Over a decade treating hepatocellular carcinoma percutaneously with radiofrequency thermal ablation. Worldwide experience

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Abstract

Hepatocellular carcinoma (HCC) is a very common malignancy. Early diagnosis plays a significant role in the management of patients, affecting survival and prognosis. Surgical resection is the treatment of choice; yet only a small number of patients are surgical candidates at the time of diagnosis. Furthermore, recurrences are very common even after a successful resection. These reasons urged the need to introduce a minimally invasive technique that can be repeated, without the fear of increasing mortality, morbidity, hospitalization and treatment-related cost. In the present article we present our long-standing experience regarding radiofrequency thermal ablation (RFA) treatment of HCC. Indications, clinical results from other investigators and complications are discussed. Additionally there is a description of the technique and the equipment used.

Key words: radiofrequency ablation, hepatocellular carcinoma, treatment, complications, indications, clinical results.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer and the fourth in overall mortality. About 372,000 new cases of HCC are diagnosed each year, with increasing incidence worldwide due to infection with hepatitis B and C virus. Since early recognition of the cancerous lesion would be of great benefit for the patients as far as their survival and prognosis are concerned, those with strong predisposing factors such as cirrhosis should be monitored quite often [1].

Although the gold standard treatment for HCC is surgical resection, in several prior studies [2-5] more than 70% of patients who underwent hepatectomy for HCC were found to have recurrent HCC in the liver within 5 years after hepatectomy despite postoperative histologic findings of no tumour cells in the resected tumour margins. Recurrences in the remnant liver originate from intrahepatic metastasis from the primary resected tumour, and/or from metachronous multicentric occurrence [6]. If repeat hepatectomy is feasible, it is recommended [7, 8]; but only 10-40% of patients can safely undergo it [2, 3, 7, 8] due to either progressive hepatic dysfunction or the presence of multiple tumours at diagnosis [2, 5, 9-11].

On the other hand, only a limited number of HCC patients are surgical candidates because of their lack of hepatic reserve, resulting from co-existing advanced cirrhosis, widespread intrahepatic involvement and concomitant diseases (heart or pulmonary failure, etc) [12]. Furthermore, liver transplantation, which eradicates HCC, is regarded as the best treatment, but the shortage of donors and its high cost limit its widespread use. Moreover, transplantation is generally contraindicated in patients with large HCC tumours [13].

Percutaneous imaging-guided ablative techniques using thermal energy sources such as radiofrequency (RF), microwaves, lasers and high-intensity focused ultrasound (HIFU) are based on the principle that decreasing tumour load or preventing new growth can lead to longer survival and potential cure in selected patients, and are considered low-risk, effective methods for treating HCC [14]. RF ablation systems with expandable monopolar electrodes are currently the most prevalent and widely accepted as a minimally invasive treatment for the management of primary or secondary liver malignancies [15]. The use of RF energy for the treatment of hepatic tumours was pioneered more than a decade ago [16, 17]. Reduced mortality, morbidity and hospitalization are considered major advantages rendering RF ablation as a promising alternative, not only in controlling malignant disease, but also in improving survival rate for patients with limited but unresectable disease [18-20].

RFA: equipment and technique

RF energy is electromagnetic energy. Heat is produced by ionic movement surrounding the electrode as the radio waves attempt to find their ground, usually a foil pad attached to the patient's back or thighs [15]. Eventually malignant cells are killed, while adjacent structures remain intact. Optimal results arise when healthy tissue of 0.5-1 cm around the tumour is ablated to ensure that all microscopic cancerous foci are destroyed as the exact margins of the malignancy are not precise. High temperatures between 60 and 100°C cause protein coagulation and therefore tissue damage [21, 22]. The aim of ablative therapies is to achieve and maintain a 50-100°C temperature range throughout the entire target volume. Temperatures above 105°C result in tissue boiling, vaporization and carbonization, usually diminishing optimal ablation due to a decrease in energy transmission [15].

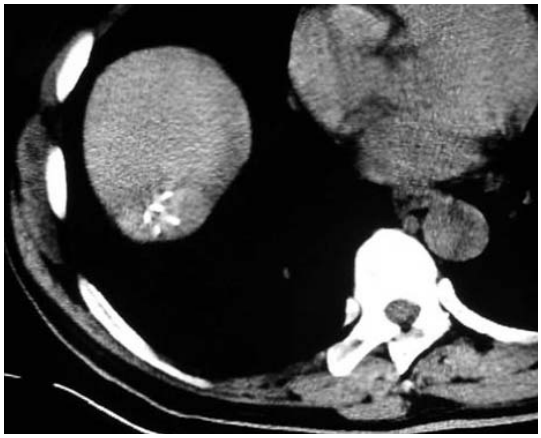

Figure 1. Case of a male patient, 77 years old suffering from HCC who was not a surgical candidate due to comorbid conditions. The tumour was located under the diaphragm; the multitined expandable electrode is inside the lesion

There are different types of generator. Most devices currently used are monopolar but bipolar devices are also used. Many electrodes modifications are now available. The type of device and electrode used clearly influences the extent of ablation. There are expandable electrodes with one tine or multiple tines, internally cooled electrodes and perfusion electrodes. Electrodes increase energy deposition by creating larger zones of coagulation and produce better lesion destruction [15].

In our department we used three different RFA systems with an expandable needle electrode and one with a perfusion electrode, all monopolar systems. The RITA Medical Systems (Mountain View, CA, USA), the Boston Scientific (Watertown, MA, USA; formerly Radio Therapeutic Corporation, Mountain View, CA, USA), and the MIRAS (Invatec S.r.l., Roncadelle, Italy) are expandable type devices.

Diagnostic imaging applications are necessary for the RFA procedures in order to target the lesion, guide the device deposition during the procedure and assess the results at follow-up. CT, MRI and U/S may be used in the case of liver malignancies. The selection depends on the availability of equipment and personal preference, the experience of the radiologist performing the RFA, the patient's somatotype, the lesion's location, and the relative cost. In patients with lesions in a difficult location (close to the dome of the hemidiaphragm) (Figure 1), or with anatomic variations (e.g. Kilaiditi syndrome) (Figure 2) and in obese individuals guidance under CT is preferable. Also CT-guided RFA is universally preferred because of better visualization of the needle inside the parenchyma, and better spatial resolution. Since CT can better ensure adequate positioning of the RF device and our experience obtained in RFA is greater with CT than with U/S, we perform ablation under CT guidance.

Before starting, all patients should undergo careful clinical examination, including laboratory (Hct, WBC, blood coagulation values, values for hepatic function and a-fetoprotein levels (it can be used as prognostic factor for the RFA result) and imaging examination (to exclude metastatic disease): a platelet (PLT) count <50,000/ml and

international normalized ratio (INR) >1.3 are contraindications for RFA and should therefore be corrected. Coumadin and aspirin must be ceased at least 3 days prior to therapy.

Anaesthesia

There is no consensus on the best anaesthetic care for liver RFA. Candidates for liver RFA frequently have a medium-to-high risk when receiving anaesthesia. They typically have been rejected for advanced age, chronic obstructive bronchopneumonopathy, or other associated diseases. In most centres the liver RFA is performed with the patient in conscious sedation by using fentanyl citrate (50 µg intravenously) and midazolam hydrochloride (1 mg intravenously) [23, 24]. Other centres use an epidural anaesthetic that consists of 5-10 ml of 2% lidocaine, 1 ml of fentanyl citrate, or both, with an epidural tube [25]. Some other teams prefer general anaesthesia with endotracheal intubation. The patients should not be so deeply sedated though since they cannot follow breathing commands, which facilitate the proper electrode placement into the tumour. Sedation should be bloused just before the current is turned on [26]. All these techniques need the presence of an anaesthesiologist, so the cost of the whole procedure is increased. During the procedure patients undergo monitoring with continuous pulse oximetry and electrocardiography, checking the blood pressure every 5 minutes [15, 22].

In our department we use an analgesic and antidepressant therapy forty-five minutes before the procedure. All patients receive one pill of 3 mg bromazepam (Lexotanil® Roche) per os and 75 mg d-propoxyphene hydrochloride (ZIDERON® Norma Hellas S.A) intramuscularly [27]. This treatment, which includes bromazepam, allows patients to relax and eliminates the *fear of pain* they feel for the procedure. So the cost of the whole procedure is lower, it has fewer side effects and very good analgesia, which permits the patient to tolerate the ablation with the minimum of pain [28]. At the puncture site local anaesthesia is achieved with injection of a 10-15 ml 1-2% lidocaine hydrochloride solution both intradermally and into deeper tissues. If pain is intolerable early in treatment, the generator can be turned down or off and the pain should abate in about 30 seconds. Treatment may begin again after more anaesthetic is administered [26].

Authors' experience

In our department between February 1999 and January 2007, 258 patients (206 men and 52 women) with 360 HCC underwent 390 RFA sessions. The diameter of the tumours ranged from 1.5 to 5 cm (mean 2.8+0.7 cm). Prior to RFA sessions a-fetoprotein values were normal (<20 ng/ml) in 120 patients, slightly elevated (20-200 ng/ml) in 82 and markedly elevated (>200 ng/ml) in 56.

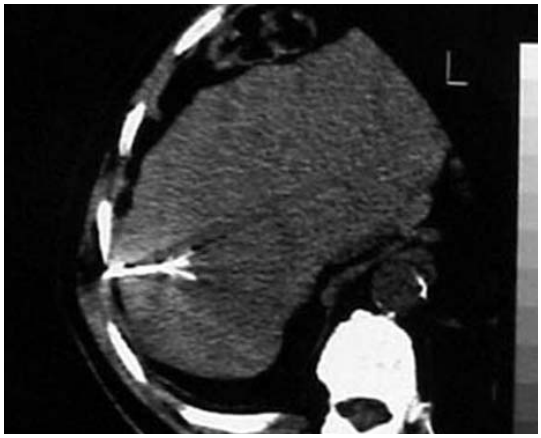

Figure 2. Male patient, 65 years old with HCC cirrhosis and Kilaiditi syndrome who refused operation. The multitined expandable electrode is in the centre of the lesion

Prior to RFA treatment, its benefits and risks were fully explained, and written informed consent was obtained from every patient. Forty-five minutes before the procedure the analgesic and antidepressant treatment consisting of 3 mg bromazepam orally and 75 mg d-propoxyphene hydrochloride intramuscularly was received [27, 28].

Computed tomography-guided RFA was started by placing the patient in the supine position. Using a Picker 5000 (Philips Medical Systems, the Netherlands) a pre-procedure CT scan was obtained. A radiolucent net device with radiopaque guides, in touch with the skin, was placed and 5-mm collimation CT of the desired area was performed. The lesion's exact location and depth, in relation to the overlying skin, were determined on the acquired CT slices, and marked with a permanent ink marker. The shortest, most vertical and safest path was chosen. The net was removed. The skin at the needle entry site was prepared with povidone iodine 10% solution. A 22G needle for syringe use was inserted into the skin, and three contiguous CT images were obtained to ensure that the chosen point was the appropriate one. Local anaesthetic (2% lidocaine hydrochloride) was then instilled through this needle for skin and subcutaneous tissue anaesthetization. The needle was removed and an incision with a surgical blade was made to facilitate electrode cannula insertion. After patient preparation was completed, two dispersive electrodes were applied to the patient's abdomen or thighs. Subsequently the device was inserted from the exact skin entry site in a stepwise fashion, while the trocar tip was controlled each time with three contiguous 5-mm CT images. Once the tip was seen on CT images at a correct position, the electrode was deployed slowly. When final confirmation of the correct positioning of the tip

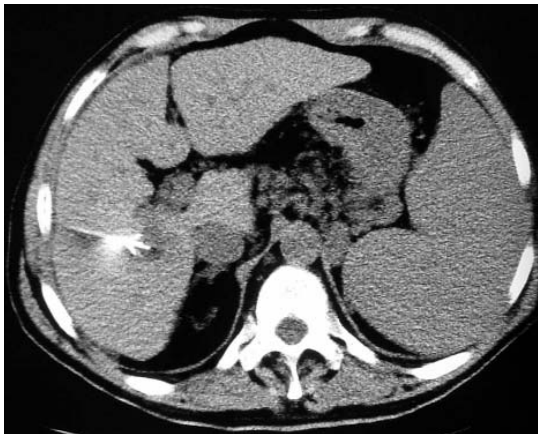

Figure 3. Male patient, aged 63 years old with cirrhosis, splenomegalia and oesophageal varices, who developed an HCC; operation was unattainable. The lesion is delineated by the IVC and liver hilum. The multitined expandable electrode is inside the lesion

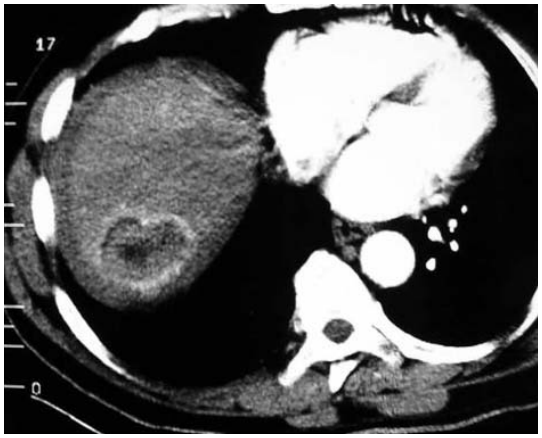

Figure 4. The result immediately after ablation in the case of the patient presented in Figure 1; note the hyperaemic halo around the tumour that presented with a little inside enhancement in the arterial phase with IV contrast material administration. A small subcapsular self-treated haematoma is noticed

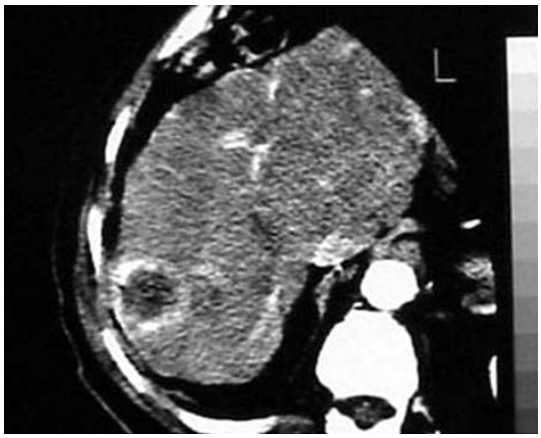

Figure 5. Arterial phase immediately after ablation in the case of the same patient as in Figure 2; the "cystic" tumour transformation that signifies necrosis (no enhancement) and the hyperaemic halo around can be seen

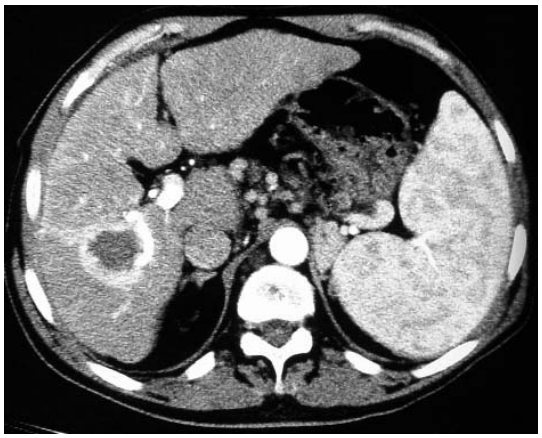

Figure 6. In the case of the patient presented in Figure 3 the immediate scan after RFA and IV contrast material administration revealed the right branch of the portal vein which demarcates the medial tumour margin. Cystic transformation of the lesion, with no inside enhancement, and hyperaemic halo around are shown

of the device was obtained (Figure 3) with additional 3-mm contiguous CT images, the dispersive electrodes and the device were connected to the RF generator.

A pulsed RF energy was applied for 13 to 20 min, depending on the size of the lesion, its location and its vascularity. The duration of the ablation was predefined according to the manufacturer's instructions and modified during ablation if necessary. After the ablation of the lesion was completed low pulsed RF energy was applied for the ablation of the track. This operation was necessary to avoid tumour seeding.

To evaluate the immediate response of the lesion to the ablation, dual-phase dynamic contrast enhanced CT was performed after the electrode's removal (Figures 4-6). If a complication occurred (i.e. subcapsular haematoma) the patient was laid on his right side. For the outpatients, observation for 3 hours was mandatory; the inpatients were hospitalized for 24 hours. All individuals were released with relevant post-care instructions.

Follow-up was performed at 1, 3 and 6 months post-RFA and every 6 months afterwards (Figure 7). A-fetoprotein measurement was also part of the follow-up. Patients were observed for recurrence of the treated lesion and for the emergence of new HCC.

RFA indications for HCC

In order to facilitate a link between tumour staging and treatment, Bruix and Llovet classified patients with HCC into 4 major categories, namely the Barcelona Clinic Liver Cancer classification [29].

1. Patients at an early stage are those who present asymptomatic single HCC <5 cm or up to 3 nodules <3 cm. They will benefit from curative/effective therapies: resection, liver transplantation and percutaneous ablation.
   - In the case of a single HCC and well-preserved liver function (normal portal pressure and bilirubin levels) resection is the treatment of choice; however apparently only a few patients meet the above criteria.
   - In the case of single HCC <5 cm with signs of liver deficiency or in the case of 3 nodules <3 cm, RFA is the optimal treatment when other diseases coexist, while liver transplantation is the optimal treatment in absence of other comorbidities. Properly selected candidates in this category should achieve a 50 to 75% 5-year survival rate.
2. Patients exceeding these limits, with no cancer-related symptoms and absence of vascular invasion or extrahepatic spread, fit into the intermediate stage and may benefit from palliation with chemoembolization, especially those in a Child-Pugh A stage. Three-year survival rates even without treatment may reach 50%.
3. In contrast, patients with cancer-related symptoms (pain and deterioration of their physical condition as evidenced by a performance status <2) and/or an aggressive tumour pattern (vascular invasion or extrahepatic spread) correspond to an advanced stage with a 3-year survival rate at around 10%. In this category there is no unequivocally effective therapy [30], although new anti-tumour agents may be considered.
4. Finally, individuals at a terminal stage are those who fit into stage 3 of Okuda's classification [31] and/or show severe physical impairment (performance status >2) as well as Child-Pugh class C patients. They are treated symptomatically. In the absence of general contraindications (age or associated conditions), they are candidates for LT because of their liver functional impairment.

Clinical results

Rossi et al. [32] reported a median survival of 44 months and a total of 41% recurrences, of which 5% were local tumour recurrences and 36% were new lesions. Complete necrosis was achieved in 95% of the patients, while 64% of the patients were tumour free for a mean period of 23 months. The survival rate for the first year was 94%, 86% for the second year, 68% for the third year, and 40% for the fourth and fifth years. In another study by the same investigators complete necrosis was achieved in 95%, while 71% of the patients were tumour free for a mean period of 12 months [33].

In the study performed by Ikeda et al., 23 patients with solitary HCC smaller than 3 cm were treated with RFA. Complete tumour response on imaging was achieved in all 23 patients (100%) [34].

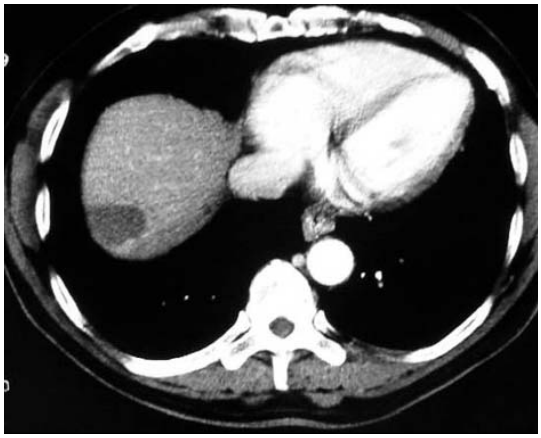

Figure 7. Two years later the aforementioned patient presented in Figures 1 and 4 was free of symptoms and the lesion appears hypodense with no signs of enhancement and smaller in size

Solmi et al. [35] concluded that RFA is a safe treatment for HCC <5 cm in cirrhotic patients; they treated 56 consecutive cirrhotic patients with 63 HCCs with RFA. The diameter of the HCCs ranged from 1 cm to 5 cm (mean 2.8 cm). Complete necrosis after single or multiple treatments was achieved in 96.8% of the tumours. However, in lesions measuring 3-5 cm, RFA with a LeVeen needle under US guidance gave acceptable results with complete necrosis at the first treatment in 64.7% of cases, whereas the remaining 35.3% required a second session for complete necrosis. During a mean follow-up of 32.3 months, recurrence rate after complete necrosis was 41%. The recurrences were local in 2 patients (8.6%) and in different segments in 21 (91.4%).

In a large study by Lencioni [36], consisting of 187 patients who were excluded from surgery and who had Child A or B cirrhosis, with either a single or multiple (as many as three) HCCs, less than or equal to 3 cm in diameter each, RF ablation was the first choice of treatment. The 3- and 5-year survival rates of patients with Child class A cirrhosis were 76 and 51% respectively and for Child class B cirrhotic patients survival rates were 46% at 3 years and 31% at 5 years. Patients with a solitary HCC had 3- and 5-year survival rates of 75 and 50%, respectively, while patients with multiple tumours had 3- and 5-year survival rates of 51 and 34%, respectively. The rate of recurrence of new tumours reached 81% at 5 years. They considered this high rate of new tumours as an expression of the inherent multicentric nature of HCC in cirrhosis and not a drawback of the ablation.

Choi et al. [37] treated 45 patients with recurrent HCC, who had previously undergone hepatectomy, with RF ablation under ultrasonographic guidance. The overall survival rates at 1, 2 and 3 years were 82, 72 and 54% respectively. After initial RF ablation, 21% of the ablated HCC showed residual tumour or local tumour progression. After additional RF ablation, complete ablation was achieved in 87% of

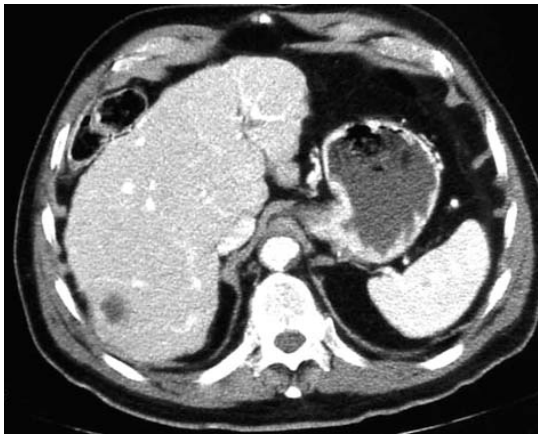

Figure 8. Eighteen months later the patient presented in Figures 2 and 5 was free of symptoms and the lesion appears totally necrotized with no enhancement and a smaller size

the tumours. Disease-free survival rates at 1, 2 and 3 years were 57, 43 and 34%, respectively.

Kim et al. examined the efficacy and safety of radiofrequency ablation in the treatment of HCC in patients with decompensated cirrhosis (mean Child score 10.7). Up to 88.5% of the patients showed complete necrosis without marginal recurrence at the 6-month follow-up. During follow-up (mean 13.3 months), one patient experienced a remote tumour recurrence in the liver. The median survival time was 12.0±1.7 months. The mean Child scores 3 weeks after RFA were similar to those before treatment. However, RFA seemed to aggravate the pre-existing hepatic dysfunction, taking into consideration the elevated levels of serum amino-transferase and bilirubin two weeks after the procedure. Thus, the investigators consider that RFA could be used selectively for the treatment of HCC in patients with decompensated cirrhosis.

In the case of tumours larger than 3 cm, data appear less satisfactory. Livraghi et al. [38] treated 114 patients with 126 HCC lesions greater than 3 cm in diameter. Complete necrosis on imaging was attained in only 60 lesions (47.6%), nearly complete (90-99%) necrosis in 40 lesions (31.7%), and partial (50-89%) necrosis in the remaining 26 lesions (20.6%). Medium and/or non-infiltrating tumours were treated successfully significantly more often than large and/or infiltrating tumours. In particular, to investigate the necrosis rate, they divided the patients with hepatocellular carcinoma nodules measuring 3.1-9.5 cm in diameter into a non-infiltrating tumour group and into an infiltrating tumour group, and each of these categories was further subdivided according to the tumour diameter: patients with a tumour diameter of 3.1-5 cm and those with a tumour diameter larger than 5 cm. They reported that the complete necrosis rate of tumours measuring 3.1-5 cm in diameter in the non-infiltrating tumour group was 71%, that of tumours larger than 5 cm in diameter in the non-infiltrating tumour group was 25%, that of tumours measuring 3.1-5 cm in diameter in the infiltrating tumour group was 45%, and that of tumours larger than 5 cm in diameter in the infiltrating tumour group was 23%.

In order to achieve better results when tumours larger than 3.5 cm were treated, Chen et al. [39] developed a mathematic protocol, using a regular prism and a regular polyhedron model, to determine how multiple ablation spheres of fixed size could overlap to provide the smallest number of RF ablations, the optimal overlapping mode, and the electrode placement process necessary to achieve a favourable outcome. The investigators treated 121 hepatic tumours (mean diameter 4.75±0.93 cm). According to the CT results obtained 1 month after the treatment, the ablation was successful in 106 (87.6%) of the 121 tumours. During the follow-up period of 3-26 months, the local recurrence rate was 24%. Recurrence rates were 15, 21 and 40% in the patients with HCC and Child-Pugh class A, B and C liver function, respectively. The estimated mean recurrence-free survival was 17.1 months.

In our department the first month follow-up revealed total necrosis in 311/360 (86.4%) tumours and a residual lesion in 49/360 (13.6%). All residual tumours were managed with a second RFA session. The 1-, 2-, 3-, 4- and 5-year survival rates were 95.8, 86.1, 77.7, 67.4 and 54.3% respectively (Figures 7 and 8). A post-RFA reduction of a-fetoprotein was noticed in all patients who had elevated values at the beginning.

Complications

Data from multicentric and unicentric studies show that RFA performed by experienced interventionalists is a safe procedure.

In the multicentre study conducted by Livraghi et al. [40], 2,320 patients were included. Mortality rate was estimated at 0.3%. Deaths were mainly attributed to thermal injury resulting in gastrointestinal perforation and liver failure secondary to bile duct stenosis. Other causes of death were *Staphylococcus aureus* peritonitis resulting in septic shock and multiorgan failure and tumour rupture resulting in massive haemorrhage. There was also one case of sudden death of unknown cause 3 days postoperatively. Major complication rate was estimated at 2.2%; in detail peritoneal bleeding was observed in 0.5%, abscess formation in 0.3%, gastrointestinal wall perforation in 0.2%, haemothorax necessitating drainage in 0.2% and neoplastic seeding in 0.5%. Other, even rarer, major complications included large biloma requiring drainage, biliary stricture requiring stent placement, cardiac arrest, pulmonary embolism and one case of left contralateral pneumothorax. Minor complications occurred in 4.7% of patients. The procedural side effects of periprocedural pain, fever and asymptomatic pleural effusion were common and

not well quantified. Other also frequently reported complications were self-limited intraperitoneal bleeding and transient liver decompensation.

In another multicentre study [41], 872 patients with 1,263 lesions were treated. Analysis of variance was used to evaluate relationships of complications with patient-, tumour- and procedure- related factors. Mortality rate was 0.1% caused by multiorgan failure following peritonitis due to colonic perforation which occurred in a cirrhotic patient with a superficially located HCC. Major complication rate was 3.1%. Tumour seeding along the needle track occurred in seven cases (0.8%).

In the study of de Baère [42], complication rate was 12% including five deaths. Major and minor complication rate was 6.3 and 5.7% respectively. Causes of death included one case of liver insufficiency, one case of colon perforation and 3 cases of portal vein thrombosis. It was observed that portal vein thrombosis was significantly ($p<0.00001$) more frequent in cirrhotic patients (2/5) than in non-cirrhotic patients (0/54) after intraoperative radiofrequency ablation performed during a Pringle manoeuvre. Liver abscess was the most common complication, observed in 7 cases. Abscess occurred significantly ($p<0.00001$) more frequently in patients bearing a bilioenteric anastomosis (3/3) than in other patients (4/223). Other complications included five pleural effusions, five skin burns, four hypoxaemias, three pneumothoraces, two small subcapsular haematomas, one acute renal insufficiency, one haemoperitoneum, and one needle-tract seeding.

In the study of Akahane [43] in which 1,000 RF ablation treatments for 2,140 lesions in 664 patients were included, the major complication rate was 1.9% and the minor complication rate was 0.82% per individual treatment session.

In a review by Mulier [44] of 3,670 patients treated with percutaneous, laparoscopic or open RFA, the mortality rate was 0.5% and the complication rate was 8.9%. Abdominal bleeding occurred in 1.6%, abdominal infection in 1.1%, biliary tract damage in 1%, liver failure in 0.8%, pulmonary complications in 0.8%, dispersive pad skin burn in 0.6%, hepatic vascular damage in 0.6%, visceral damage in 0.5%, cardiac complications in 0.4%, myoglobinaemia or myoglobinuria in 0.2%, renal failure in 0.1%, tumour seeding in 0.2%, coagulopathy in 0.2%, and hormonal complications in 0.1%. The complication rate was 7.2, 9.5, 9.9 and 31.8% after a percutaneous, laparoscopic, simple open and combined open approach respectively. The mortality rate was 0.5, 0, 0 and 4.5% respectively.

A multicentre study by Rhim [45] included more than 1000 patients; major complication rate was 2.4%. Mortality rate was 0.09%. Hepatic abscesses and biliary stricture formation were the commonest complications. Solmi et al. [39] reported that major complications rate was 4%, including right pleural effusion in 1 case, cholecystitis in 1 case and liver failure in 1 case.

Regarding tumours >3 cm in the series by Livraghi [38] et al., serious complications were encountered in two patients; one case of death and one case of bleeding that necessitated laparotomy. In the study by Chen et al. [39], that also included tumours >3.5 cm, major complications occurred in 6.4% of patients consisting of 1 case of bile leakage, 1 case of renal colic, 1 case of subacute cholecystitis, 1 case of subcapsular haematoma, 1 case of hepatic abscess, 1 case of tumour seeding and 1 case of colon perforation requiring surgery.

In our group of 258 patients who were treated percutaneously with 390 RFA sessions, no major complications were encountered. Minor complications occurred in 31 (12%) patients in all sessions, including 7 subcapsular haematomas (Figure 4), 5 partial liver infarcts, and 19 patients with pain and fever up to 38°C, requiring no further treatment but analgesics.

In the case of periprocedural pain, which may be frequent, additional analgesics are administrated. Small asymptomatic right pleural effusion that lasts for less than 1 week is also encountered in the majority of patients. Other laboratory value disorders include transaminase levels increase 2-7 times over baseline during the first 3 days following therapy, slight increase in leukocyte count and bilirubin, and a decrease in platelet count and haptoglobin. All of these tests return to baseline levels by 7 days following RF ablation [46].

Post-ablation syndrome is a known situation consisting of transient flu-like symptoms. Dodd et al. [47] found that post-ablation syndrome occurred in more than one third of patients (36%). Symptoms consist of fever (94%), malaise (70%), chills (35%), delayed pain (29.5%) and nausea (11.7%). On average, the symptoms present 3 days after ablation and last 5 days. Post-ablation syndrome is related to the volume of tissue ablated and the post-ablation AST levels; specifically it was found that statistically significant ($p<0.01$) predictors of symptoms were tumour volumes >4.5 cm diameter, ablated tissue volumes of 6.5 cm diameter, a difference between pre-ablation tumour volume and the volume of tissue ablated >125 cm^3, or post-ablation aspartate aminotransferase levels >350 IU/L.

Tumour volume was a significant predictor before the ablation, whereas volume of tissue ablated and the AST level were significant (and correlated) predictors after the ablation. Among the pre- to post-ablation change measures, the only significant (and correlated) predictors were the difference between tumour volume and the volume of tissue ablated and the increase in AST.

Furthermore, it was found that patients undergoing ablation of a single hepatic tumour less than 3.25 cm in diameter or patients with a post-

ablation AST level less than 150 IU/L are unlikely to experience post-ablation symptoms, whereas patients undergoing radiofrequency ablation of tumours greater than 7.75 cm experience post-ablation symptoms. Additionally, patients with post-ablation AST levels greater than 350 or 500 IU/L have an intermediate and high risk of experiencing post-ablation symptoms, respectively.

Discussion

Surgery remains the gold standard therapy for HCC, but as mentioned above only a few patients, less than 5%, may undergo it [48]. The 5-year survival rate in well selected patients with resectable HCC is around 50% [49, 50], reaching a 70% rate in those with normal bilirubin concentration who do not have portal hypertension [51].

However, even in cases of successful resection, recurrences are frequent. Cumulative recurrence rates after resection are estimated at 77-100%, and 80-95% of such recurrences were confined to the liver [52-55] in a 5-year follow-up.

The therapeutic approach to intrahepatic recurrence is the same as that for the first tumour appearance. Aggressive treatment of liver recurrence increases patients' survival compared to other modalities, but most frequently these patients are not suitable for surgery [56]. Most investigators have reported 3-year survival rates of 37-71% after repeat hepatectomy [3, 4, 7, 8, 57].

Table I. Complications according to the literature

	Livraghi et al. [40]	de Baère et al. [42]	Akahane et al. [43]	Rhim et al. [45]
Number of patients	2320	312	664	1139
Death rate	0.3	1.4		0.09
Major complications	2.2	5.7	1.9	2.43
Minor complications	4.7	6.3	0.82	
Peritoneal haemorrhage	0.5	0.3	0.2	0.6
Hepatic abscesses	0.3	2	0.3	0.9
Gastrointestinal wall perforation	0.2	0.3	0.15	
Haemothorax	0.2		<0.1	0.09
Neoplastic seeding	0.5	0.3	0.7	
Biloma	0.04		0.3	0.3
Biliary stricture	0.04			0.9
Vasovagal reflex	0.04			0.2
Pulmonary embolism	0.04			
Pneumothorax	0.04	0.8	<0.1	0.3
Skin burn		1.4	0.1	0.3
Haemobilia			0.1	
Portal vein thrombosis	0.04	3.1	0.2	
Pleural effusion		1.4	0.2 (requiring drainage)	
Hepatic infarction	0.04		0.1	0.09
Bile peritonitis			<0.1	
Subcapsular haematoma		0.6		
Hepatic failure	0.08	0.3		0.09
Sepsis	0.04			0.09
Bronchobiliary fistula			0.1	
Acute cholecystitis	0.04			
Diaphragmatic paresis	0.04			
Hypoxaemia		1.1		
Renal failure		0.3		
Diaphragmatic injury				0.09
Renal infarction				0.09
Transient ischaemic attack				0.09
Gastric ulcer				0.09

According to the study conducted by Matsuda et al. [6], in patients with recurrence who underwent repeated hepatectomy, the 1-, 3- and 5-year survival rates for multicentric occurrence (MC) patients after repeated operations were 100, 69.7 and 58.1%, respectively, and the 1-, 3- and 5-year survival rates for patients with intrahepatic metastases (IM) from the primary resected tumour were 57.1, 14.3, and 14.3%, respectively. The 1-, 3- and 5-year survival rates after the initial hepatic resections were 100, 94.1 and 82.4%, respectively, in MC patients and 100, 57.1 and 14.3% in IM patients. The control group included patients without recurrence or patients who had recurrent tumours treated by methods other than an operation, such as RFA and/or transarterial chemoembolization. The 1-, 3- and 5-year survival rates for the control patients were 94.3, 78.7 and 65.3% respectively. According to the above results, the MC group survives significantly longer than the IM group after initial or repeat hepatectomy. Additionally, survival rates after initial hepatectomy for the MC patients are better than survival rates for control patients, but the difference was not significant. It is remarkable that there was no significant difference between the survival of MC patients after the repeat operation and the survival of the control patients after the initial hepatic resection.

Percutaneous RFA is the best option for early unresectable HCC [32, 58, 59], and according to published data it seems to be safe and efficient. Death rate is estimated at 0.09-1.4%, major complication rate at 1.9-5.7% and minor complication rate at 0.82-6.3%. Hepatic abscesses, peritoneal haemorrhage and tumour seeding are some of the commonest complications occurring [40-45]. Regarding tumours measuring less than 3 cm, RFA achieves a high rate of complete necrosis of the tumours targeted. However, about a third of the patients developed recurrent tumour over a follow up-period of less than 2 years [32, 33, 60].

According to our experience RFA long-term results may be challenging [20]. One of our patients diagnosed with HCC underwent surgery and twice RFA. RFA was technically successful in both sessions, no complications occurred and seven and a half years after the first operation he is still alive with a good quality of life.

Lu et al. [61] identified the presence of vessels at least 3 mm in size contiguous to hepatic tumours as a strong independent predictor of incomplete tumour destruction by RF ablation. Moreover, recurrences were more common in the perivascular tumour group than in the non-perivascular tumour group. It is suggested that additional sessions or modified ablation strategies should be considered to improve destruction of perivascular tumours, as the *heat-sink* effect, caused by the blood perfusion of the vessels, results in cooling of nearby tissue, making an untreated tumour more likely [62, 63]. Reduction of flow not only to the tumour, but also to the large vessel in question, could be accomplished by arterial embolization or balloon occlusion and by temporary portal or hepatic vein balloon occlusion [62-68], concurrent ethanol or hypertonic saline solution injection into the tumour and concurrent chemotherapy [69]. Ideal technical conditions are usually considered those in which tumours are deep in the liver parenchyma, at least 1 cm from the liver capsule and at least 2 cm away from large bile ducts or large hepatic or portal veins [70, 71].

Regarding comparison between RFA and PEI, according to published reports survival rates after RFA are higher than those after PEI [72, 73]. The treatment sessions required are fewer with RFA than with PEI [14, 74] and the hospitalization period shorter with RFA [74]. RFA can achieve a higher complete necrosis rate [14]. Finally, 1- and 2-year local recurrence-free survival rates are higher with RFA [72], whereas overall recurrence risk and local tumour progression risk are smaller with RFA [74]. However, the incidence of complications is reported to be higher following RFA [14]. In contrast, compared to laser-induced thermotherapy (LITT), local recurrence was reported to be more common after RFA [75].

In comparison with surgical resection, in the non-randomized trials by Yu et al. [76] and Montorsi et al. [77], it was found that surgery was associated with a lower rate of recurrence [76, 77] and longer time to recurrence [76] compared with RFA. However, no statistical difference in long-term survival was found between surgical resection and RFA [77]. Since surgical resection and RFA are usually performed in different groups of patients, with RFA being performed in patients in a more advanced stage who cannot undergo surgical resection, a comparison between the two treatment methods is difficult. The lower recurrence rate for the surgical resection group may be due to the removal of the tumour and its portal venous territory [78].

As far as long-term survival is considered, in the study conducted by Tateishi et al. [79], 3- and 5-year cumulative survival rates were 78 and 54%, respectively, for patients receiving RFA as primary treatment, and 62 and 38%, respectively, for patients who received RFA for recurrent tumour after previous treatment including resection, ethanol injection, microwave ablation and transarterial embolisation.

Another issue that should be pointed out is the importance of the stage of cirrhosis for survival; patients with HCC in Child-Pugh class C cirrhosis are at high risk of developing decompensation of their reserved hepatic function, and thus a RFA procedure should not be carried out since it per se involves a poor prognosis for survival [80]. 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 [81, 82].

According to Lencioni et al. [36], patients with Child A cirrhosis have significantly higher 3- and 5-year survival rates than in patients with Child B cirrhosis. The 3- and 5-year survival rates were also significantly higher in patients with a solitary lesion than in patients with multiple lesions.

When it comes to tumours measuring >3 cm, results are less satisfactory; it is known that ablation of a 1 cm safety margin of cancer-free tissue around the tumour is considered to be obligatory to prevent local recurrence. In one of the latest publications on the subject, an adequate tumour-free margin was defined as being preferably 2 cm and no less than 1 cm of normal liver [83]. Given that most RFA devices produce an approximately 3 cm ablation, tumours >3 cm should not be treated by a single 3 cm ablation but multiple ablations, or a multimodality strategy with adjuvant techniques is required to increase the size of the ablation. Studies show that ablative zones that are much larger than those previously reported can be created if RF thermal ablation is performed in HCC nodules after occlusion of their hepatic blood flow [84, 85].

RFA is also to be considered as an optional treatment in the rare eventuality of tumour seeding along the needle track, occurring in 0.2-0.7% of patients [40, 42-44]. Subcapsular location of the tumour, high a-fetoprotein level, poorly differentiated grade of HCC [86, 87] and previously associated percutaneous biopsy [88] are considered the main risk factors. Surgical resection seems to be used in most instances. External radiation therapy has been reported as an alternative treatment [89]. In the case of tumour seeding along the needle track presented by Espinoza et al. [90] the seeding was successfully treated with ultrasound-guided percutaneous radiofrequency ablation. No recurrence was found after a 2-year follow-up either on contrast-enhanced computed tomography or MR imaging. Moreover, RFA of the needle track can be used as a precaution at the end of the RFA procedure or a biopsy. In the case of subcapsular tumours, it might be recommended to extend RFA to the subcutaneous tissues. However, the efficacy and safety of RFA of needle tract seeding need to be testified in further studies.

In summary, RFA seems to be very efficient and should be suggested in cases of recurrence after initial hepatectomy, since according to Matsuda et al. [6], in cases of recurrence it has comparable survival rates to repeat hepatic resection in MC patients. Given that only a few patients meet the Barcelona Clinic Liver Cancer classification criteria for initial surgical treatment [29], RFA acquires an even more significant role not only in cases of recurrence but also in the very inceptive stage. Furthermore, our long-term results regarding survival rates reaching at 1, 3 and 5 years percentages of 95.8, 86.1 and 54.3% respectively show that RFA is not to be considered only as a temporary, palliative treatment but can be established as a first line treatment along with initial hepatectomy, when the latter is attainable. Large tumour size, tumours neighbouring with vessels or ducts and tumours in a difficult to approach site are factors associated with incomplete necrosis. However, we believe that optimal results are achieved when RFA is performed by a trained and experienced interventionalist.

In conclusion, RFA used percutaneously for the treatment of HCC during a period of over ten years is established as a significant weapon. Multiple studies in different centres worldwide have demonstrated that RFA can cause destruction of tumours with low morbidity and mortality, although the best results have been seen with lesions smaller than 3 cm.

In many centres it is considered the treatment of choice in patients with HCC who are candidates for transplantation and cannot undergo surgical treatment. Further studies need to be conducted in order to establish its efficacy as far as long-term survival rates are concerned. We believe that with continuous technology improvement and increasing clinical experience, RFA may achieve even greater results and possess prominence in the treatment of early, unresectable and recurrent HCC.

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