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ORIGINAL ARTICLE

Comparison of ^{18}F-dopa PET/CT and ^{123}I-MIBG scintigraphy in stage 3 and 4 neuroblastoma: a pilot study

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Abstract
Purpose ^{18}F-Dopa positron emission tomography (PET)/CT has proved a valuable tool for the assessment of neuroendocrine tumours. So far no data are available on ^{18}F-dopa utilization in neuroblastoma (NB). Our aim was to evaluate the role of ^{18}F-dopa PET/CT in NB and compare its diagnostic value with that of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy in patients affected by stage 3–4 NB.
Methods We prospectively evaluated 28 paired ^{123}I-MIBG and ^{18}F-dopa PET/CT scans in 19 patients: 4 at the time of the NB diagnosis and 15 when NB relapse was suspected. For both imaging modalities we performed a scan-based and a lesion-based analysis and calculated sensitivity, specificity and accuracy. The standard of reference was based on clinical, imaging and histological data.
Results NB localizations were confirmed in 17 of 19 patients. ^{18}F-Dopa PET/CT and ^{123}I-MIBG scintigraphy properly detected disease in 16 (94%) and 11 (65%), respectively. On scan-based analysis, ^{18}F-dopa PET/CT showed a sensitivity and accuracy of 95 and 96%, respectively, while ^{123}I-MIBG scanning showed a sensitivity and accuracy of 68 and 64%, respectively ($p<0.05$). No significant difference in terms of specificity was found. In 9 of 28 paired scans (32%) PET/CT results influenced the patient management. We identified 156 NB localizations, 141 of which were correctly detected by ^{18}F-dopa PET/CT and 88 by MIBG. On lesion-based analysis, ^{18}F-dopa PET/CT showed a sensitivity and accuracy of 90% whereas ^{123}I-MIBG scintigraphy showed a sensitivity and accuracy of 56 and 57%, respectively ($p<0.001$). No significant difference in terms of specificity was found.
Conclusion In our NB population ^{18}F-dopa PET/CT displayed higher overall accuracy than ^{123}I-MIBG scintigraphy. Consequently, we suggest ^{18}F-dopa PET/CT as a new opportunity for NB assessment.

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Keywords ^{18}F-Dopa · PET/CT · ^{123}I-MIBG scintigraphy · Neuroblastoma

Introduction

Neuroblastoma (NB), an embryonic tumour of children that is derived from the peripheral sympathetic nervous system and is able to secrete catecholamines, is frequently metastatic on diagnosis, with a long-term survival of less than 40% [1].

Functional imaging plays an important role in the assessment of this type of neoplasm, from the initial diagnosis and staging to the evaluation of treatment response and detection of recurrent disease.

^{123}I-Metaiodobenzylguanidine (MIBG) has been recognized as the radiopharmaceutical of choice in NB assessment [2]. MIBG is a guanidine-like molecule similar to norepinephrine and is taken up by tissues of sympathetic medullary origin via the norepinephrine transporter. Once inside the cell, the tracer is accumulated in storage granules by the vesicular monoamine transporter (VMAT) types 1 and 2 [3]. The presence of these transporters is a prerequisite for functional imaging by means of ^{123}I-MIBG, and their lack is the main cause of false-negative scans. MIBG scintigraphy has been widely used for the past 25 years. However, this technique often requires adequate correlation with radiological examinations, especially in cases of doubtful uptake, and computed tomography (CT) or magnetic resonance (MR) are the best options for assessing disease extent at the primary tumour site [4].

In an effort to overcome this drawback, several pilot studies have demonstrated that ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT in NB can be used to detect primary/metastatic disease [5, 6] on staging and to monitor the response to treatment in patients with MIBG-negative tumours [7]. However, the implications of the information provided by ^{18}F-FDG PET/CT in disease staging and response evaluation have not yet been shown. In this field, the overall higher sensitivity of ^{123}I-MIBG imaging in comparison with ^{18}F-FDG, as reported by recent papers [8, 9], supports the preferential use of ^{123}I-MIBG scans for surveillance imaging in patients not receiving therapy and for response evaluation during therapy for relapse.

A metabolic imaging method that has not been described so far in NB is ^{18}F-dopa PET/CT. ^{18}F-3,4-dihydroxyphenylalanine (dopa) is the radiolabelled form of dopa, a direct precursor of dopamine and a precursor of catecholamines in general. NB cells, like those of other neuroendocrine tumours, retain the ability to accumulate and decarboxylate amine precursors, including dopa. This molecule is actively transported into cells through the transporter system of large neutral amino acids (LAT1) and then converted into dopamine by the enzyme amino acid decarboxylase (AADC) [10]. Subsequently, dopamine is stored within the intracellular vesicular storage system and converted into norepinephrine and epinephrine [11].

Promising diagnostic results in neuroendocrine tumours and pheochromocytomas have recently been reported for this imaging method [12–15]. ^{18}F-Dopa PET has been shown to have greater diagnostic accuracy than ^{123}I-MIBG scintigraphy or other conventional imaging modalities, including CT and MRI, in the study of catecholamine-secreting tumours [12, 16].

The aim of our study was to evaluate the role of ^{18}F-dopa PET/CT in NB and compare its diagnostic value with that of ^{123}I-MIBG scintigraphy in patients affected by stage 3–4 NB.

Materials and methods

We prospectively evaluated a total of 28 paired ^{123}I-MIBG and ^{18}F-dopa PET/CT scans in 19 consecutive patients with stage 3 and 4 NB [2]. Four patients underwent our protocol at the time of the first NB diagnosis and 15 when disease relapse was suspected on routine clinical and conventional radiological imaging during follow-up.

The Local Ethics Committee approved the study, and informed consent was obtained for all patients. The main characteristics of patients and tumours are summarized in Table 1. All patients with suspected recurrence of disease showed an MIBG-positive scan at the time of first NB diagnosis. No patient aged less than 1 year was included in our study.

Paired scans were obtained in fasting patients within 10 days of each other. Image acquisition was performed according to standard procedures: ^{123}I-MIBG scans were acquired 24 h after injection of tracer with an administered activity of 5.18 MBq/kg. Single proton emission computed tomography (SPECT) images, acquired at intervals of 24 h only, were available in 15 patients (Table 2).

The scan speed for whole-body imaging was 6 cm/min. The dual-head gamma scintillation camera was equipped with a low-energy high-resolution parallel-hole collimator. For SPECT acquisitions the following parameters were used: 64 projections, 128×128 matrix, 40s acquisition time per projection. SPECT data were reconstructed by standard filtered backprojection using a Butterworth filter.

Whole-body ^{18}F-dopa PET/CT was carried out 60 min after the injection of 210–370 MBq of tracer (4 MBq/kg) on an integrated PET/CT system (Discovery LS or STE, GE Medical Systems, Milwaukee, WI, USA). Whole-body ^{18}F-dopa PET acquisitions included six to ten bed positions (4-min emissions per bed position) and were reconstructed by

Table 1 Patient/tumour characteristics and therapeutic strategy at the time of ^{18}F-dopa PET/CT and ^{123}I-MIBG scintigraphy

Patient	Sex	Age (years)	Stage of disease, INNS	MYCN gene amplification (yes/no)	Clinical indication for scans	Sites of primary tumour	^{123}I-MIBG at the time of first NB diagnosis	Surgery for primary tumour (yes/no)	Systemic therapy (yes/no)	Therapeutic ^{131}I-MIBG (yes/no)	Bone marrow transplantation (yes/no)	Previous recurrence
1	M	4	4	Yes	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	Yes	No	No
2	M	4	4	No	Restaging	Thorax	Positive	Yes	Yes NB AR 01	No	No	No
3	M	9	4	No	Restaging	Abdomen	Positive	Yes	No	No	No	No
4	M	41	4	No	Restaging	Abdomen	Positive	Yes	Yes	No	No	Yes
5	M	7	4	No	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	No	Yes	Yes
6	M	30	4	Not available	Restaging	Abdomen	Not available	Yes	Yes	No	No	Yes
7	M	8	4	Doubtful	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	No	No	No
8	M	3	4	No	Staging	Abdomen	–	–	–	–	–	–
9	F	7	4	Yes	Staging	Abdomen	–	–	–	–	–	–
10	F	4	4	Yes	Staging	Abdomen	–	–	–	–	–	–
11	F	8	3	No	Restaging	Abdomen	Positive	Yes	No	No	No	No
12	M	9	4	No	Restaging	Abdomen	Positive	Yes	Yes NB 97	Yes	No	Yes
13	M	3	4	Yes	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	No	No	No
14	M	6	4	Not available	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	No	No	No
15	M	1	4	Yes	Staging	Abdomen	–	–	–	–	–	–
16	M	4	4	Yes	Restaging	Abdomen	Positive	Yes	Yes NB AR 01	No	No	No
17	M	8	3	No	Restaging	Thorax	Positive	No	NBL 99.1	No	No	No
18	M	6	4	Yes	Restaging	Abdomen	Positive	Yes	Yes NB AR 01 +TVD	No	No	Yes
19	F	9	4	No	Restaging	Thorax	Positive	No	NB unresectable	No	No	No

INSS International Neuroblastoma Staging System [2], *NB AR 01* chemotherapy protocol, *NB 97* chemotherapy protocol, *NBL 99.1* chemotherapy protocol, *TVD* topotecan, vincristine, doxorubicin: chemotherapy protocol

Table 2 Results of imaging studies in 28 paired ^{123}I-MIBG and ^{18}F-dopa PET/CT scans of 19 NB patients

Scan	Patient	Urinary catecholamines at scanning	MIBG scan results	SPECT acquisition (yes/no)	Dopa PET results	Sites and number of lesions by MIBG	Sites and number of lesions by dopa	Number of NB lesions confirmed by our standard references	Standard of reference			Change in therapeutic strategy (yes/no)	Outcome from paired scans (months)
									Histopathology	BMB	CT/MRI		
1	1	Increased	Positive	No	Positive	B=10, Total=10	B=19 Total=19	19	Not available	Positive	Negative	No	AWD (48)
2	2	Increased	Positive	No	Positive	B=7 ST=1 Total=8	B=10 ST=1 Total=11	11	Not available	Positive	Positive on ST and B	No	DOD (9)
3	3	Normal	Positive	No	Positive	ST=1 Total=1	ST=1 Total=1	1	Positive on ST	Negative	Positive on ST	No	AWD (15)
4	4	Normal	Positive	Yes	Positive	ST=1 Total=1	ST=2 P/R=1 Total=3	3	Not available	Not available	Positive on ST	No	AWD (11)
5	5	Normal	Positive	Yes	Negative	P/R=1 Total=1	0	0	Not available	Negative	Negative	Yes	NED (13)
6	6	Normal	Negative	Yes	Positive	0	ST=10 Total=10	10	Not available	Not available	Positive on ST	Yes	AWD (13)
7	7	Normal	Negative	No	Positive	0	ST=3 Total=3	3	Not available	Negative	Positive on ST	Yes	NED (12)
8	8	Normal	Negative	Yes	Positive	0	B=1 P/R=1 ST=1 Total=3	3	Positive on P/R and ST	Positive	Positive on P/R and ST and B	Yes	NED (11)
9	9	Normal	Negative	Yes	Negative	0	0	3	Positive on P/R and ST	Negative	Positive on P/R and ST	No	NED (10)
10	10	Increased	Positive	Yes	Positive	B=8 Total=8	B=12 ST=1 Total=13	15	Positive on P/R and ST	Positive	Positive on P/R and ST	No	NED (8)
11	11	Normal	Negative	Yes	Positive	0	ST=2 Total=2	5	Not available	Negative	Positive on P/T and ST	Yes	AWD (6)
12	12	Increased	Positive	Yes	Positive	B=8 P/R=1 ST=1 Total=10	B=11 P/R =1 ST=1 Total=13	16	Not available	Positive	Positive on P/T and ST	No	Lost to follow-up
13	13	Increased	Positive	Yes	Positive	B=2 P/R=1 Total=3	B=4 P/R=1 Total=5	3	Not available	Positive	Positive on P/R and B	No	AWD (48)

Table 2 (continued)

Scan	Patient	Urinary catecholamines at scanning	MIBG scan results	SPECT acquisition (yes/no)	Dopa PET results	Sites and number of lesions by MIBG	Sites and number of lesions by dopa	Number of NB lesions confirmed by our standard references	Standard of reference			Change in therapeutic strategy (yes/no)	Outcome from paired scans (months)
									Histopathology	BMB	CT/MRI		
14	14	Increased	Positive	Yes	Positive	B=13 Total=13	B=15 Total=15	15	Not available	Positive	Negative	No	Lost to follow-up
15	15	Increased	Positive	Yes	Positive	B=8 P/R=1 ST=1 Total=10	B=8 P/R=1 Total=9	10	Positive on P/R	Positive	Positive on P/RT and ST	No	AWD (48)
16	16	Normal	Positive	Yes	Negative	ST=1 Total=1	0	0	Not available	Negative	Negative	Yes	NED (50)
17	17	Increased	Negative	Yes	Positive	0	ST=1 Total=1	1	Positive on ST	Negative	Positive on ST	Yes	AWD (49)
18	18	Normal	Positive	Yes	Positive	B=9 Total=9	B=12 Total=12	12	Not available	Positive	Positive on B	No	AWD (4)
19	19	Normal	Positive	Yes	Positive	B=5 Total=5	B=5 P/R=1 Total=6	6	Not available	Positive	Positive on B and P/R	No	AW (/4)
20	3	Normal	Positive	Yes	Negative	ST=1 Total=1	0	0	Not available	Not available	Negative	Yes	AWD (11)
21	3	Normal	Negative	Yes	Negative	0	0	0	Not available	Negative	Negative	No	AWD (8)
22	3	Normal	Positive	Yes	Positive	ST=1 Total=1	ST=5 Total=5	5	Not available	Negative	Positive on ST	No	AWD (4)
23	4	Normal	Positive	Yes	Positive	ST=2 Total=2	P/R =1 ST=2 Total=3	3	Positive on ST	Not available	Positive on P/R and ST	No	AWD (4)
24	7	Normal	Negative	No	Positive	0	ST=2 Total=2	2	Positive on ST	Negative	Positive on ST	Yes	NED (10)
25	7	Normal	Negative	No	Negative	0	0	0	Not available	Negative	Negative	No	NED (7)
26	7	Normal	Negative	No	Negative	0	0	0	Not available	Negative	Negative	No	NED (4)
27	11	Normal	Positive	Yes	Positive	ST=2 Total=2	ST=2 Total=2	5	Not available	Negative	Positive on ST	No	NED (4)
28	4	Not available	Positive	Yes	Positive	ST=4 P/R=1 Total=5	ST=4 P/R=1 Total=5	5	Not available	Not done	Positive on ST	No	AWD (4)

B bone/bone marrow recurrence/metastases, *NED* no evidence of disease, *ST* soft tissue recurrence/metastases, *AWD* alive with disease, *P/R* primary/residual tumour, *DOD* dead of disease

using an iterative reconstruction algorithm. No carbidopa premedication was utilized for any PET/CT scans. ^{18}F-Dopa (IASOdopa®) was produced as previously described [17]. Non-diagnostic CT scanning (low-dose CT with 120 kV, 80 mA, 0.6 s per rotation) was used for attenuation correction and for anatomical localization of the hot spots of the ^{18}F-dopa PET study.

Although semi-quantitative scoring systems for NB have been described (body division into seven or nine sections) in order to evaluate disease extent [18], a simplified version of disease quantification was used in our study [9]. The effectiveness of ^{123}I-MIBG and ^{18}F-dopa PET/CT in detecting NB was assessed by reviewing the uptake patterns for each radiopharmaceutical in the following locations: primary and residual tumour, local and regional soft tissue recurrence/metastases, and bone and bone marrow metastases. The paired ^{123}I-MIBG and ^{18}F-dopa PET/CT for each patient were reviewed in order to determine the differences in number and distribution of disease sites in these three main locations.

When more than one paired scan per patient was performed, it was acquired at a different time as a consequence of different clinical indications. In all of these patients, between the first and the following scans, proper treatment (surgery and/or chemotherapy) was performed (Table 3).

^{18}F-Dopa PET/CT and ^{123}I-MIBG scan images were interpreted after a consensus reading by two nuclear medicine physicians in each institute who were aware of the patient's clinical history but blinded to any results of the anatomical imaging modalities (MR/CT).

Scan results were compared and the sensitivity, specificity and diagnostic accuracy of both imaging modalities were assessed by means of scan-based and lesion-based analysis.

Standard of reference

The standard of reference for primary/residual tumour and locoregional soft tissue recurrence/metastases was based on histopathology and/or diagnostic contrast-enhanced CT and /or MR findings.

The gold standards for bone and bone marrow metastases were bone marrow biopsy (BMB) and/or MR when available. The standard of reference for each scan and for each patient is shown in Table 2.

At least 4 months of clinical and imaging follow-up data were available for all patients.

Statistical analysis

Owing to the nature of the study (pilot study) no specific sample size was calculated: the number of 19 patients recruited was determined only by practical considerations, given the low prevalence of the disease.

Table 3 Clinical indication and therapy of patients who underwent more than one paired scan (^{123}I-MIBG scintigraphy and ^{18}F-dopa PET/CT)

Patient	Indication	1st paired scan (results)	Therapy	Indication	2nd paired scan (results)	Therapy	Indication	3rd paired scan (results)	Therapy	Indication	4th paired scan
3	Suspected liver relapse	Scan 3 liver metastasis	Surgery+ChT	Restaging after therapy	Scan 20 negative	BSCT	Restaging after BSCT	Scan 21 negative	No	Suspected PD	Scan 22 PD
4	Suspected peritoneal metastases	Scan 4 peritoneal metastases	ChT	Restaging after therapy	Scan 23 PD	Surgery+ChT	Restaging after therapy	Scan 28 persistence of disease			
7	Restaging	Scan 7 lymph node relapse	ChT	Restaging after therapy	Scan 24 PR	Surgery+ChT	Restaging after therapy	Scan 25 negative	BSCT	Restaging after BSCT	Scan 26 negative
11	Suspected recurrence	Scan 11 recurrence	ChT	Restaging after therapy	Scan 27 PD						

ChT chemotherapy, *PD* progression of disease, *BSCT* blood stem cell transplantation, *PR* partial response

Categorical data are reported as the number (percentage) of subjects/lesions, and continuous data as mean, standard deviation, median and range.

The two diagnostic techniques were compared in terms of sensitivity, specificity and accuracy by using histopathology, clinical and imaging follow-up as the gold standards. The chi-square and Fisher's exact tests were used to compare categorical data and to test the difference in sensitivity and specificity between the two diagnostic methods.

Statistical significance was set at a two-tailed p value <0.05. All analyses were performed by means of SPSS software (version 13, SPSS Inc., Chicago, IL, USA) and Stata software (version 11, StataCorp, College Station, TX, USA).

Results

Our final multidisciplinary diagnosis confirmed primary tumour/recurrence/metastasis of NB in 17 of 19 patients. ^{18}F-Dopa PET/CT correctly identified NB localizations in 16 (94%) of these patients, whereas ^{123}I-MIBG scintigraphy did so in 11 patients (65%).

Both disease-free patients who had been classified as positive on ^{123}I-MIBG scintigraphy were correctly re-evaluated as negative by ^{18}F-dopa PET/CT analysis.

Of 17 patients, 11 (65%) were properly classified as positive for NB localization by both ^{123}I-MIBG scintigraphy and ^{18}F-dopa PET/CT analysis. An example of ^{123}I-MIBG scintigraphy and ^{18}F-dopa PET/CT agreement is shown in Fig. 1.

Scan-based analysis

On scan-based analysis, ^{18}F-dopa PET/CT showed a sensitivity and accuracy of 95 and 96%, respectively, values which were significantly higher than those of ^{123}I-MIBG scanning (sensitivity and accuracy 68 and 64%, p=0.046 and p=0.01, respectively). No significant difference in terms of specificity was found between the two imaging modalities (p=0.2). The specificity of ^{18}F-dopa PET/CT approached 100%. In 9 of 28 paired scans (32%) and in 6 of 19 patients (32%), PET/CT results influenced the patient management and/or the therapeutic strategy that had been adopted on the basis of all available data including the initial MIBG report (Table 4, Fig. 2).

The scan-based sensitivity in detecting NB was dependent on the anatomical localization (Table 5). In this analysis, ^{18}F-dopa PET/CT seemed to be slightly more sensitive, albeit without reaching statistical significance, than ^{123}I-MIBG scintigraphy in detecting primary/residual tumour (66 vs 33%, p=0.2) and locoregional soft tissue recurrence/metastases (82 vs 47%, p=0.07), but not in the case of bone marrow/bone recurrence (100 vs 90%).

Lesion-based analysis

In all, we identified 156 NB lesions in 28 paired ^{123}I-MIBG and ^{18}F-dopa PET/CT scans, 141 (90%) of which were properly detected by ^{18}F-dopa PET/CT and 88 (56%) by ^{123}I-MIBG scintigraphy. All but one MIBG-positive NB lesion had ^{18}F-dopa uptake, showing similar pathological tracer distribution (Fig. 3), while in 53 dopa-positive NB lesions, MIBG proved negative.

In 14 of 19 patients (73%) and in 18 of 28 paired scans (64%), ^{18}F-dopa PET/CT detected more metastatic sites than ^{123}I-MIBG scintigraphy.

On lesion-based analysis, ^{18}F-dopa PET/CT displayed a sensitivity and accuracy of 90%; these values were significantly higher (p<0.001) than those found for ^{123}I-MIBG scintigraphy (sensitivity and accuracy of 56 and 57%, respectively). No significant difference in terms of specificity was found between the two imaging modalities (^{18}F-dopa PET/CT 75%; ^{123}I-MIBG scintigraphy 62%).

However, a difference in terms of regional sensitivity of the different techniques was found; this is shown in Table 5. ^{18}F-Dopa PET/CT displayed a higher sensitivity than ^{123}I-MIBG scintigraphy in detecting bone marrow/bone recurrence/metastases (96 vs 71%, p<0.001) and local and regional soft tissue recurrence/metastases (84 vs 31%, p< 0.001), whereas in the assessment of primary/residual tumour sensitivity the difference did not reach statistical significance (66 vs 33%, p=0.2) (Fig. 4).

The higher discrepancy between ^{18}F-dopa PET/CT and ^{123}I-MIBG scintigraphy was observed in the detection of soft tissue recurrence/metastases; in particular 24 dopa-positive lesions were negative at ^{123}I-MIBG scanning. The diameter of all soft tissue recurrence/metastases ranged from 8 to 78 mm (median 18 mm). The size of 19 of 31 MIBG-negative soft tissue recurrence/metastases was less than 1.5 cm (Table 6).

Discussion

^{123}I-MIBG scintigraphy is a powerful tool for diagnosing and staging NB, and it is also an efficacious means of evaluating treatment response and conducting long-term post-therapy surveillance for the early detection of recurrence [19, 20]. However, a great variability in tumour tracer uptake has been observed, and the reasons for false-negative results have not been entirely elucidated. ^{123}I-MIBG uptake may depend on several variables: (1) modifications of the active trapping mechanism due to the differentiation and maturation of tumour cells [21, 22], (2) levels of urinary catecholamine metabolites [23], (3) prevalent necrotic phenomena of the primary NB tumour, (4) pharmacological interference [24, 25] and (5) low dose

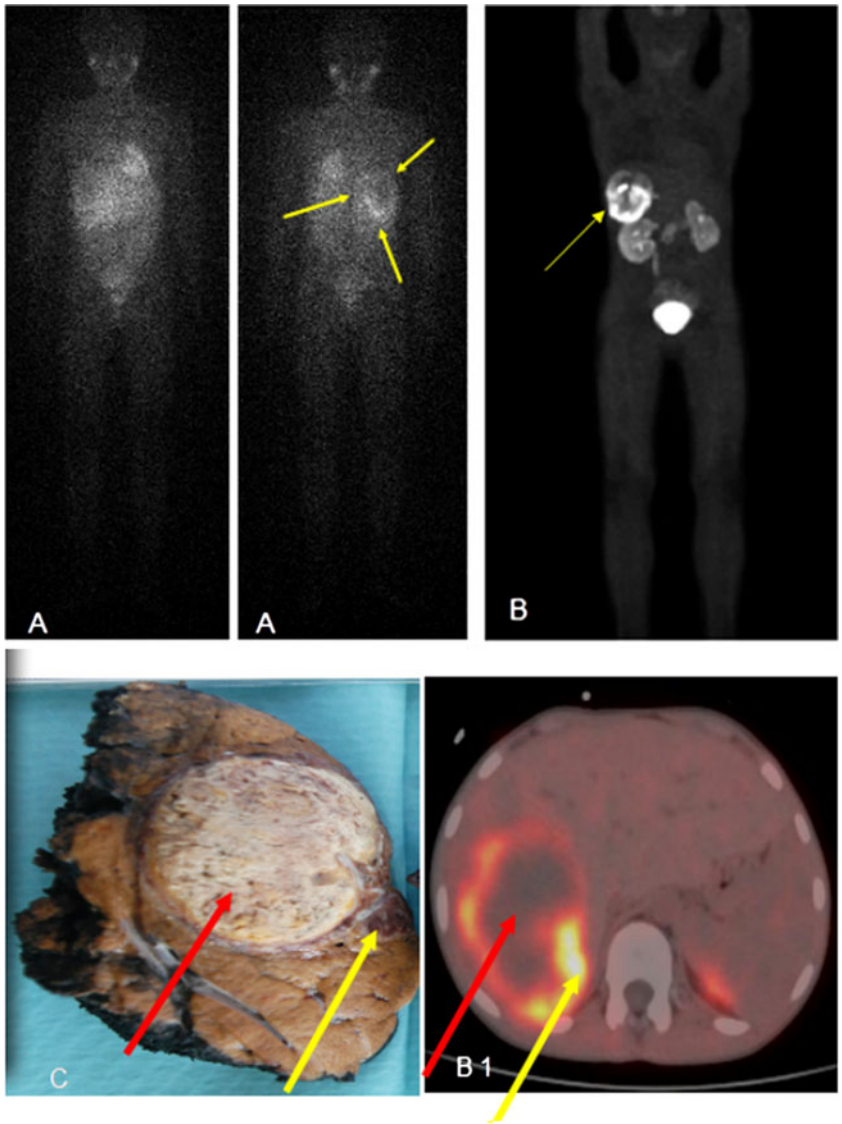

Fig. 1 Liver metastasis from NB (patient 3, scan 3) detected by whole-body ^{123}I-MIBG scintigraphy (**a**), confirmed by ^{18}F-dopa PET/CT (maximum intensity projection, MIP) (**b**) and histopathology (**c**). The large liver metastasis was characterized by necrosis inside (*red arrows* **b1**, **c**) and viable tumour outside (*yellow arrows* **b1**, **c**)

of ^{123}I-MIBG injected [26]. A further issue concerns the correct interpretation and recognition of the normal distribution pattern of ^{123}I-MIBG in children [27] often conditioned both by the low quality of ^{123}I-MIBG scintigraphy in children and by the difficult abdominal anatomy that is often present during the staging and restaging of NB. SPECT is used as a "keystone" to overcome these diagnostic limits. However, in the era of CT and MRI, a more suitable tool might increase sensitivity and provide more precise anatomical localization of the disease, especially after coregistration with radiological imaging modalities.

Considering the high quality of the images provided by ^{18}F-FDG PET/CT, the availability of high-technology tools, including coregistration with CT, and the theoretically high affinity of the tracer for NB tumours, this imaging modality might be successfully introduced in NB assessment.

In this regard, several pilot studies have demonstrated that ^{18}F-FDG PET/CT can be used in NB to detect primary/metastatic disease [5, 6] on staging and to monitor treatment response, which is especially useful in patients with ^{123}I-MIBG-negative tumours [7]. Moreover, ^{18}F-FDG PET was proved to be more sensitive and specific for the detection of NB lesions when discrepant/inconclusive findings are found on MIBG scanning/SPECT [28]. However, the principal drawback of ^{18}F-FDG PET/CT is its low accuracy, during staging and restaging, in detecting NB localization in bone and bone marrow, which are the most frequent sites of disease progression [5, 8]. This limitation means that ^{123}I-MIBG scintigraphy is still the best diagnostic option in stage 3 and 4 NB [9].

^{18}F-Dopa, a well-known catecholamine precursor, is an excellent PET/CT tracer for the detection of benign and malignant pheochromocytoma in cases of either primary or

Table 4 ^{18}F-Dopa PET/CT influenced patient management and/or treatment decisions, in comparison with all available data and the initial MIBG report

Patient	Scan	Indications	CT	MRI	MIBG	Clinical management without dopa	Dopa	Clinical management with dopa	Follow-up
5	5	Suspected recurrence in the site of previous surgery	Doubtful	Doubtful/negative	Positive	More aggressive follow-up	Negative	No therapy, normal follow-up	NED after 13 months
6	6	Suspected abdominal lymph node relapse	Doubtful/positive	Not available	Negative	More aggressive follow-up	Lymph node relapse	ChT	AWD after 13 months
7	7	Restaging	CT of the neck was not available	Cervical lymph node doubtful/positive	Negative	More aggressive follow-up	Lymph node relapse	ChT	NED after 12 months
8	8	Staging	Abdominal mass + lymph nodes	Abdominal mass + lymph nodes	Negative	Stage 3	Abdominal mass + lymph nodes + bone marrow	Stage 4	NED after 11 months
11	11	Suspected disease persistence/ recurrence in the site of previous surgery	Not available	Residual tissue in the site of surgery	Negative	More aggressive follow-up	Positive; inhomogeneous uptake on residual tissue	ChT	AWD after 6 months
16	16	Suspected liver metastases	Not available	Negative	Positive	More aggressive follow-up	Negative	No therapy, normal follow-up	NED after 50 months
17	17	Suspected disease persistence/ relapse in the site of previous surgery	Not available	Residual tissue in the site of surgery	Negative	More aggressive follow-up	Positive; inhomogeneous uptake on residual tissue	ChT	AWD after 49 months
20	3	Suspected relapse in the site of previous surgery after ChT and before BSCT	Not available	Doubtful/negative	Positive	No BSCT	Negative	HD ChT + BSCT	PD 7 months after BSCT
24	7	Response to ChT	Not available	No response	Negative	ChT	PR	Surgery and ChT	NED after 10 months

ChT chemotherapy, *PD* progression of disease, *NED* no evidence of disease, *BSCT* blood stem cell transplantation, *PR* partial response, *AWD* alive with disease, *HD ChT* high-dose chemotherapy

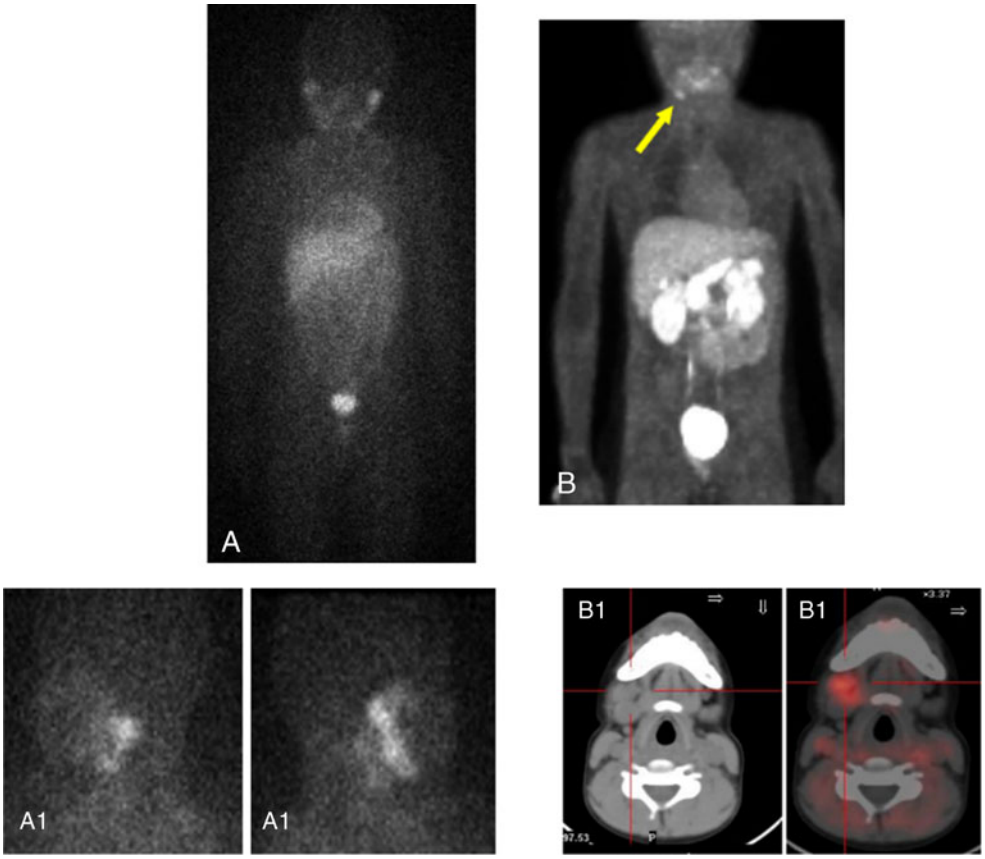

Fig. 2 Cervical lymph node metastasis from NB (patient 7, scan 7) not detected by whole-body ^{123}I-MIBG scintigraphy + planar lateral acquisitions (**a**, **a1**) but discovered by ^{18}F-dopa PET/CT (MIP) (**b**); transverse PET/CT image (**b1**). This metastasis was histologically confirmed after surgery

metastatic disease and displays greater sensitivity than ^{123}I-MIBG [12, 15, 16]. We prospectively investigated the role of ^{18}F-dopa PET/CT in 18 patients with advanced-stage NB and compared our data with those yielded by ^{123}I-MIBG scans acquired within 10 days. We used this powerful PET tracer in order to evaluate the possibility of overcoming several of the diagnostic limitations of ^{123}I-MIBG and ^{18}F-FDG PET/CT scans.

First, we found that primary/residual, recurrent/metastatic soft tissue NB and bone/bone marrow NB metastases were characterized by a specific ^{18}F-dopa uptake and that the pathological distribution of this PET tracer was similar to that of ^{123}I-MIBG. Indeed, 11 of 17 patients (65%) positive for NB localization were properly classified by both techniques, thus confirming a relatively good agreement between ^{18}F-dopa PET/CT and ^{123}I-MIBG scans, and all but one MIBG-positive NB lesion showed ^{18}F-dopa uptake. This finding confirms the high affinity of dopa for NB cells.

Second, in our population we have found that both on scan-based analysis and on lesion-based analysis ^{18}F-dopa PET/CT was more accurate than ^{123}I-MIBG in staging and restaging advanced NB. However, no significant difference in terms of specificity was found. Since this was a pilot study (i.e. small sample size), in most cases statistical significance was not reached because of the low statistical power of the test employed.

Table 5 Sensitivity of ^{18}F-dopa PET/CT and ^{123}I-MIBG scintigraphy at different locations considering scan-based analysis and lesion-based analysis. Standard of reference was based on CT, MRI, histopathology and clinical follow-up

	^{18}F-Dopa PET/CT	^{123}I-MIBG scintigraphy	*p* value
Locations (scan-based analysis)			
Primary/residual tumour	8/12 (66%)	4/12 (33%)	0.2
Soft tissue recurrence/metastases	14/17 (82%)	8/17 (47%)	0.07
Bone/bone marrow	10/10 (100%)	9/10 (90%)	1
Locations (lesion-based analysis)			
Primary/residual tumour	8/12 (66%)	4/12 (33%)	0.2
Soft tissue recurrence/metastases	38/45 (84%)	14/45 (31%)	<0.001
Bone/bone marrow	95/99 (96%)	70/99 (71%)	<0.001

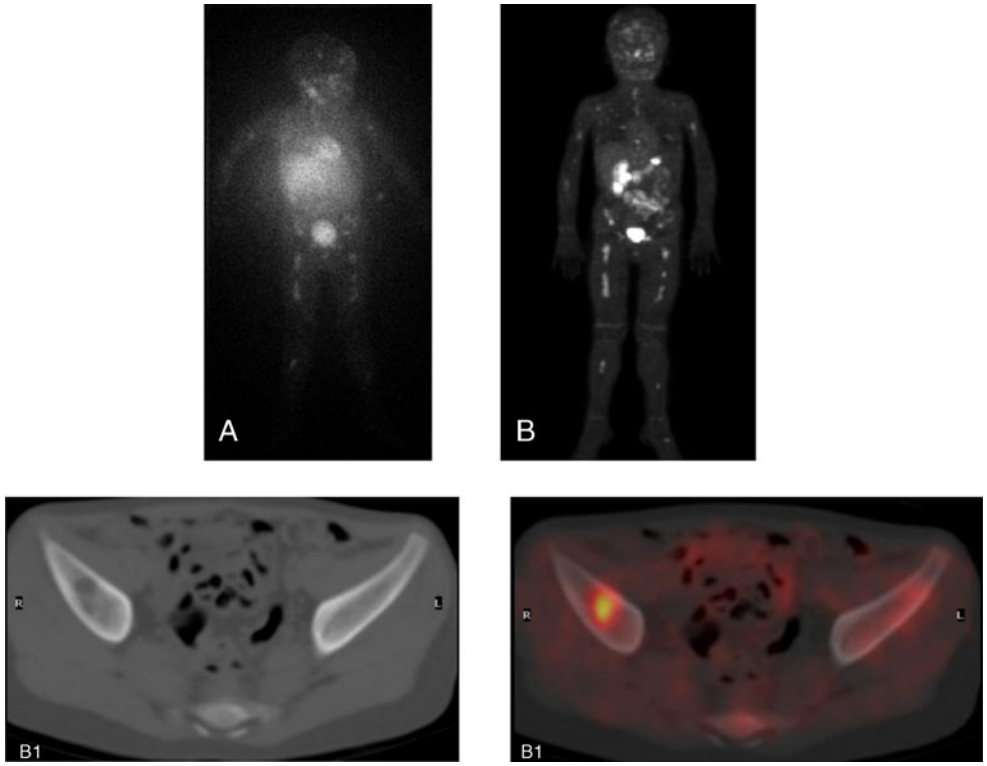

Fig. 3 Bone and bone marrow metastases from NB (patient 1, scan 1) detected by whole-body ^{123}I-MIBG scintigraphy (**a**) and ^{18}F-dopa PET/CT (MIP) (**b**). Transverse PET/CT (**b1**) was able to distinguish bone from bone marrow localizations, showing high dopa uptake corresponding to lytic bone metastasis on CT

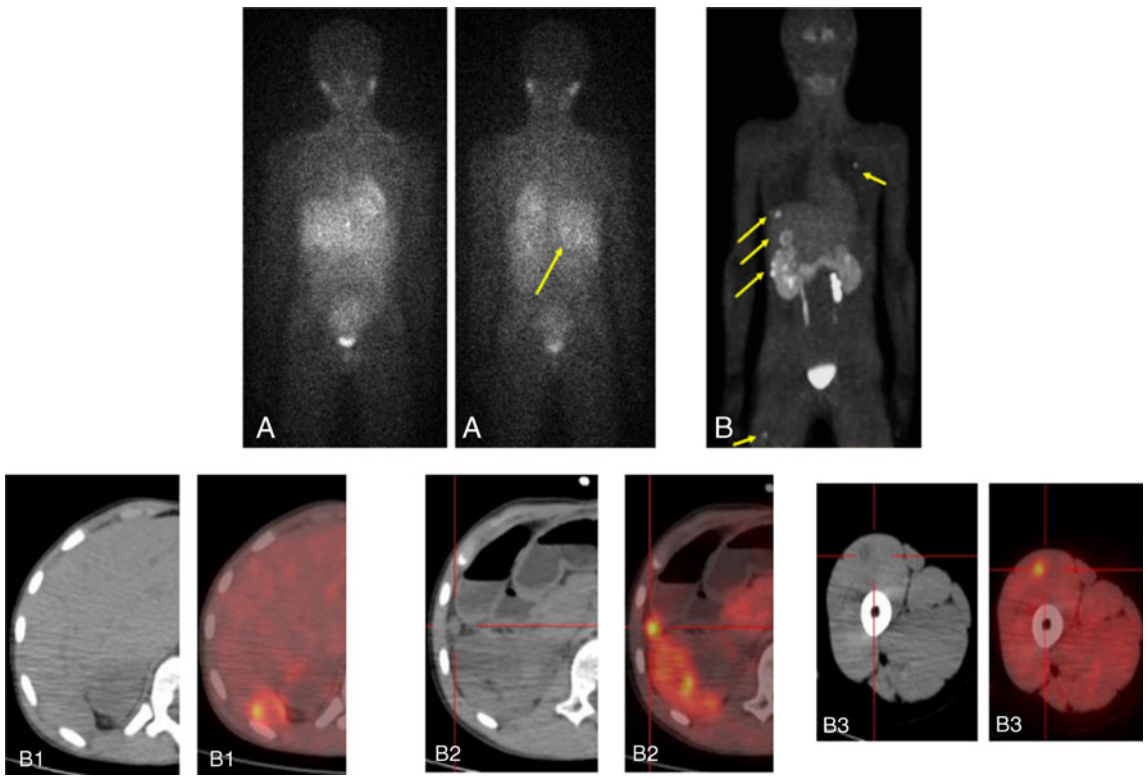

Fig. 4 Second liver relapse (*arrows*) from NB (patient 3, scan 22) detected by whole-body ^{123}I-MIBG scintigraphy (**a**) and ^{18}F-dopa PET/CT (MIP) (**b**). ^{18}F-Dopa PET/CT (MIP) and transverse PET/CT (**b**, **b2**, **b3**) revealed lung, liver, peritoneal and soft tissue metastases (*arrows*) that were undetected by whole-body ^{123}I-MIBG scintigraphy

Table 6 False-negative findings on ^{123}I-MIBG scintigraphy and ^{18}F-dopa PET/CT in relation to NB lesion dimensions. Standard of reference was based on CT, MRI, histopathology and clinical follow-up

Dimension of soft tissue recurrence/metastases	^{123}I-MIBG scan		^{18}F-Dopa PET/CT	
	Positive	Negative	Positive	Negative
<1.5 cm	0	19	17	2
>1.5 cm and <3 cm	12	11	19	4
>3 cm	2	1	2	1
Total	14	31	38	7

With regard to the uptake pattern in different anatomical regions, no significant difference in terms of sensitivity was found between ^{18}F-dopa PET/CT and ^{123}I-MIBG scanning when primary/residual tumour was considered. The principal explanations for this finding are related to the low number of primary/residual lesions in our cohort (12 lesions), involving only 4 patients at first NB diagnosis (patients 8, 9, 10 and 15), and to the presence of 3 patients with no MIBG- and dopa-avid primary/residual tumour (patients 9, 10 and 11). On the other hand, we confirmed the higher sensitivity of ^{18}F-dopa PET/CT vs ^{123}I-MIBG, especially in cases of soft tissue recurrence/metastases (scan-based analysis 82 vs 47%, $p=0.07$; lesion-based analysis 84 vs 31%, $p<0.001$). In this field we have to underline that tumour relapse was characterized by small dimension, with 50% of NB lesions being less than 18 mm. This finding may explain the low sensitivity of ^{123}I-MIBG scanning in our patients, even if it was associated with SPECT. In this setting, SPECT was performed in all but one patient (patient 7, Fig. 2) with no MIBG-avid soft tissue recurrence/metastases. In this patient, with lymph node recurrence close to physiological uptake of the right submandibular gland, SPECT imaging might have theoretically improved the sensitivity of MIBG scanning; however, the dopa uptake detected by PET/CT was well defined and easy to classify as lymph node relapse.

While confirming the high sensitivity of ^{123}I-MIBG in cases of bone/bone marrow NB infiltration (scan-based analysis 90%, lesion-based analysis 71%), we ascertained the high dopa avidity of NB bone/bone marrow metastases (100% sensitivity on scan-based analysis and 96% on lesion-based analysis). Moreover, no false-positive dopa bone marrow uptake was observed after chemotherapy as described for FDG. Thus, the principal diagnostic limitation of ^{18}F-FDG PET/CT, namely its low accuracy in bone marrow NB assessment, could be overcome by using ^{18}F-dopa PET/CT.

The uptake mechanism of dopa and MIBG for both soft tissue and bone/bone marrow metastases seems to be very similar. All but one MIBG-positive metastases (88 lesions) were well detected by ^{18}F-dopa PET/CT, thus confirming a common catecholamine pathway.

Third, the overall high accuracy of ^{18}F-dopa PET/CT influenced patient management and treatment decisions, in comparison with all available data and the initial MIBG report, in 6 of 19 patients (32%) and in 9 of 28 paired scans (32%). ^{18}F-Dopa PET/CT recognized as false-positive results one case of abdominal ^{123}I-MIBG uptake at a site of previous surgical resection (scans 5 and 20) and one case of unspecific uptake in the liver (scan 16), thus confirming remission of disease (Tables 2 and 4). In addition, it revealed NB recurrence/metastases that were deemed negative on ^{123}I-MIBG scanning, suggesting the need for further therapy (Tables 2 and 4, scans 6, 7, 11, 17 and 24). Finally, it detected one spine metastasis that was undetected by ^{123}I-MIBG scintigraphy, thus changing the stage from 3 to 4 (scan 8). These data suggest that ^{18}F-dopa PET/CT in patients with stage 3 and 4 NB is likely to influence patient management. However, in our patients, therapy modification was not based only on the ^{18}F-dopa PET/CT result, but also on the entire diagnostic workup, including clinical and conventional imaging findings (CT, MRI, MIBG scanning).

Consequently, we suggest ^{18}F-dopa PET/CT as a new diagnostic opportunity for NB assessment.

This “new” tool might be applied: (1) in initial staging, thus providing important information on disease extension, (2) in cases of suspected relapse, (3) in the evaluation of disease response after chemotherapy and probably, as the best indication, (4) to clarify doubtful MIBG results. The high sensitivity of ^{18}F-dopa PET/CT may also offer a further possibility to verify the status of complete remission after therapy to detect any minimal residual disease, which often leads to tumour recurrence [29].

Limitations

We feel that the results of the present study are encouraging. Nevertheless, some limitations should be borne in mind.

First, histological examinations of primary/residual tumour, soft tissue recurrence/metastases and bone/bone marrow NB metastases were not performed in all patients. However, we obtained histological confirmation of primary/residual tumour and soft tissue recurrence/metastases in 8 of 19 patients (8 of 12 NB-positive patients with primary/residual tumour and/or soft tissue recurrence/metastases) and BMB in 17 of 19 patients.

Second, without local histological confirmation, we cannot exclude the possibility that a positive result yielded by dopa on bone marrow, in the presence of a negative MIBG result at the same location, may be a false-positive. In order to overcome this limitation, focal ^{18}F-dopa bone marrow uptake was regarded a priori as positive for NB localization if BMB was positive, with MRI confirmation when available (Fig. 5). In this setting, our study lacks a real independent tool to correctly evaluate the extent and the number of bone and bone marrow lesions; consequently, we cannot exclude that our interpretation of bone marrow involvement was exceedingly "PET based". However, for ethical and practical reasons a bioptic or MRI evaluation on each bone/bone marrow lesion was not deemed appropriate.

Third, the difference in terms of accuracy between ^{123}I-MIBG scintigraphy and ^{18}F-dopa PET/CT depends on the relatively low sensitivity of ^{123}I-MIBG scanning found in our study (68% in scan-based analysis and 56% in lesion-based analysis), which proved markedly lower than that reported by other recent studies [30, 31]. Our low sensitivity values are probably due to the features of the study population encompassing 19 consecutive patients, probably not representing the general population of patients with NB. In fact, our study includes two adults, one of whom had ten MIBG-negative NB lesions, and three NB at the time of first diagnosis (patients 8, 9 and 10) with primary lesions not showing any MIBG uptake. In this regard, in this study there is no single patient aged less than 1 year, while infants represent the group with the highest incidence rate of NB.

Another possible explanation for low ^{123}I-MIBG scan sensitivity is probably related to the fact that most patients (15 of 19) underwent our diagnostic protocol for suspected relapse. In fact, our study is not comparable with previous literature studies [30, 31], where the study population mostly encompassed patients at the time of first diagnosis.

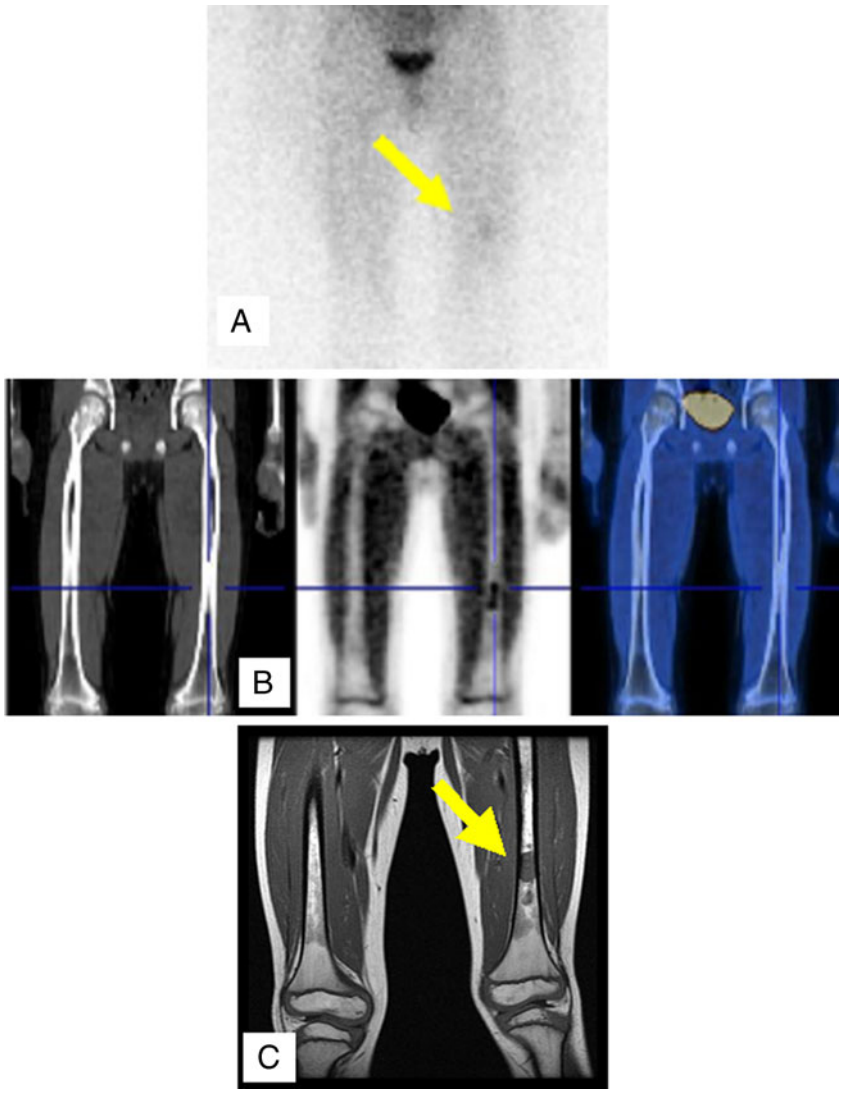

Fig. 5 Bone marrow recurrences from NB (patient 13, scan 13) detected by whole-body ^{123}I-MIBG scintigraphy (**a**) and ^{18}F-dopa PET/CT (**b**). This metastasis was confirmed by MRI (**c**)

Indeed, the detection rate of NB relapse by ^{123}I-MIBG was lower than that reported for the diagnosis of primary NB, ranging from 70 to 90% [32–34]. Moreover, difficulties assessing NB lesions at follow-up have been discussed. On the one hand, MIBG-positive lesions at the time of first diagnosis, which proved negative on ^{123}I-MIBG scintigraphy at relapse, have been reported [35–37]. This finding may be due to tumour cells which survive chemotherapy and fail to accumulate ^{123}I-MIBG [38] or to loss of differentiation at the time of recurrence with consequently low rate of MIBG-avid scans reported by recent papers [28]. On the other hand, positive MIBG scanning at the time of NB relapse may be negative at first diagnosis [39].

Another key point required to fully understand the low sensitivity of ^{123}I-MIBG scanning could be the lack of SPECT data in 4 of 19 patients as reported in Tables 2 and 3. Although SPECT was not performed in these four patients, the whole-body scan of patients 1, 2 and 3 showed no doubtful findings needing a SPECT protocol (Figs. 1 and 3). Patients 1 and 2 had clear and diffuse bone/bone marrow involvement and patient 3 was affected by a big liver metastasis characterized by MIBG uptake. MIBG SPECT, as reported by Matthay et al. [40], should be performed in cases in which uncertainty exists.

In our scans SPECT acquisitions encompassed the same field of view as PET/CT when a different number of soft tissue NB lesions were detected by ^{18}F-dopa PET/CT and ^{123}I-MIBG scanning. Of course, the availability of a SPECT/CT system might have increased the sensitivity of ^{123}I-MIBG scanning. In other words, the lack of adequate anatomical CT correlation could have influenced the false-negative ^{123}I-MIBG scan and SPECT interpretation. Thus, we suggest performing ^{123}I-MIBG SPECT/CT whenever the technique is available and when the children are able to cooperate.

Fourth, although no significant difference in terms of specificity was found, a real assessment of the specificity of ^{18}F-dopa PET/CT and ^{123}I-MIBG scanning in this population remains difficult. In fact, the number of true-negative NB lesions was low due to the high prevalence of viable disease in our population.

Finally, the number of patients in our study was limited; however: as this was a pilot study conducted on a selected population, this limitation does not seem to be very great.

Conclusion

We found that primary/residual, recurrent/metastatic soft tissue NB and bone/bone marrow NB metastases were all characterized by a specific ^{18}F-dopa uptake. The pathological distribution of this PET tracer was similar to that of ^{123}I-MIBG. ^{18}F-Dopa PET/CT displayed high overall diagnostic accuracy in stage 3–4 NB which was comparable to ^{123}I-MIBG scintigraphy results, providing outstanding information on disease extension. Consequently, we propose ^{18}F-dopa PET/CT as a new opportunity for NB assessment. Further confirmation on a larger sample population is however required.

Conflicts of interest None.

References

1. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid: Children's Cancer Group. N Engl J Med 1999;341:1165–73.
2. Braduer GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–77.
3. Vaidyanathan G. Meta-iodobenzylguanidine and analogues: chemistry and biology. Q J Nucl Med Mol Imaging 2008;52:351–68.
4. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol 2009;27:298–303.
5. Shulkin BL, Hutchinson RJ, Castle VP, Yanik GA, Shapiro B, Sisson JC. Neuroblastoma: positron emission tomography with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose compared with metaiodobenzylguanidine scintigraphy. Radiology 1996;199:743–50.
6. Kushner BH, Yeung HW, Larson SM, Kramer K, Cheung NK. Extending positron emission tomography scan utility to high-risk neuroblastoma: fluorine-18 fluorodeoxyglucose positron emission tomography as sole imaging modality in follow-up of patients. J Clin Oncol 2001;19:3397–405.
7. Kushner BH. Neuroblastoma: a disease requiring a multitude of imaging studies. J Nucl Med 2004;45:1172–88.
8. Taggart DR, Han MM, Quach A, Groshen S, Ye W, Villablanca JG, et al. Comparison of iodine-123 metaiodobenzylguanidine (MIBG) scan and [18F]fluorodeoxyglucose positron emission tomography to evaluate response after iodine-131 MIBG therapy for relapsed neuroblastoma. J Clin Oncol 2009;27:5343–9.
9. Sharp SE, Shulkin BL, Gelfand MJ, Salisbury S, Furman WL. 123I-MIBG scintigraphy and 18F-FDG PET in neuroblastoma. J Nucl Med 2009;50:1237–43.
10. Minn H, Kauhanen S, Seppänen M, Nuutila P. 18F-FDOPA: a multiple-target molecule. J Nucl Med 2009;50(12):1915–8.
11. Fottner C, Helisch A, Anlauf M, Rossmann H, Musholt TJ, Kreft A, et al. 6-18F-fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to 123I-metaiodobenzyl-guanidine scintigraphy in the detection of extraadrenal and hereditary pheochromocytomas and paragangliomas: correlation with vesicular monoamine transporter expression. J Clin Endocrinol Metab 2010;95(6):2800–10.
12. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Havekes B, et al. Comparison of 18F-fluoro-L-DOPA, 18F-fluorodeoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2009;94(12):4757–67.
13. Hoegerle S, Altehoefer C, Ghanem N, Koehler G, Waller CF, Scheruebl H, et al. Whole-body 18F dopa PET for detection of gastrointestinal carcinoid tumors. Radiology 2001;220:373–80.

14. Hoegerle S, Altehoefer C, Ghanem N, Brink I, Moser E, Nitzsche E. 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. Eur J Nucl Med 2001;28:64–71.
15. Hoegerle S, Nitzsche E, Altehoefer C, Ghanem N, Manz T, Brink I, et al. Pheochromocytomas: detection with 18F-DOPA whole body PET—initial results. Radiology 2002;222:507–12.
16. Fiebrich HB, Brouwers AH, Kerstens MN, Pijl ME, Kema IP, de Jong JR, et al. 6-[F-18]Fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with (123) I-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. J Clin Endocrinol Metab 2009;94(10):3922–30.
17. Luxen A, Perlmutter M, Bida GT, Van Moffaert G, Cook JS, Satyamurthy N, et al. Remote, semiautomated production of 6-[18F]fluoro-L-dopa for human studies with PET. Int J Rad Appl Instrum A 1990;41(3):275–81.
18. Messina JA, Cheng SC, Franc BL, Charron M, Shulkin B, To B, et al. Evaluation of semi-quantitative scoring system for meta-iodobenzylguanidine (mIBG) scans in patients with relapsed neuroblastoma. Pediatr Blood Cancer 2006;47:865–74.
19. Shulkin BL, Shapiro B. Current concepts on the diagnostic use of MIBG in children. J Nucl Med 1998;39:679–88.
20. Osmanagaoglu K, Lippens M, Benoit Y, Obrie E, Schelstraete K, Simons M. A comparison of iodine-123 meta-iodobenzylguanidine scintigraphy and single bone marrow aspiration biopsy in the diagnosis and follow-up of 26 children with neuroblastoma. Eur J Nucl Med 1993;20:1154–60.
21. Moyes JSE, Babich JW, Carter R, Meller ST, Agrawal M, McElwain TJ. Quantitative study of radioiodinated metaiodobenzylguanidine uptake in children with neuroblastoma: correlation with tumor histopathology. J Nucl Med 1989;30(4):474–80.
22. Lebtahi Hadj-Djilani N, Lebtahi NE, Bischof Delaloye A, Laurini R, Beck D. Diagnosis and follow-up of neuroblastoma by means of iodine-123 metaiodobenzylguanidine scintigraphy and bone scan, and the influence of histology. Eur J Nucl Med 1995;22:322–9.
23. Geatti O, Shapiro B, Sisson JC, Hutchinson RJ, Mallette S, Eyre P, et al. Iodine-131 metaiodobenzylguanidine scintigraphy for the location of neuroblastoma: preliminary experience in ten cases. J Nucl Med 1985;26:736–42.
24. Khafagi FA, Shapiro B, Fig LM, Mallette S, Sisson JC. Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissues. J Nucl Med 1989;30:481–9.
25. Biasotti S, Garaventa A, Villavecchia GP, Cabria M, Nantron M, De Bernardi B. False-negative metaiodobenzylguanidine scintigraphy at diagnosis of neuroblastoma. Med Pediatr Oncol 2000;35:153–5.
26. Giammarile F, Lumbroso J, Ricard M, Aubert B, Hartmann O, Schlumberger M, et al. Radioiodinated metaiodobenzylguanidine in neuroblastoma: influence of high dose on tumour site detection. Eur J Nucl Med 1995;22:1180–3.
27. Bonnin F, Lumbroso J, Tenenbaum F, Hartmann O, Parmentier C. Refining interpretation of MIBG scans in children. J Nucl Med 1994;35:803–10.
28. Melzer HI, Coppenrath E, Schmid I, Albert MH, von Schweinitz D, Tudball C, et al. (123)I-MIBG scintigraphy/SPECT versus (18) F-FDG PET in paediatric neuroblastoma. Eur J Nucl Med Mol Imaging 2011;38:1648–58.
29. Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, et al. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer 2009;45:2835–42.
30. Vik TA, Pfluger T, Kadota R, Castel V, Tulchinsky M, Farto JC, et al. (123)I-mIBG scintigraphy in patients with known or suspected neuroblastoma: results from a prospective multicenter trial. Pediatr Blood Cancer 2009;52:784–90.
31. Jacobson AF, Deng H, Lombard J, Lessig HJ, Black RR. 123I-meta-iodobenzylguanidine scintigraphy for the detection of neuroblastoma and pheochromocytoma: results of a meta-analysis. J Clin Endocrinol Metab 2010;95:2596–606.
32. Feine U, Müller-Schauenburg W, Treuner J, Klingebiel T. Metaiodobenzylguanidine (MIBG) labeled with 123I/131I in neuroblastoma diagnosis and follow-up treatment with a review of the diagnostic results of the International Workshop of Pediatric Oncology held in Rome, September 1986. Med Pediatr Oncol 1987;15(4):181–7.
33. Hoefnagel CA, Voûte PA, de Kraker J, Marcuse HR. Radionuclide diagnosis and therapy of neural crest tumors using iodine-131 metaiodobenzylguanidine. J Nucl Med 1987;28:308–14.
34. Okuyama C, Ushijima Y, Kubota T, Nakamura T, Kikkawa M, Nishimura T. Utility of follow-up studies using meta-[123 I] iodobenzylguanidine scintigraphy for detecting recurrent neuroblastoma. Nucl Med Commun 2002;23:663–72.
35. McDowell H, Losty P, Barnes N, Kokai G. Utility of FDG-PET/CT in the follow-up of neuroblastoma which became MIBG-negative. Pediatr Blood Cancer 2009;52:552.
36. Kushner BH, Kramer K, Modak S, Cheung NK. Sensitivity of surveillance studies for detecting asymptomatic and unsuspected relapse of high-risk neuroblastoma. J Clin Oncol 2009;27:1041–6.
37. Colavolpe C, Guedj E, Cammilleri S, Taieb D, Mundler O, Coze C. Utility of FDG-PET/CT in the follow-up of neuroblastoma which became MIBG-negative. Pediatr Blood Cancer 2008;51:828–31.
38. Frappaz D, Bonneu A, Chauvot P, Edeline V, Giammarile F, Siles S, et al. Metaiodobenzylguanidine assessment of metastatic neuroblastoma: observer dependency and chemosensitivity evaluation. The SFOP Group. Med Pediatr Oncol 2000;34:237–41.
39. Schwarz KB, Driver I, Lewis IJ, Taylor RE. Positive MIBG scanning at the time of relapse in neuroblastoma which was MIBG negative at diagnosis. Br J Radiol 1997;70:90–2.
40. Matthay KK, Shulkin B, Ladenstein R, Michon J, Giammarile F, Lewington V, et al. Criteria for evaluation of disease extent by (123)I-metaiodobenzylguanidine scans in neuroblastoma: a report for the International Neuroblastoma Risk Group (INRG) Task Force. Br J Cancer 2010;102:1319–22.