^{99m}Tc-MAA–Based Dosimetry for Liver Cancer Treated Using ^{90}Y-Loaded Microspheres: Known Proof of Effectiveness

TO THE EDITOR: It was with great interest that we read the study by Lam et al. entitled "Prognostic Utility of ^{90}Y Radioembolization Dosimetry Based on Fusion ^{99m}Tc-Macroaggregated Albumin–^{99m}Tc-Sulfur Colloid SPECT," published in December 2013 (*1*). In this paper, the authors described an original method based on ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) and ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) SPECT to be used for segmentation between tumors and healthy liver tissue in the context of liver metastases. Mean tumor and healthy-liver doses were then calculated using the MIRD formalism. The study findings revealed a strong correlation between tumor dose and both response to ^{90}Y-loaded resin microspheres and survival in a cohort of patients with liver metastases treated using ^{90}Y-loaded resin microspheres.

Several questions or comments can be raised in response to this publication.

The study excluded patients with mismatch between ^{99m}Tc-MAA and subsequent ^{90}Y-microsphere injection site or failure. We believe it would be worth providing a clear definition of "injection site" and "injection failure." In addition, an evaluation of the number of patients meeting these definitions would be useful for the purpose of assessing the number for which the pretherapeutic dosimetry proved accurate.

Mean tumor dose was 44.2 Gy for responding lesions, yet the authors did not establish a threshold tumor dose. We would be highly interested to see the additional results that were not reported, such as receiver-operating-characteristic analysis with tumor-absorbed dose as a marker and nonresponders as a control group (area under curve; sensitivity, specificity, and accuracy with a threshold tumor dose equal to the minimum value of the responding group). A comparison with data previously published by our group (*2,3*) could also provide helpful insight.

For the segmentation process, the authors used both a tumor map (based on ^{99m}Tc-MAA and ^{99m}Tc-SC uptake) and a fixed threshold (applied on both ^{99m}Tc-MAA SPECT and ^{99m}Tc-SC SPECT) in order to avoid manual segmentation. A fixed threshold is an interesting choice, given this method's advantages of being neither operator-dependent nor time-consuming. These benefits are of particular interest in the context of multifocal diseases such as metastases. Yet the use of a fixed threshold has been recognized as producing less than optimal results at a lesion level (*4,5*). The authors have offered an interesting clinical validation of the concept in the context of multifocal disease.

In the "Discussion" section, this publication made mention of the approach previously used by our team for hepatocellular carcinoma patients (*2*), stating that "this modified partition method has clear advantages over existing methods with regard to tumor dosimetry but has several important limitations: normal-liver tissue dosimetry and toxicity are not addressed. . . ." This is incorrect, given that for both compartments (tumors and healthy liver) the mean doses were calculated using the MIRD approach. The only difference consisted of which segmentation process was used, namely ^{99m}Tc-MAA SPECT/CT fusion in our study and ^{99m}Tc-MAA SPECT/^{99m}Tc-SC SPECT fusion in theirs. In our study, we described both normal-liver dosimetry (mean healthy injected liver dose of 79.9 ± 24.5 Gy) and liver toxicity (*2*), finding no correlation between the healthy-liver dose and liver toxicity. Seven liver toxicity cases were noted, 3 involving an injected healthy-liver dose of less than 100 Gy delivered during treatment, and 5 an injected healthy-liver dose of more than 100 Gy, without any other toxicity. These results can be accounted for by the fact that, in our study, we treated only a single liver lobe rather than the entire organ. More recently, we applied the same approach and demonstrated that the combination of a healthy-liver dose of more than 120 Gy and hepatic reserve (percentage of nonirradiated liver volume) less than 30% constituted an independent factor of permanent severe liver toxicity on multivariate analysis (*3*).

This point is of particular significance, given that it is not mandatory to perform a supplementary ^{99m}Tc-SC SPECT acquisition in order to achieve an accurate dosimetric evaluation (especially for the healthy liver), or at least not for hepatocellular carcinoma, since ^{99m}Tc-MAA SPECT/CT dosimetry may also prove accurate (*2,3,6–8*) if performed correctly (*9*). Using a fixed threshold also offers us the opportunity of achieving segmentation between tumors and healthy liver tissue with ^{99m}Tc-MAA SPECT. We would be highly interested to see a comparison of ^{99m}Tc-MAA SPECT/CT–based dosimetry using a fixed threshold versus the methodologic approach developed in this paper. This would confirm for us which approach is the most accurate, along with whether performing an additional ^{99m}Tc-SC SPECT study is mandatory in the context of multifocal diseases such as metastatic disease.

All in all, although the presented results still require confirmation using a larger patient cohort, we can still remark that this study has brought to light additional evidence supporting the predictive power of ^{99m}Tc-MAA–based pretreatment dosimetry. New additional findings have also been published concerning how tumor dose correlates with response, overall survival, and liver tolerance. This finding is of particular interest for the following 3 reasons. First, given that ^{99m}Tc-MAA dosimetry is available before therapy initiation, it can lead to a fully personalized approach in selecting patients who, according to a ^{99m}Tc-MAA–based dosimetric estimation, are most likely to respond, as well as to a more efficient identification of patients at risk of liver failure and even to an intensification of the treatment, as has recently been suggested (*3,10*). Second, a more personalized oncologic approach using ^{99m}Tc-MAA SPECT/CT dosimetry and intensification for hepatocarcinoma patients with portal vein thrombosis produced positive results, with an overall survival rate reaching 24 mo (*3*). This kind of approach may also improve metastatic patient outcome. Lastly, this type of powerful, pretherapeutic predictor of response and survival represents a clear advantage of radioembolization. This advantage is unfortunately not available with other therapeutic approaches used for liver

cancer, such as chemotherapy, biotherapy, or chemoembolization.

DISCLOSURE

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REPLY: We thank Dr. Garin et al. for their expert insights into the complex topic of radioembolization dosimetry. For ^{90}Y hepatic radioembolization, ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) administered as an intraarterial simulation imaging agent is primarily used for calculation of the lung shunt and identification of extrahepatic deposition. An emerging third reason to perform ^{99m}Tc-MAA scintigraphy is to predict intrahepatic biodistribution of ^{90}Y, facilitating estimation and modulation of the anticipated absorbed dose distribution. For maximum accuracy of intrahepatic dosimetry, the simulation dose and therapeutic dose should be administered at the exact same position, minimizing the effects of hemodynamic perturbations such as streaming and competitive flow (*1*). Thus, in our study on intrahepatic dosimetry, we included only patients for whom this was the case (*2*). All cases in which ^{99m}Tc-MAA and subsequent ^{90}Y microspheres were injected in different arteries or positions were excluded to avoid the additional variability.

Fixed thresholding was used for both ^{99m}Tc-MAA SPECT and ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) SPECT, which was performed for automatic delineation of the functional liver compartment. Accurate scintigraphic volumetry using a threshold is dependent on imaging physics, including photon count, volume, and signal-to-noise ratio. After numerous models and thresholds were tested, we decided to use fixed thresholds (10%–30%), largely because adaptive thresholding was complex and led to dramatic variability. We found that the use of fixed thresholds was highly reproducible, and the choice of the fixed threshold level had no significant effect on the dose–response relationships (*2*).

Garin et al. were among the first to show the potential benefits of more accurate intrahepatic dosimetry (*3*). They used visual adaptation of the threshold on ^{99m}Tc-MAA SPECT to match lesions identified on CT and calculated the volumes. A subtraction technique (total liver minus tumor lesions) was used to calculate the remaining liver dose (*3*). This method has clear advantages over delineation by anatomic images only, but it could not have been used in our large-tumor-burden population undergoing salvage therapy, for whom visual assessment and delineation of each and every lesion is impossible. In fact, Garin et al. showed in a preliminary study on their own population that delineation and subsequent dosimetry using only ^{99m}Tc-MAA was not possible in all cases, because not all lesions could be assessed visually (*4*). An automatic segmentation method is clearly warranted. A simple 2-compartment model based on ^{99m}Tc-MAA SPECT/CT segmentation would be insufficient, since ^{99m}Tc-MAA is distributed to both tumorous and functional liver tissue, especially when tumors are myriad, miliary, or infiltrative. These compartments need to be further segmented physiologically using a method such as ^{99m}Tc-SC SPECT.

Analogous to external-beam radiotherapy, the absorbed dose to the functional liver determines dose limit. To define the maximum tolerable dose to the functional liver compartment, the whole liver needs to be exposed. A mixed population of lobar and whole-liver treatments is not comparable, because a certain dose to half the liver (e.g., 400 Gy) is better tolerated than half that dose (200 Gy) to the whole liver. For both radioembolization and external-beam radiotherapy, a heterogeneous dose distribution is better tolerated than a lower but more homogeneous dose distribution. In the studies by Garin et al., most patients received lobar treatments only (*5*). This probably explains why Garin et al. found that the combination of the functional liver dose and the percentage of unaffected liver volume was the strongest predictor of survival, in contrast to the functional liver dose alone. However, since radioembolization dose distribution is never homogeneous, one may hypothesize that a certain volume of "unexposed" functional liver, receiving less than a certain threshold of absorbed dose, could prove to be the most important toxicity parameter. As long as these limits are respected, one could then administer excess activity to the targeted regions, such as with radiation segmentectomy (*6*). However, for dose–response toxicity analysis, anatomically subtotal treatment does not suffice.