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Radiofrequency ablation of unresectable hepatic tumors

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PURPOSE
To evaluate the efficacy and safety of radiofrequency ablation (RFA) in the treatment of primary and metastatic liver malignancies.

MATERIALS AND METHODS
Twenty-nine consecutive patients who have primary (n = 9) and metastatic (n = 20) liver malignancies were treated with RFA. The total number of lesions were 62 at the initiation of treatment and 28 new lesions were diagnosed at the follow-up period. Totally, 84 lesions were ablated with RFA technique at 46 sessions. Primary tumors that gave rise to metastatic lesion were all colorectal cancer except one with gallbladder carcinoma. The greatest tumor diameter immediately before treatment was 0.8–5 cm with a mean of 2.5 cm.

RESULTS
In the hepatocellular carcinoma (HCC) group, 1 patient was lost to follow-up, 5 deceased due to extensive disease, and 3 are still on the follow-up. In the metastatic liver disease group, 8 patients died due to progression of disease, 1 deceased due to stroke, and 3 were lost to follow-up. Nine patients with HCC had 14 nodules with a mean of 1.75 lesions/patient and 20 patients had 70 metastatic lesion with a mean of 3.1 lesions/patient. Residual viable neoplastic tissue was found at control computed tomography in 1 (1/14) lesion and recurrence occurred in 3 (3/14) lesions in HCC group. Recurrence occurred in 7 lesions (7/70) of 4 patients (4/20) in the metastatic liver disease group. Drainage requiring empyema took place in 1 patient and skin burn was observed in 2 as complications due to procedure.

CONCLUSION
RFA of primary and metastatic liver malignancies is a safe and effective tool for local control of disease in unresectable hepatic malignancies.

Key words: • *catheter ablation* • *liver neoplasms*

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Hepatic tumors, whether primary or metastatic in nature, are leading cause of morbidity and mortality (1–3). Although, the hepatic resection is still being considered as the gold standard for treatment of hepatic tumors, the majority of hepatic tumors are surgically unresectable at the time of diagnosis, due to various reasons including the number and proximity to major vascular or biliary structures of lesions, insufficient remaining functional hepatic parenchyma, and severe medical comorbidities (4).

Currently available methods for treatment of hepatic tumors include hepatic resection and a variety of ablative techniques. However, a minority of patients with hepatic colorectal metastases (10–20%) and only 13–35% of patients with hepatocellular carcinoma (HCC) are candidates for hepatic resection (5, 6).

Local ablative techniques including percutaneous ethanol injection (PEI) and transcatheter arterial chemoembolization (TACE) are well known image-guided therapies used for destruction of tumors in patients with surgically unresectable disease. However, the effect of PEI decreases with the tumor size, particularly for lesions larger than 3 cm (7) and TACE is mainly reserved for massive HCCs (8).

Percutaneous radiofrequency ablation (RFA) has received significant attention in the recent years as a minimally invasive treatment of focal malign liver disease (9). The purpose of this study was to evaluate the efficacy and safety of RFA in the treatment of unresectable malignant focal hepatic tumors.

Materials and methods

Patients

Between April 2001 and July 2004, 29 consecutive patients who had primary (n = 9) and metastatic (n = 20) liver malignancies and were referred to our department for local ablative therapy were included to the study. Inclusion criteria were histologically documented primary or metastatic hepatic tumors without any evidence of extrahepatic disease, unresectable tumor, less than 6 tumoral nodules, and each nodule having a maximum diameter of 5 cm. Bilobar location of tumors, tumor proximity to major vascular structures precluding a safe margin-negative resection, and/or presence of cirrhosis with inadequate hepatic reserve were the criteria for surgical treatment.

All patients underwent a baseline evaluation including a detailed medical history, physical examination and laboratory tests which were complete blood count, coagulation studies, liver panel, total biluribin, alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA). Ultrasound was used to define the pre-procedural quantification and location of the lesions and as the guiding imaging modality during the procedure. Contrast enhanced dual phase computed tomography (CT) was performed

at arterial and portal venous phases for staging of the disease and for the follow-up. The follow-up was done with CT using the same protocol at the first month after the procedure and then every three months thereafter. Non-enhancement at the ablation sites both at the arterial and venous phases were considered to represent succesive ablation. Any persistent contrast enhancement at or around the ablation site was considered as residual-recurrent viable tumor.

Study population included 7 female and 22 male patients with a mean age of 55 (18–81). Total number of lesions were 62 at the beginning and 28 new lesions were diagnosed at the follow-up period. Eighty-four lesions were ablated at 46 sessions. Nine patients with HCC had 14 nodules with a mean of 1.75 lesions/patient and 20 patients had 70 metastatic lesion with a mean of 3.1 lesions/patient. The ablated metastatic tumors were all from primary colorectal carcinoma except for one patient with a primary of gallbladder carcinoma. The pre-procedural tumor diameter ranged between 0.8–5 cm with a mean of 2.5 cm. All nine patients with HCC had a history of chronic liver disease due to hepatitis-B and C (HBV-HCV) in 8 patients and type I tyrozinemia in 1 patient. Follow-up periods ranged between 6–30 months with a mean of 13.3 months.

RFA technique

RFA was performed with a 150-W RITA Starburst XL radiofrequency (RF) generator (RITA Medical systems, Mountain View, CA, USA) with a 25 cm long, 14-gauge expandable needle electrode that has nine retractable curved electrodes on the tip and a large dispersive electrode. Power output, electrode temperature, tissue impedance, and procedure time were displayed continuously by the RF generator that was connected to a portable computer. A dedicated software continuously recorded the temperature and impedance curves during the procedure.

The procedure was performed percutaneously in 21 patients who had lesions suitable for this form of treatment and in the remaining 8 patients, an open surgical approach was preferred due to inappropriate localization of lesions in 3 patients, synchronous resection of primary tumor in 3 patients and synchronous resection of the multifocal metastases in 2. All patients were hospitalized before the procedure. No premedications were given pre-procedurally.

All percutaneous procedures were performed under conscious sedation. Ultrasound and CT was used in 37 sessions (80.6%) and in 9 sessions (19.6%), respectively. Patients were placed in either the supine or left lateral decubitus position, depending on lesion site and planned trajectory. For the tumors smaller than 3 cm in diameter, the multiple array was deployed in the center. For larger lesions, the array was placed eccentrically at proximal site of the lesion and subsequently withdrawn and redeployed to 4 cm and 5 cm intervals within the tumor. Optimal positioning of the electrode permited complete ablation of tumor and at least 1 cm safety margin were reserved in order to achieve tumor-negative margins. Initial power applied was at 150-W and target tissue was set to 105 ºC in the primary deployment. In this system, 5 of the 9 hooks of the needle contain thermocouples that can monitor the tissue temperature. For lesions smaller than 3 cm, a single ablation for 5 minutes at target temperature was performed. In the lesions measuring between 3–5 cm, multiple overlapping ablations in orthogonal planes around the tumor nodule were done to achieve a geometric configuration of ablation zone with a safety zone of 1 cm.

Results

Twenty-nine patients with 84 tumoral nodules were treated with RFA during the study period (Table). Fourteen HCC nodules were treated with RFA in 9 patients. One patient was lost to follow-up, 5 died due to extensive disease during the treatment and 3 are still under follow-up. Residual viable neoplastic tissue was detected at control CT in 1 (1/14) lesion and ablation was repeated in this patient. Recurrence occurred in 3 (3/14) lesions which were detected at the 6th month follow-up CT in 2 patients and at 10th month in the third. Two of these patients were 18 and 21 year old young patients who had HCCs with bilobar involvement due to type I tyrozinemia. Initial treatment included surgical resection of one lobe and RFA of the other lesions in the other lobe. However, multiple new tumoral nodules appeared in the follow-up period and both were placed on TACE protocol due to extensive involvement and died twelve and fourteen months after the initial treatment, respectively. Third patient had a solitary nodule with peripheral location under the liver capsule measuring 5 cm in the largest diameter. Ablation was done at the operating room and a nodular focus of recurrent viable tumor tissue was detected on the follow-up CT at the 6th month.

One patient aged 64 years in HCC group having two lesions had died due to myocardial infarction immediately after the procedure.

A total of twenty patients having 48 tumor nodules due to liver metastasis were treated with RFA initialy. Twenty-eight additional lesions were detected at the follow-up. Twenty-two of the new lesions were also treated with RFA. The pre-procedural diameters ranged between 0.8–5 cm with a mean of 2.5 cm.

Eight patients with metastatic liver tumor died due to progressive disease and 1 patient died due to stroke during follow-up. Three patients were lost to follow-up. Follow-up CT scans at the first and third months showed complete necrosis of all lesions except 1 lesion (1/70). Residual tumor was di-

The number of nodules, residual lesions, and recurrence

	n
Initial number of tumor nodules	62
Newly detected nodules at follow-up	28
Total number of treated nodules	84
Residual lesion	1
Recurrence	10
Total number of patients	29

Figure 1. a-g. Axial contrast enhanced CT images **(a, b)** of a 73-year-old patient with two nodular hepatic metastases secondary to colon carcinoma treated with radiofrequency ablation. Post-procedural CT images **(c, d)** show total ablation without any contrast enhancement. Follow-up CT images obtained at the 6th month reveal recurrence of both treated nodules and multiple new metastases **(e-g)**.

agnosed at third month follow-up only in 1 lesion and technical inadequacy was considered to be the reason of failure. Recurrence occurred in 7 lesions (7/70) of 4 patients (4/20). Of these, 2 were larger than 4 cm and 1 was larger than 5 cm in diameter and 1 was located near hepatic portion of inferior vena cavae, and 2 were located peripherally under the liver capsule (Fig. 1, 2). Drainage requiring empyema took place in 1 patient and skin burn was observed in 2 as complications due to procedure.

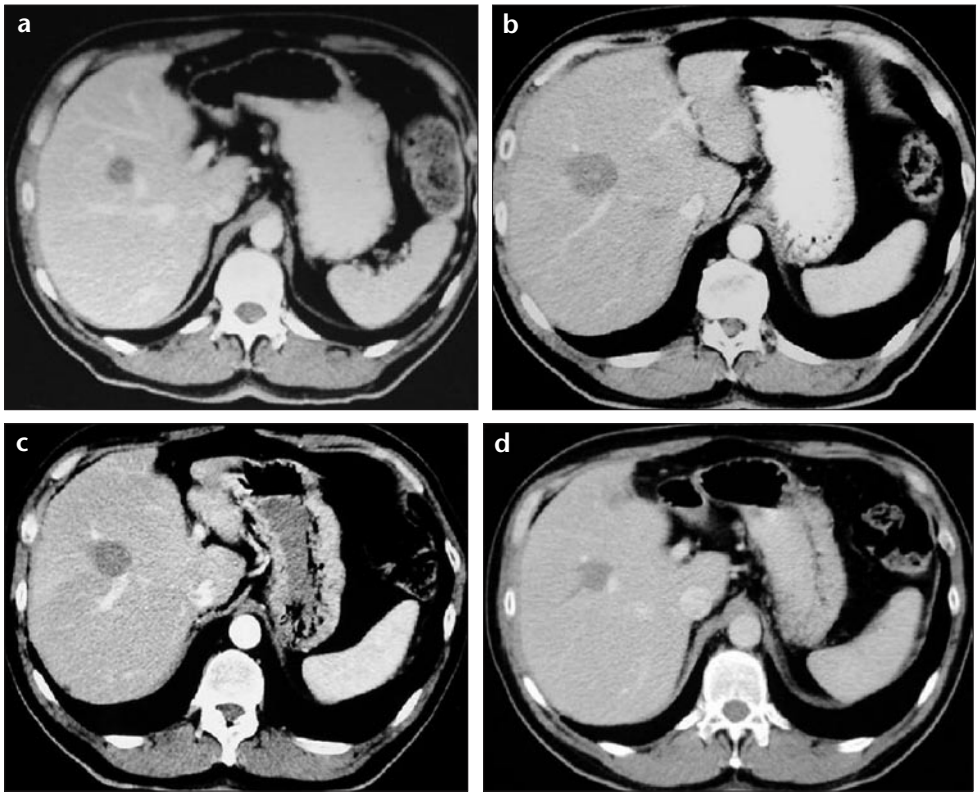

Figure 2. a-d. Axial contrast enhanced CT image **(a)** of a 50-year-old patient with solitary hepatic metastasis secondary to colon carcinoma treated with radiofrequency ablation. Post-procedural follow-up CT images obtained at the 3rd **(b)**, 6th **(c)**, and 12th months **(d)** reveal no recurrence.

Discussion

Primary liver cancer is among the most common solid cancers, causing an estimated one million deaths annually (10). Totally 140,000 new cases of colorectal cancer are diagnosed in USA in every year with a rate of 25% metastatic disease at the time of diagnosis and 25–50% develops metastasis, most commonly in liver in five year (11). Surgical resection is, currently, the only potential curative treatment for primary and secondary malignant diseases of the liver. However, with the micrometastatic and multifocal nature of the disease and impaired liver function in patients with HCC, surgery may not be possible in all patients.

Percutaneous ethanol injection is a well accepted local ablative therapy that is conventionally used for treatment of HCC. In a study based on the collected data from five centers, Livraghi et al reported 3-year survival rates of 63% and 31%, in patients with single or multiple HCC lesions smaller than 5 cm, concluding that the effect of PEI decreases with the size and the number of the lesions (12). Lencioni et al, comparing the effectiveness of RFA with that of PEI for the treatment of small HCC in patients with cirrhosis in a randomized trial, demonstrated that RFA is superior to PEI with respect to local recurrence-free survival rates that are 98% and 96% in the RFA group and 83% and 62% in the PEI group for one and two year follow-up period, respectively (13).

Untreated hepatic metastasis has an extremely poor prognosis, with a 5-year survival rate of less than 2% and median survival of less than 12 months (14). Surgical resection can provide a 5-year survival rate of less than 50% (15, 16). Furthermore, RFA in conjunction with surgical resection may increase the number of patients eligible for surgery when bilobar involvement is present. In the present study, RFA was used to treat the lesions located at the other lobe of liver synchronously with resection of one lobe in 2 patients.

Therapeutic application of RF energy has been used in surgery since the late 1920s. Newer modification of its use as an interventional radiological procedure for local tumor therapy has gained wide popularity since the early reports of RFA for tumor therapy by Rossi et al. (17) and McGahan et al. (18).

The mechanism of tissue destruction by RFA depends on the acceleration of energy created by RF generator, so that the alternating current causes the local ions to vibrate producing heat due to friction and inducing cell death by coagulative necrosis. Despite the cytototic temperature threshold is 50 ºC with RFA techniques, the temperatures may well exceed and actually reach the boiling point of water (100 ºC) leading to desiccation and thermal coagulative necrosis.

Until recently, a major limitation of RFA was the small ablation size created by conventional monopolar electrodes. Within the past couple of years, technical advances in RF systems introduced bipolar, internal cooled and multitined expandable electrodes enabling to produce heat for ablating lesions greater than 5 cm in diameter in a single session. This development makes RFA well suited for the treatment of primary and secondary liver malignancies as well as other sites in patients who are not eligible for surgery.

In our study, a RITA RFA system was used for treatment of liver tumors. Energy is delivered from the generator to the target tissue by a 14-gauge needle that has nine hook shaped electrodes inside and the system offers the advantage of a real-time local tissue temperature and impedance measurement. Duration of the treatment was adjusted according to the lesion diameter.

The main advantage of RFA is the ability to preserve the uninvolved hepatic

parenchyma with destruction of only a small rim of surrounding healthy liver tissue. Accurate image guidance for optimal placement of probe into the lesion is of vital importance to achieve complete necrosis (19). Ultrasound was used as the guiding imaging modality in 37 sessions (80.6%) and CT in 9 sessions (19.4%), in this study. Deep location of the lesion in the liver parenchyma, lack of patient cooperation, and inappropriate visualization of the lesion with ultrasound were the main reasons for CT guidance. Immediate contrast-enhanced CT scans obtained at arterial phase was also found to be useful for the evaluation of effectiveness of treatment in 2 patients with HCC by differentiating the ablated tissue and the residual viable tumor.

Immediately after RFA, treated areas appear as hypoattenuating regions on contrast enhanced CT devoid of characteristic parenchymal enhancement (20). Rim or nodular enhancement and gross expansion in diameter of the lesion are the indicators of recurrence. However, rim enhancement observed at early CT scans may be due to the irreversible damaged cells around the lesion and serial CT scan is needed for differentiation from residual tumor (21). Follow-up CT and/or magnetic resonance imging at 1–3 months has been reported to be useful for confirming the success of treatment and for detecting residual tumor that is often suitable for additional RFA therapy (22).

In our study, follow-up evaluations were done with CT at first month and then every three months after treatment. In HCC group, a residual tumor in 1 patient and recurrence was detected in 3 patients (3/14). Also, 7 recurrence (10%) was defined in the metastatic tumor group.

Tumor size greater than 2 cm and subcapsular location were reported to be the major risk factors for local recurrence of HCC by Komorizono et al. (23). One of the recurrences of HCC in our series was also measuring 5 cm in largest diameter and was located under the capsule of the liver. Clinical studies evaluating risk factors for local recurrence of metastasis treated with RFA is lacking in the literature. Of the 7 lesions with recurrence in metastatic tumor group, 2 were larger than 4 cm and 1 was larger than 5 cm in diameter and 1 was located near hepatic portion of inferior vena cava, and 2 were under the liver capsule.

A recent systematic review of 7 randomized trials by Seidenfeld et al. summarized the outcomes of RFA compared with hepatic arterial infusion or systemic chemotherapy for metastatic colorectal cancer treatment (24). Six of these studies (combined n = 150) reported the outcomes of RFA alone for unresectable colorectal metastases. The majority of the patients in these studies had more than one lesion ablated. Hepatic relapse occurred in 30-60% of these patients. Only one of the studies (n = 52) reported the 2-year and 3-year survival rates as 56% and 29%, respectively. This compares favorably to 2-year and 3-year survival rates of untreated patients with more than one hepatic lesion. Our study population had also more than one lesion, however, there was insufficient data to conclude for survival rates due to limited number of patients.

Hepatic RFA is, nonetheless, an important tool in the management of patients with liver malignancies. It is also associated with relatively low rates of complications. In the recent largest multicenter report, Livraghi et al. reported post-procedural complications from the RFA of 3554 lesions in 2320 patients (25). Overall mortality rate was 0.3%. Deaths were related to RF-induced thermal damage to adjacent viscera causing colonic perforation, hemorrhage associated with tumor rupture, peritonitis, and septic shock. Fifty (2.2%) major complications occurred within 30 days of the procedures in this report. Grounding ped skin burns were also reported and accounted for 0.2% of the cases. In our study group, 1 patient (1/29) died due to myocardial infarction immediately after the procedure, 1 patient required drainage due to empyema.

In conclusion, with the higher rates of mortality and morbidity associated with surgery and increasing numbers of patients ineligible for surgery, minimally invasive thermal ablation techniques including RFA have received tremendous attention in recent years. RFA offers a safe, effective, and relatively simple alternative treatment for liver malignancies.

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