Radiofrequency Ablation for Primary and Metastatic Liver Tumors: Indications and Therapeutic Effects

TOSHIYUKI OTSUKA, HITOSHI TAKAGI*, DAISUKE KANDA, HIROAKI NAKAJIMA, MASATOMO MORI

First Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Gunma 371-8511, Japan

Abstract: Radiofrequency ablation therapy (RFA) is considered to be a reliable alternative to surgical resection for patients with primary and metastatic liver tumors. RFA delivers energy into the tumor through non-insulated needle electrode tips, causing a high-frequency alternating current to flow and resulting in coagulation necrosis of the tumor tissue. Compared to percutaneous ethanol injection (PEI) and microwave coagulation therapy (MCT), RFA can induce a larger and more predictable area of coagulation necrosis. Therefore, this technique may reduce the number of required treatment sessions and shorten the hospital stay. Three different RFA devices are presently available, and their usefulness has been compared. Representative adverse effects of RFA include local pain, intra-abdominal bleeding, pleural complications, and needle tract seeding. Although more studies are required to precisely define the indications and to estimate the long-term effects, RFA is expected to become a major therapeutic technique for the treatment of primary and metastatic liver tumors.

Key Words: radiofrequency ablation, primary liver tumors, metastatic liver tumors

Background

As therapeutic modalities for small liver tumors, local ablative therapies such as percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), and radiofrequency ablation therapy (RFA) have recently become attractive alternatives to surgical resection because they are both effective and less invasive. RFA is a reliable method that can be used to induce thermally mediated coagulation necrosis of tumor tissues percutaneously or intraoperatively. Early clinical trials have been applied to primary liver tumors, mostly hepatocellular carcinomas (HCCs), metastatic liver tumors, and cervical intramedullary ependymomas.

This review outlines the technical considerations of RFA and describes experimental and clinical studies involving the use of RFA in the liver, including a metaanalysis of the effects and complications.
Technical overview

Radiofrequency waves of between 460 and 500 kHz are generally used in RFA procedures\(^{16,18,22}\). The converting radiofrequency waves generate an alternating current that passes from an uninsulated electrode into the surrounding tissues. The alternating current changes the direction of ions in the surrounding tissues. The resulting ionic agitation creates frictional heating, which results in the coagulative necrosis of the surrounding tissues\(^{23}\).

Three kinds of generator systems are presently available\(^{12,13}\). The RITA 500 PA generator system (RITA Medical Systems, Mountain View, CA) consists of an electrode needle, including four expandable hooks, with a thermometer (Fig. 1A) and an RF generator with a maximum output power of 50 W. The RF 2000 generator system (Radio Therapeutics Corp., Mountain View, CA) consists of a needle electrode with 8-10 expandable hooks (Fig. 1B) and an RF generator that supplies up to 100 W of power. In these RF generator systems, an insulated 15-gauge needle electrode is introduced into the tumor under the guidance of ultrasonography; the expandable hooks are then deployed from the tip of the needle electrode into the tumor\(^{16,22}\). The cool-tip RF generator system (Radionics Burlington, MA) consists of a monopolar-type needle electrode (Fig. 1C) and an RF generator that supplies a maximum of 100 W of output power. The uninsulated portion of the 18-gauge needle electrode is introduced into the tumor under sonographic guidance\(^{18}\).

RFA can be performed either percutaneously or intraoperatively\(^{24}\). To increase the antitumor effect of RFA, the combination of RFA and balloon occlusion of the hepatic artery or portal vein has been proposed\(^{25-27}\). The resulting reduction in the blood supply reduces the cooling effect of the blood flow, which is beneficial to the hyperthermia that is generated by the RF waves.

![Fig. 1](image-url)

**Fig. 1.** Three kinds of RF devices: RITA disposable hand piece, Model 30 (A), LeVeen Needle Electrode (B), and cooled-tip RF needle (C).
Indications

Although several reports on the indications for RFA in the treatment of primary and metastatic liver tumors have been published, the general consensus seems to be that RFA is suitable for cases where the tumors are less than 3 cm in diameter and three or fewer in number.\(^{11-13,16-19}\). The maximum size of tumors that can be successfully treated using RFA has been determined using animal studies. In experimental models using normal liver tissues in vivo, the diameter of tissue coagulated by the cool-tip RF generator system was limited to \(2.4 \pm 0.2\) cm\(^2\), while the diameter of tissue coagulated by the RITA 500 PA generator system was limited to 3.5-4 cm\(^2\).\(^{29}\), Otsuka, T. et al., unpublished data\(^{29}\). Therefore, RFA may replace surgical resection, especially for the treatment of small HCC (less than 3 cm in diameter) and in cases where the patient refuses to undergo surgery. Some groups have performed RFA intraoperatively for the treatment of larger HCCs.\(^{11,14,16,30}\) In these cases, the hepatic inflow is temporarily occluded to decrease the cooling effect of the blood flow on perivascular tumor cells; alternatively, transcatheter arterial embolization (TAE) can be performed prior to percutaneous RFA.\(^{30}\) Preliminary studies also suggest that the combination of RFA and intra-arterial infusion chemotherapy is effective in patients with multiple liver metastases of colon cancer.\(^{31}\) However, RFA usually does not require additional therapeutic procedures to be performed, even in cases of multiple liver metastatic lesions.\(^{32}\)

With regard to liver function tests, RFA is generally indicated in patients with a prothrombin activity of more than 50%, a platelet count of more than 50,000/mm\(^3\), a serum total bilirubin level of less than 3.0 mg/dl, and no gross ascites.\(^{10,12,16,17}\) These criteria are commonly used for all procedures involving percutaneous and transhepatic punctures, such as PEI and MCT, although some exceptions do exist.

Therapeutic Effects

Histopathologic examinations of surgically resected tumors and animal studies have revealed that sufficient coagulation necrosis of non-tumorous and tumorous tissues can be obtained using RFA.\(^{28,29,33}\) The effect of RFA for the treatment of HCC is equivalent to that for metastatic liver tumors.\(^{16,17}\)

To evaluate the therapeutic effects of RFA, imaging methods such as ultrasonography (US), enhanced color and power Doppler US, computed tomography (CT), and magnetic resonance imaging (MRI), and tumor markers such as serum alpha-fetoprotein (AFP) or protein induced by vitamin K absence or antagonists-II (PIVKA-II) have been used. If the treatment is not sufficient, RFA can be repeatedly performed. Follow-up assessment of the response to treatment can also be performed using the above-mentioned imaging methods.\(^{11-13,16,17,34-36}\) We have performed RFA for HCC and evaluated the therapeutic effect using CT (Fig. 2).\(^{35}\)

Several reports on the use of RFA for the treatment of HCCs and liver metastases have been published. Data derived from studies with a follow-up period of more than 1 year and that describe the rates of local recurrence, recurrence at other sites, and disease-free survival rates are summarized in Fig. 3. The mean follow-up period was 17.9 months for studies involving large groups of patients (varying from 15 to 123 patients, with a mean of 71.8 patients).\(^{10,11,16,17}\) The local recurrence rate varied between 0% for the study by Francica et al.\(^{10}\) (mean follow-up period of 15 months) to 5% for the study by Rossi S et al.\(^{17}\) (mean follow-up period of 22.6 months). The mean local recurrence rate was 2.6% for all
The recurrence at other sites rate varied from 27.6% for the study by Curley et al. (mean follow-up period of 15 months) to 45.5% for the study by Curley et al. (mean follow-up period of 19 months). The mean recurrence at other sites rate was 35.6% for all follow-up periods. The disease-free survival rates ranged from 48.3% for the study by Rossi et al. (mean follow-up period of 22.6 months) to 70.6% for the study by Curley et al. (mean follow-up period of 15 months). The mean

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Fig. 2. CT images obtained before and after RFA using an expandable needle electrode (RITA Medical Systems). (A) Pretreatment CT scan in a patient with a hepatocellular carcinoma (arrow). (B) CT scan after RFA treatment shows complete necrosis of the lesion.

Fig. 3. Summary of clinical studies on RFA that document the local tumor recurrence rate (black bars), the rate of recurrence at new sites (striped bars), and the rate of disease-free survival (white bars) and that have a follow-up period of more than 1 year (four groups on the left side). Our data is shown on the right side. The parentheses indicate the follow-up period (in months) and the number of patients in the study.
disease-free survival rate was 58.5% for all follow-up periods. Thus, the recurrence rates increased and the rates of disease-free survival decreased according to the length of the follow-up period. The survival rate after RFA for the treatment of small HCC reported by Rossi et al.\textsuperscript{17} was similar to that for patients with small HCC who were treated with PEI\textsuperscript{11}.

However, most of the studies, including our own data, were performed using a small number of patients and a short follow-up period. We have performed RFA in 15 patients with HCC and have followed these patients for 6 months. The rates of local and other site recurrence, and disease-free survival rate were 6.7% (1 in 15 patients), 20% (3 in 15 patients), and 73.3% (11 in 15 patients), respectively (Fig. 3). In addition to the number of patients and the period of follow-up, different tumor characteristics (location and number), different techniques (cool-tip needle electrode or needle electrode including expandable hooks), and different modalities of approach (percutaneous, intraoperative, or laparoscopic) were used in these reports on RFA. Most of the studies did not include a control group of patients who were treated with a different technique. Therefore, a randomized control study is needed to clarify the effects of RFA and to determine the therapeutic efficacy of RFA.

Complications

The most common adverse effects of RFA are pain, fever, and an elevation of transaminase levels\textsuperscript{12,13,15}. These effects are generally transient and do not require any specific therapy. Most patients complain of mild to moderate pain at the puncture site or epigastrium during the procedure but the pain can usually be tolerated by analgesics, such as pentazosine.

However, several major complications requiring specialized therapy have been reported, and the incidence of major complications is 5-10% of all patients\textsuperscript{10-13,15,16,18,28,37,38}. These complications include pleural effusion, ascites, intraperitoneal bleeding, hemorrhage in the treated tumor, pleurisy, hydro-pneumothorax, ventricular fibrillation, bleeding from the subcostal wound, jaundice, gastric ulcer, and needle tract seeding. Moreover, Livraghi et al.\textsuperscript{38} reported that RFA had a higher complication rate than PEI in a prospective randomized trial comparing RFA and PEI.

Although RFA appears to be a safe and minimally invasive procedure for the treatment of primary and metastatic liver tumors, the possibility of complications should always be kept in mind.

Conclusion

RFA is thought to be an effective and minimally invasive method for the treatment of small liver tumors less than 3 cm in diameter or liver tumors that can not be resected because of deteriorating liver function\textsuperscript{1,11,16}. RFA is useful in patients where PEI or MCT is also indicated. RFA is superior to PEI and MCT with regard to the predictability of the area of coagulation necrosis, and the ability to create larger areas of coagulation necrosis results in a reduction in the number of treatment sessions and a shortening of the hospital stay\textsuperscript{1,12,13}. Moreover, the survival rate for RFA is similar to that of PEI for small HCCs\textsuperscript{1,17}.

The most frequent complications of RFA are mild or moderate pain at the needle insertion site during RFA, a transient increase in serum transaminase levels, and a transient mild fever\textsuperscript{10,12,25}. However, major complications such as pleural effusion, intraperitoneal bleeding, and prolonged fevers
have been reported, although these complications were treated conservatively in most cases\textsuperscript{10,12,28,35}).

Although RFA appears to be an important therapeutic method for liver tumors, further studies must be performed to clarify the indications for achieving an optimal therapeutic effect and avoiding major complications.

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肝癌に対するラジオ熱凝固療法による治療：適応と効果

大塚 敏之・高木 均・神田 大輔
中島 弘明・森 昌朋
群馬大学医学部第一内科

要  旨：肝癌に対するラジオ波熱凝固療法 (RFA) は肝切除術に代わり得る有用な治療法として広く
行なわれるようになった。RFA は腫瘍内に電極を挿入し、その先端の非絶縁部から 460KHz の交流電流
を発生させて腫瘍を凝固壊死させる治療法である。経皮的エタノール注入療法やマイクロ波凝固療法に
比べ、RFA は 1 回の治療で比較的広範囲を予想した通りに凝固壊死にできる。従って、治療セッション
数を少なくし入院期間を短縮することができる。現在ラジオ波を発生させる装置は 3 種類あり、各々の有
用性が報告されている。RFA の副作用としては局所の疼痛、腹腔内出血、胸部貯留、穿刺経路への播種等
がある。今後も適応についての詳細な検討と長期予後を含んだ治療効果の評価が必要であるが、RFA は
肝癌治療の主流になると考えられる。