

## ORIGINAL ARTICLE

# ROLE OF RADIOFREQUENCY ABLATION IN THE TREATMENT OF COLORECTAL LIVER METASTASES

By

Hesham Abdeldayem,<sup>1</sup> Ibrahim Abdelkader,<sup>1</sup> Tarek Essam El-deen,<sup>2</sup> Ahmad Touny,<sup>2</sup> Maher Osman,<sup>1</sup> Ossama Elabd,<sup>3</sup> Mohamed El-Waraky,<sup>3</sup> Hesham Gad,<sup>1</sup> Essam Salah,<sup>1</sup> Amr Helmy,<sup>1</sup>

<sup>1</sup> Department of Surgery, National Liver Institute, Menoufeya University, <sup>2</sup> National Cancer Institute, Cairo University,

<sup>3</sup> Radiology National Liver Institute, Menoufeya University, Egypt

Correspondence to: Hesham Abdeldayem, Email: habdeldayem64@hotmail.com

**Aim:** Surgical resection is the standard of care for colorectal metastases isolated to the liver. However, only 10–25% are eligible for resection because of extent and location of the disease in the liver or concurrent medical conditions. Several series have shown that radiofrequency ablation (RFA) can result in tumor eradication in properly selected candidates. The purpose of this study was to determine the efficacy of RFA for treatment of such lesions

**Methods:** Thirty patients with documented colorectal liver metastases who met the following criteria were considered for RFA: metastases confined to the liver; judged irresectable due to technical considerations or co-morbidity, number of metastatic deposits no greater than 5; and size less than 10 cm.

**Results:** Median follow-up was 26 (range 9–63) months. Overall 1-and 2-year survival rates were 76 and 61% respectively. Median survival was 32 months. Disease-free survival at 1 year was 35% at 2 years 7%. Six patients developed recurrence at the site of RFA; given that the total number of RFA-treated lesions was 69 the local recurrence rate was 9%.

**Conclusion:** RFA can achieve effective local treatment for patients with colorectal liver metastases who were considered unsuitable for surgical treatment.

**Keywords:** Local-ablative therapy, Irresectable Tumor, Hepatic Secondaries.

## INTRODUCTION

Hepatic metastases are the main cause of death in patients with colorectal cancer.<sup>(1)</sup> In patients with metastatic disease confined to the liver, resection offers the best chance of cure. After resection, a 5-year survival rate of 35 per cent can be achieved.<sup>(2)</sup> However, only a minority (10–15 per cent) of patients with liver metastases is suitable for resection because of extent and location of the disease in the liver or concurrent medical conditions.<sup>(1)</sup> Attention has been focused on investigating the minimally invasive techniques in treating patients with hepatic metastases who were not surgical candidates. The first technique used

was percutaneous ethanol injection.<sup>(3)</sup> However, as opposed to hepatocellular carcinoma, alcohol diffusion within metastatic lesions was shown to be uneven, resulting in incomplete ablation.<sup>(2)</sup> Therefore, other local ablation methods including cryotherapy, laser, microwave, and radiofrequency (RFA) ablation, have been developed and tested clinically during the past few years.<sup>(4)</sup> RFA ablation has emerged as a powerful technique for tumor destruction.<sup>(1)</sup> Recent improvements in RFA technology have permitted the creation of in vivo spherical ablation zones exceeding 5 cm in diameter with a single probe insertion, thus substantially increasing the potential of the

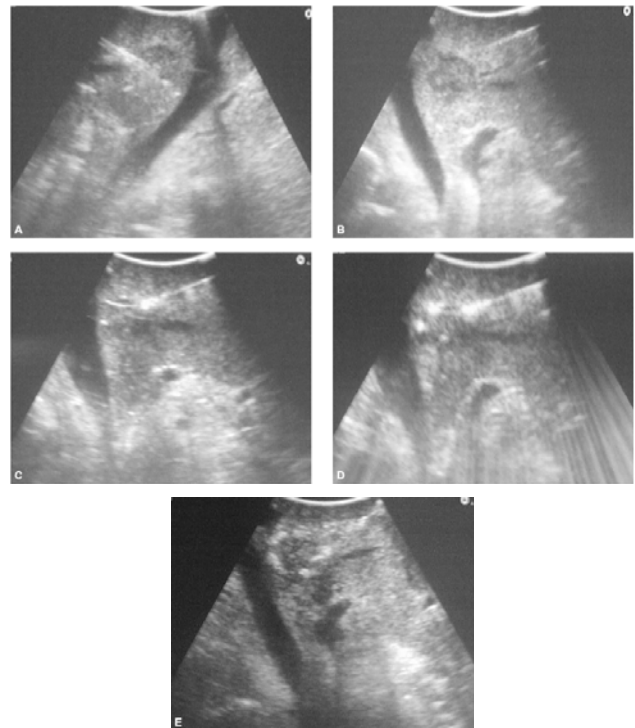
technique in clinical application.<sup>(3)</sup> The aim of this study was to evaluate the role of RFA in patients with colorectal liver metastases.

## PATIENTS AND METHODS

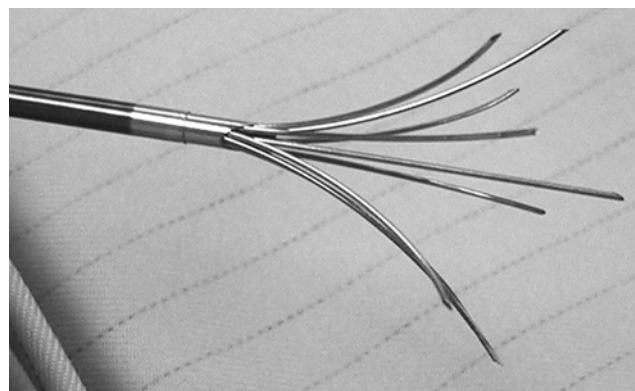
**Patient selection:** Between January 2001 and April 2006, 30 patients at the National Liver and Cancer Institutes with liver metastases from colorectal cancer who met the following prospective criteria were considered for RFA: metastases confined to the liver; judged irresectable due to technical considerations or comorbidity, number of metastatic deposits not greater than 5; and size less than 10 cm. Previous chemotherapy was not considered an exclusion criterion. All cases were discussed in details at a multidisciplinary meeting. This study was approved by the ethical committees at the National Cancer and Liver Institutes. Informed consent was taken from all cases.

To determine the extent of the disease before operation, all patients underwent spiral abdominal computed tomography (CT), chest radiography or CT of the thorax. Barium enema or colonoscopy was performed to exclude local recurrence. Liver function tests and determination of carcinoembryonic antigen (CEA) level were performed routinely.

RFA was performed percutaneously using ultrasonographic guidance. General anaesthesia was preferred but, if there was a specific contraindication to this, treatment was performed under local anaesthesia and sedation. All patients stayed overnight in hospital. Single or triple-cluster, 17-G, internally cooled electrodes (Tyco Healthcare Group, Radionics, Burlington, Massachusetts, USA) were used. Energy generated at the tip of the electrode caused ionic agitation and frictional heat, which led to coagulative necrosis of the tumor cells along with a margin of normal tissue. A single electrode with a 3-cm exposed tip was used for tumors smaller than 3 cm in diameter and a triple-cluster electrode with a 2.5-cm exposed tip for larger tumors. RF energy was applied at maximum power of less than 150 W for 5-10 min depending on impedance changes. As a rough guide, treatment for 10 min with a single electrode produced approximately a 3-cm area of necrosis and treatment with a triple electrode for the same time produced a 5-cm area of necrosis. The volume of necrosis depended on tumor position, hepatic perfusion, patient body habitus and proximity to blood vessels. Therefore it was often necessary to perform multiple placements and treatments in all but the smallest tumors (less than 1 cm). The electrode was repositioned and treatment repeated until all visible tumor had been ablated (Figs. 1,2,3).



**Fig 1. Ultrasound scan: A, Liver metastases adjacent to the hepatic vein B, View of the same lesion and a (RFA) electrode. C, The same lesion with the electrode deployed. D, Early in the RFA process, hyperechoic areas are seen at the tip of the electrode E, At the conclusion of radio-frequency.**



**Fig 2. Photograph of the tip of a needle electrode with prongs deployed.**



**Fig 3. Photograph shows percutaneous insertion of the needle electrode into the lesion.**

**Follow-up:** Postoperative follow-up was obtained at 6 weeks and then every 3 months by assessment of CEA concentration and abdominal spiral CT. The first postoperative CT scan was used as a reference to evaluate liver recurrence. Regular follow-up was reduced to twice yearly after 2 years. When new liver deposits became evident, subsequent resection or RFA was performed whenever possible. In case of doubt about recurrence at the site of RFA, an ultrasonographically guided biopsy was performed. After RFA, patients did not routinely receive chemotherapy. Chemotherapy was started only in cases of recurrence not amenable to resection or RFA.

**Statistical analysis:** Survival was estimated using Kaplan-Meier analysis; differences in survival were analyzed using the log-rank test. Differences in tumor recurrence rates were analyzed using the Fisher exact test and 2-sided [chi]2 tests. Differences were considered to be statistically significant when the P value was < 0.05.

## RESULTS

### Patient demographics Table 1.

**Table 1. Patient demographics.**

Number of patients	30
Sex ratio (M/F)	19/11
Age : mean (range) years`	62 (45-79)
Synchronous: metachronous	16:14

Out of the 30 patients there were 19 males and eleven females. Mean age was 62 years. Sixteen patients had synchronous metastases, and 14 had metachronous metastases.

The number of liver metastases per patient varied from 1 to 5 (median 3). The size of the metastases varied from 1 to 10 cm Table 2.

**Table 2. Number and size of metastases.**

	No of metastases		Size of metastases *	
	<4	≥4	< 5 cm	≥5 cm
No of patients	16	14	9	21

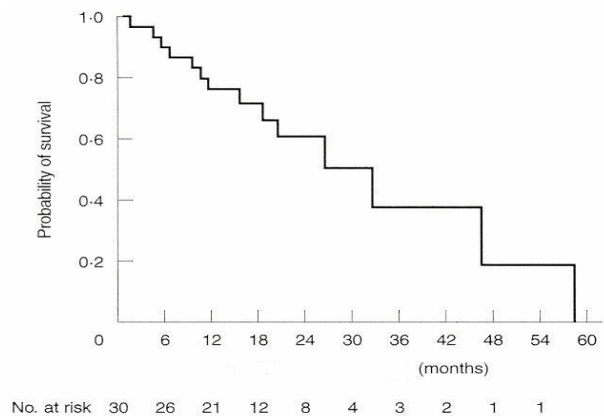
\* According to the size of the largest metastasis.

Three patients underwent repeat RFA for recurrent liver metastases. One patient was treated twice for recurrence; thus the total number of RFA procedures was 34. Median follow-up after RFA was 26 months, and the median follow-up after detection of metastases was 40 months.

The median time from detection of liver metastasis to operation was 5.5 months. In seven patients this period was more than 1 year because of delay in primary referral. Eleven of the 30 patients were initially treated by chemotherapy before referral. By that time, eight patients showed progression of the disease, noted by enlargement of the liver deposits on CT. In these patients the median duration of chemotherapy was 10.5 months. A further eight patients developed metastases during adjuvant chemotherapy. Thus, a total of 16 patients had metastases that were progressive on chemotherapy at the time of operation.

**Mortality and morbidity:** There was one postoperative death from acute myocardial infarction 14 days after an uncomplicated RFA. Only two cases developed significant morbidity because of the procedure. One patient had to be explored at the operating room because of haemorrhage; another patient developed moderate right pleural effusion that necessitated needle aspiration.

**Survival:** At a median follow-up of 26 months, 14 patients had died, 13 from metastatic disease and one postoperative death. After RFA the overall survival rate at 12 months was 76 per cent, and at 24 months it was 61 per cent (Fig. 4)



**Fig 4. Overall survival rate.**

Median survival was 32 (range 0.5-58) months. The 1- and 2-year survival rates after detection of the metastases were 83 and 68 per cent respectively. Median survival after detection of the metastases was 46 months. Patients with lesions smaller than 4 cm had an increased survival rate compared with those with lesions of 4 cm or more (Fig. 5).

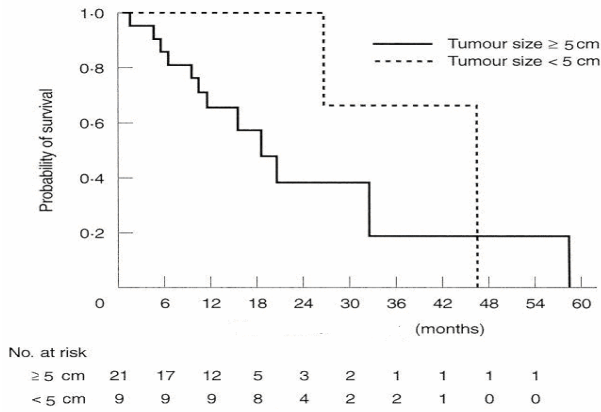


Fig 5. survival rate in relation to tumor size.

Median survival for patients with lesions smaller than 5 cm was 46 months, compared with 18 months for those with lesions of 5 cm or greater ( $P < 0.05$ , log rank test). No significant correlation was found between the number of metastases and survival.

At time of follow-up 25 of the 30 patients had developed recurrent disease. The disease-free survival rate at 1 year was 35 per cent, and that at 2 years was 7 per cent. The median time to detection of recurrence was 7 months. Of the 25 patients with recurrent disease, 18 patients presented with hepatic recurrence. In 11 cases the liver was the only site involved. Extrahepatic recurrence was observed in 14 cases: lungs (six), colon and/or rectum (three), other (nine). Six patients developed local recurrence at the site of RFA. In four of these patients the RFA-treated lesion was situated close to the portal bifurcation or inferior vena cava. With regard to the total number of RFA-treated lesions ( $n = 69$ ) in the series, the local recurrence rate was 9 per cent. Three local recurrences occurred in tumors of 5 cm or more in diameter.

## DISCUSSION

Resection of colorectal liver metastases is the treatment of choice for solitary liver metastases. This treatment is associated with an operative mortality rate of 3-5 per cent and a 5-year survival rate of 30-50 per cent.<sup>(5)</sup> There is currently no accepted alternative treatment of comparable efficacy for the majority of patients with metastatic tumors confined to the liver.<sup>(6)</sup> Most patients with colorectal liver metastases have widespread liver involvement or extrahepatic disease which precludes any surgical

approach. However, in a well defined subgroup of patients with irresectable tumors, tumor clearance of the liver can be achieved by local ablative techniques such as RFA of the liver metastases.<sup>(7)</sup>

The present study suggests that the survival rates after surgical resection and RF ablation might be comparable. RFA can reliably ablate liver tumors, leaving no residual viable tumor cells.<sup>(8)</sup> When the volume of the targeted liver metastases is too large to achieve 100 per cent ablation, the procedure can easily be repeated. The procedure is safe, well tolerated and less invasive than liver resection.<sup>(9)</sup> This study concurs with other studies on RFA of colorectal liver metastases. In these series the 1-year survival rate varied from 72 to 88 per cent, while 2-year survival rates of between 52 and 72 per cent have been reported.<sup>(10)</sup> These results compare favorably to those of chemotherapy, for which a median survival of between 12 and 17 months has been reported, depending on the schedule used.<sup>(11)</sup> Nevertheless patient selection may have contributed to the superior results in the present series, particularly as patients selected for this study had a limited number of metastases (no more than 5) and no extrahepatic disease.

Of all lesions treated by RFA, the overall local recurrence rate at the RFA site was 9 per cent. This value for local recurrence is low in comparison with a local recurrence rate of 44 per cent described by Bilchik et al.,<sup>(12)</sup> However, others have also reported local recurrence rates at the RFA as low as 2.5 and 9 per cent.<sup>(13)</sup> Inadequate coagulation was observed mainly in patients with lesions situated close to the inferior vena cava or portal bifurcation, owing to the heat sink effect of the high blood flow. Four patients with local recurrence at the RFA site had tumor situated close to these large vessels. Only two local recurrences were observed in lesions treated at other sites. Iannitti et al.,<sup>(14)</sup> reported that overall survival is significantly better in patients in whom the maximum diameter of the RFA-treated lesion is smaller than 3 cm. Temperatures reached at the edge of large lesions may be inadequate unless several probes are used in the same lesion.

In this study the overall disease-free survival rate at 1 year was 35 per cent. Most patients developed liver recurrence outside the RFA area, or presented with extrahepatic recurrence. These findings are in agreement with those of other series, which report disease-free survival rates varying from 15 per cent at 15 months to 29 per cent at 24 months.<sup>(15)</sup> As in several other series, routine postoperative chemotherapy was not used in the present study, (9 and 16) Although postoperative chemotherapy after liver surgery for colorectal metastases continues to be controversial, data from Scaife et al.,<sup>(17)</sup> suggest a potential benefit of postoperative chemotherapy by the combined administration of intra-arterial floxuridine and systemic 5-fluorouracil-leucovorin.

**In conclusion:** RFA can achieve effective tumor destruction with acceptable morbidity for patients with limited hepatic metastatic disease from colorectal cancer who are not eligible for surgical resection. The high rate of disease recurrence after RFA indicates that novel combinations of RFA with regional or systemic chemotherapy regimens are needed to improve patient outcomes. This study does not enable the conclusion that resection and RF ablation are equally effective, but highlights the need for a randomized clinical trial to determine whether RFA ablation can achieve similar survival rates to resection of colorectal liver metastases. With continuous improvement in technology and large-scale clinical experience, this technique has the potential to play an increasingly important role in the management of hepatic colorectal metastases. Finally, an appropriate use of RFA can only be done when the therapeutic strategy is decided by a multidisciplinary team and is tailored to the individual patient.

## REFERENCES

1. Pinedo HM, Van Groeningen CJ. Emerging new opportunities for patients with hepatic metastases from colorectal cancer or primary hepatocellular cancer. *Oncologist*. 2001;6:12-13.
2. Curley SA. Radiofrequency ablation of malignant liver tumors. *Oncologist*. 2001;6:14-23.
3. Erce C, Parks RW. Interstitial ablative techniques for hepatic tumors. *Br J Surg*. 2003;90:272-89.
4. Fraker DL, Soulen M. Regional therapy of hepatic metastases. *Hematol Oncol Clin North Am*. 2002;16(4).
5. Bleicher RJ, Allegra DP, Nora DT, Wood TF, Foshag LJ. Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. *Ann Surg Oncol*. 2003;10:52-8.
6. Pearson AS, Izzo F, Fleming RY. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg*. 1999;178:592-9.
7. Curley SA, Bilchik AJ, Fraker DL, McMasters KM. Symposium: radiofrequency ablation of hepatic metastases. *Contemp Surg*. 2003;59:162-72.
8. Kesmodel SB, Canter RJ, Raz DJ, Bauer TW, Spitz FR, Fraker DL. Survival following regional treatment for metastatic colorectal cancer to the liver using radiofrequency ablation and hepatic artery infusion pump placement. *Ann Surg Oncol*. 2002;9:S68-S68.
9. Bowles BJ, Machi J, Limm WML. Safety and efficacy of radiofrequency thermal ablation in advanced liver tumors. *Arch Surg*. 2001;136:864-9.
10. hung MH, Wood TF, Tsioulis GJ, Rose DM, Bilchik AJ. Laparoscopic radiofrequency ablation of unresectable hepatic malignancies. A phase 2 trial. *Surg Endosc*. 2001;15:1020-6.
11. Fischer JE. Unresectable liver metastases. *J Am Coll Surg*. 2002;195:359-60.
12. Rose DM, Allegra DP, Bostick PH, Foshag LJ, Bilchik AJ. Radiofrequency ablation: a novel primary and adjunctive ablative technique for hepatic malignancies. *Am Surg*. 1999;65:1009-14.
13. Bilchik AJ, Wood TF, Allegra D, Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. *Arch Surg*. 2000;135:657-62.
14. Siperstein AE, Garland A, Engle K. Local recurrence after laparoscopic radiofrequency thermal ablation of hepatic tumors. *Ann Surg Oncol*. 2000;7:106-13.
15. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. *Arch Surg*. 2002;137:422-6.
16. Seidenfeld J, Aronson N, Korn A. Radiofrequency ablation of unresectable liver metastases. *J Am Coll Surg*. 2002;195:378-86.
17. Bilchik AJ, Wood TF, Allegra DP. Radiofrequency ablation of unresectable hepatic malignancies: lessons learned. *Oncologist*. 2001;6:24-33.
18. Scaife CL, Curley SA. Complications, local recurrence, and survival rates after radiofrequency ablation for hepatic malignancies. *Surg Oncol Clin N Am*. 2003;12:243-55.