Repeated Radiofrequency Ablation for Management of Patients with Cirrhosis with Small Hepatocellular Carcinomas: A Long-Term Cohort Study

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In most patients with cirrhosis, successful percutaneous ablation or surgical resection of hepatocellular carcinoma (HCC) is followed by recurrence. Radiofrequency ablation (RFA) has proven effective for treating HCC nodules, but its repeatability in managing recurrences and the impact of this approach on survival has not been evaluated. To this end, we retrospectively analyzed a prospective series of 706 patients with cirrhosis (Child-Pugh class ≤B7) who underwent RFA for 859 HCC ≤35 mm in diameter (1-2 per patient). The results of RFA were classified as complete responses (CRs) or treatment failures. CRs were obtained in 849 nodules (98.8%) and 696 patients (98.5%). During follow-up (median, 29 months), 465 (66.8%) of the 696 patients with CRs experienced a first recurrence at an incidence rate of 41 per 100 person-years (local recurrence 6.2; nonlocal 35). Cumulative incidences of first recurrence at 3 and 5 years were 70.8% and 81.7%, respectively. RFA was repeated in 323 (69.4%) of the 465 patients with first recurrence, restoring disease-free status in 318 (98.4%) cases. Subsequently, RFA was repeated in 147 (65.9%) of the 223 patients who developed a second recurrence after CR of the first, restoring disease-free status in 145 (98.6%) cases. Overall, there were 877 episodes of recurrence (1-8 per patient); 577 (65.8%) of these underwent RFA that achieved CRs in 557 (96.5%) cases. No procedure-related deaths occurred in 1,921 RFA sessions. Estimated 3- and 5-year overall and disease-free (after repeated RFAs) survival rates were 67.0% and 40.1% and 68.0 and 38.0%, respectively. *Conclusion:* RFA is safe and effective for managing HCC in patients with cirrhosis, and its high repeatability makes it particularly valuable for controlling intrahepatic recurrences. (HEPATOLOGY 2010;000:000-000.)

Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer worldwide.[1] Most HCC patients have underlying cirrhosis, which complicates management of their cancer and is often the direct cause of death.[2] Internationally endorsed guidelines currently recommend surgical resection for early-stage HCCs in patients with well-preserved liver function.[3,4] When surgery is not possible,

there are several minimally invasive options for chemical or thermal tumor ablation.[5-8] One of the most effective is radiofrequency ablation (RFA),[9] which is now considered potentially curative for early-stage HCCs in patients with or without surgical prospects.[3,4,10-12]

Local tumor control and survival are the parameters most widely used to assess the efficacy of surgical and non-surgical treatments for HCC.[6-16] Data on local control are fairly easy to interpret: disease relapse at the treated tumor site is regarded as a treatment failure. Survival data are more difficult to interpret. The risk of death is influenced by the outcome of the first treatment,[3,4] but also by tumor characteristics (e.g., multifocal progression, vascular involvement, etc.) and by factors partially or wholly unrelated to tumor (e.g., liver function, performance status, age).

The most frequent event observed during the follow-up of curatively treated HCC patients is nonlocal intra-hepatic recurrence.[10-19] New HCC nodules can often be permanently eliminated, but others almost invariably appear.[10-19] The impact of nonlocal recurrence on survival is enormous, but has received little or no attention in most treatment efficacy studies. The outcome of the initial treatment, the time to first recurrence, and the overall survival are usually well documented, but limited data are available on the characteristics of the first recurrence, how it was managed, and whether or not the treatment was successful.[10-15] Even less is said about subsequent recurrences although they, too, strongly affect survival.[19] If survival is to be used as a meaningful marker of the long-term efficacy of a treatment for HCC, information must be provided on all the events observed during follow-up and management.[20]

To address this issue, we retrospectively analyzed a prospective database of 706 patients with cirrhosis who were consecutively treated for HCC with RFA. The patients were followed for up to 10 years and all episodes of recurrence were managed according to a predefined protocol.

Patients and Methods

Patients. This cohort study involved retrospective analysis of a prospective database shared by the Internal Medicine and Radiology departments of two public hospitals. The study protocol received Institutional Review Board approval, and all participants provided written informed consent before treatment. From January 1998 through January 2008, 723 patients were consecutively referred to these centers with HCC who met the following criteria for RFA treatment: (1) 1-2 treatment-naïve HCC nodules ≤35 mm (Barcelona-Clinic-Liver-Cancer [BCLC][21] stage 0-B, Liver Cancer Study Group of Ja-

pan [LCSGJ][22] stage T1-T3); (2) Child-Pugh class A5-B7[23] cirrhosis; (3) no neoplastic portal, hepatic vein thrombosis, or extrahepatic metastases; (4) prothrombin time ratio ≥50% (or international normalized ratio ≤1.7) and platelet count ≥50 × 10^9/L; (5) no high-bleeding-risk esophageal varices[24]; (6) Karnofsky score >90[25]; and (7) no comorbidities with life expectancy <24 months. Seventeen (2.3%) of these patients were excluded because of uncooperativeness ($n = 7$), poor tumor visualization on ultrasonography (US) ($n = 7$), or both ($n = 3$). The remaining 706 patients were enrolled in this study and underwent RFA.

Pretreatment Studies. The pretreatment assessment of each patient included complete history, physical examination, complete blood count (CBC), renal and liver function tests, electrocardiogram, chest x-ray, esophago-gastro-duodenoscopy, abdominal US, and either spiral computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. After June 2000, all tumors were also examined with contrast-enhanced US (CEUS). In some patients, additional diagnostic studies were performed as indicated (i.e., bone scintigraphy, selective hepatic angiography, and site-specific roentgenography, CT/MRI).

Cirrhosis diagnoses were based on histology ($n = 604$ [85.5%]) or clinical, laboratory, and US findings[26] ($n = 102$ [14.5%]). Portal hypertension was diagnosed in the presence of esophageal varices or splenomegaly with a platelets count <100 × 10^9/L, according to current guidelines.[3] HCC diagnoses were based on (1) histology; (2) positive imaging findings plus alpha-fetoprotein (AFP) levels ≥400 ng/mL (normal values: ≤20 ng/mL); or (3) concordant findings at imaging and laparoscopy (subcapsular form)[6] (Table 1).

Tumor Ablation. In both departments, ablations were performed with the same commercial RFA systems. From 1998 through 2001: Model 500 L (RITA Medical System, Mountain View, CA); from 2002 through 2008: Models RF 2000 and 3000 (Boston Scientific, Natick, MA) and Model TAG 100 (Invatec, Roncadelle, Italy). Each system included expandable-tip electrodes capable of creating thermal lesions 2.5-3.5 cm in diameter. The electrodes (14- to 19-gauge) had a stainless steel shaft (15-25 cm long) insulated with a 0.1-mm-thick layer of plastic and an exposed tip (1.0 cm long) with lateral deployable hooks (4 to 10)[27,28] or spirals (1 to 3).[29] Electrode choice was tailored to tumor size and location. In accordance with Italian Public Health System guidelines, patients were hospitalized a minimum of 1 day and 1 night (through November 2003) or 2 nights and 3 days (December 2003 to January 2008).[11]

Table 1. Characteristics of the 706 Patients* and 859 HCC Nodules Treated with RFA

Age, (years)	
range (mean SD)	58-78 (68.2 8.6)
Sex, no. (%)	
Males	462 (65.4)
Females	244 (34.6)
Cause of cirrhosis, no. (%)	
HCV	606 (85.9)
HBV	32 (4.5)
HBV-HCV	21 (3.0)
Ethanol abuse	30 (4.2)
Unknown	17 (2.4)
Child-Pugh class, no. (%)	
A5	411 (58.2)
A6	127 (18.0)
B7	168 (23.8)
Liver-related laboratory tests, (mean $\pm$ SD)	
Prothrombin time ratio (%)	77 $\pm$ 15
Serum albumin levels (gr/L)	3.8 $\pm$ 0.4
Total bilirubin levels (mg/dL)	1.1 $\pm$ 0.4
Platelet counts ($\times$ 109 L)	129 $\pm$ 35
Portal hypertension, no. (%)	
No	579 (82.0)
Yes	127 (18.0)
AFP levels, no. (%)	
$\leq$20 ng/mL	361 (51.1)
>20<400 ng/mL	296 (41.9)
$\geq$400 ng/mL	49 (7.0)
Diagnosis of HCC, no. (%)	
Imaging plus AFP levels	49 (7.0)
Imaging plus laparoscopy†	54 (7.7)
Histology	603 (85.4)
No. of HCC nodules	859
Patients with 1 nodule, no. (%)	553 (78.3)
Patients with 2 nodules, no. (%)	153 (21.7)
Size (cm)‡, range (mean $\pm$ SD)	1.2-3.5 (2.7 $\pm$ 0.6)
$\leq$2.0	159 (18.5)
>2.0$\leq$3.0	382 (44.5)
>3.0$\leq$3.5	318 (37.0)
HCC location (liver segment)§	
SI, SII, SIII, SIV, SV, SVI, SVII, SVIII	3, 75, 66, 108, 153, 118, 195, 141
BCLC stage, no. (%)	
0	57 (8.1)
A	331 (46.9)
B	318 (45.0)
LCSGJ stage, no. (%)	
T1	110 (15.6)
T2	462 (65.4)
T3	134 (19.0)

Abbreviations: HCC, hepatocellular carcinoma; SD, standard deviation; HCV, hepatitis C viruses; HBV, hepatitis B viruses; AFP, alpha-fetoprotein; S, liver segment.

* According to current guidelines, 217 of the 706 patients were potentially candidates for surgery, resection in 160 cases and liver transplantation in 57.[3] However, these options were ultimately excluded in all 217 cases. Resection was excluded in 113 cases due to age $\geq$ 75 years ($n = 82$) or comorbidities ($n = 31$); it was refused by 47 patients. Liver transplantation was excluded due to high surgical risk ($n = 54$) or patient refusal ($n = 3$).

† All patients had a Child-Pugh liver function score of B7.

‡ The largest diameter measured by US/CEUS, CT or MRI.

§ Location of HCC nodules was described by Couinaud nomenclature.[6]

Percutaneous RFA was done under local anesthesia, sometimes with conscious sedation.[6] During each session the electrode tip was inserted into the tumor 1-3 times under US guidance, and each time 1-3 thermal lesions were created (pullback technique). After withdrawal the electrode track was examined for bleeding with Doppler US. The session ended when the hyperechoic ablation area was at least as large as the tumor itself.[6,27] Laparoscopic RFA under general anesthesia was reserved for HCCs that were exophytic; located on the diaphragmatic surface of liver segments III, IV, V; or adherent to gallbladder or gastrointestinal loops. Electrodes were inserted under direct vision and 1-3 thermal lesions were produced with each insertion. The session ended when the boundaries of necrosis included the tumor.[18]

Assessment of Complications and Treatment Results. Complications were assessed with abdominal US (3 hours after RFA) and CBC, lactic dehydrogenase, aminotransferase levels, Child-Pugh-related tests, and US (24 hours after RFA). Other studies were performed as indicated. According to current guidelines,[30] complications were defined as major if they threatened the patient's life, produced substantial morbidity, or prolonged the hospital stay.

Treatment results were assessed 1 month after RFA by US with CEUS,[31] plus CT or MRI, and AFP assay if pretreatment levels were elevated. Results were classified as complete responses (CRs) (no enhancing tissue at the tumor site and normalization of AFP) or incomplete responses (IRs) (enhancing tissue at the tumor site, persistently elevated AFP levels, or both).[6,11,29] An IR to laparoscopic RFA was classified as treatment failure (TF). When IR was observed after percutaneous RFA, the procedure was repeated within 15 days. An IR to the second treatment (assessed as described above) was classified as a TF. Patients with TF underwent selective transarterial chemoembolization (sTACE)[3] and were then followed with the rest of the cohort.

Follow-up Studies. The protocol included abdominal US and CEUS, AFP assays, and Child-Pugh-related tests every 4 months (more frequently when needed) and CT or MRI every 6 months the first year after treatment and yearly thereafter (more frequently if US, CEUS or AFP suggested recurrence).[6,11,29]

Local recurrence was diagnosed when enhancement reappeared within the ablation zone or $\leq$2.0 cm from its margins or when histology was positive for viable tumor.[10-12,18] US-guided biopsies were performed: (1) when the ablation zone remained unenhanced but failed to shrink during follow-up; (2) when it remained unenhanced but AFP levels were $\geq$400 ng/mL in the absence of other intra- or extrahepatic lesions (excluded by a diagnostic work-up that included US/CEUS, bone scintigraphy, hepatic

angiography, and chest or site-specific roentgenography, CT/MRI).[6,27]

Nonlocal recurrences comprised all intrahepatic regrowth >2.0 cm from the ablation zone and extrahepatic metastases. They were diagnosed by imaging modalities and AFP assay; US-guided biopsies were used when ambiguous findings emerged.[6,10-12,27] Patients with nonlocal recurrences were classified as having limited disease (reflected by a tumor that still met the study's inclusion criteria) or advanced disease, i.e., intrahepatic HCC that was large (1-2 nodules >3.5 cm in diameter), massive (occupying an entire lobe or more), multifocal (≥3 nodules, any size), or neoplastic vein thrombosis, or extrahepatic metastases.

Treatment of Recurrences. Recurrences in patients who still met all of the inclusion criteria were treated with RFA and managed as described above, with one exception: local recurrence was treated with a single RFA session. If this session did not produce a CR or the tumor subsequently reappeared at this site, the case was classified as a TF and managed as described above. If only inclusion criterion (1) was unmet at the time of recurrence, the patient underwent sTACE (for multifocal or massive forms)[3] or RFA preceded by transarterial gelatin-sponge embolization of tumor (large forms).[27] Otherwise, treatment was exclusively supportive.

Statistical Analysis. We analyzed follow-up data collected through September 30, 2008. Quantitative variables were expressed as means and standard deviations or as medians, ranges, and interquartile ranges (IQR). Numbers and percentages were used for qualitative variables. Endpoints were recurrences, death (overall and HCC-related), and disease status at the end of follow-up. Deaths were considered HCC-related if viable tumor had been detected at the last follow-up visit. For all analyses the follow-up period started with CR to RFA of the initial HCC(s). For analyses of first recurrence and recurrence-free survival, follow-up ended at the time of first recurrence; other patients were censored at last follow-up visit and the time death without recurrence, respectively. For analysis of overall survival, follow-up ended at the time of death, censoring the remaining patients at the last follow-up visit. For tumor-specific survival analysis, follow-up ended at HCC-related death, and the remaining patients were censored at the last follow-up visit or HCC-unrelated death. In analysis of disease-free survival, follow-up ended at the time of HCC-related death or last follow-up visit in patients with active tumor. Patients who were disease-free at the last follow-up visit (taking into account the results of repeated RFA) or whose deaths were HCC-unrelated were cen-

sored. For patients lost to follow-up, data were right-censored and the disease status was that recorded at the last visit. Incidence rates per 100 person-years (and 95% confidence intervals [CIs]) were calculated for first recurrences and deaths. Recurrence and survival were described with the Kaplan-Meier method. Cox proportional hazard models were used to predict independent covariates (listed in Tables 2 and 5) associated with recurrence-free and overall survival. A competing risk model was used for cause-specific survival analysis.[32] Only variables with P-values <0.05 were retained for multivariate analysis. Results are expressed as hazard-rate ratios (HRs) with 95% CIs. Data were analyzed with the STATA statistical package (release 9.0, 2006, Stata, College Station, TX). All tests were two-sided.

Results

Table 1 shows the baseline characteristics of the 706 patients and 859 tumors. No significant differences were found between centers in terms of these characteristics.

Result of Initial RFA Treatments

Fifty-four (7.6%) patients with single subcapsular nodules underwent laparoscopic RFA, and CRs were observed in 53 (98.1%). The 652 (92.4%) who underwent percutaneous RFA included 499 (70.7%) with single nodules and 153 (21.7%) with two nodules. A total of 805 HCC nodules were treated with one ($n = 669$, 83.1%) or two ($n = 136$, 16.9%) percutaneous sessions (total sessions: 941). CRs were achieved in 796 nodules (98.8%) and in 643 patients (98.6%).

Follow-up

Median follow-up was 29 months (range, 5-128; IQR, 15-49 months). Twenty-six patients with advanced ($n = 23$) or limited ($n = 3$) nonlocal recurrence were lost to follow-up.

Recurrences

First Recurrences. During follow-up, 465 of the 696 patients who achieved CRs developed a first recurrence. The incidence of first recurrence was 41.2 (95% CI, 37.6-45.0) per 100 person-years (6.2 [95% CI, 4.8-7.8] local; 25.3 [95% CI, 22.5-28.3] limited nonlocal; and 9.7 [95% CI, 8.0-11.7] advanced nonlocal). The 3- and 5-year cumulative incidences of first recurrence were 70.8% (95% CI, 66.8-74.7) and 81.7% (95% CI, 77.7-85.3) (Fig. 1A,B). Median time to first recurrence was 18 (IQR, 7-42) months. Multivariate analysis identified age ($P = 0.030$), tumor size ($P = 0.047$), and number of nodules ($P < 0.001$) as significant predictors of first recurrence (Table 2). All three

Table 2. Cox Proportional Hazard Models Showing Predictors of First Recurrence After RFA

Predictors and Covariates	Univariate			Multivariate		
	HR	95% CI	P*	HR	95% CI	P
Age†	1.13	1.02-1.25	0.024	1.12	1.01-1.26	0.030
Sex						
Females	1‡					
Males	1.05	0.86-1.26	0.643			
Cause of cirrhosis						
HCV	1‡					
HBV	0.66	0.42-1.02	0.061			
HBV-HCV	1.50	0.37-6.01	0.571			
Ethanol abuse	1.08	0.69-1.69	0.741			
Unknown	1.55	0.89-2.71	0.119			
Child-Pugh class						
A5	1‡					
A6	1.02	0.80 - 1.30	0.874			
B7	0.99	0.79-1.30	0.916			
Child-Pugh-related tests						
Prothrombin time ratio§	1.01	0.96-1.07	0.662			
Serum albumin levels‖	1.07	0.88-1.29	0.510			
Total bilirubin levels¶	1.13	0.92-1.40	0.244			
AFP levels						
≤20	1‡					
>20<400	1.03	0.85-1.24	0.749			
≥400	1.04	0.73 -1.49	0.808			
Portal hypertension						
No	1‡					
Yes	1.19	0.95-1.49	0.130			
No. of HCC nodules						
1	1‡					
2	2.42	1.97-2.97	<0.001	2.36	1.92-2.90	<0.001
Largest nodule (cm)#						
≤3.0	1‡					
>3.0≤3.5	1.28	1.06-1.53	0.008	1.20	1.00-1.44	0.047

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; HR, hazard-rate ratio; CI, confidence intervals; AFP, alpha-fetoprotein.

* Only variables with a *P*-value < 0.05 were retained for multivariate analysis.

† Per 10-year older.

‡ Reference values.

§ Per 1 percentage-point.

‖ Per 1 unit.

¶ Per 1 unit.

Maximum diameter measured by US, CEUS, TC or MRI.

variables were independent predictors of local recurrence (Supporting Appendix 1), but only age and number of nodules correlated with nonlocal recurrences (Supporting Appendix 2). Table 3 shows the type of first recurrence as a function of time of detection and initial HCC nodule/s size.

Subsequent Recurrences. Figure 2 summarizes the events observed during follow-up and their management (details in Supporting Appendix 3). Three-fourths of the patients whose HCC recurred experienced multiple episodes of local and/or limited nonlocal recurrence, and about one-third of these ultimately developed advanced nonlocal recurrences. The median times to second, third, and fourth recurrences (measured from CRs of the previous recurrence) were 6.5 (IQR, 2.0-16.0), 4.4 (IQR, 1.0-10.0), and 2.0 (IQR, 1.0-6.0) months, respectively. Altogether, there were 877 episodes of recurrence: 134

(15.7%) local, 513 (58.1%) limited nonlocal and 230 (26.2%) advanced nonlocal. Of the 134 local recurrences, 7 (4.4%) were observed in 159 HCC nodules ≤2.0 cm, 49 (12.9%) in 378 nodules > 2.0 ≤3.0 cm, and 78 (25.0%) in 312 nodules >3.0 ≤3.5 cm.

Treatment of Recurrences. Details are shown in Supporting Appendix 3. Briefly, RFA was used to treat 110 (82.0%) of the 134 local and 467 (91.0%) of the 513 limited nonlocal recurrences. CRs were obtained in 102 (92.7%) and 455 (97.4%) cases, respectively. Of the 102 local recurrences that exhibited CRs, only seven (6.8%) had a TF. Local recurrence was detected in 54 (11.8%) of the 455 limited nonlocal recurrences with CRs.

Survival

Overall Survival. In all, 315 patients died (incidence rate: 15.4 per 100 person-years). Overall, 127
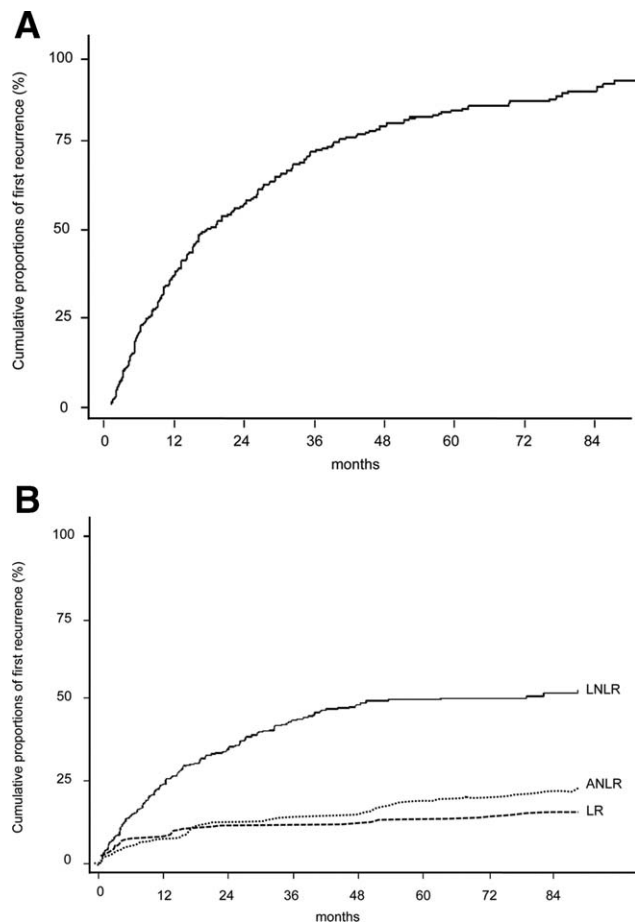
Fig. 1. Kaplan-Meier curve showing the cumulative incidence of first recurrence in 696 patients who had CR to RFA of the initial HCC nodule/s. Kaplan-Meier curves showing the cumulative incidence of first recurrences by type. The 3- and 5-year cumulative incidences were 12.1% (95% CI 7.2-15.3) and 13.2% (95% CI 8.3-20.1) for local recurrence (LR); 44.4% (95% CI 39.6-48.2) and 49.3% (95% CI 44.4-54.2) for limited nonlocal (LNLR); and 14.3% (95% CI 10.8-18.1) and 19.2% (95% CI 17.1-22.1) advanced nonlocal recurrence (ANLR).

(40.3%) deaths were unrelated to the tumor (Supporting Appendix 4); there were 188 (59.7%) HCC-related death (incidence rate: 9.2 per 100 person-years). Estimated cumulative overall survival rates at 3 and 5 years were 67.0% (95% CI, 62.7-70.9) and 40.1% (95% CI, 35.0-45.1) (Fig. 3A-C) and median overall survival was 43 (IQR, 12-124) months. Multivariate analysis identified Child-Pugh class B ($P = 0.013$), first recurrence ≤24 months after RFA ($P < 0.001$), local recurrence ($P < 0.001$), and advanced nonlocal recurrence ($P < 0.001$) as independent predictors of death (Table 4).

Tumor-Specific Survival. Estimated 3- and 5-year cumulative tumor-specific survival rates were 78.6% (95% CI 74.5-82.1) and 56.6% (95% CI 50.6-62.1), and median tumor-specific survival was 71 (IQR: 41-124) months (Fig. 3D). Multivariate analysis identified local ($P < 0.001$) and advanced nonlocal recurrences ($P < 0.001$) as independent predictors of HCC-related death (Supporting Appendix 5).

Disease-Free Survival. Estimated 3- and 5-years cumulative disease-free survival rates (after repeated RFA) were 68.0% (95% CI, 64.2-72.0) and 38.0% (95% CI, 33.2-43.1), and the median disease-free survival was 52 (IQR: 29-78) months (Fig. 3E). Of the 102 patients with follow-ups exceeding 5 years from CR of the initial HCC (median, 76; IQR, 70-84 months), 52 were disease-free at their last visit, but only 30 had never experienced recurrence. Of the 25 patients with follow-ups exceeding 7 years (median, 95; IQR, 87-115 months), 14 were disease-free but only 7 were recurrence-free.

Overall Complications

Overall, 1,326 HCC nodules were managed with 1,921 RFA sessions (percutaneous: 1,840; laparoscopic:

Table 3. Type of First Recurrence by Time of Detection and Size of Initial HCC Nodule/s

	Months after CR to RFA of initial HCC/s		
	≤ 24	> 24	
Type of recurrence - no. (%)			Total patients
Local	54 (77.5)	16 (22.5)	70 (100)
Nonlocal, limited	221 (76.3)	69 (23.7)	290 (100)
Nonlocal, advanced	70 (66.6)	35 (33.4)	105 (100)
Total patients	345 (74.2)	120 (25.8)	465 (100)

	HCC nodule diameter (cm)*			
	≤2.0	>2.0≤3.0	>3.0≤3.5	
Type of recurrence - no. (%)				Total patients
Local	6 (8.5)	22 (31.5)	42 (60.0)	70 (100)
Nonlocal, limited	67 (23.1)	110 (37.9)	113 (39.0)	290 (100)
Nonlocal, advanced	16 (15.2)	30 (28.6)	59 (56.2)	105 (100)
Total patients	89 (19.2)	162 (34.8)	214 (46.0)	465 (100)

* For patients with 2 HCC nodules, the diameter considered is that of the largest nodule measured by US, CEUS, TC or MRI.
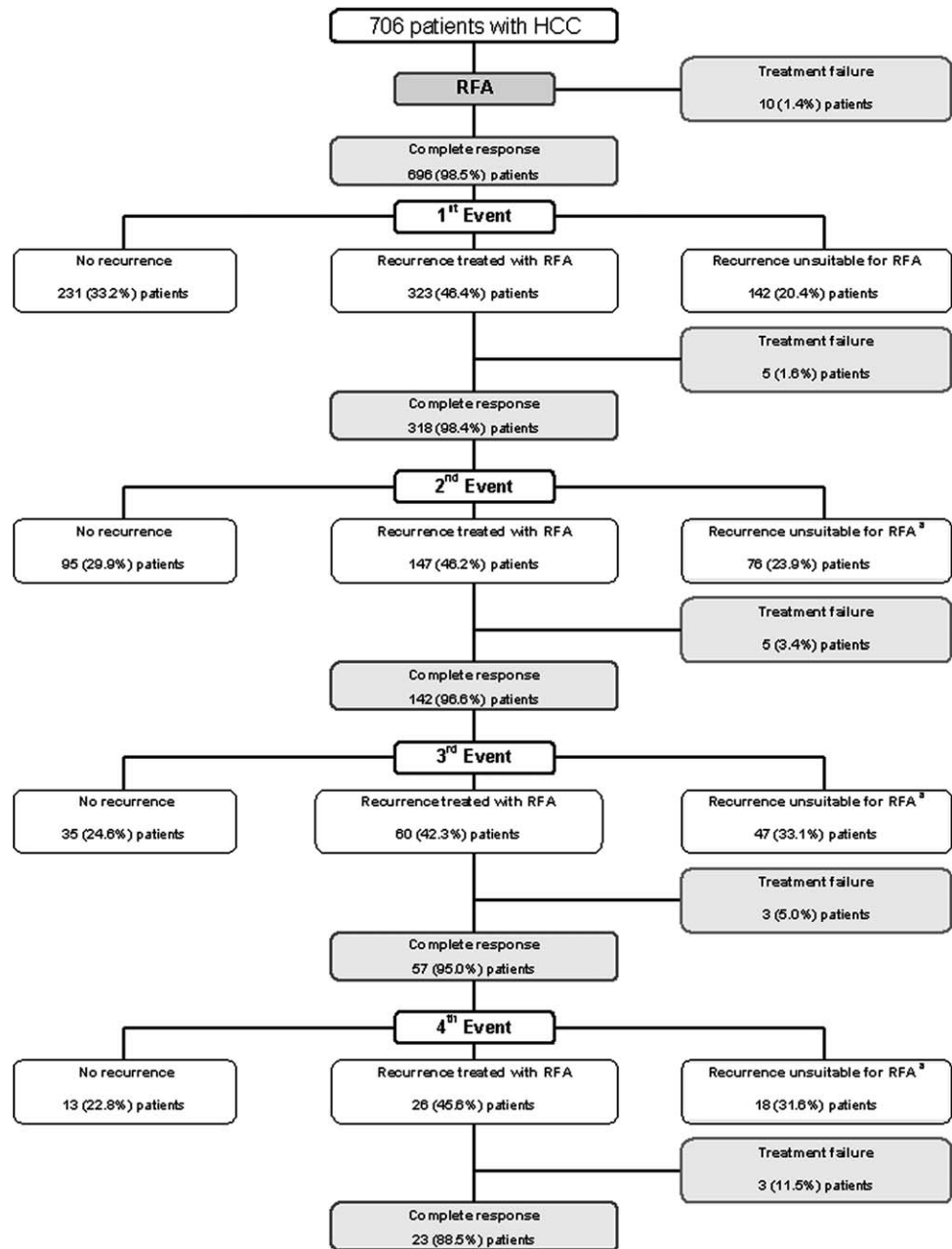
Fig. 2. Summary of follow-up events. Recurrences were treated with RFA if the patient still met all enrollment criteria. When RFA was excluded, recurrences were treated with selective transarterial chemo-embolization, RFA after tumor embolization, or palliative therapy. Patients with >4 episodes of recurrences are not shown (see Supporting Appendix 1). [a]Patient with simultaneous local and advanced nonlocal recurrence.

81). There were no procedure-related deaths, and fewer than 1.0% of the RFA sessions were associated with major complications (Table 5).

Discussion

This long-term cohort study of RFA treatment for HCC in patients with cirrhosis sheds important light on the clinical behavior of this highly prevalent and frequently fatal form of cancer.[1-3] As in previous studies,[6,10-12,16-18] RFA of the initial HCC nodules produced CRs in over 98% of the cases, with a local recurrence rate of about 15%, even if the technique used was not performed to obtain safety margins. The latter requires multiple electrode insertions and overlapping thermal lesions[28] that are difficult to create even for skilled operators. The local recurrence rate might have been slightly higher if the 83 patients (11.7%) followed for less than a year had longer follow-ups. This possible underestimation is offset, however, by the operational definition of local recurrence adopted in the study that included all tumor growth within 2.0 cm of the original ablation zone. Viable tumor tissue *within* or *continuous with* the ablation zone probably does reflect treatment failure caused by suboptimal electrode placement or undetected satellites
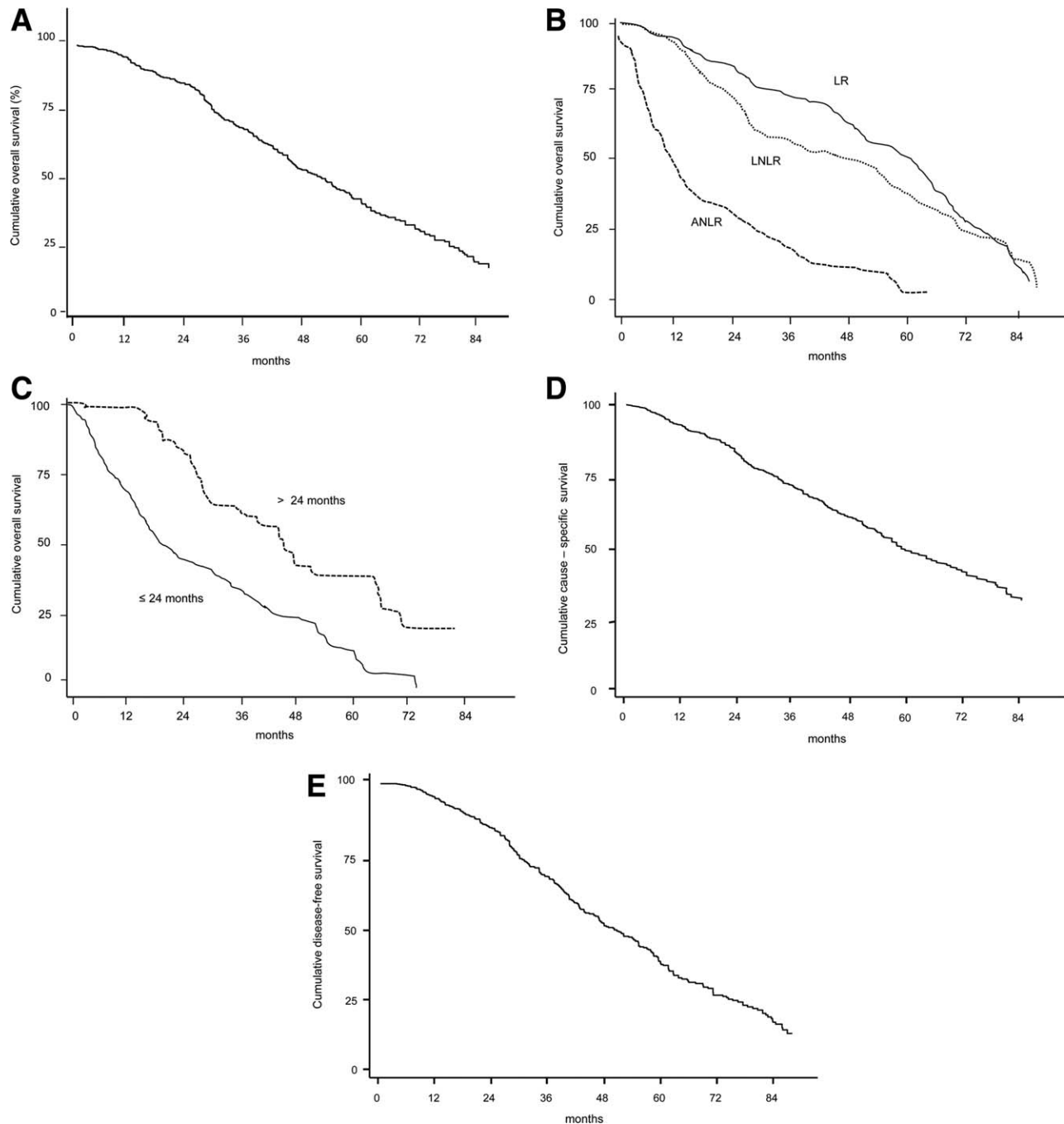
Fig. 3. Kaplan-Meier estimates of overall survival in the 706 patients treated with RFA. Kaplan-Meier estimates of overall survival by recurrence type in the 465 patients experiencing a first recurrence. (Follow-up periods started with first recurrence and ended at time of death for any cause; remaining patients were censored at last follow-up visit.) Estimated 3- and 5-year overall survival rates were 72.0% (95% CI 62.7-82.9) and 52.1% (95% CI 42.0-62.1) for patients with local recurrence (LR); 55.0% (95% CI 49.0-61.8) and 43.1% (95% CI 35.0-51.3) for those with limited nonlocal recurrence (LNLR), and 19.9% (95% CI 14.8-26.9) and 3% (95% CI 0.0-9.1%) for those with advanced nonlocal recurrence (ANLR). Kaplan-Meier estimates of overall survival in the 465 patients shown in (B) by time of detection of first recurrence. (Follow-up periods started with first recurrence and ended at time of death for any cause; remaining patients were censored at last follow-up visit.) Estimated 3- and 5-year overall survival rates were: 34.9% (95% CI 24.8-44.8) and 17.6% (95% CI 5.6-28.7) for patients who developed recurrence within 24 months and 62.3% (95% CI 52.4-72.1) and 36.0% (95% CI 26.7-46.9) for those who developed recurrence >24 months. Kaplan-Meier estimates of tumor-specific survival in the 706 patients treated with RFA. Kaplan-Meier estimates of disease-free survival in the 706 patients treated with RFA. This analysis includes results of repeated RFA treatments for 577 recurrences.

that escape ablation due to the convective effect of portal blood flow outside the tumor.[29] However, viable tumor tissue within 2.0 cm from the ablation zone but not continuous with it, particularly when it is detected more than 1 year after treatment, may well represent *de novo* carcinogenesis unrelated to the outcome of the ablation.[18]

Table 4. Cox proportional Hazard Models Showing Predictors of Death After RFA

Predictors and Covariates	Univariate			Multivariate		
	HR	95% CI	P*	HR	95% CI	P
Age†	1.18	1.04-1.35	0.011	1.08	0.93-1.28	0.306
Sex						
Females	1‡					
Males	0.99	0.78-1.25	0.923			
Cause of cirrhosis						
HCV	1‡					
HBV	0.46	0.24-0.87	0.016	0.51	0.27-0.98	0.043
HBV-HCV	5.83	1.43-23.8	0.014	9.04	2.18-37.4	0.002
Ethanol abuse	1.00	0.53-1.89	0.992	0.96	0.50-1.87	0.912
Unknown	2.17	1.23-3.81	0.007	1.84	1.03-3.28	0.039
Child-Pugh class						
A5	1‡					
A6	1.02	0.74-1.41	0.903	0.76	0.55-1.06	0.110
B7	1.29	1.00-1.66	.047	1.40	1.07-1.82	0.013
Child-Pugh-related tests						
Prothrombin time ratio§	0.90	0.87-1.00	0.050			
Serum albumin levels‖	0.73	0.58-0.93	0.010			
Serum bilirubin levels¶	1.25	0.97-1.61	0.081			
AFP levels						
≤ 20	1‡					
> 20 < 400	1.20	0.96-1.52	.144			
≥ 400	1.15	0.75-1.77	.513			
Portal hypertension						
No	1‡					
Yes	1.31	0.99-1.72	0.061			
No. of HCC nodules						
1	1‡					
2	1.42	1.09-1.84	0.009	0.89	0.67-1.18	0.425
Size of HCC nodules (cm)#						
≤ 3.0	1‡					
> 3.0 ≤ 3.5	1.29	1.03-1.61	0.024	0.87	0.69-1.10	0.246
Time of first recurrence						
None	1‡					
≤ 24 months	2.01	1.49-2.73	<0.001	1.84	1.33-2.53	<0.001
> 24 months	1.01	0.71-1.45	0.936	0.77	0.53-1.14	0.199
Type of first recurrence						
None	1‡					
Local	1.42	1.04-1.94	0.029	3.68	2.89-4.70	<0.001
Nonlocal, limited	1.31	0.86-2.00	0.208	0.96	0.86-1.06	0.400
Nonlocal, advanced	2.37	1.68-3.35	<0.001	3.27	2.86-3.73	<0.001
Type of recurrence**						
None	1‡					
Local††	4.22	3.35-5.31	<.001‖			
Nonlocal, limited††	1.14	1.04-1.25	.006‖			
Nonlocal, advanced††	7.00	5.49-8.90	<.001‖			
BCLC stage						
0	1‡	0.48-1.16				
A	0.66	0.41-1.06	0.089			
B	0.89	0.56-1.42	0.633			
LCSGJ stage						
T1	1‡					
T2	0.88	0.64-1.19	0.400			
T3	1.24	0.86-1.80	0.245			

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; HR, hazard-rate ratio; CI, confidence interval; AFP, alpha-fetoprotein.

* Only variables with a P value < 0.05 and not collinear were retained for multivariate analysis.

† Per 10-years older.

‡ Reference values.

§ Per 1 percentage point.

‖ Per 1 unit.

¶ Per 1 unit.

Maximum diameter measured by US, CEUS, TC or MRI.

** All episodes of recurrence over the follow-up period (n = 877) were considered in a time-dependent analysis.

†† Time-dependent covariates[i]; this covariate was not included in the multivariate analysis due to colinearity with the variable Type of first recurrence.

Table 5. Complications Occurred in 1,921 RFA Sessions

	no. (%)
Major	
Hemoperitoneum	6 (0.3)
Hemothorax requiring drainage	2 (0.1)
Self-limiting hemobilia	1 (0.05)
Subcutaneous seeding*	2 (0.1)
Skin burn†	1 (0.05)
Total	12 (0.6)
Minor	
Postoperative pain	18 (0.9)
Self-limiting pleural effusion	32 (1.6)
Transient worsening of liver function‡	54 (2.8)
Low-grade fever	76 (3.9)
Total	180 (9.3)

Abbreviation: RFA, radiofrequency ablation.
* Not possible to refer certainly to a US-guided biopsy or RFA.
† Occurred after a laparoscopic session of RFA.
‡ Transient change of Child-Pugh class (maximum B8).

As in previous studies, immediate posttreatment CR and local recurrence rates were better than those reported after percutaneous injection therapies.[33] The local recurrence rate observed for HCC nodules ≤2.0 cm is similar to that reported after surgical resection of HCCs of the same size,[14] and only minor differences exist between the overall local tumor control rates achieved with RFA and surgical resection for nodules >20 ≤30 mm.[13,15] However, these differences, which can be eliminated with just one additional RFA "clean-up session," need to be weighed against the relative risks of procedure-related death and morbidity. In fact, RFA is consistently mortality-free,[6,10,11] and fewer than 1.0% of our procedures were associated with major complications.[10-12,16-18] These rates are slightly higher than those reported for percutaneous injection therapies,[5,33] but they are far lower than those observed after surgical resection.[34]

Although RFA provided excellent local tumor control, ≈1 out of 3 patients developed some type of nonlocal recurrence each year, leading to a cumulative proportion of recurrence of almost 80% at 5 years. This figure is entirely consistent with the recurrence rates reported for RFA, other percutaneous ablative therapies,[10-12,16-18,33] and surgical resection of HCCs ≤3.0 cm.[14-16] These findings demonstrate that, regardless of how the first nodules are treated, recurrence and progression are the rule for HCC. However, the disease often remains confined to the liver for long periods, and this offers opportunities for radical ablation. In this setting, keeping a patient tumor-free calls for repeated interventions, therefore, the versatility and noninvasiveness of the treatment method is almost as important as its local efficacy. Like other minimally invasive techniques, RFA offers distinct advantages with respect to surgical resection in terms of repeatability. Over 65% of all recurrence episodes in our cohort were managed with repeated RFA treatments. In contrast, only 7.7%-31.0%

of first recurrences and a negligible percentage of subsequent recurrences are eligible for repeated resections.[15,19]

As previously reported,[10-12] liver function influenced overall survival, despite the limited differences evaluated in our cohort (Child-Pugh classes ranging from A5 to B7). Overall survival was also significantly related to early recurrence (i.e., ≤24 months after treatment) and to local recurrence. This may reflect the limitations of radiologic tools in staging seemingly early stage tumors.[14] However, the strongest independent predictor of death (overall and tumor-specific) was first recurrence in the form of advanced nonlocal disease, which precludes curative treatment. In some cases the early development of advanced disease may reflect tumor understaging; however, in most cases it likely reflects the intrinsic biological potential of the primary tumor that cannot be currently established before treatment. Conversely, the low risk associated with limited nonlocal recurrences—the most common event observed during follow-up—may be attributed to their early detection and to the efficacy of RFA in their local control.

The observed cumulative survival curves are entirely comparable with those reported in other series of HCCs treated with percutaneous ablative therapies[6-12,16-18,33] or surgical resection.[13-15] Recently, randomized clinical trials showed that RFA is superior to percutaneous chemical injection in terms of both local tumor control and survival.[33] Conversely, no significant differences in survival rates (overall or disease-free) were found after RFA or surgery.[35,36] However, meaningful comparison of mortality data associated with surgical and nonsurgical treatment of HCC is extremely difficult, because most patients will experience several episodes of recurrence and surgical and nonsurgical approaches differ greatly in terms of their repeatability.

Collectively, our findings indicate that the clinical course of HCC, even in very early (T1) and early stage (T2), varies widely and can be only partially predicted by current staging systems, which are mainly based on size and number of tumor nodules.[21,22] Differences in the clinical outcome of HCCs diagnosed at the same stage in patients with preserved liver function may reflect biological differences of the tumor and cirrhotic liver tissue.[37,38] This study also shows that mortality unrelated to cancer progression has an important impact on the survival of HCC patients, who in Western countries are generally elderly.[3,4,32]

In conclusion, our ability to select optimal treatment strategies for patients with cirrhosis with HCCs is currently limited by three factors: (1) unpredictability of tumor progression and *de novo* carcinogenesis[37,38]; (2) tumor understaging[14]; and (3) substantial risk of HCC-unrelated death. Safe, effective, and minimally invasive

treatments, thus, seem to be the most reasonable approach for HCC patients. Our experience indicates that RFA should be the treatment of choice for patients with one or two small HCCs, whereas surgical resection can be reserved for patients with preserved liver function whose tumors cannot be treated with RFA or in which RFA did not produce CR. It is important to recall that RFA failure does not preclude subsequent surgical resection, whereas surgery can compromise the residual liver function, making subsequent RFA useless. On the other hand, neither RFA nor surgical resection is appropriate in the group of patients who, although successful treated for early/very-early (T1, T2) HCC, develop advanced nonlocal recurrences shortly after treatment (Table 3). To improve our ability to define effective individualized strategies for the management of this complex disease, future research should focus on the identification of tumor cell markers and/or genetic profiles associated with specific patterns of HCC growth.

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