Ablation of large HCCs using a new saline-enhanced expandable radiofrequency device[☆]

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KEYWORDS

Hepatocellular carcinoma;
Ultrasound;
Interventional procedure;
Radiofrequency Ablation.

Abstract *Purpose:* Evaluation of a new device designed to achieve large volumes of necrosis in hepatocellular carcinoma (HCC) nodules by application of radiofrequency ablation (RFA). *Materials and Methods:* 29 consecutive patients with 31 HCC nodules ≥ 3 cm in diameter (range 3–7.5 cm; mean diameter 5.5 cm) underwent ultrasound (US) guided percutaneous RFA using an expandable electrode with 7 active arrays and saline injection designed to create tissue ablation in areas of up to 7 cm (Starburst XLi-enhanced RFA device). Treatment was performed in general anesthesia (6 patients) or deep sedation (23 patients). Treatment efficacy was assessed by three-phase contrast-enhanced computed tomography (CT) and bimonthly US follow-up.

Results: One to three electrode insertions (mean number 1.6) were performed in each patient. CT showed complete necrosis in 23/31 HCC nodules (74%) in 22 patients. Follow-up of these 22 patients ranged from 2 to 15 months (mean time 8.3 months). In 6/22 patients (28%) intrahepatic recurrence occurred within 5–10 months (mean time 8.3 months). Major complications were post-ablation syndrome in 7/29 (24%), peritoneal effusion in 4/29 (14%), pleural effusion in 2/29 (7%) and transient obstructive jaundice in 1/29 (3.4%) patients. One patient died 6 months after treatment because of tumor progression.

Conclusions: In the treatment of large HCC nodules, Starburst XLi-enhanced is an effective and safe device.

Sommario *Scopo:* Valutazione di un nuovo ago-elettrodo espandibile progettato per indurre ampi volumi di necrosi mediante radiofrequenza (RF) del Carcinoma Epatocellulare (HCC).

Materiali e metodi: 29 pazienti con 31 HCC > 3 cm (range 3–7.5 cm, media 5.5 cm) sono stati sottoposti a RF percutanea sotto guida ecografica usando ago-elettrodo espandibile con sette uncini attivati ed iniezione intratumorale di soluzione salina, progettato per creare

[☆] SIUMB 2007 – Award for the poster presented at the 19th National Congress of the SIUMB.

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un'ablazione tessutale fino a 7 cm (Starburst XLI-enhanced, Angiodynamics, Queensbury, NY, USA). Il trattamento è stato condotto in anestesia generale (6 pazienti) o in sedazione profonda (23 pazienti). L'efficacia del trattamento è stata valutata con TC trifasica e con follow-up ecografico ogni 2 mesi.

Risultati: Sono state praticate da 1 a 3 inserzioni (media 1.6) per paziente. La necrosi completa alla TC è stata raggiunta in 23/31 noduli di HCC (74%) in 22 pazienti. Il follow-up di questi 22 pazienti è compreso tra 2 e 15 mesi (media 8.3 mesi). 6/22 pazienti (28%) hanno presentato nuove recidive intraepatiche entro 5–10 mesi (media 8.3 mesi). Complicanze maggiori sono state: sindrome post-ablativa in 7/29 (24%), versamento peritoneale in 4/29 (14%), versamento pleurico in 2/29 (7%) e ittero ostruttivo transitorio in 1/29 (3.4%) pazienti. Un paziente è deceduto 6 mesi dopo il trattamento per la progressione del tumore.

Conclusioni: L'Ago-elettrodo Starburst XLI-enhanced ad infusione salina è un dispositivo efficace e sicuro per il trattamento del carcinoma epatocellulare di grandi dimensioni.

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Introduction

Ultrasound (US) guided percutaneous radiofrequency ablation (RFA) is a valid alternative to surgery in the treatment of small hepatocellular carcinoma (HCC) nodules in patients with liver cirrhosis [1]. However, one of the limitations of the RFA technique is that only small areas of thermal necrosis are produced by the RFA systems described in the literature; the area usually does not exceed 4 cm, which means that this treatment is inadequate in larger tumors (≥ 3 cm) [2–14].

The aim of this study was to test a new RFA device which combines multiple technological improvements in order to achieve a larger spherical volume of necrosis (up to 7 cm). This paper reports the results obtained using this new equipment in the treatment of large HCC nodules (≥ 3 cm) in patients with liver cirrhosis.

Materials and methods

Twenty-nine patients with liver cirrhosis (18 males, 11 females; age range 54–79 years) with 31 large HCC nodules (≥ 3 cm in diameter) underwent US-guided percutaneous RFA; 2 patients had 2 nodules.

Patients were selected according to the following criteria:

- Presence of up to 3 nodules ≥ 3.0 cm in diameter;
- Absence of thrombosis of the main portal trunk or one of the main portal branches, whereas thrombosis of the segmental portal vein was not considered as an exclusion criterion; malignant or benign nature of the thrombus was assessed by contrast-enhanced US (CEUS) [15–17];
- Absence of extrahepatic HCC metastases;
- Severity of liver function impairment not exceeding Child-Pugh class B-9;
- Absence of ascites;
- Patients with nodules abutting the gastrointestinal tract or hepatic hilum were excluded. Superficial nodules abutting the diaphragm, gall-bladder, kidney and right or left branch of the portal vein were not considered as exclusion criteria.

Of the 29 patients, 19 were not eligible for surgery and 10 refused surgical therapy (liver transplantation or hepatic resection). None of the patients had previously undergone other treatment for HCC.

HCC was diagnosed on the basis of characteristic enhancement patterns (arterial enhancement and late wash-out) at contrast-

enhanced computed tomography (CT) [18] and CEUS [19,20]. Eighteen patients also underwent US-guided liver biopsy which confirmed diagnosis based on CT and CEUS outcome.

Ethical approval for this study was granted by the Medical Research Ethics Committee of our Institution, and informed consent was obtained from all patients.

Before treatment all patients underwent:

- serum blood tests for liver function and hemocoagulation
- electrocardiogram
- chest X-ray
- Serum alpha-fetoprotein (AFP)
- abdominal US using commercially available US equipment (Aloka 5500 PV extended, Tokyo, Japan) and a 3.5 and 5.0 MHz convex electronic probe
- triphasic contrast-enhanced CT (Atom Fast Ring, Hitachi Medical Systems, Tokyo, Japan; Iomeron 400 [Iomeprol], Bracco SpA, Milan, Italy) (Fig. 3a).

All patients underwent US-guided percutaneous RFA using a new-generation expandable 15 gauge electrode needle (Starburst XLI-enhanced, Angiodynamics, Queensbury, NY, USA) equipped with seven active prongs (Fig. 1) and multiple channels along the needle axis for intratumoral injection of a saline solution during the treatment. The distance between the tips of two completely deployed opposite prongs is 7 cm (Fig. 2). The system was designed to create tissue ablation of areas up to 7 cm. The device is provided with channels inside the prongs. When connected to an electronic pump it allows a regular intratumoral flow of saline solution during ablation. Five prongs are also provided with thermocouples for continuous registration of the temperature in the target tissue. Characteristics of the device are reported in Table 1. Two large self-sticking plaques are attached to the patient's thighs and used as dispersive electrodes. The Radiofrequency generator (RITA 1500X system, Angiodynamics, Queensbury, NY, USA) is provided with 3 serial ports for 250 Watt power supply. Coagulation of the target lesion is obtained using high frequency alternating current produced by the RF generator. Based on temperatures registered

Fig. 1 The new Radiofrequency electrode needle Starburst XLI-enhanced.

Fig. 2 Detail of the electrode needle tip with the prongs fully deployed. The diameter of the array is 7 cm.

by the electrode thermocouples in the target tissue, specific software allows real-time modulation of the delivered energy. During exposure of the lesion to RF current, a saline solution is injected through the electrode needle into the tumor so that the neoplastic tissue around the needle tip is perfused in order to increase the electrolytic conductivity of the RF fields in the target tissue and to avoid tissue vaporization and charring, thus increasing the volume of coagulation necrosis.

The most favorable percutaneous approach was determined by US. After making a small scalpel incision of the skin and muscle, the electrode needle was percutaneously inserted into the liver until the needle tip was next to the proximal margin of the tumor (Fig. 3b). Needle insertion and deployment of the prongs were accurately monitored by US (Fig. 3c). At this point, the tumor was heated in multiple steps. The prongs were deployed at 2 cm and the current generator and the pump for the saline injection were activated for 2–5 min in order to heat a 2 cm volume to 90–110 °C. The procedure was then repeated after opening the prongs at 3, 4, 5, 6, and 7 cm in order to heat multiple concentric spheres. Time exposure to the RF field at each step is not standardized but determined by the thermocouples which register the intralesional temperature. When the equipment showed that the required temperature had been reached and the tissue had been sufficiently heated, the prongs were deployed in order to proceed to the next step. The treatment was monitored in real-time by US which showed the progressive enlargement of a hyperechoic area related to the thermal lesion within the tumor due to the saline injection and the vaporizing effect of the heat (Fig. 3d). After completed

treatment, the prongs were repositioned in the needle and the device was slowly withdrawn with the RF generator switched on in order to heat the needle track and thereby provide hemostasis and to avoid seeding of tumor cells [21].

Depending on the tumor size/shape or the position of the tumor adjacent to critical organs and structures (the hepatic hilum, colon wall, stomach, etc.) likely to be damaged by the heating, the electrode prongs can be only partially deployed in order to obtain a smaller thermal lesion. Complete deployment of the prongs is in fact possible only in case of intraparenchymal nodules which are not too close to those organs and structures.

A single insertion was planned for nodules up to 5.0 cm in diameter, whereas multiple needle insertions were planned for nodules exceeding 5.0 cm in diameter in order to produce a series of partially overlapping volumes of necrosis to obtain a large area of necrosis which included the tumor. Treatment was performed in general anesthesia (6 patients) or deep sedation (23 patients).

Abdominal US examination and blood cell count for early detection of possible hemoperitoneum were performed 2–4 h after completed treatment.

Patients were scheduled to be discharged from hospital 24 h after treatment. Fever and pain were classified as minor complications. Events requiring a prolonged hospitalization, blood transfusion or surgical therapy were considered as major complications (i.e. hemoperitoneum, pleural effusion, portal vein thrombosis, decompensated liver cirrhosis, renal insufficiency, marked jaundice, abscess, etc).

Four weeks after RFA treatment, the result was evaluated by triphasic contrast-enhanced CT (Atom Fast Ring, Hitachi Medical Systems, Tokyo, Japan) performed after administration of 150 ml iodinated contrast medium (Iomeron 400 [iomoprol], Bracco SpA, Milan, Italy) at a flow rate of 3 ml/sec. Arterial and portal phase images started 20 and 60 seconds, respectively, after the start of contrast medium injection, whereas late phase images were obtained by cluster scans starting 70 seconds after completed contrast medium injection. Tumor necrosis was considered complete when no intralesional enhancement area was evident from the early arterial phase (Fig. 3e) and throughout the portal and late contrast phases. Otherwise the response was registered as incomplete [22,23].

Post-treatment follow-up of patients consisted of abdominal US and serum AFP evaluation every 2 months [23]. US studies were carried out in order to evaluate changes in the volume of the treated lesions and to detect new nodules (recurrence) and portal vein thrombosis. If US demonstrated local or distant recurrence, CT examination was performed.

Results

The results of RFA treatment are summarized in Table 2. Fifteen patients were classified in Child-Pugh class A, and 14 in class B. International Normalized Ratio (INR) values ranged from 0.9 to 1.45 and platelet count ranged from 225,000/ μ l to 55,000/ μ l. Serum AFP levels were below 20 ng/dl in 12 patients, between 21 and 400 ng/ml in 16 patients (range 35–245 ng/dl) and exceeded 400 ng/dl in 1 patient (460 ng/dl).

Nodule diameter ranged from 3 to 7.5 cm (mean diameter 5.5 cm). Twenty-two nodules were located in the right lobe and 9 in the left lobe of the liver. Twelve nodules were superficially located under the diaphragm in the hepatic dome of the right lobe, 4 nodules were located near the main portal branches, 4 nodules were located near the right kidney and 4 nodules were located near the gall-bladder.

Malignant thrombosis of the segmental portal branch was present in 2 patients: one in segment VI and one in

Table 1 Technical characteristics of the Starburst XLI-enhanced electrode needle and RITA 1500X system generator.

- Prongs array up to 7 cm in diameter
- Saline infusion through electrical pump
- High power: up to 250 W
- Automatic heat regulation software

Fig. 3 (a) CT scan in the arterial phase showing hepatocellular carcinoma in segment V of the liver, 4.8 cm in diameter (arrows) (b) Under US guidance, the electrode needle (arrow) is percutaneously inserted into the liver until the needle tip is next to the proximal margin of the tumor (curved arrow) (c) Needle insertion and deployment of the prongs (curved arrow) can be accurately monitored by US (d) When the generator is switched on, a progressively enlarging hyperechoic area starts forming around the electrode tip (e) Post-treatment three-phase CT scan in the arterial phase showing a large area of necrosis in segment V (arrows) exceeding the extension of the tumor.

Table 2 Results of radiofrequency ablation in our series according with the diameters of the nodules (<5 cm vs. > 5 cm).

Diameter of nodules (mean)	Patients	HCC nodules	Electrode insertions (mean)	Complete necrosis (% of nodules)	Recurrence (% of patients)	Death (%)
<5 cm, 3.0–4.8 cm (4.1 cm)	10	10	Range: 1–2 (1.2)	9/10 (90%)	1/9 (11%)	0/10
>5 cm, 5.3–7.5 cm (5.9 cm)	19	21	Range: 1–3 (1.8)	14/21 (67%)	5/13 (38%)	1/19
Overall 3–7.5 cm (5.5 cm)	29	31	Range: 1–3 (1.6)	23/31 (74%)	6/22 (28%)	1/29 (3%)

segment VII. Both malignant thrombi were treated “en-block” with the related HCC nodules.

One to three electrode insertions (mean number 1.6) were performed per HCC nodule. Treatment time per session/patient (from first electrode insertion to the final withdrawal of the electrode) ranged from 12 to 55 min (mean time: 27 min).

CT showed that complete necrosis was achieved in 23/31 HCC nodules (74%) in 22 patients. With regard to the nodule size, complete necrosis was observed in 9/10 nodules (90%) measuring ≤ 5 cm in diameter (range 3.0–4.8 cm) and in 14/21 nodules (67%) measuring between 5.3 cm and 7.5 cm in diameter. RFA treatment resulted in incomplete necrosis of 8/31 nodules in 7 patients. Reasons for incomplete necrosis seemed to be proximity to large vessels in 3 cases [6] and a difficult percutaneous approach in 4 cases. All 7 patients underwent additional ablation treatments, and 5 patients underwent also trans-arterial chemoembolization (TACE). These 7 patients were not considered in the analysis of the follow-up.

Complications

After RFA treatment, fever occurred for 1–3 days in 23/29 patients (79%) and pain for 12–24 h in 5/29 patients (17%). Administration of painkillers or antipyretics was necessary in 16/29 patients (55%). Post-ablation syndrome [24] (fever and pain lasting 2–5 days) was observed in 7/29 patients (24%). Major complications were observed in 7/29 patients (24%): peritoneal effusion in 4/29 patients (14%), pleural effusion in 2/29 patients (7%) and transient obstructive jaundice in 1/29 patient (3.4%). All patients except 5 were discharged from the hospital the day after the procedure. Four patients with self-limiting peritoneal effusion and one with persistent abdominal pain were discharged within 2–4 days after treatment. None of the patients required blood transfusion or surgery.

Follow-up

Follow-up ranged from 2 to 15 months (mean time 8.3 months). One out of the 7 patients who presented incomplete necrosis of the HCC nodule died 6 months after treatment due to tumor progression. All the remaining patients were still alive at the last follow-up.

During the follow-up, US examination and subsequent CT controls showed local recurrence in 6/22 patients (28%) who presented complete necrosis of the HCC nodules after RFA treatment. Recurrence occurred in 1/9 patients (11%) with nodules < 5 cm and in 5/13 patients (38%) with nodules > 5 cm in diameter. All recurrent lesions were treated with additional ablation treatment and/or TACE. During the follow-up, none of the patients presented cutaneous or abdominal wall tumor implantations (seeding) along the electrode needle tract at clinical examination, US and CT [21].

Discussion

Limitations in the surgical treatment of HCC due to site, age and associated clinical conditions have led to the development of alternative locoregional therapies. US-

guided percutaneous RFA is a minimally invasive procedure which is considered as a valid alternative to surgery in the treatment of small HCC nodules in patients with liver cirrhosis [1]. The procedure entails the insertion of an electrode needle into the neoplastic tissue to induce a volume of necrosis by applying thermal energy without causing any systemic damage [1–5]. RFA is effective when the size of the ablation area exceeds the tumor diameter by 1–2 cm. The aim is to obtain necrosis of at least 0.5–1.0 cm of the cirrhotic parenchyma around the tumor margin to destroy the microscopic satellites responsible for a high local recurrence rate [5].

A common problem related to all types of devices used for thermoablation is the small volume of necrosis achieved [5–7]. This limitation seems to be due to increase of impedance in the tissue next to the needle electrode mainly because of dehydration and charring which limit further heat diffusion [6]. In order to obtain larger sized areas of RFA induced necrosis, two possible strategies have been developed:

1. Introduction of multiple sources of heat into the tumor by
 - (a) simultaneous insertion of multiple electrode needles (cluster) [8]
 - (b) insertion of a single large needle allowing the deployment of multiple active terminal hooks into the tumor [9]
2. Decrease of the impedance in the target tissue by
 - (a) internal cooling of the electrode needle tip to avoid charring around the needle tip [11]
 - (b) infusion of a saline solution through side holes situated in the electrode tip during the production of the thermal lesion in order to avoid dehydration [12–14].

Despite these technical improvements, the RFA systems described in the literature are inadequate in the treatment of large tumors (≥ 3 cm) since the diameter of the ablation zones does not exceed 4 cm. Moreover, so far there have been no studies demonstrating the advantage of one RFA probe over another.

In this study, a new RF device was tested which combines several of the above reported technological improvements in order to obtain areas of thermoablation of up to 7 cm in diameter. The Starburst XLi-enhanced device is designed for a progressive enlargement of the area of necrosis through multi-step deployment of the expandable electrodes, and it is provided with a system for intralesional injection of saline solution during the treatment to avoid charring and increasing impedance. These processes are accurately controlled by a system of thermocouples and software for modulating the power of the equipment. Thirty-one large HCC nodules were treated using this device. A very high efficacy rate was achieved in the treatment of nodules < 5 cm in diameter (90% resulting in complete necrosis), and relatively good results were obtained in the treatment of very large nodules ranging from 5 to 7.5 cm (67% resulting in complete necrosis).

In contrast with the good short-term results revealed at post-treatment CT, a high rate of local recurrence (28%) was

observed over a very short mean follow-up (8.3 months). However, patients with very large nodules (>5 cm) presented a statistically significant higher rate of local recurrence, in comparison with patients with nodules <5 cm.

In this study, RFA using Starburst XLI-enhanced electrode needle proved highly effective and safe. There was a high incidence (48%) of major complications, but these occurred in patients with very large tumors requiring an aggressive treatment with heating of large tissue volumes. However, all complications were self-limiting, and none required surgery or intensive care unit admission.

No cases of post-RFA tumor seeding were found [21]. The rule of keeping the RF generator switched on while the electrode needle is being withdrawn (track-ablation) probably explains the absence of these complications.

In conclusion, Starburst XLI-enhanced needle proved to be effective in the treatment of large HCC nodules in this short experience with a small series of patients. However, a study related to the use of this new device in larger series of patients is needed for proving its advantage over other currently available RFA systems.

Conflict of interest statement

The authors have no conflict of interest.

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