123Iodine-metaiodobenzylguanidine (123I-MIBG) scintigraphy is currently the tracer of choice for neuroblastoma (NB). It has high diagnostic accuracy and prognostic value for the assessment of patients after chemotherapy. A positive 123I-MIBG scan is also used for the basis of targeted radionuclide therapy with 131I-MIBG. 1-123 MIBG scan however has some limitations which should be taken into account. Moreover the reasons for false negative MIBG results have not been entirely elucidated. Meticulous correlation with radiological examinations and recognition of the normal distribution pattern of 123I-MIBG in children is vital to obtain optimal results. With its technical superiorsities, positron emission tomography/computed tomography (PET/CT) can be successfully introduced into the diagnostic worlkup of NB. Different PET tracers have been offered for imaging in patients with NB, and the efficacy of this modality has been compared with that of 123I-MIBG scan. Our review aims to analyze the present role of PET/CT imaging and radiopharmaceuticals in NB.

**Key Words:** Positron-emission tomography and computed tomography - Neuroblastoma - 1-Iodobenzylguanidine

Functional imaging with 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy plays an important role in the assessment of neuroblastoma (NB) for initial diagnosis, staging, restaging, recurrence detection and assessment. Thus, 123I-MIBG has been recognized as the radiopharmaceutical of choice in NB assessment and has been widely used in clinical practice for the past 25 years. Moreover, the presence of a positive 123I-MIBG scan establishes the basis for the use of a targeted radionuclide therapy with 131I-MIBG. This technique however requires in most cases adequate correlation with radiological examinations, such as computed tomography (CT) and magnetic resonance imaging (MRI), and necessitates precautions with image acquisition and patient preparation. Moreover, great variability in tumor tracer uptake has been reported, and the reasons for false negative results have not been entirely elucidated yet, although several explanations have been suggested. A further issue concerns the pitfalls in interpretation of images and recognition of the normal distribution pattern of 123I-MIBG in children, which is often conditioned by the low quality of 123I-MIBG-scintigraphy in these patients, especially in infants. SPECT is used as a potentially useful to overcome these diagnostic limits. However, fusing or co-registration of CT and MRI may bring convenience to image interpretation and increase sensitivity by providing precise anatomical localization.

PET/CT is now an established imaging modality
in many adult cancer types. However, their clinical role in pediatric malignancy is less thoroughly investigated. In recent years, different types of PET tracers have been used in NB, and compared with $^{123}$I-MIBG. Our review aims to analyze the present status of PET radiopharmaceuticals in children with NB.

$^{18}$F-FDG-PET-CT

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), similar to glucose, is transported to within the cells via the GLUT (glucose transporters) and intracellularly phosphorylated by hexokinase (HK) into glucose-6-phosphate and $^{18}$F-FDG-6 phosphate, respectively (Figure 1). In contrast to the downstream pathway of glucose, $^{18}$F-FDG-6 phosphate cannot be dephosphorylated, and further metabolized in the glycolytic process, and because of its reduced permeability across the cell membrane, $^{18}$F-FDG-6 phosphate is entrapped, and steadily accumulates in metabolically active cells. Like for other malignancies, $^{18}$F-FDG can be used for imaging NB in diagnostic and therapeutic management. Currently, there is no evidence to

![Figure 1](image-url)
support the use of F-18 FDG PET/CT in the initial diagnosis.

Staging

Two pilot studies have demonstrated that 18F-FDG-PET-CT can be used for staging in NB. Specifically, it was found that 18F-FDG-PET depicted disease sites in stage 1 and 2 NB better than 123I-MIBG, and detected more sites of primary tumors or loco-regional metastases. Moreover, 18F-FDG PET/CT better identified sites of disease in stages 3 and 4 when tumors did not accumulate 123I-MIBG or did so only weakly. In particular, 18F-FDG-PET/CT could provide important information about disease extent in the chest, abdomen and pelvis, and should be used when CT or MRI seem to show more extensive disease than that revealed by 123I-MIBG scan.

On the other hand, 123I-MIBG appears to be superior to 18F-FDG-PET/CT in the evaluation of stage 4 NB, due to its better detection of metastases in bone and bone marrow, which are the most frequent sites of disease progression. This situation may arise during the initial chemotherapy or under granulocyte colony-stimulating factor, when bone marrow FDG uptake may mask or mimic metastatic disease, thus reducing the sensitivity of 18F-FDG-PET techniques. Another limiting feature of 18F-FDG-PET/CT is the normal high uptake of FDG in the brain, which makes this technique less effective for imaging cranial vault lesions. Accordingly, Taggart et al. reported that MIBG imaging was significantly more sensitive than 18F-FDG-PET imaging in detecting bone lesions, both in entire skeleton and in the cranial vault.

Detection of persistent and recurrent diseases

Two studies have compared 123I-MIBG and 18F-FDG PET/CT in high-risk NB patients in the detection of persistent or recurrent disease after induction or consolidation therapy. At this stage of disease, 123I-MIBG proved superior to 18F-FDG in depicting the bone-marrow component of disease. Another Achilles' heel of 18F-FDG was that PET resulted inferior in detecting skull lesions, unless they displayed a considerable soft tissue component; this drawback was mainly due to the adjacent high physiologic 18F-FDG activity in the brain cortex as explained above. In these particular cohorts, the concordance rate for individual lesions between the two different imaging techniques was reported to be low (39.6%), the main sites of discrepancy being in bone and bone marrow lesions. This is a critical point in relapsing patients, because soft tissue involvement is expected to be low and bone and bone-marrow disease results more prevalent. However, given the fact that 18F-FDG can identify disease in 123I-MIBG-negative lesions, it might serve as a complementary imaging modality in selected patients. In this setting, 18F-FDG was able to detect soft tissue disease not seen on 123I-MIBG imaging, even in patients who had 123I-MIBG positive lesions in different sites. Although it has been hypothesized that 18F-FDG might be better in detecting liver lesions, on account of the physiologic uptake of 123I-MIBG by liver, this hypothesis was not confirmed by others.

Follow-up

There are some difficulties involved in detecting lesions during follow-up of NB. There are reports of lesions that had been 123I-MIBG-positive at the initial diagnosis, which became negative when the disease relapsed or vice versa (negative at initial diagnosis, positive when relapsed). Concerning this issue, a potential role of 18F-FDG PET/CT emerges from a paper by Kushner et al. These authors correctly report that 18F-FDG PET, despite its superiority to 123I-MIBG in detecting soft-tissue metastases, cannot replace morphological imaging modalities. CT and MRI remain mandatory, in order to better delineate masses, especially before surgery, and 123I-MIBG is needed because 18F-FDG PET/CT can miss cranial vault lesions. These authors suggest that, in the absence of cranial vault disease, 18F-FDG PET and bone-marrow biopsy might be sufficient for follow-up. However, sufficient data to support this conclusion are yet unavailable, and in the follow-up, it is prudent to repeat 123I-MIBG scans in patients deemed to be at high risk of relapse, especially those with previous cranial bone involvement.

It was demonstrated by Melzer et al. that 18F-FDG imaging is helpful during follow-up when 123I-MIBG scan/SPECT yield discrepant/inconclusive findings. In this particular setting, the sensitivity values of 123I-MIBG scintigraphy and 18F-FDG-PET were 50% and 78%, respectively, and their specificity values were 75% and 92%, respectively. The standard of reference in their study was based on
histological confirmation and clinical follow-up. Interestingly, there was no correlation between tumor size and false-negative results on $^{123I}$-MBG scintigraphy and $^{18}$F-FDG scan. In false-negative findings, the mean lesion diameter was 1.7 cm on $^{123I}$-MBG scintigraphy and 1.6 cm on $^{18}$F-FDG PET/CT. This finding confirms how the two different tracer uptake mechanisms influence the diagnostic accuracy, independently from the spatial resolution of PET and SPECT imaging.

$^{18}$F-FDG PET/CT has also been recommended during follow-up as an additional imaging modality in the event of discrepancies between $^{123I}$-MBG scan and morphological imaging.\(^{20}\)

Cola volpe et al.\(^{17}\) reported one case of metastatic NB detected by $^{123I}$-MBG scintigraphy at the time of initial diagnosis, which became $^{123I}$-MBG-negative on follow-up examination after repeated cycles of chemotherapy. $^{18}$F-FDG PET was performed in a patient with persistent bone pain and increased urinary catecholamines despite a negative $^{123I}$-MBG, and multiple hypermetabolic osteo-endothelial metastases were detected. Although tumor de-differentiation has been postulated as the cause of discrepancy, comparative histological analysis of the initial and relapsing NB did not show any difference. Cola volpe's case demonstrates that it is not entirely clear why and when some NB do not have or lose over time the $^{123I}$-MBG avidity. Consequently, it remains difficult to predict the usefulness of $^{18}$F-FDG PET in NB a priori.

**Treatment response**

$^{18}$F-FDG PET/CT imaging is able to monitor treatment response, especially in patients with $^{123I}$-MBG-negative tumors.\(^{21}\) In this setting, it has been demonstrated that the majority of NB are able to concentrate $^{18}$F-FDG both before and after cyto-reductive therapy.\(^{30}\) Kushner et al. reported that $^{18}$F-FDG PET/CT findings correlated well with disease status, and were able to properly define treatment effects and disease evolution.\(^{19}\) $^{123I}$-MBG scintigraphy is however more sensitive than $^{18}$F-FDG PET/CT in assessing the response to $^{123I}$-MBG therapy in patients with relapsed NB.\(^{14}\) On the other hand, $^{18}$F-FDG-PET/CT displayed greater sensitivity than $^{123I}$-MBG in detecting soft tissue lesions, and it was reported that $^{18}$F-FDG-PET/CT becomes negative more often than $^{123I}$-MBG scans after treatment.\(^{12}\) The principal limitation of $^{18}$F-FDG PET/CT remains the non-specific bone-marrow uptake during chemotherapy or administration of granulocyte-stimulating factor. This problem can be avoided by scheduling $^{18}$F-FDG PET just before the scheduled course of chemotherapy.

It is important to determine the prognostic implications of $^{123I}$-MBG-positive residual NB tumors. If $^{18}$F-FDG PET/CT is negative but $^{123I}$-MBG scan is still positive, biopsy might confirm whether the tumor has matured or has only been temporarily stunted in terms of metabolic activity.\(^{12}\) The combined use of $^{18}$F-FDG PET/CT and $^{123I}$-MBG scintigraphy might better depict residual disease in this clinical scenario, and thus adding important information, especially before stem cell transplantation.

**Prognosis**

Beyond disease detection, $^{18}$F-FDG PET/CT has significant prognostic implications in high-risk NB undergoing $^{131I}$-MBG therapy. Increased tumor metabolic activity, expressed by $\text{SUV}_{\text{max}}$, and the presence of extensive $^{18}$F-FDG-avid metastases have been identified as poor prognostic factors associated with decreased survival.\(^{13}\) In a study by Papathanasiou et al.,\(^{13}\) a pattern of increased $^{18}$F-FDG activity, exceeding the tumor avidity for $^{123I}$-MBG, corresponded to more aggressive disease and worse outcome.\(^{13}\) It is unknown whether this pattern may reflect NB cell de-differentiation. There is a need for a preclinical study in order to determine whether there is a specific pattern for unfavorable histology in association with neuroblast dedifferentiation that shows increased $^{18}$F-FDG activity and decreased MBG uptake.

Larger prospective studies are needed to show whether, $^{18}$F-FDG PET/CT can be used as a prognostic tool in correlation with survival.

**$^{68}$Ga-DOTA-TOC PET/CT**

Five different types of somatostatin receptors (SSTR) have been discovered so far and radiolabelled somatostatin analogs have been introduced as an imaging agent for neuroendocrine tumors in the last decade, starting with $^{123I}$-Tyr3-octreotide and 111In-pentetreotide.\(^{22}\) Somatostatin derivatives bind to SST1, like the hormone itself, and after binding to the receptor, they are internalized via endocytosis in endosomes/lysosomes (Figure 1). The tracer
is entrapped in this way, and after its release from the binding complex, the receptor is utilized for further signaling.25

Like other neuroendocrine tumors, NB can be also characterized by an over-expression of somatostatin receptors, more precisely SSTR types 1 and 2.24, 25 For this reason, 111In-pentetretide scintigraphy or somatostatin receptor scintigraphy (SRS) have been investigated in the past for the assessment of NB,26, 27 and the same concept has been readopted recently with the PET technology. SRS was not however proven to be superior to 123I-MIBG, and SRS has been accepted as a complementary method instead of a real substitute of 123I-MIBG scintigraphy. Nevertheless, it provides some prognostic information and could identify cases with different metabolic behavior. Indeed, it appears that a positive SRS can be predictive of a better outcome in patients with NB.26, 27

Recently, the rationale of SSTR expression in NB has been taken into account for the development of new potentially promising PET tracers in NB imaging, such as 68Ga-DOTA-TOC.28 In a small patient cohort (N=11), Kroiss et al. compared the accuracy of 123I-MIBG scintigraphy with that of 68Ga-DOTA-TOC-PET/CT in the diagnosis and staging of metastatic phaeochromocytoma and NB, taking CT and MRI as the reference standard. On per-lesion analysis, the sensitivity of 68Ga-DOTA-TOC PET/CT for NB was 97.2%, while that of 123I-MIBG was 90.7%. Moreover, the primary lesion was better definable on 68Ga-DOTA-TOC PET/CT than 123I-MIBG imaging which has higher background activity. These observations are relevant, considering that a positive 68Ga-DOTA-TOC-PET may well imply a further important therapeutic opportunity and, in particular, enables the selection of patients who can be candidates for therapy with radiolabelled somatostatin analogs.28

In the concept of theragnostics, recently the feasibility and safety of radiolabelled peptide based therapy in children has been reported.29 In their study, Gains et al. used 68Ga-DOTA-TATE-PET/CT for diagnosing the presence of disease and and 177-Lu-DOTA-TATE for therapy in eight patients with relapsed or refractory NB. Since there is already an established therapy method (1-131 MIBG) for NB, more comprehensive studies are needed to thoroughly assess and delineate the inclusion criteria before this new peptide based imaging-therapy model is adopted to clinical practice.

18F-DOPA-PET/CT

Although the results reported so far seem to be promising, none of the tracers discussed so far can probably be considered a real substitute for 123I-MIBG, but rather a diagnostic complement at this stage. The principal limitations of 18F-FDG and 68Ga-DOTA-peptides are probably related to the uptake mechanism, which is not disease specific and does not reflect the catecholamine metabolism of NB.

18F-dihydroxyphenylalanine (18F-DOPA) is probably a better PET alternative to 123I-MIBG in this respect, thanks to its ability, like 123I-MIBG to follow the metabolism of catecholamines. From the functional point of view, NB is characterized by an increased metabolism of catecholamines, which determines its ability to produce biologically active hormones such as norepinephrine and some of its precursors, such as DOPA and dopamine.30, 31 18F-DOPA is the formulation of radiolabelled dihydroxyphenylalanine, a direct precursor of dopamine (Figure 1). It is a multivalent molecule which is widely used for functional imaging of various neuroendocrine tumors.32-36 18F-DOPA PET/CT has been shown to have greater diagnostic accuracy than 123I-MIBG scintigraphy and other conventional imaging modalities, such as CT and MRI, in the study of tumors with high excretion of catecholamines.37-40 Indeed, the reported sensitivity of 18F-DOPA PET/CT is 90%, in comparison, the corresponding figures are 65% and 67% for 123I-MIBG and CT/MRI, respectively.10

On this basis, some pilot studies have been conducted to investigate the role of 18F-DOPA in NB patients. In a small cohort of relapsed high-risk NB patients (N=19), it was found that primary/residual tumor and all metastases were characterized by a specific 18F-DOPA uptake and that a pathological distribution of this PET tracer was similar to that of 123I-MIBG.41 All 123I-MIBG-positive metastases were well detected by 18F-DOPA PET/CT, thus confirming a common catecholamine pathway target for these two PET tracer. Moreover, 18F-DOPA-PET/CT displayed higher overall accuracy than 123I-MIBG scintigraphy; in particular, a higher sensitivity was found in case of small (≤1 cm) soft-tissue metastases (Figure 3), and the high DOPA avidity of bone/bone-marrow metastases was ascertained. No false-positive DOPA bone-marrow uptake was observed after chemotherapy, as has been described for FDG. No false-negative DOPA results regarding cranial vault localizations were reported (Figure 4). In our
own study, the overall accuracy of $^{18}$F-DOPA-PET/CT influenced patient management and treatment decisions in 32% of NB patients.\textsuperscript{41}

More recently, we compared the accuracy of $^{18}$F-DOPA-PET/CT with CT and MRI: $^{18}$F-DOPA PET performed significantly better than CT/MRI in NB and displayed an overall higher diagnostic accuracy on lesion-based analysis.\textsuperscript{42} When different sites of disease were studied, the authors found similar sensitivity values for PET/CT and CT/MRI in the case of primary location. The main discrepancies between the paired scans were found in liver lesions (with CT/MRI being significantly superior to $^{18}$F-DOPA-PET/CT) and in bone/bone-marrow, nodal and soft-tissue involvement. In these latter cases, $^{18}$F-DOPA-PET/CT performed significantly better than morphologic imaging.\textsuperscript{42}

Moreover, in recent report\textsuperscript{43} comparing $^{18}$F-DOPA-PET/CT, $^{123}$I-MIBG scan and post-therapy $^{131}$I-MIBG in a six-year-old child with multiple nodal, bone and bone-marrow metastases from NB has indicated that $^{18}$F-DOPA-PET/CT showed better delineation of the primary lesion. As compared to $^{123}$I-MIBG scan, additional sites were detected $^{18}$F-DOPA-PET/CT which corresponded to true sites of disease, as confirmed by post-therapy $^{131}$I-MIBG, which is considered to be the most sensitive method of evaluating NB extension.\textsuperscript{7} They show the same pathological distribution of both soft-tissue and bone/bone-marrow metastases. This report also suggests that the uptake mechanisms of DOPA and MIBG are similar. This result may imply a further important therapeutic opportunity in the selection of patients for $^{131}$I-MIBG therapy that could be scheduled on the basis of $^{18}$F-DOPA-PET/CT.

$^{18}$F-DOPA may therefore be the potential PET
alternative to $^{123}$I-MIBG scan. It relies on the metabolism of catecholamines, but offers the advantage of significantly better performance due to PET technology. However, the preliminary data reported were obtained in limited cohorts consisting mostly of relapsed/refractory patients. Other prospective multicenter studies are required in order to investigate the diagnostic and prognostic role of $^{18}$F-DOPA-PET/CT in NB.

$^{11}$C-Hydroxyephedrine PET/CT

$^{11}$C-Hydroxyephedrine (HED), a catecholamine analog whose uptake reflects catecholamine transport (Figure 1), storage and recycling is a PET tracer developed to image the sympathetic nervous system. and utilized both for the assessment of myocardial innervation and for imaging neuroendocrine tumors, like phaeochromocytoma and NB. Shulkin et al. first investigated the feasibility and potential utility of $^{11}$C-HED PET in localizing NB. The authors reported that HED was promptly accumulated and well-retained by NB. In all 7 patients investigated, HED was able to detect NB foci. In particular, in comparison with $^{123}$I-MIBG, which requires at least 18-24 hours to achieve tumor-to-nontumor ratios adequate for imaging, the early HED tumor uptake is relatively high, and thus the NB is visualized within minutes. In addition, whole-body exposure...
to radiation, and especially thyroid exposure is considerably lower on $^{11}$C-HED PET than on $^{123}$I-MIBG. A drawback reported by these authors, however, was that hepatic and renal uptake were prominent, and liver uptake often exceeded tumor concentration. Moreover, HED uptake proved higher than that of FDG in one pelvic MIBG-positive metastasis, and C-11 HED PET/CT detected metastases in the skull that had not been visualized by MIBG scan.17

More recently, Franzius et al.18 compared C-11-HED PET/CT with $^{123}$I-MIBG SPECT/CT in tumors of the sympathetic nervous system. With regard to NB, they found that both tracers were able to detect NB localizations with high sensitivity (96% and 100%, respectively). However, in one patient, C-11-HED PET/CT missed a large abdominal recurrence, which was confirmed on histopathology. Moreover, MIBG uptake proved to be more intense than HED uptake in 10 out of 14 soft-tissue metastases.

Despite the higher spatial resolution of PET, C-11-HED PET/CT has some disadvantages and limitations in comparison with $^{123}$I-MIBG scan. Given the high renal excretion of the tracer during imaging, tumor localization close to the kidney and ureters may be missed by C-11-HED PET/CT. Moreover, the high physiologic liver uptake may hinder the detection of small liver metastases.48 Finally, another important limitation is related to the short half-life of $^{11}$C, which requires an on-site cyclotron and a rigid time schedule.

$^{123}$I-MIBG

Iodine-124 is an emerging radionuclide for PET imaging neuroendocrine tumors, and its radiolabelled variant as $^{123}$I-MIBG currently offers a good option for pre-therapy dosimetry.49 To the best of authors' knowledge, no clinical studies on the diagnostic role of $^{123}$I-MIBG PET/CT in NB are currently available, but the tracer this represents several advantages in terms of image quantification, radionuclide characteristics ($^{123}$I half-life of 4.2 days, i.e. more similar to the 8.02-day half-life of $^{131}$I) and whole-body PET acquisition,50 that can be exploited for both diagnostic imaging and dosimetry.

In the clinical setting, $^{123}$I-MIBG has been used for dosimetric purposes since the early 1990s.51-54 Lee et al.50 reported that $^{123}$I-MIBG is significantly more advantageous than other $^{124}$I compounds, especially $^{124}$I-NaI, and that the estimated effective dose (ED) of $^{123}$I-MIBG is more than ten times lower than that of $^{123}$I-NaI (0.25 mSv/MBq radiation dose estimated for $^{123}$I-MIBG, versus 6.5 mSv/MBq for $^{123}$I-NaI). However, these ED values are tenfold higher than those obtained with $^{123}$I-MIBG (0.019 mSv/MBq).50
and become significant relevance in the paediatric population, when $^{123}$I-MIBG PET is used for diagnostic purposes. Thus, the authors recommend administering low doses, especially in small children, and that the best indication for $^{123}$I-MIBG PET is pre-therapy dosimetric study before $^{123}$I-MIBG treatment. 

Another issue to be implemented is related to the acquisition protocol. The decay scheme of $^{123}$I also contains gamma rays, 50% of which are emitted simultaneously with the positrons, thus resulting in a possible spurious coincidence with the annihilation photons. $^{53, 54}$ Unfortunately, these coincidences cannot be distinguished from true coincidences, especially if 3-D acquisition is used. The result can be a somewhat degraded spatial resolution of $^{123}$I-PET in comparison with $^{18}F$ PET. $^{55}$ In modern PET/CT scanners, spatial resolution is significantly better and part of limitations due to decreased image quality can be overcome. Moreover, the disadvantage of reduced activities, can be simply solved by prolonging bed time acquisition, which in new machines doesn’t affect significantly the overall scanning time.

More extensive investigation of $^{123}$I-MIBG is mandatory before concluding on definite use of the tracer in NB patients, because the studies carried out so far have been conducted only on animals or on a limited cohorts of human adults with NTS. $^{50, 51, 55}$

**Conclusions**

$^{123}$I-MIBG is still the tracer of choice for NB with its high diagnostic accuracy which is further improved by the introduction of SPECT/CT, and its ability to reveal important prognostic value at the end of chemotherapy, and its use as an in vivo model for $^{123}$I-MIBG therapy. $^{18}F$-FDG PET/CT may be considered an important diagnostic complement to $^{123}$I-MIBG in selected patients with negative or inconclusive $^{123}$I-MIBG scan. $^{65}$DA-DOTA-TOC PET/CT may play a role in selecting patients for therapy with radio labelled somatostatin analogs. $^{65}$DA-DOTA-TOC PET/CT may play a role in selecting patients for therapy with radio labelled somatostatin analogs. $^{65}$

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