

Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors: how important is internal dosimetry?

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We are grateful to Mr Trauernicht and Dr du Toit for their letter to the editor written on the recently published South African practice guidelines on peptide radionuclide therapy of neuroendocrine tumors.¹ In the letter, they express concern that internal dosimetry was discussed in “only a single short paragraph” and that this may create an impression that “internal dosimetry assessment is just an optional extra.” The authors drew a contrast between the South African guidelines and the joint International Atomic Energy Agency (IAEA), European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging guidelines published earlier where “a whole section on dosimetry” was included.²

The NETTER-1 trial is a phase III trial that demonstrated the superiority (regarding survival benefits) of peptide receptor radionuclide therapy (PRRT) of well-differentiated metastatic midgut neuroendocrine tumours (NETs) using Lu-177 DOTATATE over long-acting octreotide alone.³ Following the report of this trial, many regulatory authorities around the world approved the use of this radionuclide therapy option in routine clinical practice. Consequently, the demand by patients and their oncologists for this highly effective therapy with tolerable side effects increased tremendously in South Africa and elsewhere around the world. In response to this high demand, the College of Nuclear Physicians (CNP) of South Africa, on behalf of the South African Society of Nuclear Medicine (SASNM), came together to publish practice guidelines to “assist Nuclear Medicine Physicians in the evaluation, safe administration and follow-up (assessment of response and long-term toxicities) of patients with NETs referred for or considered for PRRT”.¹

Our intervention (the practice guidelines) was to provide an essential guide with everyday applicability for Nuclear Physicians to safely apply PRRT in patients’ management

with consideration of the opportunities and challenges for such application in South Africa and similar climates across the world. The practice guidelines were not meant to be a complete and exhaustive step-by-step approach to the application of PRRT. Details regarding quality control, post-therapy imaging, dosimetry, and other such matters were not included to allow practitioners some flexibility in the application of this guidance document. Our brief mention of dosimetry must not be misconstrued as indicating that it is not an important exercise or that it be regarded as an optional extra. A similar approach to ours has been adopted in other guidelines produced by other international organisations for radionuclide imaging and therapy.^{4,5}

Dosimetry ensures that a lethal dose is delivered to the tumour while keeping radiation exposure to normal organs within safe limits. It is a useful step in radionuclide therapy for safety and efficacy. Its practice has got several challenges, however. As affirmed by Trauernicht and du Toit, it is difficult to perform, and the skills required for its performance are not uniformly available in all practices. There are several methods for the performance of dosimetry assessment which vary in sophistication. OLINDA is a useful software application to estimate the mean absorbed dose to tumours and normal organs, such as bone marrow and kidneys, in PRRT. In recognising the challenges with dosimetry assessment, the joint IAEA, EANM and SNMMI guidelines recommend that patient-specific dosimetry be performed “if feasible”.²

A local South African experience and several international studies have reported on the safety and efficacy of PRRT in large patient populations with long-term follow-up treated for NETs.⁶⁻⁹ Adhering to practices reported in these studies ensures safe and effective administration of PRRT. Radioiodine treatment of well-differentiated thyroid cancer is the oldest and most commonly applied radionuclide therapy modality

in clinical practice. Decades of use have allowed a clear identification of a patient sub-population in which dosimetry is essential for therapy effectiveness and the limitation of therapy-related adverse effects.¹⁰ Such experience is, however, lacking for PRRT and it is consequently unknown for which groups of patients sophisticated individualised dosimetry may be mandatory.

In conclusion, PRRT administration requires the expertise of many professionals including the medical physicist, who, by regulation, must observe all radionuclide therapy administrations. Dosimetry is a responsibility of the medical physicist. Despite challenges to its practice, dosimetry is an essential step in radionuclide therapy planning and administration. Where the expertise is available and when feasible, dosimetry must be done in all patients to obtain an estimate of the tumour dose, and the mean absorbed dose to normal organs especially bone marrow and the kidneys. Furthermore, in centres without the expertise for this assessment, every effort must be made to ensure that it be put in place. We hope to include a section detailing dosimetry assessment in the second version of these practice guidelines planned for the near future.

REFERENCES

1. Lawal I, Louw L, Warwick J, et al. The College of Nuclear Physicians of South Africa Practice Guidelines on Peptide Receptor Radionuclide Therapy in Neuroendocrine Tumours. *S Afr J Surg*. 2018;56(3):55-64.
2. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2013;40(5):800-16.
3. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of ¹⁷⁷Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376(2):125-35.
4. Blaufox MD, De Palma D, Taylor A, et al. The SNMMI and EANM practice guideline for renal scintigraphy in adults. *Eur J Nucl Med Mol Imaging*. 2018;45(12):2218-28.
5. Ahmadzadehfard H, Aryana K, Pirayesh E, et al. The Iranian Society of Nuclear Medicine practice guideline on radioligand therapy in metastatic castration-resistant prostate cancer using ¹⁷⁷Lu-PSMA. *Iran J Nucl Med*. 2018;26(1):2-8.
6. Vorster M, Modiselle MR, Corbett CS, Lawal IO, Buscombe JR, Sathekge MM. First Results and Experience with PRRT in South Africa. *World J Nucl Med*. 2018;17(2):86-93.
7. Sabet A, Ezziddin K, Pape UF, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with ¹⁷⁷Lu-octreotate. *J Nucl Med*. 2013;54(11):1857-61.
8. Bodei L, Kidd M, Paganelli, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumors: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging*. 2015;42(1):5-19.
9. Baum RP, Kulkarni HR, Singh A, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with ⁹⁰Yttrium and ¹⁷⁷Lutetium in 1048 patients with neuroendocrine neoplasms. *Oncotarget*. 2018;9(24):16932-50.
10. Kreissl MC, Janssen MJR, Nagarajah J. Current treatment strategies in metastasized differentiated thyroid cancer. *J Nucl Med*. 2018. Epub ahead of print 6 Sept 2018. doi: 10.2967/jnumed.117.190819