Author reply: Radioembolization for colorectal liver metastases

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We thank Dr Vente and colleagues for clarification that they used ‘any response’ (AR) as an end point in their meta-analysis.¹ We apologize for this error in our discussion of their study. Although the assessment of disease by cross-sectional imaging using the Response Evaluation Criteria In Solid Tumors (RECIST)² has improved international standardization in large-scale oncology trials, the anatomical approach to measuring response can be criticized on two levels. Firstly, for many tumors, particularly those treated by radiotherapy or biological agents, there is only a weak relationship between anatomical response and patient benefit. Indeed, clinical trials that use objective response rate (ORR) or AR as their primary end point provide minimal useful information to advise individual patients on how best to improve the prognosis from their condition and direct their personalized care.^{3,4} Indeed, when patients ask clinicians for guidance about living longer or improving their quality of life, trial statistics on ORR and AR provide little comfort. Secondly, for certain therapies (including radiotherapy) there can be an apparent increase in tumor size, or even the appearance of new lesions, in the event of a favorable patient outcome to treatment. This ‘false’ increase in size has been well documented following radioembolization (RE) therapy, probably because of intratumoral and peritumoral edema and hemorrhage.⁵

Although interesting from a research perspective, we do not agree with Dr Vente and colleagues that functional imaging using fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) should be incorporated routinely into tumor assessment. The use of functional and dynamic imaging has not yet been standardized internationally, nor validated prospectively in trials of RE, and

it is certainly not recognized by regulatory authorities as a standard of care in the treatment of metastatic colorectal cancer (mCRC). It is not yet clear how ¹⁸F-FDG imaging should be incorporated into RE treatment as a means of selecting patients or assessing response, and we recommend that researchers should incorporate ¹⁸F-FDG imaging into future clinical trial design to standardize the application of this technique and to establish its utility in evaluating these parameters.

Expanding on the final point made by Dr Vente and colleagues, we strongly feel that the primary end point of large-scale trials of RE should be overall survival. However, we do recognize that overall survival data might be confounded by subsequent treatments received after participants have completed protocol therapy, for example by cross-over of a patient from the control arm to the investigational arm. Furthermore, the increasingly prolonged duration of participant survival makes completion of mCRC trials with overall survival as the primary end point impractical, due to the long time-interval required for follow-up after completion of protocol therapy, in comparison to other studies using, for example, disease free survival as the primary end point. Therefore, we believe that progression-free survival (PFS) may be a reasonable interim end point for such trials. Perhaps the most interesting aspect of the incorporation of RE into multi-modality management might be the number of first-line inoperable patients successfully down-staged to resection. Down-staging to resection is defined as a treatment regimen that renders a patient potentially curable by R0 liver resection. On the basis of contemporary data from studies such as the recent Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases

(CELIM) randomized phase II trial,⁶ in patients with an initial presentation of unresectable disease we advise potential investigators to measure treatment efficacy by the number of patients undergoing R0 resection following first-line therapy including RE.

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Competing interests

R. A. Sharma declares an association with the following company: Sirtex Medical Ltd. See the article online for full details of the relationship. The other authors declare no competing interests.

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