COMMENTARY

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Role of ablation: should it be used as primary therapy for early-stage hepatocellular carcinoma?

Hepatic Oncology

“...thermal ablation represents an essential therapeutic tool for small hepatocellular carcinoma and its favorable characteristics should be taken into account when planning therapy...”

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Liver cancer is the sixth most common cancer worldwide and hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers. The HCC incidence increases with age reaching a peak at approximately 70 years and in many cases HCC is associated with an underlying risk factor such as chronic hepatitis B and C, alcohol abuse and aflatoxin exposure. In the western world, HCC emerges in liver cirrhosis in up to 90% of the cases and surveillance programs for early detection of HCC based on ultrasound liver study performed at 6-month interval in well to moderately compensated cirrhotic patients are cost effective as the HCC incidence in liver cirrhosis is higher than 1.5% per year [1]. However, the application of such screening programs is still insufficient. In Italy, that is a country with intermediate incidence of the tumor, approximately 50% of all HCCs are diagnosed during surveillance programs at an early stage allowing the access to curative therapies [2].

One of the therapeutic options in the management of HCC is image-guided tumor ablation, which comprises the direct percutaneous application of chemical or thermal therapies to the tumor, with the

aim of inducing complete necrosis. The first ablation therapy introduced in clinical practice more than 30 years ago was percutaneous ethanol injection (PEI), which comprises the injection into the HCC lesion of absolute ethanol eliciting coagulative necrosis as a result of cellular dehydration and small arterial vessel thrombosis. The effectiveness of PEI has been shown to be reduced by the presence of intratumoral septa (preventing the homogeneous ethanol diffusion within the nodule) and/or of extracapsular tumor invasion or satellite nodules (causing a high rate of local tumor recurrence due to incomplete ablation). For this reason, PEI has been largely replaced by the thermal ablation procedures clinically developed starting from the 1990s and based on the insertion within the HCC nodule of needle devices causing tumor tissue necrosis by local heating at 60–100°C (radiofrequency ablation [RFA], percutaneous laser ablation [PLA], microwave ablation [MWA]) or freezing at -20–60°C (cryoablation [CRYO]); among them, RFA has emerged as the most popular technique and its superiority over PEI in terms of local tumor control and overall survival has been shown in prospective

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- ablation • hepatocellular carcinoma
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“...based on the currently available data, both resection and radiofrequency ablation provide excellent and comparable overall survival and tumor recurrence rates in the setting of compensated cirrhotic patients with very early or early hepatocellular carcinoma.”

randomized studies and meta-analyses mainly including patients with HCC nodules larger than 2 cm [3]. At present, PEI may still be considered for the treatment of small HCC nodules up to 2 cm in diameter located in difficult sites for RFA (e.g., near the gallbladder, main intra-hepatic vessels and bile ducts or intestinal loops) or emerging in patients with severely impaired clotting parameters. None of the other thermal ablation techniques has been definitively shown to provide results better than RFA. Percutaneous laser ablation has had a limited diffusion and a recent prospective randomized trial comparing this technique with RFA in patients with early stage HCC did not show significant differences in terms of local tumor control and overall survival [4]. Microwave ablation has the theoretical advantage over RFA of shorter ablation session duration and better effectiveness in the treatment of HCC located near big vessels but no prospective randomized trials comparing RFA and MWA are currently available and no significant advantage for MWA-treated patients has been shown in retrospective series comparing this technique to RFA in patients with very early or early HCC [5]. Finally, CRYO has been recently proven to be as effective as RFA in the treatment of HCC nodules up to 3 cm and probably more effective in case of nodules between 3 and 4 cm large in a prospective randomized study [6]. However, CRYO is technically complex, costly and still poorly diffuse.

According to the current guidelines of the European Association for the Study of the Liver for the management of HCC, the Barcelona Clinic Liver Cancer system is used to stage HCC emerging in liver cirrhosis, and ablation is considered to be the choice of treatment option for patients in very early (single nodule up to 2 cm in size) or early stage (single nodule or no more than three nodules, each smaller than 3 cm in size) who are not candidates to resection (RES) or liver transplantation [1]. Indeed, the best results of RFA ablation are obtained in patients with Child-Pugh score A and solitary nodule up to 3 cm in size in whom 5-year survival rates of 64–74% and 10-year survival rate of 41.3% have been reported in the largest available western and eastern series [7,8]. On the other hand, there is a clear evidence of a different effectiveness of RFA according to the tumor size of the treated nodule. Indeed, in the explanted liver of HCC patients undergone to RFA as a bridge treatment during the waiting period

before transplantation, the rate of complete necrosis ranges between 50 and 78% in HCCs up to 3 cm and between 13 and 43% in larger neoplasms, and tumor size larger than 3 cm has been identified as the only risk factor for HCC persistence after RFA treatment [9]. Thus, for single tumors larger than 3 cm in compensated cirrhotic patients without severe portal hypertension, RES remains the choice of treatment and transarterial chemoembolization (TACE) or combined treatments (RFA plus PEI, RFA plus sequential or single-step TACE) should be regarded as alternative options in patients who are not candidates to RES.

An open issue is whether RFA can be considered a first-line treatment option competing with surgery in cirrhotic patients with very early or early HCC. From a theoretical point of view, the higher probability of RES of achieving a radical tumor treatment is counterbalanced by the lower incidence of treatment-related complications in RFA-treated patients. Three prospective randomized studies performed in eastern countries (where cirrhosis is mainly related to hepatitis B virus infection) and comparing RES and RFA have provided conflicting results. No significant difference in 4-year overall and disease-free survival has been shown in patients with single nodule not larger than 5 cm [10] and in patients with no more than two nodules up to 4 cm [11]. Conversely, a better 5-year overall survival for RES patients has been shown in another paper including HCC patients within Milan criteria (single nodule up to 5 cm or no more than three nodules each less than 3 cm) and this result was confirmed in the subgroup of patients with single nodule smaller than 3 cm [12]. No prospective studies in this field are available in western countries. The largest European retrospective study, performed using the propensity score matching analysis, did not show a significant difference in terms of 4-year overall survival and tumor recurrence in patients with single HCC smaller than 3 cm and in the subgroup of patients in whom the HCC was smaller than 2 cm [13]. Two other recent retrospective papers performed using the propensity score matching analysis provide different results. In a group of 237 patients with very early HCC undergone to RES or RFA, RES provided better long-term overall and recurrence-free survival and the Authors stated that RES should be considered as the first-line treatment for these patients [14]. In a population of 580 patients with single HCC <3 cm, 5-year

overall survival, and disease-free survival did not differ significantly between nonanatomic RES and RFA groups but the complication rate and the hospital stay were significantly lower in the RFA group [15]. If we look at this issue using the meta-analytical method, the results remain controversial. Indeed, Cucchetti *et al.* recently performed a meta-analysis of the pertinent literature and constructed a Markov model with a 10-year perspective. RFA and RES provided similar life-expectancy and quality-adjusted life-years in Child-Pugh A cirrhotic patients with very early HCC (single tumor <2 cm) or with two to three tumors each less than 3 cm; however RFA was cheaper and than more cost effective than RES [16]. In another recently published meta-analysis, only studies including patients with early HCC treated with RES or RFA were selected. Although 1- and 3-year overall and recurrence-free survivals did not differ significantly, 5-year overall survival was higher and 5-year recurrence rate lower in patients treated with RES. However, the complication rate was lower and the hospital stay shorter in RFA group and the long-term differences in overall and recurrence-free survival did not apply to patients with very early HCC [17].

In our opinion, based on the currently available data, both RES and RFA provide excellent and comparable overall survival and tumor recurrence rates in the setting of compensated cirrhotic patients with very early or early HCC. However, according to the principles of evidence-based medicine, there are not at present sufficient arguments to support the replacement of RES with RFA not only in case of early HCC, but also in the setting of very early HCC. This difficult issue could be answered only through the implementation of large, well-designed but difficult to plan prospective studies in which the patients' stratification should include among the randomization criteria not only the HCC nodule number and size and the liver function assessment but also the site of the HCC nodule in the liver, the presence and severity of extrahepatic comorbidities, the cirrhosis etiology, the degree of portal hypertension (PH) evaluated using the hepatic vein pressure gradient and the assessment of tumor aggressiveness using α -fetoprotein serum level and histological grading.

We think that a rational approach is to tailor the choice between RES and RFA according to the individual patient's clinical and tumor features. For this reason, we think that RES

remains the choice of treatment in patients without PH whereas RFA should be preferred in patients with relevant extrahepatic comorbidities increasing the surgical risk, with severe PH (e.g., presence of large esophageal or gastric varices or previous ascitic decompensation), and with limited hepatic functional reserve. Indeed, PH is recognized as a negative prognostic factor in HCC patients undergone to RES [1], and, according to Japanese guidelines for HCC management, RES should be denied to patients with serum bilirubin >2.0 mg/dl, and only limited RES should be performed in cirrhotic patients with normal serum bilirubin but with indocyanine green retention rate at 15 min >20% [18]. Another fundamental issue to consider in the choice of treatment is the site of the tumor within the liver. Whereas RFA should be preferred in case of centrally located tumors, RES performed using a laparoscopic or laparotomic approach should be chosen in case of peripheral tumors or of tumors located near big vessels or gallbladder, main biliary ducts and bowel loops. Indeed, in all these cases the application of RFA entails an increased risk of incomplete ablation or of treatment-related complications [1]. However, it is worth mentioning that a number of such HCC lesions can be safely and effectively treated with thermal ablation if specific technical strategies are used. For instance, displacement of intestinal loops or diaphragm by means of artificial ascites allows a subcapsular nodule to be safely treated, and, to prevent thermal damage of the gallbladder wall, orientation of the electrode is crucial as if the needle device is perpendicular to the wall gallbladder injury is unlikely [19].

Finally, both treatments should be planned and performed with the aim of providing a radical result. Then, RES should be applied with the intent of preventing postoperative liver failure, using whenever possible an anatomical approach, and achieving a safety resection margin of 1 cm or more; RFA should provide a volume of necrosis higher than that of the original tumor as the failed achievement of an ablation margin equal to or higher than 0.5 around the tumor has been recognized as a risk of late local tumor progression due to the persistence of peripheral microscopic tumor foci undetectable on postprocedural contrast-enhanced imaging studies. This applies also to tumors up to 2 cm in which the occurrence of satellite nodules and microvascular invasion has been detected in 12

“...a rational approach is to tailor the choice between resection and radiofrequency ablation according to the individual patient's clinical and tumor features.”

and 27% of the cases, respectively, in a large surgical series [20].

In conclusion, even if its role as first-line therapy for very early and early HCC is still debated, thermal ablation represents an essential therapeutic tool for small HCC and its favorable characteristics (effectiveness and safety, low cost, repeatability) should be taken into account when planning therapy in the individual patient.

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