Computed Tomography-guided Radiofrequency Ablation of Hepatocellular Carcinoma: Treatment Efficacy and Complications

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Abstract

Aim: To evaluate the efficacy and complications of computed tomography (CT)-guided radiofrequency ablation (RFA) of unresectable hepatocellular carcinoma (HCC). **Methods**: A retrospective study of 282 patients (231 males, 51 females, age range: 44-76 years, mean age: 62 years) with HCC (322 lesions) who had been treated by CT-guided RFA over a period of 5 years, was performed. The diameter of the tumors ranged from 1.5 to 5cm. The tumors were considered as ablated completely, if no viability was found on dual-phase dynamic contrast enhanced CT at 1 month after RFA. The follow-up period ranged from 6 to 68 months (mean 29 months) and included a dual-phase dynamic contrast enhanced CT at 1, 3 and 6 months post-RFA and every 6 months afterwards. Patient outcome was evaluated and the survival and recurrence rates were assessed. Each case was reviewed for short-term and long-term complications. **Results**: The ablation success rate was 87.3% (281/322 HCC nodules), while 41 (12.7%) lesions were managed with repeated RFA because of tumor residue. The survival rates at 1, 2, 3, 4 and 5 years were 94.8%, 86.6%, 73.1%, 64.2% and 51.1%, respectively. A total number of 9 (2.8% per procedure) minor complications occurred. No major complications were observed. During the follow-up period, the local tumour progression rate was 22%, while the recurrence rate of new intrahepatic nodules was 48%. **Conclusion**: The results of this study support that RFA is an effective and safe technique for the treatment of unresectable HCC.

Key words

Radiofrequency ablation – hepatocellular carcinoma – liver – computed tomography – CT-guided.

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy, with an increasing incidence worldwide due to infection with hepatitis B and C virus and alcoholic liver disease [1] (Fig 1). Surgical resection remains the treatment of choice, although only a small number of patients may undergo it at the time of diagnosis [2]. Percutaneous radiofrequency ablation (RFA) is a relative new, minimally invasive technique that is considered the best treatment option for patients with HCC in whom surgery is contraindicated [3].

The improvement of equipment and the increased expertise of interventional radiologists have greatly contributed to a high level of treatment efficacy and a low incidence of complications of image-guided RFA. Reduced mortality, morbidity and hospitalization are considered major advantages rendering RFA as a promising alternative, not only in controlling malignant disease, but also in improving survival rate for patients with limited but unresectable disease [4].

Image-guided tumour ablation can be performed with a variety of imaging modalities (ultrasound, computed tomography, magnetic resonance imaging, fluoroscopy) [5]. Although ultrasound is the most common image guidance in liver RFA [6], we prefer the CT guidance for electrode placement. We believe that correct needle localization, which is very important to RFA and must be precise to the millimetre, is better achieved under CT guidance. Since CT can better ensure adequate positioning of the RF device and our experience obtained in RFA is greater with CT than with ultrasound, we perform ablation under CT guidance.

The aim of this retrospective study is to report our center's experience in the therapeutic outcome and early and late complication rates in a large series of 282 patients (322 lesions) with unresectable HHC who underwent CT-guided RFA.

Methods

In our department, 282 patients (231 males, 51 females; age range: 44-76 years; mean age: 62 years) with 322 lesions of HCC underwent CT-guided RFA from February 2002 to
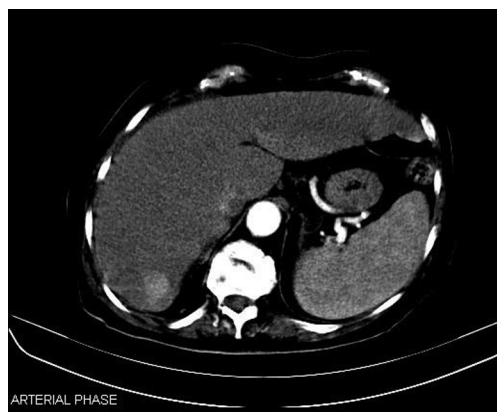
Fig 1. CT in a male patient, with cirrhosis who developed an HCC; operation was unattainable. Pretreatment arterial phase CT image reveals enhancing hepatocellular carcinoma nodule.

February 2007. All patients were diagnosed by biopsy at least on one lesion. The diameter of the tumors ranged from 1.5cm to 5cm. Prior to RFA sessions a-fetoprotein values were normal (< 20ng/ml) in 110 patients, slightly elevated (20-200ng/ml) in 91 and markedly elevated (> 200ng/ml) in 57 patients.

In this study 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.

Prior to therapy all patients had undergone laboratory examinations (hematocrit, white blood cell count, blood coagulation tests, values for hepatic function and a-fetoprotein levels): a platelet (PLT) count <50,000/ml or international normalized ratio (INR) >1.3 is a contraindication for RFA and should therefore be corrected. Coumadin and aspirin must have been ceased at least for 3 days. Ascites should be controlled. Patients with portal vein tumor thrombosis or extrahepatic metastasis were excluded. Finally, the benefits and the risks of the technique were fully explained and written informed consent was obtained from every patient.

Forty-five minutes before the procedure all patients received the analgesic and antidepressant treatment consisting of one pill of 3 mg bromazepam (Lexotanil® Roche) per os and 75 mg d-propoxyphene hydrochloride (ZIDERON® Norma Hellas S.A) intramuscularly. At the puncture site local anaesthesia was achieved with an injection of a 10-15 ml 1-2% lidocaine hydrochloride solution both intradermally and into deeper tissues.

CT-guided RFA was started by placing the patient in the supine position. Using a Somaton Emotion Duo (Siemens Medical Solutions, Germany) 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. If the lesion was small and was unable to be visualized well on plain CT, needle placement was based on nearby anatomic landmarks and the correlation to preablation CT images. In a few cases, where uncertainty existed regarding the correct needle position, a small bolus of contrast media was given and the area scanned during the procedure. 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 of the device was obtained (Figs. 2-4) 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. When the tumor was larger than 3cm in diameter, one single insertion of the electrode was performed, but during the procedure the angle of needle trajectory was changed in order to ablate another site of the lesion avoiding multiple electrode passes. 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 tumor seeding.

To evaluate the immediate response of the lesion to the ablation and check for immediate complications, dual-

Fig 2. RFA electrode inside the malignant lesion located in segment VII; RFA electrode has been inserted into the tumor under CT guidance.
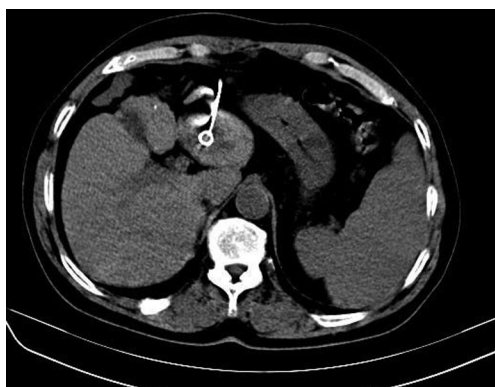
Fig 3. Hepatic lesion in the left lobe; RFA electrode inside the lesion.
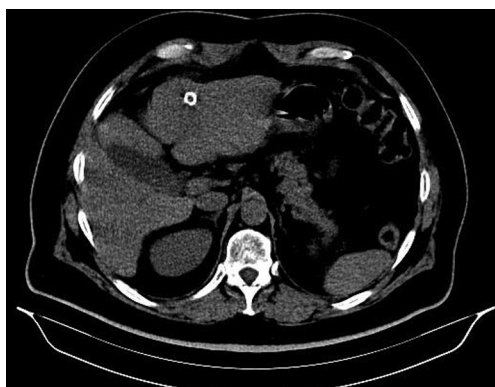

Fig 4. HCC in the left lobe in a patient who underwent RFA; because the lesion was small and was hardly visualized on plain CT, needle placement was based on nearby anatomic landmarks and correlation to preablation CT images. Electrodes are inside the lesion.

Fig 5. CT image immediately after RFA of the patient shown in Fig. 1 demonstrates no enhancement of the tumor, evidence of a good response to the RFA.

phase dynamic contrast enhanced CT was performed after the electrode's removal (Figs. 5, 6). For the outpatients, observation for 3 hours was mandatory; the inpatients were hospitalized for 24 hours. The immediate (<3 hours) and the delayed complications were recorded. Major complications were defined as those that, if left untreated, might threaten the patient's life, lead to substantial morbidity, or result in hospital admission or substantially lengthened hospital

stay. All other complications were considered minor (5). All patients were dismissed after detailed instructions were given. The follow-up period ranged from 6 to 68 months (mean, 29 months) and included a dual-phase dynamic contrast enhanced CT at 1, 3 and 6 months post-RFA and every 6 months afterwards (Figs. 7, 8). The tumors were considered as ablated completely, if no viability was found on dual-phase dynamic contrast enhanced CT at 1 month

Fig 6. Immediate CT scan after contrast media administration of the patient shown in Fig. 3; the lesion does not enhance.
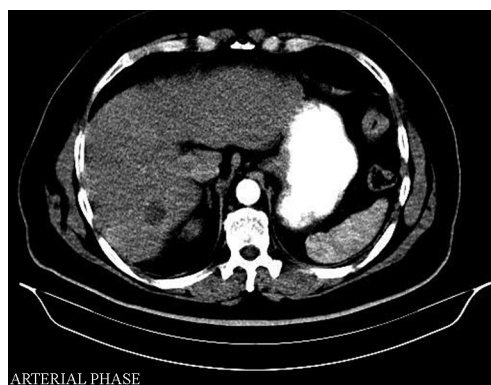

Fig 7. Follow up CT scan after contrast media administration of the patient shown in Fig. 2 after 3 months; the lesion is hypodense, evidence of a complete ablation.

Fig 8. Six months follow up CT scan after contrast media administration of the patient in Fig. 4; note the hypodense appearance of the lesion indicative of complete ablation.

after RFA. Alpha-fetoprotein measurement was also part of the follow-up.

The diagnosis of recurrence was made by dual-phase dynamic contrast enhanced CT during follow-up compared with the previous CT examinations, while magnetic resonance imaging was performed to confirm the recurrence, when necessary. HCC recurrence was classified as either local tumor progression when occurred adjacent to the treated site or intrahepatic distal recurrence when a new nodule observed remote from the margin of the ablative lesion [5]. Tumor recurrence that emerged during follow-up was treated with RFA, if the same initial inclusion criteria were still satisfied. If the patient did not meet the initial requirements for RFA or if multicentric HCC the decision of the treatment was made by the referring oncologist.

Survival analysis was performed on the patient's group and survival probabilities were calculated using the Kaplan-Meier method. For survival rates, the time from the first RFA treatment to the last follow-up CT examination or death was used. For recurrence rates, the time from the beginning of RFA treatment to the first follow-up CT examination that revealed either local tumor progression or intrahepatic distal recurrence was used.

Results

The first month follow-up revealed total necrosis in 281 tumors. The ablation success rate after the first RFA based on the CT findings were 87.3% (281/322 lesions). In this study, 12.7% (41/322 cases) of the patients had tumor residue, of which 32 cases (78.1%) were those with tumors larger than 3cm. All residual tumors were managed with a second RFA session.

The survival rates at 1, 2, 3, 4 and 5 years were 94.8%, 86.6%, 73.1%, 64.2% and 51.1%, respectively.

Minor (those not requiring medical intervention) complication rate was 2.8% (9 of 322 sessions) and consisted of subcapsular haematoma (n=6), reactive small pleural effusion (n=2) and partial liver infarction (n=1). All complications were observed on dual-phase dynamic contrast enhanced CT which was performed after the electrode removal. No delayed complications were recorded. In our group of 282 patients who were treated percutaneously with 322 RFA sessions, no major complications were encountered. No mortality was observed and no carcinoma seeding was identified.

Post-ablation syndrome occured in 120 cases (37.3%) of the 322 RFA sessions. Post-ablation syndrome is a known situation consisting of transient flu-like symptoms. Symptoms comprise fever (94%), malaise (70%), chills (35%), delayed pain (29.5%) and nausea (11.7%). On average, the symptoms are present 3 days after ablation and last 5 days [7].

A post-RFA reduction of alpha-fetoprotein was noticed in all patients who had elevated values at the beginning.

During the follow-up period, the local tumor progression rate was 22%, while the recurrence rate of new intrahepatic nodules was 48%.

Discussion

While surgical resection remains the gold standard of therapy, only a few patients are suitable candidates for curative surgical resection because of the presence of liver malignancy in unresectable locations, the number and anatomic distribution of tumor lesions, or the presence of extrahepatic disease or poor liver function [8]. Several alternative treatments to control and potentially cure liver disease have been developed for use in patients with malignant liver tumors who are not candidates for surgical resection. However, percutaneous RFA is the best option for early unresectable HCC and according to published data it seems to be safe and efficient [9-11]. As a stand-alone therapy, RFA is reserved for treatment of focal or multifocal lesions that are unresectable. RFA is not a suitable treatment for diffuse or infiltrative forms of HCC. Although the criteria for the use of RFA are not defined absolutely, most physicians select patients on the basis of the lesion size, the number of lesions, and the degree of underlying liver dysfunction. Current recommendations for RFA in HCC are Child Pugh Class A or B cirrhosis and no more than three lesions or one nodule with a diameter < 5cm [12].

There are many factors that can affect the therapeutic efficacy of RFA. The most important is the size of the tumor. Sufficient data have confirmed that RFA could successfully ablate the small liver tumors. In most large series RFA showed good control of tumors with necrosis in more than 90% of HCCs < 5cm in diameter. Larger tumors (> 5cm) were not effectively treated with RFA and results were unsatisfactory with complete necrosis in less than 30% [13, 14]. Livraghi et al [15] 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%). Our study confirms that the use of RFA results in a high rate of complete necrosis in HCC (87.3%) concerning lesions smaller than 5cm in diameter, while the majority (78.1%) of tumor residues were observed in patients with lesions larger than 3cm.

Another major factor to affect the efficacy was the undesirable location of the tumor, such as being adjacent to large vessels, hepatic hilum, gallbladder, diaphragm, gastrointestinal tract, because RFA on these tumors involves a remote risk of tumor residue or complications [16]. Lu et al [17] identified the presence of vessels at least 3 mm in size contiguous to hepatic tumours as a strong independent predictor of incomplete tumor destruction by RFA, because blood flow within adjacent blood vessels can dissipate heat and thereby affect the size and shape of the ablated zone. Moreover, recurrences were more common in the perivascular tumor group than in the non-perivascular tumor group.

In the current study, the survival rates compare favorably

with that of other studies [2, 16]. In comparison with surgical resection, in the non-randomized trials by Yu et al [18] and Montorsi et al [19], it was found that surgery was associated with a lower rate of recurrence [18, 19] and longer time to recurrence [18] compared with RFA. However, no statistical difference in long-term survival was found between surgical resection and RFA [19]. Since surgical resection and RFA are usually performed in different groups of patients, with RFA being performed in patients in a more advanced stage that cannot undergo surgical resection, a comparison between the two treatment methods is difficult. Randomized controlled trials are needed to directly compare surgical resection and RFA to determine the initial treatment of each patient group.

Possible complications after RFA of liver tumor include subcapsular hematoma, abscess, hepatic infarction, injury to the gallbladder, bile duct stenosis and biloma, hemobilia, injury to the gastrointestinal tract, pleural effusion, pneumothorax and hemothorax, tumor seeding, skin burn, but they are rare [20]. In a review of 1,000 RFA treatments for 2,140 lesions in 664 patients, the major complication rate was 1.9% and the minor complication rate was 0.82% per individual treatment session [20]. In the multicentre study conducted by Livraghi et al [21], 2,320 patients were included. Mortality rate was estimated at 0.3%. Major complication rate was 2.2%: peritoneal bleeding was observed in 0.5%, abscess formation in 0.3%, gastrointestinal wall perforation in 0.2%, haemothorax 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. Procedure-related complications were minimal to our study. No treatment related deaths and no major complications were observed. Minor complications developed in 2.8% of the cases. These complications included subcapsular haematoma (n=6), reactive small pleural effusion (n=2) and partial liver infract (n=1).

Our rate of small subcapsular haematomas (not requiring treatment) was relatively high compared with other large series using ultrasound as method for imaging guidance [21-23]. This can be explained in different ways. On the one hand, the fact that small vessels are not visualized by CT in combination with the lack of real time imaging may prompt for haemorrhage. On the other hand, patients with cirrhosis are considered to be at higher risk for haemorrhage due to coagulopathy than those without cirrhosis. Moreover, in our study an enhanced CT was performed after the electrode removal and even the small subcapsular haematomas were recognised easily, as CT is the modality of choice for the detection and evaluation of haematoma. Further studies are needed to confirm if the high rate of subcapsular haematoma may indicate the drawback of CT-guided RFA, as the use of intraprocedural CT to monitor RFA has not been extensively explored in the literature.

Post-ablation syndrome is a transient self-limiting symptom of sign complex of low-grade fever and general malaise [5]. The duration depends on the volume of necrosis produced and the overall condition of the patient. Dodd et al [7] found that this syndrome occurred in more than one third of patients (36%) and was related to the volume of tissue ablated and the post-ablation AST levels. Statistically significant ($p<0.01$) predictors of symptoms were tumor volumes > 4.5cm diameter, ablated tissue volumes of 6.5cm diameter, a difference between pre-ablation tumor volume and the volume of tissue ablated > 125cm^3, or post-ablation aspartate aminotransferase levels > 350IU/L. In our study, post-ablation syndrome occurred in 120 cases (37.3%).

Transabdominal sonography is a widely used method for imaging guided procedures in liver, while CT plays an important role in interventions which cannot be adequately guided by ultrasound [6]. Sonography has the advantage of being readily and widely available, is an excellent real-time and fast imaging technique, and is a reasonably good technique for visualizing hepatic tumours, while CT has high spatial resolution, good contrast, wide field of view, good reproducibility, and applicability to bony and air-filled structures [6, 24]. Cha et al [24] reported that during the ablation, artifacts created by thermal tissue changes limit the ability of sonography to precisely visualize the extent of necrosis and supported that this lack of concordance between imaging findings during the procedure and tissue ablation is responsible for many of the local tumor recurrences after RFA therapy. Moreover, the authors in the same study [24] reported that potential advantages of CT guidance include confirmation of probe placement in relation to the tumor, improved visualization of the extent of ablation, good correlation with actual lesion size (whereas sonography tends to underestimate lesion size) and concluded that the use of CT as guiding method may reduce the high rate of local recurrence associated with percutaneous RFA of liver tumors. Despite the advantages of CT, there are several limitations, such as the increased time that is necessary for the procedure, exposure of the patient to ionizing radiation, the fact that many liver lesions are visible only during the arterial and/or portal-venous phase of the dynamic study (although it is debatable whether liver lesions are better seen on unenhanced CT or sonography) [6, 24].

In **conclusion**, percutaneous RFA of primary liver tumors is a rapidly evolving treatment for unresectable lessions. We believe that with continuous technology improvement and increasing clinical experience, RFA may achieve even better results and possess prominence in the treatment of early, unresectable and recurrent HCC. Although surgical resection remains the gold standard treatment of HCCs, this standard may be challenged in the near future, as more results emerge from long-term studies of RFA.

Conflicts of interest

None to declare.

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