Radiofrequency Ablation for Intrahepatic Cholangiocarcinoma: Retrospective Analysis of a Single Centre Experience

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Abstract. *Purpose: To evaluate the usefulness and safety of radiofrequency ablation for primary and recurrent intrahepatic cholangiocarcinoma (ICC) in our single centre experience. Materials and Methods: Ten patients with ICC refusing or not eligible for surgery underwent radiofrequency ablation for their tumor. The ICC was primary in 9 cases and recurrent, after 2 previous resections, in 1 patient. Radiofrequency ablation was performed percutaneously under ultrasound guidance using a 15G perfused electrode. Technical success of the procedure was assessed by contrast-enhanced ultrasound (CEUS). Technical effectiveness was evaluated by CEUS and contrast enhanced CT 1 month after the last course of a defined ablation protocol. Follow-up contrast enhanced CT or MRI were performed every 3-6 months. Results: RFA was always technically successful and effective for ICC lesions ≤3.4 cm and ineffective for lesion ≥4 cm. After a median follow-up of 19.5 months (range 9-64 months), 8 patients were still alive while 2 had died due to tumor progression. The 1-, 3- and 5-year overall survival rate of all patients with ICC of our series were 100%, 83.3% and 83.3%. No major complication was observed. Conclusion: Radiofrequency ablation seems to be a safe and effective option for small (≤3.4 cm) ICC nodules. In addition it may be considered as a palliative treatment for larger tumors.*

Intrahepatic cholangiocarcinoma (ICC) is a malignant epithelial tumor arising from the small intrahepatic bile ducts. Incidence and mortality of this relatively rare tumor, which accounts for about 10%-20 of all primary liver cancer cases and 5-10% of all cholangiocarcinoma, are increasing worldwide for still unclear reasons (1-3). Diagnosis of ICC may be difficult because, unlike extrahepatic lesions typically presented with signs of biliary obstruction, symptoms of intrahepatic tumors are usually non specific and insidious. For this reason, most cases of ICC are already advanced when finally diagnosed and consequently unresectable. The median survival time for patients with advanced unresectable lesions is dismal, being reported as low as 3 months (4). After complete surgical resection, which is regarded as the only curative treatment, the survival rate is about 30% at 5 years (5, 6). Unfortunately, many patients are not eligible for surgery at the time of diagnosis and in some cases negative resection margins are not achievable because of tumor extension, thereby the overall 5-year survival rate is below 5% (1, 7, 8). The role of orthotopic liver transplantation (OLT) for ICC is still debated, especially in patients without underlying liver diseases. High recurrence rates following transplantation have been reported, and the promising results obtained with neoadjuvant chemoradiation therapy preceding OLT for hilar cholangiocarcinoma have not yet been confirmed for intrahepatic lesions (9, 10). Currently, chemotherapy has no role in adjuvant treatment, neither has it been shown to significantly increase long-term survival when used for palliative purposes in unresectable cases (11). External-beam radiotherapy seems to improve the prognosis of patients with resected and unresectable ICC; nevertheless, these results are derived from retrospective studies and need further evaluation (12, 13). Effectiveness of transarterial therapies, and in particular transcatheter arterial chemoembolization (TACE), is limited by the poor vascularity of ICC, as opposed to hepatocellular carcinoma (HCC) (14).

Over the last 15 years, radiofrequency ablation (RFA) has been increasingly used for treating HCC and liver metastasis, mainly from colorectal cancer (15). Nowadays, RFA is considered so safe and effective as to be regarded, by some authors, as the treatment of choice for patients with a single

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Table I. *Characteristics of the study population.*

Patients				Tumors						
ID	Gender	Age (years)	Comorbities	Type	N. of nodules	Location (segment)	Size (cm)	Conventional US pattern	Contrast-enhanced imaging pattern	Cause of unresectability
1	M	59	None	Recurrent	3 metachronous	VII IV/VIII V/VIII	2.4 3.4 4	Mixed echogenicity and well defined in all cases	Heterogeneous hyperenhancement in all cases	Patient refusal after two previous resections
2	F	55	Obesity	Primary	1	IV	5.5	Mixed echogenicity and infiltrating	Rim-like enhancement	Patient refusal
3	F	75	None	Primary	1	IV	4.5	Mixed echogenicty and infiltrating	Rim-like enhacement	Patient refusal
4	M	71	HCV-related cirrhosis (Child A)	Primary	1	VI	2.5	Hypoechoic and well defined	Heterogeneous hyperenhancement	Patient refusal
5	F	69	None	Primary	1	III	2.9	Hyperechoic and well defined	Rim-like enhancement	Patient refusal
6	F	72	None	Primary	1	IV	3	Mixed echogenicity and well defined	Heterogeneous hyperenhancement	Patient refusal
7	M	69	HCV-related cirrhosis (Child A)	Primary	1	VIII	2.7	Hypoechoic and well defined	Heterogeneous hyperenhancement	Patient refusal
8	F	69	None	Primary	1	VI-VII-VIII	7	Mixed echogenicity and infiltrating	Heterogeneous hyperenhancement	Not eligible (tumor extension)
9	M	72	HBV-related cirrhosis (Child A)	Primary	1	II-III	3.1	Hypoechoic and well defined	Rim-like enhacement	Patient refusal
10	M	73	HCV-related cirrhosis (Child A)	Primary	1	V	3.2	Hypoechoic and well defined	Heterogeneous hyperenhancement	Patient refusal

HCV: Hepatitis C virus; HBV: hepatitis B virus; F: female; M: male; US: ultrasound.

HCC nodule ≤2.0 cm, even when surgical resection is possible (16, 17). However, its role in patients with ICC has been, so far, evaluated in only few case reports and small retrospective series. Therefore, in this study we report our single-centre experience with the use of percutaneous RFA to treat primary or recurrent ICC with the aim of increasing the body of scientific knowledge on this subject.

Patients and methods

Patients. After Institutional Review Board approval, we retrospectively reviewed the medical records of 18 consecutive cases of histologically proven primary ICC identified among 4687 patients referred to our institution for investigation of a focal liver lesion between January 2003 and October 2010. Biopsy was performed in all cases using 18G Menghini modified needles. RFA was proposed to patients not eligible for surgery or to those refusing it. Of the 18 patients: 2 were lost at follow-up after diagnosis; 5 were referred to surgery; 2 were not eligible for surgery and refused RFA; 1 was not eligible for surgery and accepted RFA; and 8 refused surgery but accepted to undergo RFA. We included in the study group all nine patients who underwent RFA for a primary ICC and one patient, from those initially referred to surgery, who developed a recurrent ICC after two resections; this patient refused a third resection and was therefore treated by RFA. Written informed consent was obtained from all patients.

The study population was composed of 5 men and 5 women with a median age of 70 years (range 55-75 years). Six patients developed ICC in the setting of a healthy liver, while four patients had underlying liver cirrhosis due to chronic hepatitis C virus (HCV) hepatitis in three cases and (HBV) hepatitis in one case. All patients with cirrhosis had a Child A score at diagnosis. At inclusion, all patients had a single ICC nodule. The nodule size ranged from 2.4 to 7 cm (median 3 cm). On conventional ultrasound examination, nodules presented a mixed echogenicity in five cases, were hypoechoic in four cases and hyperechoic in one. The most common pattern was that of a well-defined mass. On contrast-enhanced ultrasound (CEUS), which was performed in all cases, 6 out of 10 lesions were heterogeneously hyperenhanced during the arterial phase and 4 exhibited a rim-like enhancement; all tumors hypoenhanced during portal and delayed phases. On contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), performed for staging purposes, none of patients had lymph node or extrahepatic involvement at the time of diagnosis. The same enhancement pattern shown on CEUS was confirmed on contrast enhanced CT or MRI in all cases. None of the patients had ascites and none of the nodules had a superficial location nor was close to the gall bladder. Characteristics of the study population are reported in Table I.

Table II. *Results of radiofrequency ablation fro intrahepatic cholangiocarcinoma.*

Patient no.	Tumors			RFA			Follow-up		
	No. of nodules	Location (segment)	Size (cm)	No. of sessions	Technical effectiveness	Tumor recurrence	LTP-free survival time (months)	Overall survival time (months)	Status
1	3 Metachronous	VII,	2.4	1	Complete	LTP	16		
		IV/VIII,	3.4	2	Complete	No	-	64	Dead
		V/VIII	4	1	Partial	TF	-		
2	1	IV	5.5	2	Partial	TF	0	30	Alive
3	1	IV	4.5	2	Partial	TF	0	18	Dead
4	1	VI	2.5	1	Complete	No	36	36	Alive
5	1	III	2.9	1	Complete	No	35	35	Alive
6	1	IV	3	1	Complete	No	21	21	Alive
7	1	VIII	2.7	1	Complete	No	17	17	Alive
8	1	VI-VII-VIII	7	2	Partial	TF	0	9	Alive
9	1	II-III	3.1	1	Complete	No	12	12	Alive
10	1	V	3.2	1	Complete	No	10	10	Alive

LTP: Local tumor progression; TF: technical failure.

RFA procedure. RFA was performed percutaneously under ultrasound guidance and with the patient under general anesthesia. All procedures were performed by the same operator with 32 years experience in interventional ultrasound. A 375 kHz radiofrequency generator (Elektrotom 106 HiTT, Berchtold, Germany) and a 15 G perfused electrode with an exposed active tip 2.5 cm long were used, as already described elsewhere (18). The electrode was advanced into the targeted lesion to reach the deepest margin of the tumor in order to achieve a negative margin of approximately 1 cm. We planned to use a single insertion for tumors up to 3 cm and multiple insertions for larger tumors. Radiofrequency current was applied for 10-15 min and the extent of the thermal ablation area was monitored in realtime by ultrasound. Local tissue temperature and impedance were constantly monitored. Current generator was switched-off only after the electrode had been removed from the patient's body in order to heat the needle path and to avoid tumor cell seeding.

Follow-up. Results were reported according to the standards of the Society of Interventional Radiology (19). Technical success of the procedure (*i.e.*, tumor treated according to protocol and completely covered) was assessed immediately at the end of every session by CEUS. Technical effectiveness (*i.e.*, complete ablation of macroscopic tumor including a margin of 1 cm) was evaluated by CEUS and contrast-enhanced CT at one month from the last course of a defined ablation protocol. Complete ablation of the tumor was achieved when no enhancement was shown at one month imaging follow-up, whereas any kind of enhancement at this stage was indicative of partial ablation. Follow-up contrast-enhanced CT or MRI were performed every 3-6 months. Tumor recurrence more than one month after RFA was distinguished as 'local tumor' progression whenever any kind of enhancement was evident in the same location of the ablated tumor, and 'new tumor' whenever an enhancing area was discovered in a different location. Major complication was defined as any event leading to substantial morbidity or disability; all other complications, included postablation syndrome, were defined a s being minor (19).

Local tumor progression-free survival time and overall survival time were evaluated by Kaplan-Meier analysis. Local tumor progression-free survival time was defined as the interval in months between the date of the first RFA and the date when local tumor progression was discovered; overall survival time was defined as the interval in months between the date of the first RFA and the date of death or last follow-up for censored patients.

Results

Results are reported in Table II. The patient with recurrent ICC (patient no. 1) initially presented with a nodule 2.4 cm in diameter that was treated with a single session of RFA with complete ablation. After 16 months, another RFA was needed because of local tumor progression and complete ablation was achieved again. As a new lesion 3.4 cm in size was found 19 months after the second RFA, the patient underwent a third RFA in two sessions performed two weeks apart that resulted in complete ablation. After 14 months, a new lesion 4 cm in size was detected, thereby the patient underwent a fourth RFA in a single session, which was technically unsuccessful. Overall, this patient underwent five sessions of RFA with a mean of 1.2 insertions per session (range 1-2). In the patient with the largest tumor (patient no. 8, tumor diameter 7 cm) we performed two sessions of RFA, with two needle insertions in the first session and three in the second session, achieving extensive but incomplete ablation of the lesion. In a patient with a primary ICC of 5.5 cm in diameter (patient no. 2) technical success and effectiveness were not achieved despite two sessions being performed two weeks apart with three needle insertions in the first session and two in the second session. In another

case with a primary ICC of 4.5 cm in diameter (patient no. 3), RFA was technically successful in one session with three needle insertions but not technically effective. RFA was technically successful and effective in a single session, in all six patients with a primary ICC ≤3.2 cm (patients no. 4-7, 9 and 10) (Figure 1). Overall, in our series, RFA was always technically successful and effective for ICC lesions ≤3.4 cm and ineffective for lesions ≥4 cm.

No major complications occurred. A mild and self-limiting post-ablation syndrome was observed in three cases of primary ICC.

After a median 19.5 months' follow-up (range 9-64 months), 8 patients out of 10 were still alive while 2 had died due to tumor progression. The 1-, 3- and 5-year overall survival rate of all patients with ICC of our series were 100%, 83.3% and 83.3%. Considering only patients with primary ICC, 1- and 3-year overall survival rates were 100% and 80%. Regarding the two patients that died, in one case (patient no. 1) local tumor progression occurring 16 moths after the first ablation, was effectively ablated and death was due to new lesions; in the other case, complete ablation of the tumor was not achieved in the first RFA. Local tumor progression-free survival time and overall survival time curves of patients with primary ICC and of all patients are represented in Figures 2, 3 and 4.

Discussion

Around 30-50% of patients with ICC already have advanced disease at the time of diagnosis, and thus are not eligible for surgical resection, which is the only curative treatment (10). Moreover, the recurrence rate after surgical resection is as high as 47% even in cases of patients with a solitary tumor and no lymph node metastases (20).

Since Slakey first described the use of RFA for ICC in 2002, to our knowledge, fewer than 100 patients receiving this treatment have been reported in the literature (21). Although based on a small number of patients, our results are comparable to those reported by other studies and show that RFA appears to be able to destroy small-sized tumours more effectively than large-sized ones (22, 23). All ICC nodules of our series ≤3.4 cm receiving RFA were shown to have been completely ablated on contrast-enhanced CT one month after the procedure and remained necrotic for up to 36 months of follow-up. By contrast, in all three cases with tumors ≥4.5 cm (patients n 2, 3 and 8) it was not possible to achieve complete ablation. Similarly, Carrafiello *et al*. obtained complete necrosis of all four tumors of their series ≤4 cm but were unable to achieve the same result in the two patients with tumors ≥5 cm despite the association of transarterial embolization during RFA to increase the area of ablation (22). Kim *et al*., in the largest series reported so far to our knowledge, of primary ICC treated with RFA,

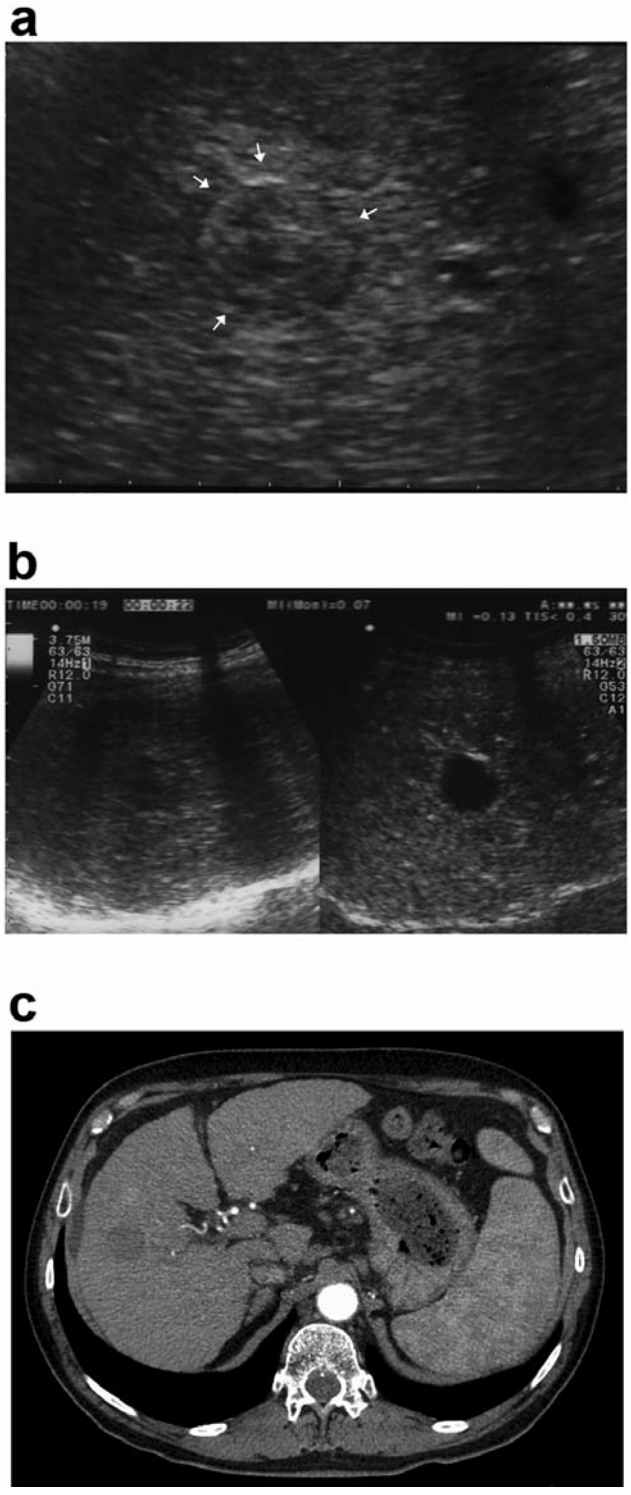

Figure 1. *A 71-year-old man with primary intrahepatic cholangiocarcinoma (patient no. 4). Conventional ultrasound shows a well-defined mass 2.5 cm in size in the VI segment (white arrows) (a). One month after a single session of RFA, the absence of enhancement during the arterial phase of contrast-enhanced ultrasound indicates complete ablation (b). Complete ablation is also confirmed in the arterial phase of contrast enhanced computed tomography (c).*

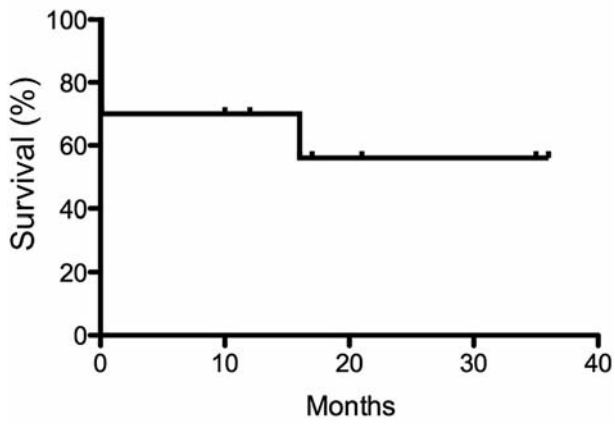

Figure 2. *Local tumor progression-free survival time of all patients.*

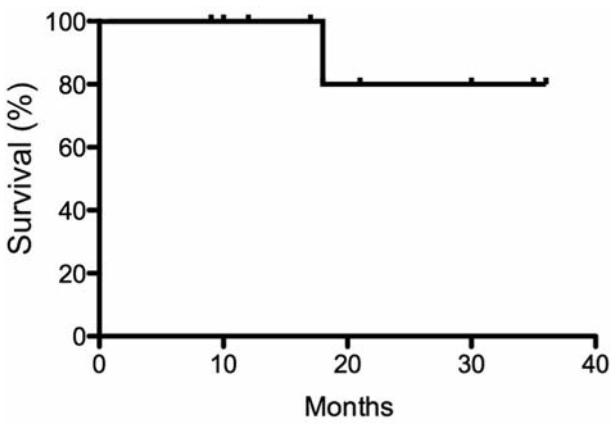

Figure 3. *Overall survival time of patients with primary intrahepatic cholangiocarcinoma.*

achieved technical effectiveness in all 11 patients with tumours <5 cm but in none of the patients with larger lesions (23). These findings are inadequate as conclusive evidence but give support to the idea that, as for HCC, in cases of small ICC, percutaneous RFA should have a higher chance of success.

Considering the only patient of our series with recurrent ICC after surgery (patient no. 1), several sessions of RFA for the small-size recurrences that developed in a metachronous fashion allowed his survival to be prolonged for over 5 years from the first ablation. At the opposite end of the spectrum, is a patient with an ICC nodule of 5.5 cm in diameter; despite incomplete ablation due to tumor size, the patient survived 30 months following RFA. Although these are single cases, of anecdotic value, our results suggest that RFA may be considered as an effective palliative option for ICC as it seems to be able to control tumors with a dismal prognosis for a relatively long time.

An increasing number of ICC develops in the settings of a cirrhotic liver (3). Four of our patients had underlying liver cirrhosis with good functional reserve: in all cases complete necrosis was achieved without complications and the patients are still alive. Kim *et al*. also included patients with liver cirrhosis in their series, although their nine patients all had poor hepatic reserve (23). If we consider both case series, we can speculate that RFA is safe and can also prolong survival in the case of ICC patients with underlying liver cirrhosis, as long as the hepatic functional reserve is still good, and that its effectiveness is markedly reduced if the hepatic reserve is poor.

The 1-, 3- and 5-year survival rates reported by Kim *et al*. are far lower than our rates. However this difference is probably due to the fact that these authors selected all patients with unresectable ICC and poor hepatic reserve for their study, whereas all patients in our study were eligible for surgery and had good hepatic reserve (23).

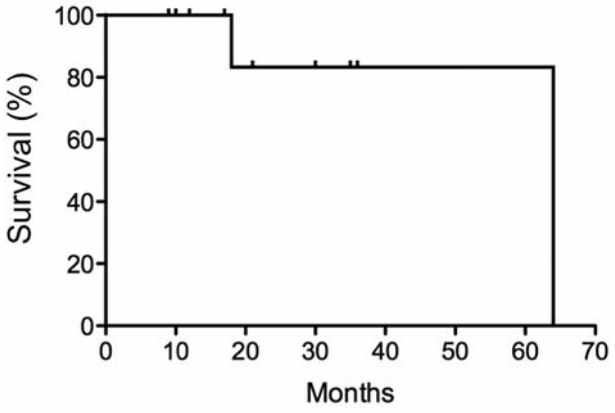

Figure 4. *Overall survival time of all patients.*

As far as complications are concerned, no major event was recorded in our series. Minor complications (post-ablation syndrome) were observed in three cases and all spontaneously recovered. Caraffiello *et al*. shared this experience, whereas Kim *et al*. reported one liver abscess (22, 23).

As for other reports on the same subject, the present study has two main limitations. The first is the lack of comparison with a control group and the second is the small number of patients. Despite these limits, our results add support to the growing body of literature that suggests a potential role of RFA for the treatment of ICC. Randomized controlled trials on a larger numbers of patients are needed to confirm these preliminary results.

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