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EDITORIAL

Beyond ^{68}Ga-labeled somatostatin analogues: *is it time to say goodbye to [^{68}Ga]DOTA-conjugated peptides for neuroendocrine neoplasms?*

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Positron emission tomography (PET) imaging with ^{68}Ga-labeled somatostatin analogues (SSAs) is the standard functional imaging modality currently used in the management of neuroendocrine neoplasms (NENs) in different settings of the disease, as reported in the European guidelines [1]. Nonetheless, the high production costs and short half-life ($t1/2 = 67.8$ min) of ^{68}Ga greatly limit the applications of ^{68}Ga-labeled radiopharmaceuticals. In this scenario, ^{18}F-labeled radioligands are emerging as attractive alternatives for molecular imaging of NENs. Compared to ^{68}Ga, ^{18}F is characterized by a longer half-life ($t1/2 = 110$ min), a lower positron energy, and higher rate of photon emission, thus resulting in an improved spatial resolution and better overall image quality. In patients with NENs, few studies have investigated the role of ^{18}F-labeled SSA so far, with encouraging preliminary results [2, 3]. However, additional evidence is eagerly needed to validate the potential clinical relevance of these novel radiotracers.

In this issue of EJNMMI, Chen D. and colleagues [4] reported the results related to the clinical value of [^{18}F]F-AlF-NOTA-octreotide ([^{18}F]-OC), a novel ^{18}F-labeled SSA, in a retrospective cohort including patients with either a suspected NEN, a confirmed NEN with suspected metastases, or recurrent disease ($n = 93$, 276 lesions). All NEN diagnoses were proven by histopathological examination after surgery or biopsy. The majority of NENs were grade 1 and 2 (85%), and most of the lesions were located in the pancreatic gland or in the liver (66.7%). In patients with suspected NENs ($n = 45$, 117 lesions), [^{18}F]-OC PET/CT demonstrated a sensitivity of 96.3%, a specificity of 77.8%, and an accuracy of 88.9% in detecting and differentiating NENs from other conditions, including pancreatic adenocarcinoma, inflammatory processes, accessory spleen, and other neoplasms. Also considering patients with suspected NEN metastases or recurrence ($n = 93$, 276 lesions), [^{18}F]-OC PET/CT showed a sensitivity of 90.5%, a specificity of 82.1%, and an accuracy of 88.8% in discriminating NEN lesions from other etiologies. In all settings, [^{18}F]-OC PET/CT demonstrated a superior diagnostic performance compared to contrast-enhanced CT and MRI, especially in terms of specificity. Notably, the smallest diameter of NEN lesions identified by [^{18}F]-OC PET/CT was 0.4 cm in the pancreas and rectum and 0.3 cm in the liver and lymph node.

Chen D. et al. performed this single-center retrospective study on a relatively small cohort of patients, with inter-patient heterogeneity in terms of clinical setting, previous treatments, site of primary lesions, NEN grade, imaging protocols, and scanners; all these issues may have resulted in potential sources of undetected bias. Additionally, contrast-enhanced CT and MRI were available for comparison with [^{18}F]-OC PET/CT in a limited number of patients, and histopathological confirmation was present in only 164/276 (59%) of lesions with 1-year imaging follow-up being used as reference standard for diagnosis in the remaining cases.

Despite the above-mentioned limitations, this study clearly demonstrates the clinical value of [^{18}F]-OC PET/CT and raises hope for future research in this area. The most valuable finding is the optimal performance of [^{18}F]-OC PET/CT in detecting NEN lesions, including those with a diameter < 1 cm; moreover, this novel functional imaging modality demonstrated higher accuracy in differentiating neuroendocrine neoplasms from other conditions. These results are also in concordance with a recent prospective study by Pauwels et al. [3] that reported a superiority of [^{18}F]-OC PET over ^{68}Ga-DOTATATE/NOC PET in a cohort of 75 patients with NENs of all grades.

So that gives rise to the question: will ^{18}F-labeled SSA replace their ^{68}Ga-labeled counterparts?

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Current evidence is encouraging, although being still insufficient to take the leap. Firstly, very few studies testing the clinical value of ^{18}F-labeled SSAs are currently available, including only one prospective investigation [3] on a relatively small cohort of patients. Secondly, ^{18}F-labeled SSAs other than [^{18}F]-OC should be further explored: similar radiopharmaceuticals are indeed emerging in the panorama of molecular imaging of NENs, most notably [^{18}F]F-SiFAlin-TATE ([^{18}F]SiTATE) [2, 5]. To further intricate the picture, ^{18}F-labeled somatostatin receptor antagonists are currently under investigation in the pre-clinical setting [6] and might exhibit even superior sensitivity compared to SSAs.

Future efforts in this field should be focusing on prospective and multi-center clinical trials including larger and more homogeneous cohorts of patients with NENs, in order to accurately investigate the usefulness and added value of different ^{18}F-labeled SSAs compared to ^{68}Ga-labeled SSAs and conventional imaging.

In conclusion, according to recent literature, ^{18}F-labeled SSAs surely represent an innovative and valuable imaging approach, being a promising alternative in the clinical management of patients with suspected or recurrent NENs.

Therefore, we might be prepared to say goodbye to [^{68}Ga]DOTA-conjugated peptides for neuroendocrine neoplasms in the next future.

Author contributions The authors confirm that no paper mill and artificial intelligence was used.

Declarations

Ethical approval Institutional Review Board approval was not required because the paper is an Editorial.

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Conflict of interest The authors declare no competing interests.

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