



RAPID COMMUNICATION

Therapeutic effectiveness of echo-guided percutaneous radiofrequency ablation therapy with a LeVeen needle electrode in hepatocellular carcinoma

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Abstract

AIM: To investigate the results of radiofrequency ablation (RFA) in obtaining the necrosis of hepatocellular carcinoma (HCC) in cirrhotic patients and to assess the results of RFA in relation to recurrence of HCC and survival of the treated patients.

METHODS: Fifty-six consecutive cirrhotic patients with 63 HCCs were treated with RFA between May 2000 and May 2004. The diameter of the HCCs ranged from 1 cm to 5 cm (mean 2.8 cm). In all cases RFA was performed with percutaneous approach under ultrasound guidance using expandable needle electrode (LeVeen needle). Treatment efficacy and recurrence were evaluated with dual-phase spiral computed tomography (CT).

RESULTS: Complete necrosis after single or multiple treatment was achieved in 96.8% (61/63) tumors. We observed recurrence after complete necrosis in 23 patients (41%) during a mean follow-up of 32.3 months. The recurrences were local in 2 patients (8.6%) and in different segments in 21 (91.4%). Major complications occurred in 3 patients (4%). During follow-up period, 32 (57.1%) patients died; 15 due to progression of HCC, 11 from liver failure, 3 from esophageal varices bleeding and 3 from the causes not related to liver disease.

CONCLUSION: RFA with LeVeen needle is an effective and safe treatment for HCC < 5 cm in cirrhotic patients. It has yet to be established how far this treatment influences the survival rate of patients. It becomes important to establish treatments to prevent recurrences in different segments, such as interferon therapy.

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Key words: Hepatocellular carcinoma; Radiofrequency ablation; Complication; Recurrence

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignant neoplasm throughout the world and surgical resection is thought to be the best curative approach in the treatment of HCC^[1-3]. However, few patients with HCC are suitable for resection due to age, location of the lesion, advanced cirrhosis of the liver and concomitant diseases; as a consequence less invasive treatment methods have been pursued, especially echo-guided percutaneous ethanol injection (PEI) and radiofrequency (RF) thermal ablation^[4-9]. PEI was the first method used starting in the eighties, followed by the introduction of RF in order to overcome some of the limitations of PEI, such as the difficulty in ensuring the distribution of ethanol throughout the lesion and the need for multiple sessions due to the reduced volume of necrosis that can be achieved in the single session^[10]. At present RF is certainly the first choice of interstitial therapy method in the majority of cases of HCC that can not be treated surgically. The two types of RFA needles most used are the cool-tip needle with internally circulating cool saline (Radionics, Burlington, MA, USA) and the expandable 10-hooks LeVeen needle (Radio Therapeutics Corporation, Sunnyvale, CA, USA). Compared with the Cool-Tip, the LeVeen needle electrode can theoretically create a more even flux of the radiowave, producing thermal effects with a greater spherical area. Because this needle uses a gradual augmentation sequence of the RF output to prevent excess heating of the target tissue, this RFA system does not require circulation of cool saline in the needle electrode for preventing charring of the target tissue as in the Cool-Tip RFA system^[9]. The LeVeen needle has a larger diameter than the Cool-Tip (15 Gauge vs 18 Gauge), but no significant differences in complications have been reported in the literature between the two types of needle electrodes^[11].

Herein, we report our experience in performing

percutaneous echo-guided RF thermal ablation of HCCs with the LeVeen needle electrode system in a gastroenterological Italian service. We aimed to assess the efficacy of the system in obtaining the necrosis of the target tissue and the clinical outcome of the treated patients.

MATERIALS AND METHODS

From May 2000 to May 2004, a total of 56 consecutive cirrhotic patients (37 males and 19 females, age range 45-81 years, mean age 68.7 years), who underwent RFA for non-surgically resectable HCC due to the location of the tumor, severity of the cirrhosis, age, associated diseases or refusal of surgery, were enrolled in the study. Inclusion criteria were HCC diameter < 5 cm, absence of portal thrombosis or extrahepatic diffusion, absence of significant ascites, prothrombin activity > 50% and platelet count more than 50 000, and a maximum of three HCCs, each not more than 3 cm in maximum diameter.

The etiology of the cirrhosis was viral in 51 cases (48 due to HCV infection and 3 due to HBV infection), alcoholic in 4 and autoimmune in 1 case (primary biliary cirrhosis). On the basis of the Child-Pugh classification, 16 patients were class A, 37 class B and 3 class C (Table 1).

As regards the characteristics of the HCCs, 50 patients had a single tumor, 5 had two tumors and 1 had three tumors; a total of 63 tumors were detected in the 56 patients studied. None of the HCCs had an infiltrating appearance at imaging. The dimensions of the HCCs were between 1 and 2 cm in 19 cases, between 2 and 3 cm in 27 cases, between 3 and 4 cm in 12 cases and between 4 and 5 cm in 5 cases; the mean size was 2.8 cm (Table 2). The pre-treatment diagnosis of the nature of the lesion was histological with echo-guided fine needle biopsy in 42 patients, performed in 19/19 nodules <2 cm, 20/27 nodules <3 cm, 3/12 nodules <4 cm and 0/5 nodules <5 cm. In the remaining 14 patients, the diagnosis was based on non-invasive criteria, radiological with typical arterial hypervascularization at color power Doppler ultrasound, contrast-enhanced ultrasound, computerized tomography (CT) or magnetic resonance (MR) (11 patients) or combined with one typical imaging technique associated with AFP levels >400 ng/mL (3 patients). Starting in October 2000, as far as the non-invasive diagnosis was concerned, we followed the indications of the EASL Conference on clinical management of hepatocellular carcinoma, held in Barcelona, Spain in September 2000^[12]. It should however be pointed out that all the patients underwent pre-treatment contrast dual-phase spiral CT for the staging and baseline assessment of the vascularization of the HCC.

Technique

The RF delivery system was an RF 2000 generator system (Radio Therapeutics) in monopolar mode, used in conjunction with a LeVeen monopolar array needle electrode and two large dispersive electrodes. The RF generator supplies voltage at a frequency of 460 KHz and a maximum power output of 100 W. The RF generator display indicates power, tissue impedance and procedure

Table 1 Characteristics of 56 cirrhotic patients with HCC treated with RFA

Parameters	Numbers
Total patients	56
Gender	
Male	37
Female	19
Age (yr)	
Range	45-81
Mean	68.7
Type of cirrhosis	
Viral HCV-related	48
Viral HBV-related	3
Alcoholic	4
Autoimmune	1
Child-Pugh classification	
A	16
B	37
C	3

time. The active expandable needle electrodes have a 15 gauge, 15 cm long stainless steel insulated cannula with 10 retractable lateral hooks each oriented at an angle of 36° from the two adjacent hooks. The maximum deployment diameter of the hooks was 3.0 or 3.5 cm. We used the 3.0 cm hooks for lesions equal to or less than 3 cm in diameter and the 3.5 cm hooks for lesions greater than 3 cm.

Treatment was performed only in inpatients, fasting 12 h before treatment, and they received mild sedation with an intramuscular administration of 10 mg of diazepam and 0.5 mg of atropine sulphate 30 min before the procedure. If necessary during treatment, 40 to 50 mg of pethidine was administered intravenously for analgesic purposes.

Using a multifrequency convex probe, RF ablation was performed with real-time ultrasound guidance (HID 3000, ATL, Bothell, WA, USA) by the same gastroenterologist (L.S.) with longstanding experience in interventional ultrasound. The needle was inserted using free-hand technique with subcostal or intercostal approach depending on the easiest access route according to the ultrasonographic picture. Once the needle electrode was located in the correct position, the hooks were deployed and the RF generator was activated. After maintaining the baseline power output at 50 W for 1 min, the output was increased by 10 W every minute until the power output reached 90 W, and then it was kept at 90 W until "roll-off" occurred. After a 20 to 60 s pause, power was reapplied at 75% of the maximum power achieved until power "roll-off" again occurred. If the "roll-off" did not occur within 15 min of the RF power output application, the RF power stopped automatically. After a 20 to 60 s pause, power was reapplied following the same procedure as before. Hematologic assays, such as red blood cell count and hemoglobin, serum alanine aminotransferase, serum aspartate aminotransferase and total serum bilirubin levels, were measured 24 h after treatment. The patients were discharged from the hospital 48 h after the treatment, if there were no any complications.

Assessment of therapeutic efficacy

To evaluate the response to RF therapy, contrast-enhanced

Table 2 Characteristics of HCCs in 56 cirrhotic patients treated with RFA

Parameters	Numbers
Number of HCCs	63
One HCC	50
Two HCCs	5
Three HCCs	1
Type of HCCs	
Nodular	63
Infiltrating	0
HCC diameter (cm)	
> 1 < 2	19
> 2 < 3	27
> 3 < 4	12
> 4 < 5	5
Mean	2.8

CT with the same parameters as the pre-treatment scanning was performed 1 mo after the procedure; tumor necrosis was considered complete when no foci of enhancement were seen within the tumor or at its periphery on CT scans. Safety margin surrounding the ablated tumor was obtained in all the cases where tumor necrosis was considered complete. Every three months, the patients subsequently underwent color power Doppler ultrasound associated with AFP dosage; and in the event of modifications of the ultrasound picture or a progressive increase in AFP value, a CT scan was performed.

RESULTS

A total of 63 HCCs were treated with RFA in the 56 patients enrolled in the study. Two HCCs, measuring 3.5 and 4 cm in diameter, were non-responders to the treatment with RFA with persistence of the vascular signal after two sessions together with an increase in volume in the second (4-4.7 cm in maximum diameter). They were therefore subjected to chemoembolization with a positive result for the first but a progression of the disease in the second despite the additional therapy. The overall percentage of complete necrosis was 96.8% (61/63 of the lesions treated). In 54 HCCs, corresponding to 85.5% of the total, complete necrosis was achieved with just one session with a single insertion of the needle, while a second session was carried out in the remaining 7 HCCs after the first control CT scan due to persistence of vascularized areas of the tumor, again with a single insertion; a total of 68 treatments were necessary to achieve complete necrosis of the 61 responder HCCs. The diameters of the HCCs that required two sessions for complete necrosis were 3 cm in one case, 4 cm in one case and larger than 4 cm in the remaining 5 cases. The RF application time ranged from 2.5 to 15 min for each electrode insertion; the mean RF time was 10.4 min per session. All patients had an increase of echogenicity in the ablated region during RFA, suggesting generation of microbubbles in the ablated hepatic tissue.

As regards complications, 34 (60.7%) patients reported pain requiring the administration of analgesics during the treatment, while practically all subjects presented a moderate and transitory increase in transaminases at the

Table 3 Clinical findings in 23 cirrhotic patients with HCC recurrence after RFA

Parameters	Numbers
Total patients	23
Time of recurrence (mo)	
Range	3-30
Mean	13
Type of recurrence, <i>n</i> (%)	
Local unifocal	2 (8.6%)
Different segments unifocal	5 (21.8%)
Different segments multifocal	16 (69.6%)
Treatment of recurrences	
RFA	7 (unifocal)
TACE	5 (multifocal)
Supportive treatment	11 (multifocal)
Results of treatment	
RFA	Complete necrosis 7/7
TACE	Complete necrosis 1/5

24 h hematological checks with no other laboratory test alterations. Major complications occurred in 3 of 72 cases (4%), including right pleural effusion in 1 case, cholecystitis in 1 case and liver failure in 1 case.

The post-treatment follow-up varied from 8 to 56 mo with a mean of 32.3 mo; during the follow-up, we detected 23 cases of recurrence (41%), with onset varying from 3 to 30 months after treatment and a mean of 13 mo. The recurrence was unifocal in 7 cases and multifocal in 16 cases; two of the unifocal cases were local recurrences, while the remaining five were localized in another segment. Of the 23 cases of recurrence, the previously treated HCC was a single lesion in 22 cases and two lesions in 1 case; there was no relationship with the dimensions of the primary HCC which varied from 1.5 cm to 4.5 cm. Of the 22 previously treated single lesions, recurrence was unifocal in 7 cases and multifocal in the remaining 15 cases. In the unifocal recurrences, we carried out a new cycle of RFA therapy. Of the 16 multifocal cases, chemoembolization was performed in 5 cases, while treatment was limited to support therapy in view of the tumor diffusion and the general clinical conditions in the remaining 11 cases. The seven patients who underwent a new cycle of RFA therapy had positive results and were disease-free with a follow-up varying from 4 to 15 mo (mean 9 mo); four of the five patients treated with chemoembolization died due to progression of the HCC, while the other patient had a stable tumor situation 5 months after the treatment (Table 3).

Finally, 32 (57.1%) patients died during the follow-up, 15 from HCC, 11 from liver failure, 3 from esophageal varices bleeding, 1 from head stroke, 1 from cerebral hemorrhage and 1 from esophageal carcinoma. Among the patients who died from liver failure, 9 were Child-Pugh B and 2 were with Child-Pugh C (Table 4). Twenty-one patients were alive and disease-free at the end of the study.

DISCUSSION

The limitations to the surgical treatment of HCC due to site, age and associated clinical conditions have led to

Table 4 Clinical findings in 32 deceased cirrhotic patients treated with RFA for HCC

Causes of death	Number of patients	Child-Pugh status		
		A	B	C
HCC recurrence	15	4	12	
Liver failure	11		9	2
Esophageal varices bleeding	3		3	
Head stroke	1		1	
Brain hemorrhage	1	1		
Esophageal cancer	1	1		

the development of alternative locoregional therapies of which PEI is the first and most widely used example. RF was subsequently introduced by Rossi *et al*^[8] in the attempt to overcome some of the limits of PEI, such as the need for multiple sessions, the difficulty in foreseeing the diffusion of the ethanol, and is now being used more and more as the first choice technique in the locoregional treatment of HCC^[13]. Also, in our department, RFA has gradually replaced PEI which we had been using since the mid 80 s and which is now reserved for selected cases. Our experience in RFA with the LeVein needle electrode has given us satisfactory results in terms of therapeutic efficacy, achieving complete necrosis in 85.5% of the lesions with just a single treatment, increasing to 96.8% with a second session, which are in agreement with the data reported in the literature^[10,14,15]. Necrosis was not achieved with RFA in two cases of HCC, as shown by the post-treatment CT scan, and we were unable to identify the reason for the lack of response with certainty; the diameters were 3.5 and 4 cm and the lesions were not close to large vessels whose blood flow could have dispersed the heat^[16]. Both were localized immediately under the hepatic dome and we therefore think it probable that the site interfered with the correct positioning of the electrode, reducing the efficacy of the treatment as previously reported^[15]. Among the 7 HCCs which required a second session, 6 cases had a diameter of 4-5 cm, while only in one case had the diameter of 3 cm; therefore, if we consider only the HCCs up to 3 cm in diameter, the percentage of complete necrosis with just a single treatment would rise to 97.8%. Our experience also confirms that diameter < 3 cm is the ideal condition for locoregional treatment with RFA as with PEI^[13,14,17]. However, in lesions measuring 3-5 cm, RFA with a LeVein needle gave acceptable results with complete necrosis at the first treatment in 64.7% of cases, the remaining 35.3% required a second session for complete necrosis. As previously reported by Livraghi *et al*^[10], the lesser number of treatment sessions with respect to PEI makes it possible to reduce the time employed by the hospital staff and to considerably shorten the duration of the treatment and eliminate the stress of repeated sessions in most cases. One factor that can increase the volume of the area of necrosis and reduce the number of necessary treatment sessions is represented by what Livraghi *et al*^[10] defined as the “oven effect” caused by the fact that cirrhotic liver surrounding individual HCC nodules acts as a thermal insulator that increases tissue heating during RF therapy, making it possible to treat non-

infiltrating tumors in a single treatment session in the majority of the cases.

The LeVein needle electrode we used in this study has ten expandable inner hooks in a single outer sheath to obtain even greater flux of the radio wave in the ablated tissue. Through this, the needle produces a greater spherical area of thermal ablation than can be obtained by the previous four expandable hooks needle, assuring a safety margin if the tumor is within the range of ablation. Furthermore, the LeVein needle can hold itself securely within the area of ablation by expanding the hooks; this may help in the treatment of tumors in areas susceptible to the respiratory movement of tissue. The LeVein needle has some limitations, the first represented by the 15 gauge caliber and a greater risk of bleeding can be expected; however, we did not experience any hemorrhagic complications, and the literature also has not reported a greater incidence of hemorrhagic complications with respect to smaller gauge needles, such as 18 gauge cool-tip needle^[11]. An 18-gauge LeVein needle with 2.5 cm and 3 cm maximum deployment diameter of the hooks has recently become available, eliminating the difference in gauge; in the two cases treated with this finer needle, we did not encounter problems compared to the traditional one. A second limitation is the low visibility of the tips of the hooks under ultrasonography which sometimes makes it difficult to assess the correct location of the hooks with possible unexpected complications^[15].

In our experience, not only was RFA with the LeVein needle effective, it also proved safe with a low incidence (4%) of major complications, similar to the percentage reported in the literature^[3,11,18,19,20]. In two cases (pleural effusion and cholecystitis), the complication was because the HCC was close, respectively, to the diaphragm and the gall bladder with consequent thermal irritation of the pleura and of the gall bladder wall. In spite of being quickly resolved with medical therapy and without sequelae, this confirms the need to take particular care in treating lesions in the sites at risk as previously described^[21]. In the third case, functional liver failure occurred with ascites after treatment of a 2.3-cm HCC of liver segment III in a Child-Pugh class C patient. The HCC had been subjected to a single session of RFA lasting 7.8 min. Medical therapy achieved a partial improvement of the clinical conditions; however, the patient subsequently died 4.5 months after treatment from liver failure without HCC recurrence. It should be further stressed that in patients with HCC on Child-Pugh class C cirrhosis locoregional treatments should not be carried out due to the greater risks and the advanced stage of the cirrhosis which *per se* involves a poor prognosis for survival^[22]. The exception to this rule is treatment of patients on the waiting list for orthotopic liver transplant (OLT) when there is a long waiting time, as is frequently the case in almost all the transplant units in Italy^[23,24]. Two of the three Child-Pugh class C patients that we treated, including the one in whom the complication occurred, were on the waiting list for OLT. The second patient on the waiting list underwent OLT 15 months ago and is alive and free of recurrence.

We did not find any cases of post-RFA tumor seeding. In contrast, a study by Spanish authors has reported a high

incidence of post-RFA seeding^[25] which has not, however, been confirmed in any of the other studies reported in the literature. A recent study has demonstrated an incidence of post-RFA seeding even lower than that of post-PEI, both with expandable needles and with cooled needles^[11].

As far as complications are concerned, a recent Italian study showed that despite achievement of complete local necrosis, rapid intrahepatic neoplastic progression was observed in four patients (4.5%) after treatment. The authors experienced that high AFP levels and location of the tumor near the portal vein branches were associated with this complication^[26]. Moreover, 75% (3/4) patients had a poor differentiation of the tumor^[26]. This is the only report of this type in the literature to date and, while attention should be paid to this possibility, further studies are necessary for its confirmation. However, in our series, we have not found any similar occurrences to date.

Evaluation of the tissue necrosis is fundamentally important in order to decide whether further treatment is necessary and is currently mainly based on imaging techniques to assess the persistence of lesion vascularization, rather than on a biopsy which can not give a complete sampling of the lesion. The gold standard technique is certainly the contrast-enhanced CT scan, and we, based our post-treatment evaluation on this technique, performed it in all patients after thirty days. This is the most common interval as it allows any remaining vital tissue to be detected within a period of time that is short enough to prevent significant progression of the disease and to not burden an already overloaded radiology service with an excessive number of CT scans. It also prevents the risk of interpreting the hyperdense rim present in the majority of cases on CT scans obtained in a earlier period after RFA. This hyperdense rim is the expression of the early parenchymal inflammatory rim around the treated tumor as proved in resected specimens^[27]. In our series, the HCCs with signs of activity at the one-month CT scan underwent a second session of RFA with complete necrosis in 100% of cases; the time lapse did not have any negative effect on the result of the treatment. The first data on the use of contrast-enhanced ultrasound (CEUS) with second generation contrast medium have recently been reported and are extremely encouraging, particularly as regards early 24 h evaluation of post-RFA persistence of activity^[28-30]. The possibility to obtain by CEUS data comparable with the ones obtained by CT would make it possible to use a more rapid method and, if necessary, to carry out a second treatment during the same session, thus further reducing the duration of the therapeutic cycle with advantages for both patients and hospital staff.

In our series, HCC recurrence occurred in 41% (23/56) patients, a lower percentage than those reported in the literature^[31]. This may be due to the lower number of patients and to the shorter follow-up compared to other studies. The percentage of local recurrence was only 3.1% (2 patients), in line with what was reported by other authors^[31], while recurrence occurred in other liver segments with respect to the initial one in the remaining 21 patients, thereby confirming the validity of RFA in achieving complete necrosis of the treated HCCs. In both cases of local recurrence, the lesion diameter was > 3 cm

(4 cm and 4.5 cm), confirming the limits of locoregional therapy in larger tumors. One factor that may contribute in determining recurrence is the presence of satellite nodules that can not be identified by imaging^[32]. Livraghi *et al*^[13] supposed that the “oven effect” may partially explain the limited success in treating satellite lesions. They believe that peritumoral fibrotic tissue that is interposed between the main tumor and satellite lesions may limit heat diffusion from the tumor center to the satellites. The association of RFA and transcatheter arterial chemoembolization (TACE) has been proposed as a means of reducing the number of local recurrences and the initial results seem encouraging^[33,34]. The problem is different for recurrence in other sites, which remains high regardless of the type of treatment used, with values ranging from 60% to 80% after four years follow-up in series reported by Japanese authors^[31].

In our experience, it was possible to treat all 7 patients with unifocal recurrence with RFA, achieving complete necrosis of the lesion in all cases, but only 5 of the 16 multifocal recurrences with TACE and with a positive result in only one case. It is becoming important in the clinical setting to establish treatment methods to prevent recurrences at other sites, such as the use of interferon or anti-inflammatory therapy particularly to decrease the incidence of multicentric recurrences^[35-38]. Therefore, even after achieving the local curative ablation by RFA, it is important to closely follow-up the patients for early detection and treatment of recurrence.

The rather limited number of patients and the too short mean follow-up period in our study do not allow us to draw conclusions on the efficacy of RFA of HCCs in improving survival. Nevertheless, by analyzing the causes of death in the patients who died during follow-up, it can be seen that while none of the Child-Pugh class A patients died from cirrhosis-linked causes, 9 patients in class B and 2 out of 3 in class C died as a result of progression of the cirrhosis, and the third patient in class C is alive after OLT. In addition, another 3 patients in class B died as a result of bleeding from esophageal varices. This further confirmed the importance of the stage of cirrhosis in patient survival, so as to exclude class C patients from any ablation treatment except for those on the waiting list for OLT. In our series, however, 46.8% (15/32) patients died as a direct result of the HCC; our data also indicated that, as mentioned earlier, it is extremely important to improve the prognosis of patients who have undergone local ablation therapy by treating the background liver disease, using chemopreventive drugs, such as interferon. Regarding the previous data on the long-term survival of patients treated with RFA for HCC, it should be pointed out that although the history of RFA is not long enough for analysis, when analysis was limited to cases of primary liver cancer in which local curative therapy was achieved, the 5-year survival rate was relatively high (66-82%), comparable to that of resection^[17,31,39-41].

In conclusion, percutaneous RFA by means of the LeVeen needle electrode appears to be an effective, safe and relatively simple procedure for the treatment of HCC lesions in patients with cirrhosis, obtaining the best results in HCCs < 3 cm in diameter. We currently prefer to use

RFA rather than PEI because RFA is capable of achieving complete tumor necrosis in fewer treatment sessions compared with multi-session PEI, reserving PEI for HCCs that are difficult to approach or located in areas where RFA is considered unsafe, such as HCC adjacent to large vessels, the main bile duct or the gall bladder. Despite the good results as regards the necrosis of the HCC lesions, it is not yet possible to define the effect of RFA on the long-term survival of treated patients, even though the initial data are encouraging. Notwithstanding the importance of the stage of cirrhosis for survival, HCC recurrence after RFA is a significant cause of death in these patients. On the basis of the recent data reported in the literature, it is probable that in the future the prognosis can be improved by the use of chemopreventive drugs, such as interferon for the prevention of recurrence after curative local treatment.

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