



Effectiveness and safety in radiofrequency ablation of pulmonary metastases from HCC: a five years study

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Abstract

Hepatocellular carcinoma (HCC) is a frequent tumor that may be treated with radiofrequency thermal ablation (RFA). RFA has been used with success also in treatment of pulmonary metastases from a wide range of primitive tumors, especially colorectal. Previous studies have shown that RFA can be used in treating HCC pulmonary metastases. Purpose of our study was a retrospective evaluation of overall survival and complication rates of percutaneous CT-guided radiofrequency ablation of pulmonary metastases from hepatocellular carcinoma (HCC). Data were collected from 40 CT-guided ablation sessions performed on 42 lesions in 26 patients (16 M and 10 F; mean age 62.5 years) with pulmonary metastases from HCC (size range 0.3–4 cm, mean diameter 1.4 ± 0.98 cm) from February 2012 to December 2017. All patients, as in advanced stage of illness (stage C), were treated according to Barcelona Clinic Liver Cancer (BCLC) criteria, with Sorafenib. They had no active HCC foci in the liver and no more than three metastases in the lung. Patients did not discontinue medical therapy with Sorafenib and pulmonary relapses were treated up to three times. In two patients two lesions were treated during the same procedure. Each lesion was ablated under CT guidance. Follow-up contrast-enhanced CT at 1, 3, 6, 12-month and every 6 months after treatment were reviewed. A total of 42 metastatic lung lesions from HCC in 26 patients (57% male, 43% female) were treated with CT-guided radiofrequency thermal ablation procedures. Immediate radiofrequency ablation-related complications (subtle pneumothorax) were observed in 9 of 40 procedures (22.5%). Only one patient developed a pneumothorax requiring drainage tube insertion (2.5%). No other major complications occurred. Moreover, no significant worsening of pulmonary function was observed. In all patients the overall survival rates were 88.5% at 1 year, 69.8% at 3 years and 26.2% at 5 years. Our retrospective assessment confirmed that percutaneous CT-guided radiofrequency thermal ablation in 23 patients with pulmonary metastases from HCC represents an effective and safe alternative treatment option in patients not considerable as potential candidates to surgery.

Keywords Hepatocellular carcinoma · Lung · Metastases · RFA · Radiofrequency · Ablation · Survival · Interventional radiology

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and the third leading cause of cancer-related mortality worldwide [1–3], with an average survival rate lower than six months if untreated and a 5-year survival of only 5–9% since time of diagnosis [4–6].

Untreated advanced HCC has a poor prognosis, with a median survival of 4–8 months, and chemotherapy alone provides a modest improvement in survival, with an overall survival nearby 6–11 months [7].

Hepatectomy and liver transplantation still represent the essential radical treatments for HCC, though that only

10–20% of patients actually have the chance to receive them [8–10].

Although 66% of patients with extrahepatic metastasis die from hepatic causes, 22% of these die because of the progression of extrahepatic metastasis [11, 12].

The most common sites for HCC metastases are lungs (55%) [13, 14], through an hematogenous dissemination to the pulmonary capillary network [15]. HCC patients will develop metastatic pulmonary disease in 39% of cases [13].

Patients with pulmonary metastases may also potentially benefit from surgical therapy, though the prohibitive surgical risk due to either a poor pulmonary function or severe medical comorbidities. In addition, current usual practice for surgical metastasectomy of lung metastases is limited to a specific subset of patients, hence the most of them cannot undergo resection [14]. As an alternative, these patients could be treated with minimally invasive ablative therapies, like radiofrequency ablation (RFA), microwave or cryoablation, which preserve unaffected the lung parenchyma.

Radiofrequency consists in a thermal energy delivered in the target tissue through a system which applies an alternating current supplied by an energy generator through a needle electrode. The alternating current generates ionic agitation, creating a temperature up to 95 °C and resulting in coagulative necrosis and tissue destruction at the top of the probe [15].

RFA has been extensively used in lung lesions treatment in patients not eligible for resection and is now widely accepted as a safe and effective therapy of pulmonary metastases from different primary tumors, based on clinical and radiological research [16, 17].

Aims of our study are to retrospectively evaluate overall survival and complication rates of RFA as a treatment of pulmonary metastases from HCC.

Materials and methods

Patients

This retrospective study was done with the approval of our Ethics Committee of AORN Ospedali dei Colli (No. 311/18) and in accordance with the 1976 Declaration of Helsinki and its later amendments. All patients provided written informed consent before each RFA procedure.

From February 2012 to December 2017 a total of 26 patients [16 M and 10 F; mean (\pm SD) age, 62.5 \pm 9.4 years; range 36–78 years) underwent pulmonary RFA associated to Sorafenib as first line treatment for lung HCC metastases (Table 1).

Data were collected from 40 CT-guided ablation sessions performed on 42 lesions in 26 patients with pulmonary metastases from HCC. None of them had a second

Table 1 Diameter of the 42 lesions

Pt. No	Age	Sex	Cirrhosis	Pulmonary Metastases (n.)
1	57	F	Yes	1
2	62	F	Yes	1
3	75	M	Yes	2
4	78	M	Yes	3
5	65	M	Yes	1
6	50	M	Yes	1
7	44	M	No	2
8	69	F	Yes	1
9	56	M	No	3
10	64	F	Yes	1
11	61	M	No	1
12	73	F	Yes	2
13	68	M	Yes	1
14	66	M	Yes	3
15	72	M	Yes	3
16	67	M	Yes	1
17	52	M	Yes	1
18	64	F	Yes	1
19	59	M	Yes	2
20	58	F	Yes	1
21	67	F	Yes	1
22	65	M	Yes	2
23	60	F	Yes	2
24	36	F	No	2
25	70	M	Yes	2
26	67	M	Yes	1

primary malignancy in addition to HCC. All patients were previously treated for primary liver HCC either with surgical resection, liver transplant, liver RFA, and they had no active HCC foci in the liver. All of them were in chemotherapy with Sorafenib, according to BCLC criteria. Sorafenib was not discontinued during RFA treatment. All patients with lung metastases were evaluated for RFA by a multidisciplinary team including diagnostic and interventional radiologist, gastroenterologist, medical oncologist and a thoracic surgeon. Specific inclusion criteria consisted of (i) age between 18 and 85 years; (ii) patients with lung metastases from HCC proved by elevation of serum α -fetoprotein (AFP) or biopsy; (iii) no active HCC foci in the liver; (iv) Child–Pugh score A; (v) evidence of up to three metastases per lung; (vi) lesions accessible by percutaneous route. Exclusion criteria were: (i) a diameter of metastases > 4 cm; (ii) more than three lesions per lung; (iii) lesions immediately adjacent to major pulmonary vessels or major bronchi; (iv) patients with Child–Pugh score B or C; (v) bleeding

disorders (international normalized ratio (INR) more than 1.5; platelet count less than $50 \times 10^9/L$) not responding to medical treatment, (vi) presence of pace-maker.

Before the procedure patients' previous medical history, chemistry and coagulation panels were analyzed; physical examination was compared with radiological imaging acquired by contrast-enhanced CT. The diagnosis of lung metastases from HCC was made with enhanced CT features and the elevation of serum AFP during patients' follow-up for HCC. Just two patients in 38 RFA sessions (5.2%) underwent percutaneous biopsy for cytological analysis before RFA procedure.

Treatment

All RFA procedures were performed percutaneously with CT guidance (Brilliance CT 16-slice Philips, Healthcare Philips Medical Systems, Best, The Netherlands) by one senior interventional radiologist (F.L., who has more than 10 years of experience with RFA of lung lesions). Scanning parameters were 120 kV, 100 mA; collimation: 1.5 mm. All patients were administered local anesthesia with Lydocaine and analgo-sedation, using Remifentanyl and Midazolam, with continuous monitoring of vital parameters (oxygen saturation, ECG, respiratory rate). After localization of the nodules, the skin entry site allowing the shortest and safest pathway, which avoided great blood vessels or major bronchi, bronco-vascular bundles, bullae and/or inter-lobar fissures was chosen. The successful central placement of the needle electrode into the center of the lesion was confirmed. Time of RFA procedures was calculated to obtain an ablation area large enough to cover the entire focus with ablative safety margins around the nodules of at least 0.5 cm.

In the 5 years period study we used three different devices: a multiple tines device, the Rita Starburst CL probe by using a 250 W generator Model 1500X (Rita Medical, Mountain View, CA, USA), which could use power-controlled mode and temp-controlled mode based on impedance; a single tip disposal, the Cool-Tip RF Ablation system by using a 200 W power source pulses energy delivery (Medtronic, Minneapolis, MN, USA); a single tip probe, AMICA, by using an automatic energy delivery mode generator 200 W max (HS, Italy). Dispersion pads were applied on patients' thighs.

After ablation the electrode was retracted with cauterization of the electrode path from the tumors to the subcutaneous tissues to prevent bleeding and tumor seeding. Diagnostic post-procedural imaging was performed immediately to document technical success and intraoperative complications.

Follow-up

The follow-up period was defined as the duration from the date of enrollment in the RFA procedure until death or the last visit. In our study, this period was considered from February 2012 to December 2017. Follow-up visits were scheduled at 1, 3, 6, 12-months and every 6 months after treatment. Each follow-up appointment included a physical examination, serum alpha-fetoprotein (AFP) assay, liver function tests and tumor recurrence monitoring by contrast-enhanced CT scan. The efficacy of RFA was assessed by the change in contrast enhancement and the size of the target tumors according to mRECIST criteria [16–18], considering as baseline the first post-treatment CT at 1-month, and normal a precocious enlargement of the tumor after the ablation, which may mimic a true neoplastic progression [19]. When enhanced CT scanning showed that abnormal enhancement could still be detected in lesions, tumor residue or local recurrence was considered.

All the lesions were independently assessed by two radiologists, each of them with more than 10 years of clinical and radiological experience.

Complications, such as pleural effusion, pneumothorax, pneumonia, abscess, bleeding or worsening of pulmonary function, were monitored and reported, whether present. The definition of minor and major complications was assigned according to the Society of Interventional Radiology Classification System for Complications by Outcome [17].

Statistical analysis

Overall survival (OS) was calculated by Kaplan Meier analysis.

Results

A total of 42 metastatic lung lesions from HCC in 26 patients were treated with CT-guided RFA procedures, with a size range 3–40 mm, mean [\pm SD] diameter, of 13.57 ± 8.44 mm (Table 2).

Data were collected from 40 CT-guided ablation sessions, and in two patients two lesions were treated during the same procedure (Fig. 1).

All patients had no active HCC foci in the liver, 1 lesion was present at the time of RFA treatment in 53.8% of cases, 2 lesions in 30.8%, 3 lesions in 15.4%. 8 of 26 patients (30.8%) had bilateral disease. Median length of stay for patients treated with RFA by the percutaneous approach was 2.5 days (range 1–5 days). Each lesion was ablated under CT guidance. Immediate radiofrequency ablation-related complications (subtle pneumothorax) were observed in 6 of 40 procedures (15%).

Table 2 Diameter of the 42 lesions

CT Ablation session (No.)	Largest metastasis diameter (mm)
1	8
2	9
3	8; 14 ^a
4	13
5	6
6	9
7	10
8	23
9	21
10	6
11	11
12	13
13	40
14	16
15	18
16	3
17	10
18	17
19	9
20	40
21	5
22	8
23	6
24	10; 5 ^a
25	22
26	28
27	7
28	9
29	13
30	17
31	5
32	15
33	9
34	14
35	6
36	26
37	8
38	17
39	22
40	14

^aIn two cases, two lesions were treated in the same procedure

Only one patient developed a pneumothorax requiring drainage tube insertion (2.5%). No other major complications (aseptic pleuritis, pneumonia, lung abscess, hemothorax, bleeding requiring blood transfusion, bronchopleural

fistula, tumor seeding) occurred. No significant worsening of pulmonary function was observed.

OS rates were 100% up to 6 months, 88.5% at 1 year, 74.5% at 18 months, 69.8% at 24, 30 and 36 months, 34.9% at 42, 48 and 54 months, 26.2% at 5 years. (Fig. 2).

Discussion

Thermal ablation therapies are commonly used in HCC treatment not amenable to surgical therapy [9, 10, 20–24]. Data from large case-series studies show excellent results in terms of OS and quality of life [20, 24]. Furthermore, such therapies have a minor economical and personal impact compared to surgical treatments, due to their mini-invasive character [25, 26]. Thermal ablation is also repeatable over time in case of either HCC recurrence or appearance of new lesions [27].

Local ablation therapies are also successfully used to treat metastatic lesions from various neoplasms [28]. These are especially performed on liver metastases [29], though there is a growing experience on ablative treatment of lung metastases with thermal ablation [28]. Most of current literature on the topic regards colorectal pulmonary metastases and findings are really encouraging [28]. In this scenario it looks reasonable to treat HCC metastasis with thermo-ablation.

At present, metastatic HCC patients are considered in an advanced phase and classified as class C in the BCLC flow-chart. According to BCLC flow-chart, metastatic HCC patients are treated with systemic therapy with Sorafenib [30, 31]. Prognosis is very poor in these patients, with a median survival of C3a patients (no portal invasion, extrahepatic extent, Child–Pugh A) of 5.2 months [32].

However, several patients experience side effects of Sorafenib [29], which reduces their compliance to the therapy.

With regard to a tumor board dedicated to HCC, we decided to associate Sorafenib therapy to RFA treatment in patients with good liver function (Child–Pugh A), a limited number and dimension of lesions, to better control the illness.

Our data are in good agreement with the few data in literature [11] and with our expectation of a prolonged life and a better quality of life, without relevant side effects.

We did not discontinue Sorafenib treatment to perform thermal ablation and, though some derangement in hemostasis could be expected [33], we did not observe any hemorrhagic event in any of our patients. We conducted the procedure in analgo-sedation and local anesthesia in free breathing. Our patients never required intubation. Recovery was always immediate as soon as the procedure ended. The

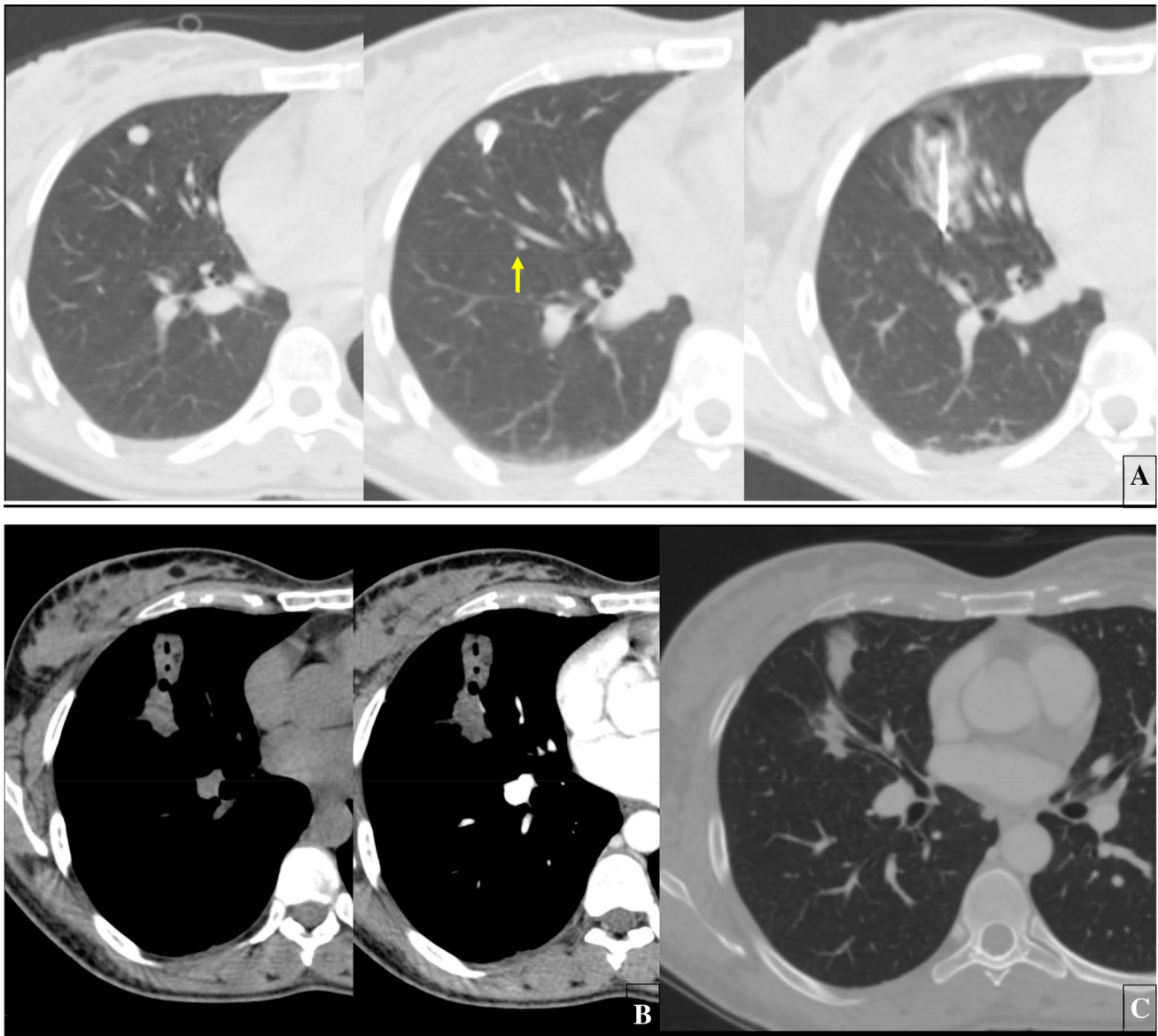


Fig. 1 In Fig. 2a, one of the two cases in which two lesions were treated in the same session. The second lesion is indicated by the yellow arrow. In Fig. 2a the 6 months later follow-up, with no contrast

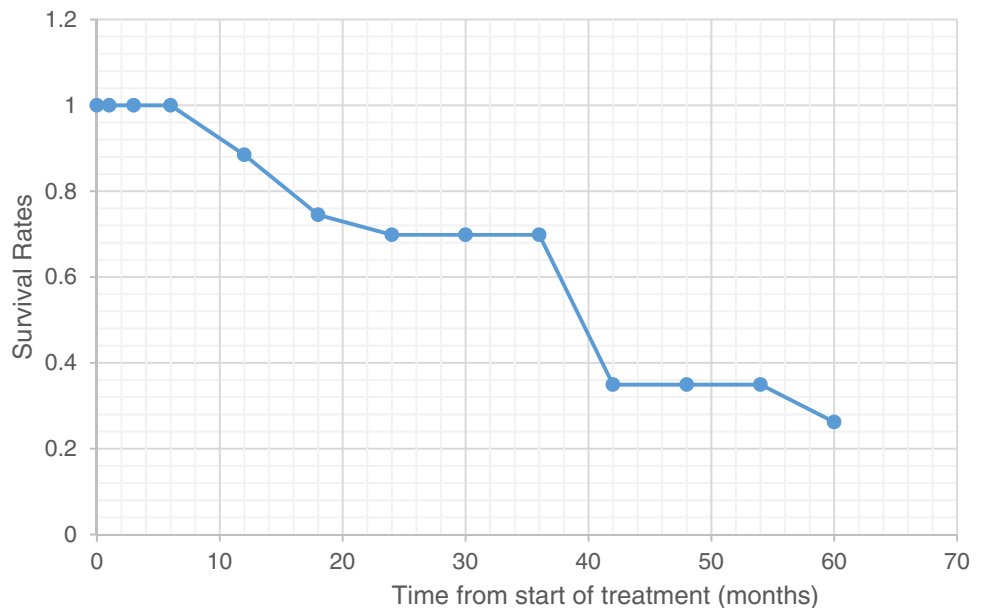
enhancement; in Fig. 2a, the one year later CT scan, with a fibrotic regression of the two metastases

only complication was pneumothorax, which was observed in 15% of cases, anyway we did not consider it significant. The duration of hospitalization of these patients was very short, with the longest stay of 5 days in just one patient, who experienced the large pneumothorax. We did not observe any other significant complication related to the procedure, such as hemorrhage, infections, seeding of lesions.

In conclusion, we consider RFA associated to Sorafenib a valid alternative to chemotherapy alone, prolonging OS and ameliorating quality of life in metastatic HCC patients without either relevant side effects or complications.

The main limitations of our study are the retrospective study design and the small sample size. A large prospective study with standard therapy would be necessary in order to validate RFA to treat pulmonary metastasis from HCC.

Fig. 2 Kaplan–Meier plot: Overall survival of 26 patients after RFA of pulmonary metastases from HCC



Compliance with ethical standards

Conflict of interest We declare that we have no conflicts of interest.

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