Dual-Integrin $\alpha_v\beta_3$- and Gastrin-Releasing Peptide Receptor–Targeting PET Radiotracer (^{68}Ga-BBN-RGD)

TO THE EDITOR: Zhang and colleagues recently published their interesting work in *The Journal of Nuclear Medicine* (*1*). Both integrin $\alpha_v\beta_3$ and gastrin-releasing peptide receptors are important markers in the biology of cancer as evidenced by the plethora of such PET radiopharmaceuticals, including arginine-glycine-aspartate (RGD) peptides for imaging angiogenesis (*2*) and bombesin analogs for imaging gastrin-releasing peptide receptors (*3*).

Although the use of RGD PET radiopharmaceuticals in prostate cancer is limited (*4*), bombesin analogs have been used successfully in this disease (*5,6*). We now know the expected biodistribution of the two classes of PET radiopharmaceuticals when injected separately. Therefore, in reviewing the methods and results reported by the authors, one may notice an incomplete evaluation of the new radiotracer because a comparison was not made with the ^{68}Ga-RGD injected separately. RGD dimers have normal distribution in the choroid plexus and thyroid gland (*7*), which is not observed in the images published for ^{68}Ga-bombesin-RGD. Can this be an indication that the new tracer may behave differently from the two injected separately? Our group uses the combined administration of ^{18}F-FDG and ^{18}F-NaF for detection of skeletal lesions. However, we compared the combined scan with both ^{18}F-FDG and ^{18}F-NaF in each participant included in the protocols before concluding that the combined scan provides similar information (*8*). A similar scrutiny should be the authors' goal for future use of ^{68}Ga-bombesin-RGD.

More importantly, readers may have difficulty identifying the optimal clinical use of ^{68}Ga-bombesin-RGD. Both angiogenesis and gastrin-releasing peptide receptors can be targets for therapies such as bevacizumab or ^{177}Lu-labeled bombesin analogs (*9*), respectively. How would a treating physician decide on the use of one versus the other based on a ^{68}Ga-bombesin-RGD PET scan? How would a theranostics approach be possible?

Lastly, the important task of identifying disease heterogeneity within patients will not be possible using ^{68}Ga-bombesin-RGD PET. Clinicians need to know whether all or what lesions demonstrate increased angiogenesis versus gastrin-releasing peptide receptor expression.

We are now fortunate to have multiple targets for detection and treatment of prostate cancer (*10*). Although the appropriate use of each class of PET radiopharmaceutical still needs to be evaluated in this disease, the information about cancer biology that each provides is of high merit. Bundling such information in a single examination may negate its usefulness. To quote from an editorial that accompanied our previous published work, technical feasibility versus clinical utility may be a question of "can we?" versus "should we?" (*11*)

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REPLY: I would like to respond to the wonderful commentary from Dr. Andrei Iagaru regarding a paper my colleagues and I recently published in *The Journal of Nuclear Medicine* (*1*). The heterodimer comprises two monomers that target two distinct types of receptors and are covalently linked. Consequently, one major advantage of the heterodimer over the corresponding monomers is the multivalency effect, resulting in improved binding affinity and an increased number of effective receptors (*2*). However, after covalent conjugation, the heterodimer is a new compound, which would show different in vivo pharmacokinetics from the monomers. Thus, it is not surprising that bombesin–arginine-glycine-aspartate (RGD) showed different distribution patterns within normal organs and tissues from either RGD or bombesin alone. If we mix RGD and bombesin, the similarity of the background would be improved, but that is not the purpose of this study.

I and my coauthors agree with Dr. Iagaru that it is challenging to reflect distinct pathways through imaging with heterodimers since the imaging intensity relates to both tumor angiogenesis by the RGD

moiety and gastrin-releasing peptide receptor level by the bombesin moiety. However, the major goal of the study was to provide a better detection rate for primary lesions and metastases of prostate cancer instead of knowledge of tumor angiogenesis and gastrin-releasing peptide receptor level. From this point of view, the study was successful because bombesin-RGD PET is better than bombesin PET in lesion detection (*1*). As pointed out in Dr. Iagaru's commentary, the imaging results from bombesin-RGD cannot be used to guide therapy using either RGD or bombesin directly. Because of the high tumor uptake and retention of bombesin-RGD, we are planning to label the heterodimer with β- or α-emitting radioisotopes for endoradiotherapy, which manifests the theranostic value of the heterodimer.

Most clinical trials are a natural consequence of promising preclinical investigations with the purpose of better serving patient management, and bombesin-RGD is not an exception. Both preclinical studies and the pilot clinical study demonstrated the potential of this heterodimer as a PET imaging probe. We are also aware that only a few of the plethora of candidate pharmaceuticals will eventually be approved in clinical trials. Sufficient caution is needed, but exploration is also needed to expand the arsenal for the diagnosis and treatment of malignant diseases. As has been said, it doesn't matter whether a cat is white or black, as long as it catches mice.

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Errata

In the article "Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines" by Gelfand et al. (*J Nucl Med.* 2011;52:318–322), Webster's formula in Table 2 should read as follows: (Age (y) + 1) × (adult dose)/(age (y) + 7). The authors regret the error.

In the article "^{68}Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Metaanalysis" by Graham et al. (*J Nucl Med*. 2017;58:1452–1458), two values of *n* were incorrect in the paragraph providing sensitivity and specificity results. The corrected paragraph appears below. The authors regret the error.

Sensitivity and Specificity (Metaanalysis)

The findings of the metaanalysis on the first 7 papers (*8–14*), which reported true-positive, true-negative, false-positive, and false-negative results (n = 300), show an overall sensitivity and specificity of 92% (95% confidence interval [CI], 85%–96%) and 82% (95% CI, 69%–90%), respectively (Fig. 2). The diagnostic odds ratio for these papers was 61 (Fig. 3). When we included the 5 papers (*15–19*) that reported only true-positive and false-negative results (n = 132), the metaanalysis resulted in an overall sensitivity of 93% (95% CI, 87%–96%) (Table 2).