

Pretreatment Dosimetry in HCC Radioembolization with ^{90}Y Glass Microspheres Cannot Be Invalidated with a Bare Visual Evaluation of $^{99\text{m}}\text{Tc}$ -MAA Uptake of Colorectal Metastases Treated with Resin Microspheres

TO THE EDITOR: We read with great interest the paper by Ulrich et al. (1) reporting on the predictive value of $^{99\text{m}}\text{Tc}$ -macroaggregated albumin ($^{99\text{m}}\text{Tc}$ -MAA) uptake in patients with colorectal liver metastasis scheduled for selective internal radiation therapy (SIRT) with ^{90}Y -loaded resin microspheres. Despite the inclusion of an impressive amount of work (66 patients and 435 lesions), the results are disappointing as they found no association between patient- or lesion-based response and the overall degree of $^{99\text{m}}\text{Tc}$ -MAA perfusion ($P = 0.172$). The authors conclude that the response cannot be predicted by the degree of perfusion on $^{99\text{m}}\text{Tc}$ -MAA scintigraphy.

This study raises several important methodologic and general concerns that have to be clarified. In our opinion, conclusions made by the authors cannot be supported by data presented in this paper.

From a methodologic point of view, we have 4 major concerns: the insufficient quantification method, lack of dosimetric evaluation, inappropriate radiologic evaluation of response, and inadequate definition of catheter position.

First, the main issue about imaging $^{99\text{m}}\text{Tc}$ -MAA perfusion is that it does not sufficiently evaluate the true degree of implantation in small lesions. Mazzaferro et al. (2), using the same Siemens software as Ulrich et al., needed to apply 120 projections, 8 iterations, and 8 subsets without any gaussian postfiltering to maximize the SPECT spatial resolution (7 mm in full width at half maximum measured in water), keeping a reasonable noise level. Nevertheless, under these circumstances, because of the well-known partial-volume effect, a 20% underestimation of activity was reported for a 1.8-cm-diameter sphere (3 mL in volume) with a $^{99\text{m}}\text{Tc}$ contrast ratio of 4:1 between sphere and background. The smaller the lesion, the larger the underestimation. For this reason, Mazzaferro et al. excluded lesions with a diameter smaller than 1.8 cm from their voxel dosimetry analysis. The reconstruction parameter described by Ulrich et al. implies worse spatial resolution than that achieved by Mazzaferro et al., with a consequently more pronounced underestimation of the degree of $^{99\text{m}}\text{Tc}$ -MAA perfusion even in lesions larger than 1.8 cm, whereas their lesion size was 3.39 ± 2.12 cm at baseline. Moreover, they adopted the Chang attenuation correction, which is valid for uniform objects and for which accuracy should be validated in regions of nonuniform attenuation (slices containing liver–lung interfaces). The lesion-based analysis relies on MR imaging/SPECT registration, and no description of the registration process is given. Since liver deformation can occur in 30 d, an image mismatch could occur without an elastic deformation registration method.

Second, SIRT is a kind of radiation therapy. As such, efficacy should be discussed in terms of absorbed dose and radiobiologic

models, not merely in qualitative terms of degree of $^{99\text{m}}\text{Tc}$ -MAA implantation, which is image- and operator-dependent.

The third methodologic concern relates to the response evaluation. According to our experience, the 6-wk interval is definitely too short to observe an appropriate morphologic response. Metabolic assessment of tumor response using ^{18}F -FDG PET can be applied early (6–8 wk) and would probably have been more accurate as an endpoint for assessing a dose–response relationship. In addition, the Response Evaluation Criteria in Solid Tumors (RECIST) are not at all a validated method for the assessment of treatment response in SIRT. “The most common change in the CT-appearance of the liver after SIRT is decreased attenuation in the affected hepatic areas” (3). In these situations, response evaluation must take into account the vascularization of the lesion, as in the criteria of the European Association for the Study of the Liver (EASL) or in modified RECIST.

Fourth, regarding catheter position, identification of the vessel by merely specifying right or left artery is not sufficient. The distance between the tip of the catheter and the origin of the artery should also be carefully reproduced, since a 5- to 10-mm difference in catheter position can have a major impact on flow distribution (4).

In addition to these 4 methodologic issues, 3 general concerns have to be raised.

First, the results of this study contradict previously published results on resin microspheres (SIR-Spheres; Sirtex). Using an appropriate dosimetric approach (5), a preliminary study (8 patients) found a good correlation between the tumor-absorbed dose and the response of metastatic disease to ^{90}Y -resin microspheres. On the other hand, more than one study (Wondergem et al. (4), for instance) found a poor correspondence between $^{99\text{m}}\text{Tc}$ -MAA and ^{90}Y -resin microsphere biodistributions, suggesting that the degree of $^{99\text{m}}\text{Tc}$ -MAA perfusion could not predict response. Indeed, $^{99\text{m}}\text{Tc}$ -MAA particles and ^{90}Y -resin microspheres may not have the same distribution, since the number of injected therapeutic particles is about 300 times higher than the number of $^{99\text{m}}\text{Tc}$ -MAA particles. Moreover, $^{99\text{m}}\text{Tc}$ -MAA is injected as a bolus, whereas the resin microspheres are given as a series of small injections interleaved with checks with contrast medium. In hepatocellular carcinoma (HCC), the results seem more concordant. Using the partition model applied to planar $^{99\text{m}}\text{Tc}$ -MAA images, Ho et al. (6) reported a response rate of 37.5% for a tumor dose of more than 225 Gy versus only 10.3% for a tumor dose of 225 Gy or less ($P < 0.006$). Similarly, Kao et al. (7) reported a good correlation between $^{99\text{m}}\text{Tc}$ -MAA SPECT/CT dosimetry and response after ^{90}Y -resin microsphere therapy.

Second, the fact that in Ulrich’s study 26% of the lesions with a low degree of $^{99\text{m}}\text{Tc}$ -MAA perfusion effectively responded may be explained by at least one factor other than quantification underestimation. Although quantification of bremsstrahlung images of ^{90}Y distribution was not performed, the authors conclude that even in hypovascularized lesions the amount of ^{90}Y -resin microspheres is sufficient to induce an antitumoral effect. We wonder whether, for some patients, this antitumoral effect might have been embolic rather than induced by radiation, once properly quantified. Indeed, even though the absence of histologic signs of embolization in normal liver was demonstrated in a preclinical study (8), the potential embolic effect on tumoral neovascularization is still a matter of debate.

Third, Ulrich et al., despite their poor methodology, suggest that “. . . in $^{99\text{m}}\text{Tc}$ -MAA SPECT no prediction of response in colorectal

carcinoma is possible. Therefore, pretherapeutic dosimetric calculations based on ^{99m}Tc -MAA imaging, as reported with HCC, . . . should be seen critically.” This statement about HCC cannot be based on a study dealing with a different pathology and a different kind of microsphere. Metastases and HCC are different types of tumors (more peripheral vascularization in HCC and a higher proportion of small lesions in metastases). Results observed with one type of lesion cannot be extrapolated to the other. Ulrich et al. extend their conclusions from results obtained with resin spheres (SIR-Spheres) to glass spheres (TheraSphere; BTG), as if the two medical devices were identical. This is absolutely not the case from the dosimetric and biologic point of view (9). Activity per sphere is 50 times lower for the resin spheres than for the glass ones, requiring a 50 times higher number of particles to give the same mean absorbed dose, with a consequent increased real embolic effect. Because of this tremendous difference between the number of injected particles, we cannot agree about extrapolating results concerning the predictive value of ^{99m}Tc -MAA scintigraphy from resin to glass microspheres.

The evidence on HCC treatment provided by the teams of Rennes (10) and Milan (2), both of which used glass spheres, in contradiction to what is reported by Ulrich et al., was not discussed adequately. In the first study (mean lesion size of 7.1 cm), ^{99m}Tc -MAA SPECT/CT was predictive of response with an accuracy of 90% (10). The lesion-absorbed dose was the only parameter associated not only with response but also with overall survival at multivariate analysis (10). Also, the second study found a dose–response relationship in HCC (2). Mean tumoral absorbed dose significantly correlated with the EASL response (Spearman $r = 0.60$, $P < 0.001$).

In conclusion, when reporting on the predictive value of ^{99m}Tc -MAA scintigraphy in SIRT, one should pay attention to the type of microspheres, the quantification method for estimating the ^{99m}Tc -MAA degree of perfusion, dosimetry issues, tumor type, lesion size, and the method of response assessment. At present, there is confirmed evidence that ^{99m}Tc -MAA SPECT–based dosimetry is predictive of response in HCC when glass microspheres are used. Published results with resin microspheres, especially in metastases, require additional studies to assess the predictive power of ^{99m}Tc -MAA scintigraphy. Conclusions from a methodologically weak study about the lack of predictive value of ^{99m}Tc -MAA uptake in liver metastases treated with resin microspheres should not be extrapolated to HCC treated with glass microspheres.

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REPLY: Thank you for giving us the opportunity to respond to the letter to the editor. Chiesa and coauthors raise sincere concerns over the study’s methodology and deny the negative outcome reported for the use of pretherapeutic ^{99m}Tc -macroaggregated albumin (^{99m}Tc -MAA) uptake for prediction of response after radioembolization in liver metastases of colorectal cancer (CRC). Some aspects raised in the letter represent meaningful concerns, which we address and set aside through detailed comments as well as an additional data analysis performed for that precise purpose. Other concerns expressed in the letter reflect a personal opinion on debatable points. The references mentioned to support these opinions direct the reader to review articles and through these, if analyzed in depth, to studies based on very small patient cohorts reporting on tumor biologies other than CRC (as in our study) or to studies involving no radioembolization at all.

To address the concerns expressed in the letter about a resolution-induced partial-volume effect on ^{99m}Tc -MAA uptake in small lesions, we performed an additional analysis of our data. In this analysis we included only lesions larger than 18 mm, as requested by the letter’s authors. In total, 233 of 290 lesions (45 of 48 patients) from our original publication were evaluated. To address doubts expressed with regard to the appropriate follow-up time point, we refer to MR imaging data at 3 mo. There was no significant correlation between the ^{99m}Tc -MAA uptake and lesion-based therapy response by changes in tumor diameter (responding/nonresponding lesion), by lesion-based Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or by patient-based RECIST