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Radiofrequency ablation of liver metastases from cancer of unknown primary site

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PURPOSE
This retrospective study was performed to review the efficacy of local radiofrequency ablation (RFA) in all the management of liver cancer of unknown primary site (CUP), and to identify possible prognostic features and complications that affect the efficacy of this treatment on survival.

MATERIALS AND METHODS
From April 2003 to December 2007, 22 patients (15 men, 7 women) with a total of 36 liver metastasis of CUP and poor response to prior systemic chemotherapy were treated with computed tomography-guided RFA. The median age of patients was 66 years. All patients (22/22) had 1-, 3-, and 6-month follow-up and 8/22 of them had a 12-month follow-up.

RESULTS
The overall median survival of all 22 patients was 10.9 months. Survival was better in patients with lesions 3 cm or smaller. No severe complications, including local seeding, were occured.

CONCLUSION
Our study revealed that RFA appears to be an effective, safe and relatively simple alternative procedure for the local ablation of these lesions. These results are more encouraging for lesions 3 cm or smaller, all of which were successfully treated, as proved by the imaging criteria and the statistical analysis. Further prospective trials are needed to determine whether RFA should be proposed for standard protocols.

Key words: • *neoplasms, unknown primary* • *liver* • *radiofrequency ablation*

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Metastatic cancer of unknown primary site (CUP) accounts for 3% of all malignant neoplasms and is therefore one of the 10 most frequent cancers diagnosed in humans (1). CUP refers to metastatic disease for which the site of origin cannot be identified at the time of diagnosis (1, 2), and the whole patients' control, including the percutaneous biopsy of the lesion, does not reveal signs of a potential primary tumor.

Extensive work-up with modern imaging technology, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), has resulted in some improvements in diagnosis, showing sometimes the primary and allowing a better definition of the extent of the disease. However, in almost 70% of CUP syndromes, the primary tumor remains unknown after autopsy investigation (1).

Many clinicopathological entities have been recognized, including metastatic CUP to lymph nodes, peritoneal cavity, lungs, bones, brain, and liver (1). Since liver metastasis was found to lead to a worse prognosis (3–5), the establishment of their effective treatment, is compulsive. Surgical resection is not always applicable or effective tool because of the number and location of lesions, and comorbid conditions (6, 7). This may lead oncologists to use other treatment modalities, including radiofrequency ablation (RFA) (6), systemic chemotherapy (8), or local lesion therapy (9).

The objective of this study was to evaluate the impact of RFA as local treatment in 22 patients with liver CUP showing poor response to chemotherapy, and to identify possible prognostic features and complications that affect the efficacy of this treatment on patients' survival.

Materials and methods

Twenty-two patients with CUP over four-year period were reviewed. This retrospective study was approved by the institutional review board. Thirty-six liver metastases of CUP in 22 patients (15 men, 7 women) treated with RFA. Their age ranged between 52 and 84 years (mean age 66 years). The final diagnosis of the metastatic nature of these lesions had been confirmed by percutaneous core needle biopsy (CNB). The biopsy had been performed percutaneously using an 18G/10 cm automated gun, under CT guidance. The histopathological result in all biopsies was metastatic cancer (13 from adenocarcinoma, 3 from squamous cell carcinoma, 2 from transitional cell carcinoma, and 4 from unidentified carcinoma); there was no histopathological diagnosis tumor of the primary tumor in any case (Table). The primary origin had not been detected even after the extensive work-up with specific clinical, laboratory, and imaging tests. In each case, the only known site of malignancy was the liver, as demonstrated by dual-phase contrast enhanced spiral CT. PET was not routinely used, as its value is still controversial in these cases (2).

All patients had been referred by their oncologists or liver surgeons to our department for RFA, since all of them had poor response to prior systemic chemotherapy, and not being considered candidates for surgical resection, because of technical difficulties (site and number of lesions) or clinical comorbidities [chronic renal failure (n = 2), chronic obstructive pulmonary disease (n = 3), or congestive heart failure (n = 5) respectively].

Ten patients presented with single hepatic metastasis, 10 patients with two lesions, and the remainder with three. Lesions ranged in diameter from 1.1 cm to 4.8 cm (mean diameter, 2.74 cm). Twenty-one of 36 lesions were located in the right lobe, and the remainders were located in the left. Four lesions (4/36) were exophytic, two were next to inferior vena cava (>3 mm in diameter) (2/36), and three next to gallbladder (>1 cm) (3/36). These 36 lesions were treated in 30 RFA sessions (we named session a single intervention episode that consisted of one or more ablations performed on one or more tumor (1) (Table).

In all patients, a pre-procedural physical examination was performed, and screening blood tests included measurements of internationalized normalized ratio (INR), partial thromboplastin time (PTT), platelet count, and blood cancer indices. Blood cancer indices were normal or mildly high, without giving a specific diagnostic orientation. Informed consent was obtained from all individuals after detailed discussion of the whole procedure, the

Table. Clinical and radiological data for 22 patients with cancer of unknown primary site treated with RFA percutaneously under CT guidance

	Patient Data		Number of	Tumor size of		Date of 1st RFA	1-month follow-up		3-month follow-up	6-month follow-up		12-month follow-up			
N	Sex	Age	lesions (sessions)	each lession (cm)	CNB results	(month/ year)	Tumor necrosis	2nd RFA	Tumor necrosis	Tumor necrosis	Metastases	Tumor necrosis	Metastases	Survival (months)	Cause of death
1	M	55	2 (1)	1.6 2.0	adeno Ca	04/02	+ +	– –	+ +	+ +	–	death		11	disease
2	M	58	1 (1)	4.0	adeno Ca	06/02	–	+	+	+	–	death		8	disease
3	M	65	1 (1)	3.5	squamous cell Ca	07/02	+	-	R	–	(new) liver	death		9	disease
4	F	53	1 (1)	4.8	adeno Ca	11/02	–	+	+	–	(new) liver	death		8	disease
5	F	72	2 (2)	1.9 3.5	unidentified	12/02	+ +	– –	+ R	+ +	(new) liver	+	–	12	ventricular fibrillation
6	M	68	1 (1)	3.2	squamous cell Ca	03/03	+	–	R	–	extrahepatic	+	-	14	car accident
7	F	80	3 (2)	1.5 1.8 2.6	adeno Ca	07/03	+ + +	– – –	+ + +	+ + +	extrahepatic	death		9	disease
8	M	78	2 (1)	1.1 2.7	adeno Ca	10/03	+ +	– –	+ +	+ +	–	death		10	disease
9	M	61	1 (1)	3.3	adeno Ca	11/03	–	+	+	–	(new) liver	death		9	disease
10	M	69	3 (2)	1.1 2.5 2.6	adeno Ca	12/03	+ + +	– – –	+ + +	+ + +	–	death		11	disease
11	F	64	1 (1)	2.5	unidentified	03/04	+	–	R	+	–	+	–	15	disease
12	M	71	2 (2)	2.5 3.0	unidentified	04/04	+ +	– –	+ +	+ +	–	+	–	13	disease
13	M	84	1 (1)	4.8	adeno Ca	06/04	–	+	+	–	–	death		8	heart attack
14	F	52	2 (2)	3.3 1.2	adeno Ca	11/04	+ +	– –	+ +	+ +	–	death		10	disease
15	M	60	2 (1)	1.5 2.0	transitional cell Ca	03/05	+ +	– –	+ +	+ +	–	+	–	14	disease
16	F	72	2 (2)	3.0 3.5	adeno Ca	05/05	+ +	– –	+ R	–	– extrahepatic	death		9	disease
17	F	61	2 (2)	2.8 3.3	squamous cell Ca	07/05	+ +	– –	+ R	+ +	–	+	–	12	hemorrhagic infarct
18	M	52	2 (1)	1.2 2.0	transitional cell Ca	07/05	+ +	– –	+ +	+ +	–	+	–	14	disease
19	M	62	1 (1)	2.9	unidentified	09/05	+	–	+	+	–	+	–	17	disease
20	M	68	1 (1)	3.3	adenoCa	11/05	–	+	+	+	–	death		9	disease
21	M	77	1 (1)	3.9	adenoCa	11/05	–	+	+	–	extrahepatic	death		8	disease
22	M	70	2 (2)	3.5 4.8	adenoCa	12/05	– –	+ +	+ +	+ +	–	death		9	disease

N, number of patients; RFA, radiofrequency ablation; M, male; F, female; Ca, carcinoma; R, recurrence; (+), present and (–), absent for each corresponding lession.

possible complications, and the potential result. All ablations were performed under local anaesthesia. For this reason all patients, for better cooperation, had received an analgesic and sedative treatment (3 mg benzodiazepine by mouth and a 0.05 g intramuscular injection of pethidine hydrochloride) 45 min prior to the procedure. None of the patients required additional intravenous sedatives or analgesics during the procedure.

The imaging modality of choice for the percutaneous electrode guidance was spiral CT (Picker 5000, Philips Medical Systems, Best, The Netherlands). Two types of applicators were used: (a) RITA 1500 (RITA Medical Systems Inc., Mountain View, California, USA) with multi-tined expandable electrodes (7 or 9 tines 10 cm or 15 cm long), and (b) MIRAS (Inavatec, Roncadelle, Italy) with a spiral expandable electrode. The selection of the applicator and electrode type was based on tumor size and location. The controls were set to the desired settings for the initiation of the procedure, and changes were made during ablation, according to manufacturers' instructions. Pulse RFA energy was applied for 10 to 20 min (mean ablation time 12 min) for each lesion, depending on size, location, and vascularity of the lesion. Of the 10 patients with hepatic metastasis, four were treated in one session and the rest in two different sessions. The two patients with three lesions were also treated in two sessions. The decision to treat more than one lesion in one session was based on the lesion size and location and patient cooperation during the ablation. MIRAS spiral expandable electrode was used in 17 of 36 lesions [12/36 lesions with diameter ≤2 cm; 5/36 lesions with diameter >2 cm, but close to inferior vena cava (n = 2) and gallbladder (n = 3)] and RITA multi-tined expandable electrode in 19/36 (all 19/36 lesions with diameter >2 cm, in 5 lesion the 7-tine electrode, and in 14 the 9-tine electrode). The ablation sessions lasted from 10 to 20 min. The maximum tissue temperature ranged from 90°C to 110°C (thermal coagulation begins at 70°C and tissue desiccation at 100°C, producing coagulation necrosis of tumor tissue and surrounding hepatic parenchyma). The ablation was designed to provoke caseation of the lesion 0.5 cm to 1 cm outside its imaging borders. All tracks were ablated during electrode exit from the lesion in order to avoid dissemination of the disease.

To evaluate the lesion's immediate response to ablation and to identify any complications, a dual-phase contrast enhanced spiral CT was performed immediately after the procedure. All patients were hospitalized for 24-hour monitoring. Follow-up was performed with the same modality at 1, 3, 6, and 12 months.

Outcomes were examined in respect to a number of prognostic factors. Survival analysis was performed using Kaplan-Meier for all patients and separately for patients with one, two, and three hepatic lesions. Statistical results were considered significant at $P < 0.05$.

Results

Twenty-two patients with a total of 36 liver metastases were treated in 30 RFA sessions.

The technical success of the ablation was reflected in the spiral dual-phase CT scan as cyst-like appearance of the lesion. The hypervascular halo around it, in the immediate control, was due to tissue reaction (10). The final result for the total tumor necrosis was estimated at the one-month follow-up, was performed with the same imaging modality and the same technique. All imaging follow-ups were accompanied by blood cancer indices values that compared with the pre-procedural ones.

All 22 patients had 1-, 3-, and 6-month follow-ups, and 8/22 had a 12-month follow-up. The one-month follow-up demonstrated total necrosis (referred as the absence of lesion vascularity in contrast enhanced CT scan and cyst-like appearance of the lesion) in 28/36 lesions (77.7%) and partial necrosis (referred as residual enhancing viable tumor in contrast enhanced CT scan) in 8/36 (22.2%). All these last lesions were greater than 3 cm; five of them were hypervascular, and two were next to great vessels (>3 mm). A complimentary session with complete technical success (total cystic appearance on the one-month follow-up) was performed in those tumors. The three-month follow-up revealed in 6/36 (16.6%) lesions (in different patients), hypodense nodules with no enhancement contiguous with the ablated tumor. This was considered as recurrence because of the contiguity, and a new RFA session was performed. All recurrences noted were in patients with aggressive histopathological type of cancer. None of these lesions had a previous second RFA treatment (Table).

The six-month assessment revealed new liver metastasis in 4/22 patients (18.1%) and extra-hepatic disease in other 4/22 cases (18.1%) (Figs. 1, 2). The remaining 14/22 patients were "free" of disease. Patients' survival time (measured from the time of first RFA session) ranged from 8 to 17 months, with estimated median survival of 10.9 months.

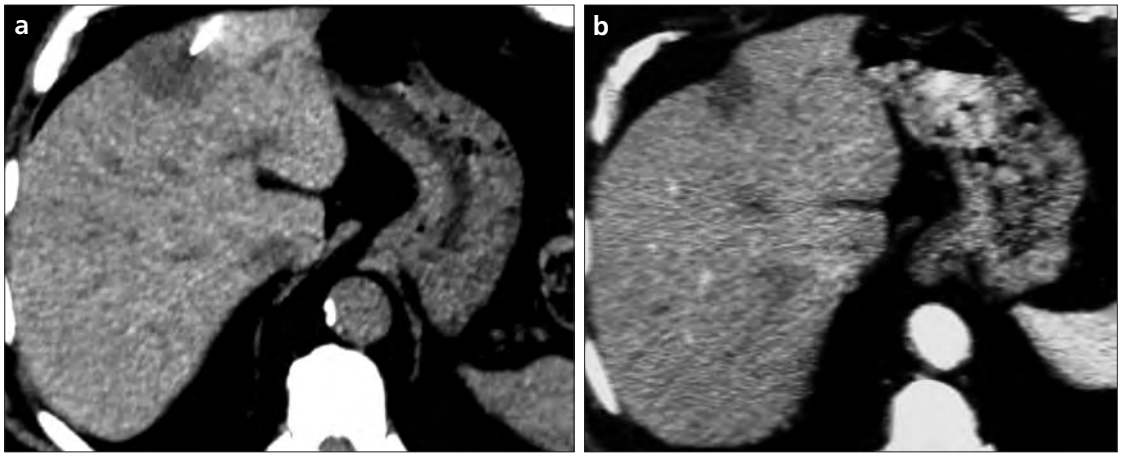
Patients with one lesion had a mean survival time of 3.50 ± 3.44 months; those with two lesions 4.40 ± 1.89 months; while patients with three lesions had 3.00 ± 1.41 months mean survival time (± standard deviation). The comparison of the results of these three groups was not statistically significant ($P = 0.11$).

Eighteen patients died from dissemination of their disease. In each patient who presented with new metastases to other viscera, a new percutaneous CT guided biopsy was performed for possible primary site of cancer identification with no diagnostic success. The remaining 4 patients died from car accident (n = 1), ventricular fibrillation (n = 1), heart attack (n = 1), and from hemorrhagic brain infarct (n = 1) (Table). Survival was better in patients with lesions 3 cm or smaller. Multivariate analysis (age, gender, lesion diameter) identified one prognostic factor: the lesion diameter ($P = 0.001$). Age ($P = 0.168$) and gender ($P = 0.232$) had no significant effect on survival.

In a total of 44 RFA sessions, none of our patients developed major complications. Three patients (13.6%) complained of mild pain at the ablation site requiring oral analgesic treatment, and one (4.5%) had fever (up to 38°C) for one day. Only one self-limited subcapsular hematoma was recorded (3.33%). No extrahepatic seeding was occurred due to RFA treatment.

Discussion

Liver is a frequent site of metastasis in many malignancies, and metastatic disease represents the most common hepatic neoplasm in Western world (11). About 40% to 50% of malignancies are complicated by liver metastasis (11, 12). The high frequency of metastasis is partly due to the vast blood



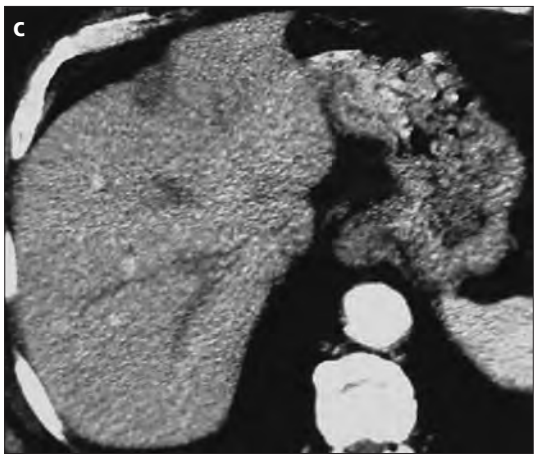
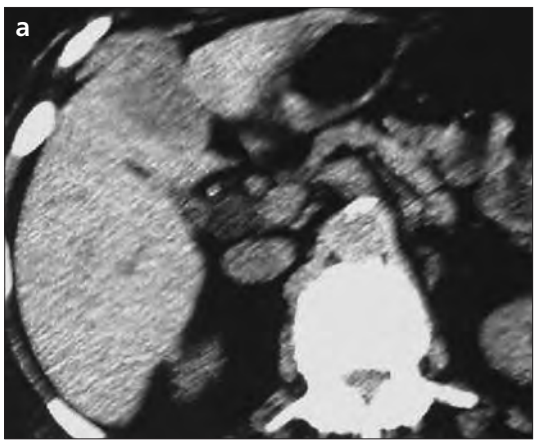
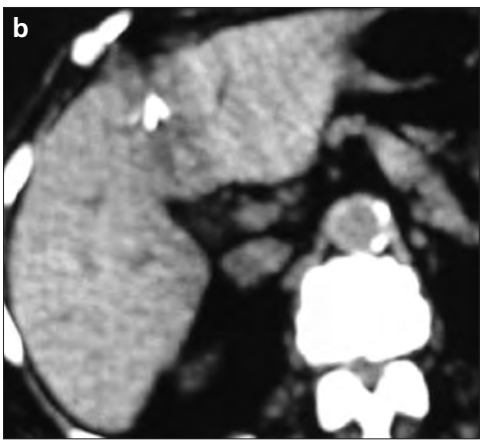
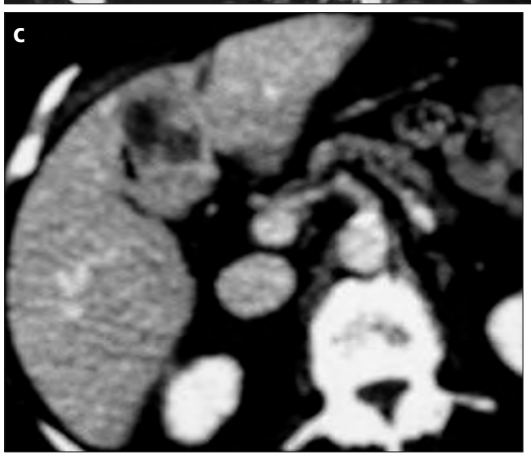


Figure 1. a–c. CT images of a 62-year-old man with single hepatic metastatic nodule from unidentified carcinoma. CT image **(a)** demonstrates a lesion in the right liver lobe being treated with radiofrequency ablation. The lesion gradually decreased in size in the 3-month **(b)** and 6-month **(c)** follow-up CT scans.







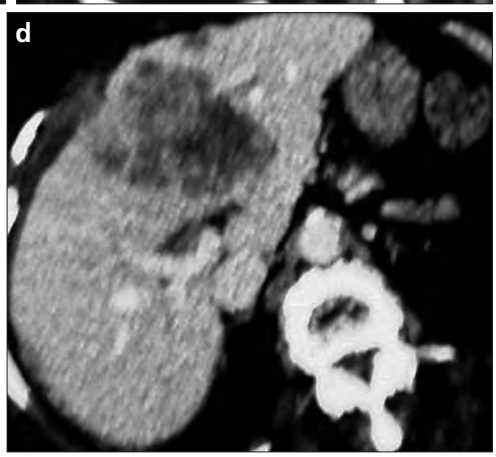


Figure 2. a–d. CT images of a 61-year-old man with a liver metastasis (in segment IV) of adenocarcinoma type. The lesion was treated by radiofrequency ablation (RFA) **(a, b)**. Needle electrode insertion lines are visible **(b)**. Dynamic CT scan obtained after RFA **(c)** shows a coagulated lesion with the hypervascular ring enhancement. The 1- month follow-up CT-scan revealed residual enhancement, due to lesion recurrence and a second RFA was performed (not shown here). Six months later, follow-up CT-scan **(d)** shows a larger mass near the ablated area, representing lesion recurrence, and a new subcapsular lesion.

supply of the liver, originating from portal and systemic circulation (13). In many patients with hepatic metastasis, clinical identification of the site of origin is not feasible despite the complete physical, imaging, laboratory and histopathological tests (13). Extensive work-up with specific examinations (gastroscopy, bronchoscopy, etc.), extended imaging technology (CT, MRI, PET), and specific pathology investigations in core biopsy specimens (immunohistochemistry, electron microscopy, molecular diagnosis), do not lead to detection of the primary malignancy site (1). These liver metastases make the entity of "hepatic metastasis of CUP" (1, 2).

PET scan can be used in the diagnosis of CUP but its value is controversial. In general, the PET scan reveals a primary tumor in 8% to 53% of patients with CUP, and has a false-positive rate of approximately 20% (2). According to Ambrosini et al., PET scanning allows detection of 24% to 40% of primary cancers, whereas the detection rate with 18F-FDG-PET/CT (18F-FDG is the most widely used radiotracer in oncology) in 20 cases is 53%, showing higher sensitivity than that reported for any other imaging modality, including PET (14). Some newly discovered immunohistochemical markers further assist in narrowing the differential diagnosis (2).

According to the literature, carcinoma of the lung and pancreas are the most common primary carcinomas that initially present as CUP (15, 16). Other common malignancies such as colorectal, breast, and prostate cancer infrequently present as CUP (15, 16). The anatomic location, size, and number of the lesions (inadequate viable liver tissue that could remain after operation), or patient's comorbid conditions (i.e., cardiac, pulmonary, or renal failure), each one alone or in combination, makes operation unsafe or impossible (17). Alternative options are limited for these patients. Systemic chemotherapy (including immunotherapy) may be beneficial for some group of patients and should be considered as an initial treatment option, prior to other local treatments (1, 11, 12, 18).

Since the 1990s, RFA, a minimally invasive technique, was gained a great deal of attention as an alternative to standard therapies for primary and metastatic liver tumors (13, 19–21). In our study, we retrospectively reviewed all liver metastasis of CUP treated with RFA, secondary to poor response to initial combined chemotherapy. The decision was up to the oncology team treating each patient. Complications, possible prognostic features, and method-efficacy were identified.

During a follow-up period of 17 months, local tumor control after single treatment, was achieved in 28 of 36 lesions (20 lesions ≤3 cm, 6 lesions >3 cm). In the eight lesions with partial necrosis, a second RFA session was obtained. New liver metastasis occurred in four patients. The only significant prognostic factor for overall RFA success and survival (as proved by imaging criteria and statistical analysis) was lesion diameter.

The procedures were free of major complications, and median disease-free-intervals were very well tolerated from all individuals, with no adverse effects.

The overall survival time of 10.9 months (although referred to a small group of patients) represents a promising outcome, compared to the published literature (4, 22, 23).

Solbiati et al. (21) reported a series of 29 patients with 44 hepatic metastases from colorectal cancer who were treated with RFA. No evidence of local recurrence was seen in 84% of these lesions. With a mean follow-up duration of 7.9 months (range, 3–15 months); disease-free survival was seen in 66.7% of patients. Hogan et al. (4) evaluated the impact of therapy and survival rate for 88 patients with hepatic metastases and CUP over a 10-year period and reported that the median survival time for the adenocarcinoma group was 49 days, with no significant difference between the treated (surgery, chemotherapy, radiotherapy, combination protocol, or palliative care alone) and untreated patients ($P = 0.128$). Briasoulis et al. (23) confirmed the poor outcome of patients with CUP metastatic to the liver, treated with chemotherapy. Greco et al. reported that the median survival time for the entire group was 9 months (24).

However, our study revealed that RFA may be a promising alternative and may join successfully a multitreatment protocol for these types of malignancies, as it is minimally invasive and does not aggravate patient's life quality. Larger studies with a great number of patients need to be organized in order to have more valid results with high statistical power.

The appropriate management of patients with liver CUP remains unclear. This study shows—although referred to a small number of patients—that RFA could be a promising treatment modality in this group of patients, especially in those with small hepatic lesions. Further prospective trials are needed to determine whether RFA should be proposed for standard protocols.

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