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Radiofrequency and microwave ablation of subcapsular hepatocellular carcinoma accessed by direct puncture: Safety and efficacy

Giampiero Francica[a,*], Maria Franca Meloni[b,1], Ilario de Sio[c], Amanda R. Smolock[d], Christopher L. Brace[d], Maddalena Diana Iadevaia[c], Roberto Santambrogio[e], Sandro Sironi[f], Mariano Scaglione[a], Fred T. Lee Jr.[d]

[a] Department of Imaging, Interventional Ultrasound Unit, Pineta Grande Hospital, Castel Volturno, Italy
[b] Department of Diagnostic Radiology, Valduce Hospital, Como, Italy
[c] Department of Internal Medicine, School of Medicine, 2nd University of Napoli, Napoli, Italy
[d] Department of Radiology and Department of Biomedical Engineering, University of Wisconsin School of Medicine and Public Health, Medison, United States
[e] 2nd Surgery Department, Hepato-bilio-pancreatic and digestive Surgery Unit, San Paolo Hospital, Milano, Italy
[f] Department of Diagnostic Radiology, School of Medicine, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy

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ABSTRACT

Objectives: Direct puncture of subcapsular hepatocellular carcinoma (HCC) for tumor ablation has been considered high risk due to a perceived increased incidence of hemorrhage or tumor seeding. The purpose of this retrospective multicenter study was to identify the rate of tumor seeding, hemorrhage and local tumor progression (LTP) associated with direct puncture radiofrequency (RF) and microwave (MW) ablation of subcapsular HCC.
Methods: A multicenter, retrospective review of direct-puncture RF and MW performed on subcapsular HCC was conducted. Complications and local tumor progression were documented. Data was analyzed using Kaplan–Meier and log-rank tests.
Results: The study group consisted of 60 cirrhotic patients (M/F = 43/17; mean age 69.6 years) with 67 subcapsular HCC (mean diameter 2.3 cm ± 1.0 cm) that were directly punctured for RF ($n = 40$) or MW ($n = 27$) under ultrasound (US) guidance. The mean follow-up period was 30.8 months. There were no hemorrhagic complications. The overall LTP rate was 13.4%. There was one case of tumor tract seeding in a patient who had undergone a percutaneous biopsy two weeks prior to RF.
Conclusions: Thermal ablation of HCC by direct puncture appears safe and effective. There were no cases of intraperitoneal hemorrhage, and tumor seeding was seen in a single case in which a preceding percutaneous biopsy had been performed.

1. Introduction

Thermal ablation therapies such as radiofrequency (RF) and microwave (MW) ablation are playing an increasingly important role in the management of hepatocellular carcinoma (HCC) [1]. Ablation is now widely accepted as first-line therapy for very early and early HCC due to a lower complication profile and an overall survival equivalent to surgery in several randomized controlled trials [2,3].

Historically, percutaneous treatment of HCC in certain locations (i.e., nodules located in contiguity with Glisson's capsule, exophytic tumors, or those in close proximity to critical vulnerable structures) has been considered high-risk due to a greater potential for incomplete ablation, tumor seeding, hemorrhage, and damage to adjacent organs [4–6]. A subcapsular location has therefore been considered a relative contraindication to ablation.

Some studies have demonstrated that treatment of subcapsular tumors using a needle path traversing normal hepatic parenchyma combined with tract cautery is associated with a low rate of hemorrhagic complications and tumor seeding and local tumor progression (LTP) rates similar to ablation of more central tumors

* Corresponding author at: Interventional Ultrasound Unit, Pineta Grande Hospital, SS Domitiana, Km 30,00, Castel Volturno (CE), Italy.
E-mail addresses: giampierofrancica@gmail.com, giampierofrancica@libero.it (G. Francica).
[1] Present address: Casa di Cura IGEA, Milano, Italy.

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[7–11]. The use of artificial ascites does not appear to increase the risk of hemorrhage or tumor seeding in these patients [8,11].

However, treating exophytic and subcapsular tumors with an approach that includes traversing normal hepatic parenchyma is not always possible due to tumor position and the available angles of entry. The purpose of this study was to evaluate our results with direct puncture of subcapsular HCC treated with both radiofrequency and microwave ablation at multiple centers, with specific attention to the rates of hemorrhage, tumor seeding and LTP.

2. Materials and methods

2.1. Patients

This multicenter retrospective study was approved by the institutional review boards of all participating centers. All subcapsular (defined as within 5 mm of liver capsule) or exophytic HCC that underwent ablation between January 2000 and August 2013 were reviewed. Inclusion criteria were the presence of at least one subcapsular HCC nodule up to 4 cm that had been directly punctured because of a lack of other feasible approaches and compensated cirrhosis. Sixty patients with a total of 67 HCC nodules met the inclusion criteria (M/F = 43/17; mean age 69.6 years). These nodules represented 2.6% of 2380 HCC tumors treated by percutaneous ablation at the partecipating centers over this time period.

Diagnosis of HCC was based on American Association for the Study of Liver Diseases (AASLD), European Association for the Sudy of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) imaging guidelines, and in only two cases was biopsy deemed necessary [12–14]. All patients had absence of vascular invasion or extrahepatic spread at the time of pre-treatment imaging.

2.2. Thermal ablation techniques

Percutaneous RF or MW procedures were performed by one of the physicians (G.F., M.F. M., I. D., F.L., S.S.) at the involved centers with experience ranging from 1–20 years in ultrasound-guided interventional diagnostic and therapeutic procedures.

All procedures were performed under real-time US guidance with 2.5–6 MHz transducers (Aplio SVG, Toshiba, Japan; H21Hitachi, Japan; alpha 10-Aloka, Tokyo, Japan; Sequoia, Siemens, USA; IU-22 Philips Healthcare, USA; Logiq 9, GE Healthcare, USA). All procedures were carried out in the operating room with the patients under either general anesthesia with endotracheal intubation or conscious sedation according to local policy.

Hydrodissection was used in 13 patients with the purpose of shielding the body wall from unintended thermal damage. The hydrodissection technique consisted of placement of an 18 gauge spinal needle into the peritoneal space under real-time US guidance, followed by the injection of approximately 1000 ml of 5% dextrose-in-water or normal saline.

2.3. Ablation equipment

RF ablation of 40 HCC was performed using one of two straight internally cooled electrodes (E Series-Covidien IIC—MA, USA; RFA-HS-AMICA, Hospital Service, Aprilia, Italy). The algorithm of energy deposition followed the manufacturers' recommended protocol for their device. More than one insertion was planned if nodule size exceeded 3.0 cm. The remaining 27 tumors were treated using one of two 2.45 GHz MW systems at powers between 40 and 140 W using 14–17 gauge internally cooled antennas (HS Amica, Hospital Service, Aprilia, Italy; Certus 140, NeuWave Medical, Madison WI, USA). The power, number of antennas, number of insertions and total treatment time varied according to the size of the tumor and the response to treatment based on real-time US imaging. In all cases, the goal of treatment was complete ablation of the targeted tumor and a 5–10 mm margin.

In all cases a direct puncture of the tumor was performed without passing through a cuff of normal liver parenchyma (Fig. 1), and the entire needle path was cauterized upon completion of the ablation with manufacturer recommended parameters. The presence of residual viable tumor was evaluated between 5 and 10 min from the end of the procedure using either contrast enhanced US (SonoVue, Bracco, Milan, Italy) or contrast enhanced CT (Omnipaque 300, Lightspeed Xtra, GE Healthcare, Waukesha, WI). If residual enhancing areas were detected, immediate re-treatment was performed.

Table 1
Main demographic and clinical characteristics of the patients studied.

No. Patients	60
M/F	43/17
No. nodules	67
Mean age (SD) years	69.7 (8.9)
Mean nodule size (SD) mm	2.3 (1.0)
No exophytic nodules 10–50%/>50%	14/5
HCV+/HBV+/alcohol/other	43/7/6/4
Child's class A/B	55/5
Mean value of serum AFP (SD) ng/ml	116.5 (229.3)

Abbreviations: HVC = hepatitis C virus.
HBV = hepatitis B virus.
AFP = alpha-fetoprotein.

2.4. Complications

The type and number of complications were recorded and classified according to Society of Interventional Radiology (SIR) guidelines [15]. Patient medical records and follow up CT and MRI studies were examined for evidence of peritoneal hemorrhage and tumor seeding. Follow-up protocol included clinical assessment, measurements of liver function and alpha-fetoprotein levels, and US examination every 3 months and abdominal CT or MRI exam once or twice in a year according to local policy. Local tumor progression (LTP) was defined as evidence of residual, enhancing untreated tumor, the development of new enhancing nodules on the periphery of the ablation zone during follow-up CT or MRI, and interval growth of the ablation zone after the initial post-procedure imaging session.

2.5. Statistics

Means, standard deviations, ranges, and frequencies were used as descriptive statistics for patient baseline characteristics. The cumulative rates of LTP during the follow-up period were estimated using the method of Kaplan–Meier and reported with 95% confidence interval. All statistical analyses were performed using NCSS 2007 Statistical Software (http://www.ncss.com/).

3. Results

3.1. Clinical characteristics

Table 1 summarizes the main demographic and clinical characteristics of the study group. The mean tumor size (s.d.) at diagnosis was 2.3 cm (1.0 cm). Nodules with an exophytic component comprised 25.3% (17/67) of all tumors in the study population.

3.2. Tumor control

Patients were followed for a mean of 30.8 months post-ablation (range 1–162 months). Local tumor progression was observed in 9

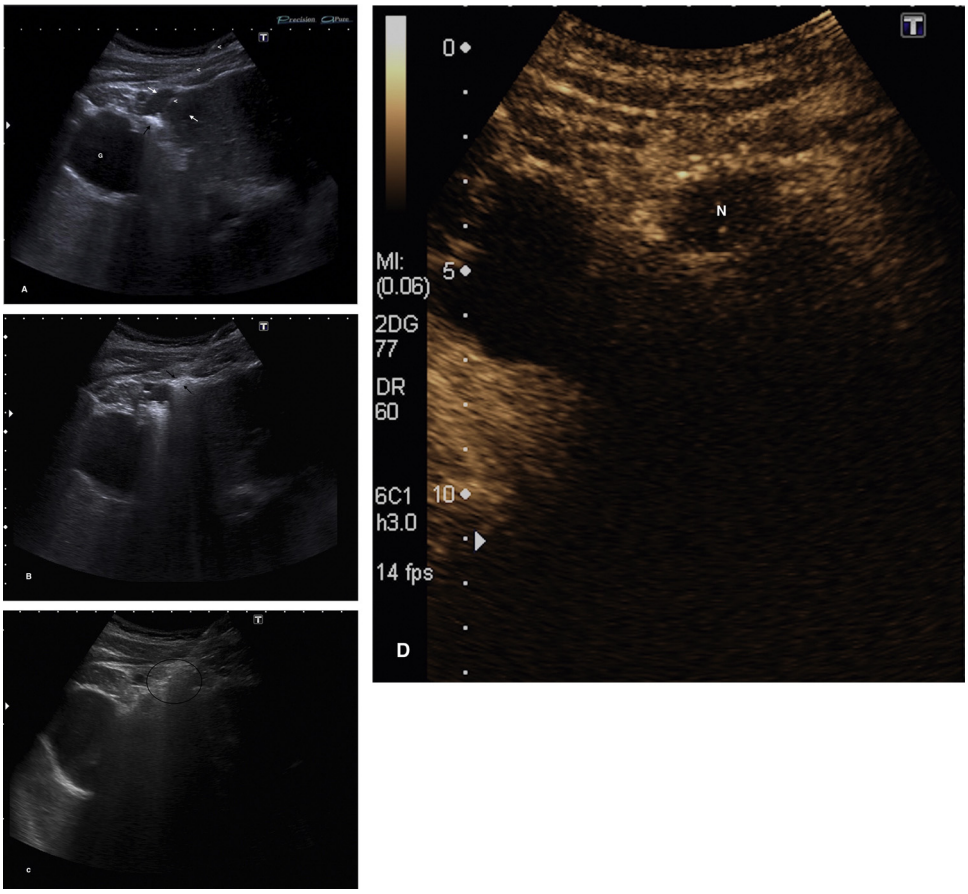

Fig. 1. Direct—puncture thermal ablation technique in a 25 mm subcapsular HCC nodule: (A) A cool-tip RF needle (arrowheads) trespasses the target nodule (between white arrows). Ablation starts at the neddle tip (black arrow). (*G* = Gallbladder). (B) After 1 min ablation starts at the proximal part of the exposed tip just at the Glisson's capsule (black arrows). (C) Ablation ends after 12 min: the target nodule is covered by hyperechogenicity due to vaporization gas (encircled area). (D) Contrast-enhanced Ultrasound 5 min after completion of ablation: the treated nodule (N) appears entirely avascular.

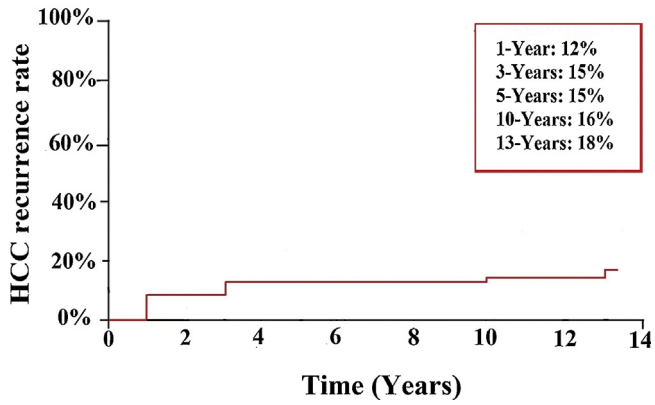

Fig. 2. Rate of local tumor progression in treated HCC tumors.

treated nodules (13.4%). Four of these cases were successfully re-treated with RF, and one was treated with chemoembolization. The cumulative rate of LTP was 12%, 15%, and 16% at 3, 5, and 10 years, respectively (Fig. 2).

Currently, 46 patients are alive and 14 are deceased (2 from non-HCC related causes and 9 from tumor progression and/or liver failure). Eight of the patients had undergone liver transplantation during the follow-up period.

3.3. Complications

No hemorrhagic complications were recorded for any patients in this series. No procedure related deaths or major complications were encountered. Post-procedure pleural effusions were observed in 5 patients (8.3%) but were asymptomatic and did not require further intervention.

3.4. Tumor seeding

One case of tumor seeding along the needle tract in the subcutaneous tissues (1.5%) was detected six years after treatment. The implant was located at the puncture site and was successfully removed at surgery. The patient remains alive without signs of recurrence 13 years following ablation (Fig. 3). Peritoneal neoplastic dissemination was not seen in any patient. There were no cases of seeding or symptomatic intraperitoneal bleeding in any of the hydrodissection cases.

4. Discussion

Treatment of subcapsular HCC has historically been approached with caution due to the theoretical risk of seeding along the needle tract or peritoneal cavity, uncontrolled hemorrhage, and an increased risk of local tumor progression [4–7,16,17]. In the past, these reports have been used as an argument against offering percutaneous ablation to patients with subcapsular tumors [11]. More recently, treatment of subcapsular HCC has been consid-

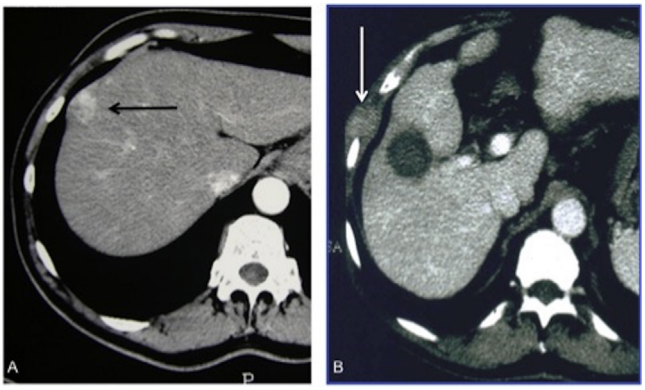

Fig. 3. 63 year old male with a 3.1 cm subcapsular HCC. (A) Pre-RF CT (hepatic arterial phase) demonstrates a hyper-enhancing HCC in segment 8. The tumor underwent percutaneous biopsy and subsequent RF ablation using a direct puncture. (B) Subcutaneous tumor seeding at puncture site six years post ablation. The seeding is located in both the biopsy needle and RF ablation antenna track. The seed was surgically excised, and the patient survived 7 years after surgery.

ered safe, but only when approached with an indirect puncture or using a "no touch wedge" technique [10,18]. In contrast, the results of this study suggest that directly puncturing subcapsular tumors when necessary is associated with a low rate of hemorrhage and tumor seeding. There were no cases of peritoneal seeding or intraperitoneal hemorrhage in our study and only a single case of subcutaneous seeding.

The local tumor progression rates for subcapsular tumors in this study were similar to prior large RF and MW series treating tumors in all anatomic locations [19–21]. Our single seeding case was in a patient who had undergone percutaneous biopsy two weeks prior to ablation. The seeding became apparent six years post ablation, and after surgical removal the patient remains alive without evidence of disease 13 years after ablation.

While the rate of seeding in this study is higher on a percentile basis (1.5%) in relation to the largest studies (<1%), this is most likely an artifact due to the small sample size. It is worth noting that in a recent large-scale study, the only risk factor for tumor seeding was concomitant biopsy [22]. Therefore, it is plausible that our single seeding event was not due to ablation, but rather the preceding biopsy.

Recent data suggests that the high seed rates seen in earlier studies were most likely due to prior biopsy or ablations performed without tract cautery [9,23]. Based on the seed and hemorrhage rates of the largest ablation and biopsy studies, ablation now appears to be safer than biopsy—likely due to the ability to cauterize the track with most modern ablation devices [10,24].

As more centers have gained experience with thermal ablation techniques, successful treatment of subcapsular tumors has become more common. However, most authors are careful to state that subcapsular tumors were punctured traversing a cuff of normal liver, biopsy was avoided, and/or post procedure track cautery was performed [7–9,11]. Another method that is likely to decrease or eliminate the risk of tumor seeding is to create a wedge shaped ablation by consecutively (single probe system) or simultaneously (multiple probe system) puncturing and ablating on each side of the tumor at an oblique angle, avoiding tumoral puncture, and creating a conglomerate ablation zone which both encompasses and undermines the tumor [18]. This technique has been referred to as a 'thermal wedge'. To date, there has been no comparison of direct puncture vs. thermal wedge techniques.

The rate of local tumor progression in this study (13.4%) is well within the range of LTP reported for both RF and MW ablation [20,25–28]. Thus, the direct puncture technique did not appear to compromise adequate tumor treatment.

The main limitations of this study relate to the retrospective nature of the data that was obtained over several years from three different centers with different radiofrequency and microwave systems. As the overall risk of seeding and hemorrhagic complications is low, pooling of data from the various centers was necessary to gather a sufficient number of cases for analysis. The use of both RF and MW ablation technology reflects the inevitable advances in ablation devices over the long time period of the study. Since the mechanism of cell death with both RF and MW is thermal, and a similar puncture of all tumors was performed with both technologies, any differences in the mechanism of tissue heating are unlikely to alter the conclusions of this study [29]. The low seeding rate, lack of peritoneal bleeding, and absence of significant complications across different ablation systems, centers, and operators appear to strengthen the generalizable nature of the study results. Another limitation of this study is the use of artificial ascites in a subset of patients to decrease post-procedure pain due to body wall burns, improve the ultrasound window to the liver, and decrease the risk of non-target thermal damage [30]. The number of cases with artificial ascites in this study is too low to draw definitive conclusions, but our results suggest that the risk when directly puncturing tumors in the presence of fluid is not high.

In summary, direct puncture and ablation of capsular and subcapsular tumors was associated with a low seed rate, no cases of peritoneal seeding or intraperitoneal hemorrhage, and local treatment effectiveness consistent with historical controls. The only patient with tumor seeding in this study had a percutaneous biopsy, a known risk factor for seeding—performed two weeks prior to the ablation.

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