

# Radiofrequency Ablation for Resectable Colorectal Hepatic Metastases

## *Is It Time for a Randomized Controlled Trial?*

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The role of radiofrequency ablation (RFA) in patients with colorectal hepatic metastases has been a heavily debated topic among liver surgeons, with a small number of authors arguing that this technique may be as effective as standard surgical resection in carefully selected patients.<sup>1-4</sup> No randomized controlled trials have been reported comparing RFA to the gold standard, surgical resection, and RFA has shown variable results in nonrandomized retrospective studies, with most reports showing inferior outcomes for RFA.<sup>5-7</sup> RFA has been an especially difficult technology to assess in terms of efficacy because of dissimilar treatment cohorts, for example comparing RFA of unresectable metastases to surgical resection. In addition, variability in defining resectability, as well as variation in use of chemotherapy<sup>8</sup> further cloud outcome results. Thus, with no level I evidence to support its use, most liver surgeons have adopted the view that RFA should only be used in patients with unresectable malignancy or as an adjunct to resection.<sup>5,6,8</sup>

In the current issue of "Annals of Surgery," Otto et al<sup>9</sup> detail results of a novel strategy in which RFA was used on a highly selective basis in preference to surgical resection in patients with "early," presumed high-risk, colorectal metastases. Their aim was to avoid operative intervention in patients who had a significant likelihood of returning with additional metastatic disease in follow-up, in other words, patients in whom liver resection may have been futile. According to their standardized clinical pathway, all patients with early colorectal metastases, (ie, detected within the first year after colorectal resection), were preferentially treated by RFA, where possible. Hepatic resection was only performed in patients who were deemed not amenable to this approach. Patients were considered for RFA if the number of lesions did not exceed 5 and the maximum diameter of the largest tumor was under 5 cm. In patients with 4 or 5 lesions in the liver, the RFA procedure was staged with an interval of several weeks between each RFA session. RFA was performed using the percutaneous approach whenever feasible, in an attempt to minimize operative intervention. Patients were managed surgically with open liver resection only if metastases were 5 cm or larger in diameter, if there were more than 5 metastatic sites, if lesions were superficial (with risk of adjacent bowel injury during attempted RFA), or when tumors were in proximity to large vessels or bile ducts where RFA may have either been ineffective or resulted in injury to major biliary radicals.

The authors claim that the 2 treatment groups were similar in overall demographic features, except for total tumor diameter where, not surprisingly, the surgery arm had larger tumors. Tumors treated with RFA had a median diameter of 30 mm compared with 50 mm in the resection group ( $P = 0.004$ ). A total of 110 patients fulfilled selection criteria for analysis between 2002 and 2008, with 28/110 (25.5%) patients treated with RFA and 82/110 (74.5%) treated by open hepatic resection. Impressively, there was no mortality in either arm of the study related to the RFA or surgical treatment. The authors found that, compared with surgical patients, patients treated with RFA had a significantly higher rate of local recurrence and at a more rapid rate than patients treated with surgical resection. The median time to disease progression was 203 days in the RFA group and 416 days in the surgical arm ( $P < 0.001$ ). Local recurrence per lesion treated by RFA was 16% and local recurrence per patient occurred in 32% of patients treated with RFA versus only 4% of patients treated with surgery ( $P < 0.001$ ). Total hepatic recurrence, ie, local recurrences plus new liver metastases that appeared elsewhere in the liver occurred in 18/28 (64.3%) after RFA versus 30/82 (36.6%) after surgery ( $P = 0.014$ ). However, almost twice as many patients, 50% from the RFA group versus 27% from the surgery group, were amenable to repeated local treatment. The estimated 3-year overall survival was not different between the 2 treatment groups, 67% in the RFA group and 60% in the surgical arm ( $P = 0.93$ ). Multivariate analysis demonstrated 2 independent predictors of overall survival, the number of hepatic metastases at initial treatment and the development of new liver metastases. The authors conclude that, despite striking differences in local tumor recurrence and shorter time to progression in patients undergoing RFA, survival in patients with early colorectal

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**TABLE 1.** RFA Treatment of CRM, Either a Comparison to Resection (Rxn) or RFA Alone

Author	Year	Patients (n) RFA Vs. Rxn	Median Follow-Up (mo)	LR (%) RFA Vs. Rxn	Overall Survival RFA Vs. Rxn
Elias et al <sup>11</sup>	2002	47 (RF only)	18	34	—
Oshowo et al <sup>1</sup>	2003	25 vs. 20	—	—	53 vs. 55% (3 yr)
Livraghi et al <sup>10</sup>	2003	88 (RF only)	33	40	—
Aloia et al <sup>5</sup>	2006	30 vs. 180	31	37 vs. 5	27 vs. 71 (5 yr)
White et al <sup>6</sup>	2007	22 vs. 30	17(RF), 68(Rxn)	55 vs. 12	0 vs. 58 (5 yr)
Lee et al <sup>7</sup>	2008	37 vs. 116	38	30 vs. 7	49 vs. 66 (5 yr)
Otto et al <sup>9</sup>	Current	28 vs. 82	—	32 vs. 4	67 vs. 60 (3 yr)

LR = Local Recurrence.

metastases does not seem to depend on the mode of treatment. They also suggest that consideration should be given to a phase 3 prospective randomized trial, modeled after the current report, to compare RFA to standard surgical resection.

The current report introduces a unique patient group for consideration of RFA, namely patients presenting with hepatic metastases within 1 year of surgery and presumed to be at high risk of additional recurrences (in the liver and elsewhere). The essential question is whether the preferential use of RFA in all suitable patients allowed for local control of the visualized liver tumor sites to determine what additional metastatic sites of disease might develop in follow-up, in other words the “test of time approach.”<sup>10</sup> Liver surgeons stress that 30% to 60% of patients undergoing hepatic resection of colorectal metastases will be alive at 5 years, but this means 40% to 70% of patients will have died, usually with additional sites of malignancy and disease progression. Use of RFA, as in the current report, could allow patients doomed to develop additional metastatic disease, either in the liver or at an extrahepatic location to be spared futile liver surgery, potentially reducing overall health care costs and treatment-associated morbidity. This risk has to be balanced against any potential inferior treatment risk to the patient with this approach, namely the allowance of recurrence or potential tumor dissemination. The authors of the current report argue that since overall survival was similar (but at only 3-years survival follow-up), then this strategy does not appear to have had an adverse effect, despite earlier and increased recurrence in the RF group. Table 1 lists some prior reports using RFA for colorectal liver metastases. While several studies assessing overall 3-year survival appear to have similar results, this has not been true when 5-year outcomes are included.

Unlike prior reports where RFA is reserved for patients with unresectable tumors (more advanced disease), in the current report, RFA is used in patients with potentially less advanced disease (smaller tumors, less in number) than in the surgery arm. The authors suggest that the larger tumor diameter and allowance for a greater number of metastatic sites in the surgery arm did not skew this group to a more advanced stage cohort. Perhaps, there is a significant possibility that selection bias has influenced study results. If the overall survival results are equal as suggested by the authors based on 3-year outcomes, could the surgery arm results have been improved if patient groups were completely equivalent at study entry? Said another way, would the RFA patients have had a better long term survival if they had undergone initial surgery? The answer to this question is speculative and unknown at this time, but will be an important consideration if designing a prospective randomized trial.

On the surface, results of the current report appear to provide some support for a randomized controlled trial of RFA versus resection in patients with resectable colorectal metastases. However, this will require very careful oversight and may be impossible to complete on a logistical basis. Use of percutaneous RFA is a highly technical proce-

ducing requiring careful needle guide placement in the volumetric center of the intended tumor target, or worse in the case of larger tumors, precise overlapping fields for complete tumor destruction, and has been associated with increased recurrence compared with surgical techniques.<sup>4,12</sup> Local recurrence after RFA is likely the result of misalignments in tumor targeting and variations in local blood flow, and was still 16% on a per lesion basis from this group of experienced interventionists at a center highly focused on this technique in the current report. By our estimates, design of a phase 3 randomized trial could require a very large number of patients for trial completion. For the sake of argument, let us assume the higher rate of disease progression in the RFA arm resulted in decreased survival by 5-years, for example, 35% overall survival for the RFA arm versus 45% in the surgery arm. By our calculations, a prospective trial with an 80% power to detect this difference and at 2-sided 5% significance using the log-rank test would require 354 patients in each arm of the study (assuming there is no loss to follow-up during study period). In case of loss to follow-up, which is inevitable in any study, the number of patients needed would be larger, and a trial designed to prove noninferiority of RFA, compared with surgical resection, could require substantially more patients. In the current report by Otto et al, only 28 (25.5%) of the 110 treated patients met criteria for treatment with RFA. If one were designing a phase 3 randomized trial, then only patients initially meeting the RFA selection would be eligible for randomization. Thus, in the current study, taking place at a high volume European liver surgery center over 6 years in duration, only 28 patients would have been eligible for randomization leaving only 14 in each arm of the study, or less than 5 patients per year accrued to the clinical trial.

Interestingly, the authors called the current approach a “clinical pathway” and deemed that it did not require institutional review board (IRB) approval. Whether or not one should debate the authors’ logic in the current report,<sup>13,14</sup> suffice it to say that based on the available data, a randomized investigation of RFA versus surgical resection of colorectal metastases to the liver would almost certainly not be amenable to such patient treatment assignment and would require informed consent under the auspices of an IRB. This would probably reduce patient accrual to even less than the 5 per year at the authors’ center, since many patients would already have preconceived notions of their preferred treatment strategy, some wishing to have a less invasive percutaneous RFA of their liver tumor (s) and others wishing for “more proven” standard surgical resection. From this point of view, accrual of 700 patients for randomization would likely require a very large multicenter trial, on the order of at least 50 sites, which would introduce its own set of challenges for standardizing the RFA approach and follow-up.

The above estimates assume that patients receive a standardized adjuvant chemotherapy regimen, following resection of their colorectal primary and that this is able to be controlled. In the current report, 83/110 (75.5%) patients overall had stage III/IV

primary tumors, and 68/83 (82%) received systemic chemo. However in patients who did receive systemic adjuvant therapy, 41/68 (60.3%) were treated with a 5-FU based regimen, outdated by almost any standard even in 2002 at the time of initiation of the standard clinical pathway. Whether or not, use of a more modern chemotherapy regimen would impact the results of a phase III trial is unknown, but should be anticipated in any trial design. Variability in chemotherapy usage would likely result in patient exclusions, further hampering the ability to complete such a trial.

The authors of the current report are to be commended for developing a novel management strategy for patients with early hepatic metastases from resected colorectal cancer. Use of this approach was associated with a significantly higher disease progression rate as well as a higher rate of local recurrence in patients treated with RFA, but when recurrence did occur, patients in the RFA arm of the study had a significantly greater likelihood of undergoing repeated local treatment. Thus far, 3-year overall survival is similar in both arms of the study, but additional follow-up is required before definitive conclusions can be reached. Results from this phase I/II trial suggest that RFA is feasible for use in this setting and provide support for the authors' contention that a phase III randomized controlled trial should be considered. Unfortunately, the logistical and patient accrual issues appear to be insurmountable for such a trial to take place at this time. Until such data become available, surgeons and physicians should not conclude that RFA offers outcomes that are equivalent to surgical resection, even in patients with early recurrence.

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#### REFERENCES

- Oshowo A, Gillams A, Harrison E, et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. *Br J Surg*. 2003;90:1240–1243.
- Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. *J Vasc Interv Radiol*. 2008;19:712–717.
- Mulier S, Ni Y, Jamart J, et al. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol*. 2008;15:144–157.
- Mulier S, Ruers T, Jamart J, et al. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? An update. *Dig Surg*. 2008;25:445–460.
- Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. *Arch Surg*. 2006;141:460–466; discussion 466–467.
- White RR, Avital I, Sofocleous CT, et al. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. *J Gastrointest Surg*. 2007;11:256–263.
- Lee WS, Yun SH, Chun HK, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. *J Clin Gastroenterol*. 2008;42:945–949.
- Stang A, Fischbach R, Teichmann W, et al. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. *Eur J Cancer*. 2009;45:1748–1756.
- Otto GD, Düber C, Hoppe-Lotichius M, et al. Radiofrequency ablation as first line treatment in patients with early colorectal liver metastases amenable to surgery. *Ann Surg*. In press.
- Livraghi T, Solbiati L, Meloni F, et al. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the “test-of-time approach.” *Cancer*. 2003;97:3027–3035.
- Elias D, De Baere T, Smayra T, et al. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. *Br J Surg*. 2002;89:752–756.
- Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg*. 2005;242:158–171.
- Parvizi J, Tarity TD, Conner K, et al. Institutional review board approval: why it matters. *J Bone Joint Surg Am*. 2007;89:418–426.
- Department of Health E, and Welfare. The Belmont Report: Ethical Principles and Guidelines for the protection of human subjects of research. 1979. Available at: <http://ohsr.od.nih.gov/guidelines/belmont.html>.