

Radiofrequency ablation or resection for small colorectal liver metastases - a plea for caution

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Submitted Mar 08, 2013. Accepted for publication Apr 11, 2013.

doi: 10.3978/j.issn.2223-4292.2013.04.01

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Colorectal cancer (CRC) is among the leading causes for cancer death worldwide (1) and remains a serious problem for the public healthcare systems due to continuously growing costs of the treatment, and relatively low cure rates, especially in advanced stages of disease. The liver is secondary only to lymph nodes as a site for metastasis from primary CRC - about 50% of the patients developed liver metastases (CLM) during their course of disease, and in approximately $\frac{3}{4}$ of these the liver is the only site of distant spread (2). To date, resection of the metastases (LR) is the only proven potentially curative treatment option for the patients with CLM. However, despite the current advances in the concepts and techniques in liver surgery, the vast majority of the patients with CLM as well as those with other liver malignancies are not amenable to curative surgery. There is a growing need for efficient and minimally invasive techniques for the treatment of unresectable primary and metastatic liver cancer. In these circumstances several liver-directed local treatment modalities were developed and intensively explored during the years, with the aim to achieve local control, initially in patients with unresectable liver tumors, and eventually to compare further the results with those of hepatic resection. Among these local treatment options, the radiofrequency ablation (RFA) has become most popular and widely accepted local ablation modality during the past two decades. The accumulated evidence from several studies, including randomized trials, proved the safety and efficacy of RFA in the treatment of patients with hepatocellular carcinoma on cirrhosis (HCC) and even the superiority of RFA over hepatic resection in some subgroups of patients with HCC (3). None of these evidences can be directly applied to the patients with CLM.

The benefit from RFA for the patients with unresectable CLM in terms of prolonged progression-free survival (PFS) can be regarded as proven by several nonrandomized and one randomized study - EORTC 40004 (4). In the latter, RFA plus systemic chemotherapy are compared with systemic treatment alone. The median overall survival (OS), 30-month OS, and PFS are respectively 45.3 months, 61.7% and 16.8 months for the combined treatment *vs.* 40.5 months, 57.6% and 9.9 months for systemic treatment group. The EORTC 40004 does not demonstrate OS advantage from RFA and all non-randomized studies which demonstrate the OS benefit from adding RFA to systemic treatment have used historical and/or not well matched control groups. There is no any prospective, randomized trial comparing the efficacy of RFA with that of LR for CLM currently available. The literature data suggests that if local control is achieved by RFA as a sole procedure or as an adjunct to LR, the combination with current systemic therapy can reflect in prolonged OS compared to chemotherapy alone (5). Some authors go further ahead and propose RFA as a first-line treatment for the patients with resectable CLM, in order to "spare" patients from "unnecessary" LR if local control is achieved by RFA (6,7), however they have been criticized by several arguments (8,9).

Recently Solbiati *et al.* (10) reports the long-term results of the treatment of small CLM with percutaneous RFA plus irinotecan- or oxaliplatin-based systemic therapy. This report includes 99 patients with minimum of 3 years follow-up. No patient has had liver dysfunction or poor performance status and has been included in the study because of ineligibility (80.1%) or refusal (19.9%) of LR. The vast majority of the patients in this report - 73.7% have had one or two CLM, and the mean size of metastases has

been 2.2 cm. The authors report 88.1% overall complete ablation rate in this highly selected group of patients. At a median follow-up of 53 months, 40.4% of the patients have developed new CLM and almost each third patient (32.3%) has reported to have local tumor progression at the ablation site. 67.7% of the patients have died (67 of 99), and 18.1% have been disease-free at last follow-up. The median survival of the patients with incomplete ablation in this study has been 30 months. Estimated 1-, 5- and 10-year OS rates have been 98%, 47.8% and 18% respectively. The authors conclude that these results are equivalent to results from surgical resection. Is it really true?

Strong scientific evidence is needed in order to propose a change in the paradigm of the treatment of CLM, and all the published results should be carefully interpreted, keeping in mind available evidence about the effectiveness of RFA, as well as some important rules when comparing results with those of LR. In concordance with the available evidence, the above study confirms the benefit from RFA for patients with unresectable CLM, when complete ablation is achieved. But the reported difference between incomplete ablation rate of 11.9% and local tumor growth at the ablation site of 32.3% ultimately demonstrates the limited possibilities to evaluate the effectiveness of RFA with current imaging. As the tumor progression at the RFA site is a consequence of incomplete ablation, this report shows again that even in the treatment of small CLM with percutaneous RFA by most experienced team, the local control is not achieved in about one third of the patients. This result is too far from the reported local control rate of any study of LR of CLM. The oncologic safety and efficacy of RFA is further questioned by the meta-analysis of the percutaneously treated 3046 CLM, because of the lack of safety margin at the ablation site in 88.4% of treated lesions (11). Furthermore, there is no clinical data to confirm strong radiological/pathological correlation when the local control after RFA of CLM is estimated. Another limitation for percutaneous RFA comes from the inability of the current imaging studies to detect small hepatic and/or extrahepatic lesions compared with intraoperative staging, which includes intraoperative ultrasound (12). The latter fact adds unpredictable bias in estimating “new” lesions in any study of percutaneous RFA of CRLM.

The argument that even an incomplete tumor ablation can be beneficial is also questionable - the median survival of 30 months achieved in this group of patients in Solbiati's report compares unfavorably with the median survival of 40.5 months in patients with comparable extent of disease in

EORTC 40004 study, treated with systemic chemotherapy alone. When comparing long-term oncologic outcomes of percutaneous RFA of CLM with those of LR it is important also to follow some rules to avoid misleading conclusions. Most of the reported series of LR of CLM include patients with various extents of disease which have had different prognosis according to widely accepted and externally validated prognostic scoring systems as Fong's score or Basingstoke predictive index (13,14). By these, the number and the size of CLM both are independent predictors of outcome. In almost all of the studies of percutaneous RFA for CLM these variables are limited by exclusion criteria. So, the comparison with the results of LR should be done with carefully matched groups. The team from the MD Anderson Cancer Center reported the results of such nonrandomized comparison of RFA to LR in patients with solitary CLM: 5-year overall- and disease-free survival 27% versus 71% and 0% versus 50% for RFA versus resection, respectively (15). Apart from the clear demonstration that resection determines outcome, the latter report opens again the question about the influence of the RFA on the natural course of disease as even if in 60% of the patients RFA achieves local control, there have been no 5-year disease-free survivors. Finally, as the estimated 18% 10-year survival in the above RFA study by Solbiati *et al.* is compared with those of LR of CLM without any attempt for matching the extent of disease, the authors' conclusion that their results are equivalent to results from surgical resection should be questioned. Moreover a median follow-up of 53 months is too short to draw such conclusion. The need for longer follow-up was noted by all the studies of 10-year survival after LR of CLM, as substantial part of the patients can develop new metastases even after 5-year of disease-free survival (16-19). A report of the long-term results of a randomized study of adjuvant treatment after LR of CLM with a follow-up of minimum 6 years (median 10.3 years) demonstrates that 38.7% 10-year survival can be achieved with combined aggressive treatment of resectable CLM (20). Importantly this study also confirms that patients with limited disease (Fong's score 0 to 2) have better prognosis after LR irrespective of the adjuvant treatment regimen - median survival has been 82.8 months in the fluorouracil monotherapy group. These figures are still much better than any reported results of RFA of CLM.

The evidence-based use of RFA in CLM is still evolving and is far from definitive conclusions. There is still no strong evidence that RFA of CLM can be beneficial in terms of overall survival, as selection bias regarding the

number and size of the CLM exists in all of the RFA studies. However the PFS benefit from RFA has been considered proven, even in the presence of limitations regarding the estimation of completeness of the ablation of CLM. Comparison between well matched groups of patients with CLM demonstrates that LR offers significant advantage over RFA in terms of local control, long-term overall- and disease-free survival. As it is still not clear whether incomplete ablation is beneficial or harmful, larger-scale randomized studies on patients with unresectable CLM are needed to draw conclusions. The currently available data does not justify proposing RFA as an alternative to LR in resectable CLM, even in order to use RFA as a part of “test of time” approach. In these circumstances it is also highly unlikely for any design of a randomized trial aiming to compare LR to RFA in resectable CLM to pass the institutional review boards. The oncologic safety and efficacy of RFA should be further carefully explored in unresectable CLM.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Julianov A. Radiofrequency ablation or resection for small colorectal liver metastases - a plea for caution. *Quant Imaging Med Surg* 2013;3(2):63-66. doi: 10.3978/j.issn.2223-4292.2013.04.01