General Theory of Predictive Dosimetry for Yttrium-90 Radioembolization to Sites Other Than the Liver: Reply

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We have read the comments to our recently published article about Y90-radioembolization of lung metastases via the bronchial artery with great interest, and we welcome the additional perspective on dosimetry for Y90-radioembolization outside the liver [1, 2]. However, some thoughts must be added. First, it should be noted that the authors of the letter deduce their approach from a systematic description of the compartmental distribution as utilized in radioembolization of liver malignancies [2]. This model is then extended to cater different application scenarios (lung, kidney). However, other than implied in the letter dosimetry for Y90-radioembolization of the liver generally remains highly controversial with no uniform conclusions between numerous research groups [3–6].

We wish to highlight the fact that while dosimetric considerations naturally are a hallmark of radioembolization, in case of lung treatment gaining more basic knowledge must be prioritized to ensure patient safety. Radiobiological effects and kinetic properties of the compartments and substances for dosimetric modeling are widely unknown—not in regard to the target volume, but also to normal lung tissue. As we have learned from radioembolization of liver malignancies, dosimetry predicting activity patterns and uptake in different morphologic structures (tumor, liver tissue, extrahepatic tissue) is challenging. In contrast to the letter's authors, we challenge the predictive value of Tc-99m-MAA as a surrogate for pretherapeutic dosimetry. The essential correlation between the distribution of the surrogate (Tc-99m-MAA) and the distribution of the therapeutic agent (Y-90-SIRspheres) is

generally weak. Several groups have discussed discordant accumulation patterns for both substances [7–9]. Just recently, we have published a patient series where Tc-99m-MAA accumulation in colorectal liver lesions did not correlate with clinical response [10]. In light of these assumptions supplemented by the different morphology of lung tissue compared with liver the eligibility of the Tc-99m-MAA as surrogate for radioembolization of lung malignancies must be reevaluated.

In addition, we do not believe that in lung tissue glass spheres with a higher Y90 load and lower embolic potential compared with resin spheres have theoretical advantages in safety and efficacy. As a matter of fact, the bronchial artery blood pool comprises a very low volume compared with the hepatic artery. We hypothesize that the temporary embolic effect of resin particles has been an integral part of the observed strong activity accumulation in the lung tumors. During fluoroscopy, it became apparent that the resin spheres almost immediately embolized (temporarily) the capillary bronchial artery system, resulting in a low-dose exposure of bronchus or lung tissue given the relatively low Y90 load per particle compared with glass spheres. This might explain why relatively low activity applied in our patients led to an objective response; it seems that due to the embolic effect described most of the dose accumulated in the tumor blood pool rather than the bronchial artery system. For that reason, vascular stasis must not be excluded *a priori* by a dosimetric model as proposed by the authors of the letter, but it is part of the treatment success. However, this aspect seems of utmost importance and must be clarified before tumor dosimetry can be considered.

It is our conviction that dosimetric models for radioembolization should commit themselves more to the effects of the 3D-dose distribution. Establishing a mean dose does

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not at all reflect the inhomogeneous dose coverage of tumor volumes and the occasional high-dose activity in some parts of normal tissue, as frequently observed in clinical practice. In addition, these effects do at least in part explain our inability to accurately predict tumor response after radioembolization. A possible methodology to overcome these limitations is a dose volume histogram (DVH) based evaluation of the dose distribution for the clinical target volume and organs at risk. This approach is well known from other radiation-based ablative therapies, such as CT-guided brachytherapy [11–13] and recently has been demonstrated in radioembolization as well [4, 14].

In summary, we believe that numerous open issues unfortunately do not allow the conclusion that “Modern advances in interventional radiology and nuclear medicine may now allow for safe and effective 90Y radioembolization to sites other than the liver.” [2]. Again, the case series described in our paper represents a pilot study at best, and the experiences made have only helped us to design a Phase I study, which currently is under review by government authorities. Further basic research is essential to move radioembolization to the lung. Key aspects are: (1) safe prevention of extensive radio pneumonitis, (2) development of validation procedures to prevent the flow of microspheres into non-lung structures (e.g., spinal cord), and (3) reliable prediction of the accumulation pattern following Y90-radioembolization. Finally, the clinical value of treating diffuse metastatic lung disease in solid tumors or the role of downstaging advanced lung cancer must be established before considering the method for routine clinical use.

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