Efficacy and safety of radiofrequency ablation as first-line treatment of early hepatocellular carcinoma.

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**Purpose**

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third after lung and gastric in cancer-related-deaths [J Ferlay et al, Globocan 2008]. HCC is the most frequent liver neoplasm; its incidence is increasing worldwide due to expansion of hepatitis C virus infection and NASH (non alcoholic steato hepatitis). The aim of the screening programs is the detection of HCC at an early stage, in order to apply therapies with curative intention. Radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) is the first choice of treatment of single tumors=20 mm, if not candidates to liver transplantation, according to current BCLC-guidelines.

The objective of this study was to evaluate the efficacy and safety of RFA as first-line treatment in the first 31 patients treated at our Hospital.
Methods and Materials

- **Patients**

From 03-Dec-2007 to 19-Dec-2011 we have selected 31 HCC naïve cirrhotic patients in which RFA was applied at first therapy. We have excluded those patients in which RFA was applied in combination with percutaneous ethanol injection, surgical resection or transarterial chemoembolization (TACE). They presented 36 nodules, mean size 21.7 mm (95% CI 18.8-24.5). There were 23 men, mean-age 68 years, Child-Pugh class A5, (29% alcohol, 42% hepatitis C, 29% other), median AFP 6.7 ng/mL (IC range 2.9 - 26). There were 13 patients with single nodules ≤ 20 mm (BCLC-0, 42%), 13 patients with single nodules > 20 mm and 5 cases with a second nodule (Fig. 1 on page 6). There have been applied 37 sessions of RFA, 34 percutaneously. Diagnosis was made in the setting of a screening program in 24 patients. In 5 cases histology was necessary to confirm HCC, because of atypical pattern of enhancement in the studies with dynamic imaging techniques.

- **Follow-up**

Patients were followed prospectively: after an initial CTMD at 1-month to be sure that HCC was completely ablated, all patients underwent CTMD or MRI every 4 months. mRECIST criteria were applied to assess response to treatment [R Lencioni and JM Llovet, Seminars in Liver Disease 2010].

- **RFA Procedure**

All cases were assessed by a multidisciplinary team that includes Surgeons, Radiologists and Hepatologists. All percutaneous procedures were performed by Radiologists under deep sedation and analgesic with Anesthesiologist management. Laparoscopic RFA was performed under general sedation by Surgeons and Radiologists.

Patients were placed in either the supine or left lateral decubitus position, depending on lesion site and planned needle track. Patients were connected to the radiofrequency generator by the dispersive electrode placed on the leg. Local anesthesia was achieved by injecting a 1% lidocaine solution from the insertion point on the skin to the peritoneum along the planned puncture line. The skin was pricked with a small lancet, and the electrode needle was then advanced precisely to the chosen area of the lesion using sonographic guidance.

We applied a 480-kHz generator, maximum power of 200W, (CC1; Radionics, Burlington, Mass) through 16g needle monopolar an active tip of 3cm, guided by ultrasound, of 3.5-5.0 MHz.
After the tip had been deployed inside the lesion, the radiofrequency generator was activated, and the power was set to reach a minimum temperature of 60°C.

The average length of each session was 10 minutes.

Each ablation created an approximate 3-cm thermal injury. Tumor measuring less than 3 cm was treated with one or two ablations; for larger tumors, we performed multiple overlapping ablations. Treatment was considered complete when an RF induced hyperechoic region totally covered the initial location of the tumor.

After RF ablation, patients were under observation for 24 hours. Liver function and complete blood count tests were performed within 24 hours after the procedure.

• Imaging methods

After signed informed consent, most patients were followed up with serial dynamic three-phase contrast enhanced CT by using 64 MDCT (Toshiba Aquilion) after intravenous injection of 125 ml of nonionic contrast medium (Ioversol, Optiray Ultrayet® 320mg I/ml) at a flow rate of 4ml/s. The scanning parameters 64 MDCT: tube voltage 120kV, 180-400mAs intensity modulated dose, slice thickness 1mm, reconstruction interval 5mm. Images were acquired during the late arterial, portal, and delayed phases.

Any of the patients were evaluated with MR imaging performed with a 1.5-T MR system (Signa LX; GE Medical Systems). All MR images were obtained in the transverse plane with a phased-array multicoil for the body. MR imaging protocol included unenhanced T1- and T2-weighted imaging and multiphasic contrast-enhanced 3-dimensional of whole liver with suppression, before and after contrast injection. Arterial, portal venous and delayed phases images were acquired at 20, 60 and 120 seconds after Gd-BT-DO3A (Gadovist®, Bayer Schering Pharma AG, Berlin, Germany), 1 mmol/kg. The contrast was administered with a power injector at 1mL/sec. In all cases MDCT or RM imaging were done before and after intervention.

• Image analysis

All Images were analyzed independently by two radiologists on a Workstation Vitrea® 2 version 4.1.2.0 and evaluated using axial and multiplanar reconstructions by means of MIP and VR.

The follow findings were evaluated:

1. Enhancement pattern post RFA
2. Reactive hyperemia
3. Intrallesional hematoma
4. Air pockets within the ablated lesion
5. Size of nodules (longest diameter)
6. Volume of the ablated area.
The enhancement pattern was classified:

- A nonenhancing area of low attenuation was considered to be necrotic tissue and therefore complete response. (Fig. 2 on page 6).
- An area of enhancement in arterial phase: Nodular-type, defined as a focal enhancement along the inner or outer margin of the treated lesion (Fig. 3 on page 7) or halo-type, as a crescentic enhancing portion in outer margin of the treated lesion. All contrast-enhanced foci with nodular or crescentic shape in arterial phase on CT or MR with wash out in portal venous or delayed phase, were considered as viable tumor.

When this pattern of enhancement is not present viable tumor was confirmed on the basis of an increase in size during the imaging follow-up.

- Reactive hyperemia: defined as peripheral rim-like enhancement, usually uniform in thickness, envelops the ablated lesion on the arterial phase of contrast-enhanced CT or MRI. (Fig. 4 on page 8). It is shown as isoattenuation on the delayed phase of CT, but may show persistent enhancement on the delayed phase of MRI.
- Presence of intralesional hematoma, as a central area of high attenuation in the ablated lesion and along the electrode needle tract (Fig. 5 on page 9).
- Volume of the treated area was evaluated at each imaging follow-up on both CT and MR images. It was measured on portal venous phase by using an area measure tool and summation of areas technique.

- **Statistical analysis**

Continuous variables were described using mean and standard deviations. Nominal variables were described by relative and absolute frequencies. To check the relationship between nominal variables we used Fisher test. All statistical tests were 2-sided, and a significant difference was considered when \( p < 0.05 \).
Fig. 1: Size of the first nodule of each patient (n= 31) according BCLC, in millimeters

Fig. 1

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Fig. 2: Complete tumor necrosis. Axial dynamic hepatic contrast-enhanced helical CT on arterial (a) portal (b) and delayed (c) phases after RF ablation shows an unenhanced oval ablated area with low attenuation.

Fig. 2

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Fig. 3: Viable tumor after radiofrequency ablation. Axial contrast-enhanced helical CT on arterial (a) and delayed (b) phases after RF ablation show nodular-type enhancement with low attenuation in delayed phase (arrows).
Fig. 4 : **Reactive hyperemia**: Axial contrast-enhanced hepatic arterial phase helical CT 1 month after RF ablation shows oval-shaped ablated lesion with surrounding hyperemia (arrow).

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Fig. 5: Intralesional hematoma: axial arterial phase CT obtained 1 month follow-up shows a central area of high attenuation in the ablated lesion (arrow).

Fig. 5

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Results

Reactive hyperemia was seen in 5.7% of nodules (n=2) and a central area of high attenuation is showed in 17 ablated lesions (48.55%) on studies performed 1 month follow-up imaging and resolves at follow-up.

Air was not detected within the ablated areas.

The volume of the ablated areas ranged from 52 to 5,9 cc (mean 14.8 cc) with a gradual decrease in long-term follow-up CT and MR.

**Efficacy:** Median time at hospital was 2 days in case of percutaneous RFA and 8 days in case of laparoscopic RFA. Response to treatment was analyzed in 35 nodules (30 patients): globally 25 patients achieved a complete response after the first RFA (Fig. 6 on page 12): 12 BCLC-0 and 13 BCLC-A, p=0.664. At the end of follow-up only 8 patients have progressive disease. Progressions were treated either with new sessions of RFA or with TACE. One patient was included in the waiting list and finally transplanted 8 months after RFA. Time to progression (TTP) was slightly longer in patients with very early disease (BCLC-0, n=4): median 10.5 months, IC range 6.25 - 23; versus patients with early disease (BCLC-A, n=4), median 9 months, IC range 6.25 -11.75, p=0.137(Fig. 7 on page 12).

**Safety:** We have performed 37 sessions of RFA to 31 patients, 81% of them were uneventful. However, there were 4 moderate adverse events: 2 pain, 1 radiological liver infarct and 1 radiological ascites. By contrast, there were 3 severe adverse events: 1 case of laparoscopic RFA that required re-intervention due to bleeding from a small artery from the abdominal wall and two deaths: 1 following an acute myocardial infarction at fifth day and 1 after hemoperitoneum.

**Survival:** After a mean follow up of 13 months (95% CI 9-17) (Fig. 8 on page 13), 3 patients have died: 2 by severe adverse events related to RFA and one due to HCC progression after 23 months.
Fig. 6: Complete response at first control.

Fig. 6

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Fig. 7: Time of progression (months).

Fig. 7

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Fig. 8

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Conclusion

With regards to the first 31 patients treated in our centre, less than 20% of patients submitted for RFA present a complication related to the procedure. The rate of complete response after the first session of treatment is higher than 83%. These figures encourage us to continue with this therapy.


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