High Impact of Preferential Flow on ^{99m}Tc-MAA and ^{90}Y-Loaded Microsphere Uptake Correlation

TO THE EDITOR: It was with great interest that we read the article entitled "Predictive Value of ^{99m}Tc-MAA SPECT for ^{90}Y-Labeled Resin Microsphere Distribution in Radioembolization of Primary and Secondary Hepatic Tumors" by Ilhan et al. in the November 2015 issue (*1*).

The goal of their study was to evaluate the capacity of ^{99m}Tc-labeled macroaggregated albumin (MAA) uptake to predict ^{90}Y-labeled resin microsphere uptake on posttherapeutic ^{90}Y bremsstrahlung SPECT imaging. The authors found a significant yet low correlation between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake in the different tumors tested. When ^{99m}Tc-MAA uptake was found to be high, high ^{90}Y-microsphere uptake was almost always observed (i.e., 97% of cases), whereas low ^{99m}Tc-MAA uptake correlated with high ^{90}Y-microsphere in 67% of cases.

These results are in clear contradiction to those of several other studies that have demonstrated the accuracy of ^{99m}Tc-MAA–based dosimetry in the prediction of response and survival, suggesting a good correlation between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake (*2–5*).

This study therefore requires further discussion and clarification. For many years now, there has been debate surrounding the question of whether ^{99m}Tc-MAA is a good surrogate for ^{90}Y-microsphere distribution, as ^{99m}Tc-MAA particles are not of exactly the same size and density as ^{90}Y-microspheres.

The first point clearly recognized when considering ^{99m}Tc-MAA as a surrogate for ^{90}Y-microsphere distribution is the fact that ^{99m}Tc-MAA and ^{90}Y-microsphere injection should be performed precisely at the same site, meaning the same artery and at the same distance from the arterial bifurcation, with application of the same angulation of the microcatheter in the arterial lumen. In this study, no details were provided on either the exact microcatheter positioning or the accuracy of the repositioning. Where there were discrepancies between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake, this point should have been further assessed. A second key point to carefully monitor is the vasoactive status of the arterial tree at the time of ^{99m}Tc-MAA or ^{90}Y-microsphere injection. Less is known on this subject than on microcatheter positioning, yet there have been cases of huge discrepancies between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake related not to inaccurate catheter repositioning but to vasospasm observed on only 1 of the 2 angiographies performed, namely the diagnostic angiography (*6*). However, this issue has not been addressed in the Ilhan et al. study.

Presently, the debate centers not only on whether ^{99m}Tc-MAA alone is a good surrogate for microsphere distribution but also on whether the treatment simulation (including preferential flow at diagnostic angiography and ^{99m}Tc-MAA scintigraphy) is a good surrogate for ^{90}Y-microsphere distribution. This is of major interest, as it means that during the diagnostic angiography, special care should be taken to use ^{99m}Tc-MAA as a ^{90}Y-microsphere surrogate.

Figure 3 of this interesting paper illustrates the probable uncertainties of real microcatheter positioning or different arterial vasoactive statuses. On the ^{90}Y-microsphere scan, after injection of the tracer into the right hepatic artery we can see uptake only in the right lobe, with clear uptake in the tumor. On the ^{99m}Tc-MAA scan, however, no uptake at all is observed in the tumor and uptake is only faint in the right lobe, whereas strong uptake is seen in the left lobe. There are only two possible explanations for this result: either the microcatheter position has moved during ^{99m}Tc-MAA injection from the right hepatic artery into the left hepatic artery because of instability, or vascular flow in the right hepatic artery during ^{99m}Tc-MAA injection was dramatically impaired (such as through a huge vasospasm or an arterial dissection) and ^{99m}Tc-MAA flowed back toward the left hepatic artery. In this example, the discrepancy is more than likely accounted for by an abnormality occurring in the diagnostic angiography rather than by the difference between ^{99m}Tc-MAA particles and ^{90}Y-microspheres.

Arterial vasospasm can be provoked by any intraarterial procedure and is especially common in prolonged procedures, cases involving anatomic difficulties, or interventions such as coil embolization. When radioembolization is involved, arterial spasm is considered more likely in diagnostic angiography, which consists of full arterial mapping and coil embolization, as necessary.

When using resin microspheres, as in this study, it is generally recommended that systematic coiling of digestive arterial branches be performed in order to avoid gastrointestinal irradiation due to resin microsphere backflow during injection. In the Ilhan et al. study (*1*), systematic coiling and arterial spasm should have been documented and analyzed, at least when discrepancies between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake were observed. Almost all the discrepancies observed in this study involved an association between low ^{99m}Tc-MAA uptake and high ^{90}Y-microsphere uptake, strongly favoring the occurrence of vasospasm during ^{99m}Tc-MAA injection. Indeed, for lesions with low grade 4 ^{99m}Tc-MAA uptake, 21% had grade 1 ^{90}Y-microsphere uptake and 45.6% had grade 2 ^{90}Y-microsphere uptake.

Lastly, in their discussion, the authors presented the hypothesis that discrepancies between their results and those previously published could be explained by their use of glass microspheres (*1*). The type of microsphere used may, indeed, affect the correlation between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake, as glass microspheres are less embolic than resin ones. Nevertheless, it is our experience that the gentler diagnostic angiography approach we use could, once again, account for this discrepancy. As glass microspheres carry a lower risk of backflow during injection and do not require systematic coiling, coiling is used in less than 10% of procedures in our institution. Elsewhere, Lau et al. (*2*) published on hepatocellular carcinoma and Lam et al. (*5*) on metastatic disease (taking specific care with the catheter repositioning), and both reported a good dose–response relationship based on ^{99m}Tc-MAA dosimetry using resin microspheres, indicating that the kind of microsphere used may not be the key parameter in reproducibility between ^{99m}Tc-MAA and ^{90}Y-microsphere uptake.

To conclude, one must keep in mind that many confounding factors may affect the correlation between ^{99m}Tc-MAA uptake and ^{90}Y-microsphere uptake. The use of ^{99m}Tc-MAA as an accurate ^{90}Y-microsphere surrogate has to be anticipated. To avoid spasm,

the gentlest approach possible should be taken during diagnostic angiography, and effort should be taken to ensure the exactness of catheter repositioning.

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Published online May 5, 2016.
DOI: 10.2967/jnumed.116.175943

REPLY: With great interest we have read the letter of Garin and colleagues, who question our study results showing only a moderate correlation between pretherapeutic ^{99m}Tc-MAA SPECT findings and distribution of ^{90}Y-SIR-spheres in more than 500 patients (*1*). Obviously, the assumption that a high ^{99m}Tc-MAA uptake is followed by a high ^{90}Y-microsphere uptake, which translates into a high dose to the tumor and, therefore, a good response to radioembolization, sounds straightforward and striking. However, obvious assumptions also have to be proven, even more so as biology has taught us that the least tumor-related issues follow simple mechanistic correlations. Garin et al. cite 3 studies and 1 review that reported contradicting results in terms of a good correlation between ^{99m}Tc-MAA uptake and treatment response (*2–5*). However, most studies suggesting a good correlation between ^{99m}Tc-MAA SPECT and bremsstrahlung SPECT are dealing with hepatocellular carcinoma (HCC), which is different from secondary liver tumors in some aspects. Most cases of HCC are highly perfused, have distinct tumor-feeding arteries, and are either solitary or oligometastatic. These properties might account for the reported higher correlations in our view. Indeed, pretherapeutic angiography in HCC is often done in a selective fashion with injection of ^{99m}Tc-MAA into tumor-feeding arteries and not into the right and left hepatic arteries, as done in most secondary liver tumors because of the disseminated distribution of lesions. Injection of both ^{99m}Tc-MAA and microspheres mainly into tumor-feeding arteries makes discrepancies between ^{99m}Tc-MAA and microsphere distribution less likely. Consequently, in our study the correlation of ^{99m}Tc-MAA and microsphere uptake was markedly higher in HCC ($r = 0.398$, $P < 0.001$) than in secondary liver tumors such as metastases from colorectal cancer ($r = 0.22$, $P < 0{,}001$), breast cancer ($r = 0.308$, $P = 0.001$), and neuroendocrine tumors ($r = 0.197$, $P = 0.008$) (*1*). The lower correlation between ^{99m}Tc-MAA and microsphere uptake in non-HCC liver tumors is supported by several studies, partly with high numbers of included patients. Ulrich et al. found no significant correlation between response and ^{99m}Tc-MAA uptake in 66 patients with colorectal liver metastases (*6*). Also, Wondergem et al. reported significant differences in ^{99m}Tc-MAA and microsphere uptake (*7*). Finally, our group has reported in another study that cholangiocellular carcinomas with a high ^{99m}Tc-MAA uptake did not differ from those with low uptake in terms of survival (*8*). Cholangiocellular carcinomas with a high ^{99m}Tc-MAA uptake even showed a trend toward shorter survival (51 wk) than those with low uptake (median survival not reached). Similar results were reported by two other studies (*9,10*). These findings underline the complexity of tumor biology. The delivered tumor dose seems to be only a single factor in the prognosis of patients treated with radioembolization; not considering other important factors influencing the prognosis of tumors means significantly ignoring the complexity of cancer. Neoangiogenesis is a definite hallmark of cancer aggressiveness and prognosis (*11,12*) that might outweigh even the higher achievable dose in those tumors.

A second important issue related to the discrepant results reported in several studies is the kind of microsphere used. Although glass microspheres do not have a relevant embolizing effect, resin microspheres—because of the much higher number of injected particles—are embolizing a significant part of the vessels in the treated part of the liver, and therefore, the blood flow is changing over time. In a significant proportion of patients—up to 20%—the treatment even has to be stopped prematurely because of treatment-induced stasis (*13*). Of course, this embolizing effect is likely to change the blood flow and sphere distribution over time.

Garin et al. (*3*) have identified differences between diagnostic and therapeutic angiography such as catheter position and vasospasm as a probable reason for the reported low correlation. Most angiographies in our study were performed by the same experienced interventional radiologist, who has more than 20 y of experience. Therefore, differences in the catheter position cannot be ruled out with certainty but seem quite unlikely and cannot be considered a major confounding issue. This is also supported by the results of Ulrich et al., who did not find any correlation between catheter position, ^{99m}Tc-MAA uptake, and therapy response (*6*). Second, we experienced only a very limited number of vasospasms during angiography. We did coil embolization of aberrant vessels in only a limited proportion of patients and only during therapeutic angiography (*14*); therefore, vasospasms caused by prolonged diagnostic angiographies cannot explain the low ^{99m}Tc-MAA uptake and higher microsphere uptake as proposed by Garin et al. Furthermore, in most cases 1–3 wk elapse between diagnostic and therapeutic angiography. Considering the highly dynamic biology of cancer, it is not likely that tumor perfusion stays stable over time, and this instability is also a factor impairing the comparability of ^{99m}Tc-MAA and microsphere uptake.