Tumor Ablation with Radio-frequency Energy[1]

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Abbreviations:
HCC = hepatocellular carcinoma
PEI = percutaneous ethanol injection
RF = radio frequency

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[2]**. Multiple body systems

Tumor ablation by using radio-frequency energy has begun to receive increased attention as an effective minimally invasive approach for the treatment of patients with a variety of primary and secondary malignant neoplasms. To date, these techniques have been used to treat tumors located in the brain, musculoskeletal system, thyroid and parathyroid glands, pancreas, kidney, lung, and breast; however, liver tumor ablation has received the greatest attention and has been the subject of a large number of published reports. In this article, the authors review the technical developments and early laboratory results obtained with radio-frequency ablation techniques, describe some of the early clinical applications of these techniques, and conclude with a discussion of challenges and opportunities for the future.

Percutaneous, image-guided, in situ tumor ablation with a thermal energy source, such as a radio-frequency (RF), laser, or microwave source, has received increasing attention as a promising technique for the treatment of focal malignant disease. These techniques permit the destruction of tumors without necessitating their removal (hence, "in situ") and, in many cases, can be used in place of more invasive and expensive surgical techniques. Potential benefits of percutaneous in situ tumor ablation include decreased cost and morbidity, the possibility of performing the procedure in outpatients, and the possibility of treating patients who would not be considered candidates for surgery due to age, comorbidity, or extent of disease.

Until recently, an important limitation of all thermally mediated tumor-ablation techniques was the extent of coagulation that could be produced with a single application of energy; that is, the size of tumor that could be practically targeted and destroyed at a single treatment session. Early experience showed that thermal ablation by means of laser or RF energy could reliably create foci of tissue necrosis no larger than approximately 1.6 cm in diameter. However, because most tumors are larger than this by the time they are detected, successful treatment has, until recently, necessitated the use of either multiple treatment probes, multiple treatment sessions, or both. A major focus of research has, therefore, been on the development of techniques for achieving single-session large-volume tissue necrosis in a safe and readily accomplished manner.

In the clinical arena, RF ablation has been used for the treatment of a variety of neoplasms, including osteoid osteoma; hepatocellular carcinoma (HCC); renal cell carcinoma; hyperfunctioning parathyroid adenoma; and hepatic, cerebral, and retroperitoneal metastases from a variety of primary tumors. The procedures are generally performed by using 14–21-gauge partially insulated electrodes that are placed with imaging guidance (computed tomography [CT], magnetic resonance [MR] imaging, or ultrasonography [US]) into the tumor to be ablated. When attached to an appropriate RF generator, RF current is emitted from the noninsulated portion (ie, exposed tip) of the active electrode, and the current attempts to find the path to ground.

RF ablation can be performed with either monopolar or bipolar techniques; monopolar techniques are more commonly used for tumor ablation. When a monopolar technique is used, a large dispersive electrode (grounding pad) is usually placed on the patient's thigh. When a bipolar technique is used, a second (passive or ground) electrode is placed within 5 cm of the active electrode. With either approach, current passing through tissue from the active electrode leads to ion agitation, which is converted by means of friction into heat. The process of cellular heating induces almost immediate and irreparable cellular damage, which leads to coagulation necrosis. Because ion agitation, and thus tissue heating, is greatest in areas of highest current density (ie, closest to the active electrode tip), necrosis is limited to a relatively small volume of tissue surrounding the RF electrode.

In most cases, percutaneous RF ablation can be performed in patients with conscious sedation by using medications and techniques similar to those used with any other interventional radiologic procedure. In our experience, the majority of these procedures have been performed with administration of a combination of midazolam maleate and fentanyl citrate; however, other medications can be equally effective. The choice of medication is made largely on the basis of operator preference and local experience. The procedures can also be performed with general anesthesia, which can be helpful when lesions are unusually large and/or difficult to target and when the patient has low tolerance for pain.

Several approaches have been used to increase the diameter of coagulation necrosis achieved during RF ablation. These include the use of (*a*) multiprobe, hooked, and bipolar needle arrays; (*b*) intraparenchymal injection of saline before and/or during RF application; (*c*) internally cooled RF electrodes; and (*d*) algorithms for RF current application that maximize energy deposition but avoid tissue boiling, charring, or cavitation.

In this article, we will review the technical developments and early laboratory results obtained with RF ablation techniques, describe some of the early clinical applications of these techniques, and conclude with a discussion of challenges and opportunities for the future.

TECHNICAL DEVELOPMENTS: THE QUEST FOR LARGER LESIONS

Monopolar Electrode Techniques

Until recently, the principal use of RF ablation was for neurosurgical and cardiac applications, such as the treatment of benign hyperactive neurologic foci or aberrant intracardiac conductive pathways. For these conditions, the principal advantage of RF techniques is the ability to create precise small regions of coagulation necrosis. The limitations imposed by the use of conventional RF electrodes (ie, maximum ablation lesion diameter of approximately 1.6 cm) are, therefore, not critically important.

Initial descriptions of RF for the treatment of malignant neoplasms involved the use of monopolar electrode techniques in animal liver (1–3) or brain (4) and resulted in the induction of coagulation necrosis measuring no larger than approximately 2 cm in diameter. Although the authors of these reports suggested that RF ablation might be useful for tumor ablation in humans, their studies did not involve a detailed investigation of the factors that determine ablation size or treatment effectiveness.

To better understand the factors that influence ablation size, Goldberg et al (5) investigated the effects of electrode size, tip temperature, and treatment duration on the extent of coagulation necrosis. Using a 500-kHz sinusoidal waveform generator (series 3; Radionics, Burlington, Mass) and conventional monopolar RF electrodes and techniques in ex vivo liver and muscle, they demonstrated that lesion diameter is well correlated with the diameter of the electrode and the duration of RF application but that lesion length (measured parallel to the length of the electrode) is correlated only with the length of the exposed electrode tip. The diameter of coagulation necrosis was also found to be influenced by electrode diameter.

Subsequently, the effect of electrode surface temperature on coagulation diameter was investigated (6). This study demonstrated that electrode surface temperatures are not uniform during RF application. Temperatures are highest at the proximal and distal ends of the electrodes. Furthermore, as tip temperature and/or electrode tip length are increased, the variation in temperature along the electrode shaft also increases. Coagulation diameter is well correlated with local mean temperature during the application of RF energy. No necrosis is seen when surface temperatures are less than 50°C. As electrode surface temperature increases, the diameter of coagulation necrosis increases, reaching 1 cm at 71°C and 1.6 cm at 80°C. Temperatures higher than 110°C are associated with inconsistent results and often reduced coagulation necrosis as a result of tissue charring, gas formation, and/or cavitation, all of which result in increased circuit impedance and thus limit current flow.

Goldberg et al (6,7) subsequently performed in vivo studies that demonstrated the feasibility of performing RF ablation in normal pig muscle and liver and rabbit lung. Using RF electrodes and techniques that were comparable to those used in previous ex vivo studies, they found that the length of coagulation necrosis achieved in vivo is comparable to what had been observed ex vivo. However, the diameter of coagulation necrosis in vivo is considerably smaller than that which was observed ex vivo, measuring 1.3 cm for pig muscle, 0.9 cm for pig liver, and 0.8 cm for rabbit lung. The general relationship of coagulation diameter to electrode surface temperature was similar to that observed ex vivo; however, the minimum temperature required to induce coagulation is approximately 8.5°C higher than that for ex vivo specimens, and the variation in temperature along the electrode shaft is much greater than was observed ex vivo. It was postulated that so-called perfusion-mediated tissue cooling (by which heat is rapidly carried away from tissues by means of flowing blood) is largely responsible for the decrease in coagulation necrosis seen in vivo.

Multiprobe Arrays

The study results described for monopolar electrodes demonstrated that a larger volume of tissue can be destroyed at a single treatment session by modifying the treatment probe and/or the manner in which RF energy is applied to the probe. However, most of this increase in necrosis volume is related to an increase in the length, rather than the diameter, of coagulation necrosis (ie, is achieved by increasing electrode tip length). Thus, and despite the substantial progress that had been made, only relatively small tumors can be ablated, owing to their generally spherical shape. To increase the diameter of coagulation necrosis, Goldberg et al (8) studied the feasibility of simultaneous application of RF energy to arrays of two to five electrodes (with 3-cm tip exposure) in ex vivo calf liver for 6 minutes at 70°–90°C. Probe configuration and spacing were varied. The volume of coagulation necrosis obtained with simultaneous application of RF energy to all electrodes in an array was compared with that obtained when RF energy was applied sequentially to each of the individual probes within the array. In all cases, the volume of coagulation necrosis obtained with simultaneous RF application is greater than that resulting from sequential application. However, spacing of probes more than 1.5 cm apart results in discontinuous coagulation in central areas between the probes.

Another variation of the multiprobe array system, "hooked needle" or "umbrella" electrodes, has been advocated by some investigators (9,10) and made available by two commercial vendors (RITA Medical Systems, Mountain View, Calif; Radiotherapeutics, Sunnyvale, Calif). With these systems, an array of multiple, stiff, curved wires in the shape of an umbrella is deployed from a single 14- or 16-gauge cannula by using a control mechanism on the handle of the needle. LeVeen (9), using a 12-hook array (Radiotherapeutics) in in vivo porcine liver, was able to produce spherical regions of coagulation necrosis measuring up to 3.5 cm in diameter by applying 80 W of power for 10–12 minutes. Similar results were obtained by Siperstein et al (10), who applied 30–50 W for 15 minutes to a four-pronged umbrella needle system (RITA Medical Systems). Siperstein et al, performing a Pringle maneuver (clamping of the hepatic vascular pedicle) to decrease hepatic inflow during ablation, were able to achieve 3.5–4.0 cm of coagulation necrosis in piglet liver.

Bipolar Arrays

Most work with RF ablation has been performed with monopolar needle electrode systems. However, McGahan et al (11) described their experience with bipolar techniques in which they placed a second, or ground, electrode within approximately 4 cm of the active electrode in ex vivo liver. This results in heat being generated not only at the active electrode but also adjacent to the ground needle and between the two electrodes. With such a system, the resulting focus of coagulation necrosis is larger than when a conventional monopolar electrode system is used. However, the induced coagulation necrosis is elliptic rather than spherical in cross-section. Therefore, the clinical importance of this gain in the volume of induced coagulation necrosis is difficult to estimate, because most tumors are roughly spherical in shape.

Saline Solution Injection during RF Ablation

Several investigators have attempted to increase the volume of coagulation necrosis by injecting saline into tissue before, during, or both before and during RF application. Miao et al (12) investigated the effects of various regimes involving the injection of 5% hypertonic saline at a rate of 1 mL/min into freshly excised swine liver before and/or during RF ablation. Lesion diameter increased to larger than 5.5 cm with saline infusion, while electrode tip temperature and tissue impedance decreased. They postulated that these effects are due to the increased conductivity of hypertonic saline, as compared with that of blood or other tissues.

Livraghi et al (13) described ex vivo and in vivo animal experiments, as well as preliminary human studies, in which RF ablation was performed with intraparenchymal saline injection. For the ex vivo studies, RF ablation was performed after direct intraparenchymal injection of 1–20 mL of saline into calf liver. Subsequently, in vivo animal experiments were performed in Yorkshire pigs by using a similar (ie, bolus injection) technique, as well as during continuous intraparenchymal saline infusion at 1 mL/min. Saline pretreatment results in larger foci of coagulation necrosis both ex vivo and in vivo. With continuous saline infusion, ablation lesion diameter is highly dependent on energy deposition, with lesion diameters ranging from 1.8 to 4.1 cm. A total of 24 metastases (14 patients) and one intrahepatic cholangiocarcinoma were also treated by using continuous saline infusion (results described in more detail later). The authors hypothesized three potential effects of saline injection that might explain the significant increase in the volume of necrosis that is observed: (*a*) enlargement of the effective electrode surface area by means of augmented tissue tonicity; (*b*) improved tolerance of sustained high generator output due to tissue cooling, decreased tissue impedance, or both; and (*c*) direct effects of heated saline that subsequently diffuses into tissue (13). However, it was noted that the resulting foci of coagulation necrosis are irregular in shape and, particularly in the clinical series, the volume of tissue necrosis is often difficult to predict.

More recently, Polascik et al (14) performed saline-augmented RF ablation of VX2 nodules implanted beneath the renal capsule in rabbit kidneys. The results obtained with saline-augmented RF ablation were not directly compared with those obtained with conventional RF ablation techniques; however, the authors were able to achieve foci of coagulation necrosis averaging 1.4–1.8 cm with only 30–45 seconds of RF application.

Internally Cooled Electrodes

An important advance in RF energy delivery was recently achieved with the development of internally cooled RF electrodes. These 14–18-gauge electrodes have an internal lumen through which chilled perfusate is circulated during RF application. By cooling the electrode tip during the application of RF energy, it is possible to increase generator output and at the same time prevent tissue boiling and cavitation immediately adjacent to the needle tip. This in turn prevents the deleterious increases in circuit impedance that result from cavitation and thus results in greater tissue necrosis.

Lorentzen et al (15) provided an early description of the use of internally cooled RF electrodes. He used a specially designed, custom-made, 14-gauge needle electrode through which cooling water could be circulated during RF application and reported a significant increase in delivered energy and ablation lesion size in ex vivo calf liver, as compared with that achieved with a conventional needle electrode. Goldberg et al (16) developed a slightly smaller (18-gauge) internally cooled electrode system and studied its effects in ex vivo calf liver and in vivo pig liver and muscle. For these experiments, procedure duration, RF output, electrode tip length, and electrode cooling were varied to determine the effect of these parameters on lesion size. Both energy deposition and coagulation necrosis were found to be significantly greater with electrode cooling than without it. For example, in vivo experiments in normal liver demonstrated that electrode cooling results in an increase in the diameter of coagulation necrosis from 1.2 to 2.4 cm. Tissue necrosis in vivo is substantially less than that ex vivo, particularly in the liver. Perfusion-mediated tissue cooling was postulated as an explanation for this finding.

Clustered Electrodes

Early experiments with multiprobe arrays were focused on determining the maximum distance that the electrodes could be spaced apart while still ensuring contiguous coagulation necrosis. Goldberg et al (17), however, subsequently investigated the effects of the application of RF energy to three electrodes positioned close to one another, hypothesizing that closely spaced electrodes might act as a single large electrode and thus result in increased coagulation necrosis. On the basis of their results, it was determined that arrays of three 2-cm exposed-tip internally cooled electrodes spaced 0.5–1.0 cm apart can produce a spherical focus of coagulation necrosis measuring up to 4.1 cm in diameter. By comparison, simultaneous application of RF to arrays of otherwise similar electrodes spaced 1.5–2.5 cm apart produce somewhat smaller and/or more irregular zones of coagulation necrosis. On the basis of these initial results, the effects of electrode tip length and the duration of RF application were studied by using electrode clusters that consisted of three internally cooled electrodes placed equidistantly 0.5 cm apart. RF energy was applied to ex vivo liver and in vivo liver and muscle for 5–60 minutes (1,400–2,150 mA), resulting in coagulation necrosis 4.7–7.0 cm in diameter. In vivo experiments demonstrated 3.1 and 7.3 cm of coagulation when RF is applied to electrode clusters placed in liver and muscle, respectively.

The use of clustered electrodes offers the potential to substantially increase the volume of coagulation necrosis obtained at a single treatment session. By placing electrodes no more than 1 cm apart, large spherical regions of coagulation necrosis can be created. The resulting coagulation necrosis is greater than that achieved with otherwise similar electrodes used alone or in arrays spaced 1.5–2.0 cm apart. These results are best explained by considering that the closely spaced electrodes function together as if they were a single large electrode, rather than simply heating the same volume of tissue, as occurs with the multiple probe arrays in which individual electrodes are spaced further apart.

Pulsed Application of RF

In effect, each attempt to increase the volume of tissue that can be coagulated at a single treatment session sought to balance the need to apply more energy against the deleterious effects of tissue charring and cavitation, which occur when too much energy is applied too rapidly. To explore alternative methods for delivering energy to RF electrodes, Goldberg et al (18) investigated the possibility of applying RF in a pulsed, rather than continuous, manner. The goal of these experiments was to increase RF current density surrounding the electrodes while allowing brief periods for heat dissipation, to prevent charring and cavitation. RF was applied to ex vivo liver by using internally cooled electrodes with peak currents of 1,500–2,000 mA. These peak currents were maintained for approximately 15 seconds, alternating with periods during which RF current was intentionally reduced to 500 mA for approximately 15 seconds, for a total "duty cycle" of approximately 30 seconds. Overall treatment duration was 15 minutes. With this technique, the diameter of coagulation necrosis achieved is 3.6–4.0 cm when 3–5-cm-long electrodes are used. By comparison, continuous application of the maximum current that could be sustained without increases in impedance to the same electrodes (750–1,350 mA) result in foci of coagulation necrosis that are 2.9–3.5 cm in diameter ($P < .01$). Similar in vivo liver experiments (12-minute treatment duration) with a 3-cm-long electrode tip produced coagulation necrosis 2.8 cm in diameter with the pulsed technique but 2.4 cm in diameter with maximal continuous current ($P < .01$). Remote thermometry performed in these experiments demonstrated both more rapid temperature increases and higher overall tissue temperature when the pulsed technique is used. Further work remains to optimize the algorithms for applying RF energy to treatment electrodes; however, it appears at this time that pulsed application of RF energy can increase the volume of tissue necrosis that can be achieved at a single treatment session.

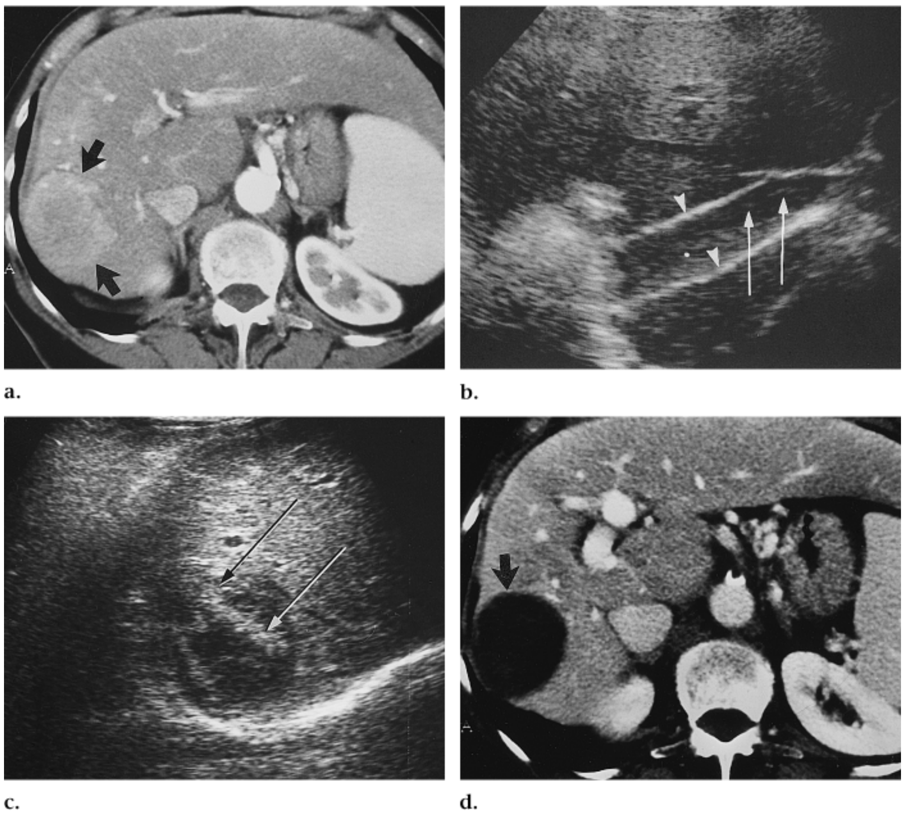


Figure 1. Successful treatment of a large HCC lesion. **(a)** Transverse contrast agent–enhanced CT scan obtained in the hepatic arterial phase shows a large hypervascular tumor (arrows) located in Couinaud segment 7. **(b)** Oblique subcostal US image obtained during RF ablation with an internally cooled cluster electrode system shows two of three electrodes (arrowheads) well positioned in the tumor. Hypervascularity is related to microbubble formation during treatment. Also note small bubbles (arrows) escaping into an adjacent hepatic vein, a fairly common occurrence. **(c)** Lateral oblique US image obtained 6 months after treatment shows that electrode tracks (arrows) remain visible. **(d)** Transverse contrast-enhanced arterial phase CT scan obtained 6 months after treatment shows uniform hypoattenuation (arrow) and absence of contrast enhancement, which are evidence of successful treatment.

EARLY CLINICAL RESULTS

Liver Tumor Ablation

To date, much of the interest related to the development of techniques for RF tumor ablation has centered on liver malignancies, both primary (Figs 1–3) and secondary (Figs 4, 5). For these tumors, minimally invasive techniques such as RF ablation have the potential to dramatically alter patient outcomes. In situ ablation techniques are markedly less expensive and invasive than surgical techniques and may have comparable effectiveness. For example, HCC is frequently seen in the setting of hepatic cirrhosis, particularly in geographic areas such as Italy, Japan, and Korea. Surgical resection in these patients is often an unacceptably risky procedure due to the combination of liver dysfunction and associated coagulopathy. In situ tumor ablation with percutaneous ethanol injection (PEI) has already been proved to be an acceptable alternative to surgery due to its comparable effectiveness and markedly decreased risk of morbidity and mortality in this high-risk patient population (19).

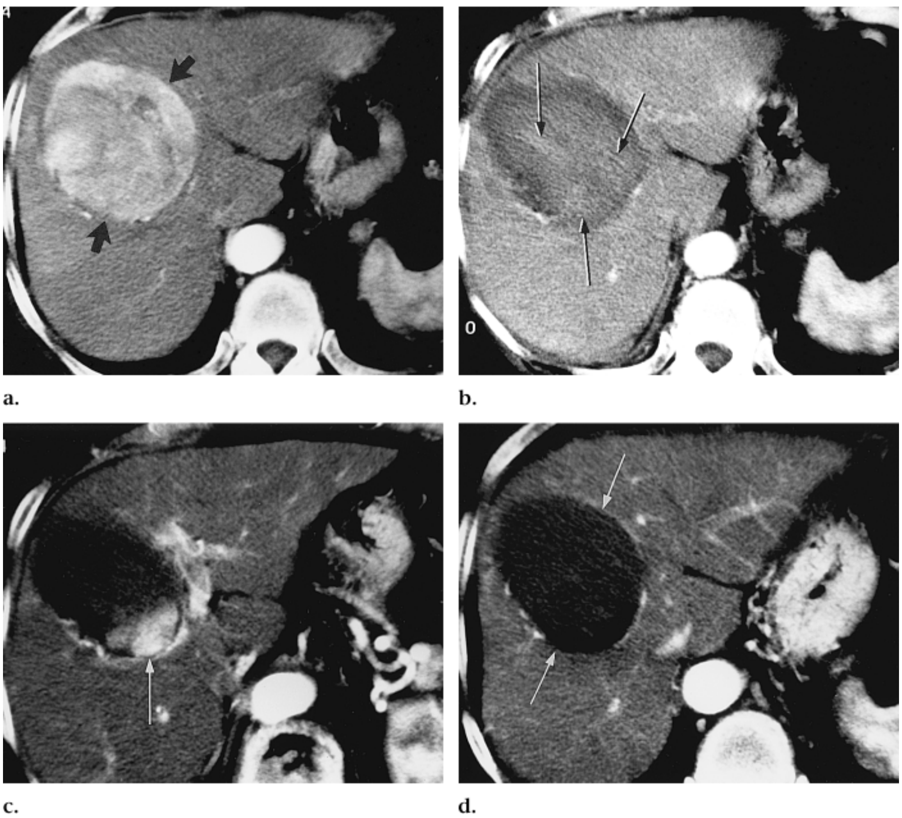


Figure 2. Successful treatment of locally recurrent HCC. **(a)** Transverse contrast-enhanced arterial phase CT scan demonstrates a large hypervascular tumor (arrows) in Couinaud segment 8. **(b)** Transverse contrast-enhanced CT scan obtained 1 month after treatment with an internally cooled cluster electrode system shows internal hyperattenuation (arrows), which likely represents blood. The lack of contrast enhancement suggests that there is no residual viable tumor. **(c)** Transverse contrast-enhanced CT scan obtained 6 months after treatment demonstrates marked hypoattenuation throughout the majority of the tumor; however, a single crescentic focus of enhancing tissue posteromedially (arrow) indicates local tumor recurrence. **(d)** Transverse contrast-enhanced CT scan obtained 3 months after repeat treatment with a single internally cooled electrode demonstrates uniform hypoattenuation (arrows), suggestive of a complete response.

In situ ablation of hepatic metastases has thus far been less successful than has surgical treatment. The rationale for percutaneous treatment of limited hepatic metastases from certain primary malignancies is based on the success that has been achieved with the use of surgical techniques. Without resection, for example, patients with hepatic metastases from colorectal carcinoma are reported (20–27) to have a median survival of less than 1 year. Systemic chemotherapy, radiation therapy, and PEI offer little to these patients in terms of improved survival. Thus, hepatic resection is the only currently available potentially curative technique.

Authors of several surgical series (23,28–48) have reported 5-year survival rates of 25%–40% when careful patient selection and optimal techniques are used. Despite its success in improving patient survival, however, hepatic resection is associated with substantial morbidity and a risk of surgical mortality of approximately 5% (31,32,36,37,42,48–53). Furthermore, the technique has thus far been applied only in patients with limited (generally fewer than four or five) hepatic metastases (41,44,49,54,55) and generally cannot be used in patients with recurrent hepatic metastases (owing to the difficulty in performing repeat hepatic resection). Many patients may represent a poor surgical risk and thus may not be candidates for hepatic resection. Nevertheless, the success of hepatic resection has prompted speculation that an effective percutaneous ablation therapy might result in similar gains and life expectancy without the morbidity, mortality, or cost of surgery.

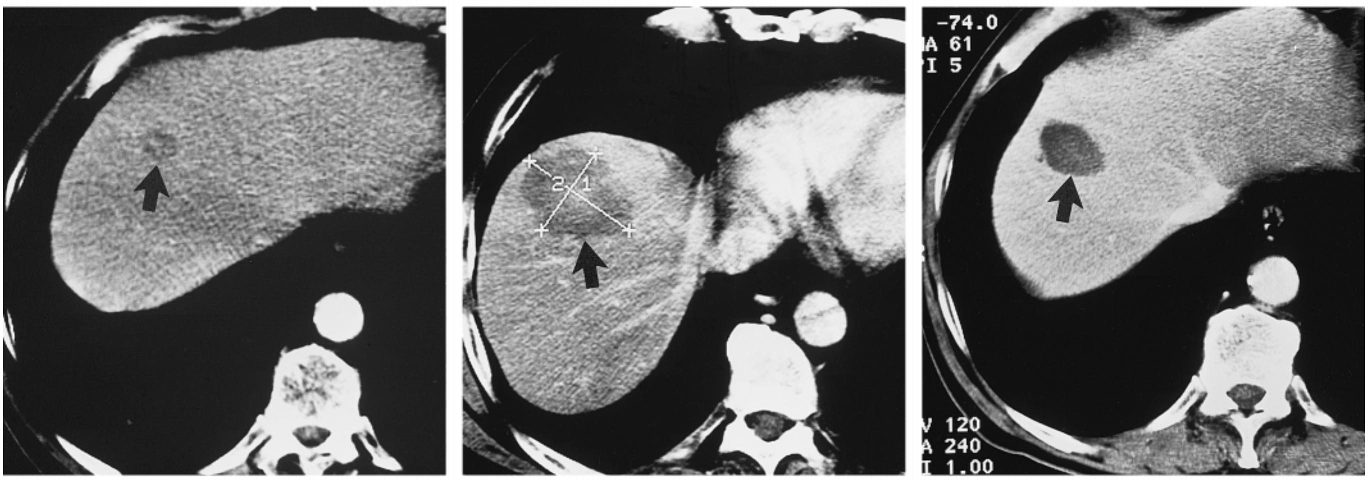
To date, there have been at least 14 series published in the English-language literature (10,13,56–67) in which the results of RF ablation of hepatic malignancies have been described. Several additional series have been presented at scientific meetings. The technique has also been described in case reports and more narrowly focused feasibility trials. However, these results must all be viewed as preliminary—principally as assessments of safety and short-term efficacy—because long-term follow-up has only recently begun to be available. The following paragraphs will summarize the results of the published series.

Rossi et al (56) treated 50 patients, 39 of whom had 41 small HCC nodules and 11 of whom had 13 hepatic metastases. They used both monopolar and bipolar RF electrodes and performed multiple percutaneous probe insertions and multiple treatment sessions. All but one of the tumors treated in their series were smaller than 3.5 cm in diameter. In the 39 patients with HCC, the mean number of treatment sessions was 3.3, and mean follow-up was 22.6 months. The authors reported a median survival of 44 months. A total of 16 (41%) of 39 patients developed recurrent tumor: Two (5%) developed local recurrences, and 14 (36%) developed new lesions. In the 11 patients with metastases, the mean number of treatment sessions was 3.1. Two of these patients underwent surgery within 35 days of RF tumor ablation. Histopathologic examination of the resection specimens showed complete tumor necrosis in one (50%) of these two patients. Mean follow-up was 11 months in the remaining nine patients. In this group, one (11%) of nine patients was without evidence of metastases at 1 year after treatment. Of note, however, local recurrence was seen in two (18%) of 11 patients in whom metastases were treated: one who underwent surgery, and one who developed both local recurrence and other liver metastases. No complications were reported.

In a subsequent series, Rossi et al (57) treated 37 patients, 23 of whom had 26 HCC nodules and 14 of whom had 19 hepatic metastases. The mean diameter of the tumor nodules was 2.5 cm. The treatments were performed by using percutaneously placed hooked-needle electrodes and required an average of 1.4 treatment sessions per lesion. Five patients in their series ultimately underwent surgery 20–60 days after RF tumor ablation. Histopathologic examination of the resected specimens showed recurrent tumor in one (20%) of these patients (a patient with an HCC lesion larger than 2.5 cm). The remaining 21 patients with

a. b. c.

Figure 3. Successful treatment of multifocal HCC. **(a)** Transverse contrast-enhanced CT scan obtained 1 month after RF ablation demonstrates an apparent complete response, indicated by the hypoattenuating area (arrow). **(b)** Follow-up transverse contrast-enhanced CT scan obtained 1 year after treatment demonstrates four small satellite lesions (arrows) but apparently complete necrosis of the initially treated lesion. **(c)** Transverse contrast-enhanced CT scan obtained 3 months after successful treatment of satellite lesions by using internally cooled electrodes. Treatment required two separate electrode insertions. Three additional small lesions (not seen on this image) in different hepatic segments were present in this patient and were successfully treated with RF ablation.

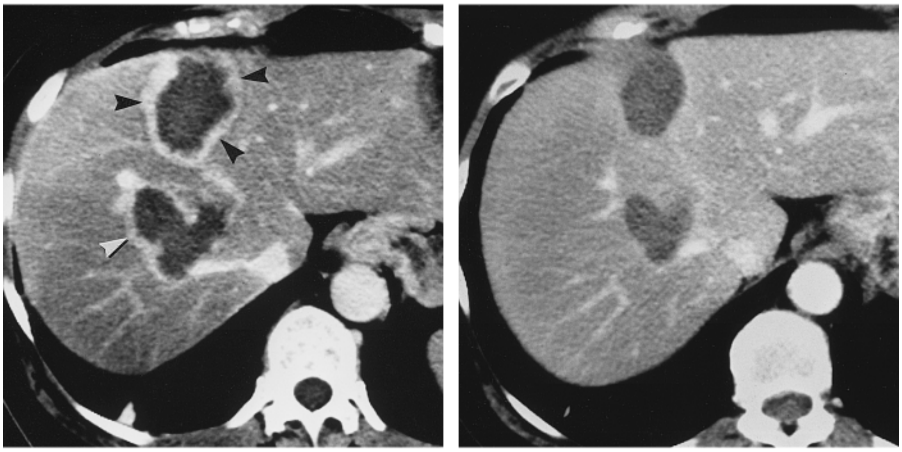


a. b. c.

Figure 4. Successful treatment of a single small metastasis from colon cancer. **(a)** Transverse contrast-enhanced CT scan obtained before treatment shows a single small tumor (arrow) in Couinaud segment 8. There was no other evidence of metastatic disease. **(b)** Transverse contrast-enhanced CT scan obtained 1 month after RF ablation with two insertions of a single internally cooled electrode shows a 4.5 × 6.0-cm zone (indicated by cursors and *1* and *2*) of hypoattenuation without contrast enhancement (arrow), suggestive of a complete response. **(c)** Transverse contrast-enhanced CT scan obtained 10 months after treatment demonstrates decreased size of the zone of coagulation necrosis (arrow), without evidence of local recurrence. At many centers, this patient might have been considered a candidate for hepatic resection. Successful treatment with RF obviated surgery and allowed a period of observation to confirm that no other metastatic lesions were present.

HCC and 11 patients with metastases were followed up for a mean of 10 and 12 months, respectively. The authors reported disease-free survival in 15 (71%) of 21 patients with HCC and in two (18%) of 11 patients with metastases. Of note, local recurrence was seen in three (8%) of 37 patients: two with HCC (one who subsequently underwent surgery) and one with metastases. No major or fatal complications were reported. Eight minor complications were reported: Six patients experienced mild abdominal pain during the procedures, one developed intense and persistent postprocedural pain and was subsequently found to have capsular necrosis, and one developed postprocedural fever (>38°C). No patients required additional therapy for their complications.

Solbiati et al (59) treated 16 patients with 31 metastases from gastrointestinal carcinoma. These tumors measured 1.5–7.5 cm in diameter, with 27 (87%) smaller than 3 cm in diameter. The treatments were performed by using percutaneously inserted conventional monopolar techniques with single electrodes or multiple electrode arrays and required a mean of 2.4 treatment sessions per lesion. A complete response (defined as no evidence of local tumor growth at CT and/or MR imaging 6 months after treat-



a. b.

Figure 5. Successful treatment of two metastases from colon cancer. **(a)** Transverse contrast-enhanced portal venous phase CT scan obtained 1 month after treatment of two large tumors by using internally cooled cluster electrode systems. Note the thick rims of enhancing tissue (arrowheads), which were thought to be somewhat suggestive of residual viable tumor versus posttreatment hyperemia. Repeat treatment was not performed at this time due to unfavorable geometry and because of the possibility that the rims of enhancement were related to hyperemia rather than tumor. **(b)** Transverse contrast-enhanced CT scan obtained 6 months after initial treatment demonstrates reduction in peripheral hyperattenuation, confirming that the rims represented hyperemia rather than tumor.

ment) was achieved for 18 (58%) of 31 lesions, all smaller than 3 cm in diameter. Partial tumor necrosis was seen in 13 (42%) of 31 lesions. Necrosis was estimated to be more than 80% of the tumor volume in nine of these lesions (six of which were larger than 3 cm) and less than 80% of tumor volume in the remaining four (all of which were larger than 2 cm). Disease-free survival was achieved in 50% of patients at a mean follow-up of 16.6 months. The overall survival rate was 100% at 1 year and 61.5% at 2 years. Only one complication was observed in this series: self-remitting intraperitoneal hemorrhage after treatment of a peripheral exophytic lesion. Neither transfusion nor surgical repair were necessary in this patient.

Solbiati et al (58) subsequently reported on a series of 29 patients in whom 44 hepatic metastases from gastrointestinal malignancies (primarily colorectal carcinoma) were treated by using percutaneously placed 18-gauge internally cooled electrodes. All lesions in this series measured 1.5–4.5 cm in diameter. Thirty-seven (84%) of 44 lesions were treated at a single treatment session; the remaining seven lesions required a second session. The authors reported "technical success" (absence of residual unablated tumor at follow-up CT or MR imaging 7–14 days after completion of treatment) in 40 (91%) of 44 tumors. Two patients could not be followed up beyond 3 months: One underwent surgery 60 days after RF ablation, and one was lost to further follow-up after 3 months. Overall, complete tumor necrosis was achieved in 33 (75%) of 44 lesions after a mean follow-up of 7.9 months. In this series, treatment outcome was significantly better in patients with small tumors: Local recurrence developed in none of 12 lesions smaller than 2 cm, in 14 (70%) of 20 lesions 2–3 cm in diameter, and in seven (58%) of 12 lesions larger than 3 cm. Disease-free survival was achieved in 16 (76%) of 21 patients at 6 months, in nine (50%) of 18 patients at 12 months, and in three (33%) of nine patients at 18 months. One patient in this series developed severe abdominal pain and orthostatic hypotension 3–4 hours after the procedure. This patient was subsequently found to have developed a small intraperitoneal hemorrhage. He was admitted for observation but was discharged without any additional therapy.

Livraghi et al (13) treated 14 patients with 24 hepatic metastases and one patient with hepatic cholangiocarcinoma by using percutaneously placed conventional monopolar RF electrodes and simultaneous intraparenchymal saline injection. The metastases measured 1.2–4.5 cm (mean, 3.1 cm) in diameter; the cholangiocarcinoma was 2.6 cm in diameter. Complete necrosis was observed at 6-month follow-up in 13 (52%) of 25 treated lesions. All of the successfully treated lesions measured less than 3.9 cm in diameter. Even in the successfully treated lesions, however, the authors noted that zones of coagulation necrosis are often irregular in shape and unpredictable. This finding, in combination with the relatively poor results, led them to abandon this technique in favor of the use of internally cooled electrodes. No major complications were observed. Two patients with lesions located near the diaphragm developed small pleural effusions and fever; these resolved without additional therapy. Another patient reported severe postprocedural pain and was found to have developed a small perihepatic rim of gas and fluid; this also resolved spontaneously.

Livraghi et al (60) subsequently compared RF ablation and PEI for the treatment of small HCC lesions. They treated 86 patients with 112 small (≤3-cm-diameter) HCC lesions by using RF ablation with percutaneously placed 18-gauge internally cooled electrodes (42 patients with 52 tumors) or PEI (44 patients with 60 tumors). The patients were examined with dual-phase spiral CT at least 4 months after treatment. The authors reported complete necrosis in 47 (90%) of 52 tumors treated with RF ablation and in 48 (80%) of 60 tumors treated with PEI. Treatment with RF ablation required fewer sessions per tumor than did treatment with PEI (1.2 vs 4.8). The results of this study suggest that RF ablation is at least as effective as PEI in the treatment of small HCC lesions. The authors also noted that the size and shape of RF-induced tumor necrosis generally conform to the size and shape of the tumors that were treated, and, in many cases, the area of necrosis is larger than might have been expected on the basis of prior experience with animals and humans. They postulated the "oven effect," whereby cirrhotic liver surrounding a tumor treated with RF acts as a thermal insulator and facilitates thermally mediated tissue necrosis. One major complication was reported in this series: hemothorax resulting from damage to an intercostal vessel located along the electrode track, which necessitated surgical drainage. Four minor complications also were reported: one episode each of self-remitting intraperitoneal bleeding, pleural effusion, hemobilia, and mild cholecystitis.

Most recently, Livraghi et al (64) described their experience in treating 126 HCC lesions measuring 3.1 cm or larger in diameter (mean diameter, 5.4 cm) in 114 consecutive patients with cirrhosis or chronic hepatitis. All tumors were treated by using percutaneously placed 18-gauge internally cooled electrodes. The authors reported achieving complete tumor necrosis in 60 (47.6%) of 126 lesions, near-complete (90%–99%) necrosis in 40 (31.7%) lesions, and partial (50%–90%) necrosis in the remaining 26 (20.6%) lesions. Both tumor size and morphology were found to be highly significant predictors of treatment success: Tumors smaller than 5.1 cm in diameter and/or those that were considered to be noninfiltrating were successfully treated significantly more often than were larger and/or infiltrating tumors.

Siperstein et al (10) treated six patients with 13 liver metastases from primary neuroendocrine tumors. The metastases measured 1.5–7.0 cm in diameter. These authors used a laparoscopic approach with a hooked-electrode needle system. To treat these lesions, one to eight applications of RF, each lasting 5–15 minutes, were needed. The overall procedure time was between 1 hour 45 minutes and 7 hours 5 minutes. Follow-up CT findings suggested complete ablation of all 13 lesions at 1 week and of 11 (100%) of 11 lesions in four patients who were followed up for 3 months. Longer term follow-up was not reported. The authors also reported symptomatic improvements in these patients with functional tumors. No complications were reported.

Siperstein et al (65) subsequently reported their experience in treating 66 patients with 250 primary and secondary hepatic tumors. The procedures were performed by using a laparoscopic approach with a hooked-electrode needle system. The authors reported achieving local control in 156 (88%) of 178 lesions for which at least 3 months of follow-up results were available. On the basis of their experience, they identified four predictors of local treatment failure: (*a*) ablation size smaller than original tumor size, (*b*) adenocarcinoma or sarcoma, (*c*) tumors larger than 3 cm, and (*d*) laparoscopic US evidence of vascular invasion. The authors also noted that most local tumor recurrences were evident by 6 months after treatment.

Elias et al (62) reported their experience with a combined (liver resection and RF ablation) approach to treat seven patients with extensive liver metastases who could not be treated with surgery alone: five patients with bilateral liver metastases deemed unresectable with conventional approaches and two who had previously undergone extensive hepatic surgery and associated central liver metastases. All RF ablation procedures were performed intraoperatively at the time of liver resection by using 18-gauge internally cooled electrodes. In all cases, the hepatic pedicle was cross-clamped (Pringle maneuver) during RF ablation to decrease hepatic perfusion, and thereby heat conduction, from tissues surrounding RF-treated lesions. The metastases treated with RF ablation measured 0.8–1.9 cm in diameter (mean, 1.1 cm). All patients were disease free at 1–10-month follow-up. No complications were reported.

Jiao et al (61) treated 35 patients with primary and secondary liver tumors who were not considered to be candidates for curative hepatic resection: eight with HCC and 27 with metastases (17 of these were from colorectal carcinoma). Treatment was performed by using 18-gauge internally cooled electrodes placed either percutaneously with US guidance (five patients) or at laparotomy guided with manual palpation and intraoperative US (30 patients). Intraoperative procedures were performed during a Pringle maneuver. Seventeen (57%) of 30 patients treated intraoperatively underwent RF ablation alone; 13 (43%) underwent combined RF ablation and surgical resection (including two who initially underwent percutaneous RF ablation). Overall, 24 (69%) of 35 patients were found to have "stable disease" at a mean follow-up of 10.1 months. Of note, 11 (41%) of 27 patients with hepatic metastases were initially judged not to be candidates for resection but subsequently underwent resection in combination with RF ablation of tumors in the remaining liver. The authors reported "serious complications" in three (60%) of five patients who underwent percutaneous tumor ablation but in none of those who underwent intraoperative RF ablation. They further reported that in patients undergoing percutaneous ablation, "the treatment always had to be discontinued owing to severe discomfort and pain" and "fever and rigor subsequently occurred in all patients." No explanation was given for the unusual (in comparison with results reported by other investigators) frequency or severity of complications observed.

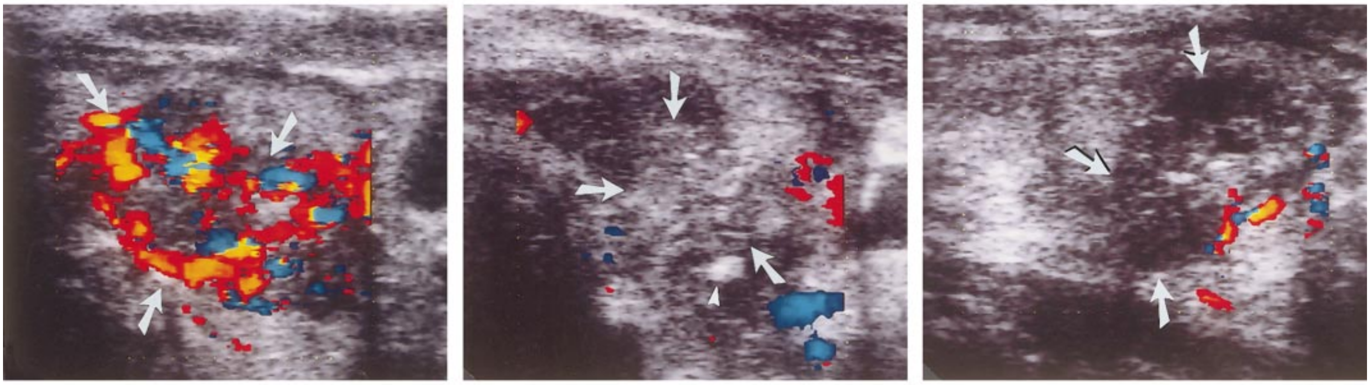
Francica and Marone (63) treated 20 HCC nodules in 15 patients with cirrhosis by using percutaneously inserted 18-gauge internally cooled electrodes. The tumors measured 1.0–4.3 cm in diameter (mean, 2.8 cm). Nine lesions were larger than 3 cm. Complete tumor necrosis was achieved in 15 (75%) of 20 lesions after a single treatment session. After a second treatment session (in patients with partial response), complete tumor necrosis was achieved in 18 (90%) of 20 lesions. Five (33%) of 15 patients developed recurrent HCC during a median follow-up of 15 months. Complications were reported in four patients: self-limited pleurisy and a five-fold increase in transaminase levels in one patient and a transient three-fold increase in transaminase levels in three patients.

Curley et al (67) treated 169 tumors (mean diameter, 3.4 cm) in 123 patients (48 with primary HCC, 75 with liver metastases). Treatment was performed either percutaneously or intraoperatively by using LeVeen monopolar hooked-needle electrodes. The majority of the procedures were performed with US guidance at laparotomy. The authors reported no treatment-related deaths and an overall complication rate of 2.4%. Complete tumor necrosis was achieved in 166 of 169 treated lesions, with a median follow-up of 15 months, but progressive metastatic disease was observed in 34 (28%) patients.

Finally, Bilchik et al (66) treated 132 unresectable hepatic metastases in 50 patients. The tumors measured 0.5–9.0 cm in diameter. Treatment was performed with US guidance either percutaneously or intraoperatively by using 15-gauge hooked-needle electrodes. The majority (37 [74%] of 50) of patients were treated during laparotomy or celiotomy. RF ablation was the sole therapy in 28 (56%) patients. For the remaining 22 (44%) patients (those with multiple lesions), RF ablation was combined with cryosurgery, resection, and/or hepatic arterial infusion chemotherapy. The authors reported that at a median follow-up of 6 months, 27 (54%) of 50 patients were alive and disease free, 17 (34%) were alive with disease, and six (12%) died of their disease.

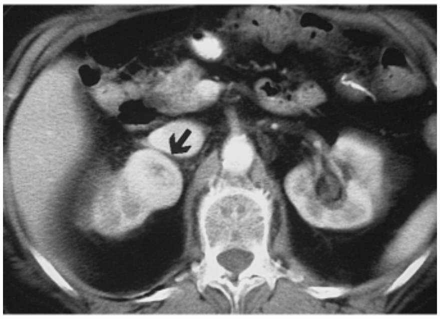
Extrahepatic Tumor Ablation

Tumors in multiple other organ sites have also been treated with RF (Figs 6, 7) (68–79). Rosenthal et al (68,69) treated over 100 osteoid osteomas by using percutaneously placed conventional monopolar electrodes. For these treatments, a 15-gauge Ackerman needle is used to bore through the surrounding cortical bone, with CT guidance. An 18-gauge RF electrode with a 2.3–5.0-mm tip exposure is inserted through the Ackerman needle by using a coaxial technique. RF is then applied for approximately 6 minutes, adjusting generator output to maintain a tip temperature of 80°–90°C. Pain, the primary clinical manifestation of this le-

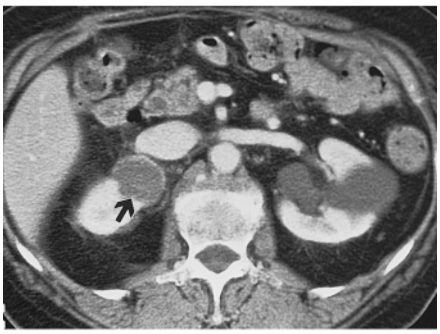


a. b. c.

Figure 6. Transverse color Doppler US scans demonstrate treatment of hyperfunctioning parathyroid adenoma by using combined PEI and RF ablation. **(a)** Pretreatment scan shows a hypervascular parathyroid mass (arrows). **(b)** Scan obtained during RF ablation shows hyperechogenicity within the mass (arrows), which is related to microbubble formation due to tissue heating. The tip of the RF electrode (arrowhead) can be seen as a pinpoint focus of increased echogenicity. **(c)** Posttreatment scan shows hypoechogenicity (arrows) replacing the mass and elimination of hypervascularity. The small focus of color signal is related to an adjacent blood vessel.



a.



b.

Figure 7. Transverse contrast-enhanced CT scans demonstrate RF ablation of a 3.5-cm renal cell carcinoma in a patient with ovarian cancer in regression after treatment with systemic chemotherapy. **(a)** Pretreatment scan demonstrates a hypervascular mass (arrow) in upper pole of the right kidney. **(b)** Scan obtained 1 year after RF ablation with a single internally cooled electrode demonstrates hypoattenuation (arrow) and no evidence of local recurrence.

sion, was eradicated in more than 95% of cases; 12 recurrent lesions were successfully re-treated with percutaneous techniques. In addition, the length of hospital stay compared with that after surgical excision, previously the therapy of choice, decreased from 6.8 to 2.6 days (70).

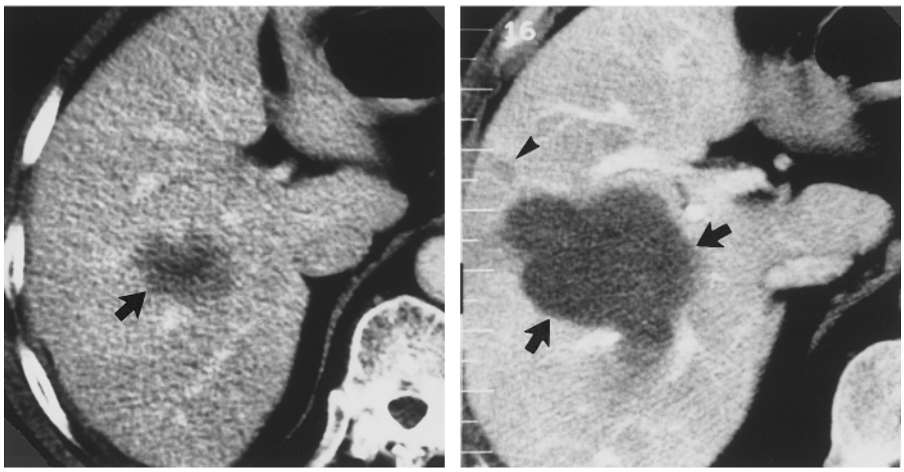
In the earliest reported application of RF ablation for the treatment of malignant human neoplasms of which we are aware, Anzai et al (80) treated 14 lesions in 12 patients with primary and metastatic brain tumors. They were able to achieve local control, documented with MR imaging, of all treated lesions for up to 10 months of follow-up.

Dupuy et al (71) reported treating 10 patients with painful metastatic bone lesions measuring 1–8 cm by using CT guidance and 18-gauge internally cooled electrodes. Subjective pain relief was reported in 90% and lasted a minimum of 4 months without further treatment.

RF ablation has also been used to treat head and neck lesions that would otherwise require extensive or repetitive surgical procedures (Fig 6). In an attempt to reduce the number of sessions necessary for percutaneous treatment of parathyroid hyperplasia and recurrent secondary hyperparathyroidism, Solbiati et al (72) performed PEI and RF ablation at a single session to treat six patients with uremia. RF was applied to 18-gauge internally cooled electrodes with a 1–2-cm tip exposure immediately after injection of 1–2 mL of ethanol. In all six patients, a greater than 50% reduction in parathyroid hormone level and normalization of bone alkaline phosphatase level were achieved at 3-month follow-up. By comparison, a less favorable clinical response was achieved in six control patients who underwent PEI alone and required a minimum of four treatment sessions. These preliminary results suggest that RF can be used to eliminate hormonally active tissue even in cases in which complete ablation of an entire lesion is not possible and that this method may reduce the treatment schedule, as compared with the results of other percutaneous injection therapies.

Solbiati et al (73) also treated two recurrent 1.5–2.0-cm metastases to supraclavicular lymph nodes from papillary thyroid cancer in patients who had previously undergone multiple operations and were deemed to no longer be surgical candidates. US guidance was used to place 18-gauge internally cooled electrodes. RF was applied for 12 minutes at 1,000–1,200 mA. Complete necrosis of all lesions was observed at 1-year follow-up. These results suggest that it may be possible to treat slow-growing lymph nodes adequately and safely and thereby achieve local control of disease without the need for extensive surgery.

Additional reports have begun to appear describing the use of RF ablation in other sites and organs (Fig 7). Polascik et al (14) reported their experience with saline-enhanced RF ablation treatment of VX2 tumors that had been implanted beneath the renal capsule in rabbits. Zlotta et al (74) reported the treatment of three focal renal tumors in two patients by using hooked electrodes. Extensive coagulation necrosis was found throughout these tumors at subsequent nephrectomy. McGovern et al (75) reported the successful treatment of a single 3-cm renal carcinoma by using an 18-gauge internally cooled RF electrode placed percutaneously with US guidance. Birdwell et al (76) used hooked electrodes to treat five large breast tumors prior to surgical excision. They were able to document contiguous ablation of tumor tissue at histopathologic examination. Lewin et al (81) described their experience in treating retroperitoneal metastases in an open MR imaging environment. Dupuy et al (82) reported their experience in treating lung malignancies. Results of preliminary animal studies have also been reported for lung (77) and pancreas (79). As clinicians gain greater familiarity with RF techniques, it is likely that additional organ sites will be treated and other treatment indications identified.



a. b.

Figure 8. Transverse contrast-enhanced CT scans demonstrate successful treatment of a solitary metastasis from colorectal carcinoma, with a surgical margin obtained. **(a)** Before treatment, a single small lesion (arrow) is present in Couinaud segments 5 and 6. **(b)** Scan obtained 3 months after treatment with an internally cooled clustered-electrode system shows a large focus of hypoattenuation (arrows) devoid of contrast enhancement and completely enveloping the previously seen tumor. A small adjacent focus of hypoattenuation (arrowhead) is related to placement of the RF electrodes.

LESSONS LEARNED, FUTURE CHALLENGES

Although the long-term clinical benefits of RF ablation for the treatment of malignant tumors remain relatively unproved, the extensive laboratory and animal experience in combination with the results from preliminary clinical series suggest that these techniques may have an important role to play in the treatment of patients with a variety of primary and secondary neoplasms. However, much additional research is needed to further optimize RF equipment and ablation techniques.

On the basis of laboratory and clinical research results reported to date, it appears that the single most important determinant of tissue heating (and thus the extent of coagulation necrosis that is achievable) is RF current density: The greater the current density surrounding the needle electrode, the more energy is deposited in tissue and the more tissue can be heated to lethal temperatures. If too much energy is applied too rapidly, however, biologic tissues can be heated to temperatures greater than their boiling point. This in turn results in gas production, charring, and cavitation, which lead to increased circuit impedance and thus limit further energy application. The development of techniques that maximize tissue heating and at the same time prevent charring and cavitation will likely permit larger volumes of tissue to be destroyed at a single treatment session. To date, several approaches have been used, including the use of hooked-needle electrodes, perfusion-cooled electrodes, multielectrode arrays, and clustered-needle electrodes and the development of algorithms for pulsed energy delivery.

The amount of tissue that can be ablated—the "lesion size"—is determined by more than simply the amount of heat that can be deposited in tissue. For example, factors such as perfusion-mediated tissue cooling can influence the rate at which heat is dissipated and ultimately determine the size of the resultant focus of tissue necrosis. This has been confirmed in animal studies where tissue perfusion has been manipulated by using mechanical or pharmacologic means and in clinical studies where ablation has been performed during the Pringle maneuver (83,84). On the basis of these preliminary study findings, it appears that decreased tissue perfusion results in an increase in the volume of coagulation necrosis that can be achieved with RF ablation techniques. A better understanding of the effects of tissue perfusion and the development of methods to overcome its cooling effects are necessary to optimize results.

It has also become clear that for successful destruction of focal hepatic neoplasms (particularly metastases), it is essential that a rim of normal tissue surrounding the tumor be destroyed. Surgeons have generally attempted to remove at least 0.5–1.0 cm of normal tissue surrounding tumors that are resected; it is likely that a similar tumor margin will be required for successful in situ tumor ablation (Fig 8). There are two potential explanations for the importance of achieving surgical treatment margins, even with in situ ablation: (*a*) Tumor cells probably extend beyond the actual tumor margins into normal tissue, and (*b*) currently used diagnostic liver imaging techniques may not accurately define actual tumor margins. Whatever the explanation, it appears clear that the failure to achieve an adequate treatment margin will be accompanied by a high local recurrence rate.

The issues of tumor margin and perfusion meeting perfusion-mediated tissue cooling are closely related. This is particularly true with respect to liver metastases, where tumor margins often contain the most rapidly growing and well-perfused cells. The cooling effects of tissue perfusion are thus greatest at the periphery of most metastases. Tissue heating, on the other hand, is less effective at the tumor margin owing to the increased distance between the margin and the electrode tip and, therefore, the decreased current density at the margin. In contrast, tumor neovascularity (and thus tissue perfusion) is more evenly distributed within HCC nodules. In addition, the surrounding cirrhotic liver is thought to act as a thermal insulator (the "oven effect") (60), resulting in decreased heat dissipation from, and thus enhanced heating at, the tumor margins. These factors may explain some of the differences in success rates that have been observed between liver metastases and HCC nodules.

Beyond optimization of technical and physiologic parameters, it is clear that to treat patients successfully with focal neo-

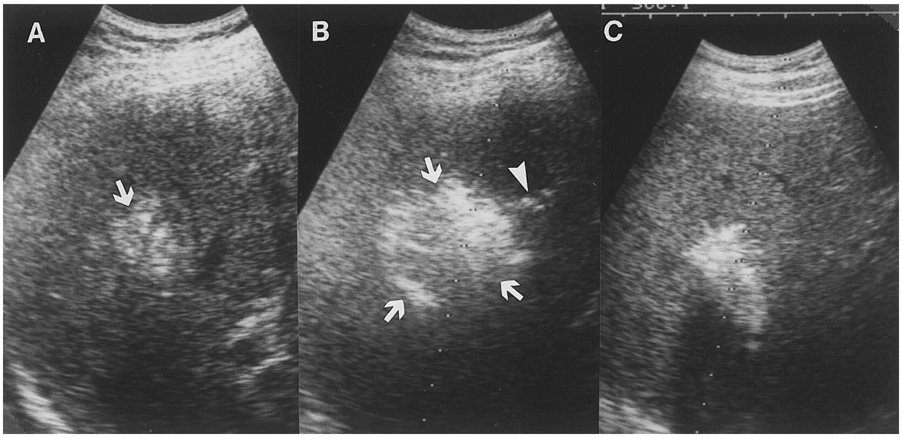


Figure 9. Oblique subcostal US scans show the evolution of US findings in HCC treated with RF ablation. *A,* Before treatment, a somewhat hyperechoic tumor (arrow) in the right lobe is visible. *B,* During RF ablation with a single internally cooled electrode, increased echogenicity secondary to microbubble formation completely envelops the tumor (arrows). The electrode (arrowhead) can be seen as a faint line of increased echogenicity. *C,* At 30 minutes after RF ablation, the focus of increased echogenicity has decreased markedly in size. The rapid change in appearance illustrates the difficulty in using US to determine the extent of treatment effect.

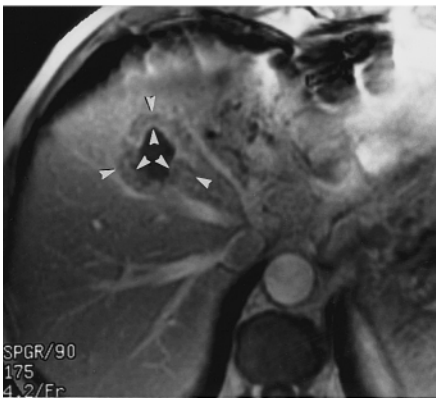


Figure 10. Transverse gradient-echo MR image (repetition time, 125 msec; echo time, 4.2 msec; echo train length, one; one signal acquired) obtained 6 months after RF ablation with a single internally cooled electrode shows unsuccessful treatment of metastasis (arrowheads) from colorectal carcinoma, with unfavorable geometry for re-treatment. The tumor completely surrounds a central area of coagulation necrosis, resulting from inadequate tissue margins. When a complete rim of locally recurrent tumor is present after unsuccessful RF ablation, successful re-treatment is often impossible because of the difficulty in adequately covering the entire surface of the now-larger sphere of tumor.

plasms by using percutaneous in situ ablation techniques, these treatments must be applied with accurate knowledge of not only the number and location of the lesions but also the biologic characteristics and natural history of the specific tumor(s) being treated. Patients with primary tumors prone to the development of numerous metastases in multiple organs (unfavorable tumor biologic characteristics) are unlikely to be successfully treated with local therapies such as in situ ablation, regardless of how successfully individual lesions are targeted and destroyed. Treatment failure in these cases is due largely to the development and uncontrolled growth of new and/or previously undetected metastases.

Despite the considerable progress that has been made to date, a number of challenges remain for the future. These include (*a*) the development of techniques that can increase the volume of tissue destroyed at a single treatment session, (*b*) the development of more suitable and accurate imaging tests, and (*c*) a better understanding of how to integrate in situ ablation techniques into the overall care of patients with different specific neoplasms.

Much progress has been made toward the development of techniques to ablate large volumes of tissue at a single treatment session. Even with optimized techniques, however, the largest focus of coagulation necrosis that can be created with a single application of RF is approximately 3–4 cm. Even if one wishes to achieve only 0.5-cm treatment margins, a 3–4-cm "kill zone" means that the largest tumor that can be successfully treated with a single probe placement is approximately 2–3 cm. This is consistent with the results reported in clinical series (13,58,59,64,65), where local recurrence rates increase considerably when tumors larger than 3 cm are treated. Obviously, larger tumors can be treated by using multiple probes and/or probe placements; however, each of these approaches increases the technical complexity of the procedure. Therefore, and despite the progress that has been made to date, if larger lesions are to be successfully targeted and eliminated at a limited number of treatment sessions, techniques that will allow the destruction of even larger volumes of tissue must be developed. This may well require combination therapies; for example, chemotherapy and/or transcatheter embolization combined with RF ablation (85) or ethanol injection followed by RF ablation (86). Experience with such combined treatment regimens is currently limited, however, and the available data are far too sparse for determination of the relative or absolute merits of combination therapies.

Accurate imaging is essential for successful in situ tumor ablation. Tumors that are not seen cannot be targeted, and residual foci of untreated tumor will continue to grow. With respect to tumor detection, and despite remarkable progress in US, CT, and MR imaging over the past several years, no currently available imaging technique is perfectly sensitive for the detection of liver tumors, which means that some lesions will undoubtedly be overlooked with all imaging techniques. Generally, these overlooked lesions are small and will grow to a size that allows them to be detected, targeted, and treated. Because currently available imaging techniques also may not precisely depict tumor margins, however, small foci of untreated tumor may not be identified. These will continue to grow in size and result in "local recurrence" after treatments that initially appeared to be successful. Improved imaging techniques should result in not only improved detection of additional lesions (which would thus permit earlier treatment) but also more accurate determination of tumor margins. Recent and ongoing developments in contrast agents for US and MR imaging coupled with technical innovations in US, CT, and MR imaging may provide the much needed improvements. Additional research will be needed to determine their effect on the efficacy of in situ tumor ablation with RF.

In situ tumor ablation is virtually always performed with imaging guidance. Currently, US is most commonly used for guidance in probe placement, owing to its flexibility, widespread availability, relatively low cost, and real-time imaging capabilities. RF ablation can also be performed with CT or MR imaging guidance; however, until recently, the static nature of CT and the complexity of the MR imaging environment have limited their use. The recent development of CT fluoroscopic systems may result in a larger role for CT in the future. Similarly, the developments of open-architecture MR imaging systems and MR-compatible interventional equipment have resulted in increased interest in the use of this modality to help guide interventional procedures. Preliminary experience now suggests that MR imaging may be useful for in situ ablation procedures with RF (4,79,81,87,88).

Imaging is used not only to help detect potentially treatable tumors and guide probe placement but also to monitor the effects of therapy. When procedures are performed with US guidance, hyperechogenicity is generally seen surrounding the probe tip during the application of RF energy. This has proved to be only marginally useful for monitoring the effects of therapy because the hyperechoic zones correspond only roughly to the regions of eventual tissue necrosis. Furthermore, these changes evolve rapidly over time and can disappear within minutes of ablation (Fig 9) (57–60). Acoustic shadowing from more superficial treated areas can also preclude visualization of deeper portions of the tumor if one is not careful to treat deeper areas first (as with PEI). The use of US contrast agents may improve the accuracy of US with respect to monitoring the acute effects of therapy; to our knowledge, however, only preliminary human and animal experience is available (89,90). Contrast-enhanced CT, which is probably the most widely used technique for the follow-up of treated lesions, is less useful for the immediate assessment of treatment results. Although no study has directly addressed the accuracy of CT in this setting, it has been our experience that CT is not particularly helpful for confirming successful treatment or identifying a small focus of untreated tumor. MR imaging appears to be more accurate than US or CT for monitoring the acute affects of therapy; however, once again, only preliminary experience has been reported (4,79,81,87,88), to our knowledge.

It is also important to note that the requirements for intraprocedural monitoring of tissue necrosis will likely change as capabilities for producing a larger volume of tissue necrosis are developed. Currently, however, there is little need to use imaging to determine the stopping point of therapy. In most cases, given the limited volume of tissue that can be coagulated, ablation is continued until the largest possible zone of coagulation necrosis has been created. Possible exceptions to this rule are when the tumor being targeted is small and/or is located in proximity to vital structures that might be damaged by heating (eg, gallbladder, bowel) or for treatment of tumors located in the brain, where "collateral damage" must always be limited. In our experience, these exceptions represent a minority of cases referred for RF ablation.

With respect to postprocedural imaging follow-up, it is critical to detect focal areas of untreated or locally recurrent tumor at an early stage, when such lesions can be successfully treated. The failure to detect these small focal areas of residual and/or recurrent tumor at an early stage results in peripheral regrowth, often with unfavorable geometry for successful re-treatment (Fig 10). As with pretreatment imaging, the optimal method for postprocedural follow-up has yet to be determined. In our experience, follow-up at 3- to 6-month intervals has proved to be acceptable, because such follow-up allows detection of untreated regions of viable tumor before they grow to such a size where re-treatment would be infeasible.

Follow-up imaging is most frequently performed by using contrast-enhanced CT; however, recent evidence suggests that contrast-enhanced MR imaging may be a useful alternative (91). Follow-up imaging studies are generally performed in combination with laboratory tests such as carcinoembryonic antigen and α-fetoprotein assays, which can provide a general indication of the overall status of malignant disease but relatively little useful information regarding the status of specific lesions that have been treated.

In conclusion, success in the use of in situ ablation techniques can be achieved only with improved understanding of the biologic features and natural history of tumors. It is critical for physicians performing RF ablation to work in concert with oncologists and oncologic surgeons to ensure careful selection of the treatment options that best serve individual patients and/or are best suited to their tumors. At this point, it seems clear that some tumors may be better treated surgically (eg, single large metastases from colorectal carcinoma that are unlikely to be successfully treated with currently available in situ ablation techniques), whereas others will likely be better managed percutaneously (eg, a single small metastases from colorectal carcinoma that, in all likelihood, can be successfully treated with percutaneous RF ablation; HCC in a patient with severe cirrhosis).

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