Radiology

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Index terms:
Liver neoplasms, CT, 761.1211
Liver neoplasms, MR, 761.1214
Liver neoplasms, therapy, 761.12168, 761.32, 761.33
Liver neoplasms, US, 761.1298
Radiofrequency (RF) ablation

Published online before print
10.1148/radiol.2262012198
Radiology 2003; 226:441–451

Abbreviations:
ANOVA = analysis of variance
HCC = hepatocellular carcinoma
INR = international normalized ratio
PEI = percutaneous ethanol injection
RF = radio frequency

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Guarantors of integrity of entire study, T.L., L.S., S.N.G.; study concepts, T.L., L.S., G.S.G., S.N.G.; study design, T.L., L.S., M.F.M., G.S.G., S.N.G.; literature research, T.L., M.F.M., S.N.G.; clinical studies, T.L., L.S., M.F.M.; data acquisition, T.L., L.S., M.F.M.; data analysis/interpretation, T.L., L.S., M.F.M., G.S.G., S.N.G.; statistical analysis, T.L., G.S.G., E.F.H., S.N.G.; manuscript preparation, T.L., G.S.G., S.N.G.; manuscript definition of intellectual content, editing, and revision/review, T.L., L.S., M.F.M., G.S.G., S.N.G.; manuscript final version approval, all authors.

Treatment of Focal Liver Tumors with Percutaneous Radio-frequency Ablation: Complications Encountered in a Multicenter Study[1]

PURPOSE: To report complications encountered by members of a collaborative group who performed radio-frequency (RF) ablation in patients with focal liver cancer.

MATERIALS AND METHODS: Members of 41 Italian centers that were part of a collaborative group used a percutaneous internally cooled RF ablation technique and a standardized protocol for follow-up. They completed a questionnaire regarding number of deaths, presumed cause of death, and likelihood of its relationship to the RF procedure; number and types of major complications; and types of minor complications and side effects. Enrollment included 2,320 patients with 3,554 lesions (size, 3.1 cm ± 1.1 [SD] in diameter): 1,610 had hepatocellular carcinoma with chronic liver disease; 693 had metastases, predominantly from colorectal cancer (n = 501); and 17 had cholangiocellular carcinoma. Number and characteristics of complications (ie, deaths and major and minor complications) attributed to the procedure were reported. Data were subsequently analyzed with analysis of variance to determine whether the major complication rate was related to tumor size, number of ablation sessions, or electrode type (single or cluster).

RESULTS: In total, 3,554 lesions were treated. Six deaths (0.3%) were noted, including two caused by multiorgan failure following intestinal perforation; one case each of septic shock following *Staphylococcus aureus*-caused peritonitis, massive hemorrhage following tumor rupture, liver failure following stenosis of right bile duct; and one case of sudden death of unknown cause 3 days after the procedure. Fifty (2.2%) patients had additional major complications. The most frequent of these were peritoneal hemorrhage, neoplastic seeding, intrahepatic abscesses, and intestinal perforation. An increased number of RF sessions were related to a higher rate of major complications ($P < .01$), whereas the number of complications was not significantly different when tumor size or electrode type were compared. Minor complications were observed in less than 5% of patients.

CONCLUSION: Results of this study confirm that RF ablation is a relatively low-risk procedure for the treatment of focal liver tumors.

Percutaneous radio-frequency (RF) ablation for the treatment of focal liver cancer is a relatively new image-guided procedure that is rapidly gaining acceptance in the radiologic and surgical community, particularly as therapy for patients who have inoperable tumors (1,2). This procedure is being rapidly adopted in favor of other minimally invasive therapies, such as percutaneous ethanol injection (PEI) (3,4), and in some cases, it is chosen over surgery because of its potential benefits, including reduced morbidity and mortality. Further, its potential use in the treatment of patients who are not candidates for surgery (1,2) is particularly important. Although findings in encouraging preliminary reports suggest that this procedure is both safe and effective, thus far results in only a

limited number of studies (3–14) in which this technology was assessed have been published.

While findings in these studies suggest that RF ablation is a relatively safe procedure, these studies include samples that are too small to allow clinicians to clearly establish the true complication rate, especially for rare but potentially morbid consequences, for the procedure. Nevertheless, this information is absolutely essential for every new intervention to permit an accurate assessment of the risks and benefits of the procedure and to determine its relative and absolute contraindications. Additionally, the complication rate of RF ablation must be compared with the 15%–30% morbidity and the approximately 5% mortality of surgery (15–17), as well as with the complication rate for PEI (with a mortality up to 0.7% and a major complication rate of 3.2%–4.6% [18]) to permit an objective assessment of the risks versus the benefits of this technology. The purpose of this article is, therefore, to report the complications encountered by members of a large collaborative group of 41 centers who have performed RF ablation in a large number of patients with focal liver cancer.

MATERIALS AND METHODS

Participants and Ablation Technique

Forty-one Italian centers where it was known that RF ablation of hepatic malignancies was performed with one RF ablation system (internally cooled electrodes and a generator [CC-1; Radionics, Burlington, Mass]) and a well-defined standardized protocol for RF ablation and follow-up participated in this study (3,6). Among these were 17 radiologic centers (16 interventional radiology sites and one nuclear medicine department), 17 medical centers (10 internal medicine departments, five gastroenterology departments, and two oncology centers), and seven surgical centers (a full listing appears at the end of this article). To our knowledge, all centers at which 10 or more patients were treated by using this RF ablation system were represented in the study, as was confirmed by correspondence with the sole Italian distributor (Hospital Service, Rome, Italy) of the system.

The time for this study was from July 1995 to January 2001. At these centers, RF ablation was performed according to well-defined guidelines. These guidelines were previously published in articles about early studies (3–6) regarding the use of ablation in the treatment of hepatocellular carcinoma (HCC) and colorectal metastases. With real-time ultrasonographic (US) guidance, either single and/or cluster internally cooled electrodes were placed in single or multiple locations within the tumor on the basis of tumor size (19,20). At all centers except one surgical center, a percutaneous approach was used for the placement of the electrode. At the surgical center, however, the procedure was performed at laparoscopy to permit laparoscopic US imaging to help guide the electrode in cases in which the lesion was poorly visualized percutaneously.

Single electrodes were used in 1,909 patients, whereas cluster electrodes were used in 421 patients, and both electrode types were used in separate lesions in 10 patients. RF energy was applied for 10–12 minutes to a maximum of 2,000 mA by using a well-defined pulsing algorithm (21) from one to three times for lesions smaller than 4 cm and as many as five times for larger lesions. Inclusion criteria for this study were as follows: disease limited to the liver, fewer than three lesions at initial presentation, and no evidence of active infection or substantial coagulopathy (international normalized ratio [INR] > 1.8). The decision to treat lesions larger than 5 cm in diameter was left to the discretion of the individual treatment center.

Two variations in protocol, those pertaining to the anesthetic regimen and those pertaining to the prophylactic antibiotic administration, were left to the discretion of the investigators. Thus, 1,002 (43.2%) patients underwent general anesthesia, 907 (39.1%) patients underwent RF ablation with conscious sedation, and 411 (17.7%) underwent both at different treatment sessions. Many centers converted to a policy of prophylactic antibiotic administration during the study because of the awareness of the possible risk of sepsis or abscess. All centers obtained permission for performing RF ablation and for detailed chart review from their appropriate investigational review boards as a requirement for obtaining the RF equipment.

Patient follow-up also was performed in a standardized fashion on the basis of previously published recommendations (3–6). Briefly, patients were evaluated clinically and with contrast material–enhanced computed tomography (CT) at 1 month after ablation and at every 3–4 months thereafter.

Questionnaire

The questionnaire sent to all 41 centers included seven questions in regard to the following: the total number of patients who underwent RF ablation; the diagnosis of the treated tumor; the number and size of lesions treated (determined by obtaining a preprocedural contrast-enhanced CT scan or a magnetic resonance [MR] image and confirmed by obtaining an immediate preprocedural US scan); the type of coagulation tests performed prior to the procedure and the threshold value considered to be safe for the performance of RF ablation at that institution; the number of deaths, the presumed causes, and the likelihood that the deaths were related to the RF procedure; the number and types of major complications; and the types of minor complications and side effects encountered. The questionnaire further specified that multiple RF applications to the same lesion were to be considered as a single treatment when the total number of lesions treated was calculated.

For major and minor complications, we used the definitions recently outlined by the Society for Cardiovascular and Interventional Radiology (22,23). Briefly, the definition of a major complication was a complication that, if left untreated, might threaten the patient's life, lead to substantial morbidity and disability, or result in a lengthened hospital stay. All other complications were considered minor. Side effects were considered common untoward consequences that did not require therapy or a prescription medication. Side effects were categorized as common undesired consequences of the procedure that rarely if ever resulted in substantial morbidity, although they occurred frequently. An RF ablation–related complication was any problem encountered within the periprocedural (30 days) time, as well as additional complications that were identified at delayed follow-up imaging and were judged to be likely caused by the RF ablation. Two physicians (T.L., M.F.M.) with substantial experience in the treatment of patients who underwent RF ablation contacted the centers.

Once the physicians collated the data and identified specific complications, one of them (M.F.M.) recontacted the centers to obtain specific additional information regarding the complications. This included the use of prophylactic antibiotic therapy for patients with abscesses, the coagulation parameters in patients with complications related to bleeding, and the location of the tumor (superficial vs deep) for cases of bleeding or tumor seeding.

Data Analysis

By using analysis of variance (ANOVA), one of the authors (E.F.H.) further analyzed the data to determine whether differ-

TABLE 1
Summary of Patients and Lesions Treated with RF Ablation according to Location and Center

Location and Center in Italy	No. of Patients	No. of Lesions	Primary Tumor		Metastases							
			HCC	Cholangiocellular Carcinoma	Colon	Pancreas	Breast	Lung	GI System	GU System	NE System	Other
Vimercate, General Hospital	455	704	363	1	56	1	24	2	3	3	0	2
Busto Arsizio, General Hospital	330	534	210	0	103	0	8	0	3	2	2	2
Clusone, San Biagio General Hospital	153	288	136	1	12	1	1	2	0	0	0	0
Romano di Lombardia, Santa Trinità General Hospital	100	143	89	1	9	1	0	0	0	0	0	0
Roma, San Camillo General Hospital	80	145	24	0	40	3	8	0	3	0	2	0
Roma, Policlinico Umberto I, Department of Radiology	79	97	50	0	16	1	6	3	2	1	0	1
Franciacorta, Clinica San Rocco	77	148	38	0	27	2	8	0	2	0	0	0
Cremona, General Hospital	69	115	39	0	18	1	6	0	2	0	0	3
Pisa, General Hospital	68	108	27	0	30	0	4	1	4	0	1	1
Cosenza, Annunziata General Hospital	66	105	57	0	9	0	0	0	0	0	0	0
Bari, Policlinico, Department of Surgery	64	95	54	1	7	0	0	0	0	0	1	1
Pietra Ligure, Santa Corona General Hospital	61	100	31	0	20	1	5	0	0	1	1	2
Milano, San Paolo General Hospital	54	77	54	0	0	0	0	0	0	0	0	0
Bologna, Policlinico Sant' Orsola	45	52	40	0	3	0	0	0	0	1	0	1
Napoli, Ascalesi General Hospital	43	50	37	0	3	0	1	1	0	0	0	1
Milano, Istituto Humanitas	43	60	33	1	7	0	0	0	0	1	0	1
Varese, Macchi General Hospital	41	70	28	1	7	1	3	0	1	0	0	0
Milano, Fatebenefratelli General Hospital	41	50	23	2	13	1	1	0	1	0	0	0
Pordenone, Santa Maria degli Angeli General Hospital	38	61	27	1	9	0	0	0	0	0	0	0
Comacchio, General Hospital	36	42	30	0	5	0	1	0	0	0	0	0
Firenze, Careggi General Hospital	33	61	10	0	17	2	1	0	0	0	0	3
Dolo, General Hospital	32	50	10	0	17	1	0	2	2	0	0	0
Perugia, Coppito General Hospital	28	30	23	0	3	0	1	0	1	0	0	0
Foggia, General Hospital	28	34	18	4	3	0	2	0	1	0	0	0
Pavia, Fondazione Maugerie	25	31	15	0	6	1	2	0	0	0	1	0
Torino, Molinette General Hospital	23	36	12	0	7	1	1	0	0	0	0	1
Senigallia, General Hospital	20	21	20	0	0	0	1	0	0	0	0	0
Roma, Tor Vergata University	18	20	8	0	8	1	1	0	0	0	0	0
Roma, Cattolica University	18	24	11	1	5	0	0	1	0	0	0	0
Napoli, Policlinico Federico II	16	18	13	0	3	0	0	0	0	0	0	0
Este, Ospedale USLL 17	15	24	13	0	2	0	0	0	0	0	0	0
Bari, Di Venere General Hospital	15	18	10	0	2	0	1	1	0	0	1	0
Mestre, Umberto I General Hospital	15	20	13	0	1	0	1	0	0	0	0	0
Roma, Vannini General Hospital	14	31	3	1	7	0	1	0	0	1	1	0
Roma, Policlinico Gemelli	13	17	10	1	0	1	1	0	0	0	0	0
Roma, Policlinico Umberto I, Department of Surgery	11	12	4	0	6	0	1	0	0	0	0	0
Avezzano, General Hospital	11	15	2	0	6	0	2	0	0	1	0	0
Pistoia, General Hospital	11	14	9	0	2	0	0	0	0	0	0	0
Conegliano, General Hospital	11	13	1	1	8	0	1	0	0	0	0	0
Aquila, General Hospital	10	11	8	0	1	0	1	0	0	0	0	0
Bari, Policlinico, Department of Gastroenterology	10	10	7	0	3	0	0	0	0	0	0	0
Total	2,320	3,554	1,610	17	501	20	94	13	25	11	10	19

Note.—GI = gastrointestinal; GU = genitourinary; NE = neuroendocrine.

ences existed between centers at which members were experienced (ie, centers at which members performed procedures in more than 25 or 50 patients) and centers at which members were less experienced (ie, centers at which members performed procedures in fewer than 25 or 50 patients) and to determine whether differences existed between the types (ie, surgical, radiologic, or medical) of centers at which the procedure was performed. This author used ANOVA with post hoc pairwise comparisons to determine whether the tumor size, the number of RF ablation sessions, and the RF electrode type (single vs cluster) were related to the rate of complications. For the analyses of rates, the arc-sine square root transformation was used to convert all data into normalized variables.

RESULTS

All 41 centers responded. The number of patients treated per center ranged from 10 to 455, and the total was 2,320 patients. In total, 3,554 lesions were treated (Table 1). In this group, 1,610 patients had HCC in the presence of cirrhosis and or chronic liver disease; 683 patients had intrahepatic metastases, predominantly from colorectal cancer (Table 1); and 17 patients had cholangiocellular carcinoma. Tumor sizes ranged from 1 to 13 cm for HCC and from 0.7 to 9.6 cm for metastatic lesions, with approximately 3,000 (approximately 85%) being smaller than 5 cm.

Cases of a total of 217 of 2,320 patients were previously reported in the literature (3–7).

Coagulation Guidelines

At all centers, routine coagulation tests were performed prior to the procedure and included prothrombin time (as measured by percentage of activity), partial thromboplastin time, and platelet count. General consensus among the centers was achieved on the basis of the guidelines used for performing other interventional procedures, such as biopsy or PEI; that is, that a prothrombin time greater than 40% (ie, corresponding to an INR of 1.8), a partial thromboplastin time greater than 40 seconds (ie, a 5-second elevation above a 35-second upper normal boundary), and a platelet count greater than 40,000 $\times$ mm^3 were viewed as the minimum threshold for safety in performing RF ablation. Hence, patients whose values were within these guidelines, particularly patients with cirrhosis and splenomegaly, were treated without an attempt to correct any mild coagulopathy (INR $<$ 1.8) within the accepted practice guidelines of Italy. None of the patients in this study had an abnormal coagulation profile corrected with blood products in an attempt to perform RF ablation.

Mortality

A total of six (0.3%) patients died (Table 2). Five of these patients had HCC, and one had metastatic disease. In three of the five patients, these deaths were attributed to RF-induced thermal damage; in two patients, colonic perforation occurred with infiltrating HCCs that were 3.5 and 4.2 cm in diameter. Both of these patients had lesions adjacent (within 1 cm) to the colonic wall. They developed feculent peritonitis and multiorgan failure within several days following the procedure.

Despite surgical intervention within 24 hours of the development of clinical signs of peritonitis, these patients died. One of these patients had multiple adhesions from a previously resected cholecystectomy, and the second patient had had inflammatory calculous chronic cholecystitis, which suggested that the liver may have been adherent to the local bowel. In the third patient with Child class B cirrhosis, an infiltrating 4.5-cm HCC was treated although it was adjacent to the hepatic hilum. The patient died 25 days following the procedure secondary to liver failure, which was induced in part by thermal damage and subsequent stenosis of the right bile duct, as detected with contrast-enhanced CT performed 17 days following the RF ablation.

TABLE 2
Deaths after RF Ablation

Complications	No. of Deaths	Pathologic Diagnosis
Intestinal perforation, peritonitis, multiorgan failure; in patients with cirrhosis	2	HCC
Peritonitis (*Staphylococcus aureus*), septic shock, multiorgan failure; in patient with obesity, cirrhosis, and diabetes	1	HCC
Tumor rupture, massive hemorrhage	1	HCC
Stenosis of right bile duct, liver failure; in a patient with Child class B cirrhosis	1	HCC
Sudden death of unknown cause occurred 3 days after RF ablation; in a patient with metastases from pancreatic cancer (presence of gas in biliary tree)	1	Metastases

As previously reported, one patient with obesity and diabetes mellitus who had two huge HCCs died 8 days following RF ablation of septic shock and multiorgan failure (6). These symptoms developed 3 days following ablation. US-guided paracentesis yielded abundant *S aureus*. This death was attributed to a break in sterile technique (ie, inadvertent introduction of pathologic organisms into the sterile field by unknown means) during the procedure and not to the RF ablation.

One patient with Child class B cirrhosis had an infiltrating and superficial HCC nodule that was 6.5 cm in diameter. During the procedure, this tumor ruptured, resulting in massive peritoneal hemorrhage. Despite massive blood transfusions (8 units of red blood cells), the patient died of hepatic coma 3 days after the procedure.

A sixth patient with three metastases from pancreatic cancer died suddenly at home of unknown cause 3 days following the procedure. Because an autopsy was not performed, the actual cause of death could not be ascertained. Nevertheless, one interesting and potentially discriminating feature was the presence of gas within the biliary tree that was caused by a previous surgical enteric loop anastomosis that was detected at CT prior to RF ablation.

Major Complications

Fifty (2.2%) major complications were reported in 2,320 patients (Table 3). The number of major complications, including deaths, was 56 (2.4%) of 2,320. Almost all of these occurred during the periprocedural time (ie, within 30 days of the RF ablation). The most common complications included 12 (0.5%) cases of intraperitoneal hemorrhage requiring therapy; 11 of these cases occurred in patients with HCC (Figs 1, 2). Seven (64%) of the 11 patients with HCC had an INR between 1.4 and 1.8, and the patient with metastases had normal coagulation test results.

Nine of these HCCs and the metastasis (10 [83%] of 12 in total) were superficial in location (ie, abutting or protruding the liver capsule). Transfusion was necessary in nine (75%) of 12 cases, and surgical intervention was required in three (25%). In one of these cases, arterial embolization was required to correct an iatrogenic arterioportal shunt that was complicated by an intrahepatic hematoma (Fig 2). In one patient, the development of strong hiccups during general anesthesia led to laceration of the superficial tumor and tearing of the hepatic capsule because of malpositioning of the electrode. This led to bleeding that required laparotomy.

Six (0.3%) patients with intrahepatic abscesses were identified; in four of these, percutaneous image-guided drainage was required in addition to intravenously administered antibiotics, and in one, surgical intervention was performed on the basis of surgical preference (Fig 3). Intravenous antibiotic administration alone was sufficient for treatment of the abscess in one patient. Three of these patients did not receive prophylactic antibiotics at the time of ablation; two of these patients had diabetes mellitus. Three received prophylactic antibiotic therapy: Two had pneumobilia due to prior gastrointestinal surgery (ie, bilioenteric anastomoses), and one had diabetes mellitus.

In addition to the two previously mentioned cases of gastrointestinal tract perforation in which the patients died, five (0.2%) additional cases were identified (Figs 4–6). Perforation occurred as fol-

TABLE 3
Major Complications after RF Ablation

Complication	No. of Complications	Pathologic Diagnosis
Peritoneal bleeding requiring surgery (n = 3), blood transfusions (n = 9), and arterial embolization (n = 1)	12	11 HCCs, 1 metastasis
Seeding*	12	8 HCCs, 4 metastases
Hepatic (tumoral) abscesses requiring surgery (n = 1), drainage (n = 4), or antibiotic therapy alone (n = 1)	6	3 HCCs, 3 metastases
Perforation of gastrointestinal wall requiring surgery (4 in patients with prior colon resection)	5	4 metastases, 1 HCC
Hemothorax requiring drainage	3	2 HCCs, 1 metastasis
Rapid hepatic decompensation	2	HCCs
Diaphragmatic paresis (lesion in liver segment VIII)	1	Metastasis
Portal hypertension, portobiliary fistula, hemobilia, phlebitis, and acute thrombosis, with portal venous cavernous transformation	1	HCC
Stenosis of common bile duct requiring stent placement	1	HCC
Cardiac arrest requiring cardiac massage	1	HCC
Pulmonary embolism from venous thrombosis (after 3 h of RF procedure)	1	HCC
Pneumothorax requiring drainage	1	Metastasis
Large biloma requiring drainage	1	Metastasis
Multisegmental hepatic infarction, with liver decompensation	1	HCC
Acute cholecystitis requiring antibiotic therapy	1	HCC
Septicemia (Enterococcus) requiring antibiotic therapy	1	HCC

* This complication was delayed.

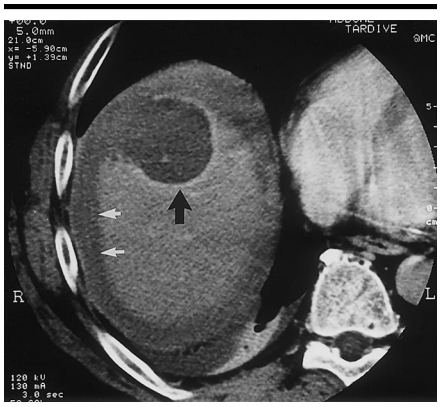


Figure 1. Transverse CT scan shows hemorrhage caused by rupture of a superficial 4.5-cm HCC. Scan was obtained because of a decrease in hematocrit level 24 hours following RF ablation. High-attenuation fluid, denoting hemorrhage, is observed surrounding the liver (white arrows). Black arrow points to the ablated hepatoma. The patient was successfully treated with a blood transfusion. Follow-up CT scans showed complete resolution of this complication.

lows: in three patients, in the colon; in one, in the stomach; and in one, in the jejunum. At surgery in these five patients, thermal damage into the gastrointestinal wall was documented, and repair of the defect was performed at that time. In these patients, symptoms that included pain, fever, and increased white blood cell count were noted approximately 2–4 days following RF ablation.

In a retrospective review, it was noted that six (86%) of seven cases of perforation occurred in patients with prior colonic resection, and at surgery, most of these patients had fibrotic adhesions that affixed the gastrointestinal tract to the liver. One case of gastric perforation occurred in a patient who had received relatively aggressive treatment (ie, eight prolonged RF applications) for a 7.2-cm superficial HCC in the left lobe adjacent to the stomach (Fig 6). Hemorrhage requiring transfusion was noted following treatment. Findings at CT performed 4 days following the procedure for recurrent persistent pain indicated perforation. At surgery, both gastric perforation and rupture of the tumor surface were documented.

Hemothorax that necessitated drainage was documented in three (0.1%) cases. In all three cases, an oblique intercostal approach was used for the RF electrode insertion, which suggested that the needle may have severed an intercostal vessel. For at least two of these cases, the thicker 0.5-cm-diameter cluster electrode system was used.

Two major complications regarding the biliary tree were noted. These included a case of a large biloma that required drainage and another of a biliary stricture that required stent placement.

Other major complications included cases of cardiac arrest and pulmonary embolism and a case of left contralateral pneumothorax. These were largely attributed to poorly defined iatrogenesis that was caused by performance of image-guided interventional procedures with the patient receiving general anesthesia, but they were not specifically caused by the RF thermal ablation.

In 12 (0.5%) of 2,320 patients, a single delayed major complication, neoplastic seeding, along the course of the original electrode track (Fig 7) was documented. These foci of seeding were noted 4–18 months following therapy. Nine (75%) of the 12 tumors were superficial in location, and six (50%) of the cases of neoplastic seeding (four with HCC and two with colorectal metastases), including the three deeper lesions, occurred in patients who had undergone prior biopsy. Brief RF heating of the electrode track (ie, "hot withdrawal") was performed for the three deeper lesions, which were all cases of highly undifferentiated HCC.

Minor Complications and Side Effects

In total, minor complications, as reported in Table 4, occurred in 110 (4.7%) of the patients. The procedural side effects of periprocedural pain, fever, and asymptomatic pleural effusion were common and not well quantified. Intraprocedural pain was generally seen when a lesion had a superficial or parahilar location. This pain usually occurred only during RF application, particularly when the pulsed technique was performed at high generator output. The level of pain usually depended on a personal pain threshold and was therefore unpredictable. Pain within the first several days following the procedure occurred less frequently and was usually associated with aggressive treatment of superficial lesions, particularly those adjacent to the diaphragm.

Fever with a temperature to 39°C often was documented during the first days and has been previously reported as a part of the postablation syndrome (24). Although not formally quantified, in general, the likelihood of fever was related to the amount of tissue necrosis, with more ag-

gressive procedures resulting in greater increases in temperature. Pleural effusion was a common feature, especially when an intercostal approach was used or the lesions were situated high in the dome of the liver (Fig 8). These effusions were asymptomatic and resolved without therapy within 1–2 weeks.

Most of the five (0.2%) cases of grounding pad burns occurred early in the collective experience before multiple grounding pads were used. All of these were second-degree or mild third-degree burns that healed with topical therapy and did not require surgical intervention.

One delayed minor complication, stenosis with dilatation of small bile duct radicals (ie, branches), was occasionally seen as an incidental finding at routine follow-up imaging, and it was usually distal to the location of the tumor. This complication occurred at 3 months or longer after initial RF therapy (Fig 9). In these cases, the dilatation of these focal small regions of the biliary tract did not result in marked complications, since none of these patients had subsequent bouts of cholangitis.

Influence of Electrode Type

Three (0.2%) deaths in 1,909 patients were observed with the use of the single electrode, and three (0.7%) deaths in 421 patients were observed with the use of cluster electrodes. Single electrodes were used in 38 (2.0%) of 1,909 patients with 50 major complications, and cluster electrodes were used in the remaining 12 (2.9%) of 421 patients with major complications. These differences did not approach statistical significance ($P > .1$). No complications were observed in 10 of 2,320 patients in whom both electrode types were used to treat separate lesions.

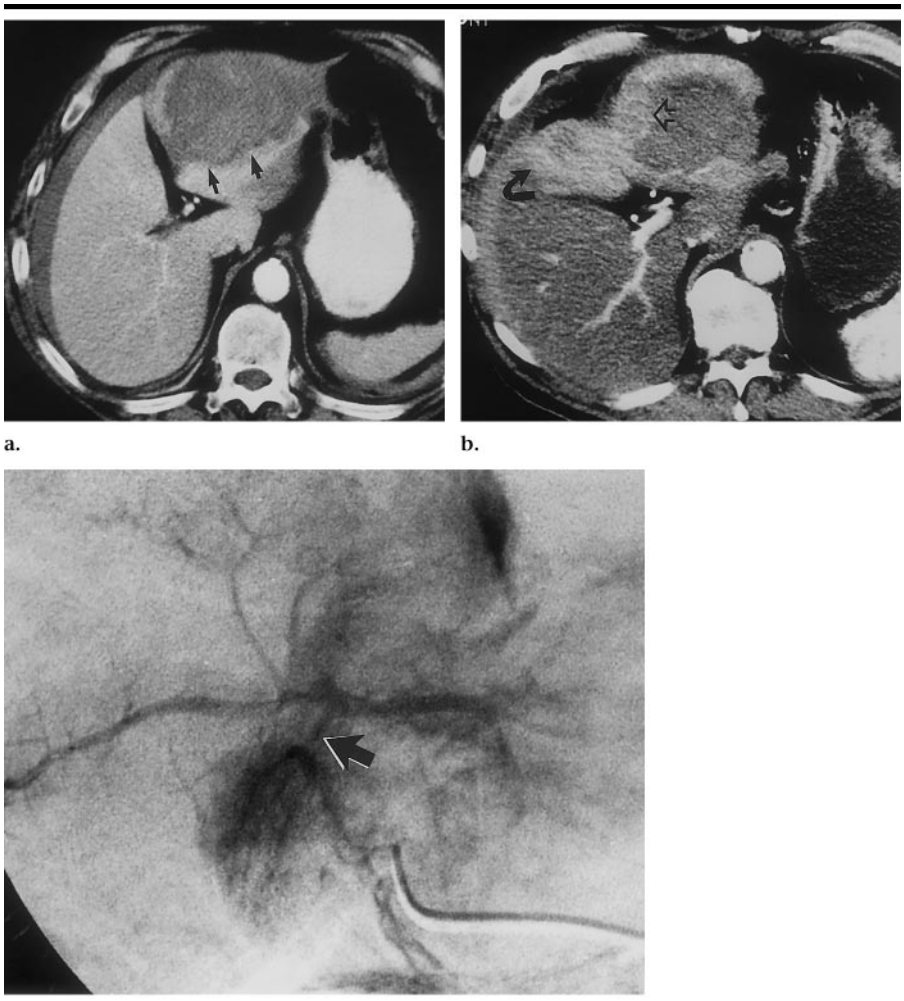


Figure 2. **(a–c)** Images show hemorrhage following RF ablation. **(a)** Transverse CT was performed immediately following RF ablation of a 5.8-cm hepatoma (INR, 1.3), and a large intrahepatic hematoma (arrows) superior to the treated lesion was identified. **(b)** Transverse CT scan shows high-attenuation intraperitoneal (solid arrow) and subcapsular hemorrhage (open arrow). **(c)** Angiographic image demonstrates iatrogenic arterioportal shunt (arrow) that was successfully embolized.

Influence of Lesion Size and Number of Sessions

Mean tumor diameter was 3.1 cm ± 1.1 (SD) in the global study population, 3.2 cm ± 1.4 in patients with major complications, and 2.6 cm ± 1.0 in those with minor complications. Thus, there was no statistically significant difference among these three groups (ANOVA), suggesting that lesion size cannot by itself be used to predict the occurrence of complications.

Overall, a mean of 1.3 sessions ± 0.8 was required to ablate a lesion. However, patients experiencing major complications were treated during a mean of 2.2 sessions ± 1.0 ($P < .01$). Patients experiencing minor complications were treated during a mean of 1.3 sessions ± 0.9 ($P > .5$ compared with the global population). Thus, a statistically significant difference in the number of sessions was noted between these three groups of patients, with a greater number of ablation sessions being performed in patients with major but not minor complications (ANOVA of post hoc pairwise comparisons).

Influence of Center Experience and Type

With ANOVA, significant differences in the rate of death or in the rate of major or minor complications could not be identified on the basis of the level of experience of the members of the centers. However, a significantly greater complication rate was found at the surgical centers when compared with the medical and radiologic centers. The rate of combined death and other major complications was 16.7 per 1,000 patients for the radiologic centers, 23.0 per 1,000 patients for the medical centers, and 60.2 per 1,000 patients for the surgical centers ($P = .01$) (Table 5). Given that the one surgical center at which laparoscopic assistance was used had only one major complication (bleeding) in 42 (2.4%) procedures, the use of laparoscopy did not contribute to this observation.

DISCUSSION

Regardless of the resulting benefits, the performance of image-guided interven-

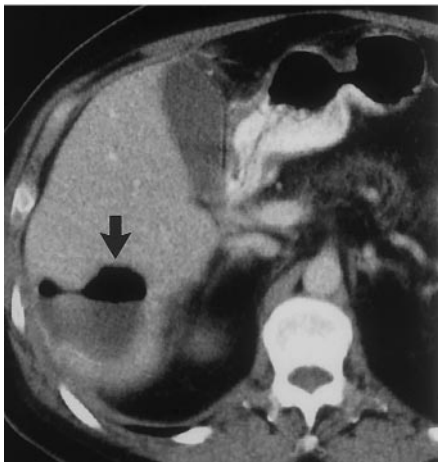
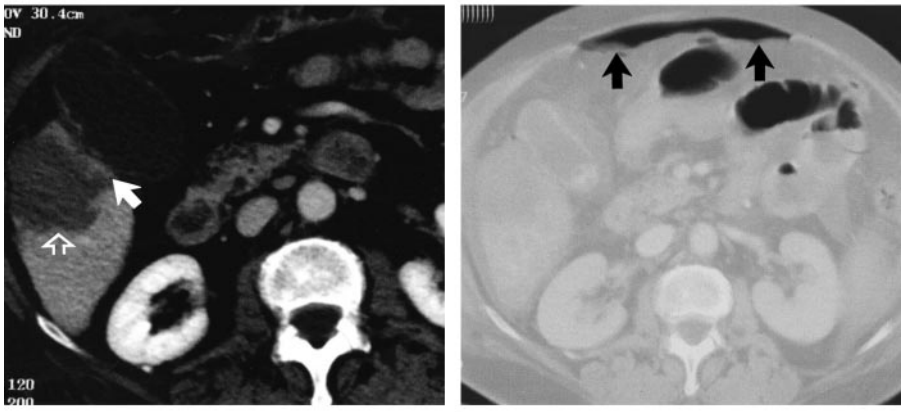


Figure 3. Transverse CT scan shows a hepatic abscess in a 64-year-old man who had a fever and an increased white blood cell count 4 days following RF ablation of two colorectal metastases. CT scan shows a large fluid- and air–filled cavity (arrow). This *S epidermis* abscess was successfully treated with percutaneous drainage and intravenous antibiotic therapy.



a. b.

Figure 5. **(a, b)** CT scans show colonic perforation with associated hepatic decompensation. A 3-cm HCC in a 72-year-old woman was treated with a single 3-cm RF electrode. **(a)** Transverse CT scan obtained 24 hours after RF ablation demonstrates adequate coagulation necrosis surrounding the original tumor (open arrow) and a clear margin of viable liver tissue (solid arrow) separating the treatment zone from the hepatic flexure. **(b)** Transverse CT scan obtained 72 hours after treatment because of severe hypotension without peritoneal signs revealed intraperitoneal fluid and gas (arrows). Entire liver was hypoperfused as manifested by multiple diffuse small foci of hypoattenuation. Surgery performed 1 day later revealed perforation of the colon where adhesions had affixed it to the liver surface near the ablation site.

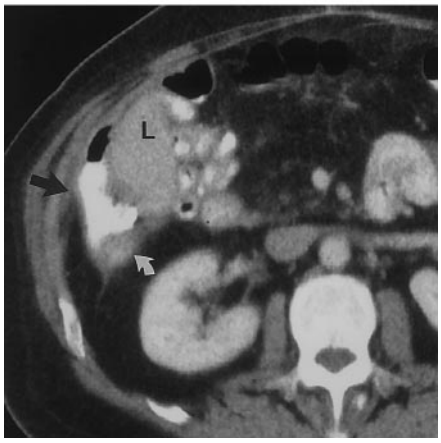


Figure 4. Transverse CT scan obtained 5 days after RF ablation of a 2.7-cm colorectal metastasis demonstrates colonic perforation represented by an area of high attenuation (black arrow) between the liver *(L)* and ascending colon (white arrow). At the time of the procedure, the superficial lesion abutted the colon.

tional procedures will always entail some degree of risk. Characterization of these risks and determination of methods to avoid these complications are of extreme importance whenever a new procedure is established. For example, when PEI was initially introduced for the treatment of small hepatic lesions, complications caused by the introduction of the needle (ie, those occurring with the performance of fine-needle biopsy, such as bleeding and infection) were foreseen. However, other risks caused by the instillation of ethanol, such as chemical portal thrombosis, were less predictable (25).

Hence, a large multicenter experience of several years was required to characterize rarer complications and to objectively quantify the expected complication rate in the hands of a skilled physician (25,26). Only from this experience were we able to appropriately assess exclusion criteria and determine absolute and relative contraindications to the PEI procedure with any degree of certainty. The treatment of liver tumors with RF ablation also requires a similar safety evaluation. Although complications caused by needle placement are expected to be similar to those of biopsy and PEI, the absolute rate of these complications for RF ablation with larger needles is currently incompletely determined. Additionally, complications specific to thermal ablation, particularly those due to untoward heating, require evaluation in a large population.

RF ablation is a complicated procedure, and substantial experience is required for it to be performed safely. Indeed, we attribute the fact that surgical centers had more complications to their more limited experience in the use of percutaneous image-guided techniques. Yet, we did not note a significant difference in the rate of major complications or death on the basis of the experience of the centers. Although it is likely that some complications will be idiosyncratic (ie, the more cases performed, the more likely one will observe a given complication), this finding also may be attributed to the fact that the centers with the greatest experience were the first to perform RF ablation; hence, they had a greater number of complications during a learning curve over which many of the relative contraindications emerged.

Alternatively, with the exception of the initial two centers, all investigators were required to observe a minimum of 10 patients at a center with more experience prior to commencing RF ablation at their own institution, and this may have provided the critical threshold knowledge to master the RF technique. Yet, our analysis is further confounded by the fact that many of the smaller centers performed this procedure only in straightforward cases and referred more difficult cases to the larger centers. Regardless, given that this study includes much of the global learning curve of the RF ablation procedure, it is possible that the rate of complications will be further reduced in the future.

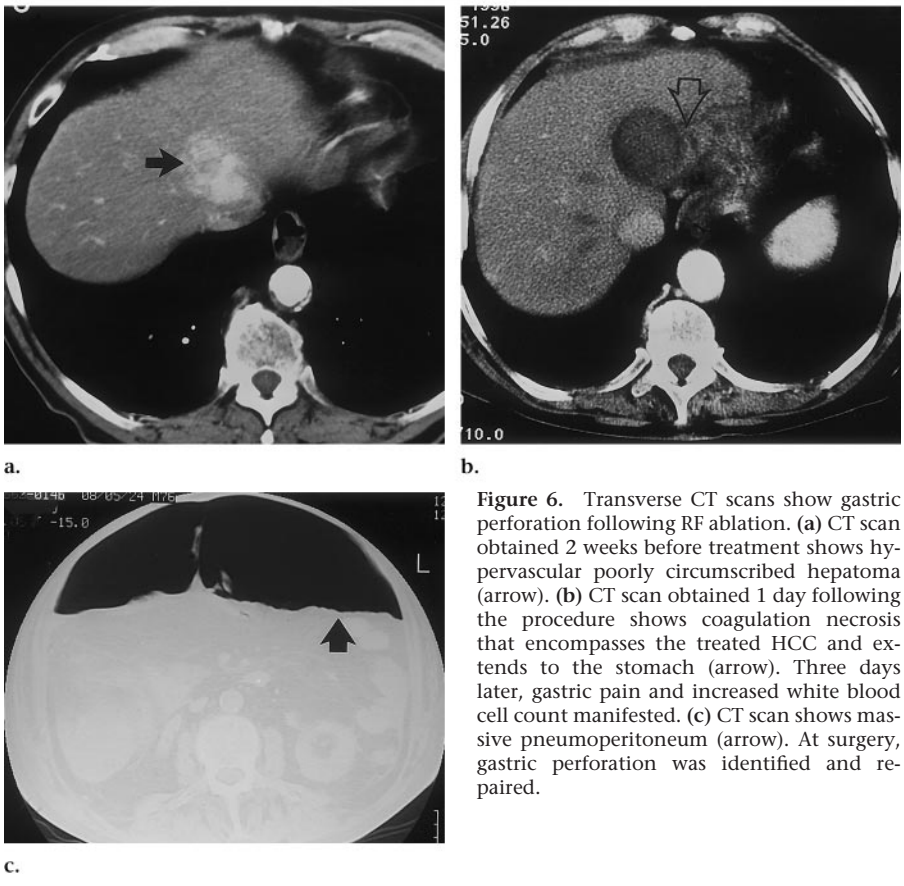
Four different types of complications were reported: thermal damage from heating and mechanical, septic, and other unexplained causes. The latter three types of complications cannot be attributed directly and specifically to RF thermal ablation alone but are likely caused by the performance of any image-guided needle procedure in patients who are receiving general anesthesia. Thermal damage included cases of gastrointestinal perfora-

tion, biliary stenosis, and grounding pad burns. Mechanical complications were injuries to the vessels and the biliary tract, including hemorrhage and bile leakage with or without arterioportal or biliary-portal shunt formation, and tumor seeding. Septic complications included abscess formation, septicemia, and peritonitis. Other complications included cases of cardiac arrest, pulmonary embolism, and left pneumothorax, which all occurred in patients who received general anesthesia.

Although it is likely that we did not detect a few rare complications that did not occur in this patient population but which will undoubtedly be observed in future patients, the large number of patients whose cases were analyzed in this survey is almost certainly sufficient to determine the relative risks of RF ablation. Indeed, one case of a thermal burn to the diaphragm with an associated abscess that led to sepsis and multiorgan failure and one case of bile leakage that required laparotomy have been previously reported (8,11), but they were not observed in this study. Nevertheless, given the large number of centers and the variety of physicians performing the procedure, it is likely that this study is representative of complications that may be encountered by different operators.

The most important major complication due to thermal damage was that of perforation of the gastrointestinal wall, which occurred in 0.7% of patients. This complication was particularly dangerous in fragile patients (ie, those with advanced cirrhosis) and led to the death of two patients. Perforation was observed only when the tumor was within 1 cm of the liver capsule and adjacent to a gastrointestinal lumen. An additional risk factor was prior abdominal surgery or chronic cholecystitis in the region adjacent to the tumor; these conditions led to documented fibrotic adhesions between the bowel and liver. Tight adhesion of the bowel to the liver may have precluded the normal peristalsis and migration of the bowel away from the liver, which in turn heated the bowel during the procedure.

Clinical symptoms of perforation usually manifested several days after the procedure, and this delay was likely due to the fact that several days are required for the dead cells within the bowel wall to slough. Alternatively, surrounding inflammation contained the perforation for some time prior to clinical declaration. Early signs of perforation, an increase in white blood cell count and fever, were nonspecific. Hence, it may be prudent to perform CT of the abdomen in patients with an increased white blood cell count that develops several days following RF ablation.



a. b. c.

Figure 6. Transverse CT scans show gastric perforation following RF ablation. **(a)** CT scan obtained 2 weeks before treatment shows hypervascular poorly circumscribed hepatoma (arrow). **(b)** CT scan obtained 1 day following the procedure shows coagulation necrosis that encompasses the treated HCC and extends to the stomach (arrow). Three days later, gastric pain and increased white blood cell count manifested. **(c)** CT scan shows massive pneumoperitoneum (arrow). At surgery, gastric perforation was identified and repaired.

On the basis of these observations, we recommend that patients who have undergone prior right upper quandrant surgery and who have lesions within 1 cm of the capsule in the region adjacent to the bowel should be treated with RF ablation either with laparoscopic guidance or at laparotomy, when separation of the bowel from the liver can be ascertained with direct visualization prior to RF heating (12) or, alternatively, when the pathologic diagnosis is HCC with PEI or other nonthermal ablation methods. Nevertheless, it is important to stress that these complications do not always occur. Indeed, we have successfully treated more than 20 lesions adjacent to the gallbladder without the introduction of cholecystitis (3,6). Thus, the risk of thermal damage to adjacent structures needs to be weighed in terms of potential risks versus benefits on a case-by-case basis. Additionally, in centers with limited US experience, it may be wiser to perform these riskier procedures with the assistance of CT guidance (in addition to US) whenever possible in an attempt to maximize the visualization of the adjacent bowel.

Figure 7. Follow-up transverse US scan obtained 6 months following RF ablation of a 3.5-cm hepatoma shows tumor seeding. A small 2-cm mass was revealed between the cursors outside of the peritoneal cavity and within the intracostal muscles. This lesion was located along the track of the initial electrode insertion, which suggested iatrogenic seeding from the procedure.

The colon appears to be at greater risk for thermally mediated perforation than are the stomach and the small bowel, since only one case each of gastric and small intestinal wall perforation were reported

TABLE 4
Minor Complications after RF Ablation

Complications	No. of Complications
Acute	
Skin burn (hip prosthesis, entrance point, grounding pad too small)	5
Asymptomatic thickening of gallbladder wall	6
Self-limiting intraperitoneal bleeding	19
Arterioportal shunt (asymptomatic CT imaging finding)	9
Biliary portal shunt with hemobilia	8
Thickening of diaphragm	3
Transient liver decompensation (in cirrhosis)	11
Biloma	2
Subcapsular hematoma	3
Intratumoral (intrahepatic) hematoma	3
Direct damage of renal tissue (without clinical sequelae)	1
Pain developing 3 d after procedures	35
Delayed	
Biliary duct stricture	5

Figure 8. CT scan shows pleural effusion in a patient with multifocal HCC who was treated with RF ablation. At 24 hours after RF ablation, pleural effusion (arrow) with compressive atelectasis was noted. This asymptomatic finding resolved within 1 week.

despite numerous treatments of tumors located adjacent to these organs. We attribute the rarity of gastric complications to the greater wall thickness of the stomach, the rarity of surgical adhesions along the gastrohepatic ligament, or to both. The mobility and peristalsis of the small bowel also may provide greater protection of this organ, compared with the fixed nature of the colon. The bile ducts also appear to be at risk for injury that can lead to delayed stenosis. Thus, for hepatomas adjacent to the portal hilum, PEI should be seriously considered as an alternative to RF ablation. On the other hand, dilatation of small, peripheral biliary radicals distal to the treated tumor did not result in any clinically meaningful complications for the patient.

Eleven of 12 cases with clinically important intraperitoneal bleeding occurred in patients with cirrhosis, which suggests a higher risk for bleeding in these patients, given the high percentage of clinical or subclinical coagulation disorders in patients with liver disease and the higher vascularity of hepatomas compared with metastases. However, the rate of bleeding complications for patients with HCC was 0.7% in this study, which is not substantially increased compared with the 0.5% reported in large studies of patients treated with PEI and thinner needles (26).

Two risk factors that led to septic complications were the presence of diabetes mellitus and/or the presence of air in the biliary tract. This latter risk factor likely arises from possible enteric contamination that results from the communication between the biliary tree and the nonsterile gastrointestinal tract. Given the low incidence but serious nature of these complications, we now have collectively agreed to the use of antibiotic prophylactic therapy for patients with these two conditions. Additionally, following the first death that was attributed to peritonitis from a break in sterile technique, many centers now routinely administer antibiotics prior to the performance of RF ablation in all patients.

Yet, it must be noted that at many centers the practice of and protocol for antibiotic administration evolved during the time of the study; as a result, the exact number of patients receiving antibiotics was not assessed. Also, the type and regimen of antibiotic therapy were not uniform among the centers, and consensus on a well-defined protocol has yet to be determined. Thus, one potential limitation of this study is that we cannot provide a definitive relative risk for performance of RF ablation in the liver with or without antibiotic prophylactic therapy.

The risk of tumor seeding occurred primarily in superficial tumors (where heating of the needle track is not possible) and in deeper lesions in which a biopsy was previously performed and that were poorly differentiated HCC. Llovet et al (9) reported a similar set of risk factors. Indeed, half of the cases of tumor seeding occurred in patients who had had a percutaneous needle biopsy, and that may have contributed to or caused this complication. For the cases in which biopsy was not performed, given that the RF ablation destroys the tumor surrounding the electrode, we speculate that seeding in these cases probably occurred because of the repositioning of unsatisfactory initial electrode insertions without intervening RF heating. Thus, a meticulous technique should be performed when the electrode is initially placed, with careful attention to the technique to ensure optimal positioning on the first pass.

Additionally, physicians should consider the application of a small amount of heat surrounding the electrode prior to repositioning (ie, "hot withdrawal"), which may also reduce the complication of bleeding by inducing tissue coagulation. A high rate (12%) of seeding after RF ablation of HCC was recently reported in a study at one center (9). The high rate of seeding in that study, in comparison with our 0.5% rate of seeding, was probably caused by many factors, including the small number and types of lesions treated (ie, sample bias of many superficial tumors and learning curve) and the additional biopsy performed by those investigators; in Italy, biopsy usually is performed only in cases in which the diagnosis is in doubt.

Liver decompensation from overtreatment in patients with cirrhosis was a theoretical complication that fortunately was observed only twice (<0.1%) in 2,320 patients. In both cases, multiple sessions of RF ablation were necessary to include the entire lesion, and destruction of surrounding cirrhotic tissue occurred. Thus, the local focal induction of tumor necrosis may constitute an important advantage for thermal ablation over conventional transarterial chemoembolization in which toxic therapeutic agents are diffused throughout the already damaged and poorly functioning liver.

Complications caused by the direct damage of vascular structures were also rarer than initially anticipated, as only three cases of intrahepatic vascular damage were reported. This finding can be attributed to the protective heat-sink mechanisms of vascular-mediated tissue perfusion that prevent tissues adjacent to big vessels from becoming thermally damaged. Indeed, this cooling effect has

been reported to have negative effects on the extent of desired tumor necrosis, with persistent residual tumor observed adjacent to vessels (26–28).

Several minor complications observed in this series deserve discussion. Although findings of this study did not help in the full quantification of cases of the commonly noted side effect of mild periprocedural pain, such cases have been noted with RF during the treatment, immediately after therapy, and during the first 3 days after the procedure. Delayed pain or fever (ie, that which occurs more than 3 days after the procedure) is uncommon and raises the possibility of complications such as perforation. For these cases, imaging should be performed to search for more serious underlying complications. When all findings appear to be within normal limits, the pain is most likely caused by peritoneal irritation from the inflammation that results, especially after treatment of a superficial tumor.

Skin burns were noted particularly early in the experience when insufficient grounding pads were used. This complication has become a rarity because of the use of larger grounding pads and the awareness of the recently published guidelines that promote grounding pad safety (29). In addition, the two other cases of skin burns also provide insight into ways to minimize complications. A burn near a metallic hip prosthesis suggests that the energy concentrated around the implanted metal and that grounding pads should likely be placed at a distance from these prostheses. Additionally, a burn along the track of one electrode in a thin patient with a superficial lesion suggests that care should be taken to ensure that the entire active electrode tip is embedded well into the liver and does not course through the skin, the muscle, or the diaphragm.

Our global experience has led to the adoption of some guidelines for performance of RF ablation that will hopefully reduce complication rates further. These guidelines are as follows: RF ablation is contraindicated when lesions are abutting the bowel (particularly when adhesions are suspected) or the main biliary ducts or when pneumobilia is present. Unlike with PEI, which has been used to successfully treat many patients with diabetes mellitus without the need for antibiotics (18,26), patients with diabetes mellitus who are treated with RF ablation require prophylactic periprocedural antibiotic therapy. Application of RF to coagulate tissues surrounding the electrode following incorrect insertion into the tumor should be considered to avoid tumor seeding, and the same maneuver should be used for patients at risk of bleeding to avoid hemorrhage. Patients with advanced liver disease or with large tumors that require aggressive therapy are at risk of liver decompensation. The superficial location of a tumor, a difficult targeting approach, the length of the procedure, and the number of treatment sessions are factors that will influence the occurrence of complications.

TABLE 5
Complication Rate according to Center Type

Death or Complication	Center		
	Radiologic	Medical	Surgical
Death	2.3	1.4	7.5
Complication			
Major	14.4	21.7	52.7
Combined	16.7	23.0	60.2

Note.—Data are presented as a rate per 1,000 patients. Statistically higher complication rates were observed at surgical centers.

Although findings of this study are helpful in identification of the potential complications that are associated with RF ablation, the retrospective design of our study precludes determination of the absolute risk for many of these associations. For example, many lesions with bleeding and tumor seeding were superficial, suggesting that the superficial location of a tumor may increase the relative risk of the need for performance of ablation. However, it is important to note that at least 100 superficial tumors were successfully treated without bleeding. Yet, we did not prospectively record the position of each tumor treated in regard to peripheral or deep location for all tumors, because the importance of this variable was not known at the time of the study.

Likewise, information about the exact number of RF applications and the total duration of heating were not available from many centers, which thereby limited our ability to correlate procedural risks with these variables. Similar limitations also apply equally to the issue of performance of RF ablation in patients who have diabetes mellitus. Clearly, half of the patients with an abscess had this underlying condition, but an unquantified greater number of them underwent the procedure without any complications. Now that these likely risk factors have been identified, the accurate assessment of the absolute risk can be determined from an ongoing prospective study.

In conclusion, results of this large multicenter study indicate that RF ablation is a relatively safe procedure with a very low death rate of 0.2% and a major complication rate of 2.2%. By comparison, this complication rate is lower than that reported for surgery (ie, 15%–30% morbidity and approximately 5% mortality [15–17]) and is equivalent to that for single-shot PEI. While further refinement in technique and patient selection is necessary to achieve safety equivalent to that for multisession PEI, this negative factor must be balanced on a patient-by-patient basis versus the increased risks and discomforts of multiple sessions and the potentially slightly lower effectiveness (4–6). It is anticipated that additional expertise and knowledge in regard to the use of the technique will help to better elucidate the causes of these negative outcomes and

Figure 9. Coronal MR image obtained 9 months after RF ablation of a 5.3-cm colorectal metastasis. Image shows the development of marked intrahepatic biliary ductal dilatation (solid arrows) distal to the zone of RF tumor ablation (open arrow). Ablation extended to the bile duct, the stricture was not present prior to ablation, and the region of coagulation decreased in size during the follow-up interval, suggesting that the thermal coagulation was responsible for this observation. This asymptomatic finding did not require therapy for more than 24 months of conservative treatment.

therefore will help to determine standardized criteria for RF ablation that will enable this procedure to become even safer.

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Acknowledgments: The authors thank Dario Giusti of Hospital Service, Rome, Italy, for financially supporting this study and Stefania Improta for her help in disseminating the questionnaires and collecting and tabulating the data.

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