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REPLY: I would like to thank Schneider et al. for their compliments regarding our article (*1*), and I value and appreciate their time in submitting their concerns regarding our recommendations at the end of the article.

For the reader, the correct quotation of our recommendation from our article was "the use of rhTSH is appropriate for patients who cannot. . .increase their endogenous TSH because their metastases are producing significant thyroid hormone." As Schneider et al. point out correctly, our article does not address the appropriate or inappropriate use of recombinant human thyroid-stimulating hormone (rhTSH) in those rare patients with differentiation thyroid cancer whose endogenous thyroid-stimulating hormone (TSH) cannot be increased because their metastases are producing a significant amount of thyroid hormone. In retrospect, I believe that I could have chosen a better phrase to have communicated my original intent in that "the use of rhTSH injections is still appropriate to *consider* in patients who cannot increase their endogenous TSH because their metastases are producing significant thyroid hormone." Again, I appreciate the time and effort of Dr. Schneider et al. in bringing this to the readers' and my attention.

Having said that, I believe an even more important point is noted by Schneider et al. in their original case report, in which they emphasize that "even standard activities of 7.4 GBq (200 mCi) [of] ^{131}I may constitute a crucial dose in the rare combination of thyroid hormone secreting metastases and rhTSH-stimulation. . ..(*2*)" And as they further state, "higher standard [fixed] activities of ^{131}I should not be used without pretherapeutic dosimetry in patients with such large functioning metastases." I certainly agree with and support this comment. In addition, I believe that pretherapeutic dosimetry should not just be performed in a patient, like theirs, who is being considered for a fixed prescribed activity higher than 7.4 GBq (200 mCi), but pretherapeutic scans and pretherapeutic dosimetry should also be performed in all patients who are being considered for ^{131}I therapy and have documented or suspected functioning metastatic differentiated thyroid cancer. As has been reported by multiple authors, including Leeper (*3*), Tuttle et al. (*4*), and Kulkarni el al. (*5*), as many as approximately 10%–20% of patients may receive over 200 cGy (rad) to the blood (e.g., bone marrow) if prescribed activities of ^{131}I ranging from 3.7 GBq (100 mCi) to 7.4 GBq (200 mCi) are administered. (Additional restrictions apply, including not administering a prescribed activity of ^{131}I that would result in more than 4.44 GBq [120 mCi] of ^{131}I whole-body retention at 48 h in patients without pulmonary metastases and 2.96 GBq [80 mCi] of ^{131}I whole-body retention at 48 h in patients with pulmonary metastases.) In fact, as reported by Schneider et al. and using the OLINDA/EXM software, they calculated that the patient's blood-absorbed dose was 320 cGy (rad). If full dosimetry is not available, then the use of one of the simplified dosimetric alternatives such as percentage 48-h whole-body retention as proposed by Hänscheid et al. (*6*) or Van Nostrand et al. (*7*) should be considered in order to identify those patients whose prescribed activity of ^{131}I should be reduced. These simplified methods can be performed in almost any nuclear medicine facility.

Again, I thank Schneider et al. for their compliments, comments, and time.

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Palliation and Survival After Repeated ^{188}Re-HEDP Therapy of Hormone-Refractory Bone Metastases of Prostate Cancer: A Retrospective Analysis

TO THE EDITOR: We read with great interest the article by Biersack et al. published in the November 2011 issue (*1*). Because our group shares with the authors a similar interest in the potentials of therapeutic bone-seeking radiopharmaceuticals not only for palliation of bone pain but also for some objective antitumor activity (especially when administered in combination with other therapies) (*2,3*), this article constitutes for us an additional source of inspiration and stimulates further impetus to our ongoing investigations in this field.

Considering this evolving scenario, we believe that clarifying somewhat further some of the issues addressed by Biersack et al. would contribute to enhancing the value of the overall information that the nuclear medicine community (as well as the medical

oncology community at large) would derive from reading the article by Biersack et al. This need is felt by all specialists involved in the management of patients with bone metastases and is in fact spurring a growing number of systematic reviews and metaanalyses (*3–10*).

In the perspective of future reviews taking into account the works by Bonn's group (*1*) along with other original contributions, it is essential (for the sake of clarity and for the purpose of statistical evaluation) to specify whether the patient population with long-term follow-up described in the latest publication (*1*) is totally independent from the population included in an earlier article by the same group describing the clinical benefit of repeated ^{186}Re-hydroxyethylidenediphosphonate (^{186}Re-HEDP) administrations (*11*); this seems to be the case upon reading the last paragraph under "Discussion," but perhaps a specific statement would help in this regard.

We certainly understand that there are some intrinsic limitations due to the retrospective nature of the study by Biersack et al. and to the fact that the patients' response to ^{188}Re-HEDP therapy in terms of bone pain palliation was reported with a crude, simplified scale by the referring physician (rather than recorded directly by patients according to, for example, the Visual Analog Scale). For instance, it would help the scientific community to know if the patient population described in this work represents a consecutive series or only those patients for whom the referring physician returned the questionnaire, and what percentage of questionnaires were correctly returned with respect to the total sent.

Still, for review and analysis purposes the results reported by Biersack et al. would be even better appreciated if they described in greater detail the duration of pain palliation and, above all, the reproducibility of the palliative effect after subsequent ^{188}Re-HEDP administrations in the same patient, an issue that has already been addressed for other bone-seeking radionuclide agents, such as ^{153}Sm-ethylenediaminetetramethylenephosphonate (*12*). Furthermore, Biersack et al. do not specify the reason for repeated ^{188}Re-HEDP therapies: was treatment repeated because of prior planning (perhaps as part of an ongoing protocol with the experimental drug ^{188}Re-HEDP) or because of recurrent pain after palliation? In the latter instance, could retreatment of patients responding to the first treatment introduce a selection bias as to subsequent response to repeated therapy? Did the authors observe bone palliation after repeated treatment even if the first treatment was ineffective? Finally, for completeness of analysis the authors could provide the average number of administrations in the group receiving more than 3 ^{188}Re-HEDP therapies (they only mention a maximum of 8, which is quite a bit greater than 3) and, above all, the overall duration of treatment from first to last administration. A further issue that is usually of great concern to medical oncologists is the possible hematologic toxicity of bone-seeking radiopharmaceuticals, especially after repeated administrations (and at relatively short intervals such as ~8 wk); a specific statement by the authors in this regard would be greatly welcome.

Concerning instead objective response to ^{188}Re-HEDP therapy (as shown by declining levels of serum prostate-specific antigen [PSA] after radionuclide treatment), it would greatly help the reader to know on which occasion such a reduction was observed for patients treated more than once; in other words, do the data reported in Table 3 for groups B and C refer to the best response observed, and was such best response observed after treatment 1, 2, or 3? Conversely, it would help future analysis to know how the authors set thresholds defining serum PSA as "decreased," "unchanged," or "increased," as well as to know how reproducible the serum PSA response was in each patient after repeated therapies.

Concerning survival analysis, the data provided by the authors would optimally be complemented by adequate information not only on the approximate burden of metastatic skeletal involvement (i.e., more precisely than simply "more than 5 lesions documented by a bone scan") but also on the possible presence and extent of concomitant visceral metastatic disease. Still with reference to survival, as reviewed recently a crucial issue that is the object of increasing interest and attention in hormone-refractory prostate cancer patients with skeletal metastasis is possible combination therapy of bone-seeking agents with other proven or putative antitumor treatments, usually chemotherapy (*3*). In this regard, even if based on a retrospective study rather than on a prospective protocol, information on possible concomitant chemotherapy received by the patients described by Biersack et al. (or at least by a fraction of that population) would add to our understanding of the impact on survival of repeated ^{188}Re-HEDP therapy per se compared with such a regimen in association with other antitumor agents.

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