivered to distal vessels where they obstruct collateral channels [38, 39, 41].

Han et al. [42] performed a meta-analysis comparing DEB-TACE and cTACE with 217 and 237 patients, respectively. The results showed that DEB-TACE tends to have better results for disease control, although differences were not significant.

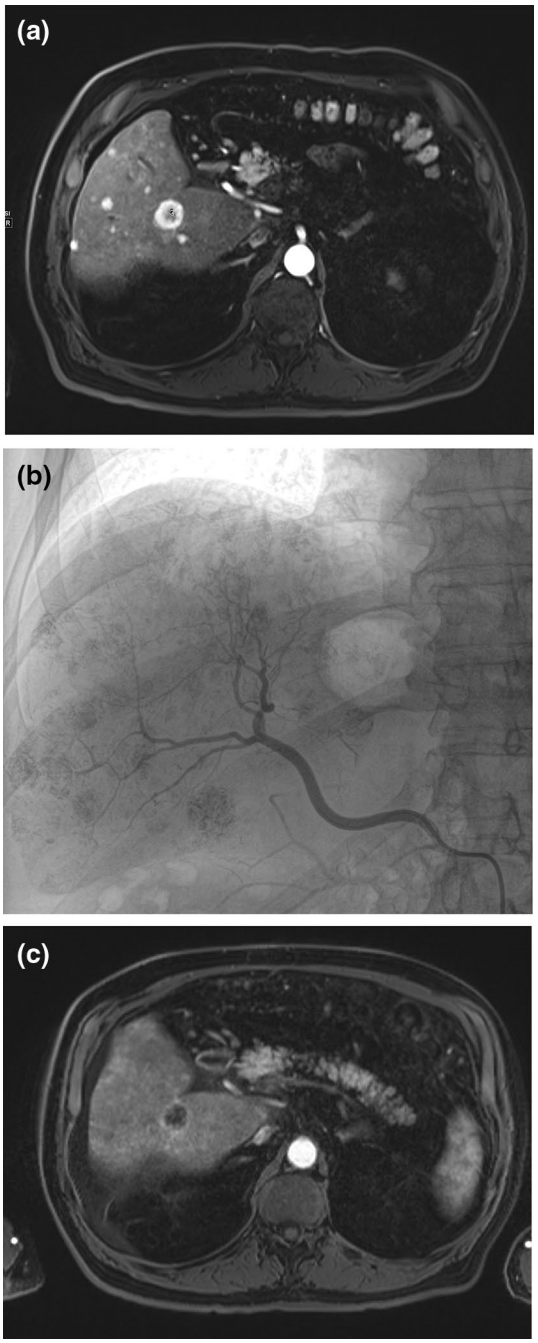

Fig. 2 A 66-year-old patient with NASH-related HCC underwent selective internal radiation therapy (SIRT) of multiple HCC liver lesions. The patient had recurrence of HCC after the initial curative left hemihepatectomy and was in BCLC B stage. Eight weeks after SIRT, complete response according to mRECIST was documented. **a** Pre-treatment transverse contrast-enhanced T1-weighted MR image shows multiple HCC liver lesions. **b** Digital subtraction angiogram image during SIRT procedure shows the presence of arterial hypervascularity of multiple HCC lesions. **c** Post-treatment transverse contrast-enhanced T1-weighted MR image obtained 8 weeks after radioembolization (SIRT) shows the elimination of tumor vascularity and completely necrosis of intrahepatic lesions

Selective Internal Radiation Therapy (SIRT)

Another treatment option for HCC in BCLC stage B is 90Y radioembolization, which delivers high-dose ß-emitting radiolabeled microspheres through a microcatheter to the HCC lesions via its arterial supply [33, 43, 44]. This technique is a combination of brachytherapy and embolization. Radioembolization uses the same technical principle as cTACE.

A randomized phase II study statistically observed a significantly longer time to progression for patients treated with SIRT when compared to those treated with cTACE [45]. Indications for SIRT are diffuse HCC, diffuse non-hypervascularized HCC, and HCC without response to TACE [46].

Yttrium-90 is the most common isotope for radioembolization. It is a ß-emitter which has a penetration of 2.5 mm and a half-life time of 64.2 h. Radioembolization using resin or glass microspheres has shown promising initial results.

Preparatory arteriography is required before radioemolization. The purpose of this arteriography is to determine where to inject the 90Y labeled microspheres by identifying the main artery which supplies the tumor and by confirming that there are no arteries arising close to the injection location which could lead to an extrahepatic spread of particles, primarily into the gastrointestinal tract. During preparatory arteriography, those arteries can be preventively occluded with coils [47]. After preparatory arteriography is finished, albumin particles labeled with 99mTc (99mTc-MAA) are injected, and subsequent scintigraphy ensures that there are no sites of extrahepatic gastrointestinal hyperactivity and that the hepato-pulmonary shunt remains low with the objective that the dose delivered to the lungs should be less than 30 Gy per treatment session, with a maximum cumulative dose of 50 Gy [47].

In the time of SIRT, selective injection of microspheres is achieved through closed circuit delivery using a proprietary delivery system specific to that particular device [27, 48]. Close monitoring using angiography during microsphere delivery is recommended to ensure that there is no significant inadvertent reflux into normal hepatic tissue or elsewhere, which may lead to inadvertent tissue damage. Due to the low tissue penetration, SIRT does not require isolation of the patient and requires only limited radioprotection measurements after the treatment.

Following SIRT, the HCC lesions are monitored using either contrast-enhanced CT or MRI to ensure that the lesions have undergone total necrosis and ruling out residual tumor, which would otherwise continue to grow (Fig. 2).

SIRT has only few risks of complications. It can cause unspecific symptoms such as fever, nausea, pain, fatigue, and anorexia. If the microspheres accidentally enter the gastrointestinal system, they can cause local inflammation including

pancreatitis, cholecystitis, ulcerations, and radiation-induced pneumonia [27, 49].

The safety of Y90 radioembolization has been documented in phase I and phase II clinical investigation [50]. In several retrospective studies, the efficacy of SIRT in the treatment of HCC has been reported (Table 1).

Salem et al. [51, 52] documented in a large prospective study that there was no significant difference regarding median survival between TACE group versus radioembolization group with 20.5 and 17.5 months, respectively [51]. A meta-analysis including 14 studies about radioembolization showed response rates of HCC ranging from 78 to 89% [53].

The relevant costs and effort associated with SIRT may limit a wider use of this technique.

Transarterial Therapies as Part of a Sequential Treatment of HCC

A combination of locoregional transarterial therapies might offer a good tool for the treatment of HCC, especially in a neoadjuvant setting. Neoadjuvant treatment is defined as a clinical situation in which the previous treatment with transarterial locoregional therapy caused a significant decrease in the size and number of HCC lesions so that a possible curative local treatment, such as hepatic resection or ablation with curative intent, could be performed.

Conclusion

The findings in the recent literature indicate that intraarterial therapies play an important role in the treatment of HCC and include multiple treatment options such as cTACE, TAE, DEB-TACE, and SIRT. Management of HCC requires a multidisciplinary approach for optimum, patient-tailored treatment in centers with excellent expertise in liver tumor treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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