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FIELD OF VISION

Resection *vs* thermal ablation of small hepatocellular carcinoma: What's the first choice?

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Abstract

Nowadays, hepatocellular carcinoma (HCC) is frequently diagnosed at an early stage, opening good perspectives to radical treatment by means of liver transplantation, surgical resection, or percutaneous ablation. Liver transplantation is considered the best option, but the lack of liver donors represents a major limitation. Therefore, surgical resection, offering a 5-year-survival rate of over 50%, is considered the first-choice treatment for patients with early stage HCC, whereas percutaneous ablation is usually reserved to patients who are not candidate to surgery. However, in the recent years some trials showed that percutaneous radiofrequency ablation (RFA) can be as effective as surgical resection in terms of overall survival and recurrence-free survival rates in patients with small HCC, and a retrospective comparative study reported 1-, 3-, and 5-year overall survival rates and recurrence-free survival rates significantly better in patients with central HCC measuring 2 cm or smaller treated with RFA than in those treated with surgical resection. RFA is less expensive, less invasive, with lower complication rate and shorter hospital stay than surgical resection, and on the basis of the results of these studies it should be considered the first option in the treatment of very early HCC. However, RFA is size-dependent, so at present the need to achieve an adequate safety margin around the tumor limits to about 2 cm the diameter of the nodules that can be ablated with long-term outcomes comparable to or better than surgical resection. The main goal of the next technical developments of the thermal ablation systems should be the achievement of larger ablation areas with a single needle insertion. In this regard, the recent improvements in microwave energy delivery systems seem to open interesting perspectives to percutaneous microwave ablation, which could become the ablation technique of choice in the next future.

Key words: Hepatocellular carcinoma; Thermal ablation; Radiofrequency thermal ablation; Microwave thermal ablation; Treatment

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INVITED COMMENTARY ON HOT ARTICLES

Peng *et al*[1] recently published a quite interesting retrospective comparative study between radiofrequency thermal ablation (RFA) and hepatic resection for the treatment of small hepatocellular carcinoma (HCC), and we strongly recommend it to the readers of *World Journal of Radiology*.

Nowadays, HCC is diagnosed at an early stage with increasing frequency, opening good perspectives to radical treatment by means of liver transplantation, surgical resection, or percutaneous ablation[2]. Liver transplantation is considered the best option, as it allows to eliminate

both tumor and cirrhosis at the same time, but the lack of liver donors represents a major limitation[3]. Therefore, surgical resection, offering a 5-year-survival rate of over 50%, is considered the first-choice treatment for patients with early stage HCC, whereas percutaneous ablation is usually reserved to patients who are not candidate to surgery owing to impaired liver function or co-morbidity, or who refuse surgery[1]. Even though with the main limit of its retrospective nature, the study of Peng *et al*[1] suggests that the strategy for the treatment of small HCC could change in the next future. Reviewing a series of one hundred forty-five consecutive patients with a resectable HCC measuring 2 cm or smaller, who underwent surgical resection (74 patients) or percutaneous RFA (71 patients), they found that the 1-, 3-, and 5-year overall survival rates were better in RFA group than in surgical resection group (98.5%, 87.7%, and 71.9%, respectively, for RFA *vs* 90.5%, 70.9%, and 62.1%, respectively, for surgical resection; $P = 0.048$). No difference was observed in the corresponding recurrence-free survival rates, whereas major complications were significantly more frequent in surgical resection group. Furthermore, analysing the subgroup of sixty-six patients with "central" HCC, defined as tumor located at least 3 cm from the liver capsule, also the 1-, 3-, and 5-year recurrence-free survival rates resulted significantly better in RFA group than in surgical resection group (86.5%, 74%, and 67% *vs* 68%, 40%, and 40%, respectively; $P = 0.33$). Indeed, patients with central HCC are usually not good candidates for surgical resection because of the risk of more injury to normal liver tissue and blood loss, which may induce more complications with a negative effect on treatment outcome. Conversely, RFA preserves the liver parenchyma, and has a low risk of blood loss. For these reasons, the authors concluded that for patients with HCC measuring 2 cm or smaller percutaneous RFA might be a better treatment than surgical resection, in particular in presence of central location of the tumor.

We strongly agree with the conclusion of Peng *et al*[1], which confirms and reinforces the findings of some prior reports. In a prospective randomized trial on one hundred and eighty patients with solitary HCC $\leqslant$ 5 cm, percutaneous RFA resulted as effective as surgical resection in terms of 1-, 2-, 3-, and 4-year overall survival rates and recurrence-free survival rates[4], and the results of a large single institution retrospective study suggested that RFA could be used as first-line treatment for early-stage HCC[5]. Moreover, in a retrospective survey of 218 patients with very early HCC $\leqslant$ 2 cm who underwent percutaneous RFA, Livraghi *et al*[6] reported sustained complete local response with 5-year survival rate of 68.5%, historically comparable to the rates reported by most studies on surgical resection of HCCs of the same stage, suggesting that RFA could be considered the treatment of choice for very early stage HCC $\leqslant$ 2 cm, even when surgical resection is possible. The main argument against the role of RFA as a first treatment option for patients with small HCC is represented by the lack of adequate randomized clinical trials (RCTs) proving that its effectiveness is comparable to that of surgical resection. However, there are also no RCTs proving a superiority of surgical resection in this subgroup of patients, and to our knowledge the only two RCTs published on this topic in the last years reported that RFA is at least as effective as surgical resection in the treatment of small HCC, even though with the limit of the small number of patients enrolled[4,7]. In other words, it is true that a strong evidence of the superiority or equivalence of RFA in comparison with surgical resection is lacking, but it is also true that there is no evidence that surgical resection is better than RFA for the treatment of small HCC. Furthermore, the difference in the long-term outcome between the two treatments is likely to be fairly small, and the sample size required to ensure meaningful results to a RCT should be quite large, probably too large to make the planning of such a RCT feasible. Indeed, two RCTs planned to evaluate the effectiveness of RFA for the treatment of liver metastases from colorectal cancer were recently closed as a result of nonaccrual, and the results were not published[8]. Therefore, as a consequence of a too strict and dull observance of the criteria of the evidence-based medicine - in this case paradoxically based on the lack of evidence of the superiority of surgical resection - RFA could be condemned to indefinitely remain a second choice in the treatment of very early HCC. RFA is less expensive, less invasive, with lower complication rate and shorter hospital stay than surgical resection, and in our opinion it should be considered the first option for the treatment of small HCC. However, RFA is size-dependent, so the need to obtain an adequate safety margin around the tumor limits to about 2 cm the diameter of the nodules that can be successfully ablated with sustained complete response. An at least 1-cm safety margin is recommended by many authors for patients undergoing surgical resection[9,10], as even at an early T stage micrometastases can spread either along or against the direction of the portal venous flow, and the incidence of micrometastases has been found to be closely related to the distance from the primary HCC[11]. Therefore, an adequate safety margin might improve the chance of clearance of micrometastases, reducing the chance of recurrence. At present, RFA can produce a necrotic area of about 4 cm, so it can be effective in achieving this safety margin only in presence of HCC measuring 2 cm or smaller. Multiple overlapping insertions of the needle electrode are often used to achieve larger necrotic areas, but the insertions following the first or second ones can be inaccurate owing to the steam generated by the ablation procedure. Moreover, multiple insertions increase the risk of complications. Therefore, technical developments allowing to achieve ablation areas of 5 cm or more in diameter with a single needle insertion could represent the keystone to make percutaneous thermal ablation a valid alternative to surgery even for tumors measuring 3 cm or more.

Microwawe ablation (MWA) offers some theoretical advantages over RFA, including an instantaneous temperature increase, consistently higher intratumoral temperatures, deeper penetration of MW energy, propagation across poorly conductive tissues, and larger tumor ablation volumes[12]. Despite these advantages, some previous comparisons between MW and RF ablation gave disappointing results[13-15]. MW energy is more difficult to distribute than RF energy. MW must be carried in wave guides, such as coaxial cable, which are more cumbersome than the small wires used to feed energy to RF electrodes, and are prone to heating when carrying large amounts of power. It follows that higher MW powers increase ablation zone size, but excessive power in the antenna shaft can lead to injuries to normal liver parenchyma, peritoneum, and skin[16]. Subsequent technical developments showed that adding a cooling jacket around the antenna reduced cable heating, allowing for the increase of the irradiation time and the amount of power that could be safely delivered[17]. In a recent experimental and clinical study comparing a cool-tip RF ablation system and a MW ablation system using a generator with a frequency of 2450 MHz and maximum power output of 100 W, and a 14-gauge cooled shaft antenna, MW ablation produced larger ablation zones than RF ablation in either porcine livers (irradiation time: 12 min) or patients with small HCC (irradiation time: 10 min)[18]. The introduction into the distal portion of the antenna of a choke coil was also proposed to reduce back heating effects, but at the expense of increased invasiveness, as such a remedy caused remarkable thickening of the antenna (9-10 gauge), making the device not suitable for percutaneous applications[19]. Quite recently, a new MW technology with interesting technical aspects has been marketed in Europe. In particular, the system uses a 2450-MHz generator (AMICA-GEN, HS Hospital Service SpA, Aprilia, Italy) delivering energy through a 14- or 16-gauge internally cooled coaxial antenna (AMICA PROBE, HS Hospital Service SpA, Aprilia, Italy), featuring a miniaturized quarter wave impedance transformer (referred to as mini-choke®) for reflected wave confinement. The mini-choke antenna design is an industrial patent (PCT/IB2002/00299) property of the Italian National Council for Research, which seems to ensure a quasi-spherical radiation pattern, while not increasing the probe gauge (14 G at most), making the device suitable for percutaneous applications. A recent study showed complete histological necrosis in the explanted liver in six cases of HCC up to 5 cm treated with this MW ablation system before transplantation; the goal was to bridge or down-stage[20]. A multicenter retrospective survey on 736 patients reported a major complication rate of 2.9%, comparable to that observed for RFA[21], and in our preliminary prospective experience the minichoked MW ablation system achieved significantly larger necrotic areas than the internally-cooled RF ablation system (unpublished data). Some prospective randomized trials are ongoing to evaluate the long-term outcome of this promising technology, and the first results are expected in the next two years.

In conclusion, we believe that to date percutaneous thermal ablation should already be considered the first option for the treatment of small HCC measuring 2 cm or smaller, and it is likely that in the next future the ongoing technical developments of the ablation systems will make thermal ablation (in particular MWA) the first treatment option even for HCC up to 4-5 cm.

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