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tion.

DISCLOSURE

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

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REPLY: We thank Dr. Garin et al. for their expert insights into the

complex topic of radioembolization dosimetry. For 90Y hepatic

radioembolization, 99mTc-macroaggregated albumin (99mTc-MAA)

administered as an intraarterial simulation imaging agent is pri-

marily used for calculation of the lung shunt and identification of

extrahepatic deposition. An emerging third reason to perform

99mTc-MAA scintigraphy is to predict intrahepatic biodistribution

of 90Y, 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

99mTc-MAA and subsequent 90Y microspheres were injected in

different arteries or positions were excluded to avoid the additional

variability.

Fixed thresholding was used for both 99mTc-MAA SPECT and

99mTc-sulfur colloid (99mTc-SC) SPECT, which was performed for

automatic delineation of the functional liver compartment. Accu-

rate 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 adap-

tive 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 99mTc-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 sal-

vage therapy, for whom visual assessment and delineation of each

and every lesion is impossible. In fact, Garin et al. showed in a pre-

liminary study on their own population that delineation and subse-
quent dosimetry using only 99mTc-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 99mTc-MAA SPECT/CT segmentation would

be insufficient, since 99mTc-MAA is distributed to both tumor-

ous and functional liver tissue, especially when tumors are

myriad, milary, or infiltrative. These compartments need to be

further segmented physiologically using a method such as

99mTc-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 segmentec-
tomy (6). However, for dose–response toxicity analysis, anatom-

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

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