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REVIEW

Role of radiofrequency ablation in the treatment of small hepatocellular carcinoma

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Abstract

Radiofrequency ablation (RFA), one of the most advanced loco-regional ablative therapeutic methods, is widely utilized in the treatment of hepatocellular carcinoma (HCC). Because of its minimal invasiveness and high efficacy, RFA has been regarded as a curative therapy as alternative to surgical resection and liver transplantation. It brings new hope and a new treatment pattern for small HCC. In this article, we summarize the important role of RFA in the treatment of small HCC according to our clinical experience over six years. The prognosis of small HCC after RFA is comparable to that of surgical resection but with higher safety, less complications, wider applicability, and good long-term survival. RFA will play a more and more important role in the clinical treatment of small HCC.

Key words: Hepatocellular carcinoma; Radiofrequency ablation; Hepatectomy; Prognosis; Complication; Recurrence; Therapy

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world[1]. Although the majority of cases are still found in Asia and Africa, recent evidence has shown that the incidence and mortality rate of HCC are rising in North America and Europe[2,3]. The prognosis of HCC is generally poor. Apart from liver transplantation, partial hepatectomy remains the best hope for a cure but is suitable for only 9% to 27% of patients[4,5]. The presence of significant background cirrhosis often precludes liver resection in patients with HCC. Recurrence of tumor within the liver remnant is also common in patients who have undergone 'curative' liver resection[6].

In the past two decades, percutaneous local ablative therapy has emerged as a safe and effective treatment for small HCC[6]. Of the various percutaneous local ablative therapies, radiofrequency ablation (RFA) has attracted the greatest interest because of its effectiveness and

safety for small HCC ≤ 5.0 cm, with a 3-year survival rate of 62% to 68%, a low treatment morbidity of 0% to 12%, and a low treatment mortality of 0% to 1%[6-11]. RFA now is regarded as a curative therapy for small HCC (sHCC) as alternative to liver resection and liver transplantation. The present article is focused on the percutaneous use of RFA in the treatment of sHCC.

PRINCIPLE AND DEVELOPMENT OF RFA

RFA is a physical thermal ablation technique. The goal of RF ablation is to induce thermal injury to the tissue through electromagnetic energy deposition. In RF ablation, the patient is part of a closed-loop circuit, that includes a RF generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode, because the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode. The local temperature can reach to 90-120℃, which leads to immediate tissue death and thermal coagulation necrosis, thereby destroying the tumor[12].

Three stages can be defined in the development of RFA since its first application in clinical treatment for HCC, according to the development of radiofrequency electrodes: In the first stage, during the early 1990s, a single and solid-center needle electrode was applied in RFA, and the ablative region was only about 1.6 cm in diameter. It utilization was very restricted because of the limitation of ablative region. During the second stage, in the middle 1990s, the electrode had been greatly upgraded. A multiple electrode, the LeVeen electrode (Radiotherapeutics) and an internally cooled needle electrode (Radionics) were invented. Both increased the ablative region to 3.5-5.0 cm in diameter, dramatically improving the therapeutic efficacy and resulting in RFA becoming widely applied in treatment of HCC. RFA gradually became the preferred method for local ablative therapies and attracted more and more attention. In the current third stage a new generation electrodes is being developed on the base of the second-generation electrodes. Most of them have integrated two-different mechanisms, such as a combined cluster needle electrode and saline enhanced electrode. For example, Celon Power (Olympus) has integrated 2-3 kinds of mechanism from second-generation electrodes, resulting in a further increase in the ablative region to 5.0-7.0 cm in diameter. Furthermore, by applying multi-electrode ablation systems and locating the electrodes according to tumor shape; precise "conforming ablation" may be achieved. All these developments will further improve the therapeutic efficacy of RFA.

EFFICACY AND SAFETY OF RFA FOR SHCC

In 1995, Rossi *et al*[13] in Italy firstly introduced RFA as a palliative therapy for HCC. In the middle 1990s, the appearance of the second-generation electrode made RFA widely utilized and attracted more and more attention to the technique. RFA was considered to be a "potential curative" therapy for sHCC. In 1996 the long term survival rates of RFA for sHCC were first reported by Rossi S *et al*[14]. In their study, 39 patients with sHCC ≤ 3.0 cm in diameter were treated with percutaneous RFA, with overall 1-, 3- and 5-year survival rates of 97%, 68% and 40%, respectively. Since then, more and more studies about RFA in the treatment of sHCC have been reported with gradually improving results. Most results showed that RFA was almost as effective as liver resection for sHCC. In the largest study to reported by Tateishi *et al*[15] in 2005, 303 patients with HCC ≤ 5.0 cm in diameter were included, and the 1-, 3- and 5-year survival rates were 93.0%, 74.3% and 45.2%, respectively[8].

Tumor size, location and stage, Child-Pugh class and so on are considered contribute to the prognosis of sHCC after RFA[16]. Tumor size seems to be the most important factor. A study reported by Livraghi *et al*[17] showed that the complete ablation rate of HCC after RFA declined dramatically with increasing tumor diameter. The complete ablation rate was ≥ 90% when tumor was ≤ 3.0 cm in diameter, but sharply decreased to 71% and 25% for tumor 3.1-5.0 cm and > 5.0 cm. So for HCC ≤ 3.0 cm, complete ablation can be reached by RFA alone, whilst for HCC 3.0-5.0 cm, RFA combined with other therapies or multiple overlapping ablation methods appear to be necessarily[15].

Various reports have shown the safety of RFA in the treatment of HCC. A study[18] including 2320 patients with 3530 HCC tumors reported that the mortality rate after RFA was 0.3%. The major complications rate was 2.2%, including bleeding, tumor implantation, hepatic abscess, enterobrosis, whilst the minor complications rate was 4.7%, including fever, pain, skin burning, and pleural effusion. The number of ablation sessions was the major factor which contributed to complications. Thus, diminishing ablation sessions was the most important ways of decreasing complications[18]. RFA was previously considered contraindicated for HCCs located on the surface of the liver, or close to vital organs, large vessels. However, in past decade, with the development of equipment and improvement of techniques, these types of HCCs were also reported to have been treated with RFA safely. So we believe that RFA may now be safely performed whenever patients have good preserved liver function.

RFA can be guided by different methods, such as ultrasound, computer tomography, laparoscopy or laparotomy. The percutaneous method is much less invasive than other methods. It allows patients to recover more rapidly and can even be performed in the day-surgery clinic. However, there may be some tumors where it is difficult to perform RFA percutaneously or where there is a risk of adjacent organs burning. For laparoscopy or laparotomy RFA, it was easy to gain entry, protect adjacent organs, and furthermore enlarge the ablative region by use of hepatic inflow blood clamping. However, this was much more invasive and required a longer hospital stay. Reports[18] have shown that open RFA may contribute to high a complete necrosis rate and low local recurrence rate, although it involved more complications and risks. Therefore, the percutaneous method is the preferred method, whilst the laparoscopy or laparotomy method can be carried out when the percutaneous method is difficult or where there is risk of adjacent organs burning.

RFA VERSUS OTHER LOCAL ABLATIVE THERAPIES FOR SHCC

Clinical trials comparing RFA with PEI demonstrated the clear superiority of RFA[19-23]. Livraghi *et al*[19] reported the first prospective nonrandomized comparative study of these 2 techniques in 1999. RFA resulted in a higher rate of complete necrosis (90% *vs* 80% of tumors) and required fewer treatment sessions (mean, 1.2 *vs* 4.8 sessions) than PEI. However, the complication rate was higher with RFA than with PEI. Since then, these 2 techniques were further evaluated in a randomized trial setting. In the RCT of Lencioni *et al*[20], RFA was superior to PEI in local recurrence-free survival. The 1- and 2-year local recurrence-free survival rates were 98% and 96% in the RFA group and 83% and 62% in the PEI group, respectively. Lin *et al*[21] performed a RCT comparing RFA with PEI and percutaneous acetic acid injection (PAI) in patients with HCC less than 3 cm in diameter. RFA was superior to PEI and PAI in local recurrence, overall survival, and cancer-free survival rates. However, RFA resulted in significantly more major complications than PEI or PAI. Major complications occurred in 4.8% of patients in the RFA group and in none of the other 2 groups. In another RCT, Lin *et al*[22] compared RFA with conventional PEI regimens and with high-dose PEI regimens, and showed RFA required fewer treatment sessions to completely ablate tumors. RFA was also associated with a significantly lower rate of local tumor progression, and higher overall and disease-free survival. In the RCT of Shiina *et al*[23], RFA resulted in a 46% decreased risk of death, a 43% decreased risk of overall recurrence, and an 88% decreased risk of local tumor progression when compared with PEI. There was no significant difference in the complication rates between the 2 groups of patients.

The superiority of RFA over MCT was supported by the RCT of Shibata *et al*[24]. In this study, 72 patients with 94 HCC nodules were randomly assigned to RFA and MCT. Both groups showed similar therapeutic effects, complications, and residual disease rate. However, the number of treatment sessions per nodule was significantly lower in the RFA group than in the MCT group (1.1 *vs* 2.4). Complete therapeutic effect was achieved in 46 (96%) of 48 nodules treated with RFA and in 41 (89%) of 46 nodules treated with MCT[24].

RFA VERSUS LIVER RESECTION FOR SHCC

Liver resection remains the gold standard therapy for sHCC. However, the presence of significant background cirrhosis often precludes liver resection for sHCC especially in China, and the 5-year recurrence rate after liver resection is as high as 43.5%. In recent decades, RFA has emerged as a new treatment modality and attracted great interest because of its effectiveness and safety for sHCC, with a 3-year and 5-year survival rate of 50% to 80%, 40%-60%, respectively, and a 5-year recurrence rate of 40%-50%. This has challenged the role of liver resection. Recently, we conducted a RCT on 180 patients with a solitary HCC $\leqslant$ 5 cm who received either percutaneous RFA or surgical resection[10]. This RCT showed percutaneous RFA to give similar overall and disease-free survivals as surgical resection for patients with solitary and small HCC. The 1-, and 4-year overall survival rates after percutaneous RFA and surgery were 95.8%, 67.9% and 93.3%, 64.0%, respectively. The corresponding disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6%, respectively. As a less invasive procedure, percutaneous RFA had the advantage over liver resection in giving better short-term postoperative results. There were, however, some limitations in our study as the sample size was small and the follow-up was not sufficiently long term. It is, therefore, still unclear whether or not RFA can actually replace surgery in the treatment of sHCC and a large sample, multi-center prospective randomized trial is needed. We believe that RFA could at least partly replace liver resection in the treatment of sHCC, especially for center tumors or recurrent tumors.

Compared to liver resection, RFA has showed some advantages: (1) Minimally-invasive; It takes about ten minutes to ablate a tumor $\leqslant$ 3.0 cm completely, and patients recover in a few days, which is much better than liver resection; (2) No significant impact on liver function and quality of life; (3) Safety; The mortality is only 0% to 1% and mobility 2.2% to 4.7%; (4) More indications: Patients with multi-nodule HCC or deranged liver function are still suitable for RFA; (5) Easily repeatable: Making it available for multi-nodule or recurrent HCC; (6) Cost-effectively: The procedure can wvwn be performed even in the day clinic; and (7) Necrosis tumor tissue also can serve as an autologous vaccine, which will enhance the immune response to cancer.

RFA COMBINED WITH OTHER THERAPIES FOR SHCC

A major limitation of RFA is the small volume of tumor that it can treat. The rate of complete ablative necrosis decreases with the size of the tumor, particularly for those larger than 3 cm. There is general consensus that complete response of RFA therapy in patients is associated with improved outcome. Therefore, initial complete tumor necrosis should be considered a relevant therapeutic target irrespective of tumor size and liver functional status. It has been suggested that a larger area of coagulative necrosis could be created if RFA was performed in HCC after occlusion of the arterial supply or in combination with another ablative therapy.

RFA combined with TAE has been widely utilized to date, and the results are encouraging. During TAE, the tumor feeding arteries are embolized and the blood infusion thereby reduced. This diminishes the "heat sink" effect during the following RFA. Furthermore, this combined therapy not only increases the ablative region, but also destroys the potential microscopic tumors by TAE. In the RCT of Cheng *et al*[25] on sHCC, patients were randomly assigned to treatment with a combination of TACE-RFA (n = 96), TACE alone (n = 95), or RFA alone (n = 100). During a median follow-up of 28.5 mo, the median survivals were 24 mo in the TACE group (3.4 treatment courses), 22 mo in the RFA group (3.6 courses), and 37 mo in the TACE-RFA group (4.4 courses). The rate of objective response sustained for at least 6 months was higher in the TACE-RFA group (54%) than either the TACE alone (35%) or the RFA alone (36%) groups. The authors concluded that TACE-RFA was superior to TACE alone or RFA alone in improving survival for patients with HCC larger than 3 cm. More RCTs with survival data are needed to validate these techniques.

RFA combined with PEI is another effective method. PEI had been utilized in the treatment of HCC for a long time. It usually requires to be repeated several times and with the disadvantages of long treatment cycle, high local recurrence rate etc. During RFA combined with PEI therapy (PEI followed by RFA) the injected ethanol embolizes vessels $\leqslant$ 5mm, so that blood infusion is reduced. Meanwhile, the ethanol can disperse to areaa which RFA failed to reach , such as perivascular tumors. In this way, the ablative effect is enhanced. In our RCT[26], 133 patients were randomly assigned to receive RFA-PEI (n = 66) or RFA alone (n = 67). The 5-year overall survival rates for the RFA-PEI group and the RFA alone group were 49.3% and 35.9%, respectively. The RFA-PEI offered significant survival advantage over RFA alone for patients with tumors of 3.1 to 5 cm in diameter, but not for those with tumors equal or less than 3.0 cm in diameter, or for those with tumors 5.1 to 7 cm in diameter. Moreover, some reports have suggested that RFA combined with injection of cytotoxic drugs will improve the efficacy although this remains to be proved. Combination of different loco regional therapies is a simple, easy way to improve prognosis.

In conclusion, RFA offers a new option for sHCC, and the initial results are encouraging. RFA is more effective than the other modalities of local ablative therapy. It has been shown to achieve effective and reproducible tumor destruction with acceptable morbidity. RFA is accepted as the best therapeutic choice for patients with early stage HCC when resection or transplantation is precluded. Moreover RFA can be used as an alternative treatment to surgery for resectable HCC of less than or equal to 3 cm in diameter. However, more long-term outcomes and prospective randomized control trials are needed to define the role of RFA in the treatment of sHCC, especially in comparison to liver resection.

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