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Combined Ethanol Injection Therapy and Radiofrequency Ablation Therapy in Percutaneous Treatment of Hepatocellular Carcinoma Larger than 4 cm

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Abstract

Background: Optimal treatment of large-sized hepatocellular carcinoma (HCC) is still debated, because percutaneous ablation therapies alone do not always achieve complete necrosis.
Objective: To report our experience in the treatment of patients with HCC larger than 4 cm in diameter by combined percutaneous ethanol injection and radiofrequency thermal ablation.
Methods: In a 5-year period there were 40 consecutive patients meeting the inclusion criteria (24 men and 16 women; age range 41–72 years, mean 58 years). These subjects had a single HCC larger than 4 cm. Twelve subjects also had one or two additional nodules smaller than 4 cm (mean 1.2 nodules per patient). Patients were submitted to one to three sessions consisting of ethanol injection at two opposite tumor poles (mean 12 ml) and then of radiofrequency application through one or two electrodes placed at the tumor center (mean treatment duration 30 min).
Results: Complete necrosis was obtained in all cases with one to three sessions (mean 1.3 sessions per patient). All patients experienced pain and fever but one only subject had a major complication requiring treatment (abscess development and fistulization). Overall follow-up was 7–69 months. Two patients showed local recurrence and 9 developed new etherotopic HCC nodules. Seven subjects died during follow-up while 33 were free from recurrence 8–69 months after treatment.
Conclusion: A combination of ethanol injection and radiofrequency ablation is effective in the treatment of large HCC.

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Percutaneous ablation therapies (PATs) such as percutaneous ethanol injection (PEI) and radiofrequency thermal ablation (RFA) have been widely employed in the nonsurgical, local treatment of hepatocellular carcinoma (HCC). Nevertheless, PATs have some well-known limitations and drawbacks. One of the main problems with PATs is the inability to achieve adequate control of large-sized tumor [1–3]. Consequently, several possibilities have been suggested in the treatment of HCC larger than 4–5 cm. These treatment modalities include use of more destructive PATs, such as hot saline injection therapy [4] and single-session ''one-shot'' PEI [5]. Alternatively, a combination of different locoregional treatments has been hypothesized, such as combined use of PEI and segmental chemoembolization (TACE) or embolization (TAE) [1, 6–8], of RFA and TACE [9–12], of microwave coagulation therapy and TACE [13], of laser interstitial photocoagulation and TACE [14], of high-intensity focused ultrasound ablation and TACE [15], of external radiation therapy and TACE [16], and of PEI and RFA [17–20]. Another possibility is to improve PAT by concomitant occlusion of arterial inflow and/or venous outflow from the involved liver area [2, 3, 21].

Multimodal HCC treatment is now a major trend, whose main purpose is to obtain adequate local control of this tumor, with special reference to those patients with large HCC [22–24]. In addition, multimodal management allows the various therapeutic tools to be employed in a less ''aggressive'' fashion, reducing for example the number of treatment sessions or the number of percutaneous needle/electrode insertions for each session [9, 19]. The purpose of

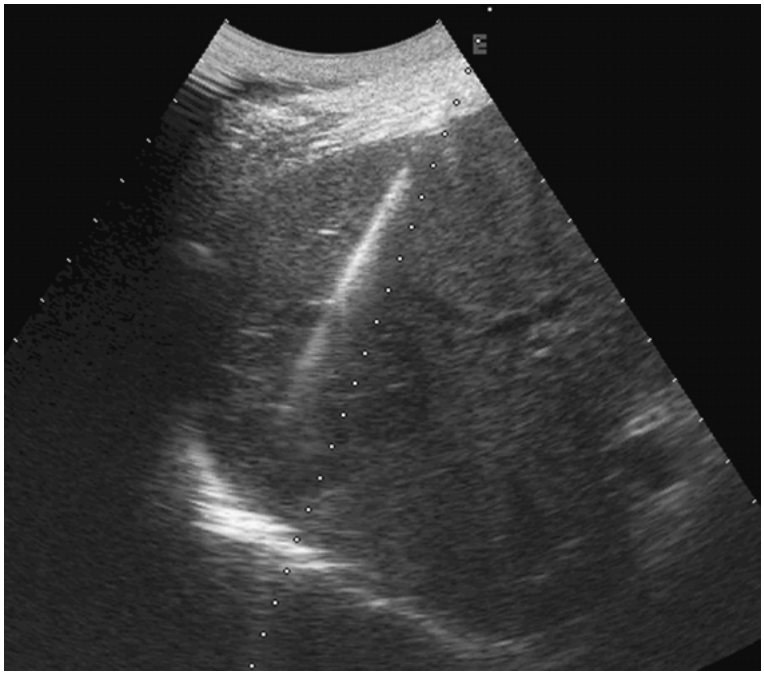

Fig. 1. The RFA electrode is introduced within the large hypoechoic lesion (HCC).

this paper is to report our preliminary experience in the treatment of HCC larger than 4 cm by means of a combination of PEI and RFA.

Materials and Methods

The study was approved by our institution's ethics committee. Our study group included 40 consecutive patients with a single HCC larger than 4 cm in diameter (and a maximum of two satellite lesions). These subjects were treated between January 1999 and December 2003.

The group consisted of 24 men and 16 women aged 41–72 years (mean 58 years). All patients had chronic liver disease, related to hepatitis C virus in 27 cases, hepatitis B virus in 4, combined hepatitis B and C virus in 1, combined hepatitis B and delta virus in 1, and ethanol abuse in 3. Four patients had cryptogenetic cirrhosis. Liver function status according to the Child-Pugh system was Child A in 7 subjects and Child B in 33. Inclusion criteria met by our study group were: HCC nodular growth, a maximum of two additional smaller nodules (all <40 mm), no evidence of extrahepatic spread, absent or minimal peritoneal effusion, Child A or B class, prothrombin time ratio greater than 50%, and a platelet count higher than 40,000/μl.

All tumors had been recognized by imaging techniques, including sonography (40/40), CT (40/40), or MRI (9/40). Pretreatment investigation included sonography, helical CT, and an alpha-fetoprotein (AFP) assay in all subjects. All CT studies were carried out with the same single-slice scanner (Somatom Plus 4 Expert, Siemens, Erlangen, Germany), contrast medium (iomeprol, Iomeron, Bracco, Milan, Italy), power injector (CT9000, Liebel-Flarsheim, Cincinnati, USA), and parameters, including a 0.75 sec revolution time, 120 kVp, 180 mA, 5 mm slice thickness, 5 mm/sec table feed, 3.1 mm reconstruction interval, 120 ml contrast volume, 350 mg I/ml contrast concentration, 4 ml/sec injection rate, 25 sec delay for arterial-phase acquisition, and 60 sec delay for portal-phase acquisition.

All HCCs had a well-demarcated, hypervascularized appearance on pretreatment CT scans. There were 40 lesions, ranging in size from 41 to 70 mm (maximum diameter measured on axial CT scans), with a mean of 47 mm. Tumor volume ranged from 41 to 190 cm^3 (mean 88 cm^3). In 8 patients with low or relatively low AFP level (<200 ng/ml) and in 2 patients with nonspecific CT findings diagnosis was confirmed with cytological or microhistologic sampling. This was done in accordance with the EASL criteria from the Barcelona conference [25]. In 12 cases there were coexistent HCC nodules smaller in diameter than 40 mm (1–2 nodules per patient, mean 1.2 nodules per patient). These additional lesions ranged in size from 9 to 33 mm (mean 28 mm) and were treated by using PEI alone or RFA alone. This was done during the same treatment session of the larger HCC.

All treatments were carried out with the patient under general anesthesia and tracheal intubation, in the operating room, under sonographic guidance. One grounding pad was placed on the posterior surface of each thigh (none of these patients had a history of hip prosthesis placement). First, RFA electrodes (LeVeen needle electrode, Radiotherapeutics) were put in place (Fig. 1). A single electrode was employed in 17 patients with an HCC diameter ranging from 41 to 50 mm while two eccentrically located electrodes were employed in the remaining 23 patients with tumor larger than 50 mm. Subsequently, ethanol was injected through a 21G, 20 cm long, multihole needle (PEIT needle, HS Hospital Service, Pomezia, Italy). This injection of dehydrated, sterile, 98% ethanol was done at the peripheral aspect of the lesion. Specifically, two ethanol injections were performed: one at a peripheral pole of the tumor and the second at the opposite pole (Fig. 2). PEI needles were placed deeply within each tumor pole but, during injection, we retracted the needle for 1–2 cm and we carefully assessed the effective, adequate spread of ethanol through the peripheral aspect of the mass. Ethanol volume ranged from 10 to 20 ml (mean 12 ml) and was arbitrarily established on the basis of the overall size of the original tumor and the adequacy of ethanol diffusion within the tumor periphery itself. In general, we injected

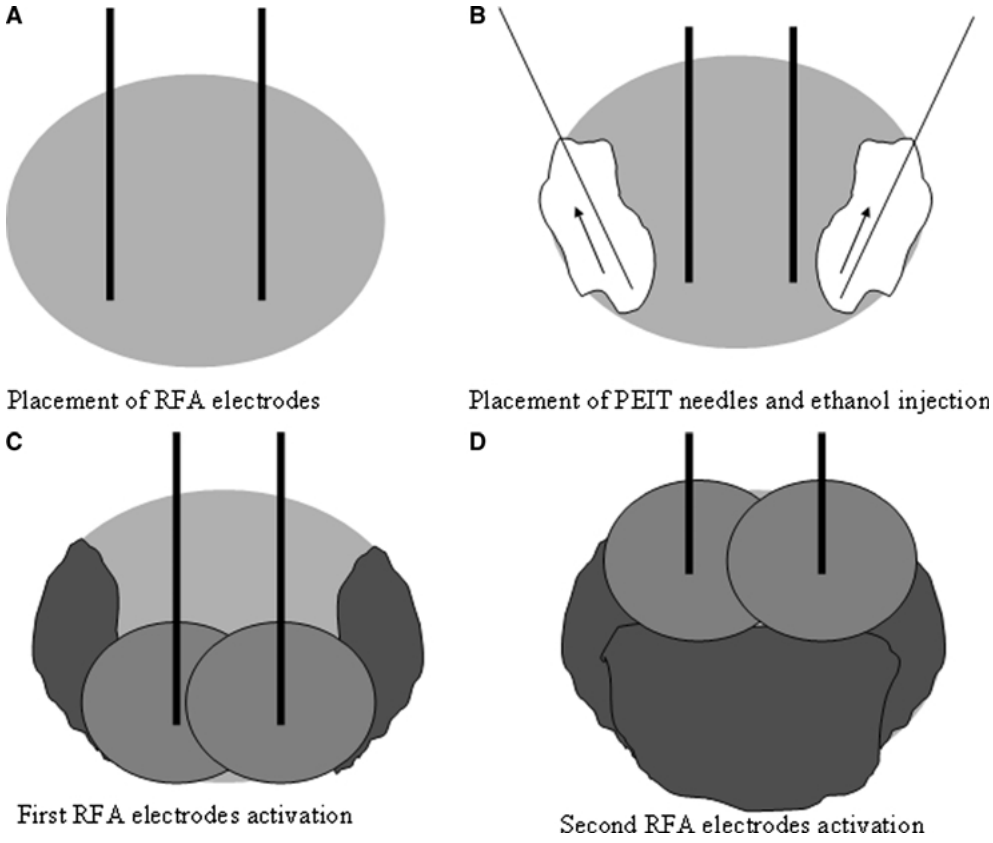

Fig. 2A–D. Our ablation protocol. **A** Two RFA electrodes are inserted. **B** PEI needles are inserted and ethanol injected. **C** Deep RFA ablation is carried out. **D** More superficial RFA ablation is carried out.

as much ethanol as we could into the tumor without causing leakage from the sides.

RFA treatment was performed 2–4 min after the completion of PEI. We employed a 250 W monopolar instrument (Radiotherapeutics, Mountain View, CA, USA), with a 12-hook 14G electrode generating a 4 cm array diameter. RFA treatment consisted, eventually for each electrode alternatively, of two phases with a 1 min cooling interval. The first radiofrequency application lasted about 7 min while the second lasted about 2 min. Subsequently, the single electrode or the two electrodes were withdrawn for 2–3 cm and the entire cycle, (consisting of a 7 min first application, a 1 min interval, and a 2 min second application) was repeated. The overall durations of PEI and RFA were up to 15 min and up to 45 min (mean 30 min), respectively.

Ablation effectiveness was checked with sonography and triple-phase CT evaluation 1, 6, and 12 months after treatment and every 12 months thereafter. Postinterventional CT studies were carried out with the same technique as the preinterventional studies. Absence of intralesional contrast enhancement was used to define complete necrosis [26, 27]. Serum AFP level was also tested at the same intervals. The pretreatment AFP level was normal (<20 ng/ml) in 3 patients, slightly increased (21–200 ng/ml) in 5, and significantly increased (>200 ng/ml) in the remaining 32.

Overall patient survival was defined as the time from treatment to death. For patients who were lost at a given time during follow-up or were alive at the time of the last visit, survival was conservatively defined as the time between treatment and the last date on which the patient was known to be alive. Progression-free survival was defined as the time from treatment to disease progression or to death from disease progression or other causes. For patients who were lost before disease progression or were progression-free at the time of the last visit, progression-free survival was conservatively defined as the time between treatment and the last date on which the patient was known to be free of progression. Survival curves were drawn using the Kaplan–Meier product limit method [28].

Results

All scheduled treatment sessions were carried out without any technical failure. During RFA treatment, a gaseous hyperechogenicity was clearly visible within the treated area (Fig. 3). This effect was more dramatic than is usually observed after RFA alone, as already noted by other authors (using CT guidance) [19].

The overall follow-up of the 40 patients treated was 7–69 months (mean 35 months). Helical CT follow-up demonstrated complete necrosis (absence of enhancing tissue during arterial-phase acquisition) in 28 of 40 cases (70%) (Fig. 4). A partial necrotizing effect was noted in the remaining 12 large HCCs (patients), all being larger than 50 mm in diameter. In these 12 subjects a 5–30% area of residual viable enhancing tissue was noted and complete necrosis was obtained only after a second treatment session (11 cases) or a third treatment session (1 case). Ultimately, complete (100%) necrosis was obtained in all our patients with one to three treatment sessions (mean 1.3 sessions per patient) (Table 1).

Injecting ethanol prior to RFA application did not caused major side effects. All patients experienced pain and fever lasting 3–7 days after treatment. Additionally, in 1 subject

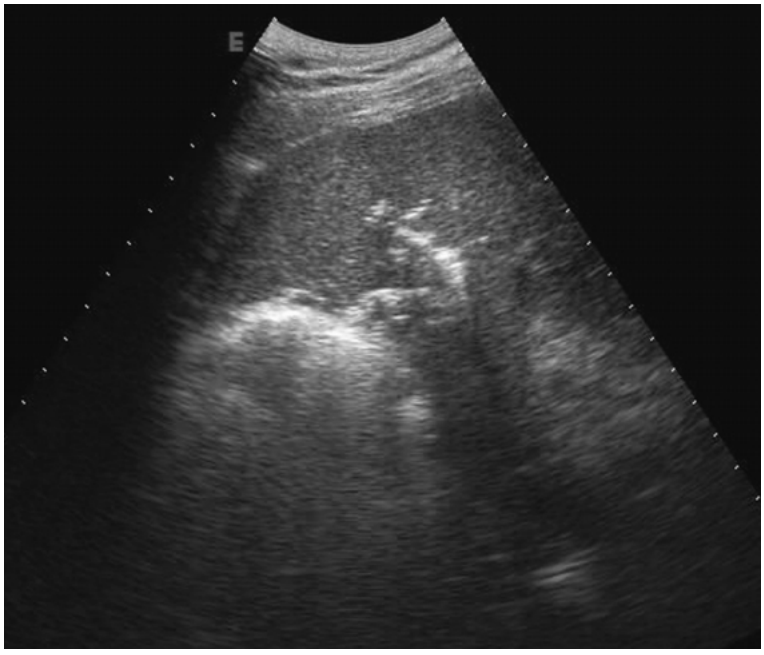

Fig. 3. Diffuse hyperechoic appearance of the HCC immediately after RFA and PEI treatment. Same patient as in Fig. 1.

an abscess developed on the treated necrotic HCC. In this patient the subcapsular location of the abscess on the anterior liver margin subsequently determined development of a cutaneous fistula. This complication was successfully managed with intravenous antibiotic therapy and surgical curettage. Other complications included reactive pleuritis (4 cases), small (<2 cm wide) subcapsular liver hematoma (2 cases), small (<2 cm wide) hematoma at the needle insertion on the abdominal wall (1 case), and hydropneumothorax (1 case). All these complications were treated conservatively without any specific therapy.

No patient underwent further loss in liver function as an immediate consequence of the treatment (Table 2). Seven patients died 7–45 months after treatment because of end-stage cirrhosis (6 cases) or unrelated cause (1 case). Local recurrence developed in 2 patients (5%) while new HCC nodules in untreated liver segments developed in 9 patients (23%). The remaining subjects were still free from tumor recurrence 8–69 months after treatment. Overall survival was 92% at 1 year, 87% at 2 years, and 83% at 3 years (Fig. 5). Progression-free survival was 80% at 1 year, 69% at 2 years, and 59.5% at 3 years (Fig. 6).

Discussion

An increasing number of cirrhotic patients with HCC undergo treatment with a locoregional ablation procedure, to avoid risks related to surgical or transcatheter management of subjects with impaired liver function [1–3]. Patients with large HCC are usually treated with TAE or TACE but, in these cases, complete necrosis is seldom achieved. Moreover, global transcatheter techniques have a significant adverse effects on nontumoral parenchyma [2, 3, 6, 22].

All currently employed PATs obtain very effective necrotizing effects in encapsulated, small primary liver tumors. PEI, and indirectly all other PATs, have been validated as a curative treatment for HCC smaller than 3 cm whereas percutaneous ablation of larger lesions still needs validation [2, 3]. One reason for failure in the treatment of larger lesions is the difficulty in determining the optimal number of ablations needed and the exact location of needle or electrode placement that is necessary to obtain homogeneous necrosis [24]. Large tumors should be treated with multiple overlapping ablations or by combining different PATs.

Experimentally, it has been shown [29] how combined use of ethanol and radiofrequency ablation causes a synergistic necrotizing effect, with coagulation volumes clearly larger than those usually obtained with PEI or RFA alone. In two different studies [17, 19] a large necrotic effect was obtained by combining PEI and RFA. In addition, this combined use allowed treatment of tumors in critically locations, such as those immediately below the liver capsule, adjacent to the gallbladder, inferior vena cava or hepatic hilum, or immediately below the diaphragm [17]. Finally, Poggi et al. [30] reported a single case where PEI was employed to treat malignant portal thrombosis and RFA to treat HCC.

In one series [19] of 30 patients with lesions larger than 5 cm (mostly metastases), the mean ablation effect in a group of subjects treated with combined PEI and RFA was almost triple that in the group of controls undergoing RFA therapy alone. At the same time, a smaller number of radiofrequency applications per session was needed in the group undergoing combined treatment compared with that undergoing RFA alone. A lower tissue impedance during radiofrequency application and a lower incidence of complications was noted in the patients treated with PEI plus

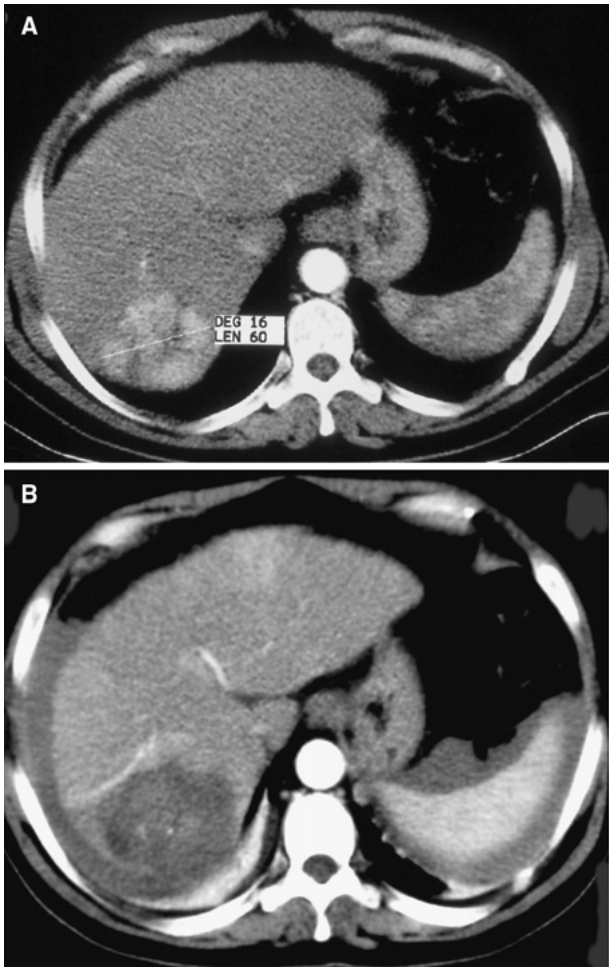

Fig. 4. Preprocedural **A** and postprocedural **B** arterial-phase CT scans. The HCC is seen as a hyperattenuating mass within liver segment VII, becoming larger and nonenhancing 8 days after treatment with PEI plus RFA. Same patient as in Figs. 1 and 3.

Table 1. Treatment results

Patient no.	Child stage	HCC size (mm)	No. of sessions	Local recurrence	New etherotopic Lesions	Death
1	A	41	1			
2	A	53	2			
3	B	41	1			
4	B	68	3		+	
5	B	42	1			
6	A	42	1			
7	A	42	1		+	
8	A	54	2			
9	B	41	1	+		
10	B	68	2		+	
11	B	41	1		+	
12	B	42	1			+
13	B	43	1			+
14	B	49	1			+
15	B	47	1			
16	B	58	2		+	
17	B	45	1			
18	B	51	2			
19	B	42	1			
20	B	70	2			
21	B	41	1			+
22	B	42	1			+
23	B	67	2		+	
24	B	41	1	+		
25	B	47	1		+	
26	B	44	1	+		
27	B	49	1			+
28	B	50	2			
29	B	45	1		+	
30	B	43	1		+	+
31	B	41	1			
32	B	45	1		+	+
33	B	58	2			
34	B	42	1			
35	B	42	1			+
36	B	47	2			
37	B	43	1			
38	B	45	1			
39	A	50	2			
40	A	42	1		+	

RFA. Nevertheless, in the above-mentioned article [19] results were not described in term of short-term or long-term therapeutic effect.

In our experience too, combined use of PEI and RFA proved effective in achieving necrosis of large HCCs. We were able to use a slightly shorter duration of ablation in comparison with our usual practice when using RFA alone. In the present series, ablation with a 4 cm electrode lasted 7 plus 2 min (with 1 min cool-down interval), which is a rather short duration. Nevertheless, also owing to the use of a 250 W instrument, we noted an adequate necrotizing effect with an overall 9 min ablation time from the beginning of our experience with combined PEI and RFA, and we continued with this standardized protocol.

We injected the ethanol within the peripheral aspect of the HCC, while other authors [19] have located the ethanol injection needle centrally (two or three needles placed deep within the tumor center and then slowly retracted by 1–2 cm increments). In our opinion a peripheral injection guarantees complete necrosis and an adequate security margin. It is well known [1, 2, 3, 26, 27] that residual viable tumor tissue is almost always located at the lesion periphery. In fact, while RFA produces spherical, thermal-based coagulation necrosis around electrode tip, PEI causes necrosis because of intravascular spread of ethanol, reaching the tumor periphery more easily. Additionally, the coagulative effect of initial ethanol injection facilitates thermal ablation, also allowing a shortening of the radiofrequency application time and consequently its toxicity. Ethanol probably also causes thrombosis of small venous branches and tissue cooling that improves the necrotizing effect of RFA [19]. In fact, its is known that ethanol may damage tumor-related vessels [1–3] and that, conversely, radiofrequency is significantly hindered by persistent tissue perfusion [2, 3]. Finally, it can be hypothesized that ethanol may be warmed by subsequent RFA and consequently increase its necrotizing effect and/or that ethanol may spread subsequently through areas that survived RFA application, such as perivascular cuffs [19].

Table 2. Liver functionality before and after treatment

	Albumin (g/dl)		Total bilirubin (mg/dl)		AST (units/l)		Alkaline phosphatase (units/l)		Prothrombin time (%)	
Patient no.	Before	After	Before	After	Before	After	Before	After	Before	After
1	3.6	3.5	1.3	1.2	69	52	47	51	77	67
2	2.7	2.8	0.5	0.7	55	55	40	49	120	119
3	2.8	2.9	1.0	0.9	33	65	48	51	60	76
4	2.8	3.0	1.1	0.9	26	32	56	59	65	61
5	3.3	3.0	1.5	1.2	66	40	67	65	71	70
6	3.0	3.1	1.6	1.7	67	69	69	62	54	52
7	3.0	3.0	3.2	2.9	45	41	43	46	50	47
8	3.0	3.2	2.1	2.7	40	41	40	45	60	58
9	3.7	3.6	1.9	2.0	50	39	147	128	65	66
10	3.0	3.1	1.9	2.0	52	42	76	81	69	71
11	2.8	3.1	2.0	2.0	49	46	45	52	71	72
12	2.9	2.7	1.0	1.3	40	37	40	49	61	63
13	2.9	2.7	1.3	1.5	23	30	50	55	51	48
14	3.1	3.0	0.7	0.9	22	29	48	49	56	53
15	3.2	3.2	0.8	0.7	27	29	49	66	64	60
16	3.3	3.2	1.1	1.2	32	30	41	77	111	102
17	3.0	2.8	1.2	1.4	32	31	43	58	56	71
18	2.7	2.6	1.3	1.3	30	40	49	52	51	50
19	2.8	2.6	1.1	1.1	66	49	50	61	88	71
20	3.1	3.4	1.2	1.1	76	71	46	44	66	62
21	3.6	3.4	1.6	1.4	25	28	50	51	60	56
22	3.5	3.4	1.7	1.4	29	33	46	65	71	67
23	2.9	3.0	1.3	1.3	30	34	43	44	56	51
24	2.9	2.9	1.2	1.1	31	35	44	47	63	60
25	2.9	2.7	1.3	1.0	30	33	102	99	53	62
26	3.0	2.7	1.4	1.1	31	37	165	161	56	52
27	3.3	3.2	1.5	1.3	59	61	77	90	59	56
28	3.2	3.2	1.5	1.4	69	77	41	54	60	56
29	4.0	4.1	1.5	1.5	39	41	139	143	51	45
30	2.9	3.0	1.5	1.1	32	28	45	52	55	54
31	3.0	3.1	1.1	1.9	29	31	202	197	56	52
32	4.1	4.2	1.2	1.2	23	26	99	108	58	51
33	3.1	3.2	1.1	1.6	28	33	80	91	60	52
34	3.6	3.3	1.0	1.0	53	48	65	67	50	46
35	3.4	3.3	0.9	1.0	45	44	76	77	112	102
36	3.3	2.9	0.9	1.1	54	49	87	89	100	102
37	3.2	3.6	0.6	1.0	51	50	88	91	78	67
38	3.4	3.5	0.6	0.8	22	20	91	102	72	66
39	3.4	3.3	1.0	1.1	28	33	98	103	67	65
40	4.0	3.6	1.2	1.1	28	22	43	54	68	70

AST, aspartate aminotransferase

In our practice, as also mentioned in other reports [19], we carry out the ethanol injection first and then the radiofrequency application. We chose to place the RFA electrode before injecting the ethanol. This is done because of the ethanol-induced diffuse hyperechogenicity, which may create difficulty in subsequent proper placement of RFA electrode. RFA electrode design may also play a relevant role, since different ablation devices produce different shapes of necrosis with different efficiency [24, 31, 32]. Application of ethanol may theoretically change the heat distribution and, consequently, the shape of the necrotic area.

The overall incidence of complications in our series was 22.5%. This is a rather high rate but it should be noted that 4 of the 9 patients with complications had only reactive pleural effusion due to ablation of liver dome tumors. In the end only 1 subject required specific treatment for a complication of PAT.

A clear limitation of our technique is that ethanol is injected empirically at the peripheral aspect of the HCC and that radiofrequency ablation is applied empirically at its center. It would be preferable to have a more defined modality in guiding the first or the second therapeutic option to targeted tumor areas. Currently we are starting to employ a sonographic contrast medium to recognize persistent tumor areas within the treated nodule [33]. This will probably allow a more effective treatment of residual tumor within the same therapeutic session, although overall session time may increase significantly.

In our institution, as in almost all centers in Italy, we employ sonographic guidance. Since sonography is a real-time, multiplanar technique and can be performed in the operating room it represents in our practice the most appropriate tool. Nevertheless it should be mentioned that other institutions employ CT [19] or MRI [34] guidance. Both these techniques are more panoramic than sonography

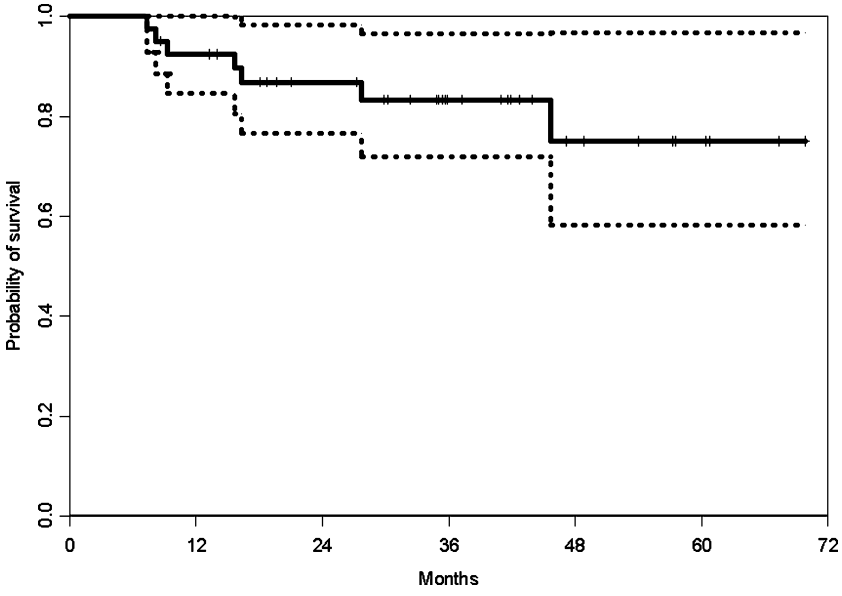

Fig. 5. Kaplan–Meier estimated overall survival. Dotted lines represent 95% confidence intervals.

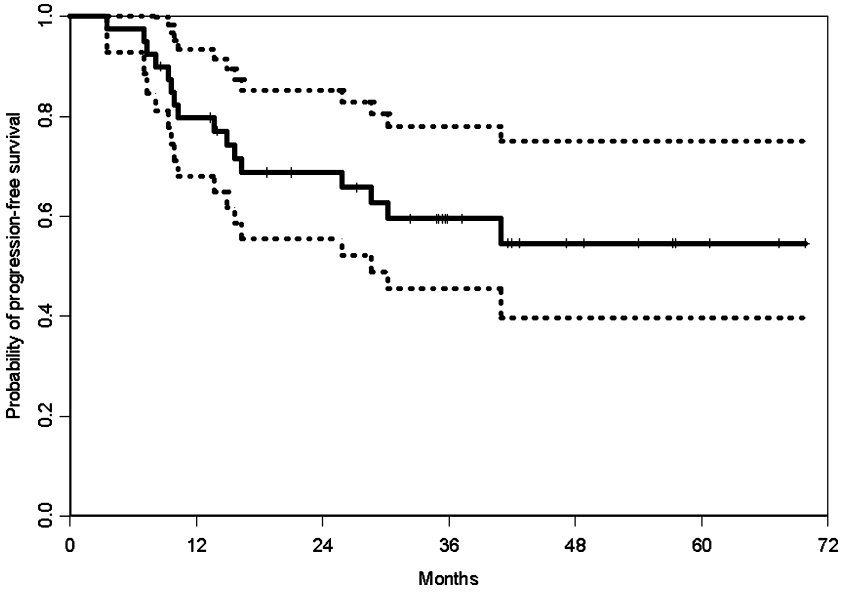

Fig. 6. Kaplan–Meier estimated progression-free survival. Dotted lines represent 95% confidence intervals.

and allow optimal targeting of almost all hepatic lesions in all parenchymal areas. In particular, MR-guided RFA in a closed-bore high-field scanner has been proven feasible and safe, being advantageous in locations unfavorable for CT guidance or in patients in whom iodized contrast media are contraindicated.

In our experience, the combination of PEI and RFA allows effective treatment of large HCC located in proximity to risky anatomic structures such as diaphragm, gallbladder, portal branches, or biliary ducts. In fact, we were able to inject the ethanol at the tumor periphery close to the above-mentioned structures and subsequently carry out a protected RFA (with a secure distance between the RFA electrode and the structure at risk). Some of these patients would have not been treated in our institution with PAT and would probably have undergone TACE.

In summary, combined PEI-RFA treatment is effective in the management of patients with large HCC. Necrosis is greater than that achievable with any PAT alone [19]. Consequently this therapeutic option may be considered a valid alternative to the surgical, TACE, or ''no treatment'' approaches to large HCC. In particular, combined PATs can be used when TACE is not feasible or has failed. Prognosis and survival of patients with large HCC can be improved because of a reduction in eventual further treatment sessions and consequently improved patient compliance and lower overall costs. Control of large, non-nodular HCC is still a challenge.

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