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Biomedicine & Pharmacotherapy 62 (2008) 667–671

Original article

Evaluation of unusual neuroendocrine tumours by means of ^{68}Ga-DOTA-NOC PET

Stefano Fanti [a], Valentina Ambrosini [a], Paola Tomassetti [b], Paolo Castellucci [a], Giancarlo Montini [a], Vincenzo Allegri [a], Gaia Grassetto [c], Domenico Rubello [c,*], Cristina Nanni [a], Roberto Franchi [a]

[a] *Unità Operativa di Medicina Nucleare, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[b] *Unità Operativa di Medicina Interna, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[c] *Unità Operativa di Medicina Nucleare, Centro PET, Ospedale 'S. Maria della Misericordia', Istituto Oncologico Veneto (IOV)-IRCCS, Viale Tre Martiri 140, 45100 Rovigo, Veneto, Italy*

Received 8 January 2008; accepted 22 January 2008
Available online 3 March 2008

Abstract

^{18}F-FDG PET value for the assessment of neuroendocrine tumours (NET) is limited. Preliminary studies indicate that somatostatin receptor PET using ^{68}Ga-DOTA-peptides is more accurate for disease assessment and provide additional data on receptor status, that are crucial for targeted radionuclide therapy. At present, however, few papers investigated the role of ^{68}Ga-DOTA-NOC PET in NET, especially in unusual situations. The purpose of the present study was to evaluate ^{68}Ga-DOTA-NOC for the evaluation of NET of uncommon presentation. Patients with biopsy-proven NET were scheduled for ^{68}Ga-DOTA-NOC PET; we excluded from further evaluation cases with most common NET tumours (gastro-entero-pancreatic and pulmonary localization of primary lesion, MEN syndromes, medullary thyroid carcinoma, pheochromocytomas). PET results were compared with findings of conventional imaging, including CT, ultrasonography, MR and somatostatin receptor scintigraphy; finally PET results were compared with follow-up data with respect to the impact on patient management. Fourteen patients were finally enrolled; primary tumours were located at uterine level (3 cases), prostate (3 cases), ovary (1 case), kidney (1 case), breast (1 case), ear (1 case); also 3 cases of paraganglioma (at neck, abdominal and mediastinum level) and 1 case of lymphoma were included. ^{68}Ga-DOTA-NOC PET was positive, showing at least 1 lesion, in 6/14 cases while 5 cases turned out negative and 2 inconclusive. On a clinical basis, ^{68}Ga-DOTA-NOC provided additional information in comparison to conventional imaging procedures in 7/14 cases, and was considered useful in 12/14 patients, with 8 patients in which ^{68}Ga-DOTA-NOC PET was determinant for patient's management. Although the number of patients studied is limited, our data show that ^{68}Ga-DOTA-NOC can be usefully applied for the evaluation of NET of uncommon presentation; in particular very promising results were obtained in paraganglioma. On the other hand, care has to be paid when studying lesions localized at sites of physiological concentration of the tracer, and in presence of inflammation.
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Keywords: ^{68}Ga-DOTA-NOC; PET; Neuroendocrine tumours; NET

1. Introduction

Neuroendocrine tumours (NET) are a heterogeneous group of slow-growing rare neoplasms, occurring in 1–4/100,000 people per year [1–4], mostly represented by carcinoid lesions, accounting for approximately 50% of all NET [5]. Most frequently NET occurs in the gastro-entero-pancreatic tract, where pancreatic endocrine tumours are less frequent than endocrine gastrointestinal forms. Other relatively common form of NET is bronchial carcinoid (about 20% of all carcinoid) and medullary thyroid carcinoma (about 5–10% of all thyroid cancers) [5–7]. Also NET can be a part of multiple endocrine neoplastic (MEN) syndromes; finally

* Corresponding author. Tel.: +39 0425 39 4427; fax: +39 0425 39 4434.
E-mail address: domenico.rubello@libero.it (D. Rubello).

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doi:10.1016/j.biopha.2008.01.010

pheochromocytoma and paraganglioma can be considered as NET [8].

NET tumours arise from cells derived from the neural crests and therefore primary lesions can be occasionally located in unusual sites [9]. Furthermore a neuroendocrine component can frequently be observed in common cancers, such as breast and prostate, with cases in which the neuroendocrine differentiation can be prevalent at immunohistochemistry.

Diagnosis of NET may be difficult because they often present as small lesions and with variable anatomical locations. The diagnosis and initial work-up of NET patients mainly relies on morphological imaging techniques such as computed tomography (CT), ultrasound (US) and magnetic resonance (MR) [10] combined with functional imaging, namely whole-body somatostatin receptor scintigraphy (SRS) [11]. However, all these approaches can have several limits [12–14] and this may be particularly relevant in case of uncommon site of presentation.

Positron emission tomography (PET) has also been suggested for the diagnosis of NET. It is well-known that ^{18}F-FDG is certainly not a well-suited tracer for the assessment of NET patients [15], because it identifies only highly metabolic undifferentiated tumours: therefore alternative radiotracers such as ^{18}F-DOPA [16,17] and ^{68}Gallium-peptides [18,19] have been used with encouraging results.

In particular ^{68}Ga-DOTA-peptides rely on a receptor-based mechanisms to visualize NET. Indeed the identification of novel somatostatin analogs labelled with ^{68}Gallium allows the visualization of SSR on the tumour cell surface, that are over-express in NET, and ^{68}Ga-DOTA-peptides PET has been successfully applied to evaluate NET [20,21].

Since at present only data regarding ^{68}Ga-DOTA-peptides to study common localization of NET are available, the aim of our study was to evaluate the result of this approach to study unusual NET.

2. Methods

2.1. Study population

We started enrolling NET patients to be studied with ^{68}Ga-DOTA-peptides in August 2006, with the approval of the Ethical Committee; between August 2006 and November 2007, 110 patients were scheduled for ^{68}Ga-DOTA-NOC PET. We retrospectively evaluate all available data and, for the purpose of this study, we excluded case with most common localization of primary tumour, namely gastro-entero-pancreatic NET, bronchial carcinoid, medullary thyroid carcinoma, MEN syndromes and pheochromocytoma. In all cases a complete history, throughful clinical examination and biochemical exams were carried out before PET image acquisition; pathologic diagnosis was based on WHO criteria.

Several imaging procedures, including ultrasound (US), contrast-enhanced US, abdominal and chest CT, whole-body SRS and MR were performed in all cases: the choice of the exams was essentially based on clinical consideration depending on the site of disease. Evaluation of these procedures was based on final report: in case of uncertain or inconclusive findings, the exam was retrieved and an expert radiologist was asked to make a definitive report.

Indications to perform PET included suspect relapse (3 cases), therapy planning (8 cases) and indeterminate finding at other imaging procedures (3 cases). In 6 cases the primary tumour was excised by surgery before the PET scans.

2.2. PET scans

^{68}Ga-DOTA-NOC was synthetized at the Radiopharmacy of the Nuclear Medicine Unit. ^{68}Gallium was eluted from a ^{68}Ge/^{68}Ga generator and the labelling of DOTA-NOC with ^{68}Gallium was performed following the procedure described by Meyer et al. [21].

^{68}Ga-DOTA-NOC PET scans were carried out with using a dedicated hybrid PET/CT tomograph (Discovery LS scanner, GE Medical System, Waukesha, WI). Scans were carried out in the 6 h-fastened patient (intravenous injected dose 185 MBq, uptake time 60 min). PET scan emission images were recorded for 4 min per bed position; for non-uniform attenuation correction, CT images were used (acquisitions parameters: 140 kV, 90 mA, 0.8 s tube rotation, 5 mm thickness). PET images were acquired from the skull basis to the middle part of the thigh.

2.3. PET image evaluation

Any area with an intensity greater than background and that could not be attributable to physiologic activity was considered to be indicative of tumour tissue. Physiologic ^{68}Ga-DOTA-NOC uptake areas include the spleen, the liver, the adrenal glands, the urinary pathways and the pituitary gland. PET results were compared with other imaging procedures; the time frame between the investigations was in all cases less than 40 days. In all cases a clinical follow-up of 6 months (range: 6–12) was carried out.

As reference standard to finally evaluate PET results we used all available data (clinical follow-up, concordance of at least 2 imaging modalities at follow-up, and pathology); finally PET results were compared with follow-up data with respect to the impact on patient management.

3. Results

The study group finally included 14 patients (M:F = 6:8; mean age 61 years; age range: 45–74 years). Primary tumours were located at uterine level (3 cases), prostate (3), ovary (1), kidney (1), breast (1), ear (1); also 3 cases of paraganglioma (at neck, abdomen and mediastinum level) and 1 case of lymphoma were included.

^{68}Ga-DOTA-NOC PET was positive, showing at least 1 lesion, in 7/14 cases while 5 cases turned out negative and 2 inconclusive. In detail PET was positive in 1/3 prostate NET, allowing to detect a relapse suspected at CT. The 2/3 negative cases were studied for suspect relapse in patients already treated by radical prostatectomy, pathologic demonstration of NET tumour after intervention and recent increase of

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