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Treatment of hepatocellular carcinomas by thermal ablation and hepatic transarterial chemoembolization

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Abstract  Local tumor recurrence after thermal ablation of hepatocellular carcinoma (HCC) can impact on overall survival and are very closely linked to partial treatment of the primary lesion or to potential microvascular invasion or satellite micronodules located close to the main lesion. The diagnosis of these liver metastases close to the primary lesion on CT and MRI is difficult and their incidence, number and spread throughout the liver correlates with diameter of primary tumor. Tumor diameter is currently the key factor to predict whether or not thermal ablation of HCC will be complete or not. It has now been shown for monopolar radiofrequency ablation that this therapy alone is sufficient to effectively treat single HCCs < 3 cm in diameter provided that liver micrometastases are not present. If the HCC is >3 cm in size, multifocal or in the case of tumor recurrence, overall survival and recurrence-free survival results are better if monopolar radiofrequency ablation is combined with hepatic trans-arterial chemoembolization. The timing of this combination of treatments probably influences its effectiveness on tumor and tolerability and remains to be assessed.

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At the start of the 2000s, hepatocellular carcinoma (HCC) was the sixth most common cancer in the world, with 626,000 new cases each year, and was the third leading cause of cancer deaths [1]. In more than 80% of cases, it develops in a patient with chronic cirrhotic liver disease and, as such, cirrhosis may be thought of as a pre-malignant state [2]. The two main causes of the related liver disease in France are viral hepatitis C and chronic alcoholism.

Overall survival remains poor as the tumors are usually found at an advanced stage, in which case median survival is under six months [2]. Nevertheless, in less advanced stages, curative or palliative treatments with surgery, interventional radiology and medical treatments with targeted therapy can be offered and achieves median overall survival times of several years.

There are many classifications available to group patients according to the state of progression of the hepatic and extra-hepatic tumor disease and according to liver function. None of these have been universally validated, although the Barcelona classification (Barcelona Clinic Liver Classification [BCLC]) [3] is the most widely used. This is a decision-making algorithm, which proposes treatment options depending on the stage of the malignancy, liver function and the patient’s general health. Interventional radiology with hepatic transarterial chemoembolization (TACE) and local destruction are extensively used to treat HCCs from the very early stage (stage 0) to intermediary (stage B) and even advanced stage (stage C).

HCCs under 2 to 3 cm in diameter can be classified as very early stages of disease (under 2 cm) or early stages (BCLC stage A) for patients in good general health with preserved hepatocellular function. These HCCs can be treated first line or after postoperative recurrence by thermal ablation, which produces identical results in terms of local tumor control with less morbidity [4,5]. Thermal ablation is also more often viable than surgery, particularly because of the limitations imposed by the concomitant liver disease. As an example, a recent literature review reports possible surgery viability for recurrent HCCs of between 10.4 and 31% [6].

HCCs over 3 cm in diameter can be classified as early stage if they are single or intermediary (BCLC stage B) for multifocal disease. In these patients, both thermal ablation techniques and surgical excision are associated with greater local recurrence rates with increasing tumor diameter. The tumor diameter itself is related to two main factors, which promote recurrences: vascular micro- or macroinvasion and satellite micronodules. A tumor recurrence rate of at least 80% is seen 5 years after curative treatment [7] because of these intra-hepatic metastases, partial treatment of the main lesion or the carcinogenesis inherent to the cirrhotic liver [8] (Fig. 1).

BCLC classification intermediary HCCs are mostly treated first line with TACE since the meta-analysis published by Llovet et al. in 2003 which showed a 2-year survival benefit for patients treated with TACE compared to supportive care [9]. Treatment however is usually incomplete and the complete tumor necrosis percentage rates are between 10 and 20%, with a 5-year survival rate of under 20% [10,11].

There is a rationale for combining thermal ablation techniques with TACE in order to increase percentage complete tumor response rates and reduce local recurrences due to inadequate treatment of the tumor itself or of its neighbouring environment.

This article reviews the rationale for this treatment combination, the practical aspects of its use and its preclinical and clinical results. In our conclusion, we propose an algorithm for using this treatment combination.

Rationale of the treatment combination of thermal ablation and TACE to treat HCCs

Most tumor recurrences following surgical excision of an HCC within the segment adjacent to the excision arise from portal spread of the tumor, which can be prevented by a wide excision margin [7]. In the retrospective study reported by Poon et al. [7] surgical excision with a margin of over 10 mm was associated with the same number of local recurrences as a margin of under 10 mm and in addition to these occurrences usually occurred within the year following surgery in one or more adjacent segments rather than along the line of the liver division, suggesting that their origin is usually due to intra-hepatic metastases or multifocal carcinogenesis.

These intra-hepatic metastases are due to microvascular invasion or microsatellite nodule (MSN), which are occasionally confused and are subsumed into the same entity [12]. They correlate with the extent of tumor differentiation and alpha fetoprotein (AFP) levels [12] and also with survival. The five year survival rate for HCCs under 5 cm treated surgically has been reported to be 75.9% in patients who did not have intra-hepatic metastases and 54.1 and 20.5% respectively if metastases under or over 5 mm from the primary tumor respectively [12].

Microsatellite nodules (MSNs)

These are seen in 13 to 17% of cases of HCCs under 2 cm in diameter [13,14], in 16.7% to 27.2% in those under 3 cm [14,15]. These percentage figures increase with diameter and extent of tumor differentiation [14,15]. One study, for example, showed that they could be present in up to 72% of cases of HCCs with a median diameter of 8.5 cm [16] and are reported to occur more previously with concomitant hepatitis C than with hepatitis B [17,18]. They are usually located at least 1 cm from the primary tumor but may be further away with increasing tumor diameter [12]. They have been found 1.1 to 2 cm from the primary tumor in 17% of cases of tumors under 3 cm in size [15] and may be almost 4 cm from tumors under 5 cm in diameter [12]. They measured a few millimeters in diameter [15] and were multiple in 80% of the cases described in the study reported by Okusaka et al. [14]. They usually obtain their vascular supply from the same source as the periphery of the primary tumor, where angiogenesis is also most active, particularly in tumors under 5 cm in diameter [16,17]. As a rule, the MSNs are therefore very richly supplied by the hepatic arterial system enabling them to be diagnosed by pre-treatment imaging [19,20] although the diagnostic accuracy of imaging for these MSNs has not been extensively studied. One recent retrospective study assessing MRI in HCCs measuring an average of 2.8 to 3.2 cm in diameter revealed MSNs in 7.0 to 11.1% of cases [19]. It is
very likely that imaging methods are relatively poorly sensitive for these lesions although are highly specific because of the tumors’ rich arterial vascularization despite their small volume. In our experience, arteriography performed during TACE and CT to monitor lipiodol arteriography appears to be more sensitive than imaging alone in making a diagnosis (Fig. 2).

**Vascular microinvasion**

This term includes a broad spectrum of histological conditions ranging from tumor invasion of a single vessel close to the capsule of the tumor to macroscopic vascular tumor invasion [20].

This type of vascular invasion influences prognosis. Llovet et al. showed that microvascular invasion in explanted liver was associated with no survival without tumor recurrence at three years whereas 94% of patients with no micro- or macrovascular invasion on the explanted liver had no tumor recurrence at three years [21].

Tumor diameter clearly influences the incidence of this type of tumor extension.

Vascular microinvasion is seen in 25% of cases of tumors under 2 to 3 cm in size, in 40 to 50% of tumors under 5 cm and in 55% of tumors over 6.5 cm [20,22,23]. Tumor diameter and number of tumors, however, have no impact on survival if no microvascular invasion is present [24]. Other factors such as multifocal disease or an AFP of over 1000 ng/mL are also factors, which are associated with vascular microinvasion [23].

This can be suspected on imaging, showing enhancement of a crown around the tumor or of hepatic tissue around the tumor in the arterial phase of gadolinium enhancement on T1 weighted MRI or CT performed during liver arteriography, demonstrating arterio-portal fistulae within the tumor on CT during hepatic arteriography or by measuring the intra-tumor diffusion coefficient on MRI [19,25–28]. The diagnostic value of each of these signs, however, is not known and a regular enhancement around the tumor (Fig. 2a), appears to be the most reliable sign [25,27].

In order to reduce the percentage of local recurrences, the entire tumor volume and region around the tumor which may contain metastases therefore needs to be treated. In order to do this, it is possible to attempt to increase

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**Figure 1.** Risk factors for recurrence of intra-hepatic tumor after thermal destruction of a hepatocellular carcinoma (HCC).

**Figure 2.** Fifty-four year old man with cirrhosis from chronic hepatitis C virus infection and a biopsy proven moderately well differentiated hepatocellular carcinoma, 25 mm in size, at the tip of the left lobe. a: gadolinium-enhanced T1-weighted MRI axial view in the portal phase showing washout from the tumor and a more intense crown around the tumor which may represent vascular microinvasion. This investigation shows no microsatellite nodules; b: lipiodol arteriography during hyperselective catheterization of the left lobe of the liver. Migration of lipiodol into the veins on the periphery of the tumor and two centimeter sized Lipiodol uptake sites above and to the right of the primary lesion; c: enhanced computed tomography 15 days after Lipiodol arteriography. Confirmation of lipiodol uptake on the periphery of the primary lesion and more remotely in the right liver suggesting microsatellite nodules.
the destruction volume of the main lesion compared to what is obtained with monopolar radiofrequency ablation systems. Many techniques have been described, such as the parallel use of several bipolar [29] or monopolar [30] radiofrequency needles, some microwave systems [31] or a combination of radiofrequency ablation and alcoholization [32]. Some studies, mostly on animals, have also assessed potentiation of thermal destruction by combining it with a targeted therapy [33,34] or with drugs, which promote cell apoptosis [35,36]. None of these combinations however have been assessed in great detail and in addition they can only partially treat the region around the tumor and in particular are not very effective in treating metastases located further away from the primary tumor.

Adding TACE to thermal destruction is likely to treat a segmental or region or sector around the primary lesion where the majority of MSNs and microvascular invasions are concentrated. Combination of TACE with thermal destruction could also achieve higher destruction volumes than those obtained with thermal destruction alone. The timing of the combination has a potential impact on the mechanism of action of this treatment. Carrying out thermal destruction before TACE could help to increase the local destruction volume by reducing thermal microconvection effects due to tumor vascularization and reducing diffusion of heat within the tumor [37]. The heat produced by thermal destruction could therefore help to increase the cytotoxic effects of the antimitotic agent injected during TACE. Administering TACE immediately after thermal destruction could also increase local destruction but in this case, by concentrating the drug and emboli in the hyperemic crown around the tumor caused by thermal destruction [38–40] SS (Fig. 3). The additional advantage of this second chronological option would be in simultaneously treating possible hemorrhage after the thermal destruction [39].

Preclinical results

Many animal studies have been published assessing histological changes produced if thermal ablation is combined with hepatic arterial therapy [41–47]. The vast majority of these studies have assessed initial arterial treatment followed by thermal ablation and only two of these studies have assessed thermal ablation administered first, followed by hepatic arterial therapy [44,45]. The combination of these two treatments achieves greater reduction in liver or tumor volumes than those obtained with either of the two treatments used alone [43,44,46,47]. Administering hepatic arterial therapy first achieves greater liver and/or tumor destruction volumes than those obtained if thermal ablation is carried out first [44,45], although the standard deviations of the destruction volumes appear to be considerably greater if arterial therapy is carried out first, which may suggest greater variability in destruction volumes obtained with the arterial-thermal destruction sequences and therefore poorer pretreatment prediction of the destruction volume.

In addition, the effect of anti-cancer drugs can be increased or reduced by hyperthermia. This has been demonstrated in cell and animal studies with intravenous injection of chemotherapy [36–38,48]. No animal studies, however, are available which have assessed the impact on the cytotoxic effect of the drug when TACE is combined with thermal ablation.

This treatment combination appears to be more effective when less than 100 μm [44] of microparticles or Lipiodol ultra fluide® (LUF—Guerbet) [46] are used, or if the time between the two treatments is short [42].

Finally, this mixed treatment appears to be well tolerated, although some studies show a greater post-treatment rise in liver enzymes. This does not however have any clinical consequences [43].

Clinical results

Since the first cases reported by Rossi et al. in 2000, treatments using a combination of thermal ablation and temporary hepatic artery occlusion or TACE [49] many publications have assessed this type of combination. These are represented principally by four randomized trials [6,50–52] and many meta-analyses [53–57] some of which however have included several types of local destruction including alcoholization, radiotherapy and high intensity ultrasound [53] (Figs. 4 and 5).

Timing of the combination

In all of the randomized trials and in the vast majority of retrospective studies which have or have not compared combination with radiofrequency or microwave treatment alone [58–63], TACE was performed before the thermal ablation and only one group has assessed the reverse order,
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Figure 4. Seventy-one-year-old man with post alcohol related cirrhosis in good general health with preserved hepatocellular function and a 35 mm HCC, histologically well differentiated and developing in the left lobe of the liver: a: b1000 diffusion weighted MRI axial image showing the HCC as a hyperintensity and a satellite micronodule; b: hepatic arteriography showing the hypervascularized HCC; c: microwave thermal ablation (80 watts for 10 minutes) followed by selective TACE treatment sequence in the left lobe with 100–300 μ diameter emboli loaded with 50 mg of doxorubicin; d: frontal reconstruction of a computed tomogram with intravenous iodinated iodine enhancement performed six weeks after treatment. Dense thermal ablation region because of hemorrhagic necrosis, delineated by an area of necrosis due to the arterial treatment. Overall the treatment region measures almost 70 mm in diameter; e: gadolinium-enhanced T1-weighted axial MRI view at 6 months showing complete tumor response according to the modified RECIST criteria.

Figure 5. Eighty-year-old man with cirrhosis due to chronic hepatitis C virus infection with preserved hepatocellular function and histologically well differentiated 80 mm HCC developing in the dome of the liver. The decision was taken to treat with TACE using 100–300 μ diameter microspheres loaded with 50 mg of doxorubicin followed in the event of tumor response by thermal ablation: a: arteriography during the first TACE; b: arteriography during the second TACE performed before microwave thermal ablation showing partial devascularization of the HCC; c: gadolinium-enhanced T1-weighted axial MRI view at 12 months showing complete tumor response according to the modified RECIST criteria.
with TACE performed immediately after thermal ablation, which was also delivered with temporary balloon obstruction of the hepatic artery [39,40]. In the studies in which TACE was performed first, thermal ablation was rarely delivered on the same day [50] or on the day after [61], but usually two to four weeks later [6,58,59,62–64].

**Effects on overall survival and progression-free survival for HCCs over 3 cm in size**

Randomized trials which have included patients with uni- or multifocal HCCs over 3 cm in size [51], or under 5 cm, due to recurrences [6] have reported a significant increase in one year [6,51], three years [6,51], four years [51] and five years [6] overall survival when the combination treatment is used compared to radiofrequency ablation alone. Only the study reported by Morimoto et al. [50], which included patients with HCC between 3 and 5 cm in size, showed no benefit on three years overall survival when the combination treatment was used.

This combination is also associated with a significant increase in survival without intrahepatic recurrence [6,51] or without further progression at the thermal destruction site [50].

These results in favor of the treatment combination are also seen in non-randomized studies [40,60] and in meta-analyses [50,54,57].

**Effects on overall survival and progression-free survival for HCCs under 3 cm in size**

Although one non-randomized study has shown an increase in progression-free survival at one, three and five years with the treatment combination in patients with HCCs between 2 and 3 cm in size [58], one randomized trial which included patients with HCCs of mean diameter of 1.7 cm ± 0.5 cm showed that the combination of TACE and radiofrequency ablation offered no benefit in terms of overall survival or progression-free survival at one, two, three and four years compared to radiofrequency ablation alone [52]. This lack of benefit of the combination treatment has also been described in a meta-analysis [57] and may be explained by the low incidence of mms or microvascular invasion with HCCs under 2 cm in size when the tumor and per-tumor destruction volume are sufficient with thermal destruction alone.

**Complications**

All of the reports published in the literature are consistent in finding that the combination of TACE and thermal destruction is not associated with more major complications or mortality than thermal destruction alone [6,50–52,58–63]. One meta-analysis describes a 3.7% major complication rate for the combination of TACE and thermal ablation, which is similar to what is reported for thermal ablation alone [56]. An improvement in the quality of life of patients treated with the combination has also been described, particularly as a result of the lower incidence of tumor recurrence and fewer treatments for recurrence [65]. However, we should probably remain very cautious in treating patients with hepatocellular dysfunction, (Child-Pugh class B [66]) as there is a potential risk of decompensation in these patients.

Minor complications such as pain, vomiting, deterioration in general health and asymptomatic laboratory abnormalities have still not been assessed in detail; it is possible that the treatment combination may produce more minor complications as was found in two clinical trials which showed more vomiting [50] or discomfort with increase in the length of hospital stay [52] for patients who received the treatment combination.

The timing of the treatment combination has an impact on whether or not bleeding complications develop. TACE administered immediately after thermal ablation reduces the bleeding complications which may occur after thermal ablation because of the embolization which is performed [39,40]; with the reverse order and when thermal destruction is not followed by arterial embolization, post thermal destruction perihepatic hematomas have been described in up to 5.9% of cases [59], together with one case of fatal hemoperitoneum [58].

The timing may also be important in controlling the ultimate volume destruction obtained. If TACE is administered 24 hours before thermal ablation it may result in unpredictable destruction regions with large diameters and high standard deviations as was described in the study by Morimoto et al. [50] and ultimately promote hepatic decompensation or extensive liver infarction. This point is still not well assessed in the literature as the two treatments have usually been separated by several weeks, probably carrying a lower risk in this case as the tumor destruction volumes have rarely been reported.

**Proposed use of the HIACE-thermal destruction combination**

In light of the literature analysis and from our experience, we offer a decision-making algorithm for monopolar radiofrequency ablation and/or TACE management of patients with HCCs (Fig. 6) for those patients with preserved, Child-Pugh A hepatocellular function and good general health with a performance status of 0. This is based on the initial analysis of tumor diameter and the macroscopic multifocal or microscopic nature of tumors including vascular microinvasions and MSNs.

Radiofrequency ablation may be offered for unifocal HCC under 3 cm in size. It is essential however to ensure on pretreatment imaging that no micrometastases are present on the periphery of the tumor; if these are present or are suspected on the basis of histologic proof of poor tumoral differentiation or of high AFP level, patients should preferably be treated with a combination of TACE and radiofrequency ablation.

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In multifocal HCCs between 3 and 5 cm in size remaining within the Milan criteria (no more than three lesions, and under 3 cm in size), patients can be treated first line with the combination of TACE and radiofrequency ablation delivered in the same session if the radiofrequency ablation is performed first, or in two sessions separated by a few days or weeks if the TACE is performed first.

In unifocal HCC over 5 cm in size or in multifocal disease outside of the Milan criteria but within the indications for TACE, one or several TACE may be delivered on a neoadjuvant basis. After follow-up imaging, the decision as to whether or not to supplement treatment with radiofrequency ablation will be based on the tumor response as assessed according to the modified Recist criteria [67] and evaluating the extent of tumor devascularization [68]. If the response obtained is partial or complete, thermal ablation may be offered for the tumor component, which is still vascularized.

**Conclusion**

The combination of TACE and thermal ablation can be offered to many patients with HCC based on a strong rationale and with a good level of preclinical and clinical scientific evidence. There is still, however, considerable missing information such as, for example, the clinical impact of the choice of timing or the value of major recurrence factors such as vascular microinvasion, microsatellite nodules, the degree of tumor differentiation or in the near future, oncogenetic factors on its indications.

**Take-home messages**

- The combination of hepatic trans-arterial chemoembolization (TACE) and monopolar radiofrequency ablation (RFA) can treat some patients with hepatocellular carcinoma (HCC) more effectively.
- This combination should only be offered to patients with HCC over 3 cm or who have liver micrometastases, regardless of the diameter of the primary lesion.
- In the case of a single HCC between 3 and 5 cm in size or with multifocal disease falling within the Milan criteria, the combination should be offered and one or two sessions, chosen depending on the timing.
- In single HCC over 5 cm in size or with multifocal disease outside of the Milan criteria, the combination can also be offered, but with one or more neoadjuvant TACE and RFA secondarily only for patients who respond significantly to neoadjuvant treatment.
- This type of combination still has to be assessed, in particular a comparison between the different timings and results depending two major factors influencing for local recurrence: vascular microinvasion and microsatellite nodules.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.
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