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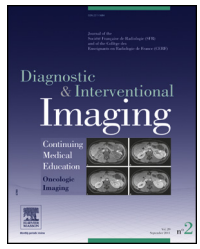

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Treatment of hepatocellular carcinomas by thermal ablation and hepatic transarterial chemoembolization

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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 ablations 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