Percutaneous Radiofrequency Ablation of Hepatic Colorectal Metastases

Technique, Indications, Results, and New Promises

Riccardo Lencioni, MD, Laura Crocetti, MD, Dania Cioni, MD, Clotilde Dellapina, MD, and Carlo Bartolozzi, MD

Abstract: Surgical resection is the standard of care for colorectal metastases isolated to the liver. However, only 10–25% of the patients are eligible for resection because of extent and location of the disease in the liver or concurrent medical conditions. Image-guided radiofrequency (RF) ablation is a minimally invasive technique that is emerging as a viable alternate treatment of nonsurgical patients with limited hepatic metastatic disease. Several series have shown that RF ablation can result in complete tumor eradication in properly selected candidates and have provided indirect evidence that the treatment improves survival. In a recent multicenter trial including 423 patients, overall survival of RF-ablation treated patients reached 47% at 3 years and 24% at 5 years. RF ablation technology is undergoing continuous improvement, and its clinical application has been successfully expanded to the treatment of colorectal metastases to the lung. Randomized trials comparing RF ablation with either surgical resection or chemotherapy protocols, however, are still missing. In this article, we review technique, indications, clinical results, and future prospects of RF ablation in the therapeutic management of metastatic colorectal cancer patients.

Key Words: colorectal cancer, liver metastases, radiofrequency ablation

(*Invest Radiol* 2004;39: 000–000)

Metastases are a frequent event in colorectal cancer natural history. Twenty percent of patients with colorectal cancer have evidence of liver metastases at diagnosis, and 50% will develop metachronous metastatic disease.[1] Of the patients who will develop liver metastases, nearly 25% will have disease isolated to the liver.[1]

Surgery is established as the standard of care for hepatic colorectal metastases. The 5-year overall survival rate after hepatic resection ranges from 27% to 58%, with the higher figures recently obtained as a result of improvement in patient selection, perioperative and postoperative care, multidisciplinary treatment, and an appropriately aggressive approach to safe hepatic resection.[2–6] Nevertheless, only 10–25% of patients with colorectal metastases isolated to the liver are eligible for surgical resection because of extent and location of the disease or concurrent medical conditions.[7] Unfortunately, conventional treatment of nonoperable or nonresectable patients with systemic or intra-arterial chemotherapy protocols is not entirely satisfactory in terms of survival outcomes.[8]

Attention has been focused on investigating the effectiveness of minimally invasive techniques for tumor ablation in treating patients with hepatic metastases who were not surgical candidates. The first technique used for local ablation therapy for liver metastases has been percutaneous ethanol injection.[9] However, as opposed to hepatocellular carcinoma, alcohol diffusion within metastatic lesions was shown to be uneven, resulting in largely incomplete ablation with necrotic areas and viable tissue irregularly mixed.[9] Therefore, other local ablation methods that seek to achieve more effective tumor necrosis, including cryotherapy, laser, microwave, and radiofrequency (RF) ablation, have been developed and tested clinically during the past few years.[10–15]

RF ablation has emerged as the most powerful technique for tumor destruction and is nowadays established as the primary ablative modality at most institutions.[16–18] In fact, recent improvements in RF technology have permitted the creation of in vivo spherical ablation zones exceeding 5 cm in diameter with a single probe insertion, thus substantially increasing the potential of the technique in clinical application.[19,20] In this article, we review technique, indications, and results of RF ablation in the treatment of colorectal

Received February 2, 2004 and accepted for publication, after revision, July 11, 2004.

From the Division of Diagnostic and Interventional Radiology, Department of Oncology, Transplants, and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy.

Reprints: Prof. Dr. Riccardo Lencioni, Division of Diagnostic and Interventional Radiology, University of Pisa, Via Roma 67, IT-56126 Pisa, Italy. E-mail: lencioni@do.med.unipi.it

ISSN: 0020-9996/04/3911-0001

hepatic metastases. Future prospects of the technique are also discussed, including its emerging role in treating colorectal metastases to the lung.

TECHNIQUE

The goal of RF ablation is to induce thermal injury to the tissue through electromagnetic energy deposition. In monopolar RF ablation, the patient is part of a closed-loop circuit that includes a RF generator, an electrode needle, and a large dispersive electrode (ground pads). An alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode because the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode.[21,22]

The thermal damage caused by RF heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50–55°C for 4–6 minutes produces irreversible cellular damage. At temperatures between 60°C and 100°C, near-immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At 110°C, tissue vaporizes and carbonizes. For adequate destruction of tumor tissue, the entire target volume must be subjected to cytotoxic temperatures.[21,22]

In the early experiences with RF treatment, a major limitation the technique was the small volume of ablation created by conventional monopolar electrodes. These devices were capable of producing cylindrical ablation zones not greater than 1.6 cm in the short axis.[23] Therefore, multiple electrode insertions were necessary to treat of all but the smallest lesions. Subsequently, several strategies for increasing the ablation zone achieved with RF treatment have been used. A major progress was achieved with the introduction of modified electrode needles, including internally cooled electrodes and multitined expandable electrodes with multiple retractable prongs on the tip.[13,24] These techniques enabled a substantial and reproducible enlargement of the ablation zone produced with a single needle insertion, and prompted the start of clinical application of RF ablation.

Internally cooled electrodes (Radionics, Tyco Healthcare Group, Burlington, MA) consist of dual-lumen electrodes with an exposed active tip of variable length. Internal cooling is obtained by continuous perfusion with chilled saline and is aimed at preventing overheating of tissues nearest to the electrode to minimize carbonization and gas formation around the tip. The tip contains a thermocouple for recording the temperature of the adjacent tissue. To increase the size of the ablation, the company placed 3 of the cooled electrodes in a parallel triangular cluster with a common hub. This device produces a significantly larger ablation than does a single cooled electrode.[10] Pulsing of RF energy (ie, alternation of very high RF current for several seconds followed by minimal RF deposition for a defined period) also has been described as a method that allows overall increased current deposition.[25]

Multitined expandable electrodes have an active surface that can be substantially expanded by prongs deployed from the tip. The number of prongs and the length of their deployment vary according to the device and to the desired volume of ablation. The commercially available devices were developed to monitor the ablation process so that high-temperature coagulation may occur without exceeding a 110°C maximum temperature threshold. One device (RITA Medical Systems, Mountain View, CA) relies on direct temperature measurement. This kind of electrode, in fact, is made by an insulated outer cannula that houses 9 curved electrodes of various lengths that deploy out from the trocar tip. Five of the electrodes are hollow and contain thermocouples in their tips that are used to measure the tissue temperature. Probe-tips temperatures, tissue impedance, and wattage are displayed on the RF generator and are graphically recorded by a dedicated software program. Maximum power output of the RF generator, amount of electrode array deployment from the trocar, and duration of the effective time of the ablation (time at target temperature) depend on the desired volume of ablation. In fact, the generator runs by an automated program and maintains the target temperature throughout the procedure. At the end of the procedure, the coagulation of the needle track can be done after retraction of the hooks with the aim to prevent any tumor cell dissemination.[20]

Another manufacturer (Boston Scientific, Natick, MA) produces a RF ablation device that relies on electrical measurement of tissue impedance rather than on tissue temperature. The electrode is made by an insulated 14-gauge outer needle that houses 10 retractable curved electrodes. The electrodes are manufactured in different lengths. In application, the tip of the needle is advanced to the target tissue and the curved electrodes are deployed to full extension. The generator is switched on and energy is administered until a rapid rise in impedance occurs. The impedance of the tissue increases as the tissue desiccates. It is assumed that an ablation is successful if the device impedes out.[22]

In addition to the previously described devices, several other designs for RF electrodes are currently being developed and clinically tested.[22] These include bipolar devices with 2 active electrode applicators placed in proximity to achieve contiguous coagulation, and perfusion electrodes that have small apertures at the tip of the prongs that allow fluids (ie, normal or hypertonic saline) to be infused into the tissue during the ablation procedure.

IMAGING

Imaging is used in 5 separate and distinct ways in RF ablation: planning, targeting, monitoring, controlling, and assessing treatment response.[24] Imaging techniques, including ultrasound (US), CT, MR imaging, and more recently positron emission tomography (PET), are used to help determine whether patients are suitable candidates for RF ablation. Pretreatment imaging planning must define tumor size and shape, number, and location within the liver relative to blood and biliary vessels, as well as critical structures (ie, gallbladder, gastrointestinal tract) that might be at risk for injury during the ablation.[24] Targeting refers to the placement of the RF electrode into the tumor, that can be achieved by using US, CT, or MR imaging. The guidance system is chosen largely on the basis of operator preference and local availability of dedicated equipment such as CT fluoroscopy or open MR systems. Monitoring is the term used to describe the process with which ablation effects are viewed during the procedure. Important aspects to be monitored include how well the tumor is being covered and whether any adjacent normal structures are being affected at the same time.[24] Although the transient hyperechoic zone that is seen at US within and surrounding a tumor during and immediately after RF ablation can be used as a rough guide to the extent of tumor destruction, MR is currently the only imaging modality with validated techniques for real-time temperature monitoring.[26] Controlling is used to describe the intraprocedural tools and techniques that are used to control the treatment. To control an image-guided ablation procedure, the operator can use the image-based information obtained during monitoring or automated systems that terminates the ablation at a critical point in the procedure.[24] Finally, imaging is used to assess the outcome of the procedure. Contrast-enhanced US performed after the end of the procedure may allow an initial evaluation of treatment effects. Contrast-enhanced CT or MR imaging are recognized as the standard modalities to assess treatment outcome, although promising initial results have been reported by using PET.[27] CT and MR images obtained after treatment show successful ablation as a nonenhancing area surrounded by an enhancing rim. The enhancing rim appears a relatively concentric, symmetric, and uniform process in an area with smooth inner margins. This is a transient finding that represents a benign physiologic response to thermal injury (initially, reactive hyperemia; subsequently, fibrosis and giant cell reaction).[28] Benign periablational enhancement needs to be differentiated from irregular peripheral enhancement because of the residual tumor that occurs at the treatment margin. In contrast to benign periablational enhancement, residual unablated tumor often grows in scattered, nodular, or eccentric patterns.[24] Later follow-up imaging studies should be aimed at detecting the recurrence of the treated lesion (ie, local tumor progression), the development of new hepatic lesions, or the emergence of extrahepatic metastases.

ANESTHESIOLOGY CARE

Patients candidates to RF ablation of colorectal liver metastases can have a medium-to-high anesthesiology risk. Most of them, in fact, have been rejected for surgery for associated diseases involving the cardiovascular system. There is no consensus on the best anesthesiology care for RF ablation. Local anesthesia does not produce adequate pain relief. Some centers use general anesthesia and endotracheal intubation. Others, including our own, prefer to preform liver RF under conscious sedation. The association of a hypnotic drug with an ultrashort half-life analgesic drug allows a mild sedation of the patient, who can co-operate with the operator and bear the pain induced by treatment. One possible protocol consists in the administration of a bolus of ketorolac (0.5–0.8 mg/kg) followed by infusion of propofol (1–2 mg/kg/h) and remifentanil (0.1 μg/kg/min). However, drug posology has to be modulated in relation to the individual patient compliance and to the different phases of the procedure. The infusion of the hypnotic drug can be varied between 0.5 and 2 mg/kg/h to achieve a patient sedation that preserves the ability to do easy actions. The infusion of remifentanil can be varied between 0.05 and 0.15 μg /kg/min to obtain an optimal analgesia. Attention has to be made to avoid bolus administration of remifentanil, as this may cause respiratory depression. The procedure is performed under standard cardiac, pressure, and oxygen monitoring. A careful post-treatment protocol is to be recommended following RF ablation. The patient is kept under close medical observation and rescanned with US 1–2 hours after treatment to detect any bleeding. An overnight hospital stay is scheduled. In most of the cases, patients may be discharged the day after the procedure.

INDICATIONS

At our institution, inclusion criteria for RF ablation require the patient not to be a surgical candidate after assessment by a multidisciplinary team. Written informed consent is obtained from all patients. A careful clinical, laboratory, and imaging assessment of the patient is necessary to establish the indication for RF ablation. Laboratory tests should include measurement of serum tumor markers, such as carcinoembryonic antigen, and a full evaluation of coagulation status. A prothrombin time ratio (normal time/patient's time) greater than 50% as well as a platelet count higher than 50,000/μL are required to keep the risk of bleeding at an acceptable low level. A standard staging protocol includes chest and abdominal CT. However, performing a more accurate imaging assessment is to be recommended: MR imaging with use of a liver-specific contrast agent and PET may be valuable complementary investigations.[29]

When considering a patient with hepatic colorectal metastases for RF ablation, a key issue is to define whether a successful treatment of the hepatic metastases will likely improve the patient's prognosis. To this aim, because RF ablation is in fact a local treatment like surgical resection, it can be assumed that all the negative prognostic factors affecting the results of surgery, will also affect the outcome of RF ablation.[4,30] The presence of extrahepatic disease is, in general, a contraindication for local ablative treatments. It is, however, of utmost importance to distinguish among different locations of extrahepatic disease. In general, anastomotic recurrence of the primary tumor should not dissuade RF treatment on liver metastases if surgery of locally recurrent primary is successful.[31] Metastases to the portal, hepatic, or celiac lymph nodes are thought to be the metastases from the secondary liver tumor and a dramatic fall in 5-year survival rate in resected patients with this kind of extrahepatic disease has been observed.[32] The lung is the second common site of metastatic spread from colorectal cancer. A minority of patients will develop isolated pulmonary and hepatic metastases. Despite limited surgical experience in this subset of patients, 30–50% 5-year survival rates after combined hepatic and pulmonary metastasectomies have been reported.[33–36] RF ablation could be a viable treatment option in patients with limited hepatic and pulmonary metastases.[37] Primary tumor stage represents another important prognostic factor. Patients with stage II colorectal cancer have improved outcomes compared with patients with stage III tumors.[4,30] Node-positive tumors are associated with reduced survival rates in surgical series and are an indication for adjuvant chemotherapy.[4,30]

As far as the characteristics of the hepatic metastases are concerned, 3 main issues—lesion number, size, and location—have to be considered. Despite it is generally accepted that the prognosis of the patient after liver resection worsen as the number of the liver metastases grows, the number of lesions should not be considered an absolute contraindication to RF ablation if successful treatment of all metastatic deposits can be accomplished. Many centers, including our own, preferentially treat patients with 4 or fewer lesions, whereas others have wider inclusion criteria. Tumor size is of utmost importance to determine the outcome of RF ablation. It has to be taken into account that, in colorectal hepatic metastases, the ablation of appropriate margins beyond the borders of the tumor is necessary to achieve complete tumor destruction.[24] When using RF systems that produce in vivo ablation spheres of 5.5–5.6 cm in diameter,[19] the tumor should not exceed 3.5 cm in longest axis to obtain a safety margin of 1 cm all around the lesion. Treatment of lesions adjacent to the gallbladder or to the hepatic hilum is at risk for thermal injury of the biliary tract. Nevertheless, in experienced hands, RF ablation of tumors adjacent to the gallbladder was shown to be feasible although associated in most cases with self-limited iatrogenic cholecystitis.[38] In contrast, treatment of lesions located in the vicinity of hepatic vessels is possible because flowing blood usually "refrigerates" the vascular wall, protecting it from thermal injury: in these cases, however, the risk of incomplete ablation of the neoplastic tissue adjacent to the vessel may increase because of the heat loss caused by the vessel itself. Lesions located along the surface of the liver can be considered for RF ablation, although their treatment requires experienced hands and may be associated with a higher risk of complications. Percutaneous treatment of superficial lesions that are adjacent to any part of the gastrointestinal tract must be avoided because of the risk of thermal injury of the gastric or bowel wall.[39,40] The colon appears to be at greater risk than the stomach or small bowel for thermally mediated perforation.[41] Gastric complications are rare, likely owing to the relatively greater wall thickness of the stomach or the rarity of surgical adhesions along the gastrohepatic ligament. The mobility of the small bowel may also provide the bowel with greater protection compared with the relatively fixed colon. The potential risk of thermal damage to adjacent structures should be weighed against benefits on a case-by-case basis. A laparoscopy approach can also be considered in such instances, as the bowel may be lifted away from the tumor.[41]

RESULTS

Early clinical experiences were conducted in the framework of feasibility studies, aimed at analyzing safety, tolerability, and local therapeutic effect of the treatment. It must be pointed out that RF ablation underwent terrific technological improvement during the past few years, with the introduction of high-power generator and newly designed electrodes. Therefore, data collected in early studies may not be comparable with recent series.

In 2 pioneer studies published in 1997–1998 by Solbiati et al[42] and Lencioni et al,[43] patients with limited hepatic metastatic disease, who were excluded from surgery, were submitted to RF ablation. In the first series, 29 patients with 44 hepatic metastases ranging from 1.3 to 5.1 cm in diameter were treated. Each tumor was treated in 1 or 2 sessions, and technical success, defined as the lack of residual unablated tumor at CT or MR imaging obtained 7–14 days after completion of treatment, was achieved in 40 of 44 lesions. However, follow-up imaging studies confirmed complete necrosis of the entire metastasis in only 66% of the cases, whereas local tumor progression was observed in the remaining 34%. Only one complication, self-limited hemorrhage, was seen. One-year survival was 94%. In the study by Lencioni et al,[43] 29 patients with 53 hepatic metastases ranging from 1.1 to 4.8 cm in diameter were enrolled. A total of 127 insertions were performed (mean, 2.4 insertions/

lesion) during 84 treatment sessions (mean, 1.6 sessions/lesion) in absence of complications. Complete tumor response, defined as the presence of an unenhancing ablation zone larger than the treated tumor on posttreatment spiral CT, was seen in 41 (77%) of 53 lesions. After a mean follow-up period of 6.5 months (range, 3–9 months), local tumor progression was seen in 12% of cases. One-year survival was 93%.

In 2000–2001, owing to the advances in RF techniques, reported rates of successful RF ablation substantially increased. de Baere et al[44] treated 68 patients with 121 hepatic metastases, mainly of colorectal origin, with 76 sessions, either percutaneously (47 patients with 88 metastases; 10–42 mm in diameter) or intraoperatively (21 patients with 33 metastases; 5–20 mm in diameter). Procedure efficacy was evaluated with CT and MR imaging performed 2, 4, and 6 months after treatment and then every 3 months. RF ablation allowed eradication of 91% of the 100 treated metastases that were followed up for 4–23 months (mean, 13.7 months). The rate was equivalent for percutaneous RF ablation (90%) and for intraoperative RF ablation (94%). One bilioperitoneum and 2 abscesses were the major complications encountered after treatment. Helmberger et al[45] reported a similar technical success rate of RF ablation (97%) in the series of 37 patient with 74 metastases. In this study, 4 cases of hematoma of the liver capsule occurred. During the limited follow-up period of 9 months, no case of local tumor progression was seen.

Recently, data on long-term survival rates of patients
T1 treated by RF ablation have been reported (Table 1). In the series of Gillams and Lees,[46] the impact of RF ablation on survival in 69 patients with colorectal metastases, with an average number of 2.9 lesions with a mean diameter of 3.9 cm, was analyzed. All patients had been excluded from surgery. Eighteen (26%) patients had undergone previous hepatic resection, and 62 (93%) received chemotherapy at some stage. One-year, 2-year, 3-year, and 4-year survival rates were 90%, 60%, 34%, and 22%, respectively. In the study of Solbiati et al,[47] 117 patients with 179 metachronous colorectal hepatic metastases were treated. Estimated median survival was 36 months, and 1, 2, and 3-year survival rates were 93%, 69%, and 46%, respectively. In 77 (66%) of 117 patients, new metastases were observed at follow-up. Seventy (39%) of 179 lesions developed local recurrence after treatment. The same authors performed an update of their series:[48] in a group of 166 patients with 378 metastases ranging from 0.7 to 5.2 cm in diameter, local tumor control (absence of tumor regrowth at the site of ablation during the follow-up) was achieved in 78% of lesions smaller than 2.5 cm, and in 17% of metastases larger than 4 cm. Only 2 major complications related to RF ablation occurred. The overall survival rates were 96%, 64%, 45%, 36% and 22% at 1, 2, 3, 4, and 5 years, respectively.

Lencioni et al recently analyzed the long-term results of RF ablation in the treatment of hepatic colorectal metastases in a series of 423 patients collected in a multicenter trial.[49] All patients had 4 of fewer metachronous metastases (overall number of lesions, 615; mean number of lesions/patient 1.4 ± 0.7), each 5 cm or less in greatest dimension (range, 0.5–5 cm; mean, 2.7 cm ± 0.9), and were free from extrahepatic disease. Surgical option had been excluded or refused by the patient. The participating centers shared diagnostic, staging, and follow-up protocols, and performed RF ablation by using the same technology (expandable multitined electrodes by RITA Medical Systems). The follow-up period ranged from 1 to 78 months (mean, 19 months ± 15). The primary effectiveness rate (percentage of tumors that were successfully eradicated following the planned treatment schedule) was 85.4% (525 of 615 lesions). During the follow-up, local tumor progression was observed in 132 (25.1%) of 525 lesions. The overall survival by the Kaplan–Meier method was 86% at 1 year, 63% at 2 years, 47% at 3 years, 29% at

TABLE 1. Survival Outcomes of Patients With Hepatic Colorectal Metastases Treated With Radiofrequency Ablation

			Survival Rate (%)		
Study	**Year**	**No. Patients**	**1 Year**	**3 Year**	**5 Year**
Solbiati et al[42]	1997	29	94	N/A	N/A
Lencioni et al[43]	1998	29	93	N/A	N/A
Gillams et al[46]	2000	69	90	34	N/A
Solbiati et al[47]	2001	117	93	46	N/A
Solbiati et al[48]	2003	166	96	45	22
Oshowo et al[52]	2003	25	00	52	N/A
Abdalla et al[51]	2004	57	92	37	N/A
Lencioni et al[49]	2004	423	86	47	24

N/A indicates not available.

4 years, and 24% at 5 years. Survival rates were significantly higher in patients with single lesion 2.5 cm or less in diameter (56% at 5 years) than in patients with single lesion larger than 2.5 cm (13% at 5 years) or multiple lesions (11% at 5 years; $P = 0.0002$, log-rank test).

The long-term survival figures obtained in nonsurgical patients who received RF ablation are substantially higher than those obtained with any chemotherapy regimens and provide indirect evidence that RF ablation therapy improves survival in patients with limited hepatic metastatic disease. In fact, in a meta-analysis of the results of chemotherapy in metastatic colorectal cancer, in which trials using fluoropyrimidine-based treatment schedules were included, mortality at 2 years was not significantly different from that observed with supportive care alone.[8] With latest advances in chemotherapy strategies and the use of combination protocols with fluorouracil–leucovorin, irinotecan, and oxaliplatin, initial promising results have been reported. However, data from 7 recently published phase III trials showed that the improvement in median survival did not exceed 3.5 months.[50]

Recent studies analyzed the role of RF ablation with respect to surgical resection. Abdalla et al[51] examined survival of 418 patients with colorectal metastases isolated to the liver who were treated with hepatic resection (n = 190), RF ablation plus resection (n = 101), RF ablation only (n = 57) or chemotherapy only (n =70). Overall survival for patients treated with RF ablation plus resection or RF ablation only was greater than for those who received chemotherapy only ($P = 0.0017$). However, overall survival was highest after resection: 4-year survival rates after resection, RF ablation plus resection, and RF ablation only were 65%, 36%, and 22%, respectively ($P < 0.0001$). In contrast, in the series of Oshowo et al[52] survival outcome of patients with solitary colorectal liver metastases treated by surgery (n = 20) or by RF ablation (n = 25) did not differ. In this study, the survival rate at 3 years was 55% for patients treated with surgery and 52% for those who underwent RF ablation, suggesting that the survival after resection and RF ablation is comparable.

Elias et al[53] used RF ablation instead of repeated resection for the treatment of liver tumor recurrence after partial hepatectomy in 47 patients. A retrospective study of the authors' database over 2 similar consecutive periods showed that RF ablation increased the percentage of curative local treatments for liver recurrence after hepatectomy from 17 to 26% and decreased the proportion of repeat hepatectomies from 100 to 39%. Livraghi et al[54] evaluated the potential role of performing RF ablation during the interval between diagnosis and resection as part of a "test-of-time" management approach. Eighty-eight consecutive patients with 134 colorectal liver metastases who were potential candidates for surgery were treated with RF ablation. Among the 53 patients in whom complete tumor ablation was achieved after RF treatment, 98% were spared surgical resection: 44% because they remained free of disease and 56% because they developed additional metastases leading to unresectability. No patient in whom RF treatment did not achieve complete tumor ablation became unresectable due to the growth of the treated metastases.

Complications after RF ablation of liver malignancies recently have been analyzed in large series. A multicenter survey included 2320 patients with 3554 lesions.[39] Six deaths (0.3%) were noted, including 2 caused by multiorgan failure following intestinal perforation; one case each of septic shock after *Staphylococcus aureus*-caused peritonitis, massive hemorrhage after tumor rupture, liver failure after stenosis of right bile duct; and 1 case of sudden death of unknown cause 3 days after the procedure. Fifty (2.2%) patients had additional major complications, defined as is those that if left untreated might threaten the patient's life, lead to substantial morbidity and disability, or result in hospital admission or substantially lengthened hospital stay.[24] In the large single-institution series of de Baere et al,[55] 312 patients underwent 350 sessions of RF ablation (124 intraoperative and 226 percutaneous) for treatment of 582 liver tumors (115 hepatocellular carcinomas and 467 metastatic tumors) during a 5-year period. Five (1.4%) deaths were related to RF treatment. The deaths were caused by liver insufficiency (n = 1), colon perforation (n = 1), and portal vein thrombosis (n = 3). Portal vein thrombosis was significantly ($P < 0.00001$) more frequent in cirrhotic livers than in noncirrhotic livers after RF radiofrequency ablation performed during a Pringle maneuver. Liver abscess (n = 7) was the most common complication. Abscess occurred significantly ($P < 0.00001$) more frequently in patients bearing a bilioenteric anastomosis than in other patients. The authors encountered 5 pleural effusions, 5 skin burns, 4 hypoxemias, 3 pneumothoraces, 2 small subcapsular hematomas, 1 acute renal insufficiency, 1 hemoperitoneum, and 1 needle-tract seeding. Among the 5.7% major complications, 3.7% required less than 5 days of hospitalization for treatment or surveillance and 2% required more than 5 days for treatment. Although these data indicate that RF ablation is a relatively safe procedure, and suggest that with increased expertise and knowledge in regard to the use of the technique it could become even safer, caution should be exercised in patients presenting with risk factors, and a careful assessment of the risks and benefits associated with RF ablation has to be made in each individual patient by a multidisciplinary team.

FUTURE PROSPECTS

RF ablation is a relatively new technique, with continuous progress in technology as well as in clinical application. A number of recent experimental studies have shown that there is further potential for this technique to improve its effectiveness.[56–60] Recent and ongoing technical refinements are not reflected in the available studies reporting survival outcomes of treated patients. Therefore, the clinical impact of current RF ablation techniques might be greater than reported.

On the other hand, clinical application of RF ablation outside the liver are promising. In the setting of patients with metastatic colorectal cancer, the use of RF ablation in the treatment of lung tumors has a special interest.[37] In fact, lung is a frequent site of metastatic disease from colorectal cancer, and surgical resection is the accepted treatment of lung metastases. Resection achieves 5-year survival rates ranging from 21% to 62% in properly selected candidates, ie, those without extrapulmonary disease or with associated resectable liver metastases.[61–63] However, surgery frequently is precluded by the number and location of metastatic nodules. Moreover, the high risk of recurrence in patients with metastatic disease and the need to remove functioning lung tissue along with the lesions limit the indications for surgery. RF ablation could represent a viable alternative to surgery for inoperable patients and for those with recurrent but limited disease.

Few preliminary clinical experiences on RF ablation of lung tumors have been published thus far. In 2000, Dupuy et al[64] first reported 3 patients with unresectable lung tumors treated with RF ablation. Steinke et al[65] described a case of a pulmonary metastasis resected after RF ablation, in which histologic proof of complete necrosis was obtained. Lee et al[66] treated a total of 32 tumors in 30 patients, and achieved complete tumor ablation at 6-month follow-up in all 6 tumors smaller than 3 cm in diameter. Lencioni et al[67] recently reported the preliminary results of an on-going multicenter trial, in which 71 patients with 117 malignant lung tumors 3.5 cm in diameter or smaller were treated. Diagnoses included nonsmall cell lung cancer in 27 patients, metastasis from colorectal carcinoma in 34, and metastasis from other primary malignancy in 10. RF ablation was technically feasible in 70 (98%) of 71 patients. Major complications consisted of pneumothorax requiring treatment (n=15) and pneumonia (n = 1). CT obtained 1 month after RF ablation showed a round, ground-glass density area encompassing the treated lesion in all cases. Sixty (91%) of 66 lesions in 41 patients who were followed up for 6 months or more after treatment showed no tumor progression on CT. Complete ablation of treated lesions was confirmed by the absence of tumor regrowth over a follow-up period of 1 year or more in 20 patients. No differences were observed in tumor response rates between patients with NSCLC and those with lung metastases.

CONCLUSIONS

In summary, RF ablation is a minimally invasive procedure that can achieve effective and reproducible tumor destruction with acceptable morbidity. RF ablation has become a viable treatment method for patients with limited hepatic metastatic disease from colorectal cancer who are not eligible for surgical resection. There are no prospective randomized studies comparing RF ablation versus surgical resection to support the indication of RF ablation in patients who are actual surgical candidates. Also, the high rate of disease recurrence after RF ablation indicates that novel combinations of RF ablation with regional or systemic chemotherapy regimens are needed to improve patient outcomes. Nevertheless, we believe that, with continuous improvement in technology and large-scale clinical experience, this technique has the potential to play an increasingly important role in the clinical management of hepatic colorectal metastases. Moreover, experiences with RF ablation of lung metastases are promising, and will likely open new prospects for colorectal cancer patients. Finally, we would like to point out that an appropriate use of RF ablation can only be done when the therapeutic strategy is decided by a multidisciplinary team and is tailored to the individual patient and to the features of the disease.

REFERENCES

1. Jessup JM, McGinnis LS, Steele GD Jr. , et al. Report on colon cancer. The National Cancer Data Base. *Cancer*. 1996;78:918–926.
2. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. *World J Surg*. 1995;19:59–71.
3. Jamison RL, Donohue JH, Nagorney DM, et al. Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch Surg*. 1997;132:505–510.
4. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230:309–318.
5. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. 2002;235:759–765.
6. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg*. 2004;239:722–730.
7. Silen W. Hepatic resection for metastases from colorectal carcinoma is of dubious value. *Arch Surg*. 1989;124:1021–1022.
8. Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Br J Cancer*. 2000;82:1789–1794.
9. Livraghi T, Vettori C, Lazzaroni S. Liver metastases: results of percutaneous ethanol injection in 14 patients. *Radiology*. 1991;179:709–712.
10. Goldberg SN, Solbiati L, Hahn PF, et al. Large volume tissue ablation with radiofrequency by using a clustered, internally cooled electrode technique: laboratory and clinical experience in liver metastases. *Radiology*. 1998;209:371–379.
11. Vogl TJ, Muller PK, Mack MG, et al. Liver metastases: interventional therapeutic techniques and results, state of the art. *Eur Radiol*. 1999;9: 675–684.
12. McGahan JP, Dodd GD III. Radiofrequency ablation of the liver: current status. *AJR Am J Roentgenol*. 2000;176:3–16.
13. Lencioni R, Cioni D, Bartolozzi C. Percutaneous radiofrequency thermal ablation of liver malignancies: techniques, indications, imaging findings, and clinical results. *Abdom Imaging*. 2001;26:345–360.
14. Morita T, Shibata T, Okuyama M, et al. Microwave coagulation therapy for liver metastases from colorectal cancer. *Gan To Kagaku Ryoho*. 2004;31:695–699.
15. Mala T, Edwin B, Mathisen O, et al. Cryoablation of colorectal liver metastases: minimally invasive tumour control. *Scand J Gastroenterol*. 2004;39:571–578.
16. Shibata T, Iimuro Y, Yamamoto Y, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology*. 2002;223:331–337.
17. Goldberg SN. Comparison of techniques for image-guided ablation of focal liver tumors. *Radiology*. 2002;223:304–307.

18. Lencioni R, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. *Radiology*. 2003;228:235–240.
19. Berber E, Herceg NL, Casto KJ, Siperstein AE. Laparoscopic radiofrequency ablation of hepatic tumors: prospective clinical evaluation of ablation size comparing two treatment algorithms. *Surg Endosc*. 2004; 18:390–396.
20. Lencioni R, Cioni D, Crocetti L, Bartolozzi C. Percutaneous ablation of hepatocellular carcinoma: state-of-the-art. *Liver Transpl*. 2004;10:S91–97.
21. Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancies: a unfied approch to underlyng principles, techniques, and diagnostic imaging guidance. *AJR Am J Roentgenol*. 2000; 174:323–331.
22. Rhim H, Goldberg SN, Dodd GD III, et al. Essential techniques for successful radiofrequency thermal ablation of malignant hepatic tumors. *Radiographics*. 2001;21:S17–S35.
23. Goldberg SN, Gazelle GS, Halpern EF, et al. Radiofrequency tissue ablation: importance of local temperature along the electrode tip exposure in determining lesion size and shape. *Acad Radiol*. 1996;3:212–218.
24. Goldberg SN, Charboneau JW, Dodd GD III, et al. ., for the International Working Group on Image-Guided Tumor Ablation. Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. *Radiology*. 2003;228:335–345.
25. Goldberg SN, Stein MC, Gazelle GS, et al. Percutaneous radiofrequency tissue ablation: optimization of pulsed-technique to increase coagulation necrosis. *J Vasc Interv Radiol*. 1999;10:907–91.
26. Quesson B, de Zwart JA, Moonen CTW. Magnetic resonance temperature imaging for guidance of thermotherapy. *J Magn Reson Imaging*. 2000;12:525–533.
27. Donckier V, Van Laethem JL, Goldman S, et al. [F-18] fluorodeoxyglucose positron emission tomography as a tool for early recognition of incomplete tumor destruction after radiofrequency ablation for liver metastases. *J Surg Oncol*. 2003;84:215–223.
28. Goldberg SN, Gazelle GS, Compton CC, et al. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. *Cancer*. 2000;88:2452–2463.
29. Lencioni R, Cioni D, Crocetti L, et al. Magnetic resonance imaging of liver tumors. *J Hepatol*. 2004;40:162–171.
30. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg*. 1999;189:291–299.
31. Sasson AR, Sigurdson ER. Surgical treatment of liver metastases. *Semin Oncol*. 2002;29:107–118.
32. August DA, Sugarbaker PH, Schneider PD. Lymphatic dissemination of hepatic metastases. Implications for the follow-up and treatment of patients with colorectal cancer. *Cancer*. 1985;55:1490–1494.
33. Murata S, Moriya Y, Akusa T, et al. Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer*. 1998;83:1086–1093.
34. Headrick JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg*. 2001;71:975–979.
35. Mineo TC, Ambrogi V, Tonini G, et al. Long-term results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. *J Am Coll Surg*. 2003;197:386–391.
36. Patel NA, Keenan RJ, Medich DS, et al. The presence of colorectal hepatic metastases does not preclude pulmonary metastasectomy. *Am Surg*. 2003;69:1047–1053.
37. Lencioni R, Crocetti L, Cioni R, et al. Radiofrequency ablation of lung malignancies: where do we stand? *Cardiovasc Intervent Radiol*., in press.
38. Chopra S, Dodd GD 3rd, Chanin MP, et al. Radiofrequency ablation of hepatic tumors adjacent to the gallbladder: feasibility and safety. *AJR Am J Roentgenol*. 2003;180:697–701.
39. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology*. 2003;226:441–451.
40. Buscarini E, Buscarini L. Radiofrequency thermal ablation with expandable needle of focal liver malignancies: complication report. *Eur Radiol*. 2004;14:31–37.
41. Rhim H, Dodd GD 3rd, Chintapalli KN, et al. Radiofrequency thermal ablation of abdominal tumors: lessons learned from complications. *Radiographics*. 2004;24:41–52.
42. Solbiati L, Goldberg SN, Ierace T, et al. Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. *Radiology*. 1997;205:367–373.
43. Lencioni R, Goletti O, Armillotta N, et al. Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. *Eur Radiol*. 1998;8:1205–1211.
44. de Baere T, Elias D, Dromain C, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. *AJR Am J Roentgenol*. 2000;175:1619–1625.
45. Helmberger T, Holzknecht N, Schopf U, et al. Radiofrequency ablation of liver metastases. Technique and initial results. *Radiologe*. 2001;41: 69–76.
46. Gillams AR, Lees WR. Survival after percutaneous, image-guided, thermal ablation of hepatic metastases from colorectal cancer. *Dis Colon Rectum*. 2000;43:656–666.
47. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology*. 2001;221:159–166.
48. Solbiati L, Ierace T, Tonolini M, et al. Long-term survival of patients treated with radiofrequency ablation for liver colorectal metastases: improved outcome with increasing experience. *Radiology*. 2003;229(P): 411.
49. Lencioni R for the Tumor Radiofrequency Ablation Italian Network (TRAIN). Long-term results of percutaneous radiofrequency ablation of hepatic colorectal cancer metastases. *Radiology*., in press.
50. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of flurouracil-leucovirin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004;22:1209–1214.
51. Abdalla EK, Vauthey JN, Ellis LM, et el. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239: 818–825.
52. Oshowo A, Gillams A, Harrison E, et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. *Br J Surg*. 2003;90:1240–1243.
53. Elias D, De Baere T, Smayra T, et al. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. *Br J Surg*. 2002;89:752–756.
54. Livraghi T, Solbiati L, Meloni F, et al. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the “test-of-time approach”. *Cancer*. 2003;97:3027–3035.
55. de Baere T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *AJR Am J Roentgenol*. 2003; 181:695–700.
56. Goldberg SN, Ahmed M, Gazelle GS, et al. Radiofrequency thermal ablation with NaCl solution injection: effect of electrical conductivity on tissue heating and coagulation-phantom and porcine liver study. *Radiology*. 2001;219:157–165.
57. De Baere T, Bessoud B, Dromain C, et al. Percutaneous radiofrequency ablation of hepatic tumors during temporary venous occlusion. *AJR Am J Roentgenol*. 2002;178:53–59.
58. Kon Kim Y, Min Lee J, Won Kim S, et al. Combined radiofrequency ablation and hot saline injection in rabbit liver. *Invest Radiol*. 2003;38: 725–732.
59. Brieger J, Pereira P, Trübenbach J, et al. In vivo efficiency of four commercial monopolar radiofrequency ablation systems: a comparative experimental study in pig liver. *Invest Radiol*. 2003;38:609–616.
60. Min Lee J, Rhim H, Han JK, et al. Dual-probe radiofrequency ablation: an in vitro experimental study in bovine liver. *Invest Radiol*. 2004;39: 89–96.
61. Pastorino U, Buyse M, Godehard F, et al. ., for the International Registry of Lung Metastases. Long-term results of lung metastasectomy: prognostic analysis based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997; 113:37–49.
62. Kandolier D, Kromer E, Tuchler H, et al. Long-term results after

repeated surgical removal of pulmonary metastases. *Ann Thorac Surg*. 1998;65:909–912.

63. Inoue M, Kotake Y, Nakagawa K, et al. Surgery for pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg*. 2000;70:380–383.
64. Dupuy DD, Zagoria RJ, Akerley W, et al. Percutaneous radiofrequency ablation of malignancies in the lung. *AJR Am J Roentgenol*. 2000;174: 57–59.
65. Steinke K, Habicht JM, Thomsen S, et al. CT-guided radiofrequency ablation of a pulmonary metastasis followed by surgical resection. *Cardiovasc Intervent Radiol*. 2003;25:543–546.
66. Lee JM, Jin GY, Goldberg SN, et al. Percutaneous radiofrequency ablation for inoperable non–small cell lung cancer and metastases: preliminary report. *Radiology*. 2004;230:125–134.
67. Lencioni R, Crocetti L, Glenn DW, et al. Percutaneous radiofrequency ablation of pulmonary malignancies: a prospective, multicenter clinical trial. *Radiology*. 2003;229(P):437.