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EDITORIAL COMMENTARY

Could ^{68}Ga-somatostatin analogues replace other PET tracers in evaluating extra-adrenal paragangliomas?

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Extra-adrenal paragangliomas (PGLs) are rare tumours that develop from neuroendocrine cells derived from the neural crest. They may arise anywhere along the paraganglion system and can be associated with the sympathetic or the parasympathetic nervous system. Extra-adrenal PGLs of the sympathetic chains usually cause symptoms of catecholamine over-secretion. Conversely, parasympathetic head and neck (H&N) and thoracic PGLs are almost always non-secreting tumours which are discovered on imaging studies or revealed by symptoms of compression or infiltration of the adjacent structures [1].

PGLs are characterized by a high frequency of hereditary forms with a propensity for multifocal disease. A specific correlation between the gene involved and tumour location has been reported [1]. Most often, extra-adrenal PGLs are benign and progress slowly. The rate of distant spread is wide, depending on tumour location, size and genetic background [1].

In extra-adrenal PGLs, pretreatment imaging including nuclear medicine techniques is crucial for providing accurate staging as well as in identifying multifocal or metastatic disease. Recent European Association of Nuclear Medicine (EANM) guidelines for nuclear medicine imaging of PGLs provided a practical algorithm for selecting the most appropriate imaging procedure based on a tailored approach, taking into account genetic mutation, location of the PGL and presence of metastases, starting from the assumption that there is no 'gold standard' imaging technique for all patients with extra-adrenal PGL [1–3].

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^{18}F-DOPA positron emission tomography (PET)/CT is suggested as first-line imaging method in H&N and abdominal non-metastatic extra-adrenal PGLs; this method may be useful in metastatic PGLs in the absence of succinate dehydrogenase B (SDHB) gene mutations or when genetic status is unknown [1, 4]. ^{111}In-Pentetreotide single photon emission computed tomography (SPECT)(/CT) may be used as first-line evaluation of H&N PGLs in the absence of ^{18}F-DOPA PET/CT. ^{18}F-Fluorodeoxyglucose (FDG) PET/CT is especially sensitive in the setting of SDH- and von Hippel-Lindau disease (VHL)-related sympathetic extra-adrenal PGLs and it seems to be the imaging modality of choice for SDHB-related metastatic PGLs; this method may also provide useful prognostic information. ^{18}F-Fluorodopamine and ^{11}C-hydroxyephedrine PET are both accurate methods in evaluating patients with extra-adrenal and metastatic PGL but, to date, these techniques have limited availability [1]. The diagnostic performance of PET or PET/CT with various radiopharmaceuticals is clearly superior to that of radioiodinated metaiodobenzylguanidine (MIBG) scintigraphy in patients with extra-adrenal and metastatic PGL; however, MIBG scintigraphy maintains a unique role in selecting patients suitable for ^{131}I-MIBG therapy [5].

Somatostatin receptor PET/CT is increasingly used in patients with known or suspected neuroendocrine tumours demonstrating high diagnostic accuracy and is superior compared to ^{111}In-pentetreotide scintigraphy in this setting [6, 7]. Recent articles in the literature assessed the diagnostic accuracy of somatostatin receptor PET/CT using different somatostatin analogues labelled with ^{68}Ga (^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATOC) in patients with extra-adrenal PGL [8–17], based on the increased expression of somatostatin receptors in PGL neoplastic cells [18].

The diagnostic performance of ^{68}Ga-DOTATATE PET/CT in patients with PGL was recently evaluated by Maurice et al. in a retrospective study including nine patients with extra-

adrenal PGL (six H&N, two abdominal and one thoracic PGL). ^{68}Ga-DOTATATE PET/CT detected more lesions compared to ^{123}I-MIBG scintigraphy and conventional imaging mainly in H&N and metastatic PGLs [8], confirming previous results of the same group in a more limited population of extra-adrenal PGL [9].

About ^{68}Ga-DOTANOC PET/CT, in 2008, Fanti et al. described the usefulness of this method in detecting neuroendocrine tumours located in unusual sites, including patients with extra-adrenal PGL [10], and these findings were confirmed in a recent article including some cases of extra-adrenal PGL [11]. In 2012, a prospective study of Naswa et al. demonstrated the higher diagnostic accuracy of ^{68}Ga-DOTANOC PET/CT compared to ^{131}I-MIBG scintigraphy in patients with extra-adrenal PGL with a sensitivity of 100 % on a per patient- and a per lesion-based analysis. A total of 29 extra-adrenal PGLs were detected on ^{68}Ga-DOTANOC PET/CT: 17 were H&N PGLs, while the rest were detected in the mediastinum, abdomen and urinary bladder [12]. A recent retrospective study of Sharma et al. evaluated 26 patients with H&N PGL by using ^{68}Ga-DOTANOC PET/CT. This imaging method was positive in all 26 patients being very useful for the baseline evaluation of patients with H&N PGL and demonstrating synchronous PGLs at other sites and distant metastases with superior diagnostic accuracy compared to ^{131}I-MIBG scintigraphy and conventional imaging [13], confirming the preliminary results of the same group reported in a pilot study about ^{68}Ga-DOTANOC PET/CT on 5 H&N PGLs [14].

About ^{68}Ga-DOTATOC, the group in Innsbruck previously reported the uptake of this radiopharmaceutical in some cases of extra-adrenal PGL [15, 16].

Due to the encouraging results obtained with somatostatin receptor PET/CT in the evaluation of extra-adrenal PGLs, a head-to-head comparison of ^{68}Ga-somatostatin analogues with other PET radiopharmaceuticals would be very useful in this setting [17].

In their retrospective study Kroiss et al. compared the diagnostic performance of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT in a series of 20 patients with extra-adrenal PGL (15 cases with single sites of disease and 5 with metastatic or multifocal lesions), most of them with H&N PGLs. Compared with morphological imaging, both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET demonstrated a detection rate of 100 % on a per patient- and per lesion-based analysis in non-metastatic extra-adrenal PGLs. On the other hand, in metastatic or multifocal extra-adrenal PGLs, the detection rate of ^{68}Ga-DOTATOC PET was 100 % compared to 56 % of ^{18}F-DOPA PET on a per lesion-based analysis. Compared to ^{18}F-DOPA PET, ^{68}Ga-DOTATOC PET showed lesions that were not detected by CT. These authors conclude that ^{68}Ga-DOTATOC PET may be superior to ^{18}F-DOPA PET and to diagnostic CT in staging of extra-adrenal PGL, particularly in metastatic or multifocal disease [19].

Prospective studies comparing ^{68}Ga-somatostatin analogues and other PET radiopharmaceuticals are needed in patients with extra-adrenal PGL to strengthen the conclusions of the study of Kroiss et al. Furthermore, future comparison between ^{68}Ga-somatostatin analogues and other PET tracers in this setting should take into account the genetic status of patients with extra-adrenal PGL. Beyond the diagnostic accuracy, an undoubted advantage of somatostatin receptor PET compared to other PET tracers is the ability to select patients potentially eligible for peptide radioreceptor therapy, which a preliminary study has described as feasible for patients with extra-adrenal PGL representing a good alternative treatment when surgical or radiation therapy are contraindicated [20].

In the current era of a growing number of available PET tracers, PGL imaging has moved beyond tumour localization towards functional characterization of tumours [3]. Therefore, it is important to compare PET radiopharmaceuticals with different uptake mechanisms not only to establish a superior diagnostic performance of a specific radiopharmaceutical but also to evaluate matched or mismatched findings, to identify possible advantages of a multidisciplinary approach or to obtain prognostic information [2]. The use of different PET radiopharmaceuticals in the same patient may be particularly useful in cases of extra-adrenal PGL; anyway, this strategy needs to be validated by specific cost-effective analyses for its introduction into clinical practice.

Conflicts of interest None.

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