

Radiodosimetric Estimates for Radioembolic Therapy of Liver Tumors: Challenges and Opportunities

In this issue of *The Journal of Nuclear Medicine*, Kao et al. describe a novel approach to estimating radiation absorbed doses during radioembolization with ^{90}Y -labeled resin microspheres in patients with liver tumors (1). Although the study includes a relatively small number of patients, nevertheless it introduces an important concept, that is, radiation dose to and the resulting effect on biologically distinct portions of the liver, namely normal tissue and tumor. This concept is at variance with considering radiation dose to the whole organ, as is generally the case when using this form of therapy, the application of which is growing throughout the world.

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Each year more than 1 million patients with liver malignancies, either primary or secondary, are diagnosed and treated worldwide (2). Although less than 15% of these patients are candidates for surgical procedures, carefully selected curative resection or liver transplantation has a definite survival benefit, especially for patients with hepatocellular carcinoma (3). For patients with inoperable hepatic malignancies, various therapeutic options (systemic or locoregional chemotherapy or chemoembolization) have been proposed. There is no consensus

or consistent agreement on which treatment option offers the greatest survival benefit and the least toxicity (4–6).

Locoregional radioembolization has been developed to deliver high radiation doses to malignant hepatic lesions while minimizing systemic toxicity. This is achieved through intrahepatic delivery of a radiation vehicle administered via a minimally invasive transcatheter route. Either lipid micellae (such as ethiodized oil labeled with ^{131}I or ^{188}Re) or microspheres loaded with radionuclides (e.g., ^{90}Y -glass or -resin microspheres) are infused into the hepatic arteries that supply the tumor (7). The efficacy of this approach is based on the fact that hepatic malignancies derive their blood supply almost entirely from the hepatic artery, as opposed to the normal liver, which depends mainly on portal blood supply (8).

After transcatheter infusion and then passing through the intrahepatic arterial circulation, different radioactive materials will localize within liver tumors by different mechanisms. In fact, lipid micellae (most commonly ^{131}I -ethiodized oil) lodge in the tumor and are retained there by pinocytosis both in the tumor cells and in the endothelial cells. Microspheres are retained at the tumor site by mechanical trapping in the capillary bed (microembolization). As a result, much higher radiation doses are delivered to liver tumors than to the normal liver, and the more tumor-selective the transcatheter infusion the higher the tumor-to-normal-liver dose ratio (9).

Considering that patients undergoing this procedure are in advanced stages of disease, radioembolization achieves favorable clinical outcomes in both primary and secondary liver malignancies (10,11). Because all these patients

have progressive disease when treated, favorable tumor response is represented by any combination of complete response, partial response, and even stable disease. After radioembolization with ^{90}Y -particles, the combined tumor response is about 80%–90% for hepatocellular carcinoma and is greater than 90% for liver metastases from colorectal cancer (when used as first-line, neoadjuvant treatment before chemotherapy). Furthermore, when an average dose of 120 ± 20 Gy can be delivered to the liver lobe bearing the tumor lesions, median survival ranges from 7.1 to 21 mo in patients with hepatocellular carcinoma and from 6.7 to 17 mo in patients with colorectal liver metastases (12).

There is nevertheless a certain variability in clinical outcomes, most likely related to different approaches used for treatment planning and for correlating radiation dose and clinical outcome (13). The most commonly used techniques for estimating radiation burdens are based on empiric models that do not separately evaluate the tumor and nontumor absorbed dose, despite the well-established correlations between therapeutic efficacy and tumor dose and between toxicity and normal-tissue dose. The goal of treatment planning for radioembolization of liver tumors is to administer the highest possible radiation dose to the tumor while keeping radiation dose to sensitive tissues (such as the lungs and normal or cirrhotic liver) as low as possible. The standard MIRD formalism is used for this purpose, using the so-called organ partition model (14–16); this strategy requires measuring the liver and tumor tissue volumes and calculating the activity localized in each of these 2 compartments and in the lungs. Accurate assessment of the target volumes of interest is there-

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fore critical because it directly affects estimates of the radiation absorbed doses, especially when selective or tumor-selective radioembolization is planned (17).

One of the most interesting and challenging facets of ^{90}Y radioembolization is its multidisciplinary nature, involving the oncologist, the interventional radiologist, the nuclear physician, and the medical physicist. Among the key issues faced by the nuclear medicine physician and the medical physicist is the accurate estimation of absorbed doses to various normal organs and tissues and to the tumor. If the lesion-absorbed dose is too low, the procedure will be ineffective; on the other hand, if the healthy liver absorbs a dose higher than 30 Gy, the risk of irreversible damage limits the overall effectiveness of radioembolization. Similar considerations apply in cases of high liver-to-lung shunting and the prohibitive risk of radiation-induced pulmonary damage.

Radioembolization differs kinetically from typical radionuclide therapies, since the ^{90}Y -particles remain permanently trapped in the lesion after their delivery through the arterial circulation. Therefore, metabolism (which is variable among different agents and even among different patients for the same agent in the case of most radionuclide therapies) does not play any role, and the physical half-life of the radionuclide corresponds to the effective half-life of the agent. In principle, this allows implementation of straightforward dosimetric models, based on the pretherapeutic intraarterial injection of $^{99\text{m}}\text{Tc}$ -macroaggregated albumin. Scintigraphy performed immediately after $^{99\text{m}}\text{Tc}$ -macroaggregated albumin injection visualizes and quantifies accumulation of the radiolabeled particles in the target lesion and in the healthy liver, thus allowing calculation of the tumor-to-nontumor absorbed dose ratio (15). Obviously, tomographic imaging (preferably SPECT/CT) yields the information required for such estimates much more accurately than simple planar imaging. Besides radioactivity ac-

cumulation and retention, mass of the target organ or tissue is another crucial datum for estimating the absorbed dose. In the supplemental material to their article (1), Kao et al. describe how catheter-directed CT hepatic angiography is incorporated into their model to identify the target volumes by better evaluating the perfused areas than digital subtraction angiography. Such improvement is achieved by co-registering the $^{99\text{m}}\text{Tc}$ -macroaggregated albumin SPECT/CT with the corresponding CT hepatic angiography, so that the target region of interest contoured in the CT hepatic angiography images can easily be transferred onto the SPECT/CT slices. The final result of such integration is the definition of a 3-dimensional volume of interest for both the target portion (bearing the tumor) and the nontumor portion of the liver (18).

Based on total injected activity and fraction of $^{99\text{m}}\text{Tc}$ -macroaggregated albumin particles shunted to the lungs, radioactivity trapped in pulmonary circulation is easily calculated and the lung-absorbed dose derived. Nevertheless, the tolerance dose for β^- particles emitted by a radionuclide lodged in pulmonary microcirculation, as is the case for microembolization with ^{90}Y -particles, is not exactly known. In principle, this dose can be estimated on the basis of external-beam radiation therapy tolerance data and the biologic-effective-dose formalism (19). Accordingly, the radiation dose to normal lung parenchyma must not exceed 30 Gy to 20% or 15 Gy to 30% of the whole lung volume. The corresponding values for the liver are 50 Gy to one third or 35 Gy to two thirds of the whole liver volume (20).

In ^{90}Y -microembolization, absorbed doses to individual tissues or organs can be calculated using the MIRD formalism, which yields the average dose to the intrahepatic lesion, as well as to the other parts of the liver lobe and to the lungs in the case of liver-to-lung shunting. In their supplemental material, Kao et al. offer for download the spreadsheet they developed for calculating the average absorbed dose to various

target zones within the liver, to nontumor liver, and to the lung (1), a potentially interesting option also for future comparison among different centers. Patient-specific dosimetry-based calculation of the administered activity is presumably more therapeutically effective and less toxic than an activity based simply on a body habitus parameter such as weight or body surface area and is therefore recommended. Unfortunately, ^{90}Y -microspheres injected intra-arterially are not uniformly distributed within the tumor or the normal liver, since the arterial vasculature does not uniformly perfuse these tissues. Calculation of the doses to the targeted tumors and to nontumor tissues could be improved further by implementing 3-dimensional voxel-based dosimetry, with the goal of taking into account, at least to some extent, the inhomogeneity of the activity distributions in volumes of interest (21,22). Nevertheless, the limited spatial resolution of current SPECT equipment (and even of PET equipment) jeopardizes the possibility of characterizing with an accuracy better than an approximately 0.4 cm^3 voxel size (or 0.07 cm^3 for PET) the inhomogeneity at the microscopic level of radionuclide distribution in the target tumor and in the nontumoral liver. Despite such intrinsic limitations, 3-dimensional voxel-based dosimetry certainly constitutes also for this form of radionuclide therapy an important advance compared with calculation of average absorbed doses, even if the latter is performed according to the novel approach described by Kao et al. (1). In addition, voxel-based dosimetry allows graphical representation, in the form of the dose-volume histogram, of the fractional volume of tissue that receives a certain absorbed dose, as is routinely done in external-beam radiation therapy. In conjunction with suitable radiobiologic (i.e., dose-response) models, this may allow one to reasonably predict the likelihood of achieving tumor control while avoiding prohibitive normal-tissue complications.

Kao et al. (1) concluded that an effective absorbed dose to the lesion of 100 Gy or greater produces a clinically

significant therapeutic effect. On the other hand, if the healthy liver tissue absorbs less than 30 Gy, no complications are to be expected; similarly, no pulmonary complications are expected in the case of liver-to-lung shunting resulting in a lung absorbed dose of less than 10 Gy. These values have been calculated by Kao et al. under the hypothesis of a homogeneous distribution of the ^{90}Y -particles in the lesions or organs. These dose values should therefore be refined under conditions of nonuniform distributions of activity in the volumes of interest. Radiobiologic modeling could then be used to derive the ^{90}Y activity required to achieve a desired reduction in tumor volume. Challenges remain, however.

One of the limitations is the fact that it is difficult to perform pretherapeutic dosimetry by administering a tracer amount of radioactivity using the same radionuclide as for therapy. ^{90}Y is a pure β -emitter that can be imaged only by using its associated bremsstrahlung; such radiation is difficult to reliably quantitate by either planar (23) or tomographic (24) imaging. In fact, accurate calibration of the imaging equipment is necessary to this purpose (23), a requirement that has so far greatly limited the routine application of such an approach. Furthermore, even the post-therapeutic bremsstrahlung images are rather poor and are generally considered only for the purpose of qualitative visual control of successful radioactivity administration. Alternatively, although emitted in low yield, ^{90}Y emissions include positrons, with the possibility of accurate activity quantitation by PET/CT (25,26).

Another limitation is that manual contouring of the regions or volumes of interest is to a certain extent operator-dependent. Nevertheless, this procedure is similar to that routinely performed in external-beam radiation therapy.

In conclusion, although a complete solution to the challenges posed by

dosimetric estimates for ^{90}Y -radioembolization is not yet available, it is nevertheless possibly brought within reach by adopting novel technical approaches, as outlined in this article.

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