REVIEW

Imaging with non-FDG PET tracers: outlook for current clinical applications

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Abstract Apart from the historical and clinical relevance of positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG), various other new tracers are gaining a remarkable place in functional imaging. Their contribution to clinical decision-making is irreplaceable in several disciplines. In this brief review we aimed to describe the main non-FDG PET tracers based on their clinical relevance and application for patient care.

Keywords Positron emission tomography · Hybrid PET/CT · Functional imaging · PET tracers · Non-FDG

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Introduction

The introduction of molecular imaging and the recent development of hybrid systems, in which both functional and morphological information are acquired simultaneously and can therefore be registered accurately, has led to a great step forward in diagnostic imaging. Positron emission tomography (PET) has paved the way for the introduction of PET/computed tomography (CT). These machines have been available since the last decade of the twentieth century [1], and PET/magnetic resonance imaging (MRI) machines are likely to be available in the near future.

Currently, 18F-fluorodeoxyglucose (18F-FDG) represents the prevailing tracer utilised in PET imaging. For this tracer oncology is undoubtedly the most important field of application, but other clinical fields in which 18F-FDG plays an important role include neurology and cardiology.

The main disadvantage of 18F-FDG is that it is not a specific oncological tracer, as several malignancies [i.e. prostate cancer, hepatocellular carcinoma (HCC), renal cell carcinoma, etc.] cannot be adequately assessed by 18F-FDG-PET. Therefore other new radiopharmaceuticals have been developed that are capable of giving more specific information, leading to a better sensitivity and specificity or just complementing 18F-FDG-PET results (Fig. 1).

At present a very wide variety of non-FDG-PET tracers have been studied. Some of them are already used in clinical practice, while others are still undergoing investigation in clinical and preclinical trials. In this paper, we will focus on some of them by selecting the principal non-FDG-PET tracers on the basis of their clinical relevance and application (Table 1).

Fig. 1 Maximum intensity projection (MIP) images of six different PET tracers and their normal distribution: (**a**) 18F-fluorodeoxyglucose (18F-FDG); (**b**) 11C-choline; (**c**) 11C-methionine; (**d** 18F-dihydroxyphenylalanine (18F-DOPA); (**e**) 68Ga-DOTA-1-NaI3-octreotide (68Ga-DOTA-NOC); (**f**) 11C-acetate

Iconography

MIP images
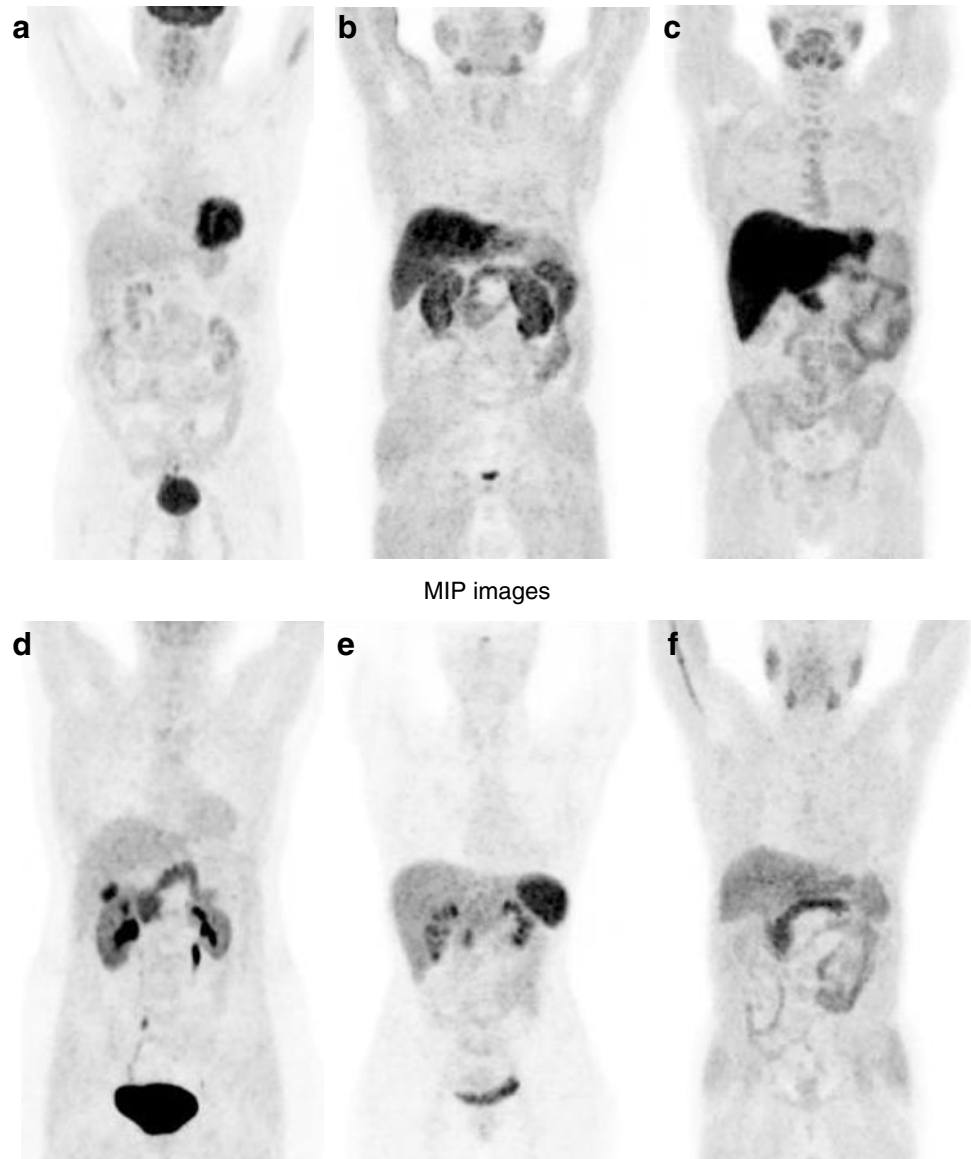
Choline metabolism

(11C-choline)

11C-Choline and its fluorinated analogue (18F-fluorocholine), as precursors for the biosynthesis of cellular membrane phospholipids (i.e. phosphatidylcholine), represent specific PET tracers capable of marking out membrane metabolism and turnover. These processes are both known to be increased in tumour cells [2]. The two tracers show no significant difference in diagnostic performance and biodistribution, except for the earlier urinary appearance of 18F-choline, probably due to an incomplete tubular reabsorption [3].

For many tumour types, choline-PET is reported to be a good diagnostic technique, although in practice its clinical value is mainly limited to prostate cancer [4].

For staging purposes, 11C-choline has been utilised in selected high-risk patients (high levels of PSA or Gleason score), with the intent to assess extra-prostatic nodal and bone metastases. For N- and M-staging, 11C-choline-PET performs better than clinical nomograms [5]: it has a patient-based sensitivity and specificity of 60.0% and 97.6% respectively, and a nodal-based sensitivity and specificity of 41.4% and 99.8% respectively [6], whereas, for staging of the primary prostate cancer (T-staging), choline-PET is not suitable [6–8].

Table 1 Main non-FDG-PET tracers and their principal indications

Tracer	Metabolic process	Diagnostic imaging	Oncological indications	Clinical value
11C-Choline	Cellular membrane turnover	**Prostate cancer**	Diagnosis/Biopsy guidance	Identification of carcinoma foci in patients with multiple negative biopsies
18F-Choline (FCH)	Phosphatidylcholine metabolism	*Other tumours:*	Staging	Assessment of proper disease extent in high-risk patients
		Bladder cancer	Suspect of relapse	Early detection of relapse in patients with biochemical failure
		Brain tumours, etc.	Restaging	Therapeutic management in patients with documented carcinoma relapse
11C-Methionine	Amino acid transport and protein synthesis	**Brain tumours**	Diagnosis	Differential diagnosis between benign and malignant lesions/Inconclusive CIT
		Other tumours:	Grading	Direct correlation between 11C-methionine uptake and tumour grading
		Head and neck, etc.	Stereotactic biopsy	Detection of more suitable sites for brain biopsy
		Non-oncologic indication:	Treatment response/ Prognostic value	Assessment of treatment efficacy/Direct correlation between uptake decline and patient outcome
		Hyperparathyroidism	Suspect of relapse or residual disease	Characterisation of suspect or inconclusive lesions at CIT
18F-DOPA	Dopamine uptake and metabolism	**Neuroendocrine tumours (NET)**	Diagnosis/ Unknown primary	Diagnosis of NET/Documented NET metastasis in unknown primary
		Non-oncological indications:	Staging/restaging	Assessment of disease extent before treatment
		Congenital hyperinsulinism Parkinson	Suspect of relapse	Early identification of relapse
68Ga-DOTA-peptides	Somatostatin receptors	**Neuroendocrine tumours (NET)**	Diagnosis	Diagnosis of NET
		Other tumours:	Unknown primary	Identification of primary tumour in patients with documented NET metastasis
		Pheochromocytoma	Staging/restaging	Assessment of disease extent before treatment
		Paraganglioma	Suspect of relapse	Early identification of relapse
		Microcytoma	Treatment response	Assessment of treatment efficacy
11C-Acetate	Lipid synthesis and energetic metabolism	**Prostate cancer**		Similar to 11C-choline indications for prostate cancer
		HCC	Diagnosis of HCC	Differential diagnosis between benign and malignant hepatic lesions
		Non-oncological indications:	Staging/restaging HCC	Assessment of disease extent
		Myocardial metabolism	Suspect of relapsed HCC	Characterisation of suspect or inconclusive lesions at CIT
18F-FLT	Cellular proliferation and	**Lymphoma**	Diagnosis/ Primary tumour	Differential diagnosis between benign and malignant lesions/T staging
TK-1 activity		**Lung**	Treatment response evaluation	Treatment response assessed with FLT-PET correlates with pathological response
		Colorectal cancer		
		Gastric and pancreatic		
18-NaF	Bone metabolism	**Bone metastasis**	Diagnosis	Identification of bone metastasis
		Non-oncological indications:	Staging	Detection of bone involvement in tumours with elevated risk of bone metastasis

Table 1 (continued)

Tracer	Metabolic process	Diagnostic imaging	Oncological indications	Clinical value
18F-FMISO	Tumour hypoxia	Orthopaedic pathological conditionsOrthopaedic pathological conditions **Solid tumours**	Pre-treatment assessment	Detection of hypoxic quota in malignant tissue for prognostic value and treatment intensity modulation
18F-FAZA				
18F-EF3 and 5				
64Cu-ATSM				

CIT conventional imaging technique

HCC hepatocellular carcinoma

The main indication for using choline-PET remains the evaluation of prostate cancer relapse in previously treated (radical prostatectomy or external beam radiotherapy) patients, who present with a rising PSA serum level [9]. PET performance in this case is reported to be superior to other conventional imaging techniques (CIT) leading to early identification of both nodal and extranodal lesions, as well as local recurrence (Fig. 2) [10–13].

The detection rate of choline-PET, however, can still be low during restaging, especially for low PSA values [12]; therefore, PSA kinetics has been studied. Utilising trigger PSA, PSA velocity and PSA doubling time [9, 14], increases the performance of the method significantly and gives clinicians useful information for a better assessment of treatment strategies and patient follow-up.

Malignancies other than prostate cancer have been studied with choline-PET, such as bladder cancer, brain tumours and multiple myeloma [4, 15]. The late urinary excretion, characterising 11C-choline, and the low background activity in the pelvic area are the main reasons for the successful use of choline-PET in bladder cancer [4]. In the other tumours, such as brain neoplasia or multiple myeloma, the utility is still questioned and there does not seem to be much improvement in diagnostic accuracy compared with other PET tracers, such as 11C-methionine for brain tumours and 18F-FDG for multiple myeloma [15].

Amino acid and protein metabolism

(11C-methionine)

Methionine is an essential amino acid and the uptake of its carbon-11 labelled form (11C-methionine) directly reflects amino acid transport and protein metabolism. These processes are known to be significantly increased in

malignant cells as a consequence of the increased cellular proliferation activity [16].

The imaging potentialities of 11C-methionine as an oncological PET tracer have already been documented in different malignancies like brain tumours, breast cancer and head and neck tumours [17–19].

11C-Methionine has a main advantage in brain imaging compared with 18F-FDG: there is almost no tracer uptake in normal brain tissue. On the other hand, malignant lesions show a significantly increased uptake of 11C-methionine, with an optimal tumour-to-background ratio. Also, other benign conditions, such as fibrosis, necrosis or oedema, which usually reduce FDG-PET specificity, show a relatively low uptake with methionine-PET. For these reasons, methionine-PET is predominantly used for the detection of brain tumours [20].

The good correlation that has been reported among the Ki-67 index, proliferating cell nuclear antigen expression and methionine uptake is used to give preliminary information on tumour grading (low- versus high-grade lesions) and provide a reliable initial prognostic value [21–23].

In gliomas, methionine-PET is reported to have good sensitivity and specificity, 89% and 100% respectively, and this can determine a change in treatment management in up to 50% of the cases. However, during acute inflammation and in low-grade forms the diagnostic performance can be suboptimal (sensitivity range 65-85%) [24, 25].

The good diagnostic performance of methionine-PET is mostly maintained in the case of post-treatment evaluation and during follow-up, when tumour recurrence is suspected [26]: sensitivity, specificity in detecting tumour recurrence range from 77.8 to 100% and 60% to 100%, respectively [26]. In recurrent disease, methionine-PET has a major advantage over conventional imaging techniques (including MRI) as it can make a proper differential diagnosis between malignant lesions and other non-pathological findings (i.e.

Fig. 2 11C-Choline PET in a patient with biochemical failure after radical prostatectomy: MIP and transaxial images document both lymph nodal (*arrows*) and bone relapse (*arrowhead*)

MIP
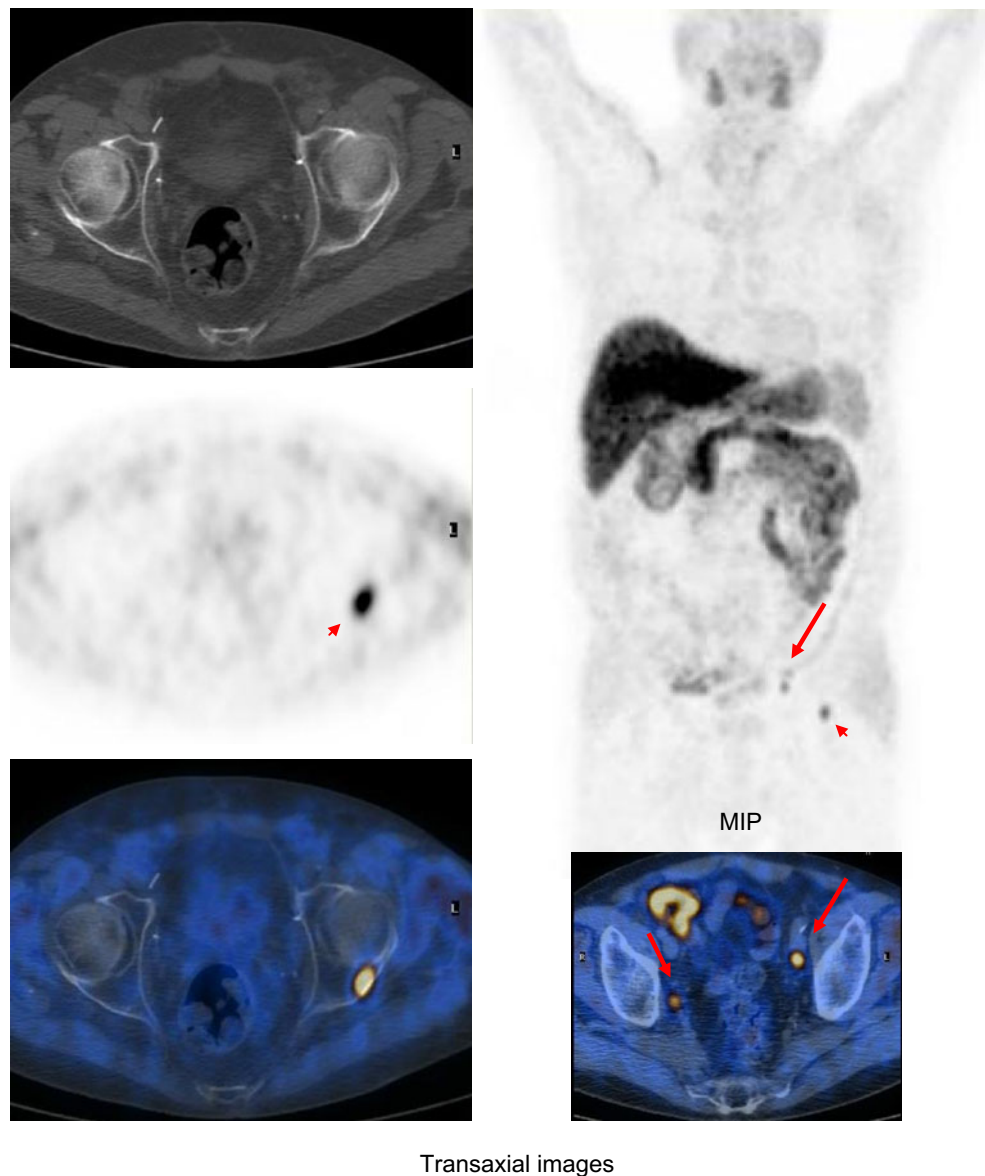
Transaxial images

infection, infarction and haemorrhage) or other brain tissue changes induced by previous surgical handling or external beam radiotherapy (Fig. 3) [23, 27].

The ability of methionine-PET to distinguish accurately between malignant tissue and necrotic areas, combined with the better delineation of tumour volumes, has found a proper use for radiotherapy planning and can be of help for stereotactic brain biopsy too [28].

Dopamine uptake and metabolism

(18F-DOPA)

18F-Dihydroxyphenylalanine (18F-DOPA) was first introduced as a marker for imaging dopamine uptake and metabolism in basal ganglia [29]. Afterwards, this tracer

was applied for the detection of malignancies such as brain tumours [30], neural crest derived (neuroendocrine) neoplasms [31], and other conditions like congenital hyperinsulinism [32].

The rationale for imaging neuroendocrine with 18F-DOPA PET is the ability of these tumours to accumulate and decarboxylate L-DOPA as a precursor of dopamine in the catecholamine pathway [33]. The increased L-DOPA transport within the cells by the large amino acid transporter system (LAT) and the increased activity of L-DOPA decarboxylase (AADC) documented in neuroendocrine tumours (NET) [34], the high signal-to-background ratio and the good spatial resolution of the PET camera system, permit the detection of both primary and metastatic lesions in many neuroendocrine malignancies. Examples for which 18F-DOPA PET imaging has proved to be successful are carcinoids, gastro-entero-pancreatic neuroen-

Fig. 3 11C-Methionine PET in two different patients previously operated on for glioma: (**a**) residual disease at the level of the surgical crater; (**b**) glioma recurrence in the contralateral brain hemisphere
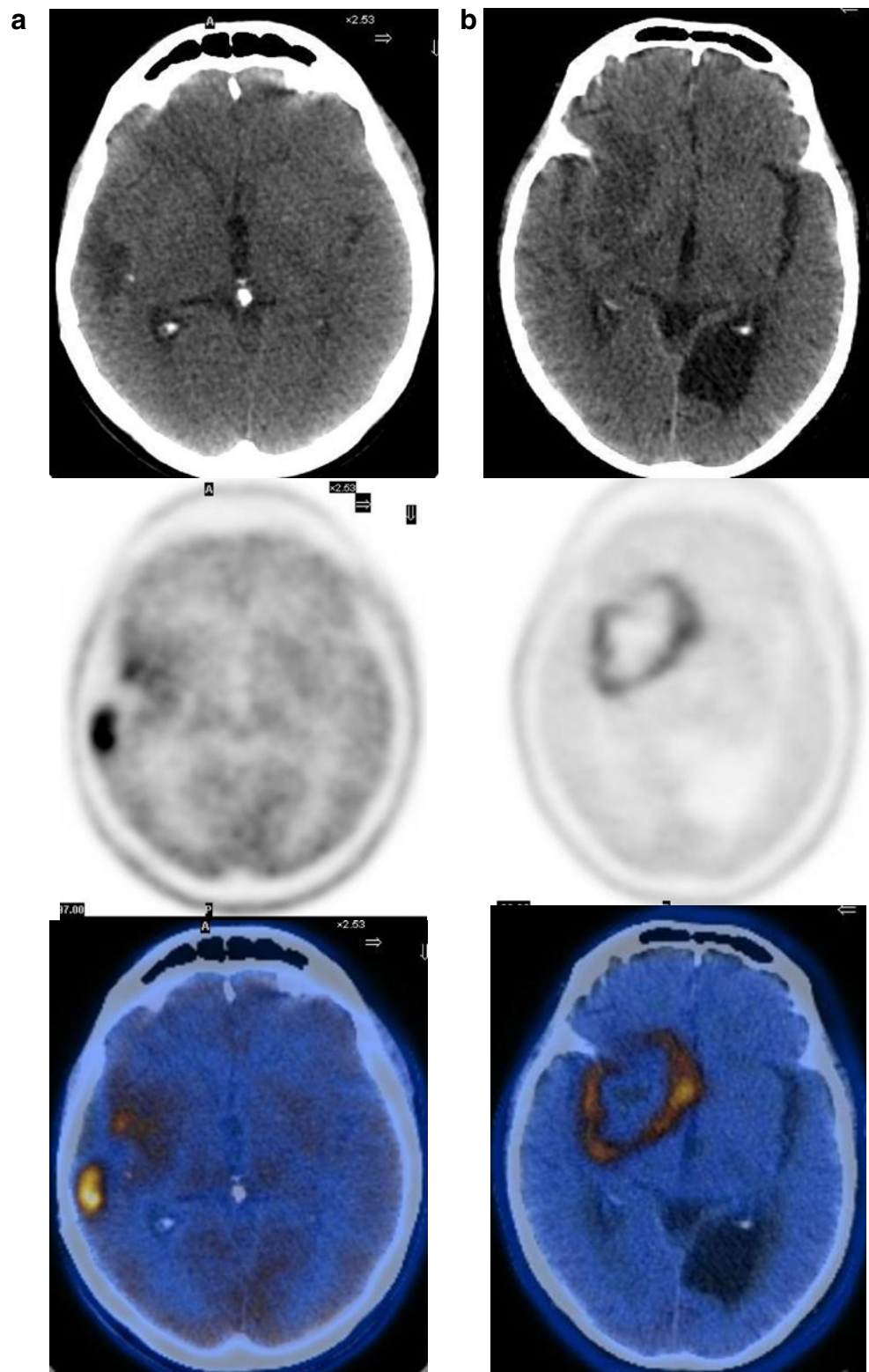
docrine tumours, glomus tumour, medullary thyroid, neuroblastoma, paraganglioma (glomus tumour) and phaeochromocytoma. [31, 35–37].

In neuroendocrine tumours with elevated catecholamine release, such as phaeochromocytomas, 18F-DOPA PET shows the best performance, with sensitivity and specificity rates of 84.6% and 100% respectively (Fig. 4) [36]. Moreover, its diagnostic accuracy for the detection of carcinoids [31, 37] and phaeochromocytoma [31, 36] was shown to be higher than that of other imaging techniques,

Fig. 4 18F-DOPA PET in a patient affected by pheochromocytoma of the right adrenal gland (*arrow*); physiological uptake of the tracer in the gallbladder (*arrowhead*)

MIP image

Transaxial images
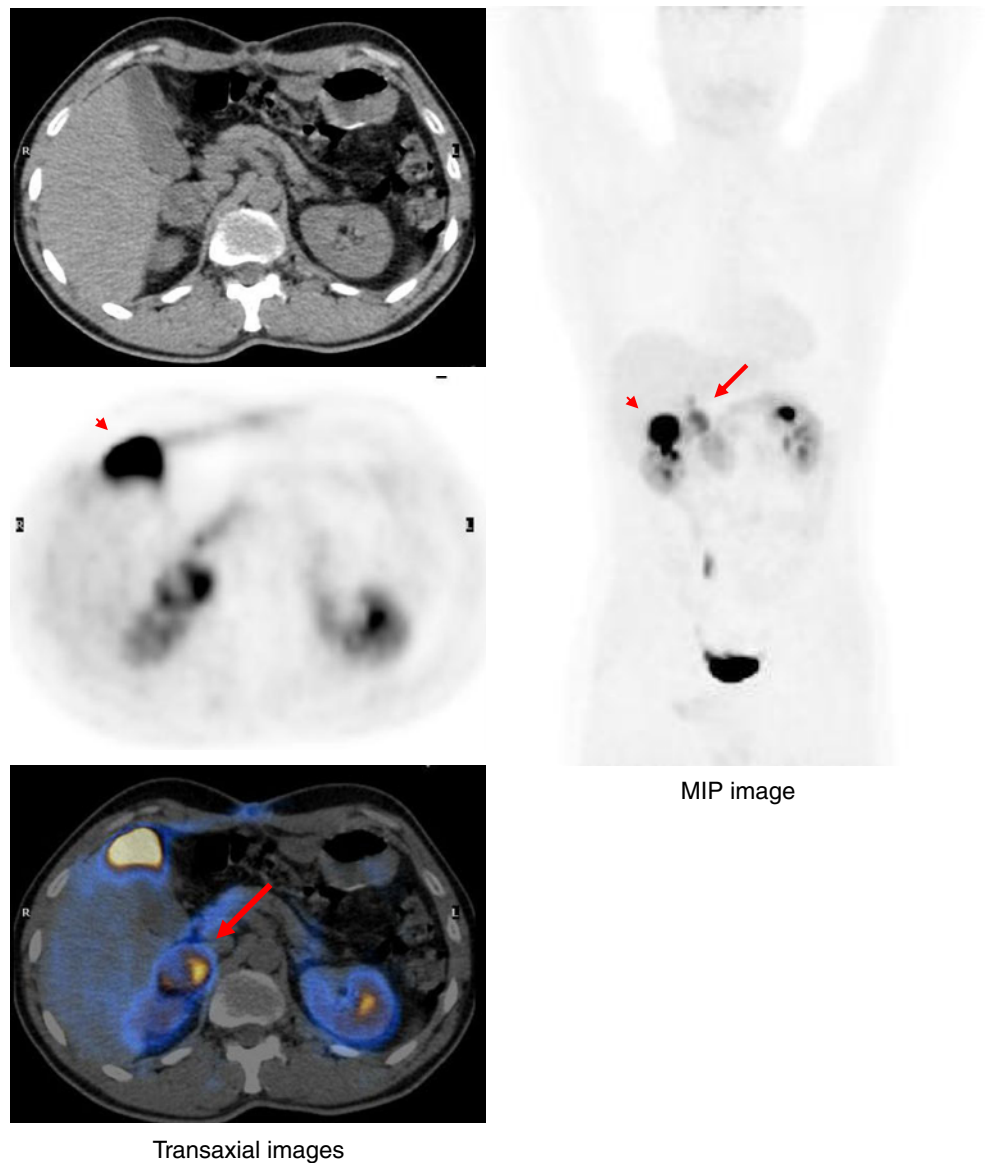
both morphological (including CT/MRI) and functional (123I-MIBG and 111In-Octreoscan) [31, 38].

Somatostatin receptors

(68Ga-DOTA-NOC and other analogues)

An important characteristic of neuroendocrine tumours is the expression of somatostatin receptors on their cell membrane. Thus far, five somatostatin receptor subtypes have been discovered: SSTR1–5. The SSTR2, SSTR3 and SSTR5 subtypes in particular [39] are often overexpressed on the cell membranes of neuroendocrine tumours (on average in 80–90% of cases).

The discovery of the overexpression of the somatostatin receptors in neuroendocrine tumours led to the development of radiolabelled somatostatin analogues. For decades, 111In-octreotide (Octreoscan) has been considered the "gold standard" for imaging and staging neuroendocrine tumours [40], but recently new PET tracers have been developed for imaging somatostatin receptors in NETs. These radiopharmaceuticals carry a somatostatin analogue labelled with the positron emitting radionuclide 68Ga, which is easily obtainable by a portable 68Ge/68Ga generator.

In 2001, the first 68Ga-DOTA somatostatin analogues were developed for clinical purposes [41] and up to now several 68Ga-DOTA-peptides have been reported. The majority show a similar affinity for SSTR2 and 5, whereas 68Ga-DOTA-NOC has also demonstrated a high affinity for SSTR3 [42, 43].

In the literature, 68Ga-DOTA-peptides are reported to be excellent candidates for imaging and staging patients with

neuroendocrine tumours, including the localisation of primary tumours in patients with known NET metastasis (carcinoma of unknown primary origin) (Fig. 5) [44, 45]. Sensitivity and specificity are documented as 97-100% and 96-100% in different papers [46, 47] and in a large series the diagnostic accuracy was reported to be higher than that of CT, 111In-octreotide or other PET tracers, such as 18F-DOPA [46, 48, 49]. PET with 68Ga-DOTA-peptides gave additional information to other instrumental investigations in 21.4% of the cases and led to a change in therapeutic management in 14% of cases [46, 47].

In addition, PET with 68Ga-DOTA-peptides gives useful information on therapeutic work-up, by providing clinicians with important pre- and post-therapeutic data on tracer uptake and receptor expression. 68Ga-DOTA-peptide uptake value (SUVmax) has been demonstrated

to correlate with clinical and pathological features in NET, by also resulting in an accurate prognostic factor for patient outcome [50]. As already reported by Gabriel et al. [46, 51], it also gives a preliminary estimation of receptor expression, thus permitting selection of patient candidates for peptide receptor radionuclide therapy (PRRT) and selection of which therapeutic agent to use (90Y-DOTATOC or 177Lu-DOTATATE).

Lipid synthesis and energetic metabolism
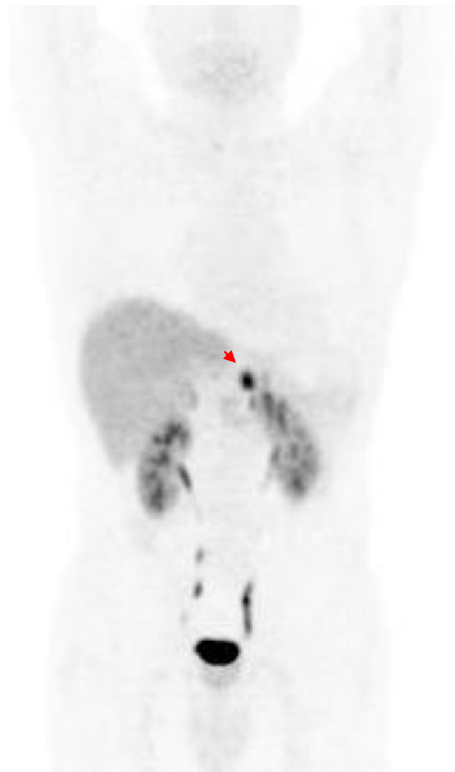
(11C-acetate)

11C-Acetate is a two-way tracer that can physiologically cover two different metabolic pathways: one is the pathway

Fig. 5 68Ga-DOTA-NOC PET in a patient with local recurrence of NET after distal pancreasectomy and splenectomy (*arrow* and *arrowhead*)
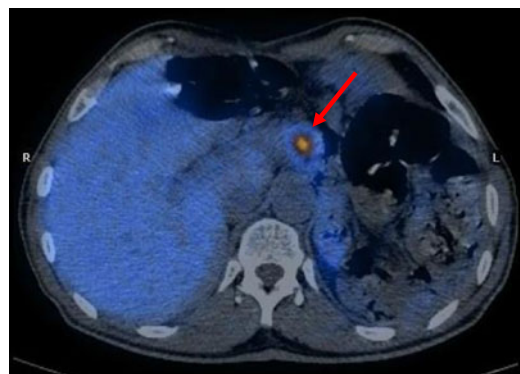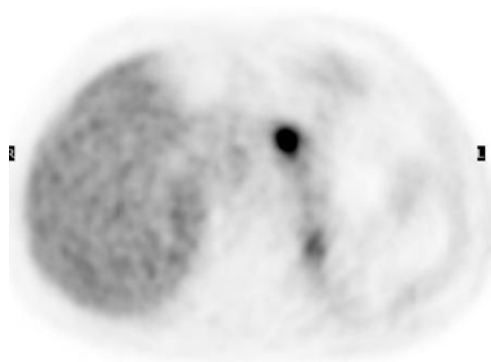
MIP image

Transaxial images

leading to the synthesis of cholesterol and fatty acids, which are then incorporated into cellular membrane [52], the other one involves energy metabolism via the tricarboxylic acid (TCA) cycle, used either for catabolic or anabolic purposes [53].

The energy pathway was the first one to be utilised for PET imaging with 11C-acetate, and consisted of cardiac studies on the assessment of myocardial blood flow and oxidative metabolism [54]. More recently, acetate-PET has been used in oncology too, for the assessment of some tumours, such as prostate cancer, renal cell carcinoma or HCC, in which FDG-PET is of limited use [55–57]. In those tumours, there is an increased uptake of 11C-acetate related to the over-expression of fatty acid synthetase, a key enzyme that entraps 11C-acetyl-CoA within different cellular structures and pathways [58].

In clinical practice, acetate-PET has a major application in imaging prostate cancer and HCC [55, 56].

In prostate cancer, 11C-acetate PET has similar indications to choline-PET and up to now no significant difference in diagnostic accuracy has been found between the two tracers [59]. Acetate-PET can be used from the diagnosis to staging/restaging of prostate cancer [60, 61], with major indications in previously treated patients presenting with biochemical failure [55, 62].

11C-Acetate has also found a proper application in the detection of HCC, which usually shows a low FDG uptake, secondary to the lower glycosidic metabolism of tumoral cells, compared with normal liver parenchyma [56, 63].

Acetate-PET has demonstrated a good sensitivity (83-87.3%) in the detection of HCC, especially in well-differentiated forms (Fig. 6) [63]. FDG-PET maintains a role in dedifferentiated HCC, but overall accuracy ameliorates when associating 18F-FDG and 11C-acetate PET, thanks to the complementary information the two metabolic tracers can give [63, 64].

Proliferation

(18F-FLT)

Introduced in 1998, 18F-fluorothymidine (18F-FLT) [65] is utilised in oncology as a marker of cellular proliferation. More precisely, 18F-FLT is entrapped in cells during the S-phase and its uptake correlates with the activity of thymidine kinase-1 (TK-1), a key enzyme that is up-regulated during DNA synthesis and cellular growth [65, 66].

The first attempts made to estimate proliferation activity in cells started almost three decades ago with 11C-thymidine, but 18F-FLT, which is derived from the cytostatic drug zidovudine [65, 67], seems to be the most suitable tracer for PET imaging.

In oncology FLT-PET is used for several malignancies, such as lung, oesophageal, gastric and pancreatic tumours, gliomas, sarcomas and lymphomas [68–71], and its uptake in tumour cells is documented to directly correlate with Ki-67 immunohistochemistry [71].

Fig. 6 Transaxial images of a patient affected by recurrent hepatocarcinoma in the paracaval region (*arrow*): (**a**) CeCT; (**b**) 11C-acetate PET images; (**c**) fused PET/CT images; (**d**) localisation CT
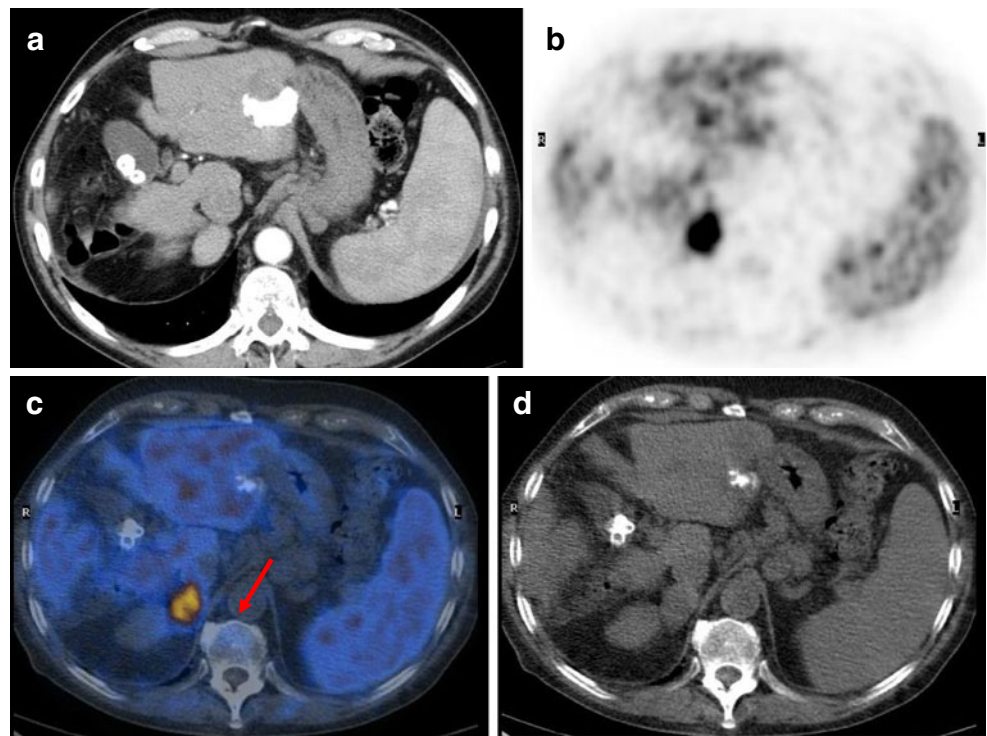
FLT-PET has a good signal-to-background rate, but the tracer is physiologically taken up in bone marrow and hepatic parenchyma, making these tissues difficult to investigate with 18F-FLT [67].

Compared with 18F-FDG uptake, 18F-FLT on average shows a lower accumulation in malignant tissue [68] and the method itself appears less accurate than FDG-PET for staging and restaging evaluation. However 18F-FLT is a more specific oncological tracer than 18F-FDG and can show a good sensitivity in the detection of primary tumour [68, 72]. As a marker of tumour cell proliferation, 18F-FLT also appears to be more accurate than 18F-FDG in treatment evaluation, by reflecting directly tumoral biological response [71].

Bone metabolism

(18F-NaF)

Thanks to the broad availability of 18F, the extremely simple synthesis of the tracer and the frequent shortage of 99mTc, PET imaging with 18F-Fluoride (18F-NaF) may represent the future of bone imaging. Similar to 99mTc-radiolabelled diphosphonates, 18F-NaF uptake reflects osteoblastic metabolism, thanks to the physiological incorporation of fluoride in bone matrix as fluoroapatite [73]. However, imaging with 18F-NaF has some major advantages over bone scintigraphy, which are related to a more rapid tracer uptake: images can be available immediately after injection, with better image quality; high image resolution is achieved, especially in hybrid PET/CT acquisitions, thanks to an optimal signal-to-background ratio [74].

In several malignancies, such as prostate cancer, lung and breast tumours, PET with 18F-fluoride has demonstrated a significantly higher diagnostic accuracy compared with bone scintigraphy [75, 76], by reaching maximal rates (100%) of sensitivity and specificity versus 92% and 82% respectively for 99mTc-MDP scintigraphy [77].

Fluoride-PET shows an elevated sensitivity for both sclerotic and lytic lesions [77, 78], but this high sensitivity rate outlines the principal drawback of the tracer: 18F-fluoride is not a specific oncological tracer, thus sometimes it can be difficult to differentiate between benign and malignant lesions. However combined morphological and functional imaging, as in hybrid PET/CT systems, and the clever recycling of the tracer cocktails concept [79] may help to overcome potential false-positive findings.

Similar to conventional bone scintigraphy, 18F-NaF can also be utilised in other fields of interest related to benign pathological bone conditions, such as orthopaedic problems [80].

Tumour hypoxia and oxygen metabolism

(18F-FMISO and other tracers)

Tumour hypoxia and oxygen metabolism represent a major task in oncology, and functional imaging with PET can make a remarkable contribution to patient management and therapeutic decisions. It is well known that tumour response to treatment is significantly related to the level of tumour oxygenation and the quota of hypoxic tissue [81].

The first PET tracer introduced for imaging tumour oxygenation was 18F-fluoromisonidazole (18F-FMISO) [82]. Initially utilised in nuclear cardiology for imaging myocardial ischaemia, the tracer was subsequently introduced into oncology for imaging several malignancies, such as lung cancer, sarcomas, brain tumours and head and neck cancers [83, 84].

The presence of a suboptimal signal-to-background ratio and the lack of 18F-FMISO uptake in necrotic tissue led to the development of further hypoxic tracers. This is the case for 18F-fluoroazomycin arabinozide (18F-FAZA) [85], 18F-fluoronitroimidazole (18F-EF3 and 5) [86, 87] or 64Cu-methylthiosemicarbazone (64Cu-ATSM) [88, 89]. All these tracers give remarkable information on imaging tumour hypoxia, although thanks to an optimal biodistribution and a high signal-to-background ratio, the most promising one seems to be 64Cu-ATSM. This tracer has already demonstrated good prognostic values in different tumours, including lung and cervical cancers [87–89].

Conclusions

This brief outlook provides only a short overview of non-FDG PET tracers and their use in a clinical setting. The potential list of tracers is continuously increasing in number and new applications can hopefully be introduced. The development of fused imaging, where anatomical and functional data are combined, has given diagnostic imaging "new eyes" for old and new indications.

Thanks to the broader availability of PET imaging, the increasing interest and development of molecular imaging and hybrid technology, the future of diagnostic imaging faces no obstacles but mankind's awareness and common sense.

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