High Impact of Preferential Flow on 99mTc-MAA and 90Y-Loaded Microsphere Uptake Correlation

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Dear 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" from Ilhan *et al.*, published in November 2015 in *J Nucl Med* (1).

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

These results are in clear contradiction with those of several other studies that have demonstrated the accuracy of MAA-based dosimetry in the prediction of response and survival, suggesting a good correlation between MAA and microsphere uptake (2-5).

This study therefore requires further discussion and clarification. For numerous years now, there has been debate surrounding the question of whether MAA is a good surrogate for microsphere distribution, as MAA particles do not possess exactly the same size and density as microspheres.

The first point clearly recognized when considering MAA as surrogate for microsphere distribution is the fact that MAA and microsphere injection should be performed precisely at the same site, meaning the same artery at the same distance from arterial bifurcation and applying the same

angulation of the micro-catheter in the arterial lumen. In this study, no details were provided regarding both the exact micro-catheter positioning and accuracy of the repositioning. Where there were discrepancies between MAA and ^{90}Y uptake, this point should have been further assessed in the study of Ilhan *et al.* (1). A second key point to carefully monitor is the vasoactive status of the arterial tree at the time of MAA or ^{90}Y injection. This subject is less known than micro-catheter positioning, yet there have been cases of huge discrepancies between MAA and microsphere uptake not related to inaccurate catheter repositioning, but rather to vasospasm observed on only one of the two angiographies performed, namely the diagnostic angiography (6). However, this issue has not been addressed at all in the Ilhan *et al.* study.

At the present time, the debate centers not only on whether MAA alone is a good surrogate for microsphere distribution, but rather on whether the treatment simulation (including preferential flow at diagnostic angiography and MAA scintigraphy) is a good surrogate for microsphere distribution. “This is of major interest, as it means that special care should be taken during the diagnostic angiography to use MAA as microsphere surrogate.

Figure 3 of this interesting paper illustrates the probable uncertainties of real micro-catheter positioning or different arterial vasoactive statuses. On the ^{90}Y scan, following injection into the right hepatic artery (RHA), we can see ^{90}Y uptake present only in the right lobe, with a clear uptake in the tumor. On the MAA scan, however, no uptake at all is observed in the tumor, yet uptake is also only faint in the right lobe, whereas a very high uptake is seen in the left lobe. There are only two possible explanations for this: either the micro-catheter position has moved during MAA injection from the RHA into the left hepatic artery (LHA) due to instability, or vascular flow in the RHA during MAA injection was dramatically impaired (huge vasospasm, arterial dissection, etc.), with MAA back-flowed towards the LHA. 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 MAA particles and microspheres.

Arterial vasospasm can be provoked by any intra-arterial procedure and is especially common in prolonged procedures or cases involving either anatomical difficulties or interventional procedures, such as coil embolization. When radioembolization is involved, arterial spasm is supposed to be more likely to occur in the 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 to perform systematic coiling of digestive arterial branches 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 occurrence should have been documented and analyzed, at least when discrepancies between MAA and ^{90}Y uptake were observed. The discrepancies observed in this study almost always refer to low MAA uptake associated with high ^{90}Y uptake, strongly favoring the occurrence of vasospasm during MAA injection. Indeed for lesions with low grade 4 uptake, 21% had grade 1 microsphere uptake and 45.6% had grade 2 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 using glass microspheres (1). The type of microsphere used may, indeed, impact the correlation between MAA and ^{90}Y uptake, as glass microspheres are less embolic than resin ones. Nevertheless, the gentler diagnostic angiography approach we used in our experience could, once again, account for this, as glass microspheres carry a lower risk of backflow during injection and do not require systematic coiling, this process 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 a specific care with the catheter repositioning), both reporting a good dose-response relationship based on

MAA dosimetry using resin microspheres, indicating that the kind of microspheres used may not be the key parameter in reproducibility between MAA and microspheres uptake.

To conclude, we have to keep in mind that a lot of confounding factors may have an impact on the correlation between MAA and ^{90}Y-microsphere uptakes. The use of MAA as an accurate microsphere surrogate has to be anticipated, and effort should be made to employ the gentlest approach possible during diagnostic angiography in order to avoid spasm occurrence and effort should also be made to ensure exact catheter repositioning.

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