Role of Radiofrequency Ablation in the Treatment of Hepatocellular Carcinoma: Experience of a Cancer Center in China

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Abstract
Radiofrequency ablation (RFA) has become an important treatment for hepatocellular carcinoma (HCC). The good candidates for RFA are patients with HCC at an early stage (solitary tumor ≤ 5 cm in diameter or ≤ 3 nodules ≤ 3 cm in diameter). Several clinical trials have shown that RFA is effective in resection for the treatment of small HCC. Until now, RFA has been widely used as a radical treatment for small HCC. RFA also plays an important role in the multidisciplinary treatment of HCC and is usually combined with other therapies such as resection, vascular intervention, intratumor ethanol injection, radiotherapy, chemotherapy, targeted drug therapy, and biological immune therapy. In this study, we will introduce our experience of RFA in the treatment of HCC in a cancer center in China.
RFA as a Curative Treatment of Small HCC

The long-term survival rates of RFA for small HCC were first reported by Rossi et al. [9] in 1996. In their study, 39 patients with HCC ≤ 3.0 cm in diameter were treated by percutaneous RFA, with overall 1-, 3- and 5-year survival rates of 97, 68, and 40%, respectively. RFA was introduced in China in 1999. Chen et al. [10] reported a study of 14 patients with small HCC treated with RFA. The follow-up was 12–18 months, and the complete ablation was 93%. From that day forward, RFA was gradually accepted as a treatment for HCC in China.

We conducted a prospective randomized trial to compare the results of RFA with surgical resection in the treatment of small HCC. The main inclusion criteria of the study were patients with solitary tumor ≤ 5 cm and Child-Pugh class A liver function [10]. Finally, there were 71 patients in the RFA group and 90 patients in the surgical resection group. The results showed that the 1-, 2-, 3-, 4-year survival rates of the RFA group and the surgical resection group were 95.8, 82.1, 71.4, and 67.9% and 93.3, 82.3, 73.4, and 64.0%, respectively, and there was no significant difference between these two groups. However, the complication rate in the RFA group was lower than that in surgical resection (3/71 vs. 50/90, p < 0.05), and the hospital stay was shorter in the RFA group (p < 0.05). We concluded that RFA had the same efficacy as surgical resection for the treatment of small HCC. Lu et al. [11] also conducted a randomized controlled trial (RCT) in 105 patients with early-stage HCC. The results showed that the 1-, 2-, and 3-year survival rates of the RFA group and the surgical resection group were 93.5, 87.1, and 87.1% and 91.3, 86.4, and 86.4%, respectively. There was no significant difference between these two groups. Also several retrospective analyses reported that RFA is an effective and safe treatment for managing small HCC [12, 13].

Tumor number, tumor size, Child-Pugh class, safety margin, hepatitis B surface antigen are considered to be the independent prognostic factors of small HCC after RFA [14, 15]. RFA has been carried out as a treatment for HCC as well as liver metastases since August 1999 in our cancer center. Up to February 2007, 803 patients had received RFA as an option of treatment. We summarized the outcome of the patients, and the rate of complete ablation was 92.5%; the tumor size and stage were important prognostic factors [16]. Tumor size seems to be the most important factor. A study reported by Livraghi et al. [18] showed that the complete ablation rate was 90% with HCC < 3 cm but decreased to 71% in medium HCC (3.0–5.0 cm) and to 45% in large HCC (5.1–9.0 cm). However, with the development of technology and equipment, for HCC ≤ 5 cm, complete ablation can be achieved by RFA alone. Wu et al. [13] analyzed 680 patients with 828 lesions; the mean tumor size was 3.6 ± 1.4 cm. After RFA, 90.8% of the patients with tumors > 3.5 cm achieved complete ablation. We conducted a study to evaluate the efficacy of RFA for large HCC using a multipin bipolar system. We found that RFA with a multipin bipolar system was effective and safe; a large ablation volume could be achieved according to the shape of the index tumor.

RFA has been shown to be safe in the treatment of HCC [18]. A study including 131 patients with 226 HCC tumors reported no treatment-related deaths [19]. The major complication rate was 4.6%. Major complications reported after RFA included bleeding, tumor implantation, bile leakage, hepatic abscess, and cholecystitis. The most common minor complications were fever and pain. In our RCT, the major complication rate after RFA was 4.2%, but it was 55.56% in the surgical resection group. The minor complication rate was 15.5%, including electrode pad burn, fever, and pain. There was no RFA procedure-related hemorrhage, infection, or needle tract seeding in the study. The results were similar to those of other large studies [20, 21]. At present, RFA is widely accepted in China and is utilized not only as a curative treatment for small HCC but also in combination with other treatments or as an adjuvant treatment.

Treatment for Recurrent HCC

The 5-year recurrence rate of HCC after resection is 77–100%. Eighty to ninety percent of this is intrahepatic recurrence [22]. The first option for treating recurrent HCC is surgical resection. However, only 10.4–27.4% of patients are candidates for surgical resection because of the characteristics of the tumor, liver function, and the risk of surgery. We analyzed a cohort of 110 patients with recurrent small HCC [23]. Sixty-six patients with 88 tu-
mors were treated by RFA and 44 patients with 55 tumors were treated by repeat hepatectomy. The 1-, 3-, and 5-year survival rates of RFA and repeat hepatectomy were 76.6, 48.6, and 39.9%, and 78.6, 44.5, and 27.6%, respectively; there was no significant difference between RFA and hepatectomy for treating recurrent HCC, but the major complications happened significantly more often after repeat hepatectomy than after RFA (68.2 vs. 3.0%). The study showed that RFA was as effective as repeat hepatectomy in the treatment of recurrent small HCC, and RFA had the advantage over repeat hepatectomy of being less invasive. We also conducted an RCT to compare the efficacy of transcatheter arterial chemoembolization (TACE) combined with RFA with RFA alone [24, 25].

We also conducted an RCT of sequential RFA and TACE (TACE-RFA) versus RFA for treating recurrent HCC; there were 139 patients with recurrent HCC ≤5 cm enrolled into the study. Sixty-nine patients received sequential TACE-RFA and 70 received RFA alone. The results showed that the 1-, 3-, and 5-year overall survival rates for the sequential TACE-RFA group were 94.2, 68.6, and 45.6%, and the overall survival and recurrence-free survival for the sequential TACE-RFA group were better than those for the RFA group for patients with intervals of tumor recurrence from the initial treatment of ≤1 year and tumors 3.1–5.0 cm but not for patients with tumors ≤3.0 cm. Moreover, both treatment groups had low rates of major complications (2.9 vs. 2.9%). Thus, we recommend sequential TACE-RFA for patients with tumors 3.1–5.0 cm or patients with intervals of tumor recurrence from the initial treatment of ≤1 year.

**Combination with TACE**

TACE is the main treatment for intermediate and advanced stage HCC. RFA combined with TACE can emerge as a new treatment mode to achieve better tumor necrosis. We retrospectively analyzed 114 patients who received TACE combined with RFA [26]. After treatment, the 1-, 3-, and 5-year overall survival rates were 90.4, 73.2, and 49.1%, respectively. The 1-, 3-, and 5-year tumor progression-free survival rates were 77.1, 54.6, and 36.4%, respectively. However, the overall survival for tumors with a size ≤5 cm was better than that for tumors with a size of 5.1–7 cm because for HCC ≤5 cm complete ablation can be achieved by RFA alone, but for HCC with a size of 5.1–7 cm it is necessary to combine RFA with other treatments like TACE to achieve a higher complete ablation. In addition, compared to the outcome of patients who received RFA treatment alone, combined RFA and TACE showed better overall survival rates than RFA alone in the group of patients with tumors >5 cm or multiple tumors [27]. Therefore, RFA combined with TACE can be an alternative for patients with intermediate HCC in cases where surgery is not feasible. Combination with TACE can improve the complete ablation rate and this may be due to the following reasons: TACE can embolize vessels that supply nutrition, level down the intratumor blood flow, and reduce the effect of heat sink [28] The image of the tumor becomes clear after TACE, which is beneficial for the treatment. TACE can control microlesions.

**Combination with PEI**

PEI has been utilized in the treatment of HCC for a long time. It usually requires several repetitions and has disadvantages such as a long treatment cycle and a high local recurrence rate.

During RFA combined with PEI therapy (PEI followed by RFA), the injected ethanol embolizes vessels ≤5 mm so that blood infusion is reduced. Meanwhile, the ethanol can disperse to areas which RFA failed to reach, such as perivascular tumors. In this way, the ablative effect is enhanced. We conducted an RCT to compare PEI combined with RFA to RFA alone; 133 patients were randomly assigned to receive RFA-PEI (n = 66) or RFA alone (n = 67) [29]. The 5-year overall survival rates for the RFA-PEI group and the RFA alone group were 49.3 and 35.9%, respectively. RFA-PEI offered a significant survival advantage over RFA alone for patients with tumors 3.1–5 cm in diameter but not for those with tumors equal to or less than 3.0 cm in diameter or for those with tumors 5.1–7 cm in diameter. Moreover, some reports have suggested that RFA combined with injection of cytotoxic drugs improves the efficacy, although this remains to be proved [30]. Combination of different locoregional therapies is a simple, easy way to improve prognosis.

**Combination with Immune-Biological Treatment**

Moreover, it is a popular approach to use immune-biological treatment as adjuvant therapy. Immune-biological treatments have commonly been used for patients after curative therapies to prevent tumor recurrence. The
methods include cytokines, infusion of immune cells, and monoclonal antibody and its conjugate, tumor vaccine, among others. We reported the combination of RFA and autologous RetroNectin-activated killer (RAK) cells in the treatment of HCC patients with a tumor size <4 cm. Seven patients received the combined treatment [31]. During the 7-month follow-up, no severe adverse events, recurrences, or deaths were observed. The preliminary results suggested the feasibility and safety of the combined therapeutic regimen for HCC, and RAK cell adoptive immunotherapy might be helpful for preventing recurrence in HCC patients after RFA. Due to the limited number of cases and short follow-up period in this study, the effects of combination treatment of RFA and RAK cells remain to be further validated, but there is hope that this will be another therapy to prevent HCC recurrence.

In China, RFA is accepted as an alternative option for patients with early stage HCC, especially when resection or transplantation is precluded. However, more long-term outcomes and prospective randomized control trials are needed to define the role of RFA in the treatment of small HCC, especially in comparison to liver resection. Besides, the advantages of RFA can give it a key role in the multidisciplinary treatment of HCC.

Disclosure Statement

References


