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EDITORIAL

NUCLEAR MEDICINE IN PRECISION ONCOLOGY

Nuclear medicine in precision oncology: a foreword

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The current issue of *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* focusses on the role of nuclear medicine in the era of precision medicine. The last two decades have seen an unprecedented increase in molecularly targeted agents available for clinical use, with many others under clinical development. Precision oncology has at its disposal a vast arsenal consisting of, amongst others, hormonal agents, tyrosine kinase inhibitors, pathway inhibitors, DNA repair inhibitors, monoclonal antibodies targeting cell surface proteins and antibody-drug conjugates, that complement classical chemotherapy agents. The presence of the target for most therapies is determined through immunohistochemistry, in situ hybridization techniques, genetic analysis or a combination of these, executed on tumor biopsies or circulating tumor material, either cells or DNA, in so-called liquid biopsies. The importance of these molecular targets for treatment opens up a range of opportunities for the nuclear medicine community, as our techniques are the current gold standard for non-invasive molecular imaging in humans.

The deep characterization of tumors at the genetic and protein level has not only lead to targets for pharmacological intervention but has also identified many potential targets for "Trojan horse" strategies, where a specific ligand with a toxic payload will bind to its target and lead to a toxic concentration of the payload solely within the tumor. Successful examples include trastuzumab emtansine, where a chemotherapeutic drug is attached to an antibody for the Her2-receptor, with proven benefit in Her2-positive breast cancer patients.[1, 2] For nuclear medicine, a range of toxic payloads is available, including β^-, α and Auger-emitters. The NETTER-1 trial has demonstrated the potential of targeted radionuclide therapy with a β-emitter in a randomized controlled trial in midgut neuroendocrine tumors, with a profound impact on progression-free survival and quality of life. The most powerful class of therapeutic radionuclides, α-emitters, which constitute some of the most potent toxic payloads known to science, can have a spectacular effect when used with the proper targeting molecules, on par with the effects of immune-oncology agents. This is exemplified by the deep molecular remission obtained in castrate-resistant prostate cancer patients treated with ^{225}Ac-PSMA-617, even after progression on ^{177}Lu-PSMA-617 therapy.[3] Seoane *et al.*[4] provide an overview of targeted alpha therapy, with an emphasis of one of the most promising radionuclides, actinium-225.

One of the oldest targets in use in nuclear medicine oncology is the human norepinephrine transporter (hNET), a molecular pump overexpressed in tumors-derived from the neural crest. Imaging with [^{123}I]MIBG was the most sensitive and specific molecular imaging test that nuclear medicine could offer, but advances in PET radiopharmaceuticals have relegated hNET imaging to second, third or even later choice of imaging agent in a range of clinical indications according to the most recent guidelines.[5] How-

ever, many of these recent trials compare conventional gamma-camera-based nuclear medicine with images obtained through PET scanners with superior physical properties. As we know from the somatostatin receptor imaging field, PET imaging is clinically superior to gamma-camera imaging[6] and this has led to widespread adoption of ^{68}Ga-DOTA-somatostatin analogues.[7] Pauwels *et al.*[8] review in detail the molecular mechanisms behind hNET imaging, the available radiopharmaceuticals with an emphasis on recently developed PET tracers which outperform [^{123}I] MIBG and that might restore the pre-eminence of hNET imaging in the management of neural crest tumors.

The next topic focused on in this special edition is radiomics. Large amounts of quantitative features extracted from medical imaging, have the potential to serve as non-invasive biomarkers for tumor characterization, prognostic stratification and response prediction, thereby contributing to precision oncology.[9] The clinical application, however, especially in nuclear medicine, is still in its infancy. Individual studies show promising results, however, due to small patient cohorts and poor standardization, validation of results is difficult.[10, 11] The review of Noortman *et al.*[12] describes the radiomics pipeline, its applications and the increasing role of artificial intelligence within the field. Furthermore, combination of radiomics with clinical data and other biomarkers is addressed and challenges in clinical translation are discussed. In the near future, radiomics can hopefully make a meaningful contribution to precision medicine by providing the right treatment to the right patient, with the right dose, at the right time.

Last but not least, we would like to show a prime example of nuclear medicine theranostics in the review by Dotinga *et al.*[13] Radioactive iodine-refractory thyroid cancer shows a poor response to iodine-131 therapy, due to its inability to accumulate iodine-131 or to radioresistance, resulting in an overall poor prognosis. The development of targeted therapies, such as tyrosine kinase inhibitors (TKIs), has shown substantial promise, leading to redifferentiation and renewed radioiodine uptake, enabling iodine-131 therapy.[14] Using pre- and post-TKI treatment dosimetry, radioiodine uptake can be quantified in order to identify patients who will likely benefit from subsequent iodine-131 therapy and to calculate individualized therapeutic doses to ensure efficacy in individual lesions and in order to limit toxicity.[15, 16] Consequently, futile iodine-131 therapy can be avoided and alternative systemic therapies can be given in an earlier stage. The review discusses the role of dosimetry and elaborates on the underlying mechanism of sodium iodide symporter function and clinically investigated targets for redifferentiation. Moreover, different dosimetry approaches, pitfalls and limitations are explained and an overview of relevant clinical studies that employ dosimetry to monitor redifferentiation is given.

In this special edition we hope to share with you our enthusiasm about the myriad of current nuclear medicine innovations which have major impact on oncology clinical practice, enabling and facilitating precision oncology. We wish you a pleasant reading!

References

1. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, *et al.*; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783–91.

2. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, *et al.*; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617–28.

3. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, *et al.* 225Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. J Nucl Med 2016;57:1941–4.

4. Castillo Seoane D, de Saint-Hubert M, Crabbe M, Struelens L, Koole M. Targeted alpha therapy: a critical review of translational dosimetry research with emphasis on actinium-225. Q J Nucl Med Mol Imaging 2020;64:265–77.

5. Taïeb D, Hicks RJ, Hindié E, Guillet BA, Avram A, Ghedini P, *et al.* European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 2019;46:2112–37.

6. Van Binnebeek S, Vanbilloen B, Baete K, Terwinghe C, Koole M, Mottaghy FM, *et al.* Comparison of diagnostic accuracy of (111)In-pentetreotide SPECT and (68)Ga-DOTATOC PET/CT: A lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. Eur Radiol 2016;26:900–9.

7. Deroose CM, Hindié E, Kebebew E, Goichot B, Pacak K, Taïeb D, *et al.* Molecular Imaging of Gastroenteropancreatic Neuroendocrine Tumors: Current Status and Future Directions. J Nucl Med 2016;57:1949–56.

8. Pauwels E, van Aerde M, Bormans G, Deroose CM. Molecular imaging of norepinephrine transporter-expressing tumors: current status and future prospects. Q J Nucl Med Mol Imaging 2020;64:234–49.

9. Wei L, Osman S, Hatt M, El Naqa I. Machine learning for radiomics-based multimodality and multiparametric modeling. Q J Nucl Med Mol Imaging 2019;63:323–38.

10. Bogowicz M, Vuong D, Huellner MW, Pavic M, Andratschke N, Gabrys HS, *et al.* CT radiomics and PET radiomics: ready for clinical implementation? Q J Nucl Med Mol Imaging 2019;63:355–70.

11. Cheze Le Rest C, Hustinx R. Are radiomics ready for clinical prime-time in PET/CT imaging? Q J Nucl Med Mol Imaging 2019;63:347–54.

12. Noortman WA, Vriens D, Grootjans W, Tao Q, De Geus-Oei LF, van Velden FH. Nuclear medicine radiomics in precision medicine: why we can't do without artificial intelligence. Q J Nucl Med Mol Imaging 2020;64:278–90.

13. Dotinga M, Vriens D, van Velden F, Heijmen L, Nagarajah J, Hicks R. Managing radioiodine refractory thyroid cancer: the role of dosimetry and redifferentiation on subsequent I-131 therapy. Q J Nucl Med Mol Imaging 2020;64:250–64.

14. Giovanella L, Scappaticcio L. Radioiodine therapy of advanced differentiated thyroid cancer: clinical considerations and multidisciplinary approach. Q J Nucl Med Mol Imaging 2019;63:229–34.

15. Weber M, Binse I, Nagarajah J, Bockisch A, Herrmann K, Jentzen W. The role of 124I PET/CT lesion dosimetry in differentiated thyroid cancer. Q J Nucl Med Mol Imaging 2019;63:235–52.

16. Verburg FA. Advantages of dosimetry in 131I therapy of differentiated thyroid carcinoma. Q J Nucl Med Mol Imaging 2019;63:253–7.

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