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Radiofrequency ablation improves survival over chemotherapy alone in patients with unresectable hepatic metastases from colorectal carcinoma.

Radiofrequency Ablation of Liver Metastases From Colorectal Carcinoma

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Background: Most patients with colorectal carcinoma will develop liver metastases. Radiofrequency ablation (RFA) has been utilized in metastatic CRC to help improve the survival gap between resectable and unresectable tumor.

Methods: The current use of RFA in selected patient populations is reviewed.

Results: RFA provides a survival benefit in patients with unresectable hepatic metastases from CRC compared with chemotherapy alone. It offers effective local tumor destruction in appropriately selected lesions and minimizes the morbidity and mortality of an open resection. Common complications are abdominal bleeding (1.6%), abdominal infection (1.1%), and injury to the biliary tree (1.0%). Mortality ranges from 0% to 0.5%.

Conclusions: Trials are underway to compare chemotherapy plus local ablation to chemotherapy alone. RFA is a tool that should be utilized by experienced individuals to achieve optimal oncologic outcomes.

Introduction

The liver plays a pivotal role in the survival of patients with colorectal carcinoma (CRC). Over 50% of patients with CRC will develop liver metastases during their

disease process. The prognosis of untreated liver metastases from CRC is universally poor, with a 5-year survival rate of less than 3%.¹ However, there is a difference in survival depending on the extent of liver metastases — patients with solitary metastasis have a median survival of 21 months, those with unilobar oligometastases have a median survival of 15 months, and those with widespread bilobar disease have a median survival of less than 12 months.¹ Interestingly, the liver can often be the only site of metastases. Autopsy studies have shown that 38% of patients who die of metastatic CRC have metastases solely in the liver.²

Therapies directed at the liver can thus have an impact on survival in the setting of metastatic CRC. Numerous cohort studies have shown a survival benefit for resection of hepatic metastases from CRC. The

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Abbreviations used in this paper: CRC = colorectal carcinoma, RFA = radiofrequency ablation.

Registry of Hepatic Metastases collected data from 24 institutions over a 37-year period and determined a 5-year survival rate of 33% after hepatic resection for CRC metastases.³ Others have corroborated this with 5-year actuarial survival rates ranging from 28% to 58%.^{4,7} These studies have identified several adverse prognostic factors in these patients. These include an initially node-positive CRC, a disease-free interval of less than 12 months, more than one liver metastasis, any metastasis greater than 5 cm in size, a carcinoembryonic antigen (CEA) level greater than 200, and a positive resection margin.^{4,5}

While surgical resection is considered the gold standard for treatment of CRC liver metastases, only 10% to 20% of patients with liver metastases are deemed resectable. These patients may not be candidates for surgery because (1) the lesion is anatomically ill-located (eg, adjacent to the confluence of the hepatic or portal veins), (2) the functional hepatic reserve after a resection would be insufficient, (3) the patient's comorbidities inhibit a major operation, or (4) extrahepatic metastases are present, further decreasing the likelihood of cure. These patients have disease that is more advanced than classical resectable liver metastases and have heretofore been relegated to receive chemotherapy. Modern regimens utilizing oxaliplatin or irinotecan have improved overall survival in this population ranging from 14.8 to 16.2 months^{8,9} but still fall short of long-term cure.

Radiofrequency ablation (RFA) has been applied in metastatic CRC to reduce the survival gap between resectable and unresectable disease. RFA produces localized tumor destruction by heating the soft tissues in the vicinity of the RFA electrode. Intraoperative ultrasonography is used to guide placement of the RFA needle and can be used to monitor the "outgassing" of nitrogen from thermally ablated cells (Fig 1). For



Fig 1. — Intraoperative photograph of RFA of a liver metastasis from CRC. An ultrasound probe is used to identify the metastasis and then guide the RFA needle into the metastasis. Alternating current passes through the needle to create local tissue temperatures between 70° and 100° C, resulting in cell death through protein denaturation and microvascular injury.

instance, when an expandable RFA electrode is used, the alternating current of approximately 400 kHz is passed across the needle electrode arrays that are deployed within the tumor. The surrounding electrons vibrate, which results in lethal temperatures ranging from 70° C to above 100° C within the tissue that instantaneously denature all molecules, including proteins and bilayered lipid cell membranes. In addition, the focal heat causes microvascular injury that leads to decreased blood flow and a zone of ischemia.¹⁰ This zone progressively enlarges and peaks at 72 hours due to secondary tissue inflammatory reaction. Under optimal conditions, current RFA devices can provide spheres of ablation up to 7 cm in diameter. The size and shape of the ablation vary with the applied device, the local environment in the liver, approximation to blood vessels, and tumor type. The area of ablation begins centrally (Fig 2) and enlarges as target temperatures are maintained over time (Fig 3). Hepatic metastases treated by RFA characteristically appear larger on postoperative computed tomography (CT) and can be mistakenly interpreted as progression of disease (Fig 4). Complete destruction of the metastasis is confirmed on CT by hypovascularity of the defect and by lack of growth of



Fig 2. — Intraoperative photograph in the initial phase of a RFA of a liver metastasis from CRC. The area of ablation begins as an area of central necrosis.

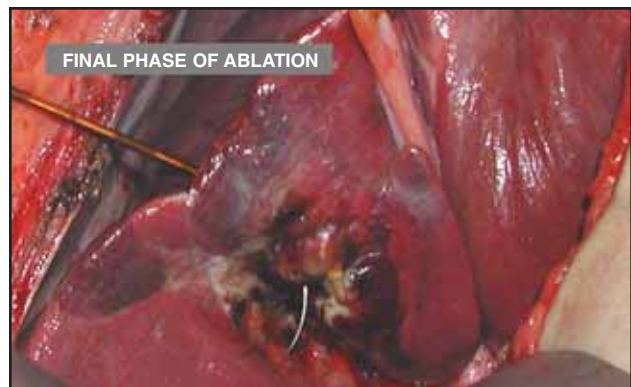


Fig 3. — Intraoperative photograph in the final phase of RFA of a liver metastasis from CRC. The area of ablation ultimately expands beyond the electrodes of the RFA needle. One of the ablation wires can be seen extending through the lesion. This emphasizes the importance of careful appreciation of the wire position as the device is fully deployed.

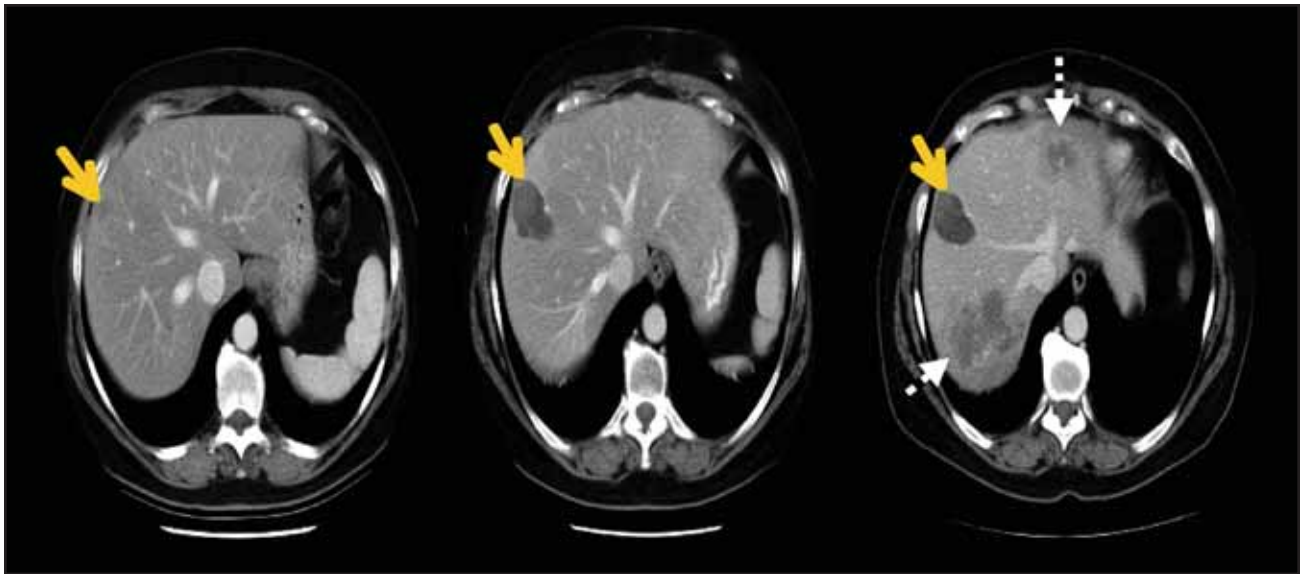


Fig 4. — Computed tomography appearance of a hepatic metastasis from CRC treated by RFA. The original lesion (arrow at left) was treated by RFA shortly after this exam was performed. Six months later, the ablation defect is characteristically larger and hypovascular. At 1 year after RFA, the defect has not increased in size or appearance, affirming destruction of the metastasis. However, new hepatic metastases (broken arrows) have developed in distant areas of the liver and appear distinctly different.

the ablation defect on subsequent CT examinations. An ablation defect that increases in size over time on serial CT scans should be considered a local recurrence.

Benefits and Complications

Much of the allure of RFA is its ability to achieve local tumor destruction with little morbidity and mortality. This is important in this patient population with unresectable liver metastases. Patients can be discharged on the same day or within 2 days.¹¹⁻¹³ Siperstein et al¹² found that quality-of-life parameters return to baseline by 1 week postoperatively. A recent meta-analysis of 95 published series reported a complication rate after RFA of 8.9%.¹⁴ The most common complications are abdominal bleeding (1.6%), abdominal infection (1.1%), and injury to the biliary tree (1.0%). Mortality after RFA is virtually zero, ranging from 0% to 0.5%.^{11,14-16}

RFA has been maligned for its high associated rate of local recurrence. Recurrence rates have ranged from 1.8% to 12% in surgical approaches^{12,13,16} and as high as 40% in percutaneous approaches.^{11,15} Solbiati et al¹¹ have shown that 96% of local recurrences occur within 12 months. The incidence of new hepatic metastases after RFA varies between 44% and 50%.^{7,13} These statistics are colored by the high-risk population in which RFA was first employed. A meta-analysis of published series found on multivariate analysis that tumor size less than 3 cm and a surgical approach (in comparison to a percutaneous approach) were associated with fewer local recurrences.¹⁷

Several large cohorts, nonetheless, have demonstrated the efficacy of RFA in the management of

traditionally unresectable liver metastases from CRC (Table 1). Solbiati et al¹¹ described their experience treating 117 patients with 179 liver metastases. Most patients (88%) had fewer than 3 lesions, with a median lesion size of 2.6 cm. A median survival of 36 months was achieved. In a prospective phase II trial, Berber et al¹⁸ treated patients with more advanced disease. With a mean number of 3.2 metastases and median size of 4.1 cm, patients had a median survival of 28.9 months. Multivariate analysis was performed to identify factors associated with increased mortality. In contrast to resection prognostic indicators, survival was not affected in those with more than three liver metastases, CEA level greater than 200 ng/mL, and the presence of extrahepatic disease. The sole predictor of increased mortality in these RFA-treated patients was lesion size greater than 5 cm, similar to patients treated by open resection.¹⁸

There has been no prospective comparison between RFA and open resection of CRC liver metastasis or between RFA and chemotherapy. Oshowo et al¹⁹ retrospectively compared patients with solitary CRC liver metastases treated by surgery and by RFA. Tumor size was smaller in the RFA group (3 cm) vs resection

Table 1. — Outcomes of Radiofrequency Ablation of Liver Metastases From Colorectal Carcinoma

| Study | No. of Patients | Local Recurrence | Median Survival (months) |
|--------------------------------|-----------------|------------------|--------------------------|
| Curley et al ¹⁶ | 61 | 3.3% | Not reported |
| Siperstein et al ¹² | 66 | 12% | Not reported |
| Solbiati et al ¹¹ | 117 | 39% | 36 |
| Berber et al ¹⁸ | 135 | Not reported | 28.9 |

Table 2. — Comparison of Radiofrequency Ablation to Other Treatment Modalities of Similarly Staged Liver Metastases From Colorectal Carcinoma

| Study | Treatment | Type of Metastasis | No. of Patients | Survival | P Value |
|----------------------------|--------------|------------------------|-----------------|--------------------|--------------|
| Oshowo et al ¹⁹ | RFA | Solitary, unresectable | 25 | Median: 37 months | Not reported |
| | Resection | Solitary, resectable | 20 | Median: 41 months | |
| Abdalla et al ⁷ | RFA | Unresectable | 57 | 4-yr overall: 22% | .005 |
| | Chemotherapy | Unresectable | 70 | 4-yr overall: <15% | |

(4 cm). Median survival for patients treated by RFA was 37 months vs 41 months for those treated by resection (Table 2). Abdalla et al⁷ reported their experience of RFA in the setting of unresectable metastatic CRC liver lesions. They found a significant improvement in survival in patients treated with RFA in comparison to patients treated with chemotherapy alone. These studies demonstrate that RFA significantly improves survival over chemotherapy alone in patients with traditionally unresectable disease. Furthermore, if the extent of liver metastases is comparable, RFA may offer a similar survival as surgical resection.

RFA has also expanded the definition of resectability. Adam et al²⁰ have described an aggressive approach to patients with unresectable liver metastases from CRC. Patients with unresectable disease underwent neoadjuvant chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin or irinotecan. Those patients who responded to such an extent that all remaining disease could be resected underwent an operation. For those with bilateral lesions, resection was performed on the most predominantly affected side while RFA was applied to the contralateral side. Utilizing this strategy, 12.5% of unresectable patients were converted to resectable and achieved a 33% 5-year survival rate.²⁰

The role of RFA in the management of hepatic metastases from CRC needs to be validated in a prospective randomized fashion. The European Organization for Research and Treatment of Cancer has initiated the CLOCC trial (chemotherapy plus local ablation vs chemotherapy), a phase III study in which patients are randomized to receive oxaliplatin, 5-fluorouracil, and leucovorin with or without RFA. No prospective trial comparing RFA to surgical resection in patients with similar extent of liver metastases has been created to date.

Conclusions

RFA provides a survival benefit over chemotherapy alone in patients with unresectable hepatic metastases from CRC. It offers effective local tumor destruction in appropriately selected lesions, and it minimizes the morbidity and mortality of an open resection. Consideration to the size of the lesions and the completeness of ablation are the key elements in reaching parity with surgical resection. RFA is a tool that requires advanced

skills, and it should be utilized by experienced individuals to yield the best oncologic outcomes.

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