cancer, such as chemotherapy, biotherapy, or chemoembolization.

DISCLOSURE

Etienne Garin is a consultant for Biocompatibles U.K. Ltd.

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Published online Jun. 12, 2014.
DOI: 10.2967/jnumed.114.137422

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.

Improved dosimetry should lead to personalized treatment and improved outcomes (*5*). Garin et al. were able to increase the therapeutic dose in many patients while keeping toxicity acceptably low. Customized activity prescription resulted in a promising increase in response to treatment, progression-free survival, and overall survival in otherwise difficult-to-treat patients. The addition of physiologic ^{99m}Tc-SC SPECT–based analysis of the functional liver compartment at risk for radiation injury should lead to even more accurate dose limits, which should subsequently be useful for individualized treatment planning.

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Published online Jun. 12, 2014.
DOI: 10.2967/jnumed.114.141465