for the specialty in the 1970s and has become insufficient when PET entered practice.

In order to support my assertion, I compared the duration of training of future specialists in Europe and elsewhere. It is 4–5 y and includes cross-sectional anatomy and basics of CT. It takes a maximum of 12 mo to learn these 2 areas. Therefore, a 1-y credit can be given to physicians coming from DR, resulting in a 36-mo training duration. A similar comparison with NM residency in the United States would result in a 24-mo training.

Finally, I ask myself (and the readers) this question. How do you expect a radiologist who learned everything in NM in 16 mo to treat and follow a metastatic castrate-resistant prostate cancer patient candidate for radionuclide therapy?

The leadership of the American Board of Nuclear Medicine should reconsider the 16-mo rule and extend it appropriately. Otherwise, the practice of NM in the United States will remain limited to diagnostic procedures with the exception of a few large academic centers. Who will suffer most? The American patient.

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Advantages and Limits of Targeted Radionuclide Therapy with Somatostatin Antagonists

TO THE EDITOR: Peptide receptor radionuclide therapy (PRRT) is highly effective in neuroendocrine tumors (NETs). In the NETTER-1 trial, progression-free survival at month 20 in patients with advanced midgut NET and treated with the somatostatin agonist ^{177}Lu-DOTATATE was 65.2% (vs. 10.8% in the control group consisting in high dose cold somatostatin analogs) (*1*). Despite these striking results, we should strive to increase also the tumor response rates, as the objective response was only 18%. Somatostatin antagonist analogs such as ^{177}Lu-DOTA-JR11 (OPS201; Octreopharm Sciences–Ipsen) may improve tumor response (*2*). In a small pilot study (4 patients with advanced NET), the absorbed doses in the tumors were approximately 3.5 times higher with ^{177}Lu-DOTA-JR11 than with ^{177}Lu-DOTATATE (*2*). The therapeutic index also favored ^{177}Lu-DOTA-JR11: the median tumor–to–kidney dose ratio was 2.1 times higher and the tumor–to–bone marrow dose ratio was 2.6 times higher than with ^{177}Lu-DOTATATE (*2*).

In a study on mice bearing tumor xenografts recently reported in *The Journal of Nuclear Medicine,* Nicolas and colleagues escalated the injected peptide mass of ^{177}Lu-DOTA-JR11 from 10 to 200 pmol without finding any tumor saturation (*3*). By contrast, the uptake in somatostatin receptor–expressing organs was greatly suppressed, and consequently the tumor-to-background ratios were enhanced. According to the authors, because 200 pmol in mice would correspond to up to 1,300 μg in humans, the injected mass of antagonists should be higher than the levels currently used for agonists (≤50 μg for imaging and ≤200 μg for PRRT) (*3*).

It is our contention that extrapolating from mice to humans is not so straightforward, and injecting a greater mass for antagonist-based PRRT is not necessarily beneficial:

- Although high doses of peptides reduced the physiologic uptake in the pancreas and stomach of mice (*3*), a human phase I/II trial showed that microdoses (15 or 50 μg) of the imaging compound ^{68}Ga-NODAGA-JR11 (OPS202) were associated with a very low uptake in the pancreas and stomach and a moderate uptake in the liver—only the kidneys and spleen displayed high uptake (*4*). Also, in the human pilot study with ^{177}Lu-DOTA-JR11 (~150 μg peptide mass), the images recorded at 24 and 72 h showed low uptake in the pancreas and stomach, and the radiation dose to the pancreas and stomach wall were about 15 times lower than that to the kidneys (*2*). The biodistribution seems to be species-dependent: for example, differently from humans, pigs displayed a high uptake of ^{177}Lu-DOTA-JR11 in the osteogenic bone, but the spleen was not visible (*5*).

  Moreover, although increasing the injected mass of ^{177}Lu-DOTA-JR11 in mice increased the tumor–to–bone marrow dose ratio, the tumor–to–kidney dose ratio decreased to a certain extent, and this may have undesired side effects during PRRT (*3*).

- Increasing the amount of injected peptide might decrease the uptake of ^{177}Lu-DOTA-JR11 in tumors that have low receptor density but may still be candidates for PRRT, such as non-NET tumors (*6*). It might also reduce the efficacy of hepatic intra-arterial administrations, because the enhanced uptake in liver metastases with this approach relies on the "first pass effect" (*7*).
- Tolerability is also an issue. Patients with metastatic NET are often treated with cold somatostatin agonist analogs in order to reduce secretory symptoms or halt tumor progression. This treatment is usually withheld before PRRT in order to avoid competition with radiolabeled peptides (*1*). The administration for PRRT of radiolabeled antagonists, rather than agonists, may induce or exacerbate symptoms, as shown, for example, in 1 of the 4 patients in the pilot study with ^{177}Lu-DOTA-JR11 (150 μg), who experienced flush (*2*). Further increasing the amount of antagonist, to levels close to those known to elicit pharmacologic response with various hormonal secretions (*8*), may be risky, especially in patients with symptomatic NET. Rather, we should aim at injecting the lowest mass of peptide that yields a satisfactory tumor uptake and also explore the possibility of maintaining the treatment with cold somatostatin analogs during PRRT with somatostatin antagonists.

At difference with somatostatin receptors, when targeting other neuropeptide receptors, such as GRPR or NTR-1, the use of radiolabeled antagonists allows avoiding stimulation of these receptors and related symptoms (*9*).

In summary, given the interspecies variations in biodistribution, the optimal peptide mass to use for imaging or therapy with radiolabeled antagonists should be determined from human data, as

previously done with agonists (*10*). Also, we think that the benefit from increasing the peptide mass of antagonist beyond the usual value of 150 μg (*2*) is still unproven.

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REPLY: We would like to thank Hindié et al. for their interest in our preclinical and clinical works on radiolabeled somatostatin receptor antagonists (*1,2*). However, we feel that the title of their letter, "Advantages and Limits of Targeted Radionuclide Therapy with Somatostatin Antagonists," is misleading because the letter does not address these 2 issues, but rather criticizes, a priori, the use of a higher mass of peptide for radionuclide therapy with radiolabeled somatostatin receptor antagonist. In our opinion, and based on our recent findings, the administration of an appropriate peptide mass is a key parameter for optimal imaging and therapy of somatostatin receptor–expressing tumors. We herein take the opportunity to respond to the valuable questions raised by Hindié et al., in addition to the already addressed points in our recent articles (*1,3,4*).

In our article presenting the outcome of animal studies (*1*), we acknowledged the complexity of translating from animal models to humans, as stressed by Hindié et al., and we cautiously stated that "considering several models, including body weight–based allometric scaling, 200 pmol *may represent* a peptide amount higher than 200 μg (up to 1,300 μg) in human." Two hundred micrograms are considered the upper limit for the agonist; however, there are indications that 200 μg might represent a starting dose for the antagonists. We understand the limitation of allometric scaling from mice to humans (*5*) and therefore agree with the authors that the benefit (safety and efficacy) of injecting larger amounts of antagonist peptide still needs to be investigated clinically. Animal experiments have been crucial in discovering the potential benefit of higher peptide mass, and these results should not be neglected because of hypotheses that have not been demonstrated. Our mass-escalation study in mice clearly indicated that an optimized amount of antagonist might further improve the safety window of radionuclide therapy by reducing bone marrow and liver doses, as well as the effective dose of ^{177}Lu-OPS201 (^{177}Lu-DOTA-JR11). However, Hindié et al. focused on the reduction of the stomach and the pancreas uptake, arguing that the uptake in these organs is rather low in the human phase I trial with 2 microdoses (15 or 50 μg) of the imaging compound ^{68}Ga-NODAGA-JR11 (^{68}Ga-OPS202).

Although we agree with Hindié et al. that decreasing gastrointestinal or pancreatic uptake/dose may only be relevant in a diagnostic setting, we think that we should take maximum advantage of the mass effect for decreasing the bone marrow and liver dose that are absolutely relevant in systemic or liver-directed radionuclide therapy, in addition to the effective dose. Unfortunately, this approach does not affect renal uptake, which is mediated by another mechanism. Nevertheless, the kidneys do not seem to be the dose-limiting organ in ^{177}Lu-based radionuclide therapy with somatostatin analogs, as shown by the NETTER-1 trial (*6*) and numerous previous other studies (*7*). In contrast and as recently presented by Reidy et al. (*8*), using a low peptide amount (100 μg) of ^{177}Lu-OPS201 and standard activity (2 cycles up to 7.4 GBq) may lead not only to excellent objective response rate (>40%) but also to substantial bone marrow toxicity. In this sense, any attempts to maximize safety and efficacy are entirely justified.

Although a pharmacologic effect of somatostatin receptor antagonist cannot be completely excluded, especially at higher mass, there are no safety concerns based on preclinical toxicity data, even with 50 times more peptide than the corresponding upper limit of 1,300 μg in humans. Although the relevance of a possible symptom exacerbation, such as flushing, in patients with preexisting carcinoid syndrome remains questionable, one may recommend slow infusion over bolus injection to prevent triggering any pharmacologic effect.

An important property of the somatostatin receptor antagonist ^{177}Lu-OPS201 is that it recognizes potentially more binding sites on tumor cells in vitro than the currently used agonists (Melpomeni Fani et al., unpublished data, 2016), similarly to previously published data (*9–11*). Organs that are physiologically expressing somatostatin receptors seem to get saturated—at least partially—earlier along the mass escalation, whereas tumor uptake remains high. Besides somatostatin receptor antagonists, these effects have also been observed for other radiolabeled peptides targeting