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REPLY: We would like to thank Drs. Lam and Smits for their concerns and comments regarding the methodology in our study (*1*).

The aim of our study was to answer the frequently occurring clinical question of whether a patient with low or no ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) uptake in metastatic lesions should undergo ^{90}Y-radioembolization. The observation in our patient cohort with colorectal liver metastasis was that therapy response after ^{90}Y-radioembolization was independent of the degree of intratumoral ^{99m}Tc-MAA uptake. Consequently, our recommendation to the reader was that "therapy should not be withheld from patients with colorectal liver metastases lacking intratumoral ^{99m}Tc-MAA accumulation" (*1*).

Our results are based on the current body-surface-area model available, taking all the insufficiencies and drawbacks of the surrogate ^{99m}Tc-MAA into account (*2*). The establishment of dose–response relationships was beyond the scope of our study. Although qualitative Bremsstrahlung or ^{90}Y-PET imaging may be feasible in clinical routine, one has to admit that a quantitative assessment of dose estimations in normal liver parenchyma in regard to liver-related adverse events and in multiple tumor lesions in both liver lobes is far more difficult (*3,4*).

However, we agree with Drs. Lam and Smits that it would be essential to establish individualized treatment planning on the basis of optimized scout-dose imaging. Besides the technical aspects, such as catheter tip position or injection flow, it is desirable to have an agent that is identical to or that better models the treatment device. The recently introduced ^{166}Ho-microspheres by Smits et al. (*5*) may be used for pretherapeutic assessment and treatment evaluation, making them a promising candidate for future application. Nevertheless, we consider flow alterations during the radioembolization process due to the embolization effect to be a significant contributor to variable microsphere distribution in the tumor and liver that cannot be estimated or overcome by any proposed approach.

An optimization of dose estimation and individual treatment planning is even more important for further evaluation of the clinical and biologic aspects of the dose–response relationship for different tumor entities, pretreatment with chemotherapeutics, or a combined treatment and sequential lobar treatment versus whole liver treatment (*6*).

An individualized dosimetry concept should improve the efficacy of ^{90}Y-radioembolization while potentially reducing cases of overtreatment and unnecessary toxicity. To define the method and role of individualized pretreatment planning, a prospective multicenter trial would be needed.

Again, we thank Drs. Lam and Smits for their comments and discussion.

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Results Confounded by a Disregard for Basic Dose–Response Radiobiology

TO THE EDITOR: Every now and then, one comes across a publication on radionuclide therapy prognosis using qualitative descriptors, without due regard for basic dose–response radiobiology (*1–3*). Like the parable of the blind men and an elephant, these authors draw erroneous conclusions based on insufficient information unbeknownst to themselves. The scientific language of dose–response radiobiology is the radiation absorbed dose expressed in grays, not the injected activity expressed in becquerels. Any prognostic study whose design does not account for absorbed radiation doses to tissue will have no reliable method of data stratification for accurate response analysis, casting doubt on the scientific validity of its results.

The recent publication by Ulrich et al. (*3*) used the semiempiric body-surface-area (BSA) method for ^{90}Y resin microsphere activity prescription in a study to determine whether the visual degree of tumoral ^{99m}Tc-macroaggregated albumin (MAA) implantation carried any predictive value for response. Use of the BSA method was not explicitly mentioned in the article but was subsequently

confirmed by its corresponding author. Unless Ulrich et al. invest additional effort in accurately translating their visual descriptors of "low" versus "high" ^{99m}Tc-MAA implantation into absorbed radiation doses to tumor, their results cannot be verified. This is because inherent to the BSA method is the assumption of a fixed and favorable mean tumor–to–normal liver ratio for all patients (*4,5*)—an assumption that confounds their results.

To illustrate this point, say we have patients A and B with advanced colorectal liver metastases, identical height (170 cm), identical body mass (65 kg), a negligible lung shunt (<1%), a 1-kg lung mass, a 300-g tumor mass, and a 1,400-g nontumorous liver mass. Both A and B have good but slightly different mean tumor–to–normal liver ratios of 2.5 and 2.0, respectively. By visual scintigraphic appearance, both patients would be classified as "high" ^{99m}Tc-MAA implantation by the study of Ulrich et al. The BSA method will prescribe an identical ^{90}Y activity of 1.73 GBq for both. However, tricompartmental MIRD macrodosimetry will show that A received a satisfactory mean tumor dose of 100 Gy whereas B received a suboptimal mean tumor dose of only 86 Gy. It follows—to no surprise—that A will have some treatment response whereas B will not, even though both been classified in the "high" group.

It is common sense that ^{99m}Tc-MAA is an imperfect surrogate for ^{90}Y microspheres. It is a tool, and the usefulness of any tool is only as good as its user and the complexity of the task at hand. To conduct a scientifically robust study on the predictive value of ^{99m}Tc-MAA yielding reproducible and radiobiologically meaningful results, one must have accurate means of, first, delineating artery-specific planning target volumes (e.g., catheter-directed CT angiography or, at minimum, cone-beam CT); second, determining technical success in accordance with the intended radiation therapy plan (e.g., ^{90}Y time-of-flight PET/CT or, at minimum, ^{90}Y bremsstrahlung SPECT/CT); and third, quantifying the predictive radiation absorbed dose of technically successful cases by ^{99m}Tc-MAA SPECT/CT (*5*). Clinical validation of predicted radiation absorbed doses by ^{99m}Tc-MAA may be achieved either indirectly by follow-up diagnostic imaging (*5*) or directly by ^{90}Y PET/CT quantification (subject of current research).

In the discussion by Ulrich et al., they showed some awareness of the importance of the radiation absorbed dose and the tumor–to–normal liver ratio but did not explain why these were not factored into their analyses. Readers of their publication are advised to be cautious of their results and conclusions.

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REPLY: First, we would like to thank Dr. Kao for his elaborate comments regarding our article (*1*).

It is a matter of common sense that in cases of radioembolization, the determination of dose distribution is a challenging task because of the complexity of quantitative imaging and the limited availability of surrogate parameters for tissue (tumor) dosimetry.

Coming back to the blind men and the elephant, however, one should not mistake the pretherapeutic evaluation of intrahepatic ^{99m}Tc-macroaggregated albumin (MAA) distribution with the posttherapeutic distribution of ^{90}Y microspheres. The work of Kao et al. (*2*) is a dosimetry study using the partition model and the ^{99m}Tc-MAA accumulation pattern to predict the accumulated dose in target regions. In Kao's study of hepatocellular carcinoma patients published in 2012, he assumes that "...^{99m}Tc-MAA scintigraphy may be considered a 'simulation study' for ^{90}Y resin microsphere predictive dosimetry" (supplemental data of (*2*)), yet he acknowledges in his letter that "^{99m}Tc-MAA is an imperfect surrogate for ^{90}Y microspheres." The latter assumption is well in line with the evidence from several other studies that investigated ^{99m}Tc-MAA and ^{90}Y microsphere distribution in different tumor entities (*3–6*). Consequently, relating ^{99m}Tc-MAA distribution to the accumulated dose is a questionable practice.

In conclusion, we have the following major concerns about the comments made by Dr. Kao:

First, the study uses the partition model (*2*), which has been validated for dosimetry in only hepatocellular carcinoma patients (*7*). The basic assumption of the partition model is the equivalency between the accumulation pattern of the therapeutic agent (^{90}Y-labeled microspheres) and the accumulation pattern of the diagnostic surrogate (^{99m}Tc-MAA). However, this equivalence has not been demonstrated for other tumor entities, especially not in colorectal carcinoma. Furthermore, several authors have reported discordant ^{99m}Tc-MAA and ^{90}Y activity distributions (*3–6*).

Second, treatment planning should be based on *a priori* information to predict the intended response and total absorbed dose before therapeutic intervention as established in external-beam radiotherapy or brachytherapy. In contrast, using information from pre- and posttherapeutic examinations (^{99m}Tc-MAA SPECT or Bremsstrahlung SPECT, for example) represents a validation process.

We agree that advanced imaging protocols using, for instance, cone-beam CT, Bremsstrahlung SPECT/CT or ^{90}Y PET/CT have an important role in the development of validation procedures for radioembolization. Nevertheless, these procedures do not compensate for the lack of an adequate diagnostic surrogate for pretherapeutic dosimetry.

In this regard, the conclusion of our study was that ^{90}Y-radioembolization-therapy "...should not be withheld from patients