



# Transcatheter arterial chemoembolization combined with radiofrequency or microwave ablation for hepatocellular carcinoma: a review

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Hepatocellular carcinoma (HCC) is the sixth most common type of malignancy. Several therapies are available for HCC and are determined by stage of presentation, patient clinical status and liver function. Local-regional treatment options, including transcatheter arterial chemoembolization, radiofrequency ablation or microwave ablation, are safe and effective for HCC but are accompanied by limitations. The synergistic effects of combined transcatheter arterial chemoembolization and radiofrequency ablation/microwave ablation may overcome these limitations and improve the therapeutic outcome. The purpose of this article is to review the current literature on these combined therapies and examine their efficacy, safety and influence on the overall and recurrence-free survival in patients with HCC.

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Hepatocellular carcinoma (HCC) is the sixth most common type of malignancy and the third most common cause of cancer-related death [1]. HCC is more frequent in males (2.4:1), with high incidence in southeastern Asia, middle and west Africa and Micronesia [2]. The incidence of HCC is increasing worldwide because of the increasing prevalence of hepatitis virus B (HBV) and C (HCV) infection [3]. The main risk factors for HCC are cirrhosis, HBV/HCV infection, alcohol abuse and metabolic syndrome [4]. Other predisposing conditions for HCC development include cigarette smoking [5], iron overload disorders such as thalassemia, hemochromatosis [6], use of oral contraceptive pills [7] and consumption of aflatoxin (produced by *Aspergillus* species) -contaminated foods in warm and humid rural areas [8].

HCC is associated with a high mortality rate, so surveillance programs have been implemented in order to screen high-risk individuals, which is more cost-effective than the treatment of HCC. Patients who are at high risk for HCC development are patients with cirrhosis of different causes (HBV/HCV infection, alcohol, primary biliary cirrhosis), Asian male HBV carriers older than 50 years, and HBV carriers with a known family member with HCC, and they should be evaluated with ultrasound (US) every 6 months [9]. The outcome will be significantly improved if treatment is initialized at an earlier stage. Early-stage HCC lesions are small and curable in the majority of cases with minimally invasive methods, so early diagnosis is critical for therapy.

## Diagnosis

Several modalities are available for HCC screening, including both serological and radiological tests. The most common biomarkers for HCC include AFP, des- $\gamma$  carboxyprothrombin and L3 fraction of AFP. For many years, AFP has been used for the detection of HCC with variable sensitivity and specificity [10,11]. Its level is increased

in patients with cirrhosis complicated by HCC but it is also elevated during pregnancy, in chronic hepatic disease without cirrhosis, in acute or chronic viral hepatitis and in various types of malignancies [12,13]. On the other hand, some small HCC tumors do not secrete AFP and the serum levels of AFP are normal [14]. For these reasons, AFP cannot be used to differentiate HCC from benign liver diseases or other malignancies and the current guidelines of the American Association for the study of Liver Diseases do not recommend AFP for screening or diagnostic purposes, and surveillance needs to be based on US examination every 6 months [9]. Over the recent years, the development of molecular biology has led to identification of new markers such as des- $\gamma$  carboxyprothrombin, glypican-3, squamous cell carcinoma antigen, human hepatocyte growth factor,  $\gamma$ -glutamyl transferase, VEGF and L3 fraction of AFP, which can be used for HCC detection and estimation of treatment success [15].

Different imaging studies are used for detection of HCC lesions. US is an operator and equipment-dependent modality. It is highly specific (97%; range: 95–98%) to detect HCC but insufficiently sensitive (60%; range: 44–76%) [16]. US can detect small tumors with a diameter of 1 cm but sometimes small HCC nodules less than 2 cm can be missed during a US examination [17]. The accuracy and sensitivity of multidetector computed tomography (CT) in the identification of HCC is very high. Usually, the lesion enhances vividly during late arterial phase and then washes out rapidly during portal venous phase, becoming hypoattenuating compared with normal liver parenchyma. Moreover CT is useful for the early diagnosis and the follow-up of the patients with HCC because it can identify lesions less than 2 cm in size with high sensitivity [9,18,19]. Magnetic resonance imaging (MRI) is also accurate in the early detection of HCC, and provides superior contrast resolution compared to CT. HCC lesions are varied hypo-, iso- or hyperintense in the T1 sequence and moderately hyper-intense in the T2 sequence. The lesions usually demonstrate arterial enhancement after gadolinium administration and become hypointense to the remainder of the liver during portal venous and delayed phases [20]. MRI is the most sensitive modality in differentiating the nature of regenerative nodules from HCC nodules in cirrhotic patients [21]. MRI is also useful in patients with renal impairment or hypersensitivity to CT contrast agents. On the other hand, it cannot be used in patients with pacemakers, ferromagnetic implants, claustrophobia and all common contraindications to MRI [22]. Liver Imaging Reporting and Data System is both a set of standardized terminology and a classification system for imaging findings in liver lesions. It was first introduced in 2011 and became widely accepted. It categorizes lesions according to their size and their characteristics (capsule presence, arterial phase enhancement, washout) into benign, HCC or alternative diagnosis. This classification system aims to decrease the variability in interpretation of liver lesions in high-risk patients [23].

The majority of HCCs are diagnosed at an intermediate to advanced stage, and less than 30% of patients with HCC are suitable for curative therapies such as surgical resection, radiofrequency ablation (RFA) or liver transplantation (LT) [24]. The median survival after diagnosis is 6–20 months [9]. Tumor staging is critical in treatment planning but prognosis is affected by the severity of liver dysfunction. The Child–Pugh classification system and the model for end-stage liver disease describe the severity of chronic liver disease but they do not assess cancer-related symptoms or the patient's clinical status [4]. The Barcelona-Clinic Liver Cancer (BCLC) staging system was based on the results from multiple cohort studies and randomized control trials (RCTs). It uses variables related to tumor stage, liver function status, physical status and cancer-related symptoms aiming to link the different stages with a treatment algorithm. This system has been recommended by liver societies from USA and Europe as the primary staging system for HCC because it provides accurate survival prediction and treatment allocation guidelines [25,26].

### Treatment of HCC

Treatment options for HCC include surgical resection, LT, RFA, microwave ablation (MWA), cryoablation, systemic chemotherapy, transcatheter arterial chemoembolization (TACE), radioembolization and radiation therapy [27]. Despite the progress in imaging studies and serum biomarkers for HCC and the widespread use of surveillance programs for high-risk patients, the majority of HCC lesions are diagnosed at an intermediate to advanced stage when curative therapies such as surgical resection, LT, RFA or MWA are not possible [28]. Surgical resection is the gold standard treatment option for early-stage HCC in patients without cirrhosis or portal hypertension symptoms. It is associated with satisfactory survival with low recurrence rates and low perioperative mortality (2–3%) [4].

Surgical resection increases the risk of hepatic decompression in cirrhotic patients, so it is important to estimate the residual liver function and the remnant liver volume [29–31]. Surgical resection is suggested in patients with early-stage disease and preserved liver function. Since the majority of HCC cases develop in cirrhotic patients, surgical intervention becomes challenging and the treatment is directed to other options.

LT is a proper treatment option for patients with earlier stage HCC and end-stage liver disease. It has the significant advantage to eliminate both the tumor and the tumor-generating environment of cirrhosis, which predisposes to further carcinogenesis. The Milan criteria (single nodule up to 5 cm, up to three nodules <3 cm, no evidence of extrahepatic spread or macrovascular invasion) are the traditional criteria for LT. Patients with HCC, within Milan criteria, who underwent LT had low rate of recurrence and significant long-term survival. However, these criteria are too stringent and exclude patients who may be suitable for LT. Expansion of Milan criteria has been studied by many centers with promising results as far as the recurrence and survival rates are concerned [32–35].

Systemic therapy for HCC is still under investigation. Until 2008, there was no systemic therapy to improve survival of patients with HCC. After the publication of two randomized Phase III trials, sorafenib is now the new standard treatment for advanced HCC. Sorafenib is an oral multityrosine kinase inhibitor, which inhibits multiple cell surface and downstream kinases and affects different pathway activations that are involved in tumor progression. Trials showed an increase in median overall survival with mild-to-moderate toxicity symptoms such as anorexia, nausea, weight loss, esthesia and hypertension [36,37]. Due to the relative chemotherapy-refractory nature of HCC and the subjacent poor liver function, systemic chemotherapy is not recommended for HCC. Other targeted molecular agents such as linifanib, brivanib or everolimus are under research or clinical development in order to treat patients who fail to tolerate sorafenib [38–40].

The role of radiotherapy for HCC has also evolved during the last years. External-beam radiotherapy can be used as a treatment option for diffuse HCC. However, it often causes radiation-induced liver disease due to the low radiation tolerance of the liver and is characterized by the lowest recommendation grade in the guidelines of EASL-EORTC [4,41]. On the other hand, stereotactic body radiotherapy (SBRT) is a noninvasive potentially curative method, which delivers high radiation dose to the target volume and minimal exposure to the surrounding healthy tissue. SBRT has comparable efficacy with other local therapies for nonresectable HCC but further studies are necessary to evaluate its indications, the optimal dose and the possible complications after SBRT [42].

Radioembolization is a potential therapeutic option for HCC and liver metastases. There are several available radioisotopes but the most commonly used is  $^{90}\text{Y}$ . Microspheres loaded with the radioactive compound are introduced percutaneously through a catheter into the target vessels and discharge local radiation with minimal exposure to the surrounding healthy tissues [43]. Different studies have shown promising efficacy and low risk for postembolization complications [44,45]. The National Cancer Institute states may recommend radioembolization in selected patients with HCC, who are not eligible for transplant or resection [46]. However, more randomized comparative studies are necessary to evaluate its role in the treatment of HCC.

Local-regional treatment for HCC such as RFA, MWA and TACE are promising therapeutic options for unresectable tumors. Combined treatments using both TACE and percutaneous ablation might overcome the disadvantages and limitations of the individual methods and improve the therapeutic outcome and survival of patients. The purpose of this article is to evaluate the efficacy and safety of combination treatments such as TACE + RFA and TACE + MWA in patients with HCC.

### Transcatheter arterial chemoembolization

TACE is the recommended treatment option for patients with asymptomatic, large or multifocal HCC without macrovascular invasion or extrahepatic metastases in whom curative treatment is not indicated [47]. According to BCLC staging, TACE is suggested as the standard of care for intermediate stages HCC [9]. TACE was first introduced by Yamada *et al.* in 1977 [48]. The role of TACE depends on the isolation of HCC from its blood supply that is mainly derived from the hepatic artery in contrast with liver parenchyma, which is supplied from the portal vein. The embolization of the right hepatic artery branch results in tumor hypoxia and eventually necrosis [49]. A study from Golfieri *et al.* demonstrated significantly higher level of tumor necrosis in patients who underwent selective/superselective TACE compared with lobar TACE [50]. Conventional TACE uses a mixture of chemotherapeutic agents and lipiodol, whereas drug-eluting beads-TACE uses embolic microspheres loaded with a chemotherapeutic agent in order to minimize systemic toxicity and provide a standardized embolic effect [51]. A meta-analysis from Llovet and Bruix showed an improvement in 2-year survival with arterial embolization and a significant benefit of chemoembolization with cisplatin or doxorubicin in comparison with embolization alone [52] and a meta-analysis from Camma *et al.* indicated that TACE improved the overall 2-year survival in patients with unresectable HCC in comparison with nonactive treatment [53]. Lammer *et al.* demonstrated that drug-eluting beads-TACE improved tolerability and decreased liver toxicity in combination with higher rates of complete response [54]. However, TACE is often associated with minor complications such as fever, abdominal

pain, nausea, leukocytopenia and impaired liver function. The risk of major complication such as irreversible liver failure, upper gastrointestinal bleeding, liver abscess, pulmonary embolism, occlusion of hepatic artery or acute renal failure is less than 5% [55,56]. Absolute contraindication to TACE are portal vein thrombosis, biliary obstruction and encephalopathy, whereas relative contraindications include a bilirubin level more than 2 mg/dl, a lactate dehydrogenase level more than 425 mg/dl, and an aspartate aminotransferase level more than 100 IU/l, which are associated with postprocedural mortality [57,58].

### Radiofrequency ablation

RFA is performed by advancing an especially designed electrode into the lesion and applying radiofrequency energy in order to create a zone of thermal destruction that encompasses the tumor. Temperatures range between 60 and 100°C. RFA is moderated by the heat-sink effect (the convective cooling by adjacent blood vessels when ablated tissues are heated), which affects RFA results. Electrodes can be monopolar or bipolar in different designs and multiple sessions may be necessary for complete tumor ablation [59–61]. RFA is considered the best therapeutic modality for very early and early-stage HCC according to BCLC staging when resection or LT is not indicated. Patients must have a single nodule smaller than 5 cm in diameter or less than three nodules with a maximum diameter of 3 cm, without vascular invasion or extrahepatic spread and good liver function status (Child–Pugh class A or B) [28,62]. Livraghi *et al.* showed that complete ablation of lesions less than 2 cm is possible in more than 95% of patients [63]. Brunello *et al.* also demonstrated the superiority of RFA compared with percutaneous ethanol injection, as far as complete response to treatment, on 139 patients with nodules less than 3 cm [64]. RFA efficacy is restricted by tumor size and location and the recurrence rate is higher in comparison with resection. Studies indicated that overall and disease-free survival was higher in patients who underwent surgical resection compared with RFA [65,66]. However, there are also studies that demonstrated significant initial response to RFA and improved overall and cancer-free survival in patients with nodules greater than 3 cm [67–69]. Major complications of RFA include intraperitoneal bleeding, infections, liver failure, pneumothorax, organ injury, bile duct stenosis and tumor lysis syndrome, but the major complication rate and procedural mortality rate is significantly low [70,71].

### Microwave ablation

MWA uses electromagnetic energy to create an electromagnetic field that heats rapidly the target tissue and induces coagulation necrosis. In comparison with RFA, MWA is more homogenous and the heat-sink effect is reduced due to the higher temperatures and the faster heating that is produced by electromagnetic energy. On the other hand, the higher elevation of temperature in the MWA field can injure the adjacent structures [72–74]. The necrosis area has a form of round or column-like shape, depending on the microwave antenna used and the amount of power generated [75]. Indications and contraindication for MWA are similar to RFA apart from the size of tumors, as MWA can be used in 5–8 cm lesions. Earlier studies showed no significant difference in efficiency in comparison with RFA but recent studies showed an advantage of this method. Lloyd *et al.* demonstrated rapid ablation and low morbidity in patients who underwent MWA [76]. Another recent study which enrolled 221 patients showed high technique effectiveness rate and well tolerance from patients [77]. The major complications of MWA are bleeding, peritoneal hemorrhage, liver abscess, hemothorax, colon perforation and bile duct stenosis [78]. The recent improvements of MWA technology improved the efficacy of the treatment that allows faster and larger ablation areas.

### Combined TACE–RFA/MWA

RFA, MWA and TACE have several limitations. RFA and MWA are curative for small tumors but their efficacy is limited in larger tumors. TACE is not restricted by tumor size, but it is not considered a curative method. The combination of these methods might improve the therapeutic outcome and prolong survival in patients with unresectable HCC. Buscarini *et al.* denoted that transcatheter arterial embolization can block hepatic arterial blood flow and attenuate the cooling effect of tumor blood flow, which is important in order to treat larger tumors that are not suitable for RFA alone [79]. Bloomston *et al.* showed that combined TACE+RFA increased mean survival and 1-year survival compared with TACE alone [80]. On the other hand, Shibata *et al.* demonstrated that combined TACE+RFA had equivalent effectiveness with RFA alone for small (<3 cm) lesions without statistically significant changes in overall and event-free survival [81]. Another study indicated that complete response in lesions 3–5 cm can be achieved with TACE+RFA. They also introduced that the association with TACE provides a way to highlight lesions, which were not recognized through other imaging modalities and enabled further treatment of residual tumor in cases with large lesions [82]. Lee *et al.* also denoted the efficacy of RFA+TACE to treat small (<2 cm)

Table 1. Study characteristics.

Study	(year)	Treatment	Number of patients	Tumor size (cm)	Mean FUP (months)
Buscarini <i>et al.</i>	(1999)	RFA + TACE	14	3.8–6.8	13.2
Bloomston <i>et al.</i>	(2002)	RFA + TACE TACE	13 24	NM	9.1
Shibata <i>et al.</i>	(2009)	RFA + TACE RFA	46 43	0.8–3	30.4
Gasparini <i>et al.</i>	(2002)	RFA + TACE RFA	24 10	<5	10
Lee <i>et al.</i>	(2009)	RFA + TACE	14	0.8–2	15
Hyun <i>et al.</i>	(2016)	RFA + TACE	14	<2	45.3
Yang <i>et al.</i>	(2009)	RFA + TACE RFA TACE	31 37 35	1.2–8	22
Cheng <i>et al.</i>	(2008)	RFA + TACE RFA TACE	96 100 95	>3	28.5
Kim <i>et al.</i>	(2011)	RFA + TACE RFA	57 66	3.1–5	42.5
Veltri <i>et al.</i>	(2006)	RFA + TACE	46	3–8	15
Tang <i>et al.</i>	(2016)	RFA + TACE RFA TACE	40 49 43	3–10	NM, total FUP period was 3 years
Seki <i>et al.</i>	(2000)	MWA + TACE	18	2–3	21.5
Yang <i>et al.</i>	(2009)	MWA + TACE	35	< 3	NM, range: 6–31
Yi <i>et al.</i>	(2014)	MWA/RFA + TACE MWA/RFA	47 47	2–5	47.5 47
Xu <i>et al.</i>	(2013)	MWA + TACE TACE	56 80	5–12	41
Liu <i>et al.</i>	(2011)	MWA + TACE TACE	16 18	5.1–10.6	8
Li <i>et al.</i>	(2016)	MWA + TACE TACE	1500 1500	Mean 6.7	NM, range: 3.5–24

FUP: Follow-up; MWA: Microwave ablation; NM: Not mentioned; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization.

HCC lesions that were not visible on US or unenhanced CT [83], whereas Hyun *et al.* treated small HCC (<2 cm) in the caudate lobe with TACE and cone-beam CT-guided percutaneous RFA not amenable to US-guided RFA with satisfactory results [84]. Yang *et al.* showed that combined RFA+TACE was an effective treatment for recurrent HCC in patients after hepatectomy with better survival rates compared to monotherapies (RFA or TACE) [85]. A meta-analysis by Wang *et al.* that included six RCT studies from China and Japan and a total number of 534 patients showed that combination of TACE and RFA in comparison with RFA monotherapy was associated with greater overall survival (HR = 0.62;  $p < 0.001$ ) and recurrence-free survival (HR = 0.55;  $p < 0.001$ ), without differences in major complications [86]. Cheng *et al.* denoted that combined RFA+TACE improves survival in patients with HCC larger than 3 cm. Patients were divided in three groups (RFA, TACE and combined TACE+RFA) and the rate of response to treatment and overall survival was higher in the combined TACE+RFA group [87]. Two separate studies also showed that combination of TACE followed by RFA provided better local tumor control in patients with lesions more than 3 cm [88,89]. In a recent study by Tang *et al.*, 132 with unresectable HCC were allocated to three groups (RFA monotherapy, TACE monotherapy and combined TACE+RFA). The 3-year recurrence-free survival was higher in the combined group (22.45 vs 20.93 vs 42.5%, respectively) [90]. Finally, a recent systemic meta-analysis by Chen *et al.* composed of eight RCTs and 648 patients also showed that RFA+TACE is more effective than RFA, especially for intermediated and large HCC lesions with a higher overall hazard ratio (HR; HR = 0.6;  $p < 0.001$ ) and recurrence-free survival (HR = 0.58;  $p = 0.001$ ) [91]. These findings are also confirmed by three several meta-analyses, which indicated that combined therapy was superior to monotherapy [92–94].

Combination of TACE and MWA improves both the efficacy of treatment and the total survival as it confirmed by several studies. Seki *et al.* demonstrated that combined MWA and TACE effectively treated lesions less than 3 cm without recurrence during follow-up and required a small number of microwave electrode insertions and

irradiations. Apart from that, no major complications associated with the combined therapy were observed [95]. Yang *et al.* treated 35 patients with 41 nodules less than 3 cm with TACE followed by CT-guided MWA. Total necrosis of the tumor was observed in 34 nodules and incomplete necrosis in seven nodules as it was confirmed in CT scans and biopsies. During follow-up, there were two cases of recurrence [96]. A study from Yi *et al.* showed that TACE before RFA/MWA was more effective than RFA/MWA alone in patients with large HCC lesions less than 7 cm. The patients in the combined TACE+RFA and TACE+MWA groups had better recurrence-free and total survival rate compared to monotherapy groups [97]. Xu *et al.* demonstrated that combined TACE+MWA prolonged overall survival in patients with large more than 5 cm HCC without serious complications [98], whereas Liu *et al.* also showed that this technique is effective for tumor reduction with better survival rate compared to TACE alone in patients with large unresectable HCC lesions [99]. The patients underwent MWA at least 2 weeks after TACE. A recent study by Li *et al.* that included 3000 cases of HCC divided into two treatment groups (TACE+MWA and TACE,) showed a better complete tumor necrosis rate and a higher survival rate with the combined treatment [100]. The characteristics of the included studies (except meta-analyses) are shown in Table 1.

### Conclusion

HCC is a common cause of malignancy worldwide. RFA or MWA are equivalent therapeutic options to surgical resection for small, early-stage HCC. TACE is a palliative therapy with satisfactory results for unresectable HCC. The limited necrosis induced by RFA or MWA and the irregular burn shape due to the heat-sink effect restricts the use of these therapies in intermediate and large lesions. The necrotic area of RFA/MWA may be increased with a combination of TACE, which might also reduce the chance of recurrence and improve the clearance of micrometastasis. As it is confirmed by several studies, the combination of these therapeutic options is superior to monotherapies, improving overall and recurrence-free survival, without significant difference in major complications between them.

### Future perspective

HCC is an aggressive cancer contributing to major morbidity and mortality. Patients frequently present in advanced stages with concomitant liver dysfunction, which impedes curative therapies. Despite aggressive local treatments, recurrence and metastases decrease overall survival. Combining different therapies may further improve therapeutic outcomes. Future RCTs have to confirm these advantageous effects of combined therapies but also to clarify the optimal technique radiation dose and interval between TACE and RFA/MWA. Other ablative methods are also available for use, such as cryoablation, laser coagulation therapy and high-intensity focused US. Future studies may assess the combination of these ablative techniques with TACE or other therapies. Moreover, the use of new molecularly targeted agents in combination with local–regional treatments may also prolong survival, and it is a serious subject for further investigation. Despite these advances, there remains much to be learned about the risk factors, the histopathology and imaging features of HCC to succeed successful surveillance and earlier diagnosis, which is critical for HCC treatment.

#### Executive summary

- Hepatocellular carcinoma (HCC) is the sixth most common type of malignancy and the third most common cause of cancer-related death.
- Different modalities are available for HCC screening including both serological tests and imaging studies.
- Treatment of HCC depends on the preserved hepatic function, the clinical status of the patients and the tumor staging using the Barcelona-Clinic Liver Cancer staging system or other staging systems.
- Local–regional treatments for HCC such as radiofrequency ablation (RFA), microwave ablation (MWA) and transcatheter arterial chemoembolization (TACE) are promising therapeutic options but have limitations.
- TACE is the mainstay of treatment for unresectable HCC.
- RFA/MWA are suitable for small tumors but they do not achieve complete response in intermediate and large tumors.
- TACE can decrease blood flow to the tumor, making RFA/MWA more effective.
- Combination of TACE and RFA/MWA is associated with higher overall and recurrence-free survival, especially in intermediate and large tumors and should be considered as therapeutic option in early-stage HCC.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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