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Review Article

PET/CT in pediatric oncology

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Abstract: The use of PET/CT in adult oncology has been consolidated by several and authoritative multicentric studies, metanalyses and systematic reviews. International guidelines help everyday nuclear medicine specialists, oncologists and radiologists in choosing the most suitable diagnostic path for each patient. Classifications based on traditional imaging and PET/CT findings define the most appropriate treatment and can predict the outcome for different types of malignancies. However, compared to adult patients the use of PET/CT in pediatric oncology is often burdened by lack of systematic and large multicentric studies and consequently accurate and precise guidelines. The cause of this shortage of large trials may be attributed to the rarity of these neoplasms and to the fear of long-term radiation effects on this peculiar category of patients. The aim of this article is to review the applications of PET/CT for imaging the most common pediatric neoplasms.

Keywords: PET/CT, oncology, pediatric

Introduction

Since its introduction in clinical practice PET/CT (Positron Emission Tomography/Computed Tomography) has increasingly became a fundamental diagnostic tool in both adult and pediatric oncology. This hybrid imaging modality not only provides morphological information (with Computed Tomography) but also allows the study of physiological and pathological processes [1]. Although in adult oncology the use of PET/CT is well consolidated, in pediatric oncology there are still shaded areas. One of the reasons may be represented by the rarity of these neoplasms and therefore lack of trials and large multicentric studies. Another problem must be considered when performing repeatedly PET/CT in pediatric patients namely the more radiosensitivity of this kind subjects. Fortunately several protocols have been developed in order to limit the radiation exposure [2], but in most cases the clinical benefits prevail the potential radiation risks [3].

The aim of this review is to provide brief references on the use of PET/CT in some of the most frequent pediatric neoplasms, i.e. brain tumors, osteosarcoma, Ewing sarcoma, neuroblastoma and Hodgkin's and Non-Hodgkin's Lymphoma.

Brain tumors

The most common pediatric solid tumors are represented by CNS malignancies [4] with a prevalence of 9.5 cases per 10,000 and an incidence rate of 29.1 cases per 1,000,000 [5].

The main limit in the use of ^{18}F-FDG/PET (^{18}F-fluorodeoxyglucose) for the diagnosis of CNS tumors is the physiologic high uptake of ^{18}F FDG in the brain cortex [3] and thus it is not routinely used for the evaluation of these neoplasms. This is particularly important in the diagnosis of low-grade malignancies (especially gliomas) [6]. On the other hand ^{18}F-FDG is more sensitive when diagnosing high-grade gliomas showing a higher uptake of the radiotracer in the tumor compared to the normal brain cortex [7]. Several radiotracers have been proposed in place of ^{18}F-FDG 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 L-DOPA is available at a limited number of centers with a limited experience regarding the others radiolabeled amino-acid PET tracers (**Figure 1**). ^{11}C-labeled tracers use is limited by the presence of a cyclotron because of the relatively short half-life of this radioisotope [8].

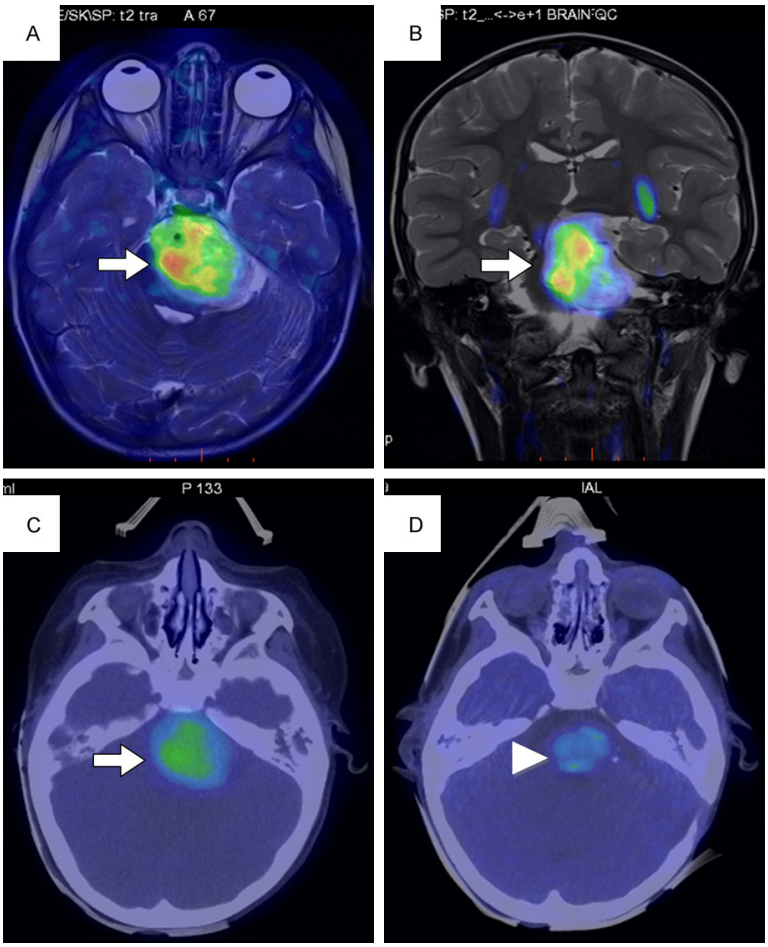

Figure 1. [^{18}F] DOPA therapy monitoring in 4-year-old patient with Neuroendocrine embryonal tumor with multilayered rosettes (ETMR). Axial (A) and coronal (B) MRI-PET fusion images and axial PET/CT (C) images showing brainstem uptake (arrow); axial PET/CT (D) after systemic chemotherapy and proton therapy shows lower brainstem uptake (arrowhead).

^{18}F-FDOPA is an amino acid analog well known and used in the evaluation of presynaptic dopaminergic neuronal function [9]. This amino acid analog has also been used in the diagnosis of brain tumors and compared to ^{18}F-FDG it showed a superior contrast between tumors and normal brain tissue. Moreover, Chen et al. demonstrated that ^{18}F-F-DOPA was a predictor of tumor recurrence [10].

MET is an essential amino acid conjugated to ^{11}C with a half-life of 20 minutes. As already explained the main limit in the use of ^{11}C conjugated tracers is the availability of a cyclotron. Nevertheless, it is still one of the most valuable and used radiotracers in the diagnosis, grading and differentiation between recurrence and radionecrosis of gliomas [8]. Magnetic resonance imaging (MRI) remains the best option in the detection of brain metastases, but it can be used to differentiate recurrent metastases and radiation injury and in the delineation of the target tissue for radiotherapy [11].

Regarding FET-PET only a small number of studies are available in literature. In particular Dunkl et al. demonstrated in a small group of pediatric patients that imaging parameters derived from ^{18}F-FET PET may be useful especially in the identification of newly diagnosed brain lesions suggestive of glioma and in the diagnosis of tumor progression or recurrence [12].

Bone and soft tissue malignancies

Soft tissue sarcomas are rare in themselves in children. Soft tissue Ewing sarcoma is even more rare (**Figures 2** and **3**).

Osteosarcoma

Osteosarcoma is a primary bone malignancy with two peaks of incidence. The first one in children and adolescents and the second one in patients >60 years old. It's the most common pediatric primary bone tumor [13]. ^{18}F-FDG PET has been used in the evaluation of tumor response to adjuvant chemotherapy even before the development of PET/CT [14]. The dual modality in addition to a higher spatial resolution allowed the use of PET/CT not only in the initial staging of disease but also in the definition of local and distant recurrence [14]. Moreover, several studies demonstrated the correlation between (Standard Uptake Value max (SUVmax) and patient's prognosis). For example, Costelloe et al. correlated SUVmax before and after chemotherapy with progression-free survival [15]. Another study considered SUVmax, Total Lesion Glycolisis and Metabolic Tumor Volume (MTV) and associated them with progression-free survival [16]. In conclusion ^{18}F-FDG PET/CT is rou-

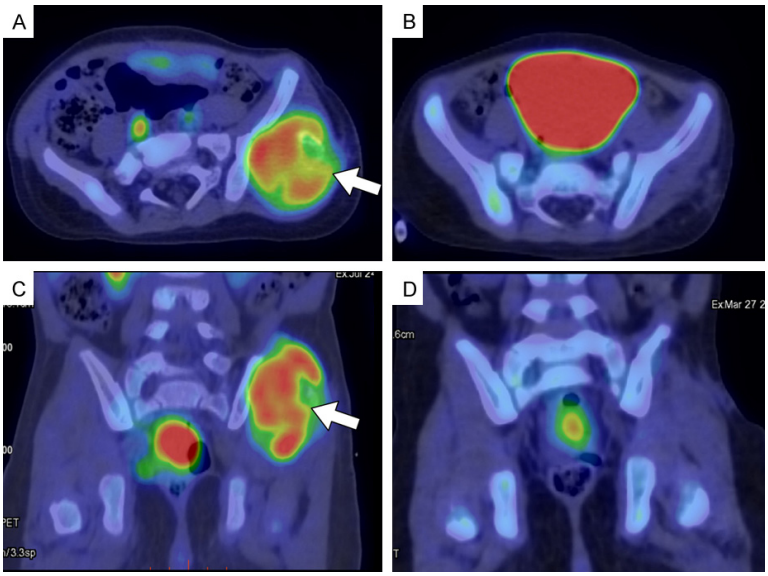

Figure 2. Therapy monitoring in 6-year-old patient with Soft tissue Ewing sarcoma of left glutei muscles. Axial (A) and coronal (C) [^{18}F] FDG images show high FDG uptake involving left glutei muscles (arrows); no more activity in the post-therapy study (B and D).

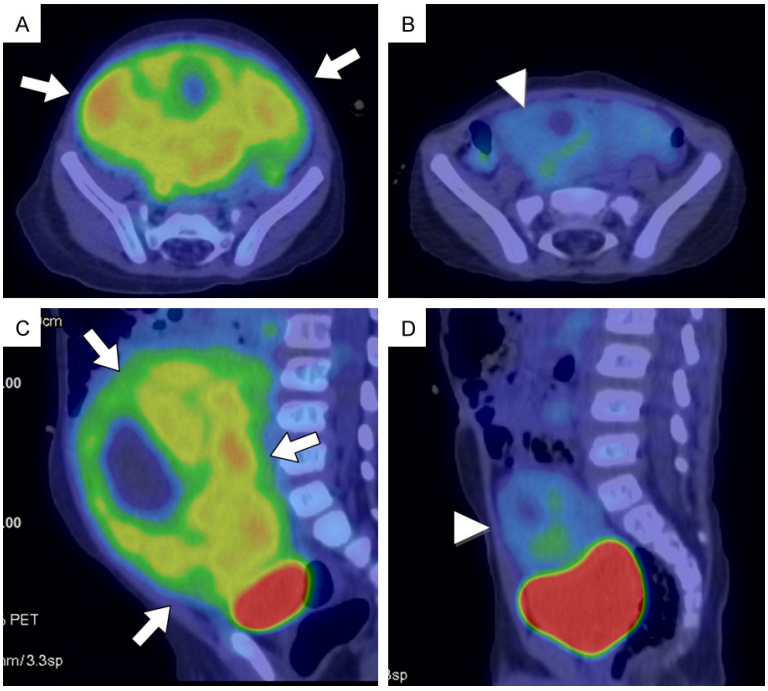

Figure 3. Therapy monitoring in 2-year-old girl with Rabdomyosarcoma of the urinary bladder with botryoid morphology. Axial (A) and coronal (C) planar [^{18}F] FDG images show a voluminous pelvic mass with high FDG uptake (arrows); partial response (arrowheads) is observed after systemic chemotherapy (B and D).

tinely used in the staging and re-staging of patients with Osteosarcoma and in the detection of skeletal metastasis, with a greater accuracy than scintigraphy bone scan [17].

Ewing sarcoma

Ewing sarcoma is the second most common bone tumor in children and adolescents. It involves not only the bones but also the contiguous soft tissues [18]. 25% of patients are already metastatic at the diagnosis, with the most frequent sites represented by lungs, bones and bone marrow [19]. Similarly to osteosarcoma [^{18}F] FDG PET/CT is regularly used in the initial staging being able to identify distant sites of disease [20]. However, ^{18}F-FDG PET is equally effective to traditional imaging when studying primary tumor site. Nonetheless PET/CT is still fundamental in therapy planning and detecting distant sites of disease [21].

Neuroblastoma

Neuroblastoma is the most common solid extracranial malignancy and occurs mostly in patients under 5 years old [22]. Unfortunately up to 50% of cases present as metastatic disease at the diagnosis [23] (**Figure 4**). Choice of treatment and prognosis strictly depend from which risk group the patient belong to [24]. In the low-risk group patients have better prognosis with less treatment needed while patients in the high-risk group require more aggressive therapies with minimal benefits and worse prognosis [25]. Several imaging modalities have been used for staging and therapy of neuroblastoma. Metaiodobenzylguanidine (mIBG) conjugated with ^{123}I and ^{131}I can be used respectively for the detection of meta-

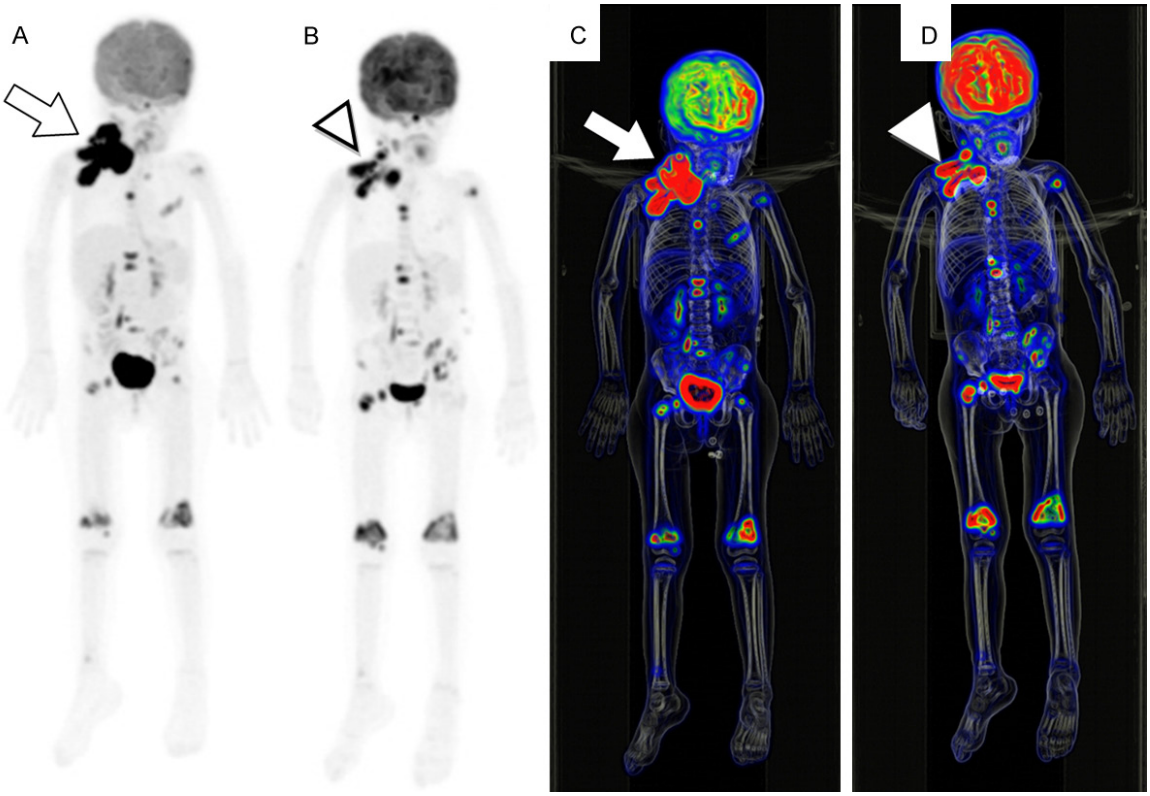

Figure 4. Therapy monitoring in 3-year-old girl with bone and laterocervical lymph nodes metastatic neuroblastoma. FDG PET maximum intensity projection image (A) and Volume Rendering (C) show high FDG uptake (arrows); partial response is observed after systemic chemotherapy (B and D-arrowheads).

static disease and for treatment of relapsed and refractory neuroblastoma. The rationale behind the use of this norepinephrine analogue is that most neuroblastomas express noradrenaline receptors [26]. As for PET/CT two types of tracers are currently used in neuroblastoma: the first one is ^{18}F-FDG [27] and the second one is the group of ^{68}Ga conjugated somatostatin analogues DOTATOC, DOTANOC and DOTATATE [28].

A potential flaw of ^{123}I MIBG is that up to 10% of neuroblastoma do not express noradrenaline receptors. These less differentiated neuroblastomas remain FDG avid so ^{18}F-FDG is particularly useful with negative ^{123}I-MIBG at the expense of specificity value [29].

The recent use of DOTA-conjugated peptides is justified by the variable expression of high-affinity somatostatin receptors (SSTRs) in neuroblastomas [30]. Moreover, the presence of SSTR-2 correlates with prognosis with a better survival for neuroblastomas with high levels of SSTR-2 [31]. Furthermore, the evaluation of SSTRs expression in patients with neuroendocrine tumors and in relapsed/refractory neuroblastomas helps selecting patients eligible to treatment with ^{90}Y- and ^{177}Lu-DOTA-conjugated peptides [32].

There are many advantages of using ^{68}Ga-DOTATATE PET/CT compared with ^{123}I-mIBG scans. These include rapid radiotracer uptake allowing acquisition of imaging in less than 90 minutes after radiotracer administration; rapid image acquisition times, often less than 10 minutes, which will shorten sedation times if necessary; noninvasive quantitation for individualized dosimetry estimates for body habitus and tumor burden for subsequent peptide receptor radionuclide therapy. Given these advantages, this agent has the potential to become the preferred molecular imaging modality for pediatric patients with neuroblastoma.

Another promising PET/CT tracer currently under investigation is the PET analogue of mIBG, ^{18}F-mFBG (meta-fluorobenzylguanidine). This compound has proven to be safe with a

favorable biodistribution, kinetics and an adequate lesion detection capacity [33].

Lymphomas

Hodgkin's lymphoma

Pediatric Hodgkin's Lymphoma (HL) occurs more frequently in adolescents rather than children mostly as nodular sclerosing HL [34]. Staging is carried out by using the Ann Harbour classification with Cotswold modifications [35], and is of crucial importance as it defines the correct treatment for each stage (Stage I involves a single group of nodes in one location, Stage II involves two regions of nodes on the same side of the diaphragm, Stage III includes nodal areas on both sides of the diaphragm, and Stage IV involves solid organs such as lung, bone or liver) [34]. ^{18}F-FDG PET/CT is systematically used not only for initial staging of HL but also for therapy response assessment [36]. Indeed, on one hand patients with negative FDG PET defined during response assessment have an excellent prognosis, on the other hand a positive FDG PET in early and late chemotherapy response assessment is not able to accurately predict HL relapse [37]. The visual interpretation of treatment response is carried out through the Deauville criteria which consists in a 5-point scale comprehending no uptake above surround background, less uptake than mediastinal blood pool, more uptake than mediastinal blood pool but less uptake than liver, moderately increased uptake compared to liver and markedly increased uptake compared to liver [38]. This method has been proven to be reproducible and easily applicable in interim evaluation [39].

In 2014 the Lugano classification incorporated the Deauville visual scale eliminating potential ambiguities. These criteria are used in diagnosis, staging, assessment of response and surveillance of patients with HL and NHL. The Lugano classification also recommends the use of FDG PET/CT in those cases of FDG avid lymphomas preferring CT in non-avid histologies [40].

The introduction of immunotherapy for HL led in 2016 to a revision of the Lugano criteria for therapy response assessment, the lymphoma Response to Immunomodulatory therapy Criteria (LYRIC). The most important modification between the LYRIC and the Lugano criteria is the introduction of a new category i.e. the Indeterminate Response. This addition comprehends inflammatory infiltrates and potential flare or pseudoprogression which can often occur during treatment with immunomodulatory agents and that could be confused with disease progression [41].

Recently a new modality for the interpretation of treatment response has been proposed. The PET Response Criteria in Solid Tumors (PERCIST) unlike the criteria described above permits a quantitative evaluation of therapy response assessment using the SUVpeak which is the average maximum SUV in four voxels, involving the maximum SUV voxel and three highest adjacent voxels [42].

Non-Hodgkin's lymphoma

Non-Hodgkin's Lymphoma (NHL) is uncommon in children and thus less investigated [34]. The most frequent subtypes in pediatric patients are represented by high grade lymphomas (with frequent extranodal involvement) of B-cell origins such as Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma [43], while the incidence of low grade subtypes increases with age. Attention must be paid when considering T-cell derived lymphomas as their behavior is similar to the one of leukaemia [44].

Recently a revised classification of NHL has been proposed next to the St. Jude classification, i.e. International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) (Stage I includes a single site, nodal or extranodal, but also designates whether there is skin or bone involved; Stage II includes multiorgan involvement irrespective of position relative to diaphragm; Stage III includes two or more extranodal sites irrespective of position relative to diaphragm, designation as to skin, bone, lymph node, ovary or kidney involvement, and intrathoracic and spinal tumor; Stage IV includes any of the previous sites with CNS or bone marrow disease and is dependent on their method of confirmation) [45]. However, this revised classification does not specifically address PET/CT as a more useful imaging modality when compared to CT or MRI.

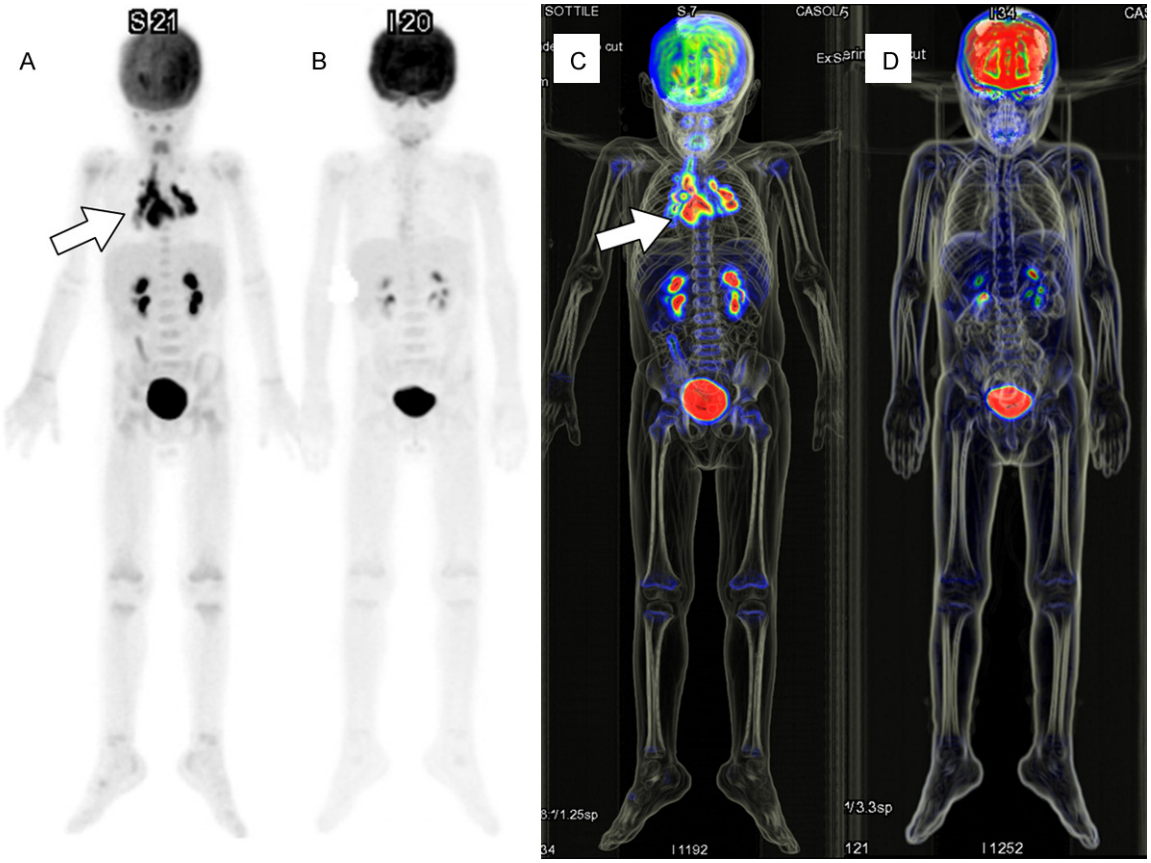

Figure 5. Therapy monitoring in 6-year-old patient with Non-Hodgkin Lymphoma. FDG PET maximum intensity projection image (A) and Volume Rendering (C) show high FDG uptake in mediastinal lymph nodes (arrowheads); no more activity in the post-therapy study (B and D).

Large trials are currently lacking given the rarity of these malignancies. Moreover, several studies in literature included not only NHL but also patients with HL making it more difficult to accurately assess the role and the importance of PET/CT in these neoplasms (**Figure 5**). For example, it is still controversial whether the use of PET/CT at interim could predict overall survival or progression-free survival [46]. Nevertheless, several centers choose to include the use of PET/CT in NHL.

Discussion

When the clinician finds himself dealing with a pediatric patient, he must face several issues. One of those issues is choosing the best diagnostic tool for these patients. The clinician should consider not only costs, invasiveness, diagnostic value but also radiation exposure and the necessity of general anesthesia that could cause neurotoxicity [47]. When using ionizing radiation for diagnosis, staging and follow-up of oncologic diseases in particular with PET/CT, extreme caution must be used considering that the most significant contribution to radiation exposure derives from the use of CT even if the administered dose is lower than adults. In fact, the radiation exposure must be justified by an actual long-term benefit [48]. It' well known that children's organs and tissues are more sensitive if compared to an adult's radiosensitivity. Moreover, children are subjected to a longer post-exposure life expectancy and consequently have a higher probability of showing post-exposure adverse effects [2]. Even if not widely available PET/MRI represents a valid alternative to PET/CT especially for brain and soft tissues malignancies. One of its advantages is the reduction of radiation exposure given by the CT component. The use of MRI has been assessed in neoplasms such as HL, sarcoma, neuroendocrine tumors and primary CNS tumors [49]. Using PET/MRI as the hybrid modality of choice could not only reduce the amount of ionizing radiations in pediatric patients, but

Table 1. Summary of the most relevant PET/CT tracers used in pediatric oncology

RADIOTRACER	PATHOLOGIES	LAST 5 YEARS PUB-MED CITATIONS	NOTES
^{18}F-FDG	Brain tumors, bone and soft tissue malignancies, neuroblastoma, NL and NHL	89	High sensibility, low cost, widely available but aspecific
^{18}F-FDOPA	Brain tumors	9	Useful in differentiation between scar and recurrent malignancy
^{11}C-MET ^{18}F-FET	Brain tumors, bone and soft tissue malignancies, head and neck lymphoma	2	Need for an in-site cyclotrone for ^{11}C-compounds, small number of pediatric studies for aminoacidic tracers
^{68}Ga-DOTA-NOC/TOC/TATE	Neuroblastoma, neuroendocrine tumors	4	High cost due to the need for ^{68}Ge-^{68}Ga generator. Potential pre-treatment evaluation with ^{90}Y/^{177}Lu-peptides
^{18}F-Galacto-RGD ^{18}F-FLT	Bone and soft tissue malignancies	1	Need for more validation studies
^{18}F-fluoride	Bone lesions	2	Useful in detecting metastatic bone lesions

also decrease the necessity for general anesthesia, giving greater anatomic, and functional/molecular information in a single imaging session.

As explained above several tracers are available, each one with its inherent strengths and weakness (**Table 1**).

A few of these tracers are more specific for certain kind of malignancies than others. The high number of radiotracers available for the management of brain lesions is both a precious resource and a potential confusing element for the clinician.

FDG PET has been and is widely used to detect brain tumors. A meta-analysis of 2014 revealed that FDG PET was able to identify malignant brain lesions with a sensitivity of 71% and a specificity of 77% [50]. Sensitivity increases up to 94% when considering high-grade gliomas [51]. The main limit of FDG is not only the physiological uptake in normal brain tissues but also the uptake in various non-malignant intracerebral lesions (for example inflammatory or infectious diseases) resulting in a not always easy distinction between the two conditions [52]. An important milestone has been achieved with the development of aminoacidic radiotracers. The most used are represented by ^{11}C-MET, ^{18}F-DOPA and ^{18}F-FET PET. ^{11}C-MET showed low uptake in healthy brain tissues and increased uptake in brain malignancies with optimal contrast [6]. Moreover, a meta-analysis confirmed its optimal performance in brain lesions differentiation [50]. When compared to FDG, MET PET is more suitable in diagnosing brain tumor especially if low-grade gliomas [52].

Although MET PET is a very used and sensitive aminoacidic tracer in malignant brain lesions imaging a potential pitfall is represented by its uptake in benign lesions [53]. As already explained the main limit of ^{11}C-labeled tracers is their short half-life, requiring the presence of a cyclotron [8]. Therefore, the necessity of using tracers with longer half-life, i.e. ^{18}F-labeled aminoacidic tracers FET and FDOPA.

In a metanalysis of 2015, Dunet compared the diagnostic value of ^{18}F-FET PET with the one of ^{18}F-FDG in brain malignancies [54]. This metanalysis revealed that FET PET was superior than FDG in diagnosing and assessing a brain lesion of recent discover. Both tracers shared similar performances in grading gliomas.

Another valid aminoacidic tracer is ^{18}F-DOPA which showed an accumulation independent from tumor grading. This feature gives this radiotracer a diagnostic accuracy higher than ^{18}F-FDG [10]. Moreover, a recent study proved that ^{18}F-FDOPA is a valuable tool when evaluating brain tumor recurrence, either glioblastoma or brain metastases [55]. Regardless of radiotracer used, PET is being increasingly used to supplement MRI in the clinical management of pediatric brain tumors [56].

PET imaging could have an important role to evaluate the response to therapy, distinguish recurrence of high-grade neoplasm from radiation effects or in in clinical trials of new strategies for the treatment of glioma, e.g. immunotherapy, where pseudoprogression is particularly challenging for MRI [57]. In these contexts combined PET/MR imaging could provide information about tumor biology, help direct biopsy,

surgery, or radiation therapy planning via precise anatomic delineation and accurate localization of viable tumor volume [58].

Both ^{18}F-FDG and MR imaging are valuable in staging, restaging, and therapy response assessment for musculoskeletal malignancies and soft tissue sarcomas. Although combined PET/MR imaging likely does not increase the diagnostic accuracy of primary tumor staging over MR imaging alone, the staging of nodal and distant metastases could benefit from the combination. The PET component could also help guide biopsies. A significant disadvantage of PET/MR imaging, however, is the limitation in detecting small pulmonary nodules, being the lung a common site of metastases for bone sarcomas. Therefore, a continued dedicated evaluation of the lungs by CT is recommended [59].

New promising tracers are under investigation such as ^{18}F-galacto-RGD, ^{18}F-fluorodeoxythymidine (FLT), ^{18}F-fluoride, ^{11}C-methionine (MET) or ^{18}F-fluoroethyltyrosine (FET).

^{18}F-galacto-RGD is a biomarker of neoangiogenesis still under investigation [60].

^{18}F-FLT accumulation depends on Tyrosine Kinase 1 high activity which correlates with cellular proliferation. A potential limitation in ^{18}F-FLT is the fact that it accumulates in replicating cells such as activated lymphocytes that require high level of thymidine [61]. However, ^{18}F-FLT could be used to overcome a flaw of ^{18}F-FDG, i.e. its accumulation in benign lesions [62]. ^{18}F-fluoride is used for the evaluation of both sclerotic and lytic metastatic bone lesions [63]. The lower background activity and the spatial resolution of PET/CT make this radiotracer an excellent alternative to ^{99}mTc-MDP.

Radiolabeled somatostatin analogues, i.e. DOTA-conjugated peptides, have gained more and more space in the diagnosis of neuroendocrine tumors in the adult population and in the management of neuroblastoma in children.

Additionally, these tracers can be used for treatment when bound with ^{90}Y and ^{177}Lu. Although ^{18}F-FDG is easily accessible in most of the centers with a PET/CT, ^{68}Ga conjugated compounds offer an advantage in terms of radiation exposure in children with neuroblastoma [64].

Moreover, a meta-analysis from 2018 compared the diagnostic rate of ^{68}Ga-DOTA-SST with the one of ^{18}F-DOPA, ^{18}F-FDG, and $^{123/131}$I-mIBG in pheochromocytomas and paragangliomas [65]. Even though more specific studies are necessary for neuroblastoma, the high detection rate of ^{68}Ga-DOTA-SST added to the more favorable dosimetry for pediatric population might suggest the greater utility of ^{68}Ga-compounds in this type of malignancies instead of ^{18}F-FDG.

Regarding HL AND NHL ^{18}F-FDG is still the most used radiotracer for diagnosis, staging, ad interim evaluation and follow-up. A viable and validated alternative is yet to be identified.

A study from 2017 compared the diagnostic accuracy of ^{11}C-Methionine and ^{18}F-FDG PET/CT in patients with lymphoma. Although ^{11}C-Methionine optimally individuated tumor sites in the head and neck, physiological uptake in abdominal healthy structures could represent an important limit to this tracer in HL and NHL [66].

Conclusion

The use and the importance of PET/CT in staging, re-evaluation and therapy planning in pediatric oncology is increasing exponentially thanks to the growing availability of ^{18}F-FDG PET/CT and to the development of more specific radiotracers. The role of the nuclear medicine physician is to assist the oncologist in choosing the best tracer for the patient as well as collaborate in order to determine the best time to perform a PET/CT to limit the exposure to ionizing radiations to the minimum necessary for pediatric patients. The most important need for the future is represented by larger studies in order to provide an even more standardized and proven methodology in this specific group of patients.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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