Regarding "Is 16 Months of Specialized Nuclear Medicine Training Enough for Best Patient Care?"

TO THE EDITOR: As the program director of the national nuclear medicine training program in Singapore (ex-British colony that just celebrated our 52nd anniversary of independence), I read with interest "Is 16 Months of Specialized Nuclear Medicine Training Enough for Best Patient Care?" I agree with the editor that my answer is also "No."

In our institution, "Nuclear Medicine and Molecular Imaging" has just joined our cousin departments "Diagnostic Radiology" and "Vascular and Interventional Radiology" to form the division of "Radiologic Sciences." In the Specialists Accreditation Board, nuclear medicine is an independent specialty with its own Residency Advisory Committee.

Let me comment on the key questions that the editor has raised. First, nuclear medicine is not a division of radiology in Singapore (I agree that cross-sectional imaging is an important part of nuclear medicine training). Second, the nuclear medicine practice will continue to grow in therapy, oncology, neurology, and cardiology in the next 5–10 y. Third, we have to increase our capacity to meet the needs of theranostic programs. And fourth, theranostics will subspecialize into systems to fit into the workflow of nuclear medicine.

I agree that nuclear medicine therapy (precision medicine) has different training demands. In Singapore, nuclear medicine is considered a senior residency program (2.5 y) where we accept applicants from medicine (after internal medicine residency) and radiology (after 4 y of diagnostic radiology residency as a dual accreditation program). Graduates of our program (previously called advanced specialist training) are highly skilled experts who have shaped the field in Singapore for more than a decade.

Image interpretation with cross-sectional imaging training is an important part of our program (more so for residents with a medicine background). We are also developing relationships with urology (prostate-specific membrane antigen–targeted theranostics), radiation oncology (theranostics), endocrinology, and oncology (somatostatin receptor–targeted theranostics, bone pain treatments), not to mention our close ties with cardiology, neurology, and medicine (infection/inflammation). We are also involved in the academic, translational, and clinical applications of imaging probe development, tracer kinetics, and molecular imaging in drug development.

The Journal of Nuclear Medicine has readership across the world and we are keen to be engaged in this discussion. In order for us to succeed, you must succeed as well.

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TO THE EDITOR: I am writing in support of the editorial written by Dr Czernin (*1*) and Dr Lam's letter (*2*) published recently.

There are 2 questions raised by the statements. The first, should nuclear medicine (NM) be an independent specialty? And second, if not is 16 mo of training adequate to accomplish the best patient care?

My answer is yes to the first question and no to the second. I practiced NM in the United States for 30 y (the last 10 as Director of Nuclear Medicine in a large academic hospital) and assumed leadership positions within the Society of Nuclear Medicine and Molecular Imaging including president of the Nuclear Oncology council between 2009 and 2011. I have returned in 2013 to my native country Lebanon, where a large number of practitioners are duly certified after training in Europe. I have witnessed firsthand the superb quality of their care. Moreover, I have participated at the meetings sponsored by the European Association of Nuclear Medicine and have noticed the excellent educational quality of the talks.

It may be useful to remind the readership of the *Journal* that NM is an independent specialty in the overwhelming majority of world regions including Europe; the Far East, including China, Japan, and South Korea; and Latin America.

Indeed, there is no compelling reason why NM should be part of Radiology (DR). Although both specialties deal with images, the divergences are more important than the similarities. We look for metabolic or molecular disturbances with the help of tracers. Radiologists look for structural abnormalities (fracture, hemorrhage, edema, and masses) that are detected through changes in physical characteristics of the tissue interrogated. Progress in NM depends mostly on progress in finding more specific tracers. Progress in DR depends on progress in technology and bioengineering. NM has emerged from Medicine everywhere, including the United States, and for this reason has successfully endeavored to quantify the image data and relate them to the patient outcome. NM tests provide not just a diagnosis but also prognostic information and help guide management. It is not surprising that PET is at the forefront of personalized medicine in cancer. I believe our perspective and success are related to our background in Medicine and our affinity with physicians from Medicine.

Finally, and most importantly, the field is moving forward toward therapeutic applications. My mentor, the late Henry Wagner, used to say: "NM is useful for Medicine people and will become increasingly so." As is often the case, his comments were prophetic. We have emerged from Medicine and we are returning to Medical Therapy, an area far away from radiologist interests and expertise. Therapeutic Interventional Radiology is only an alternative to surgery.

The American pathway is a singular experiment with uncertain results. It is the exception that confirms the rule. It is not a coincidence that this rule has been adopted by the rest of the world. The rule and the correct way are to consider NM as a fully independent specialty. The future will validate this approach and the future is here, that is, Theranostics.

However, because the American NM pioneers have decided otherwise by striking a "marriage" deal with DR, let me answer the second question.

The 16-mo duration is barely adequate for today's NM and will be inadequate when Theranostics enters practice, in the same way the 4-mo rule (which is still surprisingly valid) was barely adequate

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.

REFERENCES

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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