13 Guidance and Assessment of Interventional Therapy in Liver

Riccardo Lencioni and Dania Cioni

CONTENTS

13.1 Introduction

Hepatocellular carcinoma is the fifth most common cancer, and its incidence is increasing worldwide because of the dissemination of hepatitis B and C virus infection (Llovet et al. 2003). Patients with cirrhosis are at the highest risk of developing hepatocellular carcinoma. Currently, hepatocellular carcinoma is the leading cause of death among cirrhotic patients. Surveillance can lead to diagnosis at an early stage, when the tumor may be curable by resection, liver transplantation, or percutaneous ablation (Bruix and Llovet 2002; Bruix et al. 2001).

Resection is currently indicated in patients with single asymptomatic hepatocellular carcinoma and extremely well preserved liver function who have neither clinically significant portal hypertension nor abnormal bilirubin (Bruix and Llovet 2002; Llovet et al. 2003). However, less than 5% of cirrhotic patients with hepatocellular carcinoma fit these criteria (Llovet et al. 1999). Liver transplantation benefits patients who have decompensated cirrhosis and one tumor smaller than 5 cm or up to three nodules smaller than 3 cm, but donor shortage greatly limits its applicability (Bruix and Llovet 2002; Llovet et al. 2003). This difficulty might be overcome by living donation, which, however, is still at an early stage of clinical application.

Hepatic metastases are a frequent event in the natural history of colorectal cancer. Twenty percent of patients with colorectal cancer have evidence of hepatic metastases at diagnosis, and 50% will develop metachronous metastatic disease (Jessup et al. 1996). Of the patients who develop hepatic metastases, nearly 25% will have disease isolated to the liver (Jessup et al. 1996).

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 having been obtained recently as a result of improvements in patient selection and peri- and postoperative care, multidisciplinary treatment, and an appropriately aggressive approach to safe hepatic resection (Scheele et al. 1995; Jamison et al. 1997; Fong et al. 1999a; Choti et al. 2002; Vauthey et al. 2004). Nevertheless, only 10–25% of patients with colorectal metastases isolated to the liver are eligible for surgical resection, because of the extent and location of the disease or concurrent medical conditions (Silen 1989). Unfortunately, conventional treatment of inoperable or nonresectable patients with systemic or intra-arterial chemotherapy protocols is not entirely satisfactory in terms of survival outcome (Jonker et al. 2000).

As a result, image-guided techniques for percutaneous tumor ablation play a major role in the therapeutic management of these patients. While percutaneous ethanol injection (PEI) is a well-established technique for percutaneous treatment of hepatocellular carcinoma, several newer methods of tumor destruction have been developed and clinically tested over the past few years (Lencioni et

R. Lencioni, MD, Associate Professor of Radiology;
D. Cioni, MD, Assistant Professor of Radiology
Division of Diagnostic and Interventional Radiology, Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Via Roma 67, 56126 Pisa, Italy

al. 2004a; Livraghi et al. 1991). Among these methods, radiofrequency (RF) ablation has emerged as the most powerful technique for tumor destruction and is nowadays established as the primary ablative modality at most institutions (Galandi and Antes 2004 pp. 10–20; Goldberg et al. 1998b; Volg et al. 1999; McGahan and Dodd 2000; Morita et al. 2004; Mala et al. 2004; Shibata et al. 2002; Goldberg 2002; Berber et al. 2004).

13.2 General Eligibility Criteria for Percutaneous Ablation Treatment

A careful clinical, laboratory, and imaging assessment has to be performed by a multidisciplinary team to evaluate eligibility for percutaneous tumor ablation (Lencioni et al. 2001).

In the case of cirrhotic patients with hepatocellular carcinoma, those classified as stage 0 (very early stage) or stage A (early stage) according to the Barcelona Clinic Liver Cancer staging classification for treatment schedule may qualify for percutaneous ablation if surgical resection and liver transplantation are not suitable options (Llovet et al. 2003). Patients are required to have (a) either a single tumor smaller than 5 cm or as many as three nodules smaller than 3 cm each, in the absence of vascular involvement and extrahepatic spread, (b) a performance status test of 0, and (c) liver cirrhosis in Child-Pugh class A or B.

In the case of patients with hepatic colorectal metastases, inclusion criteria for RF ablation require the patient not to be a surgical candidate. However, all the negative prognostic factors affecting the results of surgery, such as stage III colorectal cancer and metastases to the portal, hepatic, or celiac lymph nodes, also affect the outcome of RF ablation (Fong et al. 1999a; Iwatsuki et al. 1999; Sasson and Sigurdson 2002; August et al. 1985; Murata et al. 1998; Headrick et al. 2001; Mineo et al. 2003; Patel et al. 2003). Patients are required to have four or fewer lesions not exceeding 3.5 cm in the longest axis in order to obtain a safety margin of 1 cm all around the lesion (Berber et al. 2004; Goldberg et al. 2003).

Pretreatment imaging planning must carefully define the size, shape, and location of each lesion.

Lesions located along the surface of the liver can be considered for percutaneous ablation, although their treatment requires adequate expertise and may be associated with a higher risk of complications. RF ablation 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 (Rhim et al. 2004; Livraghi et al. 2003a; Buscarini and Buscarini 2004). The colon appears to be at greater risk than the stomach or small bowel for thermally mediated perforation (Rhim et al. 2004). 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. Treatment of lesions adjacent to the gallbladder or to the hepatic hilum entails the risk of thermal injury of the biliary tract. In experienced hands, RF ablation of tumors located in the vicinity of the gallbladder has been shown to be feasible, although associated in most cases with self-limited iatrogenic cholecystitis (Chopra et al. 2003). In contrast, RF ablation of lesions adjacent to hepatic vessels is possible, since flowing blood usually protects the vascular wall from thermal injury; in these cases, however, the risk of incomplete treatment of the neoplastic tissue close to the vessel may increase because of the heat loss. The potential risk of RF damage to critical structures should be weighed against benefits on a case-by-case basis.

Laboratory tests should include measurement of serum tumor markers, such as alpha-fetoprotein (AFP) in cirrhotic patients and carcinoembryonic antigen (CEA) in patients with hepatic colorectal metastases, and a full evaluation of coagulation status. A prothrombin time ratio (normal time/patient's time) greater than 50% and a platelet count higher than 50,000/μl are required to keep the risk of bleeding at an acceptable low level.

13.3 Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) is a well-established technique for tumor ablation (Bartolozzi and Lencioni 1996). Several studies have shown that PEI is an effective treatment for small, nodular-type hepatocellular carcinoma. Hepatocellular carcinoma nodules have a soft consistency and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively, leading to complete tumor necrosis in about 70% of the cases (Shiina et al. 1991). Although there have not been any prospective randomized trials comparing PEI and best supportive care or PEI and surgical resection, several series have provided indirect evidence that PEI improves the natural history of hepatocellular carcinoma: the long-term outcome of patients with early stage tumors who were treated with PEI was shown to be similar to that of patients who had undergone resection, with 5-year survival rates ranging from 32% to 52% (Castells et al. 1993; Lencioni et al. 1995, 1997; Livraghi et al. 1995; Shiina et al. 1993). In a recent prospective comparative study, the 1-, 3-, and 5-year survival rates were almost identical between two cohorts of patients who underwent surgical resection (97%, 84%, and 61%, respectively) or PEI (100%, 82%, and 59%, respectively) (Yamamoto et al. 2001).

Although PEI is a low-risk procedure, severe complications have been reported. In a multicenter survey including 1,066 patients (8,118 PEI sessions), one death (0.1%) and 34 complications (3.2%), including seven cases of tumor seeding (0.7%), were reported (di Stasi et al. 1997). The major limitation of PEI, besides the uncertainty of tumor ablation and the long treatment times, is the high local recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm (Khan et al. 2000; Koda et al. 2000). The injected ethanol does not always accomplish complete tumor necrosis because of its inhomogeneous distribution within the lesion, especially in the presence of intratumoral septa, and the limited effect on extracapsular cancerous spread. Also, PEI is unable to create a safety margin of ablation in the liver parenchyma surrounding the nodule, and therefore may not destroy tiny satellite nodules that, even in small tumors, may be located in close proximity to the main lesion (Okusaka et al. 2002) (Table 13.1).

Table 13.1. Survival outcomes of patients with early-stage hepatocellular carcinoma receiving percutaneous ablation

Treatment	No. of patients	Survival rate (%)		
		1year	3year	5year
Percutaneous ethanol injection				
Castells *et al. (1993)*	*30*	*83*	*55*	*N/A*
Shiina *et al. (1993)*	*98*	*85*	*62*	*52*
Lencioni *et al. (1995)*	*105*	*96*	*68*	*32*
Livraghi *et al. (1995)*				
Child class A, single HCC	*293*	98	79	47
Child class B, single HCC	149	93	63	29
Radiofrequency ablation				
Lencioni et al. (2005)				
Child class A	144	100	76	51
Child class A, single HCC	116	100	89	61
Child class B	43	89	46	31
Microwave coagulation				
Shiina et al. (2002)	122	90	68	N/A

N/A not available, *HCC hepatocellular carcinoma.*

13.4 Radiofrequency Ablation

13.4.1 Hepatocellular Carcinoma

Early clinical experiences with RF ablation were conducted in the framework of feasibility studies (Curley et al. 1999; Rossi et al. 2000). These investigations had merit in showing the efficacy and safety of the procedure. However, the data were heterogeneous and unsystematically presented (Galandi and Antes 2004). Moreover, RF treatment was not compared to any established treatment for hepatocellular carcinoma. The European Association for the Study of the Liver has recommended comparison of newer methods of tumor destruction, such as RF ablation, with the well-established and accepted PEI through randomized trials (Bruix et al. 2001). In fact, methodological research has yielded convincing evidence that less rigorous study designs are likely to produce biased results and to exaggerate the estimated effect of a new therapy (Galandi and Antes 2004).

One randomized study compared RF ablation versus PEI for the treatment of early stage hepatocellular carcinoma (Lencioni et al. 2003). In this trial, 104 patients with 144 hepatocellular carcinoma lesions were randomly assigned to receive RF ablation or PEI. No statistically significant differences between RF ablation and PEI groups were observed with respect to baseline characteristics, except for patient age and albumin concentration. At the time of the analysis, the mean follow-up was 22 months. The overall survival rates at 1 and 2 years were 100% and 98%, respectively, in the RF group, and 96% and 88%, respectively, in the PEI group. Despite the tendency favoring RF ablation, the observed difference did not reach statistical significance (hazard ratio, 0.20; 95% confidence interval, 0.02–1.69; p=0.138). However, 1- and 2-year recurrence-free survival rates were clearly higher in RF-treated patients than in PEI-treated patients (86% and 64%, respectively, in the RF ablation group versus 77% and 43%, respectively, in the PEI group; hazard ratio, 0.48; 95% confidence interval, 0.27–0.85; p=0.012). RF treatment was confirmed as an independent prognostic factor for local recurrence-free survival by multivariate analysis. This trial suggested that RF ablation can achieve higher recurrence-free survival rates than PEI, thereby confirming findings in two previous comparative studies, in which higher complete tumor response rates were observed in tumors treated with RF ablation than in those submitted to PEI (Ikeda et al. 2001; Livraghi et al. 1999). However, likely because of the short follow-up period and the limited sample size, no difference was found with respect to overall survival.

Recently, a prospective intention-to-treat clinical trial reported the long-term survival outcomes of RF ablation-treated patients (Lencioni et al. 2005b). In this study, 206 patients with early stage hepatocellular carcinoma who were not candidates for resection or transplantation were enrolled. RF ablation was considered as the first-line nonsurgical treatment and was actually performed in 187 (91%) of the 206 patients. The remaining 19 (9%) had to be excluded from RF treatment because of the unfavorable location of the tumor. Noncompliant patients were treated with either PEI or segmental transcatheter arterial chemoembolization. The overall survival rates in the intention-to-treat analysis including all 206 patients enrolled in the study (67% at 3 years and 41% at 5 years) were not significantly different from those achieved in the 187 compliant patients who received RF ablation (71% at 3 years and 48% at 5 years; p=0.5094). In patients who underwent RF ablation, survival depended on the severity of the underlying cirrhosis and the tumor multiplicity. Patients in Child class A had 3- and 5-year survival rates of 76% and 51%, respectively. These figures were significantly higher than those obtained in Child class B patients (46% at 3 years and 31% at 5 years; p=0.0006). Patients with a solitary hepatocellular carcinoma had 3- and 5-year survival rates of 75% and 50%, respectively, while those with multiple tumors had 3- and 5-year survival rates of 51% and 34%, respectively; again, this difference was statistically significant (p=0.0133). Of interest, a subgroup of 116 patients in Child class A who had a solitary hepatocellular carcinoma showed 3- and 5-year survival rates of 89% and 61%, respectively. In this series, recurrence of the tumor treated by RF ablation occurred in 10 of 187 patients. Despite the absence of viable neoplastic tissue on post-treatment spiral CT images, residual microscopic nests of tumor or small undetected satellite nodules led to local tumor progression. The actuarial 5-year local tumor progression rate was 10%. However, new hepatocellular carcinoma tumors developed in 93 patients during the follow-up. The rate of recurrence with new tumors reached 81% at 5 years. Such a high rate of new tumors is an expression of the inherent multicentric nature of hepatocellular carcinoma in cirrhosis and does not seem to represent a drawback of RF ablation, being found also in cirrhotic hepatocellular carcinoma patients treated with either percutaneous therapies or surgical resection.

The data on long-term outcome of RF ablation must be compared with those obtained in patients with early stage tumors who received other potentially curative treatments. Liver transplantation was shown to be the only treatment option that consistently provided 5-year survival rates in the range of 71–75% (Bismuth et al. 1999; Jonas et al. 2001; Llovet et al. 1999; Mazzaferro et al. 1996). Surgical resection of early stage hepatocellular carcinoma resulted in 5-year survival rates in the range of 41–51% (Fong et al. 1999b; Jonas et al. 2001; Llovet et al. 1999; Wayne et al. 2002). Resection achieved substantially higher survival rates only when patients with a solitary tumor and extremely well preserved liver function, who had neither clinically significant portal hypertension nor abnormal bilirubin, were selected (Llovet et al. 1999). In large series, PEI achieved 5-year survival rates ranging from 32% to 52%. In a multicenter study, survival of 293 patients with Child class A cirrhosis and a solitary tumor smaller than 5 cm who received PEI was 47% at 5 years (Livraghi et al. 1995). Comparison of results obtained with RF ablation with those achieved in the past by using PEI, however, may be biased by the ability to better select patients with early stage tumors owing to the improvement in imaging techniques.

In most of the reported series, RF ablation was associated with acceptable morbidity. In a multicenter survey in which 2,320 patients with 3,554 lesions were included, six deaths (mortality, 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, and liver failure following stenosis of the right bile duct, and one sudden death of unknown cause 3 days after the procedure. Fifty (2.2%) patients had additional major complications. Tumor seeding, in particular, occurred in only 12 (0.5%) of 2,320 patients (Livraghi et al. 2003a). However, lesions with a subcapsular location or an invasive tumoral pattern, as shown by a poor differentiation degree, may be at risk for such a complication (Llovet et al. 2001).

Recently, following advances in RF technology, RF ablation has also been used to treat patients with intermediate stage tumors. However, results obtained by RF ablation alone were not entirely satisfactory. Livraghi et al. (2000) treated 114 patients with 126 hepatocellular carcinoma lesions greater than 3 cm in diameter. Complete necrosis (on imaging) was attained in only 60 lesions (47.6%), nearly complete (90–99%) necrosis in 40 lesions (31.7%), and partial (50–89%) necrosis in the remaining 26 lesions (20.6%). Therefore, there is currently a focus on a multimodality strategy in attempts to ensure more effective percutaneous ablation of large hepatocellular carcinoma tumors.

Of interest, recent studies have proved the influence of perfusion-mediated tissue cooling on the area of RF necrosis achievable with RF treatment. Goldberg et al. (1998a) applied RF in vivo to normal porcine liver without and with balloon occlusion of the portal vein, celiac artery, or hepatic artery, and to ex vivo calf liver. RF application during vascular occlusion produced larger areas of RF necrosis than RF with unaltered blood flow. Lees et al. (2000) showed that hypotensive anesthesia improved the effectiveness of liver RF ablation in a human study. Assuming that the volume of RF necrosis produced by RF treatment is strongly dependent on blood flow, and considering that in hepatocellular carcinoma blood flow is mainly sustained by the hepatic artery, we performed a multicenter clinical trial aimed at investigating whether interruption of the tumor arterial blood supply by means of occlusion of either the hepatic artery with a balloon catheter or the feeding arteries with gelatin sponge particles could increase the extent of RF-induced coagulation necrosis (Rossi et al. 2000). A series of 62 consecutive patients with a single, large hepatocellular carcinoma ranging from 3.5 to 8.5 cm in diameter (mean 4.7 cm) accompanying cirrhosis underwent RF ablation after occlusion of the tumor arterial supply. The RF energy was delivered by using an expandable electrode needle at the time of balloon catheter occlusion of the hepatic artery (n=40), at the time of occlusion of the hepatocellular carcinoma feeding arteries with gelatin sponge particles (n=13), or 2–5 days thereafter (n=9). Two patients underwent liver resection after the RF ablation; the remaining 60 patients were followed up for a mean of 12.1 months (range 3–26 months). During the follow-up, 49 (82%) of the 60 treated hepatocellular carcinoma nodules showed a stable complete response, while the remaining 11 (18%) nodules showed local progression. Histopathologic analysis of one autopsy and the two surgical specimens revealed more than 90% necrosis in one specimen and 100% necrosis in two. No fatal or major complications related to the treatment occurred, despite the more aggressive RF treatment protocol. The results of this study provide evidence that areas of RF necrosis that are much larger than those previously reported can be created if RF ablation is performed in hepatocellular carcinoma nodules after occlusion of their arterial supply.

The results achieved with this technique were confirmed by two recent studies. Yamasaki et al. (2002) compared the necrosis diameters obtained with balloon-occluded RF and standard RF in 31 patients with 42 hepatocellular carcinoma lesions measuring less than 4 cm in the greatest dimension. There were no significant differences between the groups in terms of the ablation conditions, such as the frequency of a fully expanded electrode, the number of needle insertions, the application cycles, or the treatment times. However, the greatest dimension of the area coagulated by balloon-occluded RF ablation was significantly larger than that coagulated by standard RF ablation. Yamakado et al. (2002) evaluated the local therapeutic efficacy of RF ablation after transarterial chemoembolization in 64 patients with 108 lesions. Sixty-five lesions were small (3 cm or less), 32 were intermediate in size (3.1–5 cm), and 11 were large (5.1–12 cm). Complete necrosis was achieved in all lesions, and there were no local recurrences in small or intermediate-sized lesions during a mean follow-up of 12.5 months (Table 13.1).

Despite these encouraging preliminary results, there are no reports showing that RF ablation, performed alone or in combination with intra-arterial procedures, results in improved survival in patients with intermediate stage hepatocellular carcinoma. A randomized trial comparing an optimized RF technology with chemoembolization would be needed to establish the potential role of the technique in this patient population.

13.4.2 Hepatic Metastases

In two pioneering studies published in 1997–1998 by Solbiati et al. (1997) and Lencioni et al. (1998), 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 one or two sessions, and technical success – defined as lack of residual unablated tumor on 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, while 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. (1998), 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 the absence of complications. Complete tumor response – defined as the presence of a nonenhancing ablation zone larger than the treated tumor on post-treatment spiral CT – was seen in 41 (77%) of the 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 increased substantially. De Baere et al. (2000) 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 similar for percutaneous RF ablation (90%) and intraoperative RF ablation (94%). One bile leakage in peritoneum and two abscesses were the major complications encountered after treatment. Helmberger et al. (2001) reported a similar technical success rate of RF ablation (97%) in a series of 37 patients with 74 metastases. In this study, four 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 treated by RF ablation have been reported. In the series of Gilliams and Lees (2000), 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-, 2-, 3-, and 4-year survival rates were 90%, 60%, 34%, and 22%, respectively. In the study of Solbiati et al. (2001), 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 the 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 (2003): 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 two 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. (2004b) 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. All patients had four or fewer metachronous metastases (overall number of lesions, 615; mean number of lesions per patient, 1.4±0.7), each 5 cm or less in greatest dimension (range, 0.5–5 cm; mean, 2.7±0.9 cm), and were free from extrahepatic disease. The surgical option had been excluded or been 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±15 months). The primary effectiveness rate (percentage of tumors 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 4 years, and 24% at 5 years. Survival rates were significantly higher in patients with a single lesion 2.5 cm or less in diameter (56% at 5 years) than in patients with a 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 (Jonker et al. 2000). With the 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 seven recently published phase III trials showed that the improvement in median survival did not exceed 3.5 months (Grothey et al. 2004).

Recent studies analyzed the role of RF ablation with respect to surgical resection. Abdalla et al. (2004) examined the 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. (2003), 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. (2002) 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 two 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. (2003b) 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, 52 (98%) were spared surgical resection: in 23 cases (44%) because they remained free of disease and in 29 cases (56%) because they developed additional metastases leading to irresectability. No patient in whom RF treatment did not achieve complete tumor ablation became unresectable due to the growth of the treated metastases.

A general assessment of complications following RF ablation of liver malignancies has been recently performed by Livraghi et al. (2003a). In this study 2,320 patients with 3,554 lesions were included. 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, and liver failure following stenosis of right bile duct, and one sudden death of unknown cause 3 days after the procedure. Fifty (2.2%) patients had additional major complications, defined as 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 (Goldberg et al. 2003). In the large single-institution series of de Baere et al. (2003), 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) over 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 five pleural effusions, five skin burns, four cases of hypoxemia, three pneumothoraces, two small subcapsular hematomas, one case of acute renal insufficiency, one hemoperitoneum, and one instance of 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. While 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 (Table 13.2).

Table 13.2. Survival outcomes of patients with hepatic colorectal metastases treated with radiofrequency ablation.

Study	Year	No. of patients	Survival rate (%)		
			1year	3year	5year
Solbiati et al.	1997	29	94	N/A	N/A
Lencioni et al.	1998	29	93	N/A	N/A
Gillams and Lees	2000	69	90	34	N/A
Solbiati et al.	2001	117	93	46	N/A
Solbiati et al.	2003	166	96	45	22
Oshowo et al.	2003	25	100	52	N/A
Abdalla et al.	2004	57	92	37	N/A
Lencioni et al.	2004b	423	86	47	24

N/A not available.

13.5 Guidance and Assessment of Percutaneous Ablation Treatment

Image-guided tumor ablation aims at tumor eradication or substantial tumor destruction using the direct application of chemical (such as ethanol) or thermal (such as RF ablation) therapies. The region or zone of induced treatment effect (corresponding to the area of gross tumor destruction) as demonstrated by radiologic studies is termed the "ablation zone." Due to the actual limitations in contrast and spatial resolution of imaging studies, the extent of the ablation zone is only an approximation to the zone of "coagulation necrosis," which means cell death at pathologic examination (Goldberg et al. 2003).

13.5.1 Contrast-Enhanced CT and Contrast-Enhanced MR Imaging

Contrast-enhanced CT and contrast-enhanced dynamic MR imaging are considered the gold standard techniques for pretreatment staging of liver tumors and for the immediate and long-term assessment of treatment outcome (McGahan and Dodd 2000).

In the setting of evaluation of treatment outcome, successfully ablated lesions appear on CT as hypoattenuating areas which fail to enhance in both the arterial and the portal venous phase. With MR imaging, necrosis induced by PEI and RF ablation is depicted as a low-intensity area on T2-weighted images. The change from hyperintensity on T2-weighted images of the native tumor to hypointensity of the lesion after the procedure is usually associated with tumor necrosis. However, unenhanced MR imaging has some limitations, with a non-negligible rate of false negative and false positive results. False negative results are caused by the difficulty in detecting small areas of residual viable tumor, especially along the periphery of the treated lesion. On the other hand, the appearance of lesions ablated by RF ablation may not be consistent on unenhanced MR imaging – especially when the examination is performed shortly after the procedure –, with mixed hyperintense and hypointense areas reflecting the complexity of the necrotic phenomena induced by the treatment. This appearance may cause false positive results and greatly reduces the radiologist's confidence in evaluating tumor response. Therefore, the use of a dynamic, contrast-enhanced study is to be recommended as a mandatory part of the MR imaging examination aimed at assessing the therapeutic effect of the procedure. Necrotic tumor will show absence of enhancement throughout the contrast-enhanced dynamic MR imaging study (Lencioni et al. 2001).

In the case of hepatocellular carcinoma, the areas of residual viable neoplastic tissue can be easily recognized with both CT and MR imaging as they stand out in the arterial phase against the faintly enhanced normal liver parenchyma and the unenhanced areas of necrosis. In the case of hepatic metastases, a confident diagnosis of successful ablation is obtained when an area of necrosis volume exceeding that of the original lesion, with a safety margin of necrosis in the liver parenchyma all around the tumor, is depicted.

If the imaging assessment of the outcome of therapy is performed shortly after the RF treatment, contrast-enhanced CT and contrast-enhanced dynamic MR imaging may show the presence of a peripheral enhancing halo surrounding the treated lesion. This halo, which may be irregular in shape and thickness, enhances predominantly in the arterial phase and is due to the hyperemia and the inflammatory reaction along the periphery of the area of necrosis. It is usually more pronounced in hepatic metastases than in hepatocellular carcinoma since metastases produce greater injury in the adjacent liver parenchyma, and the lack of a clear border between tumor and normal liver and the higher conductivity of noncirrhotic tissue facilitate progression of RF waves into the noncancerous parenchyma. The enhancing halo is depicted for a few days after treatment, and usually disappears at later follow-up studies. Awareness of this feature is, of course, of utmost importance in order to prevent misinterpretation of a peripheral inflammatory reaction associated with successful ablation as tumor progression. However, the risk of overestimation of the therapeutic effect of the procedure – with peripheral persistence of tumor – also should not be disregarded.

To make a reliable assessment, it is crucial to compare pretreatment and post-treatment studies performed by using the same technical examination protocol, and in the event of inconclusive findings to schedule close follow-up of the patient. Alternatively, when questionable enhancing areas are observed at the periphery of a treated tumor, additional information can be obtained with the use of tissue-specific MR contrast agents, such as hepatobiliary and reticuloendothelial system-targeted agents (Lencioni et al. 2001).

13.5.2 Contrast-Enhanced US

Conventional US examination is often insufficient in the detection of liver tumors and the accurate evaluation of their burden in patients with liver cirrhosis or oncology patients (Lencioni et al. 2002). Among the limitations of conventional US, one of the most important is its inaccuracy in patients with inhomogeneity of the liver parenchyma due to cirrhosis, fatty disease, previous chemotherapy, or local treatments. Conventional US examination is also often insufficient in the characterization of liver tumors due to their nonspecific US appearance (Lencioni et al. 2002).

On conventional US examination after PEI, a hyperechoic zone appears within the tumor due to ethanol deposition. During RF ablation, a zone of increased echogenicity progressively develops around the distal electrode, within and surrounding the treated tumor. This transient finding, previously known by the jargon term "cloud," lasts up to 30–90 min and corresponds to microbubbles of water vapor and other tissue products that form as a result of tissue vaporization during active heating. This US structural change is relatively independent of the tumor histotype. At the end of the treatment, the US pattern of the lesion is usually modified, and the hyperechoic zone replaces the original lesion. This US feature, however, is unreliable for assessing the outcome of PEI and RF treatment since it does not provide adequate demonstration of the areas of necrosis and residual viable tumor tissue. Moreover, US examination, even when combined with contrast-enhanced color and power Doppler US techniques, does not provide any reliable information in the pre- and post-treatment evaluation of liver tumors due to its low sensitivity in the assessment of tumor vascularity (Lencioni et al. 2002). Conventional US examination, on the other hand, is the most commonly used imaging modality for the guidance of percutaneous ablation treatments because of its availability, rapidity, and ease of use; the same procedure is more technically challenging and lengthy in CT and MR environments.

The introduction of microbubble-based US contrast agents and, more recently, the development of contrast-specific techniques that display microbubble enhancement in gray scale have substantially improved the ability of US studies to assess liver tumor macro- and microvascularity. With the advent of new-generation sulfur hexafluoride- or perfluorocarbon-filled microbubbles and low mechanical index real-time scanning techniques, contrast-enhanced US has made a significant comeback in the fields of liver tumor detection and characterization and liver tumor ablation. This is because it is an easy-to-perform and reproducible examination that appears to be ready for routine clinical application (Lencioni et al. 2002).

These developments prompted the European Federation of Societies for Ultrasound in Medicine and Biology to organize a Consensus Conference on the use of microbubble-based contrast agents in liver US. During the meeting, a multidisciplinary panel of international experts met to prepare a document giving updated guidelines on US practice. The guidelines define the indications and provide recommendations for the use of microbubble-based contrast agents in the detection and characterization of focal liver lesions and in the pre- and post-treatment evaluation of liver tumors (EFSUMB Study Group 2004).

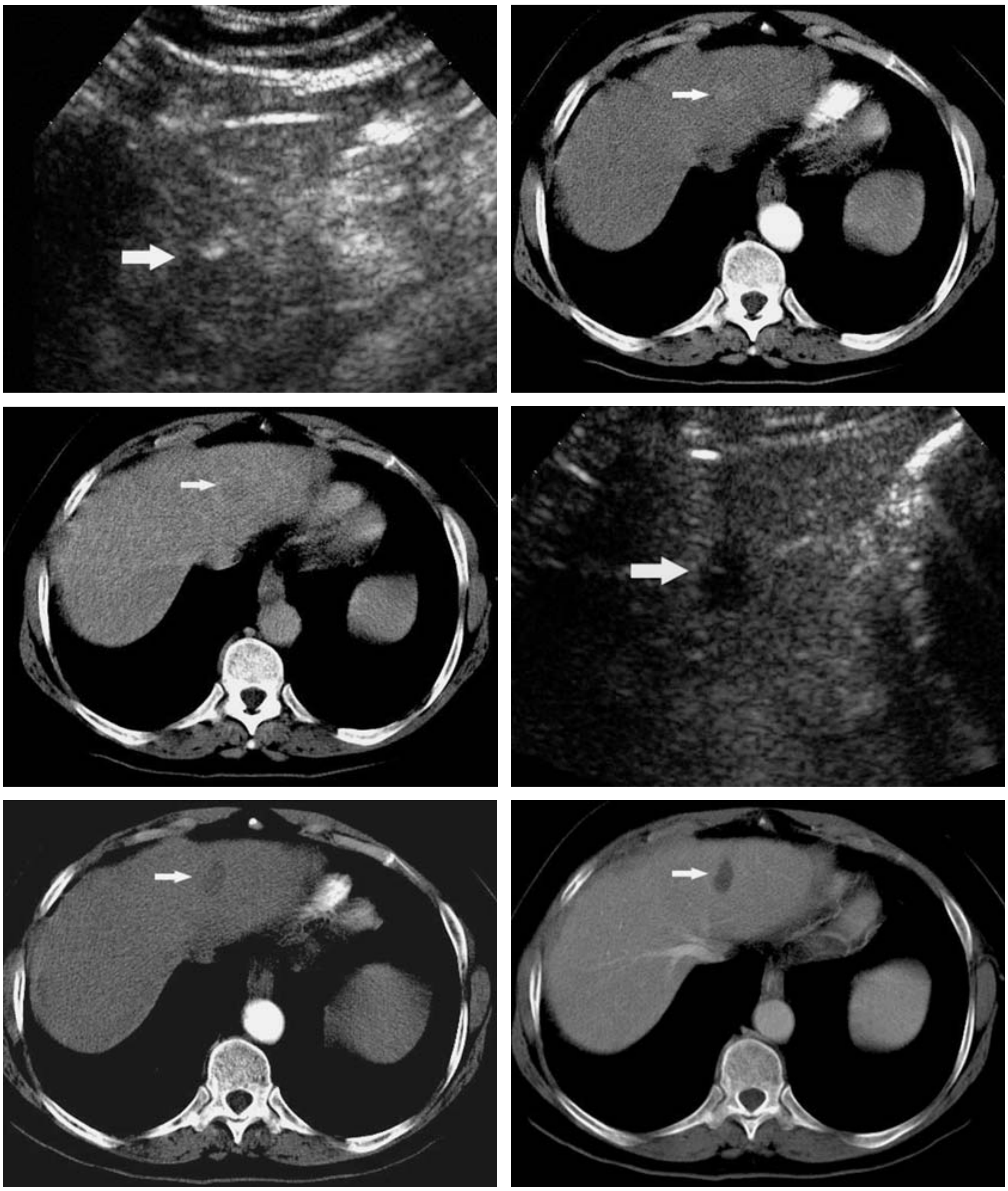
Currently, contrast-enhanced US examination of liver parenchyma is performed by using a new-generation microbubble-based contrast agent in association with a low mechanical index real-time scanning technique. This technique allows study of the enhancement pattern of each liver tumor throughout the vascular phases of hepatic parenchyma in real time. In fact, due to the dual blood supply of hepatic parenchyma by the hepatic artery (25–30%) and the portal vein (70–75%), three vascular phases can be visualized during contrast-enhanced US study of hepatic parenchyma. Hepatic parenchyma enhancement resulting exclusively from the hepatic artery supply usually starts at 10–20 s after injection of the US contrast agent and lasts approximately 10–15 s. This is followed by the tissue enhancement resulting from the portal vein supply, which usually lasts until 2 min after injection of the US contrast agent. The delayed enhancement of hepatic parenchyma persists until 4–6 min after US contrast injection. Most hypervascular hepatic tumor lesions, such as hepatocellular carcinoma, are hyperenhancing during the arterial phase, while the majority of hypovascular hepatic tumor lesions, such as hepatic metastases, are hypoenhancing during the portal and delayed phases. This approach has resulted in improved lesion detection and characterization (EFSUMB Study Group 2004).

Contrast-enhanced US examination is also highly valuable in all phases of percutaneous tumor ablation, such as treatment planning, targeting of lesions and treatment guidance, and immediate and long-term assessment of treatment outcome. Contrast-enhanced US examination allows (a) better delineation of lesions poorly visualized on conventional US, (b) guidance of the ablation needle into tumors not visualized or not well delineated with conventional US, (c) pretreatment assessment of tumor vascularity as a basis for comparison of pre- and post-treatment patterns at the end of tumor ablation, (d) immediate assessment of the treatment outcome in order to detect residual viable tumor tissue, and (e) post-treatment follow-up in order to assess locally recurrent tumor tissue or new tumor lesions (EFSUMB Study Group 2004).

Treatment planning. In the setting of patient evaluation for eligibility for percutaneous ablation treatment of liver tumors, digital storage of images and/or movie clips of contrast-enhanced US studies is employed to permit careful comparison of US contrast-enhanced findings with those of contrast-enhanced CT or contrast-enhanced dynamic MR imaging in order to maximize lesion detection. Precise knowledge of lesion number, dimensions, and localization is essential for correct judgment as to the feasibility of treatment. Tumor diameters are very important in treatment planning since the choice of ablation modality (PEI vs RF) and of RF procedure modality varies depending on the actual size and whether there is a capsulated or an infiltrating pattern.

Lesion(s) Targeting. In the setting of lesion targeting for percutaneous ablation of liver tumors, contrast-enhanced US study is performed as the initial step in the PEI or RF session, during the induction of anesthesia, in order to reproduce mapping of lesions as shown on the pretreatment CT or MR imaging study. Images and/or movie clips are again digitally stored for comparison with the immediate postablation study. The continuous contrast-enhanced US technique allows real-time targeting of the lesion(s), allowing precise needle insertion during the specific phase of maximum lesion detectability: this is the arterial phase for highly vascularized lesions such as hepatocellular carcinoma, and the portal or delayed phase for hypovascular lesions such as hepatic metastases. Real-time guidance of needle positioning during contrast-enhanced US study does not significantly prolong the total duration of the PEI or RF session. The use of contrast-enhanced US guidance is mandatory for small hepatocellular carcinomas detected by CT or MR imaging but not visible on conventional US. These lesions may only be reached during the transient arterial phase of contrast-enhanced study, during which they appear as hyperenhancing areas. The use of contrast-enhanced US guidance is also mandatory in the case of small hepatic metastases detected by CT or MR imaging but barely or not perceptible on conventional US. These lesions appear as hypoenhancing areas in the portal or delayed phase of the contrast-enhanced US study. Finally, the use of contrast-enhanced US guidance is mandatory in the context of areas of residual untreated or locally recurrent tumor, whether primary or metastatic. While conventional US almost always cannot differentiate between necrosis and viable tumor, during contrast-enhanced US study viable tumor tissue shows its native, characteristic enhancement pattern.

Assessment of Treatment Outcome. For assessment of the immediate post-treatment outcome, a contrast-enhanced US study is performed 5–10 min after completion of the PEI or RF session, with the patient still under anesthesia. Conventional US findings observed after PEI and during the RF session, represented by a zone of increased echogenicity, in fact offer only a rough estimate of the extent of induced tumor necrosis and therefore do not permit reliable assessment of treatment outcome. Comparison of immediate posttreatment images with stored pretreatment images is necessary to assess the diameter of the induced ablation zone in relation to the diameter of the treated lesion (Fig. 13.1). In the case of the RF procedure, as with CT and MR imaging, a benign periablational area of enhancement can be seen on contrast-enhanced US studies. A thin, relatively concentric and uniform enhancing rim (usually 1–2 mm thick, and no more than 5 mm) surrounding the ablation zone corresponds to a physiologic response to RF damage characterized mainly by reactive hyperemia. Residual

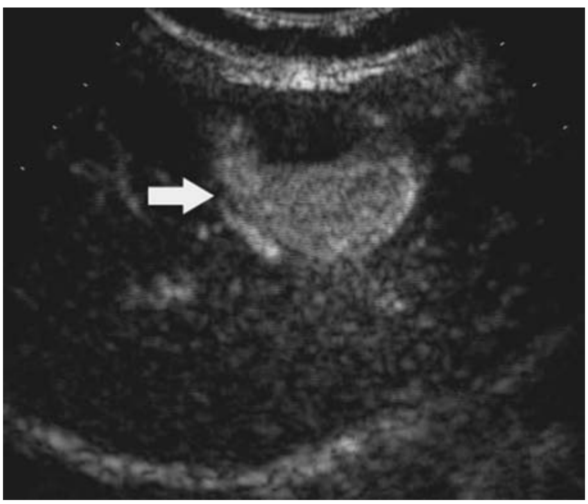


a b c d e f

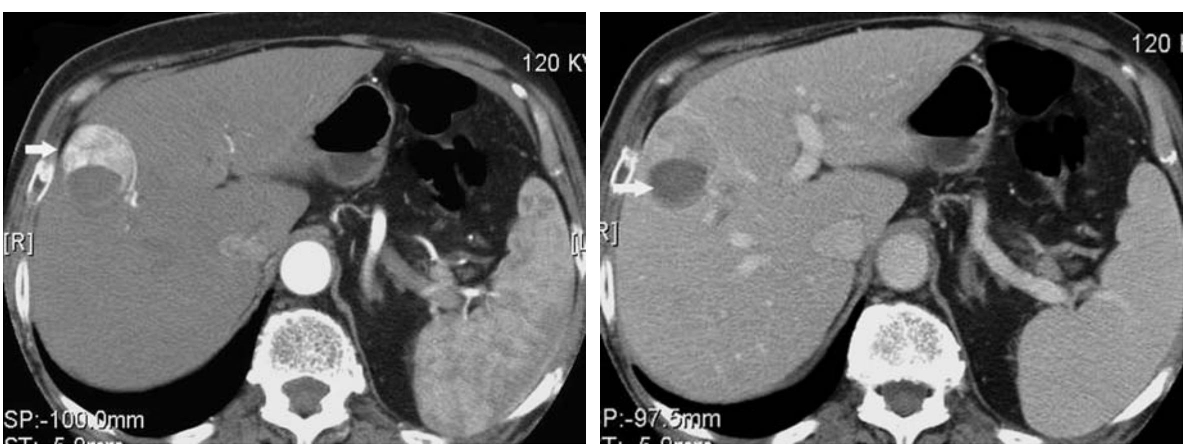
Fig. 13.1a–f. Small hepatocellular carcinoma before and after RF thermal ablation. **a** Contrast-enhanced US examination shows the lesion as a homogeneous hyperenhancing area (*arrow*), 25–35 s after the administration of US contrast agent before the procedure. **b, c** Contrast-enhanced spiral CT confirms the presence of the small hypervascular hepatocellular carcinoma (*arrow*). **d** Immediately after the procedure, contrast-enhanced US examination shows the lesion as a hypoenhancing area (*arrow*) throughout the study, suggesting complete tumor ablation. **e, f** Contrast-enhanced spiral CT, obtained 1 week after the procedure, confirms complete tumor ablation (*arrow*).

viable tumor tissue, usually recognized at the periphery of the treated lesion, maintains the enhancement behavior characteristics of native tumor as depicted on pretreatment studies. As on CT and MR imaging, residual unablated tumor tissue usually shows irregular, eccentric, or nodular peripheral enhancement. In patients with hepatocellular carcinoma, partial tumor necrosis may be confidently diagnosed when hypervascularity is maintained in a portion of the original lesion in the arterial phase (Fig. 13.2). Residual untreated hepatic metastases sometimes appear indistinguishable from tumor necrosis in the portal and delayed phases. With contrast-enhanced US, evaluation of the arterial phase is important since viable tumor tissue shows weak but perceptible enhancement. A CT and/or an MR imaging study may be performed on the first day after the procedure, mainly to check for possible complications related to the treatment and to confirm the results of the early post-treatment contrast-enhanced US study.

Long-term Follow-up. In the setting of long-term follow-up, contrast-enhanced CT and contrast-enhanced dynamic MR imaging remain the gold standard techniques. The main advantages of these modalities that render them preferable to contrast-enhanced US are their reproducibility and their panoramic quality, i.e. they offer easy coverage of the entire abdomen and extension to the lungs when indicated. Involution of tumor necrosis causes the ablation zones usually to show slow, progressive shrinkage over months and years of follow-up. Benign periablational areas of enhancement may, however, persist for a few months, and zones of altered vascularity such as arterioportal shunt tend to remain stable over time. In this setting, contrast-enhanced US study is of proven value, and is currently used to confirm or exclude doubtful or suspicious local recurrences or new metachronous lesions detected by CT and MR imaging, and to assess the possibility of retreating them under contrast-enhanced US guidance (Fig. 13.3).

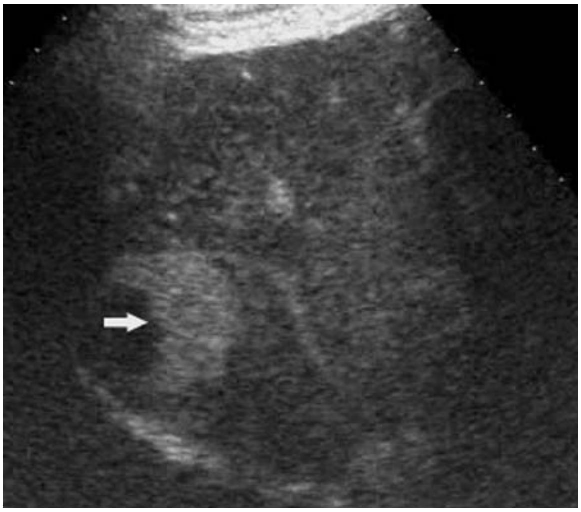


a

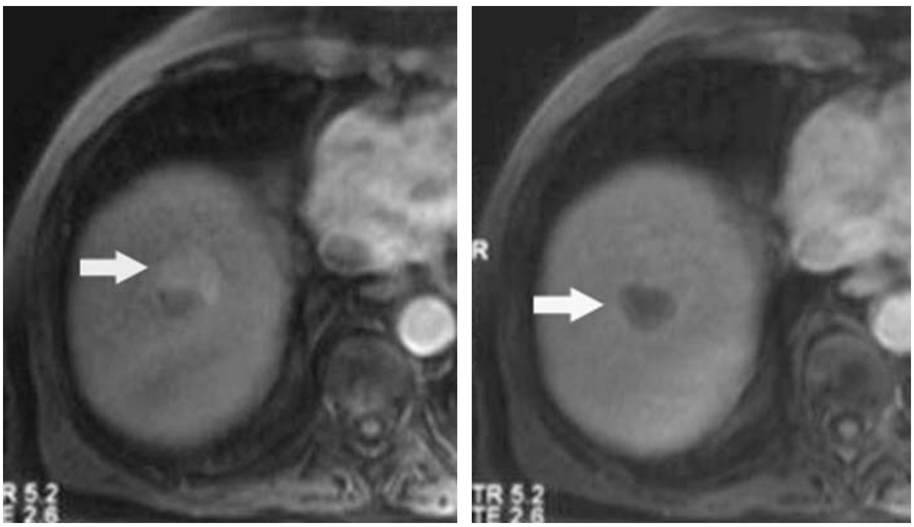


b c

Fig. 13.2a–c. Large hepatocellular carcinoma after RF thermal ablation. **a** Contrast-enhanced US examination, performed immediately after the procedure, shows peripheral residual viable tumor tissue (*arrow*) as an arterial hyperenhancing area. **b** Arterial phase CT image, obtained 1 week after the procedure, confirms the presence of residual viable tumor tissue (*arrow*) as a hyperattenuating area in the anterior aspect of the lesion. **c** The portal venous phase image better visualizes the necrotic portion of the tumor as a hypoattenuating area (*arrow*) in the posterior aspect of the lesion.



a



b c

Fig. 13.3a–c. Locally recurrent small hepatocellular carcinoma 6 months after RF thermal ablation. **a** Contrast-enhanced US examination, performed during the follow-up, shows a small peripheral arterial hyperenhancing area (*arrow*) suspicious for local recurrence. **b, c** Contrast-enhanced dynamic MR imaging confirms the presence of locally recurrent tumor tissue in the anterior aspect of the lesion (**b**, *arrow*), with evidence of the necrotic portion in the posterior aspect of the lesion (**c**, *arrow*).

13.5.3 Multimodality Navigation Tool "Navigator"

The Navigator (Esaote SpA and MedCom GmbH) enhances the images produced by a US scanner by combining them with a second modality (such as CT or MR imaging) in real time. The system consists of a US scanner (Technos ^{MPX} Esaote SpA) connected to the Navigation units (Fig. 13.4).

The connection between the two devices consists of a video cable (to grab the US screen image) and a network cable (to query the current scan geometry of the US scanner). The US system provides the US image together with its characteristics, such as the spatial dimensions, the orientation of the probe, and the field of view. Access to the US geometry is

Fig. 13.4. Navigation units.

mandatory in order to be able to compute the correct size and orientation of the virtual slice from the second modality dataset. These data are provided by the US scanner by the network connection and are automatically updated at every change on the console of the scanner. The US image is provided trough the video cable and is digitized by a standard frame grabber for presentation beside the virtual slice. An electromagnetic tracking system, composed of a transmitter and a small receiver (mounted on the US probe), provides the position and orientation of the US probe in relation to the transmitter. For this kind of application the use of an electromagnetic tracker (as opposed to an optical system) is particularly appropriate, since no special accuracy is required by the body regions under examination; the operative field is sufficiently extended and the system is not affected by tools or bodies located between the transmitter and the receiver. It can thus be easily placed in any environment and, furthermore, it has an acceptable cost. Of course, the big disadvantage of the magnetic principle is the sensitivity to metallic objects near to the receiver or transmitter. Thus, any ferromagnetic material that may disturb the field between the transmitter and the receiver must be avoided. Since neither the probe nor the biopsy needles influence the accuracy, it has been found during clinical tests that this requirement can be achieved without affecting clinical routine use in any noticeable way.

In order to start a multimodality examination, it is necessary to scan the patient with the second modality, applying at least three skin markers on the area of interest. The slices will be imported into the Navigation unit in DICOM format through PACS or data CD. The Navigation system processes every slice and, by taking into account the slice to slice distance and dimensions, generates a surface volume.

Once the patient has been positioned on the treatment couch and the transmitter fixed in a suitable position, the registration phase is commenced. The registration procedure combines the patient coordinate system, the probe position, and the 3D dataset in a known and fixed coordinate system; this is mandatory in order to compute a correct virtual slice at the current probe position. To this end it is necessary to select the same markers in the volume and on the patient skin and to register the marker position with the tracking device. During this registration step and also during the subsequent treatment, it is important to keep the patient and the transmitter in a fixed position. Once all markers have been registered, a registration matrix is computed by the software in order to correlate the probe spatial position with the second modality volume, which, after this procedure, fits with the patient body. For any probe position and, of course, for any US image, the system gives the related reference modality slice obtained by virtually cutting the volume according to the probe spatial coordinates.

At our Institution, the system is currently under investigation for the detection and characterization of liver tumors in patients with liver cirrhosis and oncology patients, and as a tool for image-guided tumor ablation. The system shows real advantages deriving from the merging of a real-time modality such as US with a static second modality such as CT or MR imaging that provides a whole organ scan. The major benefit, also due to the combination with use of a US contrast agent, lies in the ease of liver tumor detection and characterization, particularly when a tumor is hardly or not visible on conventional US. The system is also helpful in all phases of image-guided tumor ablation such as treatment planning, targeting of lesions and treatment guidance, and immediate and long-term assessment of treatment outcome. The system increases the precision of target lesion localization when the US image is not clear. A volumetric reference modality dataset allows the analysis of different planes, thereby permitting better understanding of the morphology of the target lesion and the anatomical structures that surround the target.

13.6 Conclusions

According to the EFSUMB guidelines for the use of microbubble-based contrast agents in US in the setting of percutaneous tumor ablation, contrast-enhanced US is complementary to CT and/or MR imaging for pretreatment staging and assessment of target lesion vascularity. Pretreatment optimized CT and/or MR imaging, however, is still recommended. Contrast-enhanced US facilitates needle positioning in cases of incomplete or insufficient lesion delineation on conventional US. It also allows evaluation of the immediate treatment effect after the ablation and assessment of locally recurrent tumor tissue during the follow-up when CT and/or MR imaging is contraindicated or inconclusive. Although CT and MR imaging are considered the gold standard techniques for the assessment of treatment outcome, contrast-enhanced US may be used in the follow-up protocols.

More recently, the introduction of the Navigator system increases the precision of target lesion localization when the US image is unclear. A volumetric reference modality dataset elucidates the morphology of the target lesion and the anatomical structures surrounding the target.

References

Abdalla EK, Vauthey JN, Ellis LM et al (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 239:818-825

August DA, Sugarbaker PH, Schneider PD (1985) Lymphatic dissemination of hepatic metastases. Implications for the follow-up and treatment of patients with colorectal cancer. Cancer 55:1490-1494

Bartolozzi C, Lencioni R (1996) Ethanol injection for the treatment of hepatic tumours. Eur Radiol 6:682-696

Berber E, Herceg NL, Casto KJ, Siperstein AE (2004) Laparoscopic radiofrequency ablation of hepatic tumors: prospective clinical evaluation of ablation size comparing two treatment algorithms. Surg Endosc 18:390-396

Bismuth H, Majno PE, Adam R (1999) Liver transplantation for hepatocellular carcinoma. Semin Liver Dis 19:311-322

Bruix J, Llovet JM (2002) Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 35:519-524

Bruix J, Sherman M, Llovet JM (2001) EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421-430

Buscarini E, Buscarini L (2004) Radiofrequency thermal ablation with expandable needle of focal liver malignancies: complication report. Eur Radiol 14:31-37

Castells A, Bruix J, Bru C et al (1993) Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 18:1121-1126

Chopra S, Dodd GD 3rd, Chanin MP et al (2003) Radiofrequency ablation of hepatic tumors adjacent to the gallbladder: feasibility and safety. AJR Am J Roentgenol 180:697-701

Choti MA, Sitzmann JV, Tiburi MF et al (2002) Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 235:759-765

Curley SA, Izzo F, Delrio P et al (1999) Radiofrequency ablation of unresectable primary and metastatic malignancies: results in 123 patients. Ann Surg 230:1-8

De Baere T, Elias D, Dromain C et al (2000) Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR Am J Roentgenol 175:1619-1625

De Baere T, Risse O, Kuoch V et al (2003) Adverse events during radiofrequency treatment of 582 hepatic tumors. AJR Am J Roentgenol 181:695-700

Di Stasi M, Buscarini L, Livraghi T et al (1997) Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. Scand J Gastroenterol 32:1168-1173

EFSUMB Study Group (2004) Guidelines for the use of contrast agents in ultrasound. Ultraschall Med 25:249-256

Elias D, de Baere T, Smayra T et al (2002) Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. Br J Surg 89:752-756

Fong Y, Fortner J, Sun RL et al (1999a) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230:309-318

Fong Y, Sun RL, Jarnagin W et al (1999b) An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 229:790-800

Galandi D, Antes G (2004) Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma (Cochrane Review). The Cochrane Library, issue 2. Wiley, Chichester, UK

Gillams AR, Lees WR (2000) Survival after percutaneous, image-guided, thermal ablation of hepatic metastases from colorectal cancer. Dis Colon Rectum 43:656-666

Goldberg SN (2002) Comparison of techniques for image-guided ablation of focal liver tumors. Radiology 223:304-307

Goldberg SN, Hahn PF, Tanabe KK et al (1998a) Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis? J Vasc Interv Radiol 9:101-115

Goldberg SN, Solbiati L, Hahn PF et al (1998b) Large volume tissue ablation with radiofrequency by using a clustered, internally cooled electrode technique: laboratory and clinical experience in liver metastases. Radiology 209:371-379

Goldberg SN, Charboneau JW, Dodd GD III et al for the International Working Group on Image-Guided Tumor Ablation (2003) Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. Radiology 228:335-345

Grothey A, Sargent D, Goldberg RM, Schmoll HJ (2004) 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 22:1209-1214

Headrick JR, Miller DL, Nagorney DM et al (2001) Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 71:975-979

Helmberger T, Holzknecht N, Schopf U et al (2001) Radiofrequency ablation of liver metastases. Technique and initial results. Radiologe 41:69-76

Ikeda M, Okada S, Ueno H et al (2001) Radiofrequency ablation and percutaneous ethanol injection in patients with small hepatocellular carcinoma: a comparative study. Jpn J Clin Oncol 31:322-326

Iwatsuki S, Dvorchik I, Madariaga JR et al (1999) Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 189:291-299

Jamison RL, Donohue JH, Nagorney DM et al (1997) Hepatic resection for metastatic colorectal cancer results in cure for some patients. Arch Surg 132:505-510

Jessup JM, McGinnis LS, Steele GD Jr et al (1996) Report on colon cancer. The National Cancer Data Base. Cancer 78:918-926

Jonas S, Bechstein WO, Steinmuller T et al (2001) Vascular invasion and histopathologic grading determine outcome after liver transplantion for hepatocellular carcinoma in cirrhosis. Hepatology 33:1080-1086

Jonker DJ, Maroun JA, Kocha W (2000) Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. Br J Cancer 82:1789-1794

Khan KN, Yatsuhashi H, Yamasaki K et al (2000) Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. J Hepatol 32:269-278

Koda M, Murawaki Y, Mitsuda A et al (2000) Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. Cancer 88:529-537

Lees WR, Schumillian C, Gillams AR (2000) Hypotensive anesthesia improves the effectiveness of radiofrequency ablation in the liver. Radiology 217:228

Lencioni R, Bartolozzi C, Caramella D et al (1995) Treatment of small hepatocellular carcinoma with percutaneous ethanol injection. Analysis of prognostic factors in 105 Western patients. Cancer 76:1737-1746

Lencioni R, Pinto F, Armillotta N et al (1997) Long-term results of percutaneous ethanol injection therapy for hepatocellular carcinoma in cirrhosis: a European experience. Eur Radiol 7:514-519

Lencioni R, Goletti O, Armillotta N et al (1998) Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol 8:1205-1211

Lencioni R, Cioni D, Bartolozzi C (2001) Percutaneous radiofrequency thermal ablation of liver malignancies: techniques, indications, imaging findings, and clinical results. Abdom Imaging 26:345-360

Lencioni R, Cioni D, Bartolozzi C (2002) Tissue harmonic and contrast-specific imaging: back to gray scale in ultrasound. Eur Radiol 12:151-165

Lencioni R, Allgaier HP, Cioni D et al (2003) Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. Radiology 228:235-240

Lencioni R, Cioni D, Crocetti L et al (2004a) Percutaneous ablation of hepatocellular carcinoma: state-of-the-art. Liver Transplant 10:S91-S97

Lencioni R, Cioni D, Crocetti L et al (2005) Early-stage hepatocellular carcinoma in cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology (in press)

Lencioni R (2004b) Tumor Radiofrequency Ablation Italian Network (TRAIN): Long-term results in hepatic colorectal cancer metastases [Abstract] RSNA meeting 2004

Livraghi T, Vettori C, Lazzaroni S (1991) Liver metastases: results of percutaneous ethanol injection in 14 patients. Radiology 179:709-712

Livraghi T, Giorgio A, Marin G et al (1995) Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 197:101-108

Livraghi T, Goldberg SN, Lazzaroni S et al (1999) Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 210:655-661

Livraghi T, Goldberg SN, Lazzaroni S et al (2000) Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology 214:761-768

Livraghi T, Solbiati L, Meloni MF et al (2003a) Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 226:441-451

Livraghi T, Solbiati L, Meloni F et al (2003b) Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 97:3027-3035

Llovet JM, Fuster J, Bruix J (1999) Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 30:1434-1440

Llovet JM, Vilana R, Bru C et al (2001) Barcelona Clinic Liver Cancer (BCLC) Group. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. Hepatology 33:1124-1129

Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907-1917

Mala T, Edwin B, Mathisen O et al (2004) Cryoablation of colorectal liver metastases: minimally invasive tumour control. Scand J Gastroenterol 39:571-578

Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation in the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693-699

McGahan JP, Dodd GD III (2000) Radiofrequency ablation of the liver: current status. AJR Am J Roentgenol 176:3-16

Mineo TC, Ambrogi V, Tonini G et al (2003) Long-term results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. J Am Coll Surg 197:386-391

Morita T, Shibata T, Okuyama M et al (2004) Microwave coagulation therapy for liver metastases from colorectal cancer. Gan To Kagaku Ryoho 31:695-699

Murata S, Moriya Y,Akusa T et al (1998) Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 83:1086-1093

Patel NA, Keenan RJ, Medich DS et al (2003) The presence of colorectal hepatic metastases does not preclude pulmonary metastasectomy. Am Surg 69:1047-1053

Okusaka T, Okada S, Ueno H et al (2002) Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. Cancer 95:1931-1937

Oshowo A, Gillams A, Harrison E et al (2003) Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 90:1240-1243

Rhim H, Dodd GD 3rd, Chintapalli KN et al (2004) Radiofrequency thermal ablation of abdominal tumors: lessons learned from complications. Radiographics 24:41-52

Rossi S, Garbagnati F, Lencioni R et al (2000) Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. Radiology 217:119-126

Sasson AR, Sigurdson ER (2002) Surgical treatment of liver metastases. Semin Oncol 29:107-118

Scheele J, Stang R, Altendorf-Hofmann A et al (1995) Resection of colorectal liver metastases. World J Surg 19:59-71

Shibata T, Iimuro Y, Yamamoto Y et al (2002) Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology 223:331-337

Shiina S, Tagawa K, Unuma T et al (1991) Percutaneous ethanol

injection therapy for hepatocellular carcinoma: a histopathologic study. Cancer 68:1524-1530
Shiina S, Tagawa K, Niwa Y et al (1993) Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. AJR Am J Roentgenol 160:1023-1028
Shiina S, Teratani T, Obi S et al (2002) Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology 62 [Suppl 1]:64-68
Silen W (1989) Hepatic resection for metastases from colorectal carcinoma is of dubious value. Arch Surg 124:1021-1022
Solbiati L, Goldberg SN, Ierace T et al (1997) Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. Radiology 205:367-373
Solbiati L, Livraghi T, Goldberg SN et al (2001) Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 221:159-166
Solbiati L, Ierace T, Tonolini M, Bellabuono A, Cova L (2003) Long-term survival of patients treated with radiofrequency ablation for liver colorectal metastases: improved outcome with increasing experience. Radiology 229:411
Vauthey JN, Pawlik TM, Abdalla EK et al (2004) Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 239:722-730
Vogl TJ, Muller PK, Mack MG et al (1999) Liver metastases: interventional therapeutic techniques and results, state of the art. Eur Radiol 9:675-684
Wayne JD, Lauwers GY, Ikai I et al (2002) Preoperative predictors of survival after resection of small hepatocellular carcinomas. Ann Surg 235:722-731
Yamakado K, Nakatsuka A, Ohmori S et al (2002) Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. J Vasc Interv Radiol 13:1225-1232
Yamamoto J, Okada S, Shimada K et al (2001) Treatment strategy for small hepatocellular carcinoma: comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. Hepatology 34:707-713
Yamasaki T, Kurokawa F, Shirahashi H et al (2002) Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow. Comparison with standard percutaneous radiofrequency ablation therapy. Cancer 95:2353-2360