

Bias Reduction in Correlation of Radiation-Absorbed Dose with Response

TO THE EDITOR: We read with interest the recent article on the correlation of tumor radiation dose and response in patients with non-Hodgkin's lymphoma by a dodecanetraacetic acid-conjugated ^{90}Y -labeled humanized antibody to the cluster designation 22 antigen, epratuzumab. The authors stated that "tumor response did not correlate with the radiation dose delivered. . ." (1).

We appreciate the authors' citation, in their "Discussion" section, of our report (2) on tumor dosimetry for previously untreated patients who received ^{131}I -tositumomab and on the correlation of estimated dose with response. In that section, they state: "Importantly, tumor dosimetry is biased because it can be performed only if the tumor is clearly seen, and in many instances there are tumor sites where either poor or even no targeting is achieved (1)." We agree with Sharkey et al. that if, in order to be evaluated for dosimetry, tumors must be seen on planar images, there clearly will be a bias toward the higher-uptake tumors. Such a bias can likely best be avoided if tumors are defined by methods other than scans obtained with the therapeutic agent. For example, using CT scans with registration to SPECT scans, as we have done, or using a dedicated SPECT/CT system, with the CT portion helping to define tumors, may avoid the potential bias that Sharkey et al. correctly point out as a pitfall.

Readers of our study (2) may have a misimpression concerning the measurements. The facts follow. Our method required a composite tumor to have an uptake visible on a set of tracer conjugate-view scans. The composite tumor was usually made up of more than one tumor (2). We called each tumor that composed the composite tumor an individual tumor. (By definition, the individual tumors were separated spatially on the patient's CT scan (2).) Now, all of the individual tumors in the University of Michigan study of previously untreated patients were associated with a composite tumor that met the visible-uptake requirement. (This was not a difficult restriction because uptake was generally good.) However, it was not necessary for each of the individual tumors to have easily discernible uptake, because the volume of interest for which the uptake was measured on the SPECT scan was determined by the tumor region outlined on the CT scan. The tumor outline on the SPECT image was determined by registration of the SPECT scan to the CT scan, that is, effectively by a transfer of the CT-based volume of interest to the SPECT image set (2). Thus, a characteristic of our method was that dosimetry was estimated for all the individual tumors of which a composite tumor was composed, independent of the level of uptake within the individual tumors. This characteristic reduced the bias that Sharkey et al. discussed. We regret that we did not emphasize this degree of independence from bias in our article.

Regardless of our study, if a multiple-day series of SPECT images is acquired, starting immediately after radionuclide administration, and if a SPECT/CT system or SPECT-to-CT registration is used, then the radiation dose to each tumor identified on CT can be estimated, no matter what its radionuclide uptake. Thus, there clearly would not be a bias toward preferentially including tumors that exhibit high uptake.

In conclusion, we agree with Sharkey et al. that if, in order to be evaluated for dosimetry, tumors must be seen on planar images,

there clearly will be a bias toward the higher-uptake tumors. In our study, we reduced bias by employing anatomic, CT, images and retrospective SPECT-to-CT registration. Definition of tumors on anatomic, CT or MRI, images with subsequent application to emission, SPECT or PET, images may well be the most potent approach to avoid bias in future dosimetric studies.

REFERENCES

1. Sharkey RM, Brenner A, Burton J, et al. Radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y -DOTA humanized anti-CD22 IgG (^{90}Y -epratuzumab): do tumor targeting and dosimetry predict therapeutic response? *J Nucl Med.* 2003; 44:2000–2018.
2. Koral KF, Dewaraja Y, Li J, et al. Update on hybrid conjugate-view SPECT tumor dosimetry and response in ^{131}I -tositumomab therapy of previously untreated lymphoma patients. *J Nucl Med.* 2003;44:457–464.

Kenneth F. Koral, PhD

*University of Michigan Medical Center
Ann Arbor, Michigan*

Kenneth Zasadny, PhD

*Pfizer Global Research and Development
Ann Arbor, Michigan*

Richard L. Wahl, MD

*Johns Hopkins Medical Center
Baltimore, Maryland*

REPLY: On behalf of my colleagues, I thank Drs. Koral, Zasadny, and Wahl for their comments on and clarification of any possible misinterpretation by us of their work. Indeed, we applaud the studies of this group and others who have used technologies and procedures to improve dosimetry estimates. Thus, our comment that tumor dosimetry can be biased was not directed toward their studies but, rather, toward standardized dosimetry methods based on planar imaging that have been more commonly used, such as described in our article. We fully appreciate that SPECT, and perhaps even PET in the future, can aid in the elucidation of tumors from surrounding normal tissue and therefore increase the number of tumors seen and the accuracy of predicting the radiation-absorbed dose. However, dosimetry still has inherent inaccuracies that we all recognize, primarily emanating from basic assumptions about distribution of radioactivity within a tumor or tissue. Inherent inaccuracies in tumor volume/spatial determinations also can affect the accuracy of these calculations. Therefore, although SPECT may help delineate the tumor and in so doing improve the dosimetry estimate, it is unlikely that SPECT or even PET will provide the resolution required if the radiation-absorbed dose is to be considered as anything more than an estimate. Thus, until better methods are available and easily applied clinically, the best we can do is to determine absorbed doses by a method that will at least provide reasonably reproducible results, and then correlate these values with biologic effects.

In this regard, our article was directed not so much toward the dosimetry aspects of the study but toward the fact that in a considerable number of instances, tumors could not be discerned by either planar or SPECT imaging but could be discerned by CT and were found to respond to the treatment. This finding then goes

to the heart of whether one should proceed with the treatment dose of a radiolabeled antibody when an imaging dose of the antibody fails to target the tumors. Our small study did not provide a definitive answer to this question, but these imaging results, coupled with our and others' finding that dosimetry (based primarily on planar imaging) does not appear to correlate directly with response, speak to the issue that other factors must be involved to at least partly explain the biologic effects observed. Although this might challenge the value of using dosimetry or even imaging when deciding whether a radiolabeled antibody treatment should be given, we certainly are not advocating such a radical position at this time. However, just as the outcome with chemotherapy cannot

be predicted, the mere fact that a radiolabeled compound can be traced in the body does not mean that we can fully predict the response. Thus, we need to continue efforts to improve the identification of patients who will benefit from a given treatment, including improving all aspects of the application of radiation dosimetry to radiolabeled antibodies, as well as studying other mechanisms that may ultimately influence therapeutic outcome.

Robert M. Sharkey, PhD
*Garden State Cancer Center
Belleville, New Jersey*

