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Review Article

Clinical application of ^{18}F-DOPA PET/TC in pediatric patients

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Abstract: The use ^{18}F-DOPA PET/CT for oncologic and non-oncologic pediatric diseases is well consolidated in clinical practice. The indications include brain tumors, neuroendocrine malignancies and congenital hyperinsulinism. The number of papers involving pediatric subjects is steadily growing. However, literature still lacks clinical trials and large multicentric studies in contrast with the extensive literature available for adult patients. The aim of this review is to discuss the main clinical indications of ^{18}F-DOPA in pediatric oncologic and nononcologic diseases and to analyze its role in diagnosis, staging, biopsy and surgical planning. The high resolution of PET/CT tomographs in addition to the high sensitivity and specificity of ^{18}F-DOPA imaging exceeds the downsides linked to this nuclear medicine imaging modality. In fact, few potential limitations could discourage the use of PET/CT imaging. For example, similarly to MRI studies the long acquisition time of a PET/CT scan often requires sedation especially in infants. Moreover, the radiation exposure of a PET/CT scan may be high, but the clinical benefit deriving from nuclear medicine imaging outruns the risk connected to the use of ionizing radiations.

Keywords: PET/CT, DOPA, pediatric

Introduction

^{18}F-Fluoro-dihydroxyphenylalanine (^{18}F-DOPA) is a radioactive analogue of L-dihydroxyphenilalanine (L-DOPA) used in Positron Emission Computed Tomography (PET/CT) in oncologic and nononcologic imaging [1]. This radiopharmaceutical is distributed in brain and peripheral tissues and is metabolized in the same catecholamine metabolic pathway of L-DOPA [2]. Its use is consolidated in adult patients mainly for the evaluation of the nigrostriatal dopaminergic system, in brain and neuroendocrine malignancies imaging as well as β-cell hyperplasia. The indications of ^{18}F-DOPA in pediatric patients are similar to the adult indications with the understandable exception of Parkinson's disease.

Although the radiation exposure deriving from a PET/CT scan is higher than a simple CT or MRI scan the clinical benefit always exceed the risk linked to the use of radiations [3].

The number of papers involving pediatric subjects is steadily growing. However, literature still lacks clinical trials and large multicentric studies in contrast with the extensive literature available for adult patients.

The aim of this review is to discuss the main clinical indications of ^{18}F-DOPA in pediatric oncologic and nononcologic diseases, and to analyze its role in comparison with the other imaging modalities.

Brain tumors

The most frequent solid tumors in children are brain tumors and they represent the most common cause of death among all childhood cancers [4]. Clinical presentation depends on age, location and tumor malignity. Tumors of embryonic derivation such as medulloblastoma are more frequent in younger patients while glial tumors increase in frequency with age [5].

The only proven risk factor for brain cancer is the radiation exposure [6], even if up to 8% of brain primary tumors are comprehended in germline predisposition syndromes [7].

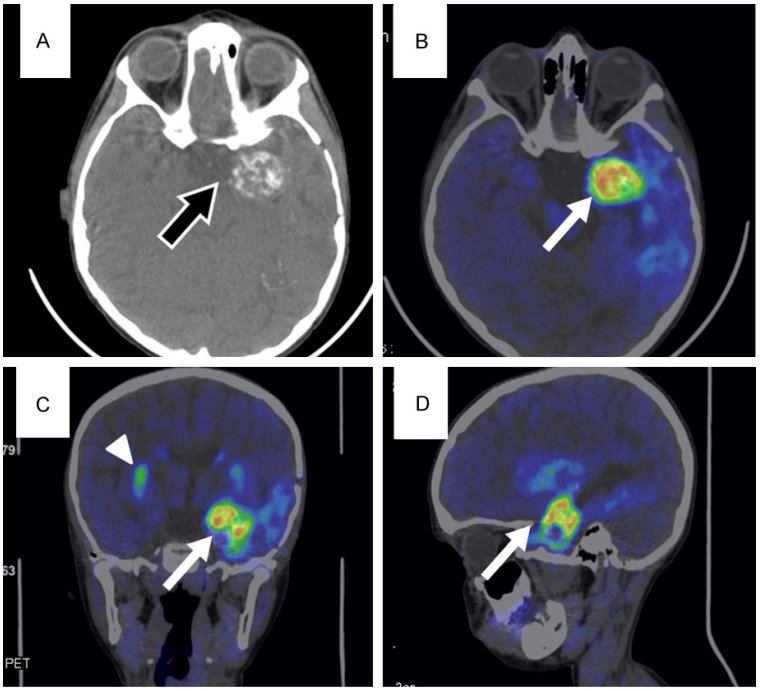

Figure 1. Anaplastic astrocytoma DH1 wildtype, grade III sec. WHO after radiotherapy. Axial CT (A) shows a calcificated left temporal mass compressing the brainstem (black arrow). Axial (B), coronal (C), and sagittal (D) PET-CT images show increased ^{18}F-DOPA uptake at the same level (arrow). Visual score indicates higher uptake of the lesion compared to striatum uptake (arrowhead), referable to recurrence.

Many radiotracers have been proposed for the diagnosis of brain tumors such as ^{18}F-fluoro-L-dihydroxy-phenylalanine (^{18}F-FDOPA), ^{11}C-methylmethionine (^{11}C-MET), ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET). However only ^{18}F-DOPA is available at a limited number of centers with a limited experience regarding the others radiolabeled amino-acid PET tracers. The uptake of ^{18}F-DOPA and amino acidic tracers in brain tumors is mainly determined by the expression of L-amino acid transporter system [8]. The status of the blood-brain barrier does not influence tracer's uptake allowing the use of ^{18}F-DOPA in both enhancing and non-enhancing brain tumors [1].

The assessment of tumor metabolism with ^{18}F-DOPA can detect high- and low-grade brain tumors independently of the blood-brain barrier breakdown. Thus, it is complementary to MRI, the current imaging gold-standard.

Gliomas

Historically WHO has divided gliomas in 4 different categories based on histopathology [9]. The incidence of pediatric high-grade gliomas are 0.8 per 100.000 and represents 20% of all pediatric gliomas [10]. The most frequent histological variants are anaplastic astrocytoma (AA), diffuse intrinsic pontine glioma (DIPG) and glioblastoma multiforme (GBM) [5]. Low-grade gliomas alone are the most frequent pediatric brain tumor mostly represented by pilocytic astrocytomas [11]. In the revised 2016 World Health Organization (WHO) classification of tumors of the central nervous system, the diffuse midline glioma (DMG) H3K27M-mutant has been introduced as a completely new entity, with a worse prognosis than that of wild-type cases [12].

The role of metabolic imaging with ^{18}F-DOPA in pediatric brain tumor is becoming more and more central, overcoming the limitations of MRI morphologic imaging [13] especially to target the biopsy (**Figure 1**) and to monitor treatment response. In fact, ^{18}F-DOPA imaging can potentially distinguish between treatment-related changes from recurrent tumor [14] or pseudo-response [15]. Pseudo-response is an MRI phenomenon in which high-grade tumors present drastic reduction of contrast-enhancement of the lesion along with reduction of perfusion and permeability. These events are due to the repairment of blood-brain barrier and can be confused with tumor response [16] to treatment. Although semi-quantitative analysis has not yet been standardized visual scales can be currently use in both diagnosis and follow-up of brain tumors [17, 18]. A comparison including only histologically defined high-grade DMG showed significant differences in the ^{18}F-DOPA PET T/S ratio between H3K27M mutant and wild-type lesions, highlighting the potential role of this parameter to non-invasively determine the H3K27M mutation status independently of histology [12].

Medulloblastoma

Medulloblastoma (MDB) is one of the most frequent pediatric brain tumor accounting for 10%

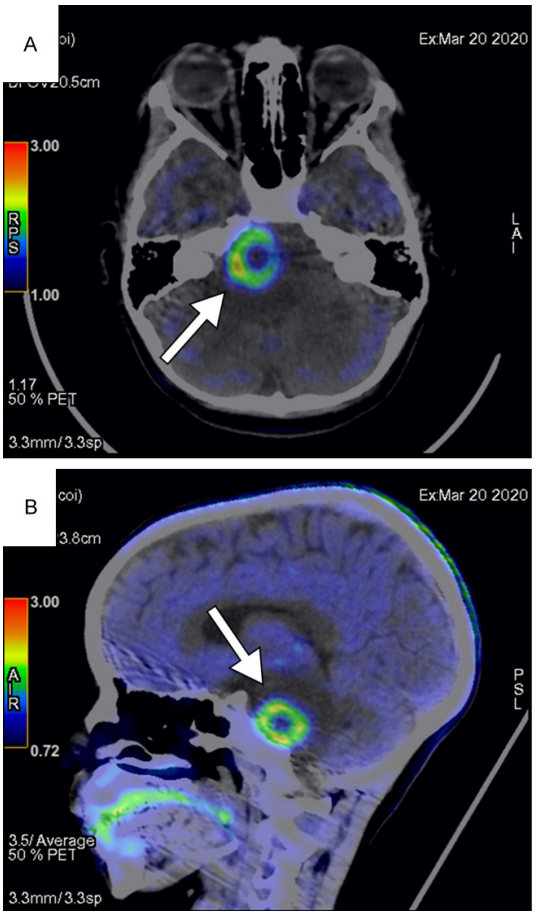

Figure 2. Medulloblastoma recurrence after systemic chemotherapy and radiotherapy. Axial (A) and sagittal (B) ^{18}F-DOPA PET/CT images show ring DOPA uptake in the brainstem (arrow).

of all brain malignancies [19]. These tumors arise from the posterior cranial fossa and spread through subarachnoid space. WHO classifies medulloblastoma as grade IV malignancies [20]. It is most frequently located in the cerebellum, particularly in the vermis. The gold standard for staging MDB is represented by magnetic resonance imaging (MRI) [21] even if secondary lesions can display different characteristics from the primary lesion [22]. However, the use of MRI is limited when considering post-treatment changes. In fact, it often cannot distinguish between disease recurrence and post-treatment modifications [14]. Chen et al. demonstrated that ^{18}F-DOPA was a predictor of tumor recurrence [1] (**Figure 2**). However, the role of DOPA PET in the management of MDB is yet to be fully defined.

Neuroblastoma

Neuroblastoma is a neuroendocrine tumor that derives from neural crest cells, the precursor elements of sympathetic nervous system. Neuroblastoma can consequently occur in adrenal glands and/or sympathetic ganglia, with more than 50% occurring in the medulla of the adrenal glands. It is one of the most frequent extracranial malignancy in pediatric patients with an early age onset and although spontaneous regression in infancy has been observed it is often metastatic at diagnosis. In fact, it shows high risk of spreading disease to bone and bone marrow, lymph nodes and liver [23] (**Figure 3**).

The median age at diagnosis is 18 months [24] with 90% of neuroblastomas arising within 10 years of age. The incidence reported is one case in 7,000 live births, and with about 700 new cases per year in the United State [25].

The age at diagnosis is a prognostic factor. Patients with less than 18 months of age have better overall survival (OS) compared to patients with more than 18 months of life [26]. Although rare in adolescent and young adults neuroblastoma tends to be indolent but much more lethal [27].

Localized disease is often an incidental finding while large masses can cause hypertension, abdominal distension and pain. Metastasis can be detected in 50% of cases at diagnosis more frequently in regional lymph nodes, bone marrow and bone. Liver and skin repetitions are more common in infants with less than 18 months of age while lung and central nervous system metastasis are rare findings [28].

The diagnosis consists of a combination of laboratory tests, radiologic imaging and histological assessment of the tumor.

The diagnosis is suggested by high urine levels of the catecholamines vanillylmandelic acid (VMA) or homovanillic acid (HVA) [29].

Increased levels of VMA and/or HVA can be found in urine in approximately 90% of patients with neuroblastoma. A valid alternative is represented by plasma free and total levels of normetadrenaline, metadrenaline and methoxytyramine [30].

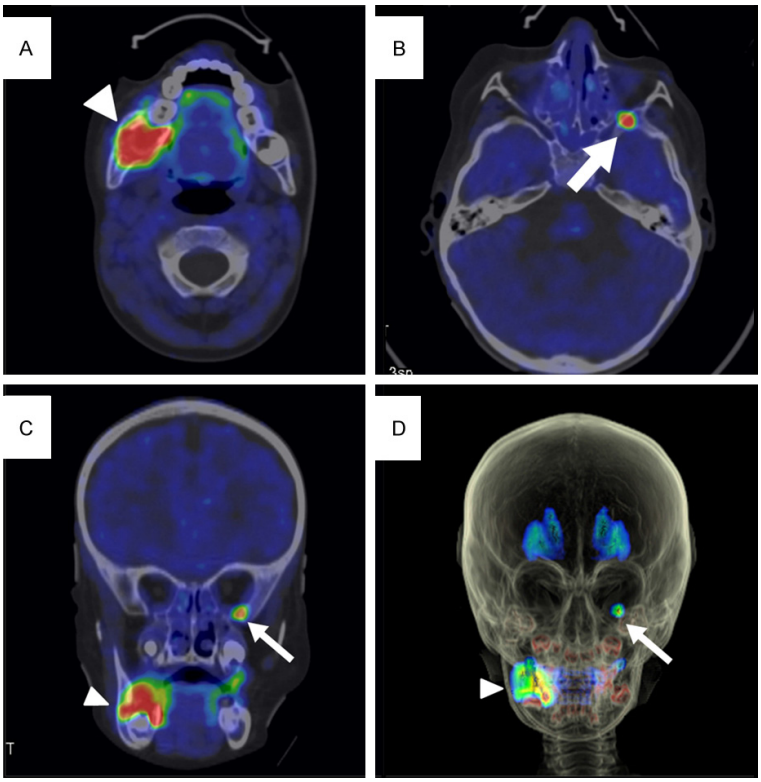

Figure 3. Axial (A and B), coronal (C) fusion PET/CT images and anterior view of 3D volume rendering fusion PET/CT image (D) showing high uptake of ^{18}F-DOPA in the right hemimandibula branch (arrowhead) and inferior orbital floor (arrow). Biopsy of the lesion in the right hemimandibula revealed bone metastasis from neuroblastoma.

The tumor grade of morphological differentiation are important prognostic factors. Peripheral neuroblastic tumors can present as neuroblastoma (with predominantly immature small round tumor cells), ganglioneuroblastoma (both immature cells and tumor cells with terminal neuronal differentiation to ganglion cells) and ganglioneuroma (tumor cells that show maturation with terminal neuronal differentiation to ganglion cells). Staging is obtained by bilateral bone marrow aspirates and trephine bone marrow biopsies, histological examination and immunohistochemistry to better assess metastatic disease [31].

Before the entrance of PET tomographs in clinical practice the nuclear medicine imaging of choice for pediatric neuroblastoma staging, was ^{123}I-meta-iodobenzylguanidine (^{123}I-mIBG) scintigraphy. The majority of neuroblastomas (90%) are mIBG-avid thanks to the expression of the noradrenaline transporter. This transporter permits the entrance of mIBG into tumor cells [32].

Radiological evaluation of neuroblastoma includes primary tumor and osteomedullary and/or soft tissue metastases assessment. Local disease evaluation is performed with CT or MRI imaging. MRI is usually preferred thanks to higher contrast resolution and the absence of ionizing radiation. However, potential limitations are represented by longer acquisition time and sedation required in younger patients. Imaging is fundamental to individuate the image-defined risk factors (IDRFs). These risk factors describe local extension through perivascular involvement with arterial encasement, infiltration of adjacent soft tissues and organs and infiltration of the neural foramina and epidural space of the spinal canal [33].

^{18}F-DOPA can be used to detect neuroblastic tumors thanks to the activity of AADC (aromatic L-amino acid decarboxylase) enzymes [34]. Piccardo et al. demonstrated that AADC was expressed 100% of neuroblastic malignancies and 0% of other pediatric tumors. AADC convert L-DOPA to dopamine, which is then converted to norepinephrine and epinephrine. VMA and HVA derive directly from norepinephrine and epinephrine metabolism [35]. The rationale of using ^{18}F-DOPA in neuroblastic tumors resides in the similarity of this tracer to L-DOPA and thus it can be metabolized in neuroblastic cells by AADC enzymes [36].

Several studies have shown that ^{18}F-DOPA has better diagnostic performance compared to ^{123}I-mIBG detecting smaller metastasis in bones, soft tissues and bone marrow [37]. Moreover, ^{18}F-DOPA is the tracer of choice in PET imaging being more accurate than alternative tracers such as ^{68}Ga-DOTA-conjugated peptides and ^{18}F-FDG [38].

Studies have investigated the role of FDG in the risk stratification and outcomes compared to DOPA performing consecutive scans with both

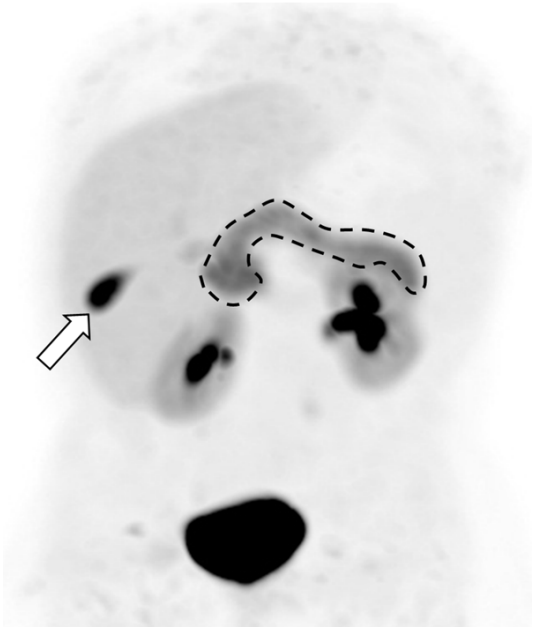

Figure 4. Diffuse Congenital Hyperinsulinism. Maximum Intensity Projection (MIP) ^{18}F-DOPA PET image shows diffuse uptake pattern in the pancreas (dashed lines). Physiological uptake in the gallbladder (arrow).

tracers. Results showed that patients with ^{18}F-FDG-avid neuroblastomas are associated with invasive tumor features and poor prognosis. In addition, lower ^{18}F-DOPA uptake is also associated with poor prognosis and distant metastases [39]. Other tracers such as ^{68}Ga-DOTA-conjugated peptides are also being evaluated for patients with neuroblastoma. However, studies have shown that ^{18}F-DOPA is more accurate in detecting distant metastasis [38].

Congenital hyperinsulinism

Congenital Hyperinsulinism (CHI) is a rare heterogenous genetic disease caused by an excessive secretion of insulin from pancreatic islet β-cells. This inappropriate production leads to hypoketotic hypoglicaemia with a wide spectrum of symptoms and high risk of brain damage in the worst cases [40]. The reported incidence of CHI is approximately 1:40-50.000 in Western populations [41]. CHI exists in two histological forms, focal or diffuse.

Focal CHI occurs in 40-50% of cases and it consists in a restricted and delimited area of adenomatous β-cell hyperplasia while diffuse CHI is caused by hypertrophy of a few β-cell nuclei scattered in most islets of Langerhans therefor involving the entire pancreatic parenchyma [42]. Imaging is the only diagnostic tool capable of discriminating focal from diffuse CHI. A correct diagnosis is fundamental because of the different therapeutic approach of the two CHI forms. Surgery is the best option when treating a focal lesion. It is in fact curative in most cases with a partial pancreasectomy without development of postsurgical diabetes mellitus [43]. On the other hand, medical treatment is preferred in diffuse CHI (**Figure 4**). In fact, in diffuse CHI surgery requires subtotal/total pancreasectomy with the risk of being not curative, or the possibility of developing iatrogenic diabetes mellitus and exocrine insufficiency [44]. Peripheral pancreatic cells are part of the neuroendocrine system (previous amine precursor uptake and decarboxylation system system) and convert L-DOPA into dopamine by the DOPA decarboxylase enzyme metabolic pathway before its entrance in β-cells [45, 46].

Currently, ^{18}F-DOPA is the most sensitive non-invasive imaging modality in identifying focal forms of hyperinsulinism.

In the Blomberg BA systematic review and meta-analysis [47], ^{18}F-DOPA PET was superior in distinguishing focal from diffuse CHI (sensitivity 75%, and the specificity 100%) compared to pancreatic venous sampling (PVS) (sensitivity 87%, and the specificity 73%) and hepatic venous sampling (ASVS) (sensitivity 71%, and the specificity 69%). Furthermore, it localized focal CHI in the pancreas more accurately than PVS and ASVS (pooled accuracy, 0.82 vs. 0.76, and 0.64, respectively). As a non-invasive and accurate modality, ^{18}F-DOPA PET replaced PVS and ASVS in the diagnostic management of CHI. However, a negative ^{18}F-DOPA PET scan should be approached with caution, because it cannot rule out focal CHI. False negative results can occur due to several reasons, including the physiological uptake of the tracer in pancreatic tissue, and the inability to visualize a pancreatic small lesion with uptake similar to that of the rest of the gland. Other potential pitfalls of ^{18}F-DOPA PET in CHI imaging include tracer accumulation in the gallbladder and duodenum, and left renal collecting system, especially when focal lesions are small in size. The smallest focal lesion detected by ^{18}F-DOPA-PET reported in the literature has measured 4 × 5 mm [48].

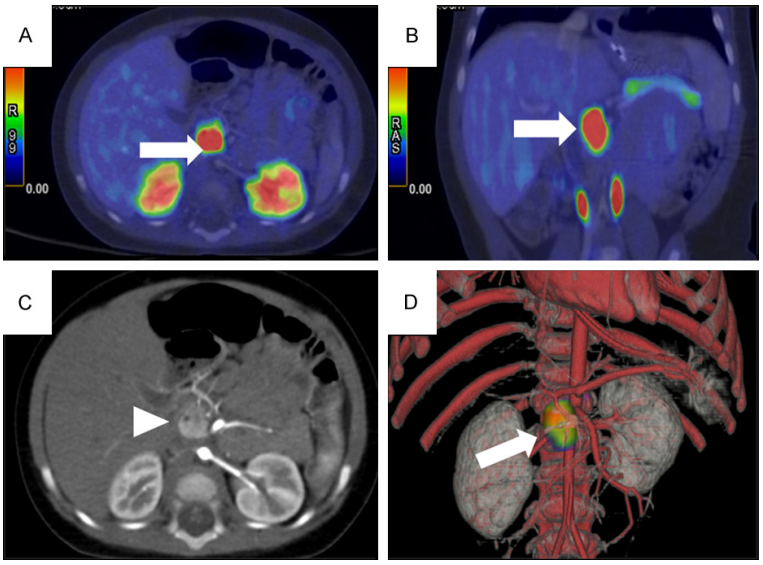

Figure 5. Focal Congenital Hyperinsulinism. Axial (A) and coronal (B) ^{18}F-DOPA PET images show focal PET uptake in the head of the pancreas (arrow). Transverse CT on the arterial phase image (C) shows hyperenhancing CT nodule in the head of the pancreas (arrowhead). Anterior view of 3D volume rendering fusion PET/CT image (D) shows the relationship between the lesion (arrow) and artery vessels.

The new integrated PET/CT method enables both exact anatomical and functional description of the pancreatic focus. When paired with CT or MRI it can individuate the exact location of the lesion increasing the probability of curative surgery [48]. Moreover, contrast enhanced CT gives the most comprehensive information in preoperative planning especially on the relationship between the lesion and important vascular structures, and sometimes on the vascularization of the lesion, as demonstrated by Hashimoto et al. [49]. Our ^{18}DOPA PET-CT protocol for CHI includes CT angiography during arterial phase, in case of focal DOPA uptake (**Figure 5**). In this way we simultaneously acquired functional and morphological data for diagnosis and surgical planning avoiding two anesthesia sessions.

Discussion

There are a limited number of pediatric multicenter studies and trials available in contrast with the extensive literature and guidelines dedicated to adult patients. One of the motivations is that the pediatric tumors described above are relatively rare. Moreover, not every center possesses a PET/CT tomograph and the possibility of using ^{18}F-DOPA PET/CT.

^{18}F-DOPA normally distributes in basal ganglia, pancreas, and adrenal glands, gallbladder and biliary tract, kidneys, ureters and urinary bladder. In children it is frequent the uptake in epiphyseal growth plates [50].

^{18}F-DOPA has been used in adult patients to evaluate the integrity of the dopaminergic system particularly when Parkinson's disease or other movement disorders are suspected [51]. This tracer is an analogue of L-DOPA and can pass the blood-brain barrier thanks to the neutral amino acid transport system [52]. The use of ^{18}F-DOPA in brain tumors is relatively recent. The first visualization of a brain tumor with ^{18}F-DOPA was an incidental finding in the 90's [53] and since then it has demonstrated to have an optimal tumor-to-background ratio due to the high expression of the amino acid transport in tumoral lesions and most importantly higher sensitivity than ^{18}F-FDG PET imaging [1]. The uptake of ^{18}F-DOPA in the brain does not depend on the blood-brain barrier disruption as opposed to what happens in contrast-enhanced MRI [14]. The fusion between ^{18}F-DOPA PET and MRI should be the modality of choice in post-treatment follow-up of frequent pediatric malignancies such as gliomas. In fact, ^{18}F-DOPA PET/MRI can potentially overcome problematics such as the differentiation between treatment-related changes, residual or recurrent disease [14]. An interesting paper analyzed ^{18}F-DOPA findings in patients with primary and/or recurrent gliomas. Results show that ^{18}F-DOPA detected most gliomas, and its activity correlated well with non-enhancing tumors. Moreover, the uptake was increased in both enhancing and non-enhancing high-grade gliomas. In one case contrast-enhanced MRI could not differentiate between post-surgical changes or residual disease. ^{18}F-DOPA PET study showed increased activity in the same area of contrast enhancement in addition to the surrounding tissues. 3 months later a second MRI demonstrated intense contrast enhancement in the same

site of ^{18}F-DOPA activity. This finding was then defined as tumor recurrence. So, ^{18}F-DOPA may be able to individuate residual disease thanks to the earliness of metabolic abnormalities [14]. While ^{18}F-DOPA semi-quantitative analysis with SUV_{max} and SUV_{mean} is not entirely standardized a visual analysis has been proposed to correctly diagnose GBM and GBM recurrence. This 5-point visual scale confronts background, lesion and striatal uptake by giving -2 points with a non-visible lesion, -1 point when the lesion is visible, but its uptake is less than striatal uptake, 0 points when the lesion uptake is similar to the striatum, 1 point with lesion uptake higher compared to striatum and 2 points when the lesion uptake is much higher than striatal uptake. ^{18}F-DOPA findings were considered positive with score 0, 1 and 2. Moreover, this score seems a good predictor of progression free survival (PFS) in patients with suspected brain recurrence [17].

Another study showed that MRI and ^{18}F-DOPA PET are complementary for early recurrence detection. In this setting, the added information brought by PET has a significant impact on patient management, leading the multidisciplinary tumour board (MNTB) to change treatment plan in one third of patients with glioblastoma and 17% of patients with brain metastases [18].

^{18}F-DOPA PET metabolic imaging demonstrates significant correlation with histopathological markers of grade and cellularity. An optimal ^{18}F-DOPA PET threshold (T/N > 2.0) can be used to reliably differentiate areas of high-grade astrocytoma not otherwise recognized with standard MRI.

^{18}F-DOPA PET SUV_{max} may more accurately identify regions of higher-grade/higher-density disease in patients with astrocytomas and showed utility in guiding stereotactic biopsy selection.

Using SUV-based thresholds to define high-grade portions of disease are valuable in RT planning of boost doses [54].

A study from 2017 conducted on patients with diffuse astrocytic tumors (DAT) evaluated the diagnostic performance of advanced MRI techniques such as arterial spin labeling (ASL) and diffusion weighted imaging (DWI) in comparison to ^{18}F-DOPA PET in terms of tumor grading and outcome prediction. The main purpose was to compare microvascular information provided by ASL, microstructural information supplied by ADC with metabolic information from ^{18}F-DOPA PET. The study found a significant correlation between microvascular tumoral density and aminoacid metabolism, and a special correlation between the area of minimum ADC and the hot-spot area on ^{18}F-DOPA PET. Moreover, data from ^{18}F-DOPA PET were different for high-grade gliomas and low-grade gliomas, supporting its capacity to differentiate low grade from high grade diffusely infiltrating glioma although statical significance was not reached [55].

^{18}F-DOPA PET can provide useful information in terms of initial diagnosis and the extent of gliomas in the context of recurrent tumors. Nevertheless, standardization of acquisition and interpretation parameters (as addressed by EANM, SNNMI and EANO) remains essential [56].

The management of neuroblastic tumors represents another application of ^{18}F-DOPA. Neuroblastic tumors such as neuroblastoma are the most frequent extracranial malignancies in children deriving from precursor cells of the sympathetic system. Their lethality is high given the possibility of bone, bone marrow, lymph nodes, or liver metastasis frequently present at diagnosis [36, 57]. The presence of AADC enzymes in neuroblastic cancer cells leads to the conversion of ^{18}F-DOPA in ^{18}F-fluorodopamine, which is then stored in vesicles [58] allowing tumor visualization. ^{123}I-mIBG and ^{131}I-mIBG scintigraphy have been the imaging modalities of choice for several years. Lu et al. demonstrated the high sensitivity value of ^{18}F-DOPA. In fact, ^{18}F-DOPA detected 41 of the 42 neuroblastic tumors with viable tumor cells, including 25 of 26 neuroblastomas, all 11 ganglioneuroblastomas, and all 5 ganglioneuromas, with a sensitivity of 97.6% (95% confidence interval, 87.4%-99.9%). Moreover, it visualized primary and metastatic neuroblastic tumors and detected all histologic types with a sensitivity of 97.6% and a specificity of 87.5% [36]. Another advantage of ^{18}F-DOPA compared to mIBG scintigraphy is the “one-shot session” scan that allows better management of non-hospitalized children.

However, it must be kept in mind that mIBG scintigraphy is mandatory in those cases where

therapy with ^{131}I-mIBG might be an option [59]. A recent prospective study of 2019 assessed not only the sensibility of ^{18}F-DOPA in detecting neuroblastoma localizations in children at the time of first diagnosis but also the evaluation of response after induction chemotherapy compared to ^{123}I-mIBG [23]. One of the most interesting features of this prospective study is that the authors investigated whether the high number of disease's repetitions detected by ^{18}F-DOPA was merely the expression of diagnostic sensibility or whether was associated to higher risk of disease persistence or progression. Indeed, at univariate analysis the stage at diagnosis and the disease burden after induction chemotherapy seemed to be associated with prognosis [23]. Further studies are needed in order to assess the prognostic value of ^{18}F-DOPA in neuroblastic tumors.

The use of ^{18}F-DOPA PET is crucial in the management of another pediatric disease, such as CHI. As explained in the section above ^{18}F-DOPA can be used not only in the diagnosis of CHI but also in the pre-operatory study guiding the clinician and the surgeon in choosing the most suitable treatment. Moreover, ^{18}F-DOPA is a non-invasive imaging modality compared to pancreatic venous sampling (PVS) used in the past in pre-operatory evaluation. This is an invasive and technically complicated tool and only few centers have acquired the experience required [60].

While in adult population pretreatment with carbidopa is necessary in order to reduce the pancreatic uptake of ^{18}F-DOPA and better identify pancreatic lesions, the physiologic pancreatic uptake in pediatric patients is significantly lower and so, the use of AADC inhibitors remains a matter of discussion [61]. For example, a study from 2006 found out that the accumulation of ^{18}F-DOPA inside the cells requires the activity of AADC and when this enzyme is blocked using AADC inhibitors the tracer could diffuse back to the extracellular department without the visualization of pancreatic cells [60]. This could potentially increase the number of false negative when looking for focal hyperinsulinism. In addition to the visual inspection of ^{18}F-DOPA uptake in CHI a semi-quantitative reproducible method was used in a multicentric Japanese case series [62].

In this method called "Pancreas percentage" the pancreas was divided in three regions i.e., head, body and tail. The SUV in the hottest area was set as 100% and the uptake of the remaining regions was then expressed as percentages compared to the one of the hottest area. The region was considered an area of focal CHI if the "Pancreas percentage" was more than 70% and the SUV_{max} was higher the 2,5. If all area investigated met these criteria the diagnosis was considered as diffuse CHI [62, 63].

The only other PET tracer used for CHI was ^{68}Ga-DOTANOC by Christiansen CD et al. [40]. In this blinded retrospective study ^{68}Ga-DOTANOC PET had a lower point estimate of the ROC AUC proving the superiority of ^{18}F-DOPA PET/CT.

^{68}Ga-NODAGA-exendin-4 is a new promising tracer for β-cell imaging using PET/CT [64]. β-cells specifically express the glucagon-like-peptide-1 (GLP-1R), which could be a promising target for diagnostic and therapeutic purposes.

Expression of the GLP-1 receptor can be quantified in vivo by ^{68}Ga-NODAGA-exendin-4 PET/CT. The value of ^{68}Ga-NODAGA-exendin-4 in comparison with ^{18}F-DOPA and contrast enhanced CT is under investigation as a potential new imaging method to distinguish between diffuse and focal forms of CHI (NCT03768518).

As explained above the use of ^{18}F-DOPA PET/CT imaging is crucial in the diagnosis, staging, pre-operative and follow-up of specific medical conditions. The main limitation of ^{18}F-DOPA tracer is its availability. In fact, not every nuclear medicine department possesses a cyclotron to produce radiopharmaceuticals in site. The relatively low number of examinations performed with ^{18}F-DOPA has led the producers/distributors of PET tracers toward the production and distribution of tracers such as ^{18}F-FDG. **Table 1** summarizes the main studies cited above which compare ^{18}F-DOPA with other imaging modalities or PET tracers.

There are some technical aspects to consider when performing a PET/CT scan on pediatric patients. The main problems when dealing with extremely young patients are the need for general anesthesia and the optimization of the radiation dose. The combination of PET and CT acquisitions and the concomitant use of iodinated contrast require strategies to optimize the radiation exposure. Pediatric tissues and organs are notably more radiosensitive com-

Table 1. Summary of studies comparing ^{18}F-DOPA and other imaging modalities or tracers

AUTHOR, YEAR	RADIOTRACER/IMAGING MODALITY	NOTES
Chen, 2006 [1]. (81+51 patients with brain tumors)	^{18}F-DOPA vs. ^{18}F-FDG	Sensitivity for identifying tumors substantially higher with ^{18}F-FDOPA PET than with ^{18}F-FDG PET as determined by simple visual inspection, especially for the assessment of low-grade tumors. The high diagnostic accuracy of ^{18}F-FDOPA PET was confirmed with the additional 51 patients. No significant difference in tumor uptake on ^{18}F-FDOPA scans was seen between low-grade and high-grade tumors or between contrast-enhancing and non-enhancing tumors. Radiation necrosis was generally distinguishable from tumors on ^{18}F-FDOPA scans.
Piccardo, 2019 [13]. (22 patients with DMG, retrospective)	Advanced MRI vs. ^{18}F-DOPA	DWI, ASL, 1H-MRS and ^{18}F-DOPA PET demonstrated significant differences between wild-type and mutant DMG prevailingly depending on the histological features of the lesions, since the results were probably influenced by the fact that low-grade diffuse astrocytomas were present only among wild-type lesions. However, a comparison including only histologically defined high-grade DMG showed significant differences in the ^{18}F-DOPA PET T/S ratio between H3K27M mutant and wild-type lesions, highlighting the potential role of this parameter to non-invasively determine the H3K27M mutation status independently of histology.
Morana, 2013 [15]. (Case report, patient with malignant transformation of ganglioglioma)	Multimodal MRI and ^{18}F-DOPA	^{18}F-DOPA PET imaging demonstrated high uptake of the residual non-enhancing lesion as well as of the nonspecific non-enhancing FLAIR hyperintensity along the anterior margin of the surgical cavity, suggesting lack of treatment response and progressive disease, as confirmed by subsequent follow-up MRI. Furthermore, ^{18}F-DOPA PET revealed an additional focal area of increased uptake without corresponding MRI abnormalities but with subsequent onset of macroscopic disease, thus seeming to anticipate disease localization.
Piccardo, 2020 [23]. (18 patients with Neuroblastoma, prospective)	^{18}F-DOPA vs. ^{123}I-mIBG	^{18}F-DOPA PET/CT was significantly more sensitive than ^{123}I-MIBG WBS in staging neuroblastoma patients and evaluating disease persistence after chemotherapy.
Liu, 2017 [39]. (25 patients with Neuroblastoma)	^{18}F-FDG vs. ^{18}F-DOPA	The avidity of primary tumors toward both tracers is correlated with various clinical and histopathologic features and may have independent prognostic values for risk stratification. Lower ^{18}F-DOPA uptake is associated with poor prognosis and distant metastases. Higher ^{18}F-FDG uptake is associated with invasive features of tumors, MYCN amplification, and poor prognosis.
Christiansen, 2018 [40]. (55 patients with hyperinsulinism, retrospective)	^{18}F-DOPA vs. ^{68}Ga-DOTANOC	^{18}F-DOPA PET/CT was excellent in predicting focal CHI and superior compared to ^{68}Ga-DOTANOC PET/CT. Further use of ^{68}GA-DOTANOC PET/CT in predicting focal CHI is discouraged.
Morana, 2017 [55]. (26 patients with DAT, retrospective)	MRI vs. ^{18}F-DOPA	DWI, ASL and ^{18}F-DOPA PET imaging provide useful complementary information for pediatric diffuse astrocytic tumor grading. ^{18}F-DOPA uptake better correlates with outcome and is an independent predictor of PFS. The combination of DWI, ASL, and ^{18}F-DOPA PET data enhances overall performance in predicting tumor progression, thus suggesting a synergistic role of these modalities and underscoring the added value of multimodal multiparametric PET/MR imaging in pediatric brain tumors.

pared to the adult population [65]. This is particularly important in oncologic patients due to the necessity of multiple radiological studies and consequently the cumulative radiation dose [66]. In the majority of cases, the clinical data derived from a PET/CT study exceed radiation risks [67]. A review article of Parisi et al. summarized the most important strategies to reduce the radiation exposure [68]. First, the nuclear medicine physician must eliminate all the unnecessary studies. The communication with the clinician is crucial and the final decision must be taken after considering the benefit-risk ratio. The second strategy requires a careful consultation of international guidelines for radiopharmaceutical dose optimization [69]. The third step involves optimization of CT scan radiation using "child-size CT protocols" with reduced parameters such as mAs and kVp and increased pitch if possible. Finally, the reduction of the extent of areas imaged. Moreover, when dealing with malignancies such as brain tumors the diagnostic CT scan of a ^{18}F-DOPA PET/CT study can be avoided when MRI is available. Fused MRI/PET images allow the use of an extremely low-dose CT scan used with the only intent of attenuation correction. General anesthesia cannot be avoided in non-compliant patients or infants. In cases with partially collaborating patients the acquisition can be carried out in a particular acquisition modality called LIST-MODE. This approach consists in a "dynamic" acquisition with multiple frames and can be used to reduce motion artifacts [70, 71].

Conclusion

In conclusion, over the years ^{18}F-DOPA has proven to be a fundamental tool in the diagnosis, preoperative assessment and follow-up of many pediatric conditions both benign and malignant. Moreover, the radiation exposure of a PET/CT study does not represent a discouraging aspect of this imaging modality in children.

Disclosure of conflict of interest

None.

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