Percutaneous Radiofrequency Thermal Ablation of Hepatocellular Carcinoma: A Safe and Effective Bridge to Liver Transplantation

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The incidence of hepatocellular carcinoma (HCC) is increasing in the United States. Although liver transplantation is an effective means of treating selected patients, pretransplantation tumor progression may preclude some patients from undergoing transplantation. The aim of this study is to determine the safety and efficacy of percutaneous radiofrequency thermal ablation (RFA) in 33 consecutive patients with nonresectable HCC and advanced cirrhosis. Mean subject age was 57.2 ± 10.6 years, mean Child-Turcotte-Pugh score was 7.0 ± 1.4, and mean maximal tumor diameter was 3.6 ± 1.1 cm. Using contrast-enhanced computed tomography and magnetic resonance imaging, 22 patients (66%) had a complete radiological response at 3 months post-RFA, whereas 11 patients (33%) had an incomplete radiological response. During follow-up, 18 patients (54%) experienced tumor progression and 9 subjects underwent repeated ablation for either residual disease or tumor progression. The overall actuarial patient survival rate of the 33 patients was 58% at 2 years, whereas the transplantation-free patient survival rate was 34% at 2 years. Fifteen of 23 transplant candidates were successfully bridged to liver transplantation after a mean post-RFA follow-up of 7.9 ± 6. 7 months. The extent of tumor necrosis in the explant varied, but no subjects had evidence of tumor seeding on post-RFA imaging, at liver transplantation, or in the explant. The 3-year actuarial posttransplantation patient survival rate was 85%. Two patients have developed posttransplantation recurrence, and both had microscopic vascular invasion in their explants. In summary, our data show that RFA is a safe and effective treatment modality for patients with advanced cirrhosis and nonresectable HCC. Although the ability of RFA to prevent or delay tumor progression requires further prospective study, its favorable safety profile and promising efficacy make it an attractive treatment option for liver transplant candidates with nonresectable HCC. (*Liver Transpl 2002;8: 1165-1174.*)

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States, with further increases projected over the next two decades.[1,2] Treatment options for patients who present with small tumors and preserved liver function include surgical resection and tumor ablation.[3-5] However, the majority of patients present with either advanced cirrhosis and/or nonresectable HCC, with a median reported survival of only 6 months.[6] Highly selected patients with nonresectable HCC may undergo liver transplantation, with 1- and 3-year patient and graft survival rates of 90% and 70%, respectively.[7-9] However, as the number of patients awaiting transplantation and time to transplantation increase, the development of tumor enlargement, vascular invasion, and intrahepatic spread may preclude many patients with HCC from undergoing curative transplantation. As a result, safe and effective means of treating and delaying the progression of HCC in liver transplant candidates are urgently needed.

Radiofrequency (RF) thermal ablation (RFA) is a novel means of treating patients with both metastatic and primary liver cancer.[10] The application of RF current through a probe inserted into the tumor leads to local tissue heating, with resultant tissue damage and coagulative necrosis. Results in patients with a maximal tumor diameter of 3 cm have shown prolonged disease- and recurrence-free survival.[11,12] Advances in RFA equipment and technology also have led to encouraging results in patients with a maximal tumor diameter up to 5 cm.[13,14] Although RFA requires puncture of the liver surface, the rate of bleeding and other serious complications in patients with cirrhosis has been low.[11-14] The primary aim of this study is to determine the safety and efficacy of percutaneous RFA in 33 consecutive patients with nonresectable HCC who were managed prospectively at a single center. Our secondary aim is to determine clinical and histological outcomes in a subset of 15 patients who underwent liver transplantation during study observation.

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Methods

Patient Selection

Patients with known or suspected HCC referred for liver transplantation evaluation at the University of Michigan Medical Center (Ann Arbor, MI) between January 1996 and July 2001 were considered for possible RFA. All patients were deemed to have nonresectable HCC based on tumor size, location, or the presence of advanced cirrhosis, with a projected life expectancy of at least 6 months. Only patients with a single tumor nodule less than 6 cm in maximal diameter or no more than three tumor nodules, each less than 5 cm in maximal diameter, were considered for RFA. Exclusion criteria were the presence of known vascular invasion on pre-RFA imaging studies, known extrahepatic tumor, subcapsular HCC, or uncorrectable coagulopathy. Histological confirmation of HCC was performed before RFA through ultrasound-guided biopsy, when possible. Written informed consent was obtained from all patients before RFA.

Baseline data collection included subject age, sex, cause of liver disease, Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) score, serum alphafetaprotein (AFP) level, and Karnofsky performance status (range, 0 to 100).[15-17] Multiphase contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) with gadolinium was performed for tumor staging before treatment in 29 of 33 patients, whereas an ultrasound examination of the liver was performed in the remaining 4 subjects.

RFA

Percutaneous RFA was performed by an interventional radiologist under real-time ultrasound guidance. Local anesthesia with conscious sedation consisting of fentanyl (Astra USA, Westborough, MA) and midazolam (Versed; Roche Labs, Nutley, NJ) was used in the first 27 patients, whereas general anesthesia was used in the last 6 patients. In 25 patients, RFA was delivered using a model 500 RF current generator and a 15-G RF probe, model 30 (RITA Medical System, Mountain View, CA) with four retractable electrodes that were deployed to a maximum diameter of 3 cm. In 8 patients, RFA was performed using a model 1500 RF generator and a 14-G RF probe, model 70 Starburst (RITA Medical System), with nine retractable electrodes that were deployed to a maximum of 5 cm.

Tumors 2 cm or less in diameter were treated with a single cycle of thermal ablation, whereas larger tumors were treated with several overlapping ablations. Each ablation cycle was maintained for approximately 10 minutes, with a target tissue temperature of 95°C to 100°C. The intrahepatic portion of the needle track was ablated during removal of the probe by using the tip of the catheter after retraction of the electrodes. Subjects with an international normalized ratio greater than 1.5 or platelet count less than 60,000/mL were administered blood products immediately before the procedure. Subjects were either admitted to the hospital for overnight observation or monitored for a minimum of 4 hours before discharge. Periprocedural complications were prospectively recorded.

Radiological follow-up consisted of CT or MRI of the liver within 6 weeks; at 3, 6, 9, and 12 months; and then every 6 months after RFA. Serum AFP levels, CTP scores, and Karnofsky scores also were assessed at these visits. All subjects were followed up until death or last available follow-up. Repeat RFA was offered to all patients when residual HCC or new tumor nodules were detected during follow-up imaging. The decision to repeat ablation was determined on an individual basis after review of tumor size and location, previous response to therapy, and patient desire to be retreated.

Efficacy Assessment

Two radiologists retrospectively reviewed all scans from CT and MRI. Before treatment, all tumors were evaluated radiologically for the presence of vascular enhancement, maximal tumor diameter, and vascular invasion. The primary end point for radiological efficacy was defined by changes in tumor vascularity on CT or MRI within 3 months of RFA. A complete response was defined as nonenhancement or a thin peripheral rim of enhancement caused by an inflammatory response within 3 months of RFA. An incomplete response was defined as persistent nodular enhancement within 3 months of RFA. Disease progression was defined as new satellite lesions arising within 2 cm of the ablated nodule or new nodules that arose more than 2 cm from the original lesion.

Liver Transplant Recipients

All liver transplant recipients underwent surveillance for HCC recurrence with serum AFP testing and imaging studies. Imaging consisted of contrast-enhanced chest and abdominal CT at 3, 6, 9, and 12 months and then every 6 months posttransplantation, as well as annual bone scans and chest radiographs. Recurrence of HCC was established by histological confirmation of new or suspicious areas on imaging studies. The primary immunosuppression regimen used in this cohort of patients included cyclosporine, mycophenolate mofetil, and corticosteroids. Steroid therapy was withdrawn gradually between 6 and 12 months after liver transplantation. In patients with proven HCC recurrence, immunosuppression was minimized, and adjuvant therapy was pursued, when possible.

All biopsy and explant specimen slides were reviewed by a single pathologist (J.K.G.). Tumors were graded according to the nuclear grading scheme proposed by the Armed Forces Institute of Pathology, with grade 1 representing bland adenoma-like features and grade 4 representing marked anaplasia.[18] Amount of tumor necrosis was estimated on a percentage basis during microscopic review. Additional factors, such as vascular invasion, satellite lesions, and margin status, also were evaluated.

Data Analysis

All statistical analyses were performed using the SAS system (SAS Inc, Cary, NC). Descriptive statistics of baseline demo-

graphics, tumor characteristics, and treatments are reported as mean ± SD, unless indicated otherwise. Overall patient and transplantation-free survival, as well as time to disease progression, in the 33 patients were calculated using Kaplan-Meier methods. Posttransplantation patient survival in the 15 liver transplant recipients also was calculated using Kaplan-Meier methods. CTP and MELD scores at death or last pretransplantation follow-up were compared with pretreatment values using two-tailed Student's *t*-tests. To determine baseline factors associated with overall survival, transplantation-free survival, and time to disease progression, Cox proportional hazards models were used. Because of the small sample size, the following pretreatment covariates were selected based on previously published studies: maximal tumor diameter, CTP score, serum AFP level, Karnofsky score, tumor grade, and MELD score. Each covariate was entered into a univariate Cox model, and those significant at the .10-level or less were evaluated in a multivariate Cox model. Likelihood ratio tests were used to determine which subset of covariates was to be included in the final multivariate model. Logistic regression was used to determine whether tumor diameter and baseline serum AFP level were associated with a complete radiological response at 3 months.

Results

Patient Population

Thirty-one of 33 patients had biopsy-proven HCC, whereas 2 patients underwent nondiagnostic biopsies of suspicious hypervascular mass lesions. The majority of subjects were men (85%) and white (91%), and mean subject age was 57.2 ± 10.6 years. Twenty-three patients (70%) were placed on the liver transplantation waiting list, and 15 patients have undergone transplantation at last follow-up. Reasons for exclusion from transplantation were advanced age (4 patients), tumor size (2 patients), medical comorbidities (2 patients), and patient noncompliance (2 patients). The most common cause of liver disease was hepatitis C (61%), and 4 of these patients had disease that previously failed to respond to interferon therapy. Twenty patients (61%) reported a history of tobacco use. Two patients had markedly elevated pretreatment serum AFP levels (patient 1, 14,971 ng/mL; patient 5, 2,453 ng/mL), leading to a median pretreatment serum AFP level of 33 ng/dL and a mean pretreatment serum AFP level of 659 ng/mL. Mean pretreatment CTP score was 7.0 ± 1.4, and 11 patients (33%) were Child's class A; 20 patients (60%), class B; and 2 patients (6%), class C.

Thirty-eight discrete HCC nodules were treated with RFA in these 33 patients. The majority of tumors were located in the right lobe of the liver, and mean maximum diameter of tumor nodules was 3.6 ± 1.1 cm (Table 1). All patients with pre-RFA imaging studies had vascular enhancement, but none of them showed evidence of vascular invasion. The RFA probe was successfully placed into all lesions under ultrasound guidance. In 25 subjects, RFA was performed using a 15-G probe with a maximal diameter of 3 cm, whereas in 8 subjects, a 14-G probe with a maximal diameter of 5 cm was used. The ablation procedure was terminated prematurely in patient 28 because of abdominal discomfort.

Table 1. Baseline Features of 33 Patients with HCC Undergoing RFA

	No. of patients (%)
Clinical characteristics	
Men (%)	28 (85)
Mean age (yr)	57.2 ± 10.6
Ethnicity (%)	
White/Hispanic/Asian	30 (91)/2 (6)/1 (3)
Cause of cirrhosis	
Hepatitis C	20 (61)
Alcohol	7 (21)
Cryptogenic	4 (12)
Hepatitis B	1 (3)
Autoimmune	1 (3)
Mean CTP score	7.0 ± 1.4
Class A	11 (33)
Class B	20 (60)
Class C	2 (6)
Mean MELD score	10.3 ± 2.5
Mean Karnofsky score	77 ± 10
Tumor features	
Tumor nodules	
1	29 (88)
≥2	4 (12)
Maximal diameter (cm)	3.6 ± 1.1 (1.5-6.0)
Serum AFP (ng/mL)	659 ± 2,608 (2-14,971)
Elevated AFP (>10 ng/mL)	26 (79)
Tumor grade (I/II/III/IV)	4/10/13/4

NOTE. Values expressed as mean ± SD (range) or number (percent).

Radiological Response

Mean duration of post-RFA follow-up to death or last available visit was 21.1 ± 13.0 months (r = 1.4 to 46.6; Table 2). At 3 months post-RFA, 22 patients (66%) had experienced a complete radiological response, whereas 11 patients (33%) had an incomplete radiological response (Fig. 1). Increased maximal tumor diameter was associated with increased odds for an incomplete radiological response (odds ratio, 2.5; 95% confidence interval [CI], 1.1 to 5.2; P = .03). However,

Table 2. Outcomes After RFA of HCC

Patient No.	Maximum Diameter (cm)	Radiologial Response	Nodules Ablated	Progression*	Time to Progression (mo)	Total Follow-Up (mo)	Outcome
1	6	CR	1	1,2	5.0	9.9	D
2	3.5	CR	1	—	—	15.8	D,T
3	4.5	CR	1	—	—	46.6	A,T
4	3	CR	1	—	—	40.5	A,T
5	6	IR	1	1	1.2	2.1	D
6	1.5	CR	1	2	4.1	38.2	A
7	5	CR	1	1,2	4.1	38.0	A,T
8	3	CR	2	1,2	9.2	37.9	A
9	4	CR	1	1,2	5.0	22.6	D
10	2	CR	1	—	—	36.1	A,T
11	3	CR	1	1,2	6.5	35.4	A
12	3	CR	1	—	—	1.5	D
13	4	IR	1	—	—	33.3	A,T
14	3	CR	1	1	12.9	42.9	A,T
15	4.6	IR	1	1,2	1.6	7.4	D
16	2.5	CR	1	1,2	3.5	22.6	D
17	5	IR	1	1,2	1.4	13.0	D
18	4	CR	1	1,2	5.4	10.5	A
19	2.6	CR	1	—	—	26.9	A,T
20	3.4	IR	1	—	—	28.0	A,T
21	5.1	CR	1	—	—	22.3	A,T
22	5	IR	1	1,2	2.9	18.8	A
23	3	CR	1	1	20.9	23.4	A
24	4	IR	2	1	3.7	20.1	D
25	3.2	IR	1	—	—	18.1	A,T
26	2.5	IR	1	1	4.1	5.1	D
27	3.8	CR	2	2	10.7	15.7	A
28	2	CR	1	—	—	16.3	A,T
29	5.0	IR	1	2	1.6	13.5	A,T
30	3.6	CR	1	—	—	15.3	D,T
31	3.5	IR	1	—	—	11.4	A
32	3.0	CR	1	—	—	1.4	D
33	2.8	CR	2	—	—	6.7	A,T

Abbreviations: CR, complete response; IR, incomplete response; A, alive; D, dead; T, transplantation.
*For progression; 1 = local, 2 = new.

baseline serum AFP level and tumor grade were not associated with radiological response at 3 months.

During post-RFA follow-up, 18 patients experienced disease progression, including 5 patients with local recurrence, 10 patients with local recurrence and new intrahepatic nodules, and 3 patients with distinct new intrahepatic nodules located more than 2 cm from the ablated tumor. Three of the 11 patients with an incomplete radiological response underwent repeated ablation during follow-up, whereas the remainder was followed up conservatively. In addition, 6 of the patients with a complete radiological response at 3 months underwent repeated ablation for tumor progression during follow-up.

Baseline features associated with tumor progression on univariate analysis included tumor diameter, serum AFP level, and pre-RFA MELD score ($P < .10$). All three variables remained significant when jointly entered into a multivariate Cox regression model of tumor progression; baseline AFP (hazard ratio, 1.005; 95% CI, 1.002 to 1.007; $P = .001$), tumor diameter (hazard ratio, 2.3; 95% CI, 1.1 to 4.9; $P = .03$), and baseline MELD score (hazard ratio, 1.32; 95% CI, 1.06 to 1.64; $P = .02$). More specifically, for each 10-unit increase in baseline AFP level, there was a 5% increase in the likelihood of tumor progression during follow-up when controlling for tumor diameter and pre-RFA MELD score. Similarly, for each 1-cm increase in pretreatment tumor diameter, there was a two-

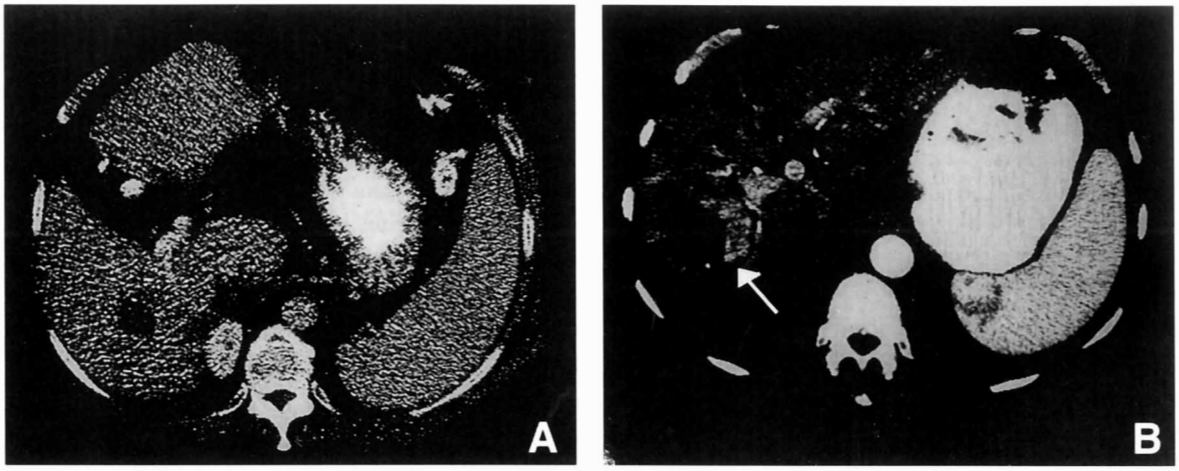

Figure 1. (A) A complete radiological response to RFA. A 49-year-old man with hepatitis C virus cirrhosis (patient 2) underwent RFA of a 3.5-cm HCC without complications. At 9 months post-RFA, the tumor remained necrotic, with no vascular enhancement on contrast-enhanced CT. (B) An incomplete radiological response to RFA. An 84-year-old man with cryptogenic cirrhosis (patient 22) underwent RFA of a 5-cm HCC without complications. At 3 months post-RFA, there was persistent nodular enhancement (arrow) on the medial side of the mass on contrast-enhanced CT, consistent with an incomplete response.

fold greater likelihood of tumor progression when controlling for baseline AFP level and pre-RFA MELD score. Last, for each 1-point increase in MELD score, the hazard of disease progression increased by 32% when controlling for other variables.

Clinical Outcomes and Survival

Clinical outcomes of the 33 patients with HCC are shown in Figure 2. Fifteen of the 23 liver transplant candidates (65%) have undergone liver transplantation, with a mean time from ablation to liver transplantation of 7.9 ± 6.7 months (range, 0.6 to 22.6 months). Five liver transplant candidates died of liver failure after a mean post-RFA follow-up of 5.1 ± 5.1 months, and 3 patients are still awaiting transplantation, with a mean post-RFA follow-up of 21.4 ± 14.7 months. Among the 10 non–transplantation candidates, 5 patients have died of progressive liver disease, whereas 5 others continue to be followed up, with a mean post-RFA follow-up of 25.4 ± 11.1 months.

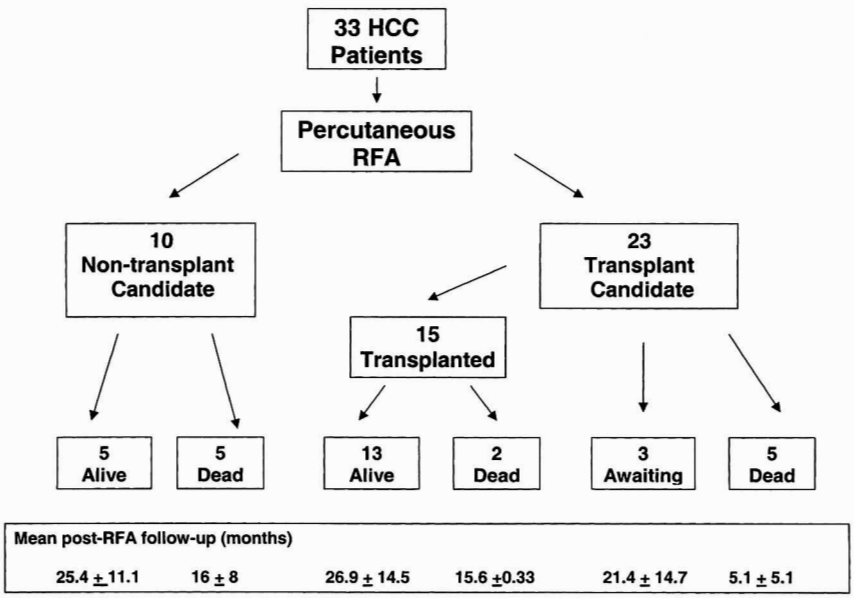

Figure 2. Clinical outcomes of 33 consecutive patients undergoing RFA (23 liver transplantation candidates, 10 non–transplantation candidates).

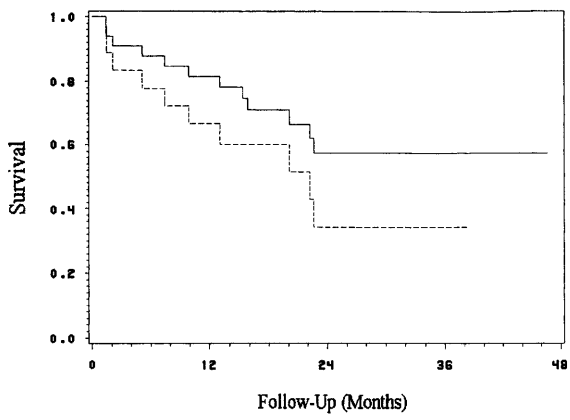

Figure 3. Actuarial patient and transplantation-free survival after RFA in 33 patients with HCC (Kaplan-Meier plot). Overall survival, (———); transplant-free survival (-----).

One-year actuarial overall and transplantation-free survival rates were 82% and 67%, respectively (Fig. 3). The only baseline feature associated with overall survival was maximum tumor diameter (hazard ratio, 1.74; 95% CI, 1.02 to 2.98; $P = .04$). On univariate analysis, baseline MELD score, Karnofsky score, and serum AFP level were significantly associated with transplantation-free survival ($P < .10$). However, on multivariate testing, only baseline MELD score remained significantly associated with transplantation-free survival (hazard ratio, 1.7; 95% CI, 1.2 to 2.4; $P = .004$).

Transplant Recipients

One-, 2-, and 3-year actuarial patient survival rates for the 15 transplant recipients were 85% (data not shown). One liver transplant recipient (patient 2) died of intraoperative cardiac complications, and another patient (no. 30) was withdrawn from support 10 days posttransplantation because of anoxic brain damage (Table 3). The remaining 13 transplant recipients are alive, with a mean posttransplantation follow-up of 26.9 ± 14.5 months (range, 5.5 to 42.1 months). Review of 14 explants showed variable amounts of tumor necrosis, with additional tumor nodules not detected on pretransplantation imaging in 6 patients (40%). Two subjects (13%) have developed HCC recurrence posttransplantation. Patient 19 had portal vein invasion in his explant and developed biopsy-proven pulmonary metastases 6 months posttransplantation. Patient 7 had portal vein invasion and an additional 4-cm tumor nodule in his explant that was not detected on pretransplantation imaging. Unfortunately, he developed biopsy-proven HCC recurrence in his allograft 3.2 months posttransplantation. In both subjects, immunosuppression has been reduced, but neither has been administered adjuvant chemotherapy; both remain alive at last follow-up.

Safety

Percutaneous RFA was associated with a low rate of periprocedural complications. Twenty-two subjects

Table 3. Outcomes in 15 Liver Transplant Recipients who Underwent RFA Pretransplantation

Patient No.	Follow-Up pre-LT (mo)	Tumor Grade	No. of Explant Nodules	Necrosis (%)	Vascular Invasion	Follow-Up post-LT (mo)	Recurrence (mo)
2	15.8	2	NA	NA	NA	0	—
3	4.5	2	1	30	PV	42.1	—
4	8.2	3	3	100	—	32.1	—
7	9.3	3	2	75	PV	28.7	3.2
10	11.0	2	1	70	—	25.1	—
13	14.2	2	1	67	—	19.2	—
14	22.6	3	1	75	—	20.3	—
19	3.9	3	1	25	PV	23.0	6.0
20	0.7	2	2	10	—	27.3	—
21	1.9	4	1	50	—	20.4	—
25	0.6	3	1	90	—	17.5	—
28	19.6	2	2	100	—	9.7	—
29	3.0	2	2	80	—	10.5	—
30	15.0	3	3	100	—	0.3	—
33	1.1	2	2	50	—	5.5	—

Abbreviations: NA, not available; PV, portal vein; LT, liver transplantation.

were electively hospitalized overnight for observation and discharged home the following day, whereas the remaining 11 patients were treated as outpatients. Two patients (6%) had transient fever with malaise after RFA that resolved with oral antibiotic therapy; 2 subjects (6%) developed an intratumoral hematoma that resolved within 3 months; and 1 subject (3%) reported short-term abdominal pain. No subject had evidence of thermal injury to adjacent structures, and there was no evidence of needle-track seeding on post-RFA imaging, at liver transplantation, or in explant specimens. Although there was a slight increase in CTP and MELD scores at last available pretransplantation visit compared with pre-RFA values, 76% of subjects had a follow-up CTP score within 1 point of their pretreatment score. Specifically, among the 15 patients who underwent transplantation, mean pretreatment CTP score did not significantly change by the time of transplantation (7.1 ± 1.4 *v* 7.1 ± 1.6). Similarly, in the 8 patients who did not die or undergo transplantation, mean CTP score did not significantly change (6.3 ± 1.6 *v* 6.8 ± 1.5). However, as expected, there was a trend toward worsening CTP scores in patients who died (7.5 ± 1.4 *v* 9.3 ± 2.8).

Discussion

As many as 40% of liver transplant recipients have evidence of HCC in their explants.[19,20] As the waiting time to liver transplantation increases, the importance of having a safe and effective means of treating and delaying the progression of HCC in liver transplant candidates is apparent. Our data show that percutaneous RFA is a safe and effective therapy for patients with nonresectable HCC. Theoretical advantages of RFA over other modalities are the localized nature of tissue destruction that can be completed in a single session and the ability to repeat the treatment if residual or recurrent disease is detected.[21] Potential risks associated with RFA include the need to puncture the liver surface, with attendant risks for tumor bleeding and seeding, and the potential to worsen global liver function.[22]

At 3 months post-RFA, 66% of our patients had evidence of a complete radiological response, whereas the remaining 33% had an incomplete radiological response. These radiological response rates are similar to those previously reported.[10,11,23,24] Possible explanations for an incomplete response in 11 of our patients include technical challenges posed by larger tumors and tumor location.[22] Because multiple overlapping spheres of tissue ablation are needed to treat tumors greater than 2 cm in maximal diameter, it can be difficult to identify borders of large HCC tumor nodules under ultrasound.[10,12] Furthermore, large HCC tumor nodules are known to have a greater proclivity for vascular invasion and high-grade histological characteristics associated with a poor response to therapy.[25] In addition, the enhanced vascularity of these large tumors can reduce the ability to maintain tissue temperatures at 100°C in all prongs of the RF probe. Consistent with these hypotheses, mean tumor diameter of patients with an incomplete radiological response in our series was 4.2 cm compared with 3.2 cm in patients with a complete radiological response. Improved efficacy with laparoscopic RFA of larger tumors has been reported, presumably because of improved visualization and access to the tumor nodule; however, this approach also is associated with a greater complication rate.[26]

The optimal time and means by which to define a post-RFA radiological response remain unclear. Imaging of the tumor cavity within 1 or 2 weeks of ablation frequently shows an enlarged, inflammatory, hypervascular mass with blood elements. However, waiting to 3 months post-RFA may allow the tumor to progress if it was incompletely treated. As a result, we and others recommend that follow-up imaging be performed 4 to 6 weeks post-RFA using either contrast-enhanced CT or MRI.[27,28] Other imaging modalities, such as semiquantitative estimation of tumor vascularity on MRI or color power Doppler measurements of tumor vascularity with contrast agents, also may prove useful, but remain investigational.[29-31] The extent of tumor necrosis in explants of our transplant recipients varied between 10% and 100% (mean, 60%). The extent of coagulative necrosis after RFA has been related to tumor size, tumor vascularity, success of the initial ablation, and duration of follow-up.[32] The significant variation in these parameters in our 15 transplant recipients, as well as the learning curve associated with a new treatment modality, may account for our observed results.

Overall, RFA was well tolerated in our patients, with a low rate of complications. Although some patients were electively hospitalized for observation, nearly all were discharged within 24 hours, and protracted abdominal pain and vascular thromboses were not observed, as reported with ethanol ablation.[28] Contrary to other reports, there was no evidence of thermal injury to adjacent structures or tumor seeding on post-RFA imaging, at liver transplantation, or in the explant specimens.[23,33] The lack of tumor seeding may have been caused by our ablation of the intrahepatic portion of the needle track before probe removal and exclusion of patients with subcapsular HCC. Although the majority

of these patients had advanced liver disease with ascites and coagulopathy, none of the patients experienced an appreciable decline in global liver function assessed by CTP scores, as reported with chemoembolization.[34,35]

During post-RFA follow-up, 54% of our patients showed either local or intrahepatic tumor progression (Table 2). The high rate of tumor progression in our series and others may relate to the biological tendency for HCC tumors to be multicentric and spread within the liver.[6] Nine of the 18 patients with tumor progression underwent repeated RFA, showing the need for close post-RFA surveillance. Although our study was uncontrolled and 45% of our patients underwent liver transplantation, pretreatment predictors of tumor progression included tumor diameter, serum AFP level, and MELD score. These observations are consistent with previous studies showing a poor prognosis in patients with large tumors and high serum AFP levels.[6,36] If confirmed in other prospective studies, these tumor characteristics may prove useful in treating individual patients and designing future trials of RFA in patients with HCC.

Overall and transplantation-free patient survival rates in our series were 82% and 67% at 1 year and 58% and 34% at 2 years, respectively (Fig. 3). Although our study was small and uncontrolled, these survival rates are better than 1-year survival rates recently reported in other large series of untreated HCC patients.[6,36,37] Contrary to our expectations, pretreatment serum AFP levels and severity of liver disease (i.e., CTP and MELD scores) were not associated with overall survival. The lack of an association may have been caused by the small number of patients studied and the use of liver transplantation at varying times post-RFA in 15 patients. However, a significant association between pretreatment MELD score and transplantation-free survival was observed, confirming the importance of liver disease severity in predicting survival in patients with HCC who do not undergo transplantation.

Percutaneous RFA was a safe and effective bridge to liver transplantation in 15 patients, with a mean pretransplantation post-RFA follow-up of 8.8 ± 7.3 months. However, 5 of our liver transplant candidates died of progressive liver failure while awaiting transplantation. Consistent with previous reports, 40% of liver transplant recipients were noted to have more tumor nodules in the explant than visualized on pretransplantation imaging studies.[7,19] However, only two patients have shown evidence of tumor recurrence posttransplantation. Both of these patients had evidence of vascular invasion in their explant, previously associated with posttransplantation recurrence.[25,38] Nonetheless, the 3-year patient survival rate of 85% in our transplant recipients is similar to that reported in other series of patients with HCC undergoing transplantation.[7-9] Serial studies using MRI and magnetic resonance angiography every 3 months to detect early portal vein involvement may prove worthwhile in liver transplant candidates with HCC; however, further studies are needed.[30]

In summary, our data show that percutaneous RFA is safe and appears to be an effective treatment modality for patients with nonresectable HCC and advanced liver disease. RFA offers several advantages over other ablative therapies in that only a single session is required and larger tumors can be treated. In a recent randomized trial involving 86 European patients with HCC tumors less than 3 cm, RFA was associated with a greater radiological response rate than ethanol injection.[28] In contrast to microwave and laser-induced thermal ablation, the development of newer RF probes has allowed larger tumors to be successfully ablated.[39,40] In comparison to chemoembolization, RFA has not been associated with a decline in global liver function.

Although 54% of our patients experienced tumor progression after a median follow-up of 4.1 months, RFA has allowed 15 of our 23 transplant candidates to undergo liver transplantation. Recent modeling studies suggest that percutaneous RFA may prove cost-effective in patients with nonresectable HCC.[41,42] The apparent ability of RFA to prevent or delay tumor progression in our patients and its excellent safety profile make it an attractive adjunctive therapy for selected liver transplant candidates with known HCC. Although all our transplant candidates underwent RFA when organ allocation was based on CTP scores, we anticipate that RFA will continue to serve as a useful bridge to transplantation under the MELD allocation scheme.[17,43]

Additional large randomized controlled trials using RFA are needed to improve our understanding of the efficacy and durability of this promising treatment modality, as well as studies incorporating antiangiogenesis agents and other adjuvant therapies in an attempt to reduce the rate of post-RFA tumor progression and recurrence.[44]

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