Hepatic Radiofrequency Ablation

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Hypothesis: Hepatic radiofrequency ablation (RFA) is effective in treating patients with unresectable hepatic malignancies.

Design: Case series of 123 patients with unresectable hepatic tumors or tumors with histological findings not traditionally treated by means of hepatic resection were considered for hepatic RFA. Median follow-up was 20 months.

Setting: Tertiary referral center.

Patients: The 123 patients underwent 168 RFA sessions from January 1, 1998, through September 30, 2001. Sixty-nine patients were male and 54, female; average age was 65 years (range, 1-89 years). Fifty-two patients had metastatic colorectal cancer; 30, hepatocellular carcinoma; and 41, cancers with other histological findings.

Interventions: A 200-W, cooled-tip RF probe system was used for all cases. Probe placement and ablation were monitored by means of real-time ultrasonography or fluoroscopic computed tomography. Final tissue temperature of greater than 50°C was achieved in all cases.

Results: Initial treatment sessions were percutaneous in 87 patients, open operations in 33, and laparoscopic in 3. Repeated sessions were percutaneous in all but 2 patients. The mean number of lesions treated per session was 2.7 (range, 1-24). Mean tumor size was 5.2 cm (range, 0.5-15.0 cm). One death occurred within 30 days of a procedure. No hepatic bleeds, bile leaks, or adult respiratory distress syndrome occurred. Overall morbidity was 7.1%. Complications included hepatic abscesses in 4 patients, transient liver insufficiency in 3, segmental hepatic infarcts in 2, diaphragm paralysis in 1, hepatic artery–to–portal vein fistula in 1, and systemic hemolysis in 1.

Conclusions: Hepatic RFA is an effective treatment option for patients with unresectable hepatic malignancies. Careful patient selection based on tumor size, location, and number and on patient clinical status should determine the choice of treatment. Further controlled trials are needed to determine the effect of hepatic RFA on long-term survival.

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Radiofrequency (RF) energy has become a popular means of tumor ablation in recent years. Radiofrequency ablation (RFA) has been used to destroy malignant lesions of the lung, kidney, bone, adrenal glands, spleen, breast, lymph nodes, pelvis, prostate, neural tissue, and liver. The concept of tumor ablation has been used for more than 100 years. Many ablation modalities have been used, including cryoablation, alcohol ablation, laser, and microwave energy. Most recently, the use of RF energy for tumor ablation is becoming commonplace, most likely owing to its ease of use and availability, the multiple approaches of probe delivery, the wide range of applications, and the effectiveness of treatment. This study reports the RFA experience with hepatic tumors at a large tertiary referral center.
PATIENTS AND METHODS

One hundred twenty-three patients with hepatic malignancies were treated with RFA from January 1, 1998, through September 30, 2001. All patients had histologically documented hepatic malignancies. We offered RFA to patients who had unresectable hepatic tumors, impaired liver function, medical conditions that would prohibit abdominal surgery, poor performance status, or tumors not traditionally treated by means of hepatic resection. We used a percutaneous approach with image guidance or surgical approaches with ultrasonographic guidance. The decision for the ablation approach used was made between the surgeon and interventionalist and was based on the patient's performance status and the size, location, numbers, and histological features of the tumor.

Procedures for patients undergoing the percutaneous approach were performed in the radiology suite with real-time transcutaneous ultrasonography (US) or fluoroscopic computed tomography (CT). Patients were treated while under conscious sedation with continuous blood pressure, cardiac, and pulse oximetry monitoring. The abdomen and chest were prepared and draped under sterile conditions. Local anesthetic was injected at the skin puncture sites. The RF probes were passed percutaneously into the hepatic tumors with real-time image guidance. Surgical approaches for hepatic RFA were performed with the patient under general anesthesia and with intraoperative US guidance in the operating room. We used US for the open and laparoscopic procedures.

An internally cooled clustered RF electrode with a 200-W RF generator (Radionics Inc, Burlington, Mass) was used for all ablations. The electrode can provide simultaneous measurements of impedance and temperature. The decision for the ablation approach used was made between the surgeon and interventionalist and was based on the patient's performance status and the size, location, numbers, and histological features of the tumor.

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The RF probe was then advanced to the desired margin of the tumor. Baseline tissue impedance was measured. Iced isotonic sodium chloride solution was then circulated through the RF probe. When the probe temperature measured less than 20°C, the RF current was begun. Maximal generator output was used for 12 minutes per electrode position. Surgical patients with hepatic vascular inflow occlusion (Pringle maneuver) were treated for 6 minutes per treatment site. Tissue impedance was measured throughout the ablation. When the time limit was reached, the circulation of the saline solution was discontinued and intratumoral temperature was measured (Figure 1).

In larger tumors, the RF electrode was then repositioned into a new site of the tumor under image guidance and with continuous temperature monitoring. When the temperature of the new position was near the cytotoxic threshold of 55°C, a second ablation was performed to create overlapping zones of thermocoagulation. The response during US guidance was also used as a rough approximation of the size of the ablation sphere when repositioning the electrode into a new region of the untreated tumor. Overlapping spheres of thermocoagulation are necessary to treat larger tumors, and this approach is important when treating tumors as large as 15 cm in this series. In patients with 4 or more lesions, operative RFA was used. Ablation was performed until final tissue temperatures of at least 50°C (the cytotoxic threshold) were achieved throughout the entire lesion. In almost all of the ablations, intratumoral temperatures exceeded 60°C.

Follow-up of patients undergoing hepatic RFA included contrast-enhanced helical CT scanning of the liver at 2 to 4 weeks, then every 3 to 6 months thereafter. Appropriate tumor markers were followed up when indicated. Postprocedural adjuvant systemic chemotherapy was offered to patients on the basis of their performance status and the histological features of their disease.

Figure 1. Radiofrequency (RF) ablation guided by means of ultrasonographic findings. A, An RF probe is inserted into a hyperechoic colon carcinoma. B, Gas is generated within the tissue during the ablation.

ease or as part of a planned staged treatment (n=11). All repeated ablations were percutaneous in all but 2 patients. The number of lesions treated per RFA session was 2.7 (range, 1-24). Mean tumor size was 5.2 cm (range, 0.5-15.0 cm).

We documented morbidity and mortality for this group of treatment sessions (Table). One death occurred within 30 days of a procedure due to a cerebrovascular accident. Hepatic abscesses occurred after 4 sessions. Two patients had cirrhosis with significant hepatic dysfunction (Child's C); of these, 1 underwent a synchronous colon resection, and 1 had underlying chronic cholangitis. All patients underwent percutaneous catheter drainage and intravenous antibiotic treatment. Three patients
with cirrhosis had posttreatment transient liver insufficiency treated by means of conservative measures. Two patients incurred hepatic infarcts of the left lateral segments (II and III) due to tumor ablation adjacent to a major left portal pedicle. Paralysis of the right diaphragm developed in 1 patient after ablation of a right hepatic dome lesion. Ascites developed in 1 patient secondary to a hepatic artery–portal vein fistula, which was successfully managed by means of selective embolization of the hepatic artery. Systemic hemolysis developed and spontaneously resolved in 1 patient. No hepatic bleeds, bile leaks, or pulmonary complications such as adult respiratory distress syndrome developed. After extensive ablations, several patients had flulike symptoms known as postablation syndrome that always resolved within 2 weeks and was treated with supportive care. Overall morbidity for the 168 ablation sessions was 7.1%.

The median follow-up was 20 months (range, 1-47 months). Follow-up for all patients included serial cross-sectional imaging every 3 to 6 months. Many patients with recurrent disease were treated with subsequent RFA sessions. Fifty-two patients had metastatic colorectal carcinoma to the liver. Overall survival at 1 year was 87% (33/38); at 2 years, 77% (17/22); and at 3 years, 50% (9/18) (Figure 2). Thirty patients with HCC underwent hepatic RFA. Overall survival at 1 year was 92% (23/25); at 2 years, 75% (9/12); and at 3 years, 60% (3/5) (Figure 3). No 5-year follow-up data are available for this patient group, because the RFA device was not approved by the US Food and Drug Administration until October 1997.

### Comment

Although other methods of thermal ablation, such as cryoablation and laser, microwave, and alcohol ablation, are performed in the liver, RFA is currently receiving the greatest attention, given its general availability and the recent technical advances facilitating its use and effectiveness. At present, more than 2500 RFA procedures for the treatment of primary and secondary liver tumors have been reported, at least in abstract form. From this vast but preliminary experience, reasonable safety of the procedure has been established, with mortality and morbidity in the largest series at 0.2% and 1.7%, respectively. The overall morbidity in this series is 7.1%, which is higher than in other published series. We believe the higher morbidity in this series reflects the aggressive treatment approach we have adopted. The mean tumor size in our series was 5.2 cm, and many tumors ranged from 10 to 15 cm, which is significantly larger than in most published series on hepatic tumor ablation. Also, we treated patients with significantly impaired hepatic function (Child’s C). Nevertheless, the overall low morbidity and mortality justify an aggressive approach to hepatic tumor ablation.

Liver RFA has been predominantly used for treatment of patients with hepatic malignancies that are not candidates for hepatic resection, and thus, most of the data have been accumulated for the treatment of colorectal metastases and HCC. The rationale for the treatment of these diseases using a minimally invasive, image-guided technique is well documented. The treatment of primary and metastatic disease of the liver is problematic for medical and surgical oncologists. Many tumors, particularly HCC, respond poorly to systemic chemotherapy. Hepatic resection has been demonstrated as beneficial for patients with colorectal metastases, with an expected 30% to 40% 5-year survival with proper patient selection. After resection of HCC, patients are expected to have a 25% to 30% 5-year survival, with an expected 70% to 80% recurrence rate in that period. Despite its success in improving overall patient survival, major hepatic resections can be associated with significant morbidity and a perioperative
Recently, Curley et al.15 demonstrated good initial results with RFA for the treatment of small HCCs (<3.5 cm in diameter).12,15,16,24 Livraghi et al.12 have also shown RFA to be as effective as percutaneous ethanol injection, with the additional benefit of fewer treatment sessions. In addition, larger HCCs can be treated, although complete eradication is less optimal compared with smaller lesions.13 Radiofrequency therapy for colorectal metastases has been promising but less efficacious than RF therapy observed for hepatomas.14,16,25 For example, Solbiati et al.17 described a series of 29 patients with 44 hepatic metastases due to colorectal cancer measuring 1.5 to 4.5 cm in diameter who were treated using internally cooled RF electrodes. In their series, no more than 2 treatment sessions were required for any patient. No evidence of local recurrence was seen in 84% of these lesions, with a mean follow-up of 7.9 months (range, 3-15 months), and disease-free survival was seen in 66.7% of patients. Results of long-term follow-up have now been presented, with an overall survival of 93%, 62%, and 41% observed at 12, 24, and 36 months, respectively.18 Recently, Curley et al.15 demonstrated good initial results in primary and secondary hepatic malignancies with a low recurrence rate of 1.8% at the treated site (median follow-up, 15 months). This group also had better results with RFA compared with cryosurgery.

A meta-analysis of the published reports demonstrates that the size of the tumor to be treated is the most important factor in determining whether complete local ablation can be achieved. This largely stems from our current limitations of the extent of achievable coagulation from a given RF application, coupled with the need for treating a 0.5- to 1.0-cm surgical margin surrounding the target lesion. In general, lesions measuring less than 2.5 cm in diameter have been reported to have a greater than 90% chance of being destroyed. For lesions measuring 2.5 to 3.5 cm, approximately 70% to 90% of these lesions can be completely treated with current RFA techniques. This range has been a moving target, with the newer modifications to RF technique increasing the likelihood of complete ablation of lesions in this size range.20 For lesions measuring 3.5 to 5.0 cm, 50% to 70% have been completely treated.13 However, many of the modifications previously described are likely to improve these results as well. Less than 50% of tumors measuring greater than 5 cm are likely to be completely ablated, even with repetitive ablation treatments. However, this has not been our experience, particularly with large, encapsulated HCC.

Location also influences the possibility of achieving complete ablation of a tumor. If a tumor is near large vessels (ie, >5-10 mm, or those visible by means of CT), all of the malignant cells adjacent to the vessel are unlikely to be completely eradicated because of the previously described perfusion-mediated tissue cooling.31,32 This area can undergo repeated treatment; however, a single RF session is unlikely to adequately treat these lesions. Other factors include the type of tumor, with greater clinical success reported in treating HCC13,15,17 and breast metastases15 compared with colorectal metastases. The tumor subtype can be equally important in determining outcome. Livraghi et al.13 demonstrated that the success in treating well-circumscribed HCC is much greater than in treating the infiltrating varieties. The underlying parenchyma is also important, as previously described, with cirrhotic tissue serving to insulate the hepatomas, thereby promoting better thermal coagulation.14

Initial reported success with RFA in liver tumors is coupled with its low morbidity rate of 7.1% for signifi-
Adequate ablation of hepatic tumors is feasible using RF energy. Percutaneous, laparoscopic, and open surgical approaches can be used to deliver RF probes to hepatic tumors. The long-term survival data for this technology are still being gathered. In this series, we reported overall survival for patients with metastatic colon cancer at 1, 2, and 3 years to be 87%, 77%, and 50%, respectively, and for patients with HCC to be 92%, 75%, and 60%, respectively. Other ablation methods such as cryoablation have reported long-term outcomes, and it is expected that outcomes for patients treated by means of hepatic RF A will most likely be similar. Most publications on RFA, including ours, report uncontrolled case series, and thus, no definitive conclusions regarding survival can be made. Multiple factors will affect patient survival, such as histological findings of the tumor, the use of adjuvant chemotherapy, and proper tumor staging. High-resolution CT and magnetic resonance imaging have clearly improved, increasing the sensitivity of these examinations. Despite use of the most current imaging techniques, unrecognized intra-abdominal hepatic disease is present in up to 15% of patients, and additional hepatic lesions are identified in up to 40% of patients when intraoperative US is used. Prospective controlled trials with long-term follow-up are clearly needed to determine more accurate patient outcomes as a result of hepatic RFA.


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Also, the RF probes treat eccentric spheres of 4 cm in diameter, and from surgical specimens, we know we need at least a 1-cm margin. Therefore, with a mean tumor size of 5.2 cm, how was your technique used to canvas these areas, and how did you use the real-time imaging to orchestrate your therapy as compared to cryosurgery, where you distinctly know your field of destruction?

In the number of tumor deposits that you report are 1 to 24, I assume the 24 and higher numbers were neuroendocrine in origin. How will we be able to compare these and other tumors in terms of outcome? Should we use number and size or volume of tumor mass to ratios of nontumor involvement areas of the liver to prognosticate our results as we use ablative and other techniques?

Lastly, I sympathize with your ideas of resection. When you achieve 29% 5-year survival of primary metastatic disease to the liver, it is not the greatest cure from large resection and large morbidity. I would echo the fact that perhaps ablative technology with adjuvant therapy can achieve the same goal.

Dr Ianitti: Could RFA be used in patients who are pretransplant with HCC? Absolutely. Radiofrequency ablation is probably the most effective ablation modality to treat HCC, particularly in cirrhosis; much more effective, we feel, than cryoablation.

Secondly, extensive colorectal carcinoma that are not candidates for hepatic resection: again, many patients have multiple metastases. These are the patients that one would want to target ablative therapy.

I definitely want to reiterate Dr Hull’s point in terms of preoperative imaging. What I presented here is an uncontrolled trial. This has been our experience over the past 3\% or so years. I agree wholeheartedly that the data clearly demonstrate that patients who undergo staging laparoscopy with laparoscopic US demonstrate that there is unrecognized occult peritoneal disease anywhere from 10% to 15%, and that holds pretty consistently across most series. Also, there is unrecognized disease that is only picked up intrahepatically by intraoperative US, so the role of intraoperative US is critical. If we were going to carry out controlled trials with curative percutaneous therapy, then those patients should have a staging laparoscopy with laparoscopic US.

Dr Ianitti: How does one determine resectability? Well, I am a hepatic surgeon, and I feel, as most hepatic surgeons do, that lesions in the liver that are resectable should be resected. We take a very aggressive approach to hepatic resection and use ablation as a means when patients are truly not resectable. Most of the patients are evaluated by myself from the surgical point of view, and all I can say is that we are fairly aggressive when it comes to resection.

Radiofrequency ablation for larger lesions: if you read the literature mostly for RFA, they mostly talk about lesions 3 to 4 cm in size. We are talking about a mean size of 5.2 cm. Most of the HCCs that get sent to us range anywhere from 10 to 15 cm in size. The difference is the technology. There are different types of RFA systems. Most of the data out there in the world talk about the jack-hook system that you just use as an impedance-based output. We use an output-based system with cool-tip electrodes. We have a lot of experience with the cool-tip system, and we know that with one 12-minute ablation or one 6-minute with a Pringle maneuver, we can develop an area of 5 to 6 cm of coagulative necrosis. When you are planning a large lesion, you plan ahead of time; you are going to do the deep margin, the medial margin, lateral margin. So again, we try to achieve the same things in surgery to achieve that greater than 1-cm margin. It is planning. You do have your tumor obscured by gas when you are doing RFA, unlike cryo. But when you know the system, you know where the margins are going to be.

What is the highest number? That is still a great question. Again, we have treated patients with 20 lesions with metastatic neuroendocrine tumors, and that question is still out there in terms of what is the highest number that is ablatable, and it is a judgment call at this point in time.