Treatment strategy and efficacy of imaging-guided radiofrequency ablation in large hepatocellular carcinoma

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Abstract

Radiofrequency (RF) ablation was recently introduced as a novel ablation modality for hepatocellular carcinoma (HCC). Several investigators have reported that percutaneous RF ablation for patients with small HCC nodules provide favorable survival with excellent local control. However, several limitations of RFA have been pointed out, such as limited coagulated necrosis and relatively frequent local recurrences in large HCC. The critical factors for treatment success in large tumors included (a) the target diameter of an ablation- or of overlapping ablations - must be larger than the diameter of the tumor that undergoes treatment; (b) reduce the negative effect of blood flow and tissue perfusion on RF heating. To overcome RF limitations, researchers developed several techniques and skills of percutaneous treatments and several studies have demonstrated that multiple RF ablation processes with overlapping of ablation zones or combination therapies are feasible for large liver tumors. In this review, we analyzed varies of treatment strategies for percutaneous RF of large tumors and summarized the efficacy of clinical application.

Key words: radiofrequency ablation, hepatocellular carcinoma, large tumor, treatment strategy

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Introduction

RF ablation was recently introduced as a novel ablation modality for HCC\(^1\)\(^2\). For adequate destruction of tumor tissue, the entire target volume must be subjected to cytotoxic temperatures. Different physical mechanisms are involved in the hepatic hyperthermic treatments in order to generate a lethal temperature. A common important factor that affects the success of thermal ablation is the ability to ablate all viable tumor tissue and possibly an adequate tumor-free margin. Ideally, a 360°, 0.5-1-cm-thick ablative margin should be produced around the tumor. This cuff would ensure that microscopic invasions around the periphery of a tumor have been eradicated. Thus, the target diameter of an ablation- or overlapping ablations - must be larger than the diameter of the tumor that undergoes treatment\(^3\)\(^4\). Most technologies enable us to produce liver thermal lesions of approximately 3-3.5 cm in diameter; RFA has consequently become an emerging percutaneous therapeutic option both for small HCC\(^5\)\(^6\). New techniques, strategies (for example, multiple RF ablation processes with overlapping of ablation zones) and combined therapies (tumor ischemia and RFA) have made it possible to treat large tumors. In this review, we analyzed varies of treatment strategies for percutaneous RF of large tumors and summarized the efficacy of clinical application.

Overlapping model and method

Because most RF device produced limited ablation area and the complete ablation of a tumor requires safety margins, these performances are clearly insufficient for the proper treatment of a tumor target larger than 3 cm in a single application. Therefore, to ensure entire coverage of the targeted zone with monopolar devices, multiple overlapping RF ablations with successive positionings of the electrode are required. Dodd et al\(^7\) reported their results of computer analysis of the thermal injury sizes created by overlapping ablations and proposed 6 and 14-ablation models. Their results demonstrated the importance of performing these types of calculations to develop tumor ablation strategies. Using a mathematical model to calculate the optimal number of RF ablation process for the target tumor, our group established a preoperative protocol for ultrasonographically guided percutaneous RF ablation of large liver tumors\(^8\). A regular prism and a regular polyhedron model were used to develop a preoperative protocol for liver tumor ablation (Fig. 1). This protocol enabled the authors to minimize the number of ablation spheres, optimize the overlapping mode, and determine the electrode placement process. The described protocol have been reported a complete tumor ablation rate of 87.6% in 110 patients with large HCC. The author also mentioned some important factors for electrode placement: (a) precise placement of the electrode with reference to the surrounding anatomic structures during the RF procedure. In large tumors at the surface of the liver or tumors in which there was no marker for reference, adjuvant measures could be used for precise positioning of the RF electrode. For example, 2 or 3 very small needles were inserted into the target sites to serve as markers for the electrode placements. (b) monitoring the actual site of the electrode tip by performing multi-plane scanning from different directions after placing the electrode. (c) Replacement electrodes or adding a number of electrode placements was required when tissue was insufficiently ablated because the electrode tip deviated from the predetermined position.

The role of Contrast ultrasound in RF of large HCC

Recently, further developments of contrast-enhanced US (CEUS) technique have significantly increased its clinical utility. Continuous mode, low MI scans performed with harmonic imaging and contrast specific software appears as a very useful technique for the visualization of both macro- and microcirculation with depiction of tumor vascularisation. Solbiati et al first reported the role of CEUS before, during and immediately at the end of RF ablation procedures to monitor and assess the therapeutic result prior to closing the treatment session\(^9\).

Our group reported identification of the exact size and extent of HCC before RFA are important for designing treatment protocols. Large infiltrative HCCs have an indistinct margin and no capsule. US can only depict the approximate shape of the hyperechoic or hypechoic tumour area, but CEUS provides functional, as well as anatomical, information
about blood flow in the tumour, and is especially useful in detecting abnormal blood vessel architecture that surrounds a tumour. Livraghi, *et al* reported the RFA results of medium and large HCC, and found that there was a distinct difference in tumour necrosis rate between invasive tumours and non-invasive tumours. One reason for this might be that conventional US could not accurately measure the size of invasive tumours before treatment, resulting in insufficient ablation. In our study, of the lesions with indistinct margins on US, 71% were larger and had better defined margins on CEUS. However, 62% of the tumours with distinct margins or capsules showed no observed changes in size after contrast agent administration. Thus, it is crucial to define the exact morphological features of HCC, especially in large and invasive tumours, before RFA treatment.

### Strategy to decrease heat sink effect

Several strategies have been used successfully to reduce the negative effect of blood flow on RF heating. Results of many clinical and experimental studies have shown that decreasing hepatic inflow or outflow by using a mechanical maneuver (balloon, clamping) or pharmacologic manipulation increases the volume and reproducibility of thermal ablation achieved with RF ablation. The main blood supply of HCC is derived from the artery. Hence, transarterial occlusion of its blood supply before heat ablation may significantly increase the size of the ablation lesion. Buscarini *et al* and Rossi *et al* have reported the use of RF to ablate large HCCs (>3.5 cm) after interruption of the tumor's arterial blood supply by segmental embolization or balloon occlusion of the hepatic artery. In a study of 62 patients with HCCs 3.5 to 8.5 cm treated by this approach, Rossi *et al* reported no major complications and a 90% complete response rate. A 1-year survival rate of 87% was reported, but the 1-year local recurrence and overall intrahepatic recurrence rates were 19% and 45%, respectively. Cheng *et al* reported randomized controlled trial conducted among 291 consecutive patients with HCC larger than 3 cm at a single center in China. During a median 28.5 months of follow-up, median survival times were 24 months in the TACE group (3.4 courses), 22 months in the RFA group (3.6 courses), and 37 months in the TACE-RFA group (4.4 courses). TACE-RFA was superior to TACE alone or RFA alone in improving survival for patients with HCC larger than 3 cm.

Obviously, TACE is an acceptable way to decrease...
heat sink effect during ablation. However, some patients were not candidate for TACE due to recurrence after surgery or poor respond to multiple TACE. Our group reported a new method -- percutaneous ablation of tumor feeding artery to control blood flow and increase coagulation effect during RF. Before RF, we used color ultrasound to detect the tumor blood supply and identify the entrance of feeding vessel. As the first step of the percutaneous RF treatment, 2-3 overlapping high energy ablating foci, 2-3 cm each in diameter, were used to ablate the entering site of the feeding vessel (Fig. 2). Color Doppler ultrasound was used to confirm the absence of feeding artery. Blocking the blood flow in the tumor is helpful in decreasing heat loss during RF, and therefore the outcome improves. In our study, percutaneous RF to block feeding vessels were performed in >3 cm and hypervascular HCC. The tumor necrosis rate at 1 and 6 month after RF was 92.6% (25/27) and 85.2% (23/27) in experiment group and 65.2% (15/23) and 56.5% (13/23) in control group (p = 0.024, p = 0.030). Combining adjuvant cytotoxic therapies

Previously, local hyperthermia was used to increase the effectiveness of chemotherapy by increasing blood flow, membrane permeability, local drug uptake, and metabolism in solid tumors. In Goldberg prior work, they demonstrated that combined RF ablation with commercially available long-circulating polyethylene glycol-coated liposomal doxorubicin preparation increases the extent of local tumor destruction and endpoint survival when compared with either RF ablation or intravenous doxorubicin alone in an animal tumor model. In a randomized pilot clinical study, Goldberg et al administered liposomal doxorubicin 24 hours before RF ablation in 10 patients with 18 intrahepatic lesions. With this combination of RF ablation with adjuvant liposomal doxorubicin therapy, the authors were able to achieve increases of 25%-30% in coagulation volume in all tumors that received combination therapy compared with RF ablation alone. Recently, Lencioni R et al reported their clinical trial results in HCC with doxorubicin-eluting bead (DEB)-enhanced RF. Twenty patients with single HCC ranging 3.3-7.0 cm (mean, 5.0 cm ± 1.4) showing evidence of residual viable tumour after standard RF ablation underwent intraarterial DEB administration (50-125 mg doxorubicin; mean, 60.2 mg ± 21.8). The volume of treatment-induced necrosis--as measured on imaging--increased from 48.1 cm³ ± 35.7 after RF ablation to 75.5 cm³ ± 52.4 after DEB administration, with an increase of 60.9% ± 39.0. The enhanced effect resulted in confirmed complete response (CR) of the target lesion in 12 (60%) of 20 patients. This result indicated DEB-enhanced RF ablation is safe and results in a high rate of CR in patients refractory to standard RF treatment.

Efficacy and complications in clinical application

The problems with ablating a large tumor are not trival. Livraghi et al described their experience treating 126 primary liver lesions 3.1 cm in diameter or larger (mean diameter, 5.4 cm) in 114 consecutive patients. On the basis of the CT results obtained at least 5 months after treatment, they reported achieving complete tumor necrosis in 60 (47.6%) of 126 lesions. Two major complications (death, hemorrhage requiring laparotomy) and 5 minor complications were observed. The single death was due to a break in sterile technic rather than to the RF procedure itself. Poon et al has evaluated the safety and efficacy of RFA in 35 patients with medium and large HCC of 3-8 cm in diameter. There were no
significant differences in the complication rate (17% vs. 12%), treatment mortality rate (3% vs. 0%), and complete tumor ablation rate (91% vs. 94%) between medium and large HCC, as well as small HCC (<3 cm in diameter). In another study by Bowles et al., 76 patients with locally advanced liver tumors (39 had colorectal liver metastases and 25 had HCC) underwent RFA. The mean tumor size was 3 cm, ranging from 0.4 to 18 cm. Local recurrence was detected in 9% of the patients at a mean follow-up of 15 months.

In our early study, we treated 121 hepatic tumors (74 HCC and 47 metastasis tumors; mean diameter, 4.75 cm ± 0.93) with mathematical protocol. According to the CT results obtained 1 month after the treatment, the ablation was successful in 106 (87.6%) of the 121 tumors. During the follow-up period of 3-26 months, the local recurrence rate was 24.0% (29 of 121 tumors). In our recent report, 172 patients who had 176 >3.5 cm HCC and were not candidates for surgery or TACE were enrolled in this study. Established strategy for >3.5 cm tumors included (1) multiple overlapping ablations based on mathematical protocol; (2) color US guided percutaneous ablation of tumor feeding artery (PAA) + RF for HCC with rich supply; (3) percutaneous arterial embolization + RF for HCC with high velocity flow. The ablation success rate was 91.5% (161/176 tumors) for all patients, 93.5% (101/108 tumors) for 3.6-5.0 cm HCC and 88.2% (60/68 tumors) for 5.1-7.0 cm HCC, respectively. Follow-up period ranged from 3 to 86 months with average 26 months. The local recurrence rate was 17.6% (31/176 tumors). The 1-, 3-, 5- overall survival were 80.4%, 52.0% and 37.5% for all patients, were 81.5%, 57.5% and 46.5% for 3.6-5.0 cm HCC patients and were 80.1%, 43.9% and 25.4% for 5.1-7.0 cm HCC patients, respectively (p = 0.174). The incidence of major complications was 3.5% (6/172 cases), including intraperitoneal hemorrhage (n = 2), hemotorax (n = 1), bowel perforation (n = 1) and needle tract seeding (n = 2). Of these, only one patient suffered from colon perforation 1 week after RFA treatment required surgical intervention.

Summary

The various techniques and protocols for large liver tumor have different advantages and disadvantages, but increased tumor destruction and long-term survivals have been reported. These results also add to the growing body of literature that suggests percutaneous Radiofrequency (RF) ablation is a safe and effective method for the treatment of focal hepatic neoplasms. However, the management of large HCC is challenging, further trials are needed to confirm the clinical value of image-guided ablation in large hepatocellular HCC and more attempts are need to explore the outcome of combined RF with adjuvant therapy.

References


