

(1–4). The results presented by Dr. Kotzerke are of high importance, suggesting that the radiometal chelated into the DOTA moiety affects the uptake and perhaps binding of both DOTA-TATE and EB-DOTA-TATE. The authors concluded that “As a consequence of the different uptake, only different isotopes of the same element (such as $^{86}\text{Y}/^{90}\text{Y}$ or $^{64}\text{Cu}/^{67}\text{Cu}$) can be used for assessment of biokinetic data.”

Although the data presented by the authors are intriguing, we would like to argue that: (1) These results are not specific to EB-DOTA-TATE but are seen with DOTA-TATE as well. It is common practice to use ^{68}Ga -DOTA-TATE to detect tumor somatostatin receptor 2 expression before radionuclide therapy with ^{177}Lu -DOTA-TATE, and so far this practice seems to prove itself. Moreover, ^{68}Ga -DOTA-TATE scanning has significantly lower radiation exposure to the patient than other longer-lived isotopes labeled with the same ligand. It would be unreasonable in our opinion to use ^{86}Y for imaging when a much safer option is available (2). The authors derive their conclusion from in vitro cell uptake and extrapolated the result to predict the in vivo pharmacokinetics. It would be more appropriate to draw a conclusion from actual in vivo studies.

We look forward to seeing data from more in-depth in vivo studies done, perhaps, by Dr. Kotzerke and colleagues.

REFERENCES

1. Tian R, Jacobson O, Niu G, et al. Evans blue attachment enhances somatostatin receptor subtype-2 imaging and radiotherapy. *Theranostics*. 2018;8:735–745.
2. Bandara N, Jacobson O, Mpoy C, Chen X, Rogers BE. Novel structural modification based on Evans blue dye to improve pharmacokinetics of a somatostatin-receptor-based theranostic agent. *Bioconjug Chem*. 2018;29:2448–2454.
3. Zhang J, Wang H, Jacobson O, et al. Safety, Pharmacokinetics, and dosimetry of a long-acting radiolabeled somatostatin analog ^{177}Lu -DOTA-EB-TATE in patients with advanced metastatic neuroendocrine tumors. *J Nucl Med*. 2018;59:1699–1705.
4. Wang H, Cheng Y, Zhang J, et al. Response to single low-dose ^{177}Lu -DOTA-EB-TATE treatment in patients with advanced neuroendocrine neoplasm: a prospective pilot study. *Theranostics*. 2018;8:3308–3316.

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Reply: Radiation Dose Does Matter: Mechanistic Insights into DNA Damage and Repair Support the Linear No-Threshold Model of Low-Dose Radiation Health Risks

TO THE EDITOR: We wish to respond to Siegel et al.’s most recent letter (1). In the interest of brevity, we confine our remarks to the evidence that refutes their first 2 points.

The vast majority of DNA double-strand breaks (DSBs) caused by ionizing radiation are repaired by nonhomologous end joining (NHEJ), which is an error-prone process (2–4). Ionizing radiation causes complex DSBs due to associated damage of the adjacent base pairs or clustering of multiple break points in the DNA backbone (5). Siegel et al. now suggest that “the repair fidelity of the damage produced by low-dose, low-LET (linear energy transfer) radiation associated with medical imaging *may* be no less than that by homologous recombination for endogenously induced damage” (emphasis added). The evidence regarding the different error rates for the various DNA repair mechanisms is critical to this discussion. DNA damage repair via homologous recombination (HR) is a high-fidelity, *template-dependent* repair pathway for complex DNA damage including DNA gaps, DNA DSBs, and DNA interstrand crosslinks (6). HR achieves this accuracy using homologous sequences found elsewhere in the genome to guide the repair process. Homologous sequences occur in sister chromatids, homologous chromosomes, or repeated regions of the same or different chromosomes.

In contrast to HR, *nonhomologous* end joining (NHEJ) leads to alterations in the underlying DNA sequence precisely because it is not template-dependent (2). NHEJ occurs throughout the entire cell cycle whereas HR primarily occurs during the late S and G2 phases. As a result, the vast majority of DSBs induced by ionizing radiation are repaired by NHEJ while HR is best suited to repairing DSBs that arise during DNA replication.

The importance of fidelity during in vivo DNA repair is highlighted by Behjati et al.’s analysis of DNA sequences obtained from radiation-associated second malignancies (7). They performed whole-genome sequencing of the tumors and compared that data with DNA sequences obtained from the same patient’s normal tissues. That comparison revealed 2 mutational signatures in the radiation-associated cancers that transcended tumor type: small deletions and balanced inversions. The structural features of the small deletions and their random distribution throughout the tumor’s genome indicated that radiation-induced DSBs and the subsequent error-prone repair by NHEJ were causal factors in these clinically relevant cancers.

When considering the evidence about whether mutations caused by ionizing radiation can cause clinically relevant cancers, Siegel et al. argue that “*only* epidemiologic studies . . . can decide the issue” (emphasis added). We disagree with this complete reliance on epidemiologic studies. Instead we suggest that data from both epidemiologic and mechanistic studies must be considered together if one wishes to elucidate the responsible causal chain.

We agree with Siegel et al. that readers are faced with a choice between 2 divergent viewpoints. Some readers might be comforted by the argument that exposure to the ionizing radiation used for medical imaging not only is harmless but also actually prevents cancer. However, the available evidence indicates that medical imaging is a double-edged sword. When properly used, medical imaging provides immense benefits. But like any tool, it can be overused and overuse of medical imaging carries risks.

REFERENCES

1. Siegel JA, Sacks B, Greenspan BS. There is no evidence to support the linear no-threshold model of radiation carcinogenesis. *J Nucl Med*. 2018;59:1918.

2. Chang HHY, Pannunzio NR, Adachi N, Lieber MR. Non-homologous DNA end joining and alternative pathways to double-strand break repair. *Nat Rev Mol Cell Biol.* 2017;18:495–506.
3. Duncan JR, Lieber MR, Adachi N, Wahl RL. Radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59:1014–1016.
4. Duncan JR, Lieber MR, Adachi N, Wahl RL. Reply: radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59:1780–1781.
5. Schipler A, Iliakis G. DNA double-strand-break complexity levels and their possible contributions to the probability for error-prone processing and repair pathway choice. *Nucleic Acids Res.* 2013;41:7589–7605.
6. Li X, Heyer WD. Homologous recombination in DNA repair and DNA damage tolerance. *Cell Res.* 2008;18:99–113.
7. Behjati S, Gundem G, Wedge DC, et al. Mutational signatures of ionizing radiation in second malignancies. *Nat Commun.* 2016;7:12605.

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Erratum

In the article “Radioiodinated Small-Molecule Tyrosine Kinase Inhibitor for HER2-Selective SPECT Imaging” by Tang et al. (*J Nucl Med.* 2018;59:1386–1391), a second corresponding author was inadvertently left out of the article. Zijing Li, Center for Molecular Imaging and Translational Medicine, School of Public Health, Xiamen University, Xiang’an South Rd., Xiang’an District, Xiamen 361102, China, E-mail: zijing.li@xmu.edu.cn, should have been listed as an additional correspondence contact. The authors regret the error.