Perspective

Radiofrequency Ablation of the Liver: Current Status

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Hepatocellular carcinoma (HCC) and metastases from colorectal carcinoma are the two most common malignant tumors to affect the liver. When these tumors are left untreated, the prognosis for both is dismal, with essentially 100% mortality at 5 years. Conventional therapies such as systemic chemotherapy or radiation have proven ineffective. Surgical resection of the tumors is considered the only potentially curative therapy [1–4]. Successful resection of targeted tumors with negative tumor margins is achieved in approximately 80–90% of patients undergoing hepatic resection [5–7]. Unfortunately, surgical resection has many factors limiting its overall usefulness. Of all patients presenting with a malignant hepatic tumor, few are surgical candidates. Contraindications to hepatic resection include too many tumors, tumors in unresectable locations, insufficient hepatic reserve to tolerate resection, and other medical conditions that make the patient a poor surgical risk. It has been estimated that only 5–15% of patients with HCC or hepatic metastases are eligible for resection [1–4]. For those patients who undergo hepatic resection, there is considerable postoperative morbidity—a small but real risk of death related to the operation—significant monetary expense, and only a modest improvement in long-term prognosis. The 5-year survival rate for patients undergoing resection of HCC or hepatic metastases is only 20–40% [1–3]. Most patients die from recurrent hepatic tumors. Although in some instances surgery may be repeated to resect recurrent tumor, at most institutions hepatic resection is a “one-shot” therapy. In light of these shortcomings, an effective, minimally invasive technique is needed for treating these tumors—one that can be repeated as necessary to treat recurring tumor.

A number of alternative therapies have been used for the treatment of malignant hepatic tumors. These include chemoembolization, ethanol injection therapy, and thermal ablation techniques. Chemoembolization has been studied extensively and is often reserved for patients with unresectable hepatic tumors [8, 9]. Ethanol injection therapy has gained fair international acceptance as a safe, inexpensive, and effective therapy for small HCC tumors [10, 11]. However, it has failed to generate much enthusiasm in the United States. This lack of enthusiasm is based in part on the need to perform multiple consecutive therapeutic sessions to completely kill even the smallest HCC tumor and the fact that the technique is typically performed under sonographic guidance [11]. Furthermore, ethanol injection therapy has been shown to be ineffective for the treatment of colorectal metastases [12].

Thermal ablation techniques for the treatment of malignant hepatic tumors include both freezing (cryoablation) and heating (radiofrequency, microwave, laser, and high-intensity focused sonography) techniques. Of these techniques, cryoablation has been the most extensively investigated [13, 14]. The two advantages of cryoablation over surgical resection are that it can be used to treat liver tumors that, by number or location, are not surgically resectable, and that it is associated with diminished morbidity and mortality relative to resection. The overall prognosis for patients undergoing cryoablation is reported to be the same as for hepatic resection. However, the limitations of cryoablation are similar to the limitations of hepatic resection—namely, it is invasive, with a laparotomy being performed in most cases [14].

During the last 10 years, considerable interest has developed in the thermal ablation techniques that produce heat. Methods that are being investigated include microwave, laser, high-intensity focused ultrasound, and radiofrequency ablation. Most of the research on microwave ablation has been performed in Japan, with minimal experience or knowledge of the technique outside that country [15, 16]. Laser ablation has been tested most rigorously outside the United States [17–19]. One group of German researchers, Vogl et al. [19], claim that the technique is highly effective for the treatment of both HCC and colorectal metastases. However, one of the primary investigators of laser ablation in England has essentially abandoned the technique in favor of radiofrequency ablation [20]. High-intensity focused ultrasound has been shown to be successful in ablating hepatic tumors in animal models but has not been used to treat liver tumors in humans [21]. Overall, the interest and enthusiasm for radiofrequency thermal ablation has far exceeded that for either microwave or laser ablation. This article will

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review the current status of radiofrequency ablation in the treatment of liver neoplasms

Background

The initial investigation of the use of radiofrequency waves in the body is credited to d'Arsonval [22] in 1891, who showed that radiofrequency waves that pass through living tissue cause an elevation in tissue temperature without causing neuromuscular excitation. These observations eventually led to the development in the early to mid 1900s of electrocautery and medical diathermy [23–25]. The best known of these developments is the surgical Bovie knife (Liebel Florsheim, Cincinnati, OH) [26]. This device is used to cauterize bleeding tissue. The device consists of an alternating electric current generator operated in the range of radiofrequency, a small knifelike electrode, and a large grounding pad. The physical principles of the operation of the device are fairly simple. The alternating electric current passes back and forth through the patient between the grounding pad and the Bovie knife. The grounding pad is applied to the patient's thigh and acts as a large dispersive electrode that allows the current to pass freely through the patient without producing any significant heat except around the point of the Bovie knife. The Bovie knife has a small tip and, when brought into contact with the patient, acts as a focal point for the electric current. The current arcs between the Bovie knife and the patient, desiccating and charring the tissue at the point of contact. Work by Organ [27] elucidated the physical principles of the interaction of the alternating electric current with living tissue. He showed that at low-power settings, the alternating current causes agitation of the ions in the adjacent tissue. The ionic agitation causes frictional heat that extends into adjacent tissues by conduction. However, at high-power settings the ions are quickly destroyed through desiccation and charring of the superficial tissue, and heat production is minimal [27, 28]. Subsequent modifications of the Bovie knife have led to its use in other superficial applications, such as destruction of the neuronal pathways in the heart in patients with intractable arrhythmias [29, 30].

In the early 1990s, two independent groups of investigators using modified radiofrequency equipment studied the percutaneous creation of focal thermal injuries deep in the liver [31, 32]. In their studies they used equipment similar to that of the Bovie knife; that is, an alternating electric current generator operated in the radiofrequency range, a grounding pad placed on the tissue, and an insulated needle as a monopolar electrode. The original needle design was simple and used standard stock needles insulated to the distal tip (Fig. 1). The studies consisted of placing needle electrodes deep in the liver and creating focal thermal injuries around the noninsulated tip of the needles. Gross and histologic examination of the ablated livers showed that the process produced a well-defined concentric region of coagulative necrosis around the exposed needle tip. This was similar to coagulative necrosis as described in prior experimentation [33]. However, the size of the thermal injuries was small; the radius of the coagulated tissue surrounding the exposed needle tip was approximately 1 cm (Fig. 2). Superficial charring around the needle tips similar to that produced by the Bovie knife limited the size of the thermal injury that could be created in the liver. Nonetheless, both investigators proposed that radiofrequency ablation might be an effective technique for destroying small malignant liver tumors [31, 32].

Subsequent research has shown that effective tissue coagulation requires local temperatures in excess of 50°C [34]. Furthermore, several factors, including a slow increase in generator power, prolonged radiofrequency application, and an increase in the exposed surface area of radiofrequency needle electrodes, have been shown to increase the volume of coagulated tissue [34–36].

Modern radiofrequency ablation equipment can create thermal lesions of sufficient size (3–4.5 cm) to be clinically relevant. In the United States, three primary companies (RITA Medical Systems, Mountain View, CA; Radiotherapeutics, Mountain View, CA; and Radionics, Burlington, MA) market radiofrequency devices for tissue ablation. Each of the companies received approval of their devices from the Food and Drug Administration under a 510K-like device exemption. The radiofrequency tissue ablation devices were deemed similar enough to the Bovie knife in design and application that a full Food and Drug Administration application was unnecessary. Each company was allowed to market its device for generic tissue ablation; however, none could market its device specifically for the ablation of hepatic tumors. However, just recently the Food and Drug Administration has approved the use of these devices for the treatment of liver tumors that are surgically unresectable.

Equipment

To overcome the problem of tissue desiccation and charring and a limited radius of coagulated tissue around the radiofrequency needle electrode, each of the three companies in the United States has experimented with different radiofrequency needle designs and generator algorithms. Each of the marketed devices uses a different radiofrequency needle design, generators of different wattage, and generator algorithms that vary significantly from each other. The following is a description of the different equipment and operating parameters.

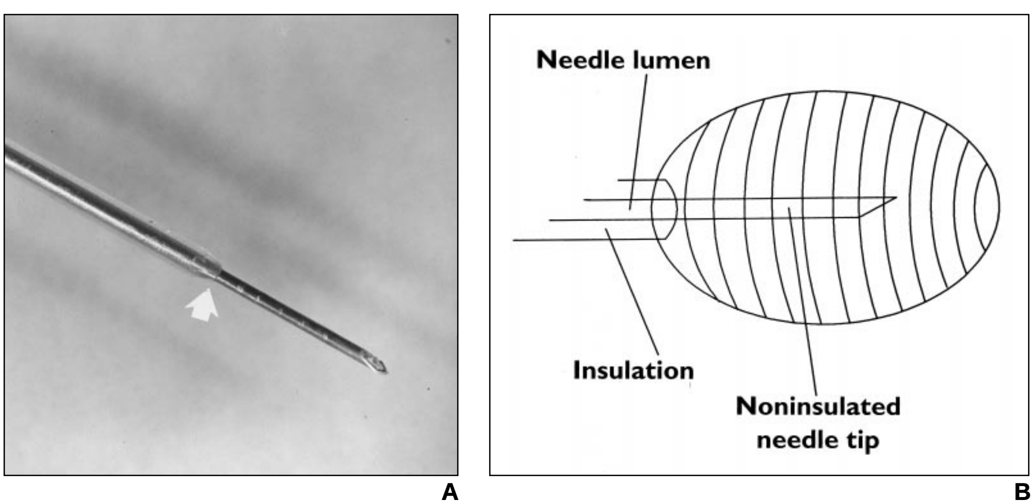
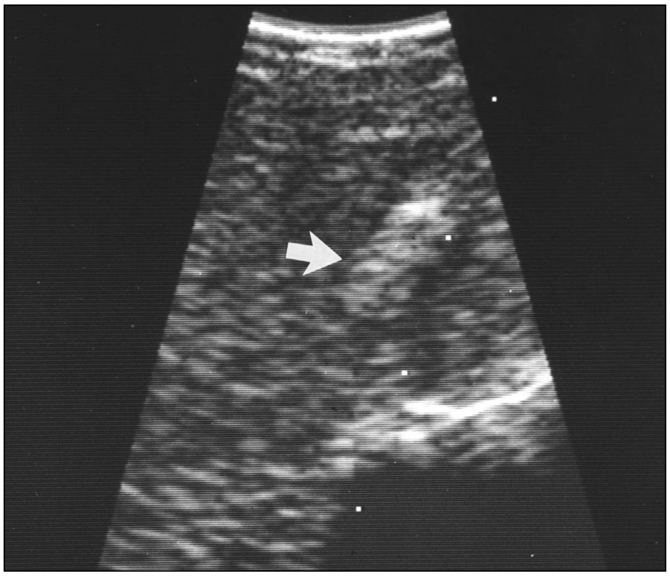


Fig. 1.—Original needle design.
A, Photograph of original needle design shows standard stock needle that is insulated (*arrow*) to distal tip. Needle tip is not insulated.
B, Drawing shows theoretic lesion that would be produced if noninsulated needle tip were used during monopolar radiofrequency electrocautery. (Reprinted with permission from [75])



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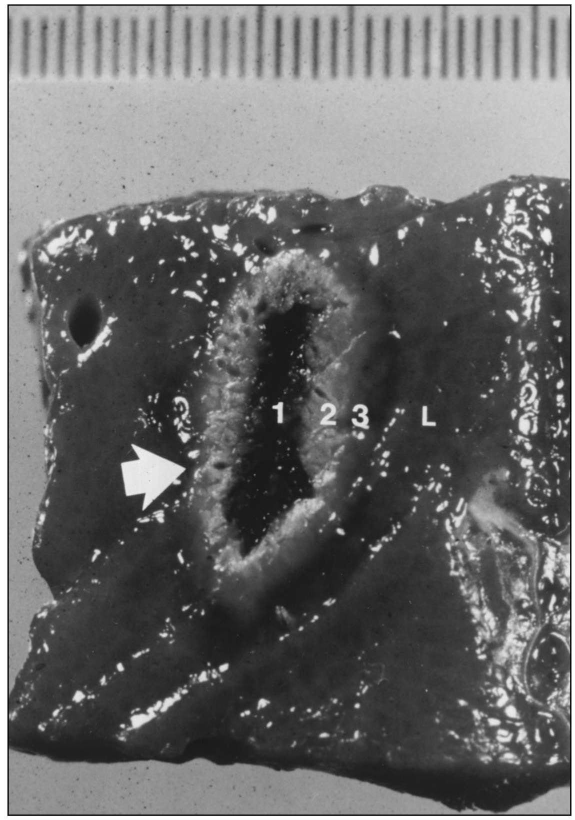
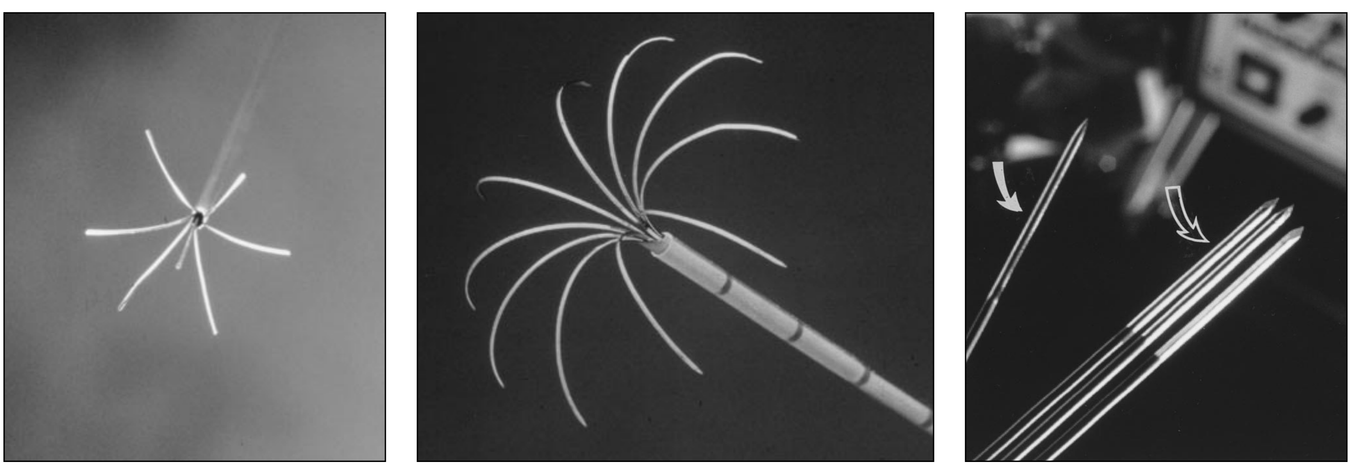


B

Fig. 2.—In vivo sonographic and histologic correlation for radiofrequency coagulation of swine liver.
A, Sonogram of monopolar radiofrequency lesion shows hyperechoic regions surrounded by hypoechoic rim (*arrow*).
B, Photograph of in vivo liver reveals central area of charred tissue (1) surrounded by coagulative necrosis (2) and hyperemic rim (*arrow*, 3). L = healthy liver. (Reprinted with permission from [28])

One of the manufacturers markets a system with two retractable needle electrodes (Model 70 and Model 90 Starburst XL Needles; RITA Medical Systems). The needle electrodes consist of a 14- or 15-gauge insulated outer needle that houses seven or nine (respectively) retractable curved electrodes of various lengths. When the electrodes are extended, the devices assume the approximate configuration of a Christmas tree, with the length and diameter of the electrode clusters measuring 3 or 5 cm, respectively (Fig. 3A). Four of the electrodes are hollow and contain thermocouples in their tips that are used to measure the temperature of the adjacent tissue. The alternating electric current generator comes in either a 50- or 150-W model; both are operated at 460 kHz. To perform a typical ablation, one or two grounding pads are placed on the patient's back or thigh. The tip of the needle (with retracted electrodes) is advanced to the desired



A B C

Fig. 3.—Photographs of radiofrequency needle designs.
A, Prongs protrude in "Christmas tree" configuration from tip of needle manufactured by RITA Medical Systems, Mountain View, CA.
B, Ten prongs protrude in umbrella configuration from tip of needle manufactured by Radiotherapeutics, Mountain View, CA.
C, Single (*solid arrow*) and clustered (*open arrow*) cooled-tip needles manufactured by Radionics, Burlington, MA.

location, and the electrodes are deployed to approximately two thirds their length. The generator is turned on and run by an automated program. The program starts the generator at approximately 25 W and then gradually increases the wattage to peak power in 30–120 sec. The program monitors the temperature at the tips of the electrodes and maintains peak power until the temperature exceeds the preselected target temperature (typically between 95° and 105°C). The operator watches the temperature display, and after the target temperature is achieved, advances the curved electrodes slowly to full deployment while maintaining the target temperature. When the electrodes are fully deployed, the program maintains the target temperature by regulating the wattage. As the tissue begins to desiccate, the amount of power needed to maintain the target temperature decreases. The company recommends that the target temperature be maintained for 8–12 min for the smaller electrode and 25 min for the larger electrode. After the ablation cycle is completed, a temperature reading from the extended electrodes in excess of 50°C at 1 min is reported to indicate a satisfactory ablation [34].

Another radiofrequency ablation device (LeVeen Needle Electrode; Radiotherapeutics) has retractable curved electrodes and an insulated 14-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella [37] (Fig. 3B). The electrodes are manufactured in different lengths (2- to 3.5-cm umbrella diameter), with most users choosing the 3.5-cm device. The alternating electric current generator is 100 W operated at 480 kHz. Two ground pads are used with the device; both are placed on the patient's thighs. In application, the tip of the radiofrequency needle is advanced to the target tissue and the curved electrodes are deployed to full extension. The generator is switched on and immediately set to 30 W. Every 60 sec the wattage is increased by 10 until peak power (90 W) is attained. The device is maintained at peak power for 15 min or until it "impedes out" (i.e., a rapid rise in impedance stops current flow and the ablation). If the device impedes out, it is turned off for 30 sec and then restarted at 70% of the maximum power attained at the time the generator impeded out. The application continues until the generator once again impedes out or for 15 min. If the device did not impede out during the first cycle, it is switched off for 30 sec and then restarted at maximum power and run until it impedes out or 15 min has elapsed. The Radiotherapeutics ablation algorithm is based on tissue impedance rather than tissue temperature. The power settings are increased slowly to minimize early tissue desiccation and charring. The impedance of the tissue increases as the tissue desiccates. It is believed that an ablation is successful if the device impedes out.

A third manufacturer has taken an entirely different approach to needle electrode design. They use an insulated hollow 17-gauge needle with a exposed needle tip of variable length (2–3 cm) (Cool-Tip radiofrequency electrode; Radionics). The tip of the needle is closed and contains a thermocouple for recording the temperature of the adjacent tissue. The shaft of the needle has two internal channels to allow the needle to be perfused with chilled water. Two groups of investigators have shown that the cooled needle produces a larger ablation than does a similar non-perfused needle [38, 39]. Conceptually, the cooling is believed to prevent desiccation and charring around the needle tip; thus, ionic agitation, frictional heat, and the size of the thermal injury produced are maximized. In an attempt to further increase the size of the ablation, the company placed three of the cooled needles in a parallel triangular cluster with a common hub (Fig. 3C). Goldberg et al. [40] tested this device and found that it produces a significantly larger ablation than does a single cooled needle.

Fig. 4.—Photograph shows clustered cooled-tip needles placed percutaneously into liver of patient using thimble guide (*arrow*) that keeps needles in correct orientation during placement.

The generator provided with the cooled-tip radiofrequency needles is the most powerful of the three commercially available generators. It has a peak power output of 200 W and is operated at 480 kHz. In clinical application, four grounding pads are placed on the patient's thighs. The tip of the single or cluster electrode is advanced to the desired location in the tissue to be treated. To maintain the correct spacing and triangular configuration of the cluster needle, a guidance thimble is used (Fig. 4). The single or cluster electrode needles are connected both to the generator and to a perfusion pump. The pump is switched on and sterile chilled water is circulated through the needle. To begin the ablation, an automated program gradually increases the power for 1 min to a peak of 200 W and maintains the power at that level until the impedance rises 20 Ω over the starting level. The power is then reduced automatically to 10 W for 15 sec and then returned to maximal power until the impedance increases again. If the power cannot be maintained for at least 10 sec without a rise in the impedance, the power is reduced for subsequent cycles to minimize elevations in impedance. Successive cycles are continued for a total ablation time of 12 min. Successful ablations usually increase the temperature of the ablated tissue to between 60° and 80°C.

Clinical Application

The clinical application of radiofrequency ablation of hepatic tumors usually includes these steps: preoperative evaluation; choice of approach: percutaneous, laparoscopy, or laparotomy; anesthesia and medications; needle placement and treatment strategy; and follow-up. The following represents a summary of the practice in our programs, but the practice may vary from institution to institution.

Preoperative Evaluation

The preoperative evaluation begins with a review of the pertinent imaging studies. Good-quality abdominal CT or MR imaging is the fundamental imaging examination on which the candidacy of a patient for radiofrequency ablation is based. These preoperative imaging studies are used to determine the number and size of tumors and their relationship to surrounding structures such as blood vessels, bile ducts, gallbladder, diaphragm, and bowel. Patients are considered potential candidates if they have fewer than five tumors, each less than 5 cm in diameter, and no evidence of extrahepatic tumor [6, 40–42]. In practice, patients with more than two tumors approaching 5 cm are poor candidates because of the sheer bulk of their tumor burden and the difficulty in completely ablating tumors of such size. By far the most common liver tumors that have been treated with radiofrequency ablation are HCC tumors and colon metastases. In addition, we have treated metastatic tumors from the pancreas, breast, stomach, and neck, as well as metastatic neuroendocrine tumors. In fact, any type of tumor isolated to the liver that meets our criteria can be treated by radiofrequency ablation. However, patients with potentially resectable tumors should be told that hepatic resection is the standard of care, and then referred for surgical evaluation.

Tumors close to the vital structures require careful consideration. We have found that ablation of tumors adjacent to the diaphragm, liver capsule, gallbladder, or main portal vessels will cause considerably more pain during and after the procedure than will ablation of tumors embedded in the hepatic parenchyma. Ablation of tumors adjacent to the diaphragm will cause transient right shoulder pain; however, if the diaphragm is directly ablated, as occurred in one of our patients, the pain can be severe and last for several months. The ablation of a tumor touching the wall of the gallbladder can lead to the development of cholecystitis, with symptoms lasting 2–3 weeks. Tumors adjacent to large vessels may be difficult to completely ablate because the blood flow in the vessel cools the tissue and may prevent adequate heating. Careful consideration needs to be given to the treatment of tumors lying in the bifurcation of the right and left portal veins or adjacent to either main portal trunk. Aside from the increased pain for the patient and diminished ability to effectively heat tumors in these locations, a very real risk exists of damaging the main right or left bile ducts. If the ducts are injured, the likely sequela is biliary obstruction. Finally, the treatment of subcapsular tumors abutting other abdominal viscera poses the risk of damage to those organs. Of greatest concern in this regard is the possibility of inducing thermal necrosis in an adjacent loop of bowel [43, 44].

If a patient is a good candidate for thermal ablation on the basis of his or her baseline abdominal CT or MR imaging, then a series of other tests is indicated before actual treatment. All patients should have histologic confirmation of a hepatic malignancy. CT of the chest should be performed to rule out the possibility of pulmonary metastases. A serum alkaline phosphatase level should be obtained; if the level is elevated without other just cause, or if the patient has new unexplained bone pain, technetium bone scanning should be performed to exclude the possibility of bone metastases. If the ablation procedure is to be performed using sonographic guidance, targeted hepatic sonography should be performed to determine if the lesions can be seen on sonography and to determine if a safe and adequate approach exists. Hematologic evaluation is necessary because the ablation needles are fairly large (14- to 17-gauge), and multiple percutaneous transhepatic needle punctures may be necessary to complete an ablation. Hematology tests should include a complete blood count, hemoglobin, hematocrit, prothrombin time, partial prothrombin time, and a platelet count. Coagulopathies should be corrected before an ablation session. A routine serum chemistry panel should be obtained to check electrolytes and liver function. A baseline serum α-fetoprotein and a carcinoembryonic antigen level should be obtained in patients with HCC and colorectal metastases, respectively. On the day before an ablation session, an ECG and blood type and match should be obtained in preparation for possible emergent surgery that may be necessary to treat a significant complication caused by the ablation. Contraindications to performing radiofrequency thermal ablation of hepatic tumors include excessive intrahepatic tumor burden, untreatable extrahepatic tumor, Child's class C cirrhosis, active infection, and inability to execute a proper consent.

Choice of Approach: Percutaneous, Laparoscopy, or Laparotomy

At our institutions, whenever possible radiofrequency ablation is performed percutaneously. Percutaneous treatment has several advantages over other approaches. The percutaneous approach is the least invasive, produces minimal morbidity, can be performed on an outpatient basis, requires only conscious sedation, is relatively inexpensive, and can be repeated as necessary to treat recurrent tumor. However, advocates of laparoscopic thermal ablation of hepatic tumors claim that the laparoscopic approach provides some distinct advantages over the percutaneous approach [45]. With the laparoscopic technique, the entire liver can be imaged with a high-frequency transducer placed directly on the surface of the liver. This technique allows the visualization (and treatment) of small tumors that cannot be detected using any other imaging technique (Fig. 5). Furthermore, with laparoscopy the extent of a tumor can be more accurately staged. The identification of previously undetected surface lesions or peritoneal implants may lead to the appropriate cancellation of the planned radiofrequency ablation [46]. This is important if the goal of the procedure is potential cure. However, Siperstein et al. [45] have also used laparoscopic radiofrequency for symptomatic relief of hormonally active liver metastasis. Additionally, advocates of a laparoscopic approach argue that they can perform a Pringle maneuver (temporary occlusion of the hepatic artery and portal vein) and thus enhance the size of a thermal ablation. The disadvantages of a laparoscopic approach include the added invasiveness of the procedure, with the associated complications and added costs, and the technical difficulties of the procedure. In particular, the placement of the needle electrode can be problematic. Unlike the percutaneous technique in which the sonographic probe and radiofrequency needle can be moved to any position over the right upper quadrant to achieve the best angle of approach to treat a tumor, the laparoscopic technique is hampered by limited access through the existing laparoscopic ports. Furthermore, no needle guides are currently available that can be attached to the laparoscopic sonographic transducers, and the radiofrequency needles cannot be placed parallel to the transducers. Most commonly, the needles are placed either perpendicular or oblique to the sonographic transducers. The manipulation of the needle from these angles is technically challenging and is not easily mastered.

Other investigators have published their experiences with radiofrequency ablation performed via open surgical treatment [42]. Disadvantages of this technique include the associated morbidity and mortality of an open procedure and general anesthetic, the added expense of the procedure and associated recovery time, and the fact that the technique is typically a one-shot therapy. Some of the advantages of the technique are the same as for the laparoscopic approach—namely, the ability to scan the whole liver with high-frequency transducers and to accurately stage the extent of the tumor [47] (Fig. 5). Additionally, the open approach allows a great deal of freedom in placing the sonographic transducer and radiofrequency needle. The radiofrequency needle can be placed through a needle guide that is attached to the transducer, or it can be placed using a freehand technique. Difficult lesions adjacent to the diaphragm, bowel, or gallbladder may be treated easily with the open technique. These organs can be removed or isolated from the mobilized liver to prevent damage during the ablation of a tumor (Fig. 6). Finally, the blood supply to the liver may be temporarily stopped during radiofrequency ablation. A Pringle maneuver, which causes temporary occlusion of the portal vein and hepatic artery, decreases blood supply to both the targeted tumor and the adja-

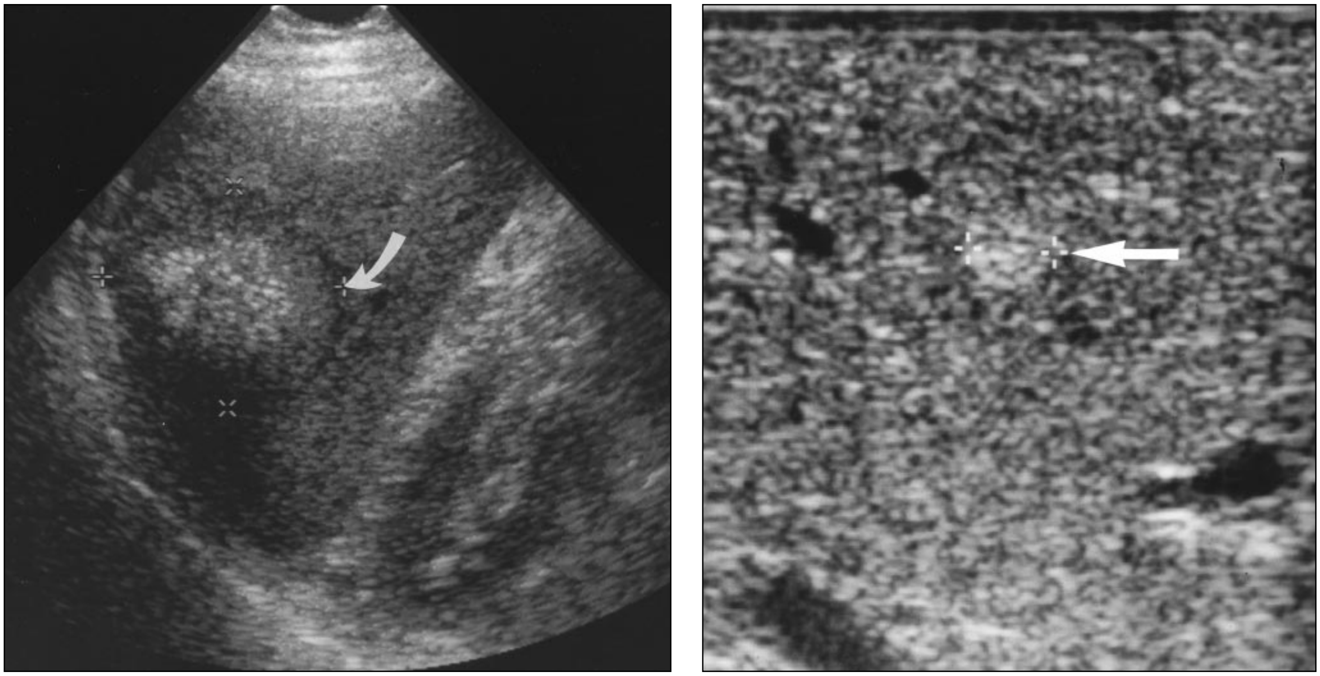


Fig. 5.—62-year-old man with metastases to liver from colon cancer.
A, Both preoperative CT scan (not shown) and sonogram show only a single large metastasis in right lobe of liver (*arrow*) that was scheduled for operative resection.
B, At surgery, intraoperative sonography revealed several 4-mm metastases scattered throughout liver (*arrow*). Resection was not performed.

Fig. 6.—58-year-old woman with multiple metastases to liver from colon cancer. Photograph shows intraoperative placement of radiofrequency needle into liver (*arrow*).

cent hepatic parenchyma. The result is a larger thermal injury than is possible with normal blood flow [42].

Anesthesia and Medications

General anesthesia is required for laparoscopy or open surgical treatment. However, conscious sedation is usually sufficient for a percutaneous approach. At our institutions, we use the services of the anesthesiology department for percutaneous radiofrequency ablation. On the morning of the procedure, an anesthesiologist or nurse–anesthetist evaluates the patient for suitability for anesthesia. The medical history is reviewed, the laboratory test results are checked, and the ECG is interpreted. If deep conscious sedation is not contraindicated, the patient is prepared for the procedure. A peripheral IV line is started, and the patient is monitored to track blood pressure, pulse, respiratory rate, and peripheral oxygenation. The site of the planned percutaneous puncture with the radiofrequency electrode is anesthetized with 1% lidocaine hydrochloride (Xylocaine; AstraZeneca, Wilmington, DE). The anesthesiologist or nurse–anesthetist administers an IV sedative. This can be a combination of the traditional drugs fentanyl (fentanyl citrate injection; El-

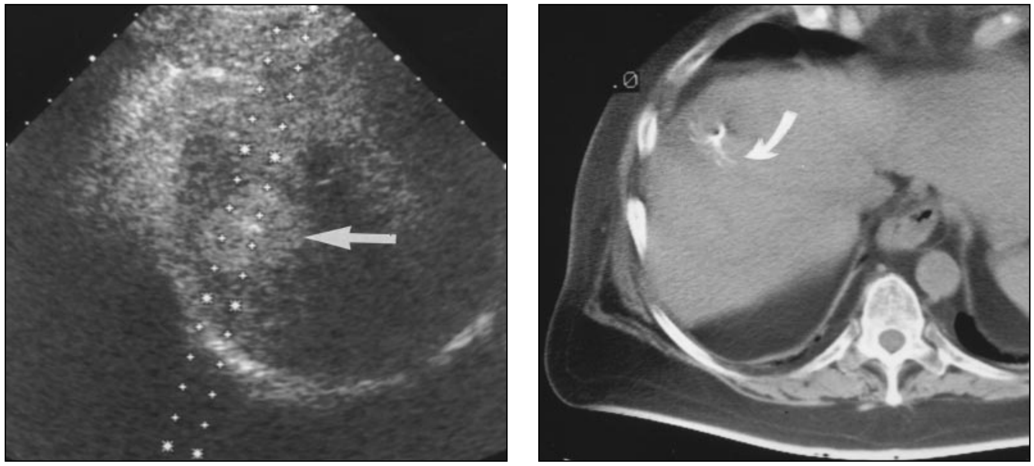


Fig. 7.—76-year-old man with colon cancer and metastases to liver.
A, Sonogram shows guide for placement of needle into isolated hyperechoic colon metastasis (*arrow*).
B, CT scan shows deployed prongs (*arrow*) in lesion.

kins-Sinn, Cherry Hill, NJ or Baxter Healthcare, Deerfield, IL) and midazolam hydrochloride (Versed; Roche Laboratories, Nutley, NJ) that are used for many percutaneous intervention procedures, or, as we prefer, the more potent and short-acting agents propofol (Diprivan; AstraZeneca) or remifentanil hydrochloride (Ultiva; Glaxo Wellcome, Research Triangle Park, NC) [48]. These newer agents are administered by a constant drip infusion. The major advantages of these agents are the deep level of anesthesia that can be obtained and their short duration of action. If the cooperation of a patient is needed to achieve satisfactory placement of the needle electrode, the patient is easily aroused within minutes of stopping the infusion of the agent. Likewise, if a patient has respiratory suppression due to oversedation, he or she is quickly recovered by stopping the infusion and ventilating the patient using a bouche bag for a few minutes.

At the end of a radiofrequency ablation session, the patient can experience severe nausea and pain with the decrease of the sedative. Because of the frequency of these two side effects, we established a routine protocol to treat these problems. Immediately after the conclusion of the procedure and before transporting the patient to the recovery area, we administer both an antiemetic and morphine IV. After the patient is transferred to the recovery area, combined oral hydrocodone bitartrate and acetaminophen tablets (Vicodin; Knoll Laboratories, Mount Olive, NJ), are given to control subacute pain. This medication regime is usually sufficient to keep the patient comfortable for 3–4 hr, at which time the side effects of the ablation have usually diminished to a tolerable level. Fewer than 50% of patients require additional analgesics during the immediate recovery period, and even fewer require analgesics after discharge. If pain persists, the patient is typically given a 3-day prescription for combined oral hydrocodone bitartrate and acetaminophen tablets (Vicodin).

Occasionally, patients may be unable to tolerate percutaneous radiofrequency ablation with just conscious sedation. This may be true for patients with cancer with chronic pain who have been taking routine analgesics, patients with a history of alcohol or drug abuse, or patients with a low tolerance for pain. General anesthesia may be indicated for these patients. Likewise, general anesthesia may be preferred if an ablation is going to be extensive and the procedure is expected to last 3 hr or longer.

Although there has been no trial to validate the use of prophylactic antibiotics, such use has become routine at some institutions. One of us routinely administers IV cephalosporin just before treatment and continues with oral cephalosporin for 5 days after treatment.

Needle Placement and Treatment Strategy

Radiofrequency needles can be placed under sonographic, CT, or MR guidance using a percutaneous approach. The needles are usually well revealed by each technique (Fig. 7). However, without question sonography is the most common method used to guide percutaneous radiofrequency tumor ablation [49–59]. Its advantages over CT and MR are its real-time capabilities, vascular visualization, availability, speed, and low cost.

The primary disadvantage of sonography is a limited ability to assess the effectiveness of an ablation. Although the ablation process produces a dense echogenic response, the size of the echogenic response provides only a rough estimation of the size of the ablation [60] (Figs. 8 and 9). Furthermore, the echogenic response obscures the margins of the tumor being treated, particularly the posterior margins (Figs. 8 and 9). Both CT and MR imaging have been reported to be more reliable in this regard [60, 61].

Regardless of the method used to guide radiofrequency tumor ablation, strategy must be established before placement of the needle. The objective in treating a tumor must be to kill the entire tumor as well as a tumor-free margin of normal liver. The surgery literature has clearly shown that an adequate tumor-free margin is mandatory to prevent local recurrence of a tumor after hepatic resection. In one of the latest publications on the subject, an adequate tumor-free margin was defined as being preferably 2

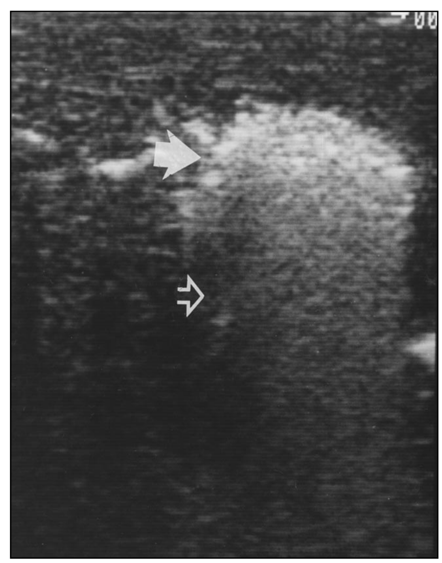


Fig. 8.—Sonographic artifact seen in swine liver. Radiofrequency ablation causes formation of microbubbles in liver. Margin near ablation becomes echogenic (*solid arrow*) and produces distal acoustic shadowing (*open arrow*). Echogenic response prevents visualization of deeper anatomy.

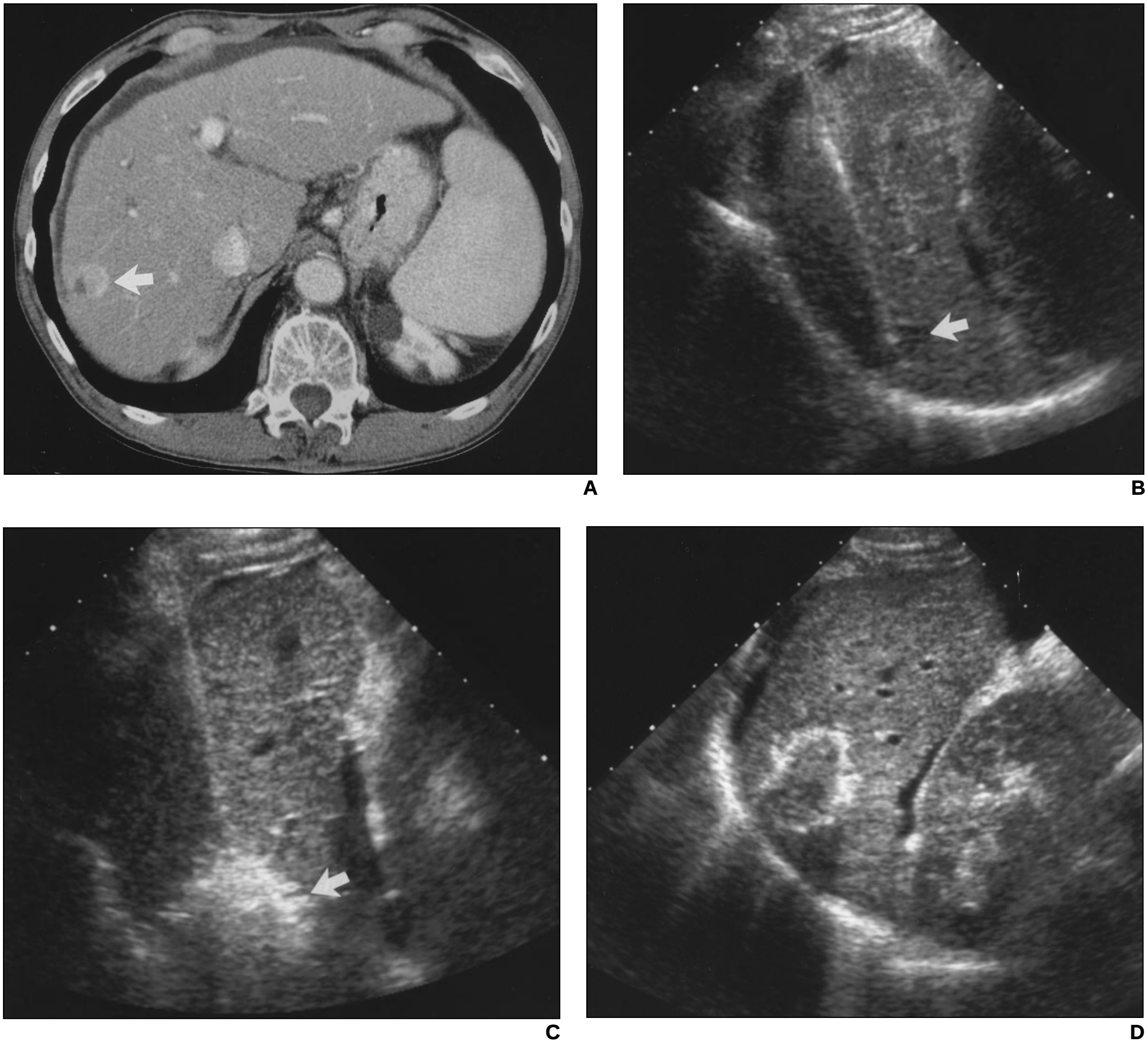


Fig. 9.—64-year-old man with hepatitis C and hepatocellular carcinoma (HCC).
A, CT scan shows 1.5-cm enhancing lesion (*arrow*) that was biopsy-proven HCC. Patient also had small amount of ascitic fluid surrounding liver.
B, Cooled-tip radiofrequency needle placed via freehand technique directly into hypoechoic HCC lesion (*arrow*).
C, Immediately after one radiofrequency treatment, echogenic microbubbles are present in area of treatment (*arrow*).
D, Echogenic response has diminished after approximately 10 min, and well-demarcated lesion measuring 2.8 × 3.8 cm with hyperechoic rim is identified in location of HCC.

cm and no less than 1 cm of normal liver [62]. If the goal of radiofrequency ablation is to duplicate the success rate of hepatic resection, then in all likelihood the same requirements for a tumor-free margin will need to be followed.

Given that most radiofrequency ablation devices produce an approximate 3-cm ablation, the largest tumor that should be treated by a single ablation should be smaller than 2 cm in diameter (Fig. 10A). A 2-cm tumor treated with a 3-cm ablation yields at most a 5-mm tumor-free margin. If error in needle placement is factored in, the margin could be much less. Certainly, 3-cm tumors should not be treated by a single 3-cm ablation. To treat a larger tumor, multiple ablations need to be overlapped to build a composite thermal injury of sufficient size to kill the tumor and to provide the desired tumor-free margin. By strict geometric analysis, six overlapping spherical ablations are necessary to create an intact composite thermal sphere of the next magnitude (Fig. 10B). If six 3-cm thermal spheres are precisely overlapped, with four in the *x*–*y* plane and two along the *z*-axis, the largest intact composite thermal sphere that can be created is just 3.75 cm, or 1.25 times the diameter of a solitary sphere. Thus, the largest tumor

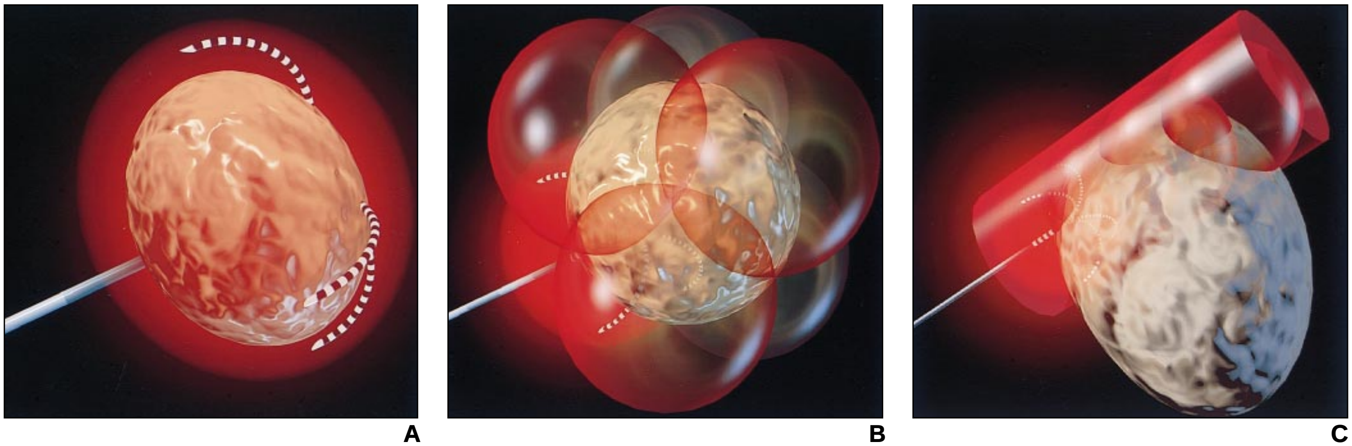


Fig. 10.—Artist's rendition of ablation schemes.
A, Solitary ablation completely envelops small tumor and circumferential rim of healthy liver.
B, Six optimally placed overlapping spheres produce composite spherical thermal injury with diameter equal to 1.25 times diameter of a single ablation sphere.
C, Overlapping thermal cylinders is effective way to treat large tumors. Each cylinder is created by overlapping serial ablations by 50% along a single needle path. Adjacent cylinders are overlapped by 50%.

that should be treated with six 3-cm overlapping ablations should be less than 3.25 cm in diameter. Larger tumors can be treated with radiofrequency ablation, but they require many more ablations or require adjuvant techniques to increase the size of an ablation. A strategy for treating large tumors consists of the creation of thermal cylinders [63] (Fig. 10C).

When performing multiple radiofrequency ablations using sonographic guidance, it is important to plan the order of ablations so that the deepest ablations are performed before the superficial ones (Figs. 8 and 9). This strategy minimizes the possibility that microbubbles might obscure visualization of the deeper portions of the tumor and thus prevent completion of the ablation session.

Follow-Up

Immediate evaluation can consist of sonography performed at the time of treatment. This may be helpful with HCC tumors that are vascular. However, it may not be helpful in metastatic disease. Solbiati et al. [58] found that use of contrast-enhanced sonography may help to detect residual tumor after radiofrequency treatment. This immediate feedback can be used for reapplication of radiofrequency in areas that are untreated.

Most institutions perform CT of the liver within a few hours of the ablation to gauge the completeness of the ablation and to look for any potential complications [61]. However, the accuracy of the completeness assessment on the immediate CT scan is often limited because of the presence of an ablation-induced hyperemic rim around the margin of the ablated tissue (Fig. 11). This hyperemia is difficult to distinguish from residual tumor. Fortunately, the hyperemia is usually resolved by 1 month after the ablation, and a more accurate assessment of the completeness of the ablation can be made at that time (Fig. 12). In some instances, CT is not performed immediately, but rather 1 month after ablation. If no evidence of residual tumor is seen on the CT scan 1-month after ablation, patients are usually followed up by repeated CT every 3 months. Each follow-up CT scan must be scrutinized for evidence of tumor recurrence in the liver, adjacent to and remote from the ablated site, and outside the liver. Typical sites of extrahepatic tumor recurrence in patients with HCC are the adrenal glands, lungs, bones, and regional lymph nodes along the porta hepatis, gastrohepatic ligament, celiac axis, and cardiophrenic sulcus. Patients with colorectal carcinoma tend to develop extrahepatic metastases at the primary tumor site, in the peritoneal cavity, and in the lungs. Because of the frequency of extrahepatic metastases in patients with colorectal carcinoma, we usually perform both abdominal and pelvic CT every 3 months and chest CT every 6 months.

The technique used to perform follow-up CT has a significant impact on the early detection of

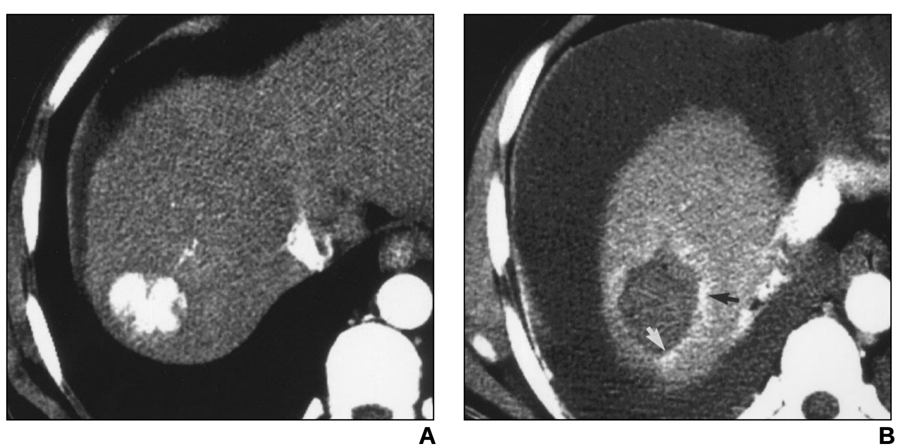


Fig. 11.—58-year-old man with hepatocellular carcinoma.
A, Arterial phase CT scan of dome of right lobe of liver before ablation shows untreated solitary hypervascular tumor.
B, Arterial phase CT scan immediately after ablation shows normal hyperemic rim (*arrows*) around ablated tumor. Hyperemic rim may prevent accurate assessment of completeness of ablation.

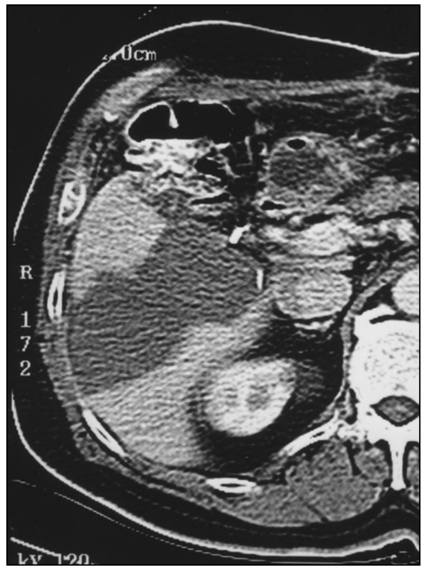


Fig. 12.—67-year-old man with two metastases from colon cancer.
A, CT scan shows two well-localized metastases (1, 2) in right lobe of liver.
B, Three-month follow-up CT scan after radiofrequency ablation shows complete ablation of tumors. Percutaneous radiofrequency approach was used for treatment of the more lateral lesion. However, because of overlying bowel and proximity to gallbladder, open radiofrequency ablation was used for the more medial lesion.

intrahepatic tumor recurrence. Most early recurrences in patients with HCC are detected only in the arterial phase of good-quality three-phase CT. Likewise, the subtle changes of local intrahepatic tumor recurrence in patients with colorectal metastases may be visualized only during a strong portal venous phase contrast-enhanced CT scan [56, 59]. We routinely perform three-phase CT in all patients with HCC and two-phase CT in patients with colorectal metastases. Additionally, we obtain repeated α-fetoprotein and carcinoembryonic antigen levels every 3 months in patients with HCC or colorectal hepatic metastases, respectively. We find the levels helpful in assessing subtle changes on the CT scans and in determining if additional evaluation is warranted. Changes in α-fetoprotein or carcinoembryonic antigen values must be assessed on an individual basis for each patient on the basis of their values before treatment and the normal levels used at each medical institution.

Several investigators prefer to use MR imaging to follow up their patients after radiofrequency ablation. One study claims that MR imaging is more sensitive than CT for the detection of early intrahepatic tumor recurrence [61]. The interpretation of MR imaging for tumor recurrence is based primarily on the premise that ablated tissue produces minimal signal on T-2 weighted sequences, whereas tumor produces high signal. Dynamic contrast enhancement of suspected tissue is further evidence of tumor recurrence.

Regardless of the technique used to follow up patients after ablation, the primary objective is to detect tumor recurrence as soon as possible so the appropriate therapy can be instituted. If recurrence is limited to the liver, reablation may be effective (Fig. 13). One of the potential benefits of percutaneous radiofrequency ablation over other more invasive forms of treatment, such as surgery, intraoperative cryotherapy, or intraoperative radiofrequency treatment, is that it can be repeated as often as necessary to treat intrahepatic tumor recurrence. In our practices, we have treated individual patients with local tumor recurrences as many as seven times during a 3-year period. Each time the tumor appeared completely destroyed, and the patient had 3–6 months of asymptomatic health between treatments. If a patient develops extrahepatic tumor or extensive intrahepatic tumor, alternative therapies such as systemic chemotherapy or hepatic chemoembolization should be considered.

Results

Long-term results of radiofrequency ablation of either primary or secondary liver neoplasms are scant because this is a fairly new technique. The goal of most of the early reported ablations is complete tumor necrosis and possibly a cure. However, some published results are available on the short-term follow-up of patients treated with radiofrequency ablation. These results are presented by tumor type and method of treatment. Many results are with prototype devices and do not reflect current refined technology. Furthermore, many early results were with conventional needles similar to the original single noninsulated needles described by McGahan et al. [31] and Rossi et al. [32] (Figs. 1 and 2).

Percutaneous Treatment of HCC

At least four series document the results of percutaneous radiofrequency treatment of HCC. The original study of Rossi et al. [56] used a conventional needle that was insulated to the distal tip. Rossi et al. [55] conducted a later series using an umbrella-type needle (Fig. 3). Livraghi et al. [53] and Francica and Marone [49] published one study each in which they used a cooled needle device. In all studies, near-complete necrosis of 90% of the treated tumors had occurred at 6 months. These results were for tumors smaller than 3 cm. However, for the study by Livraghi et al. [53] with tumors larger than 3 cm (mean, 5.4 cm,) the complete necrosis rate was only 47.6%. Complete necrosis was 71% for noninfiltrating tumors that were 3.1–5.0 cm, and only 25% for noninfiltrating tumors greater than 5 cm in diameter. Also, the rate of disease-free survival at follow-up was lower; the first study of Rossi et al. [56] found 64% at 23 months and 71% at 12 months in a subsequent study [55]. Francica and Marone reported 67% of patients to be disease-free at 15 months. Thus, with HCC, although there is a high rate of complete necrosis of ablated tumors, about a third of the patients develop recurrent tumor. Kainuma et al. [50] found it useful to monitor and perform reablation in these patients. These results are summarized in Table 1.

Percutaneous Treatment of Metastatic Liver Tumors

Radiofrequency ablation has also been used to treat tumors that have metastasized to the liver. The results of five series are summarized in Table 2. The original study by

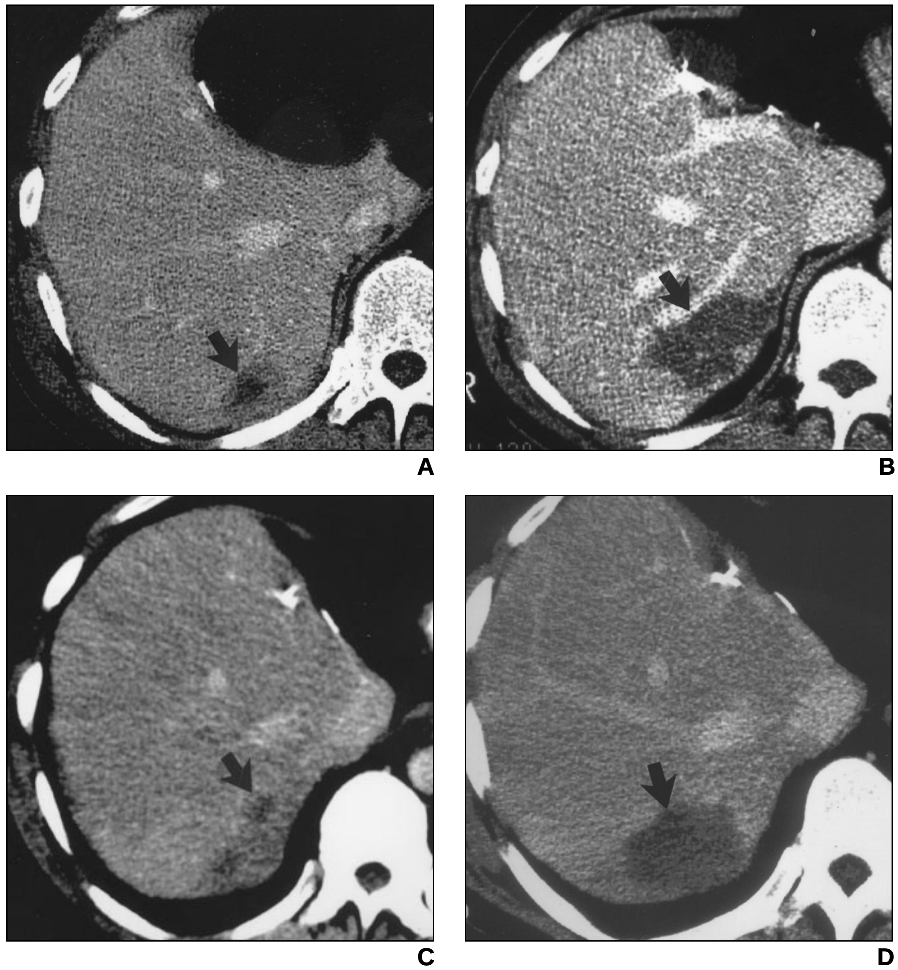


Fig. 13.—46-year-old man with metastatic colon cancer.
A, CT scan before treatment shows 3-cm metastasis (*arrow*) in posterior right lobe of liver.
B, CT scan immediately after ablation shows thermal injury (*arrow*) at site of treated tumor and no definite evidence of residual tumor.
C, Follow-up CT scan at 3 months after ablation shows recurrent tumor (*arrow*) at margin of ablated tumor.
D, CT scan immediately after reablation shows enlarged thermal injury (*arrow*) at site of treated tumor recurrence and no definite evidence of residual tumor.

TABLE 1 Percutaneous Radiofrequency Ablation of Hepatocellular Carcinoma

Researchers	No. of Patients	Needle Type	Mean Follow-Up	Percentage of Success	
				Complete Necrosis	Tumor-Free
Rossi et al. [56]	39	Conventional	23 months	95%	64%
Rossi et al. [55]	23	Umbrella	12 months	91%	71%
Livraghi et al. [53]	42	Cooled-tip	6 months	47.6%	Not stated
Francica and Marone [49]	15	Cooled-tip	15 months	90%	67%

TABLE 2 Percutaneous Radiofrequency Ablation of Metastatic Liver Tumors

Researchers	No. of Patients	Needle Type	Mean Follow-Up	Percentage of Success	
				Complete Necrosis	Tumor-Free
Rossi et al. [56]	11	Conventional	11 months	78%	11%
Solbiati et al. [57]	16	Conventional[a]	18.1 months	58%	50%
Solbiati et al. [59]	29	Cooled-tip	10.3 months	66%	76%, 6 mo. 50%. 9 mo. 33%, 18 mo.
Livraghi et al. [54]	14	Conventional[a]	6 months	52%	Not stated
Rossi et al. [55]	14	Umbrella	10 months	93%	18%
Lencioni et al. [51]	29	Cooled-tip	6.5 months	88%	52%

[a]These two studies also used saline infusion before radiofrequency was applied in hopes of increasing area of tumor necrosis.

Rossi et al. [56] used a conventional needle that was not insulated to the distal tip. Solbiati et al. [57] and Livraghi et al. [54] conducted series with a conventional needle not insulated at the tip combined with saline infusion. Ten to fifteen milliliters of saline was introduced into the tumor before radiofrequency was applied in hopes of increasing the area of tumor necrosis. Rossi et al. [55] performed a series using an umbrella-type needle. Solbiati et al. [59] and Lencioni et al. [51] reported results using a cooled-tip needle in 1997. The rate of complete necrosis in these studies ranged from 52% to 93%. However, few patients remained disease-free; the rates ranged from as low as 11% at 11 months in the series of Rossi et al. [56] to as high as 33% at 18 months in the series of Solbiati et al. [59]. The marked discrepancy between the complete tumor necrosis rate and the percentage of patients who remain disease-free is in part due to the biology of metastatic liver disease and our limited ability to detect the full hepatic tumor burden. Most patients with a few 2- to 3-cm liver metastases also have numerous subcentimeter or microscopic tumors that are not detectable with current imaging technology.

Laparoscopic Results

Siperstein et al. [45] described results of laparoscopic radiofrequency ablation of 13 neuroendocrine tumors in the livers of six patients. The tumors ranged in size from 1 to 7 cm. Follow-up CT showed complete necrosis in 11 of 11 lesions in four patients at 3 months. All patients showed improvement in their symptoms after radiofrequency ablation. Cuschieri et al. [46] used laparoscopic sonography to guide treatment of 10 patients, two with hepatoma and eight with metastases. No complications occurred. Patients were discharged within 2 days of intervention. This compares with the usual same-day discharge after percutaneous techniques, but it is a shorter hospitalization than with open techniques. At follow-up ranging from 6 to 20 months, one patient had died of progressive disease, one patient had further metastases, and eight were disease-free.

Intraoperative Results

Elias et al. [64] described the use of combined liver resection and radiofrequency ablation to treat seven patients with liver metastasis. This is an interesting approach in that these were liver metastases that were thought to be unresectable by previous approaches. Radiofrequency was used to ablate those lesions that could not be surgically resected. The Pringle maneuver was performed in all patients, and all seven patients were disease-free up to 10-months of follow-up. Jiao et al. [65] reported a series of eight patients with HCC and 27 patients with metastases in which 30 of the 35 patients underwent intraoperative radiofrequency ablation using the Pringle maneuver. Thirteen of the 30 patients had combined radiofrequency ablation and a surgical resection. At approximately 10 months of follow-up, 24 of the 35 patients were found to have stable disease.

To our knowledge, the largest series to date of intraoperative radiofrequency ablation of hepatic tumors is by Curley et al. [42]. In that study, radiofrequency ablation was used to treat 169 tumors in 123 patients. Of the 123 patients, 92 (75%) were treated with laparotomy and 31 (25%) were treated percutaneously. Forty-eight (39%) patients had HCC and 75 patients (61%) had hepatic metastases. All tumors were treated with an umbrella-type electrode, and a Pringle maneuver was used on all intraoperative cases. Overall, complete necrosis had occurred in 98% of the ablated tumors at a median follow-up of 15 months, and 72% of the patients remained tumor-free during the same time. In the series of Curley et al., the size of the tumors treated by percutaneous radiofrequency (2.4 cm diameter) was less than the size of tumors treated intraoperatively (3.8 cm). Those authors did not analyze the outcome difference in the percutaneous and the intraoperative groups. However, only three (1.8%) of 169 treated lesions had local recurrence.

Complications

As stated in the section on anesthesia, almost all patients experience pain and nausea during and immediately after ablation. These side effects are usually controllable and transient. Nausea rarely persists longer than 2–3 hr after the procedure. Approximately 25% of patients will have pain that requires continued medication at the time of discharge [66]. In 98% of patients, pain will be gone within 1 week after the procedure [66].

As reported with other types of tumor ablation procedures (chemoembolization and cryoablation), a percentage of patients (in our experience, about 25%) will develop a delayed syndrome after ablation. The frequency, severity, and time to onset appear to be directly related to the amount of tissue ablated. The typical presentation consists of flulike symptoms (low-grade fever [up to 38.8°C] accompanied by general malaise) that begin 3–5 days after the ablation and persist for approximately 5 days. With large-volume ablations we have seen the syndrome begin almost immediately, cause fever as high as 39.4°C, produce severe lethargy, and last for as long as 2–3 weeks. Several patients have reported night sweats. Appropriate treatment of the syndrome is primarily supportive. We inform patients that they may develop the syndrome after their ablation. Their fever is treated with oral acetaminophen. They are instructed to call us if their fever exceeds 38.8°C or lasts longer than 5 days. If their fever exceeds 38.8°C, a blood sample is drawn and cultured to determine if the patient is septic [66].

Radiofrequency ablation of the liver is considered safe, with an extremely low major complication rate observed by multiple groups. More serious complications have been reported in the literature. Rossi et al. [56] described capsular necrosis, and Solbiati et al. [57, 59] reported intraperitoneal hemorrhage that did not require transfusion. Solbiati et al. [57] also reported one case of fairly severe hypotension that persisted for 3–4 hr after the procedure. Livraghi et al. [53, 54] reported complications in their patients that consisted of two pleural effusions, a perihepatic hematoma, a hemothorax that required surgical repair, self-limited intraperitoneal bleeding, and hemobilia and cholecystitis in one patient each. We have experienced several complications, including three cases of intrahepatic arterial bleeding, with one requiring selective arterial embolization; one burn of the diaphragm that caused pain for 3 months; one 3-cm hepatic abscess that was treated with oral antibiotics; five 1- to 3-cm first- or second-degree burns along the edge of the grounding pads; and three instances of tumor seeding along the needle tract. Additionally, Lees and Gilliams [67] reported hepatic abscesses and a thermal burn of the transverse colon. Livraghi et al. [52] reported a single death (0.8% rate) in their series. This was the result of a *Staphylococcus aureus* infection that developed 3 days after the procedure. Because of this complication, those authors administer antibiotic prophylaxis of 1000 mg of ceftriaxone sodium (Rocephin; Roche Laboratories) to all patients.

Few reports mention complications occurring after radiofrequency ablation performed via a laparotomy. Of those that have been reported, most consist of fever and pain. Other reported complications include a perihepatic abscess and an intrahepatic hemorrhage that required arterial embolization [42].

Discussion and Future Strategies

Radiofrequency ablation of the liver has been a promising technique. The overall success of radiofrequency ablation of liver tumors has been variable. Differences in reported success rates are no doubt multifactorial and include patient selection, operator experience, and the equipment used. We have learned a great deal in the exploratory phase of radiofrequency ablation of liver tumors. Currently, tumor burden may exceed technologic ability to completely ablate the tumor, and our ability to affect long-term patient survival is thus limited. Much of the future success of radiofrequency ablation will be based on technologic advances in radiofrequency electrode and generator design, and better understanding of methods to ensure adequacy of tumor necrosis. Certainly, compared with the original single noninsulated radiofrequency needle, newer needle designs and more powerful radiofrequency generators have allowed increased tissue necrosis. Further refinements are being investigated. For instance, Goldberg et al. [68] have shown that pulsed radiofrequency current (as compared with continuous application of current) can increase coagulated necrosis. Continued refinements in technology will likely yield larger and more consistent ablation.

Understanding tissue response to radiofrequency electrocautery application is also important. For example, the complete ablation rate of HCC using percutaneous methods is about 90% [49, 53, 55, 56]. The success rate for metastatic liver disease is much lower [54, 57, 59]. The decreased success of radiofrequency ablation of metastatic liver disease compared with HCC is multifactorial. The reasons include, among other things, inadequate tumor treatment and different tissue responses to radiofrequency treatment. It has been theorized that in HCC tumor necrosis is more uniform and complete, with the margin of ablation being limited by the tumor capsule. Fortunately, tumor invasion beyond the tumor capsule is uncommon; consequently, the chance of local tumor recurrence because of missed tumor is uncommon. However, the margin of metastatic tumors is different, and local invasion of the surrounding hepatic parenchyma is common. Thus, a more aggressive approach to the ablation of metastatic tumor is required to minimize local tumor recurrence.

The need to create a surgical margin to prevent local tumor recurrence restricts successful treatment to smaller lesions. However, advances will probably allow larger volumes of tissue necrosis with radiofrequency ablation. Creation of a larger volume of tissue coagulation will ensure successful ablation of small tumors and allow us to treat patients with larger tumors who may have previously been excluded from consideration for radiofrequency therapy. Furthermore, successful ablation of all tumors may be improved in the future using MR imaging guidance or sonographic contrast agents to determine if tumor margins have been adequately treated [58, 61].

Future strategies may be aimed at changing the tumor response to radiofrequency treatment. For instance, radiofrequency tumor ablation can be increased by stopping blood flow to the tumor. Because flowing blood cools the radiofrequency thermal process, stopping the flow can potentiate an ablation. This can be performed using several methods. The Pringle maneuver can be performed intraoperatively by temporary occlusion of the portal vein and the hepatic artery. This maneuver decreases blood supply to the entire liver and the tumor, thus increasing the size of an ablation. Patterson et al. [69] showed in vivo increased liver necrosis from 6.5 cm^3 with radiofrequency ablation compared with 35.0 cm^3 with radiofrequency ablation and the Pringle maneuver. This process has been successfully used intraoperatively to treat both HCC and liver metastases [42]. In HCC the main supply to the tumor is via the hepatic artery. If the hepatic artery is embolized before radiofrequency treatment, a larger volume of tissue necrosis will occur [70–73]. Most research to date has combined intraarterial chemoembolization with percutaneous injection of ethanol [70–72]. However, Buscarini et al. [71] and Rossi et al. [73] used chemoembolization or hepatic arterial occlusion in combination with percutaneous radiofrequency ablation for the treatment of HCC. Kainuma et al. [74] used combined intraarterial infusion chemotherapy and radiofrequency thermal ablation to treat colon cancer. Thus, approaches directed at combining radiofrequency ablation with infusion chemotherapy, chemoembolization, or temporary occlusion of the tumor blood supply may improve complete tumor necrosis of small tumors and aid in the treatment of large tumors.

Summary

Radiofrequency thermal ablation of primary and secondary tumors can be performed safely using percutaneous, laparoscopic, or open surgical techniques. Technologic advances in radiofrequency equipment, methods of altering tissue response to radiofrequency treatment, and combined therapies will likely yield an improvement in the complete ablation rate of small tumors and make the treatment of larger tumors a clinically viable treatment alternative.

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