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A Place for Radiofrequency Ablation in the Treatment of Resectable Colorectal Liver Metastases?

To the Editor:

We thank de Meijer et al. for commenting on our review paper "Radiofrequency Ablation versus Resection for Resectable Colorectal Liver Metastases: Time for a Randomized Trial?".[1,2] We are pleased to see that our proposal has triggered an active discussion about the setting up of such a trial.[1,3,4]

It is not clear to us why de Meijer et al. state that our review compared apples with oranges. On the contrary, we have emphasized that results of radiofrequency ablation (RFA) for *unresectable* colorectal liver metastases (CRLM) cannot be compared to results of resection for *resectable* CRLM. Resectable colorectal metastases may have a more favorable location and a different biological behaviour than unresectable CRLM. This inappropriate comparison, resulting in the incorrect conclusion of "inferior" results after RFA, is unfortunately being made in many recent review papers and is being used as an argument against RFA for *resectable* CRLM.

We agree with the statement by de Meijer et al. that current imaging techniques in detecting incomplete ablation and local recurrence after RFA for CRLM are not perfect and that there is room for innovation and improvement.[5] Only a few studies, mostly with a limited number of patients, have compared imaging with histology (biopsy or resection) and/or long-term follow-up after RFA of liver metastases. Sensitivity and specificity were calculated for computed tomography (CT; 44–97% and 63–100%, respectively), magnetic resonance imaging (MRI; 73–89% and 100%), positron emission tomography (PET; 61% and 98%), and PET-CT (84% and 100%).[6–8] This means that the true histological local recurrence rate after RFA is probably being underestimated. The same underestimation by imaging however probably holds true for the 3.8–10.4% local recurrence rate on imaging after resection of CRLM.[2,9] In conclusion, although we agree that some degree of uncertainty exists about completeness of local eradication after RFA as well as after resection, we do not feel that this should prevent the setting up of a randomised study. Some degree of diagnostic uncertainty will always exist in all domains of medicine.

De Meijer et al. estimate that morbidity of resection will not be much higher than that of RFA. We are not so sure about this. Some small resectable CRLM are indeed superficial, and resection may be associated with limited morbidity. Other small resectable CRLM however are deeply situated and can only be removed by major resection with increased morbidity. In our paper, we showed that local recurrence rate is similar after open and laparoscopic RFA of CRLM.[2] Therefore, our trial proposal would allow both approaches for surgical RFA.[2] It is clear that morbidity of laparoscopic RFA is smaller than of open RFA.

De Meijer et al. propose to postpone a randomised trial until genomic and proteomic markers of aggressiveness of tumours are better understood. While such studies are very interesting and may hopefully contribute to therapeutic algorithms in the future, they should not prevent randomised trials from being conducted at the present. Randomised trials are currently being conducted to determine optimal chemotherapy protocols for various cancers, with inclusion, exclusion and stratification criteria based on clinical and histological criteria, without waiting for full knowledge on genomic and proteomic markers of these cancers.

De Meijer et al. emphasize the need for more standardisation in RFA research. We could not agree more and we have we have contributed to the consensus on terminology of RFA.[10,11]

They also emphasize the need for more prospective data collection before embarking on a randomised trial. Data on local recurrence rate after RFA of resectable CRLM are currently not available and we feel that it is not ethical to generate such data outside of a randomised trial with the implicit risk of patient selection and hence biased results. Moreover, even when more prospective studies find a similar local recurrence rate for resection and RFA in a selected group of patients, the profoundly different immunological and other biological effects of RFA and resection may lead to a marked difference in survival. Only a randomised trail can answer which of both treatments leads to better survival. We feel that our paper showed that sufficient scientific data exist today to justify the setting up of such a trial, and to define safe inclusion criteria to minimise local recurrence after RFA. Waiting to perform a randomised trial until we have a perfect knowledge of all background clinical and basic science data[4] carries the risk of waiting indefinitely and losing a window of opportunity. A survey from Germany reported that 25.9% of hospitals are already performing RFA for resectable tumors.[12]

A randomised trial that was very similar to our proposal has already been carried out. A group of 30 patients with multiple resectable CRLM (mean tumor diameter 3.0 cm, mean number of tumors per patient 3.5) were randomised to undergo either resection or microwave ablation through a laparotomy. Survival rate in both groups was similar; while morbidity was smaller in the open microwave ablation group.[13]

In his editorial, Steven Curley sums up many variables that limit the efficacy of RFA. We agree, as mentioned in our paper, that large tumour size, percutaneous use, earlier chemotherapy and limited experience with RFA all negatively affect treatment efficacy, and hence inclusion of such patients in a randomized trail may ethically not be justified.[3] For these very reasons we proposed that only a selected subgroup of patients (only small tumors (<3 cm), only by surgical approach, only tumors large away from vessels large, only by experienced physicians) be included in such a randomised trial. The main argument, however, of Curley against our proposal for a randomised trial is his fear that the results of a well-designed and carefully performed study might be abused to justify RFA by any approach, by any physician and for any size of tumour, leading to catastrophic results. We fully understand his argument but rather feel that the risk of improper use of RFA, as increasingly is the case, is larger in the absence of sound scientific evidence than in the presence of results of a randomised trial.

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REFERENCES

1. de Meijer VE, Ijzermans JN, Verhoef C. A place for radiofrequency ablation in the treatment of resectable colorectal liver metastases? *Ann Surg Oncol* 2008 Mar 8; doi: 10.1245/s10434-008-9843-z [Epub ahead of print].
2. 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; 15:144–57.
3. Curley SA. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol* 2008; 15:11–3.
4. Tez M, Tez S. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol* 2008 Mar 11; doi: 10.1245/s10434-008-9856-7 [Epub ahead of print].
5. Ni Y, Chen F, Mulier S, et al. Magnetic resonance imaging after radiofrequency ablation in a rodent model of liver tumor: tissue characterization using a novel necrosis avid contrast agent. *Eur Radiol* 2006; 16:1031–40.
6. Dromain C, de Baere T , Elias D, et al. Hepatic tumors treated with percutaneous radio-frequency ablation: CT and MR imaging follow-up. *Radiology* 2002; 223:255–62.
7. Mason T, Berber E, Graybill JC, et al. Histological, CT, and intraoperative ultrasound appearance of hepatic tumors previously treated by laparoscopic radiofrequency ablation. *J Gastrointest Surg* 2007; 11:1333–8.
8. Kuehl H, Antoch G, Stergar H, et al. Comparison of FDG-PET, PET/CT and MRI for follow-up of colorectal livermetastases treated with radiofrequency ablation: initial results. *Eur J Radiol* 2007 Dec 21; [Epub ahead of print].
9. Leblanc F, Fonck M, Brunet R, et al. Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. *Eur J Surg Oncol* 2008; 34:185–90.
10. Mulier S, Miao Y, Mulier P, et al. Electrodes and multiple electrode systems for radiofrequency ablation: a proposal for updated terminology. Electrodes and multiple electrode systems for radiofrequency ablation: a proposal for updated terminology. *Eur Radiol* 2005; 15:798–808.
11. Mulier S, Ni Y, Frich L, et al. Experimental and clinical radiofrequency ablation: proposal for standardized description of coagulation size and geometry. *Ann Surg Oncol* 2007; 14:1381–96.
12. Birth M, Hildebrand P, Dahmen G, et al. Present state of radio frequency ablation of liver tumors in Germany. *Chirurg* 2004; 75:417–23.
13. Shibata T, Niinobu T, Ogata N, et al. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. *Cancer* 2000; 89:276–84.

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