Hepatocellular carcinoma: asphyxiate and then cook

Hepatic Oncology

Philippe Kolly^{1,2} & Jean-François Dufour^{*1,2}

Various therapies are available for hepatocellular carcinoma (HCC) from surgical procedures to systemic therapies. Radiofrequency ablation (RFA) and transarterial embolization are two established therapies. Using electromagnetic energy deposition, the aim of RFA is to induce thermal injury to the tissue [1]. This technique has shown to achieve complete necrosis in >90% of the patients with a tumor size of ≤ 3 cm [2,3] and is therefore considered as a curative option. However, complete necrosis tends to diminish beyond the 3.0 cm limit, with rates of 71% for 3.1–5.0 cm tumors and 25% for >5 cm [4]. Transcatheter arterial embolization (TAE) is another much investigated therapy for HCC. The goal of this procedure is to achieve an ischemia by performing an intra-arterial embolization of the blood vessel with an embolic agent [1]. TAE can be combined with the local delivery of a chemotherapy such as doxorubicin (TACE). But the main effect of this procedure is due to the embolization [5,6]. TAE does rarely

achieve a total tumor necrosis [7] and is therefore considered as a palliative option. Nevertheless, this therapy has shown to increase the overall survival (OS) of patients with nonresectable HCC compared with conservative management [8]. Since RFA is limited to early HCC (because of the size limitation) and TAE does not achieve total tumor necrosis, neither RFA nor TAE alone can act as a curative therapy for intermediate HCC.

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have endorsed the Barcelona Clinic Liver Cancer (BCLC) staging system and treatment algorithm [9,10], which tags patients to various therapies depending on tumor's stage. Based on this scheme [11], RFA is suggested for very early tumors (≤ 2 cm) that are not candidate for liver transplantation (BCLC 0) and some early tumors (no more than 3 nodules ≤ 3 cm) with associated disease (BCLC A). Patients

KEYWORDS

• ablation • chemoembolization
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¹Hepatology, Department of Clinical Research, University of Bern, Bern, Switzerland

²University Clinic for Visceral Surgery & Medicine, Inselspital Bern, Bern, Switzerland

*Author for correspondence: Tel.: +41 31 632 26 95; Fax: +41 31 632 97 65; jf.dufour@insel.ch

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with an intermediate tumor burden (BCLC B) are tagged to the palliative TACE therapy. Treatment for this latter stage should probably be more differentiated because of the wide heterogeneity of patients and tumor burden in this stage [12]. Moreover, it has been argued that some patients in that stage may benefit from other treatments that could be curative instead of palliative. One of these suggestions is to combine TAE with RFA in selected cases. Two hypotheses are underlying this idea: first, applying RFA after a round of TAE should give better results than RFA alone and could therefore extend the scope of RFA. The assumption behind this idea is appealing; by reducing the blood flow to the tumor with TAE, there should be less heat loss by convection thus making RFA more effective [13]. The second hypothesis is that the TAE+RFA combination should give better results for intermediate tumors than TAE alone.

Several studies, which mainly differ in the inclusion criterion regarding the size of the tumor, explored the benefit of the TACE-RFA combination against RFA alone. An RCT conducted between 2003 and 2007 with 89 consecutive Japanese patients compared an RFA ($n = 43$) and a TACE-RFA ($n = 46$) group [14]. Inclusion criterion for tumor burden was three or fewer HCC nodules of ≤ 3 cm. Results show that the included patients in both groups mostly had a small single nodule (mean size: $1.7 \text{ cm} \pm 0.5$). There was no statistical difference in the overall survival ($p = 0.515$) and in the recurrence-free survival ($p = 0.365$). A meta-analysis of studies investigating the TACE-RFA combination versus RFA only in small HCC (≤ 3 cm) found no survival benefit for the combination treatment [15]. Those results suggest that the TACE-RFA combination does not improve OS or recurrence-free survival for small HCC. As Wang *et al.* point out [15], this result is not surprising, knowing that complete necrosis is already achieved in more than 90% of the small HCC (≤ 3 cm) treated by RFA [2,3]. Therefore, there is probably no need to add another treatment to an already successful therapy.

Two studies extended their inclusion criteria regarding the tumor burden to single HCC of 3.1–5.0 cm. An RCT performed in 2010 with 37 Japanese patients compared TACE-RFA ($n = 19$) with RFA ($n = 18$) [16]. The TACE-RFA group showed better technical success (1.1 RFA sessions vs 1.4; $p < 0.01$) and a lower rate of local tumor progression after 3 years of follow-up (6 vs 39%; $p = 0.012$). The ablated area was

also bigger in the TACE-RFA group ($p = 0.012$). According to the authors, this leads to a more spherical ablated area, which could be more effective for local tumor control. Finally, the 3-year OS was not statistically different between the two groups ($p = 0.369$). Another RCT was conducted in 2011 with 123 Korean patients, comparing TACE-RFA ($n = 57$) and RFA ($n = 66$) [17]. TACE-RFA group had a lower local tumor progression rate (40 vs 76%; $p < 0.001$). These two studies suggest that applying TACE before RFA could extend the scope of RFA to the 3.1–5.0 cm single HCC.

The inclusion criterion was extended beyond the 5 cm limit by two studies. Yang *et al.* conducted an RCT in 2008 with tumor ranged from 5.2 to 10.1 cm in 78 Chinese patients, randomized in four different treatment groups [18]. The TACE-RFA group ($n = 24$) showed 60.3% of tumor necrosis rate versus 47.8% for the RFA group ($n = 12$). Tumor relapse rate was lower in the combination group (29.0 vs 34.7%). This study provides interesting results but is statistically limited and has a small sample size in the subgroups. Another RCT was conducted in 2013 with 189 Chinese patients with single HCC of < 7 cm or multiple (up to three) each being ≤ 3 cm [19]. They compared TACE-RFA ($n = 94$) and RFA ($n = 95$). Patients in the TACE-RFA group showed better overall survival (HR = 0.525, CI = 0.335–0.822; $p = 0.002$) and better recurrence-free survival (HR = 0.575, CI = 0.374–0.897; $p = 0.009$). They concluded that TACE-RFA has a better efficiency than RFA for HCC ≤ 7 cm. This study suffers from an important limitation: while inclusion criterion regarding the size was up to 7 cm, there is no guarantee that TACE-RFA really has better outcome for tumor between 5 and 7 cm (publishing overall and recurrence-free survival results stratified by tumor size would have been of most interest).

While combining TACE to RFA for small tumors (≤ 3 cm) does not improve outcomes, evidences suggest that patients with bigger tumors could benefit from this combination. However, all these studies were monocentric and have a small sample size. Evidences are also needed to show that the RFA-TACE combination is better than the recommended TACE procedure. To achieve that, one prospective study conducted by Yin *et al.* in 2014 [20] with 211 BCLC B classified (single tumor: 5–8 cm or 2–5 nodules with diameter < 5 cm) Chinese HCC patients. They compared a TACE group ($n = 156$) and

a TACE-RFA group ($n = 55$). Patients in the TACE-RFA group had better total tumor necrosis (76.9 vs 46.5%; $p < 0.001$), a better tumor control rate after 6 months (74.5 vs 54.5%; $p < 0.001$) and a better post-treatment OS (1-, 3-, 5-year 89.8, 61.1, and 37.4% vs 67.2, 36.6, and 16.5%; $p = 0.01$). Despite the interesting result of this study, it potentially suffers from important selection bias: only patients who were considered as potential candidates underwent the RFA procedure. The RCT conducted by Yang *et al.* [18] also had a TACE arm ($n = 11$). The TACE-RFA group achieved better tumor necrosis (60.3%) than the TACE group (37.5%) and a lower tumor relapse rate (29 vs 45.8%).

The TAE-RFA combination needs stronger evidence. Especially in that setting, the use of TAE instead of TACE should be privileged, since the hypothesis for this association is the reduction of heat loss as a result of the

embolization. A multicenter RCT with intermediate HCC patients should be conducted, comparing three groups: RFA only, TAE-RFA and TAE. By finding the characteristics of patients with intermediate HCC who may benefit from a TAE-RFA combination over TAE, more patients could undergo a curative therapy.

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