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

with colorectal liver metastases lacking intratumoral ^{99m}Tc-MAA accumulation" (*1*).

Again, we thank Dr. Kao for his comments and discussion.

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