

Radiofrequency Ablation in Unresectable Hepatocellular Carcinoma

AHMAD MORSI, M.D.¹, HAZEM MOHARRAM, M.D.², IKRAM HAMED, M.D.³,
HEBA EL-ZAWAHRY, M.D.⁴ and REDA TABASHY, M.Sc.³

The Departments of Surgery¹, Radiodiagnosis³, Medical Oncology⁴, National Cancer Institute, Cairo University and Radiodiagnosis², Faculty of Medicine, Cairo University.

ABSTRACT

Purpose: Most patients with hepatocellular carcinoma (HCC) are not candidates for resection because of tumor size, location, multifocality, or liver dysfunction associated with liver cirrhosis and hepatitis. Radiofrequency ablation (RFA) offers an alternative treatment in some unresectable HCC patients with disease confined to the liver. We prospectively evaluated the local recurrence rate and the overall survival rate in patients with unresectable HCC treated with RFA.

Patients and methods: All patients with non metastatic unresectable HCC referred to the National Cancer Institute (NCI) Cairo University between Jan. 2001 and Jan. 2003 were evaluated for eligibility for treatment with RFA. Patients were treated with RFA using open or percutaneous approach with ultrasound guidance using LeVein monopolar array needle electrode and RF2000 generator. Patients were evaluated at regular intervals to determine disease recurrence and survival.

Results: A total of 50 patients, 34 men (68%) and 16 women (32%), with a median age 55.2 years (range 23-67 years) underwent RFA for 79 HCC tumors. All were followed up for at least one year (mean follow up 23.6 months). Percutaneous and open intraoperative RFA was performed in 32 (68%) and 18 (32%) patients respectively. Of the 18 patients treated with open RFA, 1 patient (5%) underwent additional resection. Median diameter of the tumors treated with percutaneous RFA was 3.5 cm while the median diameter of the tumors treated with open intraoperative approach was 5.5 cm. There was one treatment related death in the open intraoperative RFA group. During a mean follow up period of 23.6 months, disease recurred in 24 of the 50 patients (48%), including 15 (46%) treated percutaneously and 9 of 18 (50%) treated by the open intraoperative RFA. The overall survival at 1, 2 years for the percutaneous RFA group was 81.2% and 71.8%, while in the open RFA group, it was 72% and 50%.

Conclusions: Treatment with RFA can produce significant survival improvement in some patients with non-metastatic HCC who are considered unresectable because

of multifocal disease, proximity of the tumor to key vascular or biliary structure, or inadequate functional hepatic reserve to allow safe hepatic resection.

Key Words: Hepatocellular carcinoma - Radiofrequency ablation.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. HCC accounts for 90% of primary liver cancer and causes at least one million deaths worldwide per year. It is the 5th most common cancer in the world [1].

HCC is an extremely virulent form of cancer. Its onset is insidious and most patients are asymptomatic until the tumor has advanced to an extremely large size and has spread to other parts of the liver or other organ system. Because of the late presentation, the prognosis of patients with that tumor is grim. The median survival rate from the onset of symptoms is only 3 to 6 months [2].

The optimum treatment for HCC is surgical excision with curative intent. Unfortunately, only 5 to 15% of the newly diagnosed patients with HCC undergo a potentially curative resection. Patients with disease confined to the liver may not be candidates for resection because of multifocal disease, proximity of the tumor to key vascular or biliary structures that precludes a margin negative resection, or inadequate functional hepatic reserve related to coexistent cirrhosis. Thus, for the majority of patients with HCC who are not candidates for surgical resection, novel treatment approaches to control and

potentially cure the liver disease must be explored [3].

Several minimally invasive interventional techniques aiming at providing local destruction of the tumor have been developed and clinically tested over the past few years. These methods include percutaneous ethanol injection, laser photocoagulation, cryoablation and radiofrequency ablation [4].

Radiofrequency thermal ablation (RFA) is a more recently developed method for local tissue ablation. In this technology, radiofrequency energy at a frequency of 400 to 500 kHz is delivered into the tissues. A resistive heating occurs as a result of the vibrations of the electrons within the tissues caused by this high energy current. Once cells are heated above 50°C, their cell membranes melt and fuse and with continuous heating, proteins denaturation and irreversible cell death occurs. Thus unlike cryoablation, thermal ablation produces direct cytodestruction in treated tissues [5].

In this study we report our initial results in 50 patients with HCC treated with RFA of their liver tumors.

PATIENTS AND METHODS

This prospective non-randomized study was carried out in the Departments of Surgery, Radiology, Medical Oncology of the National Cancer Institute, Cairo University and the Department of Radiology, Faculty of Medicine, Cairo University, between Jan. 2001 and Jan. 2003. Patients with non-metastatic unresectable HCC who had fulfilled the eligibility criteria were treated by either percutaneous or open intraoperative RFA. Fifty patients were recruited.

Eligibility criteria for treatment with RFA included:

- 1- Patients with confirmed unresectable HCC.
- 2- No evidence of extrahepatic metastases.
- 3- Had not received radiotherapy or chemotherapy for at least 4 weeks before RFA.
- 4- WHO performance scale 0-1.
- 5- Had a serum total bilirubin level < 3 mg/dl, serum creatinine ≤ 2mg/dl, serum albumin > 3.0 gm/dl and prothrombin time not > 50% elevated above normal.

6- Had no history of hepatic encephalopathy.

7- Had minimal or no ascitis.

8- Had no active infection.

9- A detailed verbal and written description of the procedure was provided to all patients and informed written consent was obtained before treatment.

Patients were considered for RFA even if they had tumor abutting a major portal or hepatic vein branch or the inferior vena cava, but they were excluded if tumor involved the main right or left bile duct (or both) because of the probability of destruction of the major bile ducts by RFA. All patients underwent a baseline evaluation, including a history and a physical examination, serum laboratory tests consisting of a complete blood count, platelets, coagulation profile, renal panel, electrolytes, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin and alphafetoprotein, computed tomography (CT) scan of the abdomen and pelvis and a chest radiograph. All patients had histologic confirmation of HCC. The same battery of serum blood tests were obtained 1 and 7 days after the RFA procedure, then again one month after treatment. At one month and then every three months, a CT scan of the abdomen, a chest radiograph and a serum laboratory tests were obtained.

Patients with small lesions located away from the liver hilum and in a position where the needle electrode can be inserted and held safely were considered for percutaneous ultrasound guided RFA (32 patients). The other 18 patients were treated by RFA during an open surgical procedure.

Patients in this study were treated using the RF 2000 generator system produced by Radiotherapeutics Corp. (Mountain View, California, USA). The RF system consists of a generator that supplies up to 100 W of power, a LeVein monopolar array needle electrode and an indifferent dispersive electrode pad applied to the patient skin and connected to the generator to close the electric circuit. The LeVein electrode is a 15-gauge, 12 to 15 cm long insulated cannula that contains 10 individual hook-shaped electrode arms that are deployed in situ after ultrasound guided placement of the needle electrode into the liver tumor.

Impedance measurement: The principles of Ohm's law dictates the course of the ablation. When an application of RF energy begins, the RF generator measures the initial impedance level of the target tumor. This is represented by 4 bars (40-80 Ohm) being illuminated on the generator bar graph located on the front panel. As the area of the tissue around the electrode heat and become ablated, local impedance raises causing current to flow to the tissues with lower impedance. As cellular destruction occurs, the impedance rises until all the target tissue is desiccated by the RF energy. Tissue desiccation results in a rise of the impedance because the desiccated target tissue has a high resistance to current to flow to the return dispersive electrodes. The tissue impedance rises exponentially with the completion of the RF ablation. The RF generator 2000 measures this rise and illuminates the entire bar graph. Since the generator is a constant voltage system, as the impedance in the tissue rise, the current delivered to the needle electrodes decreases. The power delivered by the generator falls below 10 W, signaling the completion of the ablation.

Treatment strategy was established before placement of the needle electrode within the tumor according to the size of the tumor. The objective in treating the tumors was to ablate the entire tumor as well as at least 1-cm tumor free margin of normal liver. In this study the 3.5 cm array diameter needle was used. Tumors less than 2.5 cm in their maximum diameter were ablated with placement of the needle electrode tip in the center of the tumor. The arrays then were extended and verified by US. For tumors of 3 cm in diameter, the needle electrode tip was placed through the center of the tumor and advanced to the deepest margin between the tumor and the normal liver. The arrays were extended and were confirmed by the US to be placed correctly. This placement permits ablation of the deep part of the tumor and a rim of non-malignant liver. Following completion of RF ablation of the deep part, the arrays were fully retracted and the needle electrode was pulled back (withdrawn) to 2-2.5 cm. The arrays were redeployed and the second more superficial part of the tumor with anterior tumor free margin was ablated.

To treat larger tumors, multiple ablations were needed to be overlapped to build a composite thermal lesion with sufficient size to kill

the entire tumor and to provide a 1 cm tumor free margin. Strict geometric analysis and placement order of ablations were designed. The deepest ablations were performed before the superficial ones to minimize the possibility of those microbubbles might obscure visualization of the deepest portions of the tumor and thus prevent completion of the ablation. The hilar portion of the tumor was ablated initially to destroy the inflow of blood supplying the tumor (Fig. 1).

Application of the RF energy: After deployment of the multiple arrays, the initial power was applied at 50 Watt and then was increased in 10-W increment at 1,2,3 and 4 minutes to reach a maximum power of 90 W. The output was then maintained at this point for 15 minutes or until an increase in the circuit impedance of over 200 Ohms (roll-off) was observed, at which time the power output decreased to less than 10 Watt. After 60 seconds, a second phase was started at 75% of the maximum power reached at the first phase for 15 minutes or until power roll-off again occurred (Fig. 2). Thus, each tumor or area within a large tumor was treated with a 2 phase application of energy before retracting the multiple arrays and removing or repositioning of the needle electrode. During the first phase of ablation, if roll-off did not occur at 15 minutes, the arrays were retracted 0.5 cm and reapplication of the RF energy at output 90 Watt was started for 15 minutes or until roll-off occurred. In contrast, if roll off occurred before 5 minutes, the treatment was stopped for one minute and was restarted at 50% of the last power, then continued for 15 minutes or until roll-off occurred. During treatment, the area of tissue ablation is monitored by US to measure the zone of increased echogenicity corresponding to the coagulation of the tissues produced by the resulting nitrogen gas microbubbles. After the suggested complete ablation of the tumor was achieved, the arrays were then completely retracted.

For RFA performed during an open surgical procedure, once 90 W of power is reached, 2 to 3 minutes of vascular inflow occlusion is performed by clamping the hepatic artery and portal vein in the portahepatis. This facilitates the roll-off and increases the size of coagulative necrosis. All patients were followed after treatment to observe any acute or long-term compli-

cations related to RFA. CT scans and chest radiographs were used to detect evidence of residual or recurrent tumor in treated lesions and to monitor the development of new hepatic or extrahepatic metastatic disease.

Statistics: SPSS (statistical package for social sciences) version 10.0 was used for data analysis. The survival and disease status of all patients were evaluated at the end of the study and reported at one and two years interval. Kaplan Meier method was used for estimating the probability of survival. Comparison was made by Mann-Whitney test (nonparametric *t*-test).

RESULTS

Patient characteristics are shown in Table (1). In the group of patients who had received the RFA performed percutaneously (32 patients), RFA was used to treat a total of 51 lesions, single tumor in 20 patients (39.2%), 2 tumors in 8 patients (31.4%), 3 tumors in one patient (5.8%) and 4 tumors in 3 patients (23.6%). The median diameter of the tumors treated with percutaneous RFA was 3.5 cm with a range of 2 to 7 cm. More than one session of percutaneous RFA was done in 10 patients (31.3%) to achieve complete ablation, however, in 4 lesions (7.8%) complete ablation could not be achieved, all these lesions were > 5 cm in diameter. Treatment related complications arose in 6 patients (18.6%). One patient had post-ablation cholecystitis due to ablation of tumor adjacent to the gall bladder, one patient had symptomatic haemothorax due to ablation of subdiaphragmatic tumor and the other 4 patients developed ascitis 3-7 days after treatment and were controlled by salt restriction and diuretics, these 4 patients had Child class C cirrhosis.

Intraoperative RFA was performed in 18 patients, 9 had one lesion, 8 had 2 lesions and 1 had 3 lesions (total of 28 lesions). The median diameter of the tumors was 5.5 cm with a range of 5 to 11 cm. There was one mortality in the open intraoperative RFA group due to postoperative hepatic failure. This patient was Child class B with a lesion 9 cm in diameter in the right lobe of liver. Other complications in this group occurred in 4 patients (22%) and included, persistent ascitis in 2 patients, perihepatic abscess that was drained percutaneously in one patient and hemorrhage into the treated tumor

the day following surgery. This patient had a big lesion in the right lobe 8 cm in diameter that required 5 needle punctures to completely ablate the lesion. The bleeding was controlled by transarterial embolization of the right hepatic artery and required transfusion with 5 units of packed red cells. In one patient with a subcapsular tumor, 7 cm in diameter in the right lobe, the tumor was enucleated after complete ablation with safety margin. The tumor bed did not show any bleeding. Pathological examination of the specimen showed extensive tumor necrosis.

In the percutaneous RFA group, 6 patients (18%) died in the first year, 5 due to progressive liver cell failure, all were Child class C and one patient due to recurrent progressive HCC. In the second year, another 6 patients developed recurrent HCC, 4 of them true local recurrence at the margin of the previously ablated area and 2 in a remote areas of the liver. Three of these patients died and 3 are under supportive treatment. Twenty patients (62.5%) were alive at the end of follow up period with no evidence of hepatic or extrahepatic HCC. The disease free survival at one and two years was 81.2% and 62.5% while the overall survival was 81.2% and 71.8% respectively. The 2-year disease free survival in Child class A patients was 91%, 62.5% in Child class B and was 0% in Child class C patients with a significant difference ($p = 0.017$). No significant difference was seen in the disease free survival rates according to the size of the tumors ($p = 0.28$) or according to the multiplicity of the tumors ($p = 0.71$).

In the open intraoperative RFA group, there was one operative mortality (5%), four patients died in the 1st year due to liver failure in 1 patient and progressive recurrence at the margin of ablated area in the other one, all had lesions > 7 cm. Another four patients relapsed during the second year, one had lung metastases and 3 had liver recurrences. Nine patients (50%) were alive at the end of 2 years with no evidence of hepatic or extrahepatic HCC. The disease free survival at one and two years was 72% and 50% and the overall survival was 72% and 61% respectively. The 2 year disease free survival in patients with lesions ≤ 6 cm was 66% and in patients with lesions > 6 cm was 16.6% ($p < 0.05$). No significant difference in disease free survival rates was seen according to cirrhosis as there were no Child class C cases in the open intraoperative RFA patients.

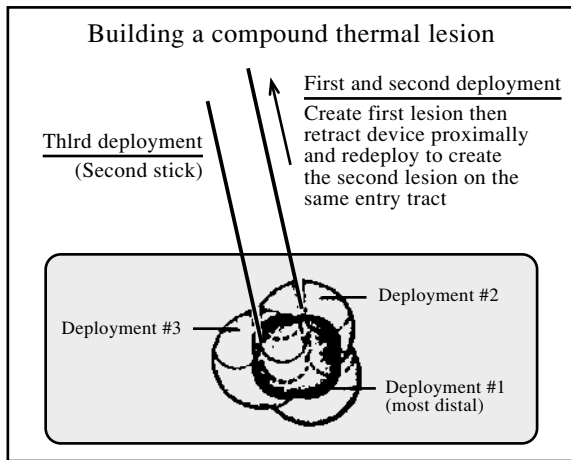


Fig. (1): Multiple electrode deployments to produce overlapping zones of thermal ablation to treat large sized tumors (Quoted from 6, with permission).

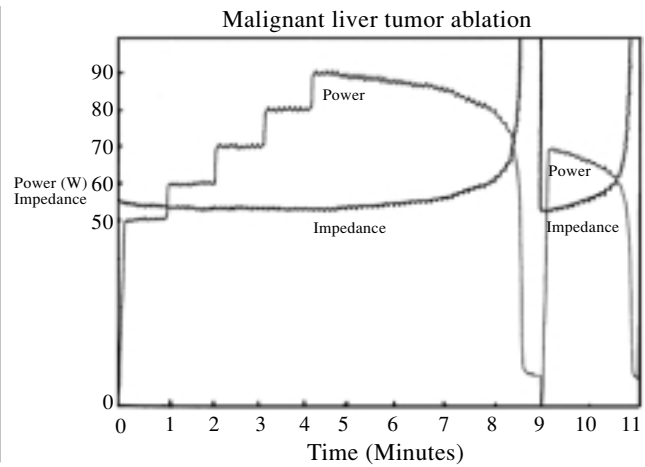


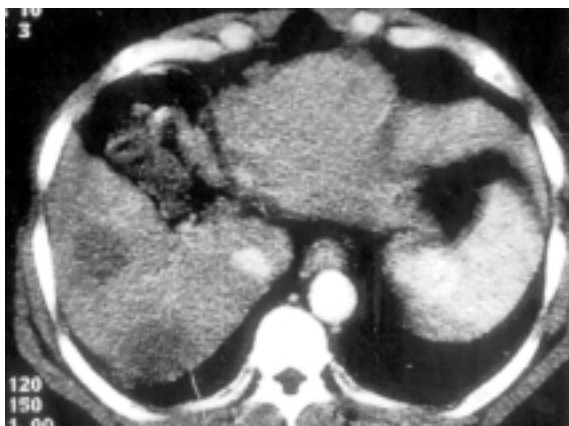
Fig. (2): A graphic display of power (in Watts) and tissue impedance (in Ohms) during RFA of a malignant liver tumor (Quoted from 3, with permission).

Fig. (3): Percutaneously ablated patient having two HCC lesions (2x2 cm) in the right lobe:

- A- Pretreatment CT (arterial phase).
- B- CT one month after RFA treatment (arterial phase).
- C- CT one month after RFA treatment (portal phase).



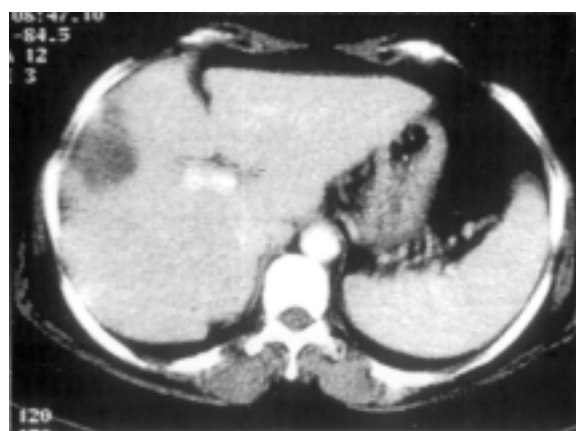
(A)



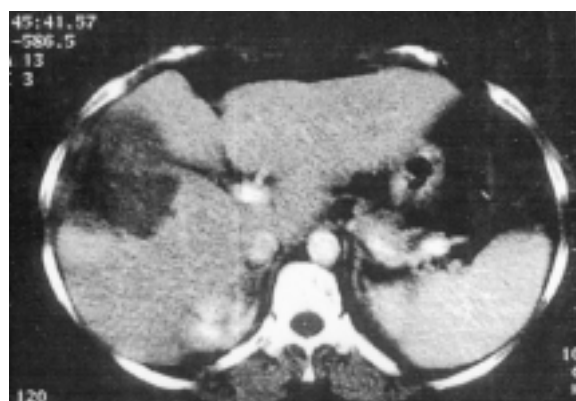
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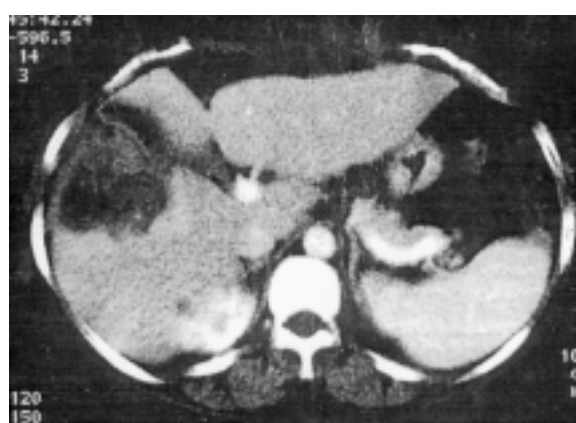
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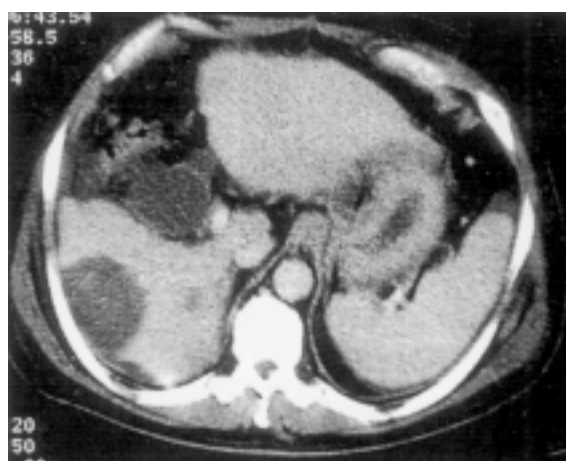


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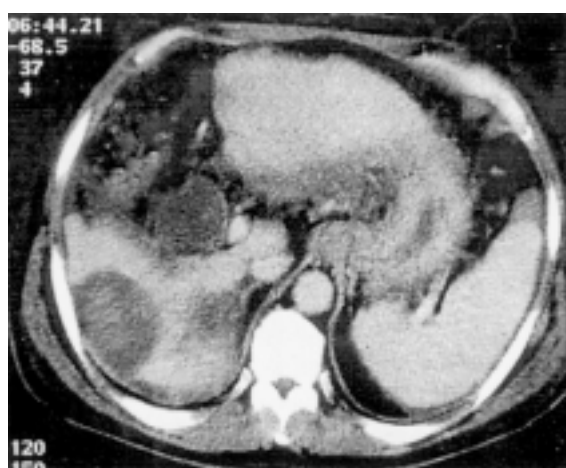
Fig. (4): Percutaneously ablated patient having a 4x4 cm HCC lesion in the right lobe:
 A- Pretreatment CT, arterial phase.
 B- CT one month after RFA treatment (arterial phase).
 C- CT one month after RFA treatment (portal phase).



(A)



(B)



(C)

Fig. (5): A big HCC lesion (6x4.5) in the right lobe close to the gall bladder ablated by open intraoperative RFA:
 A- Pretreatment CT arterial phase.
 B- CT one month after RFA treatment (arterial phase).
 C- CT one month after RFA treatment (portal phase).

Table (1): Characteristics of the 50 patients treated on the RFA protocol.

| Age | Median: 55 years (range 23-67) | |
|-------------------------------------|--------------------------------|---------|
| <i>Sex:</i> | No. | Percent |
| Male | 34 | 68 |
| Female | 16 | 32 |
| <i>Cirrhosis:</i> | All are cirrhotics | |
| Child A | 20 | 40 |
| Child B | 24 | 48 |
| Child C | 6 | 12 |
| <i>Chronic Hepatitis infection:</i> | | |
| HCV | 35 | 70 |
| HBV | 8 | 16 |
| No HCV or HBV | 7 | 14 |
| <i>RFA route:</i> | | |
| Percutaneous | 32 | 64 |
| Open intraoperative | 18 | 36 |

Table (2): The percutaneous and the open intraoperative RFA groups.

| | Percutaneous 32 patients | Open intraoperative 18 patients | <i>p</i> value |
|-------------------------------|-----------------------------|---------------------------------------|-------------------|
| Tumor number | 51 | 28 | |
| Median size | 3.5 cm (range 2-7) | 5.5 cm (range 5-11) | < 0.05 |
| Complications | 18.6% | 22.2% | |
| Ttt. related death | 0 | 1 (5%) | |
| <i>Disease free survival:</i> | | | |
| One year | 81.2% | 72.0% | |
| Two years | 62.5% | 50.0% | N.S. |
| <i>Overall survival:</i> | | | |
| One year | 81.2% | 72.0% | |
| Two years | 71.8% | 61.0% | N.S. |

DISCUSSION

Surgical resection remains the only potentially curative treatment of HCC. Unfortunately, patients with HCC are poor surgical candidates because of the lack of hepatic reserve resulting from coexisting liver cirrhosis, the presence of multiple lesions, or proximity of the tumor to key vascular or biliary structures. Additionally, because of the underlying cirrhosis, these patients are at high risk for the development of new tumor nodules [4].

Several techniques aiming at providing local destruction of the tumor have been developed and clinically tested over the past few years. These methods include percutaneous ethanol injection (PEI), laser photocoagulation, cryoablation and radiofrequency ablation [6].

Direct image guided intratumoral injection of absolute alcohol has been extensively tested around the world. PEI can destroy a relatively large area by a single session ablation technique. However, it is difficult to predict the extent of an ablated area, because distribution of the injected alcohol is affected to a large extent by the capsule and septa of the lesion. RFA has the advantage over PEI in necrotizing a large volume in one session and the therapeutic efficacy is better reproducible with RFA than PEI [7].

Although cryotherapy has the advantages of placing multiple probes at the same time and the area of frozen tissue is highly echogenic, which allows careful monitoring of the freezing process by intraoperative ultrasound, yet it has a lower efficacy than RFA (higher local recurrence rate) and a higher complications rate than RFA [8].

RF electrocautery have been used for more than 70 years to achieve direct tissue ablation, usually for hemostasis during surgical procedures. Advances in electrocautery technology led to the development of monopolar and bipolar tissue ablation devices designed to ablate larger areas of tissue, particularly malignant tumors [9].

New needles (15 to 18 gauge in diameter) have been developed with multiple array hook electrodes, like the LeVeen needle we used. The needle electrode shaft is placed into the tumor with the array retracted. Using real-time ultrasound guidance, the array is then deployed from the needle tip into the tumor. These deployed multiple array hooks create a series of electrodes with a diameter up to 4 cm across which the RF current can be passed. Using the RF current generator with a 50 to 90-W power output for 5 to 15 minutes, a 4.0 to 5.0 cm diameter tumor can be ablated with the hook electrodes fully deployed [3].

Patients must have some general characteristics to be considered eligible for treatment by RFA. First, because RFA is a local treatment, disease ideally should be confined to the liver, without evidence of vascular invasions or extrahepatic metastasis. The presence of clear and easy to detect target for needle placement is crucial for an optimal outcome. Treatment of lesions adjacent to the gall bladder or to the hepatic hilum may cause thermal injury to the

biliary tract. In contrast, treatment of lesions located in the vicinity of hepatic vessels is possible because flowing blood usually cools the vascular wall, protecting it from thermal injury [4].

RFA of liver tumors can be performed percutaneously, using laparoscopic guidance, or as part of open surgical procedure. The choice of treatment approach is individualized in any given patient. In general, patients with one to three small (less than 3.0 cm diameter) cancers located away from the hilum of the liver are considered for US-guided percutaneous RFA. Larger lesions, lesions located high in the dome of the liver near the diaphragm are not always accessible by percutaneous approach [6].

Percutaneous treatment has several advantages being less invasive, produces minimal morbidity, can be performed on an outpatient basis, requires only conscious sedation, is relatively inexpensive and can be repeated as necessary to treat recurrent tumors [10].

Although the open intraoperative technique has the disadvantages of being more invasive, with higher morbidity with the added expenses of the procedure and associated recovery time, yet it has the advantages of the ability to scan the whole liver with high-frequency transducers and to accurately stage the extent of the tumor. It also allows a great deal of freedom in placing the sonographic transducer and the needle electrode. Difficult lesions adjacent to the diaphragm, bowel or gall bladder may be treated easily with the open technique. These organs can be removed or isolated from the mobilized liver to prevent damage during the ablation. Finally, the blood supply to the liver may be temporarily stopped facilitating RFA of large or hypervascular tumors and tumors near blood vessels [6].

In our study, RFA was used to treat 50 patients, 32 via percutaneous approach and 18 via an open intraoperative approach. The most comparable study with our study was done by Curley et al., 2000 [11]. They treated 146 discrete HCC in 110 patients with RFA using the same equipment and needle size as in our study. Percutaneous or intraoperative RFA was performed in 76 and 34 patients, respectively. No incomplete ablation was noted during open RFA versus 7.9% incidence (6 patients) of incomplete

RFA in the 76 patients who were treated percutaneously (8 of 84 tumors, 7.1%). The tumors treated percutaneously were smaller than the lesions treated during open RFA (2.8 ± 0.8 cm vs. 4.6 ± 1.7 cm).

The incidence of incomplete ablation in our study was also only in the percutaneously ablated cases and it was 7.8% (4 of 51 lesions). The explanation of incomplete ablation by Curley et al. [11] was the better resolution of the tumor and RFA treatment provided by the intraoperative compared with that provided by the transabdominal ultrasound. Additional explanation can be added from our point of view, is that the occlusion of hepatic vascular inflow which is done during the open intraoperative RFA increases the efficacy of ablation, making the possibility of incomplete ablation much less likely to occur.

Curley et al. [11] reported complications in 10 of the 76 patients who were treated percutaneously (13.1%). Three patients developed hematoma, one required blood transfusion, two patients developed controlled ascitis, one patient developed hydropneumothorax which required drainage, 2 developed symptomatic pleural effusion and required drainage, one developed ventricular fibrillation controlled by cardioversion and one patient developed fever with no evidence of septic infection. Mulier et al. [12], reported complication rate 7.2% and mortality rate 0.5% after percutaneous RFA. Adam et al. [8] reported complications in 8 of 34 patients (24%) treated with percutaneous RFA. The rate of complications in our percutaneous group was 18.6%, mostly avoidable. One patient had post-ablation cholecystitis due to ablation of a tumor close to the gall bladder, and another one developed hemothorax due to ablation of a subdiaphragmatic tumor, both situations are better dealt with through an open intraoperative or laparoscopic RFA. The other 4 complications were due to the development of post-ablation ascitis in Child C patients, in whom we do not recommend any intervention in the future due to the high complication rate and the poor survival results.

In the open intraoperative RFA group, Curley et al. [11] reported 2 mortalities (5.8%) due to postoperative liver cell failure. This was similar to our 5% mortality rate. Our mortality occurred in a patient with a 9 cm lesion in the right lobe

done during the early phases of our study. In the early trials of open RFA published by Curley et al. [3], lesions as big as 12 cm were tried. In the later series published by the same author, lesions > 6.5 cm were considered too big even for open intraoperative RFA due to the high mortality rate and the high local failure rate. Other complications occurred in 4 patients (11.7%) and included hemorrhage in one patient and persistent ascitis in 3 patients. The complications rate in the present study was 22%. The higher rate of complications we had were mostly due to the larger lesions we tried to ablate by the open intraoperative RFA than that tried by Curley et al. [11] (diameter 4.6 cm) versus 6.5 cm in our cases.

In our study, 7 out of the 51 lesions treated percutaneously recurred locally during the follow up period (5/32 patients, 15.6%). Buscarini et al. [13] treated 101 HCC tumors \leq 3.5 cm in diameter in 88 patients with percutaneous RFA. Local recurrence rate was 29% in patients treated with conventional electrode and 14% in patients treated by the expandable electrode. Also, Adam et al. [8] reported local recurrence in 3 of 18 HCC patients (17%) after percutaneous RFA. In the open intraoperative RFA group, local recurrence rate was 22%.

In the percutaneous RFA group, 6 patients (18%) died in the first year, 5 due to progressive liver cell failure, all were Child class C and one patient due to recurrent progressive HCC. In the second year, another 6 patients developed recurrent HCC. Three of these patients died and 3 were under supportive treatment. Twenty patients (62.5%) were alive at the end of follow up period with no evidence of hepatic or extrahepatic HCC. The disease free survival at one and two years was 81.2% and 62.5% while the overall survival was 81.2% and 71.8% respectively. The 2-year disease free survival in Child class A patients was 91%, 62.5% in Child class B and was 0% in Child class C patients with a significant difference ($p = 0.017$). No significant difference was seen in the disease free survival rates according to the size of the tumors ($p = 0.28$) or according to the multiplicity of the tumors ($p = 0.71$). In the open intraoperative RFA group, there was one operative mortality (5%), four patients died in the 1st year due to liver failure in 1 patient and progressive recurrence at the margin of ablated area in the other

one, (all had lesions > 7 cm). Another four patients relapsed during the second year, one had lung metastases and 3 had liver recurrences. Nine patients (50%) were alive at the end of 2 years with no evidence of hepatic or extrahepatic HCC. The disease free survival at one and two years was 72% and 50% and the overall survival was 72% and 61% respectively. The 2 year disease free survival in patients with lesions \leq 6 cm was 66% and in patients with lesions > 6 cm was 16.6% ($p < 0.05$). No significant difference in disease free survival rates was seen according to cirrhosis as there were no Child class C cases in the open intraoperative RFA patients. Curley et al. [11] treated 146 discrete HCC in 110 patients with RFA, 76 patients via percutaneous and 34 via the open intraoperative technique. At a median follow up of 19 months, local recurrence, new liver tumors or extrahepatic metastases developed in 50 patients (45.5%), but 56 patients have no evidence of recurrence. Thirty one patient died. By the end of the study, 53 patients were alive with no evidence of recurrence. The disease free survival rate was 48.2% but the overall survival rate was 71.8%. Their results are close to our results.

The survival is clearly affected by the Child classification, almost all authors abandoned ablation of Child C patients. In the open intraoperative RFA ablation of lesions > 6.5 cm should also be avoided because of the high rate of mortality, morbidity and the high recurrence rates.

Conclusions:

Treatment with RFA can produce significant disease free and overall survival in some patients with non-metastatic HCC who are considered unresectable because of multifocal disease, proximity of the tumor to key vascular or biliary structure, or inadequate functional hepatic reserve to allow safe hepatic resection. Child C patients and those with lesions > 6.5 cm are poor candidates. While the survival rates were lower in those undergoing an open RFA approach, many of these patients have larger lesions. Confirmation of these results in randomized trials should be considered.

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