

carcinoma is possible. Therefore, pretherapeutic dosimetric calculations based on ^{99m}Tc -MAA imaging, as reported with HCC, . . . should be seen critically.” This statement about HCC cannot be based on a study dealing with a different pathology and a different kind of microsphere. Metastases and HCC are different types of tumors (more peripheral vascularization in HCC and a higher proportion of small lesions in metastases). Results observed with one type of lesion cannot be extrapolated to the other. Ulrich et al. extend their conclusions from results obtained with resin spheres (SIR-Spheres) to glass spheres (TheraSphere; BTG), as if the two medical devices were identical. This is absolutely not the case from the dosimetric and biologic point of view (9). Activity per sphere is 50 times lower for the resin spheres than for the glass ones, requiring a 50 times higher number of particles to give the same mean absorbed dose, with a consequent increased real embolic effect. Because of this tremendous difference between the number of injected particles, we cannot agree about extrapolating results concerning the predictive value of ^{99m}Tc -MAA scintigraphy from resin to glass microspheres.

The evidence on HCC treatment provided by the teams of Rennes (10) and Milan (2), both of which used glass spheres, in contradiction to what is reported by Ulrich et al., was not discussed adequately. In the first study (mean lesion size of 7.1 cm), ^{99m}Tc -MAA SPECT/CT was predictive of response with an accuracy of 90% (10). The lesion-absorbed dose was the only parameter associated not only with response but also with overall survival at multivariate analysis (10). Also, the second study found a dose–response relationship in HCC (2). Mean tumoral absorbed dose significantly correlated with the EASL response (Spearman $r = 0.60$, $P < 0.001$).

In conclusion, when reporting on the predictive value of ^{99m}Tc -MAA scintigraphy in SIRT, one should pay attention to the type of microspheres, the quantification method for estimating the ^{99m}Tc -MAA degree of perfusion, dosimetry issues, tumor type, lesion size, and the method of response assessment. At present, there is confirmed evidence that ^{99m}Tc -MAA SPECT–based dosimetry is predictive of response in HCC when glass microspheres are used. Published results with resin microspheres, especially in metastases, require additional studies to assess the predictive power of ^{99m}Tc -MAA scintigraphy. Conclusions from a methodologically weak study about the lack of predictive value of ^{99m}Tc -MAA uptake in liver metastases treated with resin microspheres should not be extrapolated to HCC treated with glass microspheres.

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REPLY: Thank you for giving us the opportunity to respond to the letter to the editor. Chiesa and coauthors raise sincere concerns over the study’s methodology and deny the negative outcome reported for the use of pretherapeutic ^{99m}Tc -macroaggregated albumin (^{99m}Tc -MAA) uptake for prediction of response after radioembolization in liver metastases of colorectal cancer (CRC). Some aspects raised in the letter represent meaningful concerns, which we address and set aside through detailed comments as well as an additional data analysis performed for that precise purpose. Other concerns expressed in the letter reflect a personal opinion on debatable points. The references mentioned to support these opinions direct the reader to review articles and through these, if analyzed in depth, to studies based on very small patient cohorts reporting on tumor biologies other than CRC (as in our study) or to studies involving no radioembolization at all.

To address the concerns expressed in the letter about a resolution-induced partial-volume effect on ^{99m}Tc -MAA uptake in small lesions, we performed an additional analysis of our data. In this analysis we included only lesions larger than 18 mm, as requested by the letter’s authors. In total, 233 of 290 lesions (45 of 48 patients) from our original publication were evaluated. To address doubts expressed with regard to the appropriate follow-up time point, we refer to MR imaging data at 3 mo. There was no significant correlation between the ^{99m}Tc -MAA uptake and lesion-based therapy response by changes in tumor diameter (responding/nonresponding lesion), by lesion-based Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or by patient-based RECIST

1.1 ($P > 0.05$). Thus, although lesional size admittedly is an important factor for focus visualization in SPECT imaging, this had no impact on the outcome of our analysis. In addition, in their letter, Chiesa and coauthors criticize our use of the Chang attenuation correction and attribute potential flaws in our outcome to that. The publication recommended in the letter for its technical appropriateness refers to an attenuation correction procedure quite similar to that in our protocol (1). We hypothesize that the contradictory results of that study on 8 patients may have to be attributed to the small patient cohort.

Coregistration of MR imaging data and SPECT data was performed with commercially available software (Fusion 7D; Mirada Medical) using mutual-information algorithms followed by manual fine tuning. As is necessary for any type of image coregistration, fusion results were checked for plausibility by experienced readers for every metastasis. This has been recommended even for elastic coregistration methods. In light of this diligent plausibility control, the concern expressed in the letter that “liver deformation can occur in 30 d” seems exaggerated.

The authors of the letter comment that “SIRT is a kind of radiation therapy” and “as such, efficacy should be discussed in terms of absorbed dose and radiobiologic models.” We suggest that to any clinician and his or her patient the outcome—as applied in our study—is decisive and represents a standard in clinical trials. The aim of our study was to assess the predictive value of pretherapeutic ^{99m}Tc -MAA uptake in liver metastases of CRC under the conditions of a retrospective study using the body surface area model. Several comments on our study have unfortunately ignored this aspect and suggest the use of the partition model as a favorable approach for individual dosimetry in metastatic CRC. In clinical practice the partition model is used mainly in patients with tumor lesions that are hypervascular, reasonably large, and limited in number, such as in hepatocellular carcinoma (HCC). In contrast, in CRC a high number of metastatic liver lesions with different vascularity or a frequently diffuse metastatic spread precludes clear definition of tumor and nontumor compartments (2) or reliable ratios. Furthermore, several authors have reported discordant ^{99m}Tc -MAA and ^{90}Y activity distributions as discussed in a recent reply (3), confirming that ^{99m}Tc -MAA is an imperfect surrogate for ^{90}Y resin microspheres and does not predict ^{90}Y resin distribution. In our opinion, the partition model cannot therefore be generally recommended for use in patients with liver metastases of CRC. However, neither these drawbacks nor the well-known limitations of the BSA model should stop us from searching for better solutions for individualized treatment planning and validation in radioembolization.

A further point of discussion in the letter is the follow-up protocol. The time interval of 6 wk “is definitely too short to observe an appropriate morphologic response.” Furthermore, RECIST is “not at all a validated method for the assessment of treatment response in SIRT.” The letter also quotes that “the most common change in the CT-appearance of the liver after SIRT is decreased attenuation in the affected hepatic areas” (5). All these propositions of the letter’s authors concerning response assessment are erroneous and misleading when used to comment on our study of radioembolization in CRC. First, the European Association for the Study of the Liver (EASL) criteria and modified RECIST, as suggested by Chiesa and coauthors, are validated only for HCC in the literature. There is not a single study proving that perfusion patterns such as those valid in the EASL criteria and modified RECIST are predictive in ^{90}Y -radioembolization outside of HCC.

In CRC studies, RECIST 1.1 is a validated response measure accepted by the Food and Drug Administration and the oncologic community in general. With regard to ^{90}Y -radioembolization, prospective randomized trials such as SIRFLOX (4) (a regulatory trial under Food and Drug Administration guidance) use RECIST 1.1 for the primary endpoint assessment. Thus, we do not see why the use of RECIST should be considered inappropriate for our study in the absence of data proving that RECIST is not eligible or that a valid alternative exists that is acceptable to regulatory agencies. In turn, we would ask what data the authors of the letter have in mind as proof that in patients with liver metastases of CRC and ^{90}Y -radioembolization with resin microspheres ^{18}F -FDG PET/CT is the only accepted imaging standard? No studies supporting these hypotheses are referenced by the authors of the letter. The only reference provided with regard to that point is a review article (5) describing personal opinions of the authors rather than an independent study. In addition, the section of that review article selected to emphasize that “. . .the classical approach of assessing response by measurement of tumor size may be of value only months after therapy” leads to a study assessing chemohormonotherapy in breast cancer, not ^{90}Y -radioembolization and CRC. The hypothesis put forward in the letter that “the most common change in the CT-appearance of the liver after SIRT is decreased attenuation in the affected hepatic areas” is also taken from that review article (5), which cites in support of this hypothesis a study (6) from 1993 describing 23 (!) patients with metastases of various origin (!) and without any clear correlation to prognosis. We consider the data presented by Chiesa and coauthors unhelpful for a discussion of the appropriate response criteria or time points for follow-up in a study on ^{90}Y -radioembolization and liver metastases of CRC such as ours.

To clarify the discussion we refer to recent retrospective studies that have shown a superiority of ^{18}F -FDG PET/CT in prediction of progression-free survival in comparison to RECIST, such as the study of Zerizer et al. (7). None of the authors of these studies consider RECIST to be inappropriate. In fact, Zerizer et al. conclude that the “data are encouraging and justify further evaluation in a larger study to check reproducibility” (7). We would suggest that these statements contribute better to the current debate on ^{18}F -FDG PET/CT as an imaging marker than those made by Chiesa and coauthors.

We agree that catheter position is an important factor in treatment with ^{90}Y -labeled microspheres. However, because of the retrospective character of our study, there were patients with different and identical catheter tip positions between the ^{99m}Tc -MAA and the ^{90}Y -labeled microsphere applications. In a subanalysis of our own data for patients with the identical catheter tip position (41 of the original 66 patients) for ^{99m}Tc -MAA and ^{90}Y -labeled microsphere applications at both follow-up time points (6 wk and 3 mo), there was no significant correlation between qualitative ^{99m}Tc -MAA uptake and therapy response by RECIST ($P > 0.05$). However, there are many other factors influencing the distribution of any particle released into the blood flow: number of particles, tumor biology, tumor load, pretreatment with chemotherapeutics, and physiologic hepatic blood flow, as well as flow alterations during the radioembolization process due to temporary embolization effects that cannot be estimated or overcome by any proposed approach (for further information, see our reply to the letter to the editor of Lam and Smits (8)). Further prospective basic research studies will be undertaken to answer these questions.

Finally, we would like to address the letter's statement that in our "Discussion" section we have drawn insubstantial conclusions about HCC. The quote from this section in our article is "...pretherapeutic dosimetric calculations based on ^{99m}Tc -MAA imaging, as reported for HCC, ... should be seen critically" (9). We propose that Chiesa and coauthors have misunderstood our intentions. What we meant to say was that even if pretherapeutic ^{99m}Tc -MAA-based dosimetry is valid in HCC, this cannot faithfully be extended to any other tumor biology. For liver metastases of CRC, our study underlines exactly that message.

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