REVIEW

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Radiofrequency Ablation of Liver Metastases from Colorectal Cancer: A Literature Review

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Liver metastases occur in up to 60% of patients with colorectal cancer, and the control of liver metastases is considered to be of primary importance because it is a critical factor in determining prognosis. Radiofrequency ablation (RFA) therapy is one of the least invasive techniques for unresectable hepatic malignancies and can be performed safely using percutaneous, laparoscopic, or open surgical techniques. The local tumor progression rates after RFA for colorectal liver metastases range from 8.8% to 40.0%, and 5-year survival rates range from 20.0% to 48.5%. No prospective, randomized trials comparing the efficacy of RFA with that of surgical resection for colorectal liver metastases are currently available. However, some retrospective studies have reported that patients who received RFA had a survival rate similar to that observed in surgically treated groups, while other studies have reported better survival among patients who underwent surgical resection. The use of a laparoscopic or open surgical approach allows the repeated placement of RFA electrodes at multiple sites to ablate larger tumors. An accurate evaluation of treatment response is very important for the success of RFA therapy because a sufficient safety margin (at least 0.5 cm) can prevent local tumor progression. This review critically summarizes the current status of RFA for liver metastases from colorectal cancer. **(Gut Liver 2013;7:1-6)**

Key Words: Colorectal neoplasms; Liver metastasis; Safety margin; Radiofrequency ablation

INTRODUCTION

The liver is a common site for cancer metastasis, and liver metastases occur in up to 60% of patients with colorectal cancer (CRC).[1] As one of the critical factors determining the prognosis of the patients with advanced stage CRC is liver metastasis, adequate local control of liver metastasis must be achieved. Surgery provides the therapeutic choice for cure in patients with hepatic metastases, and it has been reported that hepatic resection provides a good prognosis and a favorable quality of life in the patients with colorectal liver metastasis (CRLM).[2] However, chemotherapy following the resection of primary CRC can cause hepatic injury.[3] Repeat hepatic resection for current CRLM would be confined to the patients with good liver function. Moreover, difficulties of surgical resection may be related to the size, site, and number of tumors, vascular, and extrahepatic involvement as well as poor liver function.

There is a need for an effective and less invasive technique for the treatment of unresectable hepatic malignancies. Recently, several local ablative techniques, such as, percutaneous ethanol injection, microwave coagulation therapy, and radiofrequency ablation (RFA) have been reported to be effective in the patients, considered for liver-directed therapies, expanding the pool of patients who can be treated.[4-7] RFA, in particular, has resulted in a higher rate of complete necrosis of the metastatic lesions in the liver and required fewer treatment sessions than the other ablation therapies.[6-8] The advantage of minimal invasiveness for RFA, combined with claims of good local control and good survival have had a positive impact on the clinical management of the patients with CRLM. However, there is a need to scientifically analyze in detail the potential advantages and disadvantages of resection versus RFA for resectable CRLM. Recently randomized controlled trials have been advocated to compare RFA and hepatic resection in resectable CRLM; but to date, this has not yet been performed. In this review, we focus our discussion on the efficacy of percutaneous, laparoscopic and open surgical RFA for CRLM, and the comparison between percutaneous RFA and surgical resection.

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BACKGROUND

1. Localized application of radiofrequency energy

RFA is a localized thermal treatment technique designed to induce tumor destruction by heating the tumor tissue to temperatures that exceed 60°C.[5-7] The alternating current of radiofrequency waves passing down from an uninsulated electrode tip into the surrounding tissues generates changes in the direction of ions and creates ionic agitation and frictional heating. This tissue heating then drives extracellular and intracellular water out of the tissue, resulting in tissue destruction by coagulative necrosis. When tumor cells are heated above 45°C to 50°C, intracellular proteins are denatured and cell membranes are destroyed through dissolution and melting of lipid bilayers. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

Percutaneous RFA under local anesthesia is feasible, although intraoperative RFA under general anesthesia has also been performed to prevent severe pain and discomfort during the procedure.

2. Treatment algorithm

RFA is recommended for liver metastases with a maximum diameter of 3 cm in patients with not more than three tumors who are contraindicated for surgery, according to hepatocellular carcinoma (HCC) treatment algorithm in Japan and the West.[9-11] This algorithm has often been applied in the treatment of liver metastases. However, the number of lesions should not be considered an absolute limiting consideration for RFA, if successful treatment of all metastasis deposits can be accomplished. Most centers preferentially treat patients with five or fewer lesions. The target tumor should not exceed 3 cm in the longest axis to achieve best rates of complete ablation with most of the currently available devices.

3. Imaging of liver metastasis from CRC

Ultrasonography (US) shows multiple round and/or hypoechoic masses with irregular borders.[12] A Bull's eye appearance represents histological findings of an area showing central coagulative necrosis surrounded by a zonal area of viable tumor. However, the poorly-differentiated adenocarcinoma often appears as infiltrative, without a capsule, and the tumor border can be shown irregular on B-mode US. Contrast enhanced US can show intratumoral vascurality in the peripheral hypoechoic zone, in which viable tumor cells are proliferating.[13] It has been reported that the presence of rim enhancement with peripheral tumor vessels (sensitivity, 88.1%; specificity, 100%) is the typical pattern.[14] Contrast enhanced US in the late phase provides marked improvement in the detection of hepatic metastases as areas of hypoenhancement, and can be advantageous in detecting small metastases compared with computed tomography (CT) and magnetic resonance imaging (MRI).[15,16]

Multidetector row helical CT have further improved the performance of CT scanners in terms of speed of acquisition, resolution, and the ability to image the liver during various phases of contrast enhancement more precisely than was possible previously. CRLM are detected as hypodense lesions in the late portal venous phase on contrast-enhanced CT. In this phase the attenuation of the normal liver parenchyma increases, revealing the relatively hypoattenuating metastases, sometimes with rim enhancement.[17]

The majority of CRLM show several typical findings on MRI. The lesions appear as low signal intensity on T1-weighted images and as moderately high signal intensity lesions on T2-weighted images with fat suppression.[18] Metastases with intratumoral hemorrhage or coagulative necrosis may exhibit mixed signal intensity on T1-weighted images, and those with a desmoplastic reaction may exhibit low signal intensity on T2-weighted images. Especially, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid (Gd-EOB-DTPA) is a liver-specific hepatobiliary MR contrast agent that offers both dynamic imaging and static hepatocyte imaging. Gd-EOB-DTPA is taken up by hepatocytes in healthy liver tissue in an amount of about 50% of injected dose, and because malignant primary and secondary tumors usually do not contain functioning hepatocytes, the contrast effect the lesions will appear as dark areas against healthy liver parenchyma.[19]

4. Assessment of technical effectiveness

The area of perilesional rim enhancement shown in contrast-enhanced CT suggests microscopic tumor cell infiltration. The assessment of the therapeutic effect of RFA is very important. The technical effectiveness of ablation is commonly assessed by findings on contrast enhanced CT or MRI because of objectivity and reproducibility of the image. Contrast-enhanced US may also provide an alternative approach in assessing the therapeutic effect of RFA, in spite of having limitations in identifying the safety margin.[20] A tumor is considered to have been successfully ablated when there is at least a 0.5 cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase (Fig. 1).[21,22] Failure to establish a sufficient ablative safety margin is an independently significant risk factor for local tumor progression on multivariate analysis.[23] Basically, the local tumor progression rate following a single RFA treatment depends on how strictly the therapeutic effect is assessed.

CLINICAL OUTCOMES

1. Percutaneous approach

1) Local controllability (local tumor progression) and survival

The reported local recurrence rate after RFA for liver metastases ranges from 8.8% to 40% (Table 1).[23-35] Three-year and 5-year survival ranges from 22% to 57% and 20% to 48.5%, re-

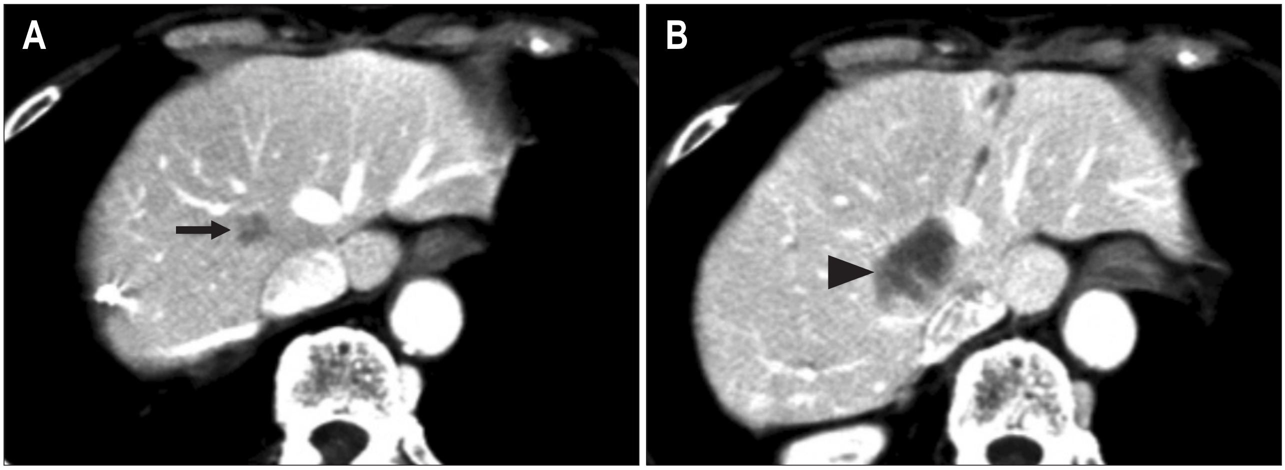

Fig. 1. An 86-year-old man with a liver metastasis from the colon measuring 1.5 cm in diameter. (A) A portal-phase dynamic computed tomography (CT) scan showing a hypovascular tumor (arrow) in segment eight of the liver. (B) A portal-phase dynamic CT scan obtained 2 days after RFA showing that the tumor and surrounding area (arrowhead) are not enhanced. Thus, this tumor is considered to have been successfully ablated.

Table 1. Local Tumor Progression Rate and Survival after Radiofrequency Ablation for Liver Metastases

Author (yr)	Origin	No.	Tumor size, mean, cm	Follow-up period, mean, mo	Local progression, %	Survival, %
Livraghi *et al*. (2003)[24]	C&R	88	2.1	33	40	-
Oshowo *et al*. (2003)[25]	C&R	25	-	-	-	53 (3-yr)
Abdalla *et al*. (2004)[26]	C&R	57	2.5	-	-	22 (3-yr)
Berber et al. (2005)[27]	C&R	135	4.1	-	-	36 (4-yr)
Aloia *et al*. (2006)[28]	C&R	27	3.0	50	31	27 (5-yr)
Machi *et al*. (2006)[29]	C&R	507	-	24.5	-	30.5 (5-yr)
Abitabile *et al*. (2007)[30]	C&R	147	-	33	8.8	57 (3-yr)
White *et al*. (2007)[23]	C&R	22	2.4	17	55	25 (3-yr)
Park *et al*. (2008)[31]	C&R	30	2.0	49	23	20 (5-yr)
Lee *et al*. (2008)[32]	C&R	37	-	-	-	48.5 (5-yr)
Reuter *et al*. (2009)[33]	C&R	66	3.2	-	17	21 (5-yr)
Gillams *et al*. (2009)[34]	C&R	309	3.7	-	-	34 (5-yr)
Knudsen *et al*. (2009)[35]	C&R	36	2.1	27	-	34 (3-yr)

C&R, colon and rectum.

spectively. Several factors can be correlated with the survival of the patients with untreated hepatic CRC metastases. The dominant effect of liver tumor involvement suggests that successful local therapy could increase life expectancy, decrease mortality, or both. Local tumor progression is related to incomplete tumor ablation. However, it is often difficult to obtain a specific safety margin in three dimensions all around a large tumor. Some researchers reported that the most important factor associated with failure of local tumor control could be tumor size.[36] Table 1 shows that local tumor progression does not necessarily depend on the tumor size; however, recurrence could occur even after a sufficient margin had been ensured. It is suggested that local tumor progression arises from the residual cancer after RFA, while recurrence from a microsatellite or by microvascular invasion other than the main nodule may also appear as a late local tumor progression. Therefore, a larger safety margin is necessary in order to obtain complete local ablation of liver metastases because of infiltrative invasion.

2) Survival: comparison with those after resection

At present, no prospective randomized trials have been reported. However, there are some retrospective reports of large numbers of patients regarding RFA versus surgical resection for hepatic colorectal metastasis (Table 2).[23,25,26,28,31-33] Some reported that patients who received RFA had survival rates similar to surgical groups, while others found that survival rates were better among patients undergoing surgical resection. Reuter *et al*.[33] conducted a comparative study on 192 patients with hepatic colorectal metastases who received either percutaneous RFA or surgical resection. Patients who underwent RFA were similar

Table 2. Survival Rates Associated with RFA versus Hepatic Resection for Liver Metastases

Author (yr)	No., RFA/resection	Mean tumor size, RFA/resection, cm	Overall survival, RFA vs resection, %	p-value
White *et al*. (2007)[23]	22/30	2.4/2.7	25 vs 82 (3-yr)	-
Oshowo *et al*. (2003)[25]	25/20	-/-	53 vs 55 (3-yr)	NS
Abdalla *et al*. (2004)[26]	57/190	2.5/-	22 vs 65 (3-yr)	<0.001
Aloia *et al*. (2006)[28]	27/147	-	27 vs 71 (5-yr)	<0.001
Park *et al*. (2008)[31]	30/59	2.0/3.1	20 vs 42 (5-yr)	0.0002
Lee *et al*. (2008)[32]	37/116	-	48.5 vs 65.7 (5-yr)	0.227
Reuter *et al*. (2009)[33]	66/126	3.2/5.3	21 vs 23 (5-yr)	NS

RFA, radiofrequency ablation; NS, not significant.

to resection patients based on mean number of hepatic lesions (2.8 vs 2.1, p=0.14), and prior chemotherapy (67% vs 60%, p=0.33). However, the median time to recurrence was shorter with ablation than with resection (12.2 months vs 31.1 months, p<0.001). Recurrence at the ablation-resection site was more common with ablation than with resection, occurring in 17% versus 2% (p<0.001) of cases, respectively. Distant recurrence in the liver was also more common with ablation, occurring in 33% of patients versus 14% for resection (p=0.002). Abdalla *et al*.[26] reported that local recurrence was most common after RFA (9% vs 2%, p<0.02). The overall survival rate was highest after resection (58% at 5 years); 4-year survival after resection and RFA only were 65% and 22%, respectively (p<0.0001). In both of the above studies, RFA alone for unresectable patients did not yield the survival rate comparable to the resected group. However, this difference probably reflects a selection bias since RFA was used in operative candidates who could not undergo complete resection of the disease. A subgroup of patients has been identified for whom local control after RFA was equivalent to the resected group. Further studies are necessary to determine the efficacy of RFA versus resection. We would suggest that the time has come for a randomized trial.

2. Laparoscopic/open surgical approach

The use of a laparoscopic or open surgical approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors.[37-39] Berber *et al*.[39] reported that local recurrence was identified in 21.7% of tumors on CT scans with a mean follow-up of 17 months (median, 12 months; range, 3 to 68 months). The local recurrence rate per tumor was highest for colorectal metastasis (34%), followed by noncolorectal, nonneuroendocrine metastasis (22%), HCC (18%), and neuroendocrine metastasis (6%). The Cox proportional hazard model identified tumor type, tumor size, ablation margin, and blood vessel proximity to be independent predictors of local recurrrence. The next advantage is the use of intraoperative US, which provides better resolution of the number and location of liver tumors. Ibrahim reported that laparoscopic ultrasound identified 19 new malignant lesions (18.4%), in comparison with the result of preoperative imaging.[40] In general, great difficulty can be encountered during laparoscopic RFA of lesions in contact with the diaphragm. However, a hand-assisted technique can offer traction while the natural diaphragmatic attachments of the liver provides countertraction. Machi *et al*.[41] discussed that the hand-assisted laparoscopic method combines the advantages of both laparoscopic and open surgical approaches for RFA treatment of liver tumors. The hand-assisted laparoscopic surgery approach has several advantages; it facilitates and expedites the procedure, reduces the stress factor on the surgeon, greatly improves exposure, and facilitates immediate and efficient control of bleeding vessels with the internal hand.

Although more invasive, open surgical RFA can be performed more easily and the puncture course of the RF needle can be more widely selected than that during a laparoscopic approach.[42,43] Radical open surgical RFA has an advantage of few ablation site recurrences, even when the nodules measure more than 4 cm in diameter or there are more than three nodules, because of fewer limitations of RF needle puncture.

3. Complications

A recent review indicated that the complication rates for percutaneous, laparoscopic, and open surgical RFA of hepatic tumors in 3,670 patients are 7.2%, 9.5%, and 9.9%, respectively.[44] Overall, the frequency of major complications of percutaneous RFA ranges from 0.6% to 8.9%.[45] In RFA of HCC, Llovet *et al*.[46] reported that dissemination along the puncture route was observed in 12.5% of their patients, so dissemination might not occur at such a high frequency. However, this complication was almost absent in many reports from Japan.[45] On the other hand, neoplastic seeding can occur after RFA of liver metastases.[47] In comparison with RFA of HCC, there are no papers on whether or not the seeding on RFA of liver metastases is frequent.

SUMMARY

The successful management of liver metastases from CRC can be obtained with RFA. RFA has a potential to achieve the same overall and disease-free survival rate as surgical resection for patients with liver metastases, while causing fewer side effects. The use of laparoscopic or open surgical approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors. In addition, an accurate evaluation of treatment response is very important for successful RFA therapy, since a sufficient safety margin (at least 0.5 cm) can prevent local tumor progression. Finally, because early and accurate diagnosis is necessary for the appropriate management of the complications, physicians should be familiar with all the features of the complications of RFA therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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