Value of ^{99m}Tc-Macroaggregated Albumin SPECT for Radioembolization Treatment Planning

TO THE EDITOR: The recent work by Ulrich et al. (*1*) discussed the value of intratumoral ^{99m}Tc-macroaggregated albumin (MAA) distribution to predict treatment outcome after ^{90}Y-radioembolization in patients with colorectal cancer liver metastasis. Their results demonstrated that response was independent of the degree of intratumoral ^{99m}Tc-MAA uptake. This is an important and interesting finding, but it should be interpreted with caution. Several studies have shown that pretherapeutic dosimetric calculations based on ^{99m}Tc-MAA distribution may lead to improved treatment planning methods based on tumor dosimetry (*2,3*). Because these developments are expected to lead to a paradigm shift in radioembolization treatment planning, from empiric methods to individualized treatment planning, it is critical that we carefully evaluate all aspects of scout dose imaging for radioembolization treatment planning. It is imperative to emphasize the importance of optimized scout dose imaging. Some additional comments may therefore be relevant to their research.

The presented study confirmed previous findings on the questionable prognostic value of pretherapeutic ^{99m}Tc-MAA distribution (*4*). In our series we found a difference in activity distribution between ^{99m}Tc-MAA and ^{90}Y of at least 10% in as many as 153 (68%) of 225 segments in 39 procedures (*5*). However, instead of correlating ^{99m}Tc-MAA distribution to posttherapeutic ^{90}Y distribution, the presented study correlated pretherapeutic ^{99m}Tc-MAA directly with parameters of efficacy. This methodology lacks an important stepwise approach.

First, the predictive value of pretherapeutic ^{99m}Tc-MAA should be evaluated to predict posttherapeutic ^{90}Y distribution, and subsequently, posttherapeutic ^{90}Y distribution should be compared with treatment outcome, both quantitatively. Otherwise, ^{90}Y distribution poses a significant confounding factor. Technical aspects of radioembolization are especially important for step 1, whereas clinical and biologic aspects of dose–response will influence step 2. Distribution differences between ^{99m}Tc-MAA and ^{90}Y are influenced by catheter tip position differences during the administration of both agents. This should be looked at in detail. Very small subcentimeter differences, as well as positioning the tip close to major bifurcations and side branches, may cause substantial differences in distribution (*4,5*). But also the in-plane cross-sectional position of the catheter tip causes distribution variations (*6*). Close attention to catheter tip positioning, possibly augmented by special catheters designed to fix the centriluminal positioning of the tip (*7*), will likely improve the predictive value of ^{99m}Tc-MAA scout dose imaging. Besides, an agent that better resembles the treatment device may replace ^{99m}Tc-MAA. For this purpose our group recently introduced new-generation microspheres for hepatic radioembolization: ^{166}Ho microspheres (*8*). These microspheres offer accurate pre- and posttherapeutic quantitative imaging by SPECT (81 keV) and MR imaging (paramagnetic properties) but also offer effective treatment by β-radiation (half-life, 27 h; 1.8 MeV).

Second, dose–response relationships have not been established yet. The previously mentioned publications on partition modeling were among the first to show such effects, but these studies were limited to hepatocellular carcinoma only. Interestingly, it was shown that the pattern of activity uptake around the tumor influenced the response to radioembolization (*3*). This was caused by variations in tumor perfusion, depending on location, and should be accounted for during treatment planning. Establishing such methods for multiple lesions in both liver lobes, such as colorectal cancer liver metastasis, is a great challenge because each tumor needs to be evaluated separately. The reported response in this cell type is very low (in the presented study only 10.4% at 3 mo). It is not yet clear whether this is caused by resistance to radiation or by underdosing, but proper dosimetry should further elucidate these issues. Nevertheless, it is expected that individualized treatment planning based on pretherapeutic dosimetry will ultimately lead to improved efficacy and toxicity. Because the response in the presented study was too little to reveal any relation with activity distribution, the authors used a nonvalidated response parameter (i.e., size change). It is also important that we stick to validated endpoints, including survival, for future investigation (*9*).

Negative results should not lead to cessation of our quest for optimized dosimetry, since these results do not necessarily imply that no relation exists. They merely, but importantly, tell us that we should overcome the limitations that lead to these negative findings, in order to establish validated methods for individualized pretherapeutic treatment planning.

REFERENCES

1. Ulrich G, Dudeck O, Furth C, et al. Predictive value of intratumoral ^{99m}Tc-macroaggregated albumin uptake in patients with colorectal liver metastases scheduled for radioembolization with ^{90}Y-microspheres. *J Nucl Med.* 2013;54:516–522.
2. Garin E, Lenoir L, Rolland Y, et al. Dosimetry based on ^{99m}Tc-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with ^{90}Y-loaded glass microspheres: preliminary results. *J Nucl Med.* 2012;53:255–263.
3. Kao YH, Hock Tan AE, Burgmans MC, et al. Image-guided personalized predictive dosimetry by artery-specific SPECT/CT partition modeling for safe and effective ^{90}Y radioembolization. *J Nucl Med.* 2012;53:559–566.
4. Jiang M, Fischman A, Nowakowski FS, et al. Segmental perfusion differences on paired Tc-99m macroaggregated albumin (MAA) hepatic perfusion imaging and yttrium-90 (Y-90) bremsstrahlung imaging studies in SIR-sphere radioembolization: associations with angiography. *J Nucl Med Radiat Ther.* 2012;3:1–5.
5. Wondergem M, Smits ML, Elschot M, et al. Technetium-99m-MAA poorly predicts the intrahepatic distribution of yttrium-90 resin microspheres in hepatic radioembolization. *J Nucl Med.* In press.
6. Kennedy AS, Kleinstreuer C, Basciano CA, Dezarn WA. Computer modeling of yttrium-90-microsphere transport in the hepatic arterial tree to improve clinical outcomes. *Int J Radiat Oncol Biol Phys.* 2010;76:631–637.
7. Rose SC, Kikolski SG, Chomas JE. Downstream hepatic arterial blood pressure changes caused by deployment of the Surefire AntiReflux expandable tip. *Cardiovasc Intervent Radiol.* December 19, 2012 [Epub ahead of print].

8. Smits ML, Nijsen JF, van den Bosch MA, et al. Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. *Lancet Oncol.* 2012;13:1025–1034.
9. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol.* 2011;22:265–278.

Marnix G.E.H. Lam*
Maarten L.J. Smits
**University Medical Center Utrecht*
3584 CX Utrecht, The Netherlands
E-mail: m.lam@umcutrecht.nl

Published online Jun. 18, 2013.
DOI: 10.2967/jnumed.113.123281

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.

REFERENCES

1. Ulrich G, Dudeck O, Furth C, et al. Predictive value of intratumoral ^{99m}Tc-macroaggregated albumin uptake in patients with colorectal liver metastases scheduled for radioembolization with ^{90}Y-microspheres. *J Nucl Med.* 2013;54:516–522.
2. Jiang M, Fischman A, Nowakowski FS, et al. Segmental perfusion differences on paired Tc-99m macroaggregated albumin (MAA) hepatic perfusion imaging and yttrium-90 (Y-90) bremsstrahlung imaging studies in SIR-sphere radioembolization: associations with angiography. *J Nucl Med Radiat Ther.* 2012;3:1–5.
3. Grober OS, Nultsch M, Laatz K, et al. Radioembolization with ^{90}Y-labeled microspheres: post-therapeutic therapy validation with Bremsstrahlung-SPECT. *Z Med Phys.* 2011;21:274–280.
4. Carlier T, Eugène T, Bodet-Milin C, et al. Assessment of acquisition protocols for routine imaging of Y-90 using PET/CT. *EJNMMI Res.* 2013;3:11.
5. Smits ML, Nijsen JF, van den Bosch MA, et al. Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. *Lancet Oncol.* 2012;13:1025–1034.
6. Seidensticker R, Seidensticker M, Damm R, et al. Hepatic toxicity after radioembolization of the liver using ^{90}Y-microspheres: sequential lobar versus whole liver approach. *Cardiovasc Intervent Radiol.* 2012;35:1109–1118.

Gerhard Ulrich*
Oliver Dudeck
Oliver S. Grosser
Holger Amthauer
**University of Magdeburg*
Leipziger Strasse 44
Magdeburg, Germany
E-mail: gerhard.ulrich@med.ovgu.de

Published online Aug. 5, 2013.
DOI: 10.2967/jnumed.113.123349

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