European Journal of
Nuclear
Medicine

Original article

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

K. Osmanagaoglu[1], M. Lippens[1], Y. Benoit[2], E. Obrie[1], K. Schelstraete[1], M. Simons[1]

[1] Department of Radiotherapy and Nuclear Medicine, University Hospital, Ghent University, De Pintelaan 185, B-9000 Ghent, Belgium
[2] Department of Pediatric Oncology, University Hospital, Ghent University, De Pintelaan 185, B-9000 Ghent, Belgium

Received 7 April and in revised form 27 July 1993

Abstract. In staging neuroblastomas, the demonstration of tumoural invasion of the bone marrow is an important criterion with regard to the therapeutic prospects and the prognosis. Iliac crest aspiration sampling has been used routinely for the detection of bone marrow metastases in neuroblastoma. However, due to the limited character of the sampling, it sometimes leads to false-negative results. Another procedure which is used to determine the extent of neuroblastoma is meta-iodobenzylguanidine (mIBG) scintigraphy. In order to establish the respective merits of both diagnostic techniques retrospectively, 148 iodine-123 mIBG scans of 26 children with neuroblastoma have been re-evaluated and compared with the results of routine bone marrow samples obtained within a 4-week period before or after scanning. Three types of mIBG uptake in the bone/bone marrow could be differentiated: (1) no visualization of the skeleton; (2) diffuse uptake in the skeleton with or without focally increased uptake, which indicates massive, diffuse bone marrow invasion by the tumour; and (3) focal tracer accumulation in one or several bones. No tracer uptake was observed in the skeleton in 91 scans. In 89 of the 91 the bone marrow biopsy was negative. Twenty-four scans showed diffuse skeletal uptake with or without foci. The bone marrow biopsies were negative for eight of those 24 scans. Hyperactive foci in one or more bones without diffuse tracer accumulation in the skeleton were detected in 33 scans. In only 7 of these 33 scans did bone marrow biopsy specimens from the iliac MDP crest contain neuroblastoma cells. Available technetium-99m methylene diphosphonate (MDP) whole-body scintigrams were also compared with the corresponding mIBG scans. Thirty-eight mIBG scans showed no visualization of the skeleton; ^{99m}Tc-MDP scintigrams were also normal. Seven patients with diffuse mIBG uptake in the skeleton appeared as normal on the ^{99m}Tc-MDP scans. Among 27 cases showing focal mIBG uptake in the skeleton with or without diffuse uptake, only 18 demonstrated a hot spot on the bone scintigram. The results of our study indicate that for the assessment of bone marrow infiltration by neuroblastoma, ^{123}I-mIBG scintigraphy is more sensitive than the conventional cytological examination of bone marrow smears routinely obtained from the iliac crest, has a very high sensitivity in excluding bone marrow invasion, has a high specificity for detecting bone marrow invasion, appears to be able to detect early tumoural deposits in the bone marrow before osseous invasion occurs as shown on the MDP scans and is superior to ^{99m}Tc-MDP bone scan in detecting bone/bone marrow metastases of neuroblastoma. In patients with a positive mIBG scan in the skeleton, bone marrow biopsy will not yield additional information.

Key words: Iodine-123 meta-iodobenzylguanidine – Neuroblastoma – Bone marrow biopsy – Technetium-99m methylene diphosphonate

Eur J Nucl Med (1993) 20:1154–1160

Correspondence to: K. Osmanagaoglu

Introduction

Neuroblastoma in children under the age of 15 years occurs at a rate of about 1/100000 per year. The median age at the time of diagnosis is around 2 years. The tumour may develop in any site where neural crest cells are present. Most of the tumours arise in the abdomen. Neuroblastoma may extend to surrounding tissue by local invasion or to regional lymph nodes via the lymphatics. Hematogenous spread most frequently involves bone marrow, skeleton and liver.

According to Evans [1], a special designation, stage IVs, is reserved for patients with small (stage I or II)

or unidentifiable primary tumours in whom remote involvement is confined to one or more of the following sites: liver, skin or bone marrow (not bone). Almost all such patients are under the age of 12 months. Patients with this form of neuroblastoma generally have a good prognosis with minimal or no therapy [1].

The degree of cell differentiation in neuroblastoma is variable. Most tumours consist of primitive neuroblastoma cells with little evidence of differentiation. Some tumours show admixtures of cells with larger amounts of cytoplasm, cytoplasmic processes, rosettes with central fibrillar material and mature ganglion cells [1].

Some neuroblastomas have a unique pattern of spontaneous regression. The spontaneous regression occurs particularly in patients under the age of 1 year who have stage I or stage IVs disease [1].

In staging neuroblastomas, the demonstration of tumoural invasion of the bone marrow is an important criterion with regard to the therapeutic prospects and the prognosis. Cytological examination of bone marrow samples has traditionally been used to establish the diagnosis.

For several years scintigraphy using meta-iodobenzylguanidine (mIBG), labelled with iodine-123 or iodine-131, which is stored in the neurotransmitter storage granules of chromaffin cells [2] and extravesicularly in the cells [3] and whose specific uptake is only provided by norepinephrine transporters in the cells [4], has been generally accepted as a very valuable and additional diagnostic tool in neuroblastoma [5, 6]. Scintigraphy using mIBG is employed for:

1. Primary diagnosis, if the primary tumour has not been localized by means of computed tomography (CT) or magnetic resonance imaging (MRI)
2. Identifying the neuroendocrine character of the tumour, even if it has been localized by other imaging procedures
3. Tumour staging to differentiate stage IV disease from lower stages as long as stage IV disease has not been established by bone marrow biopsy or ^{99m}Tc-MDP whole-body bone scan
4. Tumour follow-up (progress, recurrencies, metastases) [7]

In this paper the value of the ^{123}I-mIBG scan in the detection of bone/bone marrow invasion by neuroblastoma is evaluated in comparison with routine cytological bone marrow aspiration.

Materials and methods

In staging the neuroblastoma patients, at the time of diagnosis, we employed all the common imaging techniques (MRI, CT, ultrasonography) for detection of the locoregional extension of the tumour, ^{123}I-mIBG and ^{99m}Tc-MDP scintigraphy, and determination of catecholamines and their metabolites and neuron-specific enolase (NSE) in the blood and urine. Detection of metastasis was also done by the cytological examination of bone marrow aspiration biopsy specimens. During the follow-up the same diagnostic procedures were repeated at 3-month intervals for a minimum of 2 years. Bone scintigrams were not frequently repeated if they were negative initially.

One hundred and forthy-eight ^{123}I-mIBG scans of 26 children with neuroblastoma have been re-evaluated retrospectively. These scans, performed between 1987 and 1993 at the time of diagnosis and during the follow-up period, were compared with the results of bone marrow samples obtained within a 4-week period before or after scanning. Among 27 children, one had no mIBG uptake at the primary tumour site in the abdomen. This patient was not included in the study due to the assumption that if the primary tumour does not shown mIBG uptake, its metastases are not likely to do so.

The age of the patients ranged from 1 month to 13 years (mean 3.3 years) at the time of diagnosis. There were 14 boys and 12 girls. Seventeen of them had stage IV, three had stage IV-s, four had stage III and only two had stage I disease (staging according to the Evans classification [1]).

Unguided, unilateral bone marrow aspiration biopsies were performed at the anterior iliac crest and various smear samples were prepared from the aspiration material. These samples were cytologically analysed by an experienced hemato-oncologist. May-Grünwald-Giemsa staining was employed for morphological evaluation of the cells. Very few of the bone marrow aspirates were inadequate for evaluation. These non-evaluable smears were considered negative if they occurred during the interval between two negative bone marrow aspirations. This assumption was validated by later performed follow-up imaging and biopsy procedures. No immunocytochemical tests were performed.

Whole-body scans were performed at 6 and 24 h after the intravenous administration of 111 MBq (3 mCi) ^{123}I-mIBG (Medgenix); additional spot views were taken if necessary. Three day's premedication with a saturated solution of potassium iodide (30 mg/day) was used to block thyroid uptake of free ^{123}I.

Additionally in 22 patients 69 mIBG scans could be compared with concomitant whole-body ^{99m}Tc-MDP bone scans.

All scans were retrospectively and separately read by two residents and two experienced nuclear medicine physicians. Interpretations were compared later in order to reach a consensus.

Results

In this study only mIBG uptake in the skeleton and the bone marrow was considered. Soft tissue localizations were ignored. On the basis of our material, three types of mIBG uptake in the bone/bone marrow could be differentiated:

Table 1. Comparison of the mIBG scans with the corresponding bone marrow biopsies

mIBG	Bone marrow biopsy		Total
	Positive	Negative	
Negative	2	89	91
Diffuse uptake			
Without foci	8	0	
With foci	8	8	24
Mere foci	7	26	33
Total	25	123	148

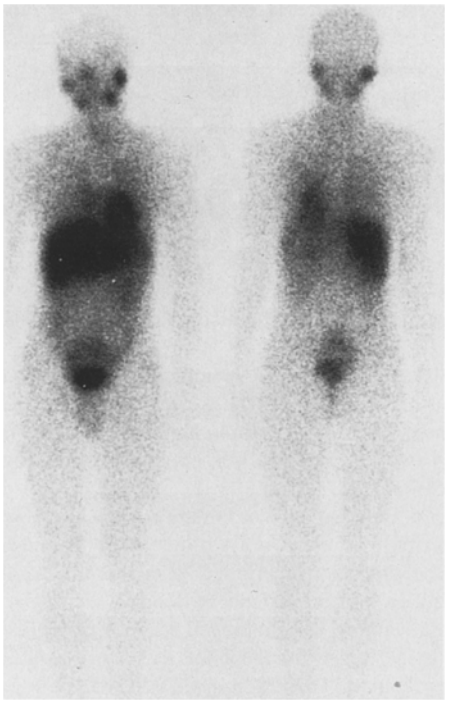

Fig. 1. The normal pattern ^{123}I-mIBG distribution; no visualization of the skeleton

1. No visualization of the skeleton (this is the normal pattern)
2. Diffuse tracer uptake in the skeleton with or without focally increased uptake, which indicates massive, diffuse bone marrow invasion by the tumour
3. Focal tracer accumulation in one or several bones.

The following results were obtained by comparison of the mIBG scans with the corresponding bone marrow biopsies (Table 1):

1. No tracer uptake was observed in the skeleton in 91 scans. In 89 of the 91, the bone marrow biopsy was negative. In only two cases could a few tumoural cells be shown.

2. Twenty-four scans showed diffuse skeletal uptake with or without foci. Among these 24, eight scans showing merely diffuse uptake correlated with positive bone marrow biopsies. Sixteen scans showed diffuse uptake with additional foci in one or more bones. In eight of these 16 scans the corresponding bone marrow biopsies appeared to be positive; the bone marrow biopsies were negative for the remaining eight scans.

3. Hyperactive foci in one or more bones without diffuse tracer accumulation in the skeleton were detected in 33 scans. For only seven of these 33 scans did bone marrow aspirates from the iliac crest reveal neuroblastoma cells.

When comparing the mIBG scans with the concomitant ^{99m}Tc-MDP whole-body bone scintigrams the folowing results were obtained:

1. Thirty-eight mIBG scans showed no visualization of the skeleton (Fig. 1); the matching ^{99m}Tc-MDP bone scans were also normal.
2. Seven cases with diffuse mIBG uptake in the skeleton appeared as normal on the ^{99m}Tc-MDP scans (Fig. 2).
3. Of 27 cases showing focally increased mIBG uptake in the skeleton with or without diffuse uptake, only 18 demonstrated a hot spot on the bone scintigram (Fig. 3).

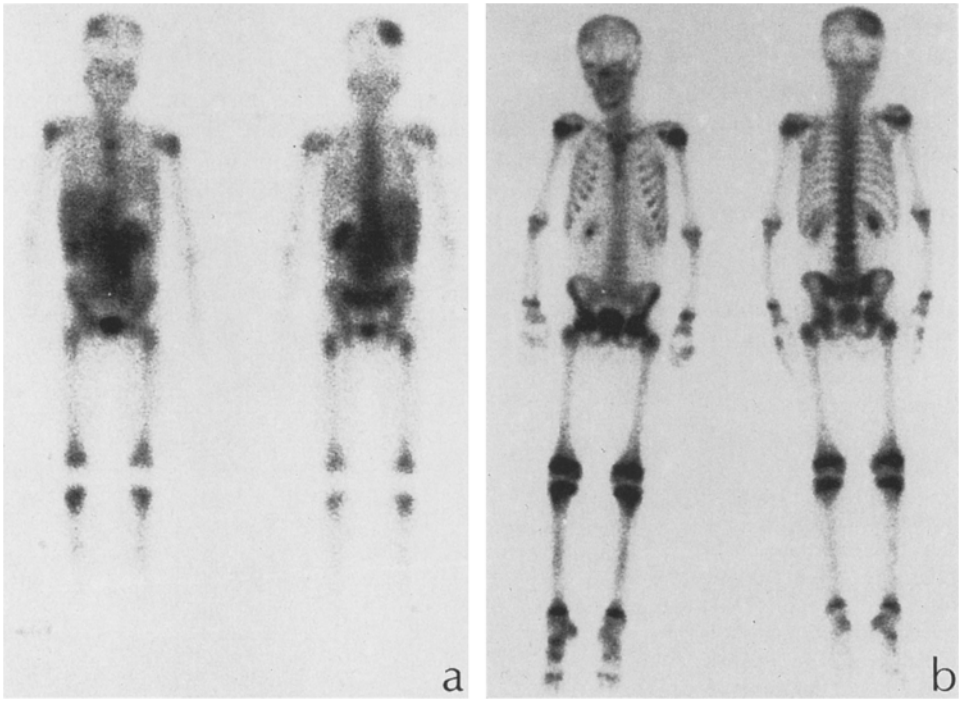

Fig. 2. a Diffuse ^{123}I-mIBG uptake in the whole skeleton with a focus in the skull. **b** Normal ^{99m}Tc-MDP uptake in the whole skeleton (with the exception of the focus in the skull) in the same patient

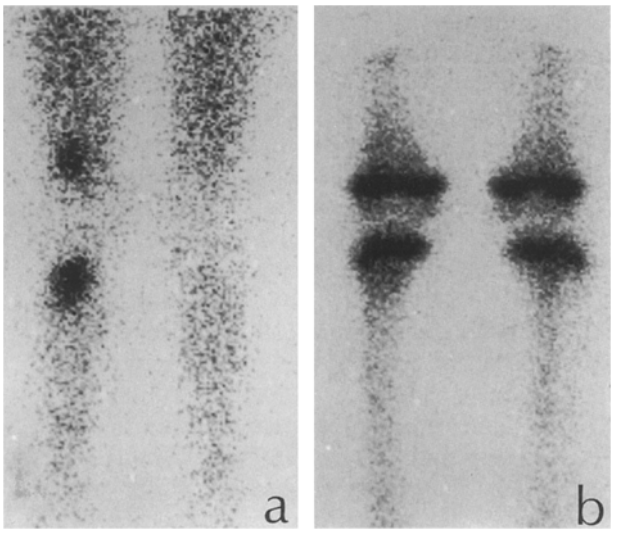

Fig. 3. a Two foci in the right distal femur and proximal tibia showing very clear uptake of ^{123}I-mIBG. **b** Bone scan of the same patient. Normal aspect of the right distal femur and only minimally increased ^{99m}Tc-MDP uptake in the right proximal tibia, not convincing for tumoural involvement

Discussion

When comparing the 91 normal mIBG scintigrams with the bone marrow smears, only two false-negative scans were detected. It is concluded that ^{123}I-mIBG scintigraphy is a sensitive method for excluding bone marrow invasion. The explanation for the false-negative scans may be the presence of only a very few tumoural cells in the bone marrow which are not able to provide sufficient tracer accumulation to be detected by the gamma camera. Other possible explanations for a negative scan are inhibition of the tracer uptake due to drug interactions or the non-secreting nature of the tumour. A similar opinion is also voiced in respect of such cases by Lumbroso et al. [8].

An abnormal increased uptake of mIBG in the skeleton may appear as diffuse and/or focal: Diffuse uptake, with or without foci, reflects massive, generalized bone marrow invasion. In these patients bone marrow biopsies were evidently mostly positive. However, in two of our patients several bone marrow biopsies at long intervals were all negative. Nevertheless the whole-body images showed an undoubtedly pathological diffuse tracer fixation in the bone marrow including the pelvis; in addition, a focus in the right parietal bone and at the base of the skull was visualized. We are therefore convinced that in these two patients bone marrow biopsies were falsely negative.

In cases where only focal localizations in the skeleton were found, only a small percentage of the bone marrow biopsies were positive. It can easily be understood that iliac crest biopsies are hardly representative for these cases. So, under these circumstances, the negativity of bone marrow biopsy is misleading. Similarly, Lumbroso et al. noted that bone marrow biopsies may be negative due to the spread of bone marrow metastases outside of commonly biopsied bones (sternum and iliac crest) [8]. The clinical evolution of these patients was unfavourable and confirmed the spread of the tumour. In addition, smears became positive in most of the cases approximately 2 months later. One the other hand, none of the patients with a negative bone marrow biopsy and a negative mIBG scintigram showed positive bone marrow smears before mIBG scintigraphy became abnormal during the follow-up.

We conclude that in the detection of bone marrow metastases of neuroblastoma, be they diffuse or localized, mIBG whole-body scintigraphy is a more sensitive method than single bone marrow aspiration biopsy. Attention should be given to the fact that routine biopsies are performed at the level of the iliac crest and represent only very limited sampling whereas mIBG uptake can be observed in the whole skeleton. It is therefore likely that bone marrow biopsies underestimate the rate of bone marrow metastases. It is not surprising that bone marrow biopsies from only one site are not capable of establishing the marrow involvement. Some studies suggest that bone marrow trephine biopsies significantly increase the detection of marrow involvement in comparison with marrow aspirates alone [9, 10]. One might suggest that multiple bone marrow biopsis be performed at different sites. However, this procedure is invasive and painful even under optimal conditions with local anaesthesia. Under general anaesthesia it is risky and not repeatable at short intervals during the follow-up. Furthermore, it has been reported that bilateral iliac crest biopsis do not significantly increase the rate of positivity for another tumour type (small cell lung cancer) [11]. A recent study by Perrin-Resche et al. [12] suggests that the combined use of MRI and bone scintigraphy is more sensitive than bone marrow biopsy for detecting bone marrow metastasis of small cell lung cancer. This raises questions as to the supposed absolute reliability and irreplaceability of bone marrow biopsy for all kinds of metastatic bone marrow disease. A recently published case report by Jonas et al. [13] demonstrates the potential of combined bone marrow scintigraphy and probe-guided bone marrow biopsy in detecting localized infiltrative lesions. A similar approach may also be utilized in neuroblastoma patients.

Our conclusion that the mIBG scan is the more sensitive method may be less valid if cytochemical techniques using monoclonal antibodies are applied in routine bone marrow aspiration analysis. It is noted in the literature that the sensitivity and specificity of the bone marrow smears for the detection of metastases of neuroblastoma are much higher when immunocytochemical techniques are used than with conventional staining methods [8, 14–18]. However, in these reports mostly non-commercially available monoclonal antibodies and freshly aspirated specimens are used, which makes the technique difficult to perform in daily routine.

The detection of metastatic neuroblastoma cells in bone marrow specimens by immunohistochemical methods without methodological constraints has been reported [19, 20]. The authors used immunochemical staining of NSE and/or chromogranin A in the demonstration of neuroblastoma cells in some histological sections that appeared normal.

Results of a study by Lumbroso et al. [8] support the view that histological and cytological examination of the bone marrow is more sensitive than mIBG scintigraphy. The authors report that one clump of metastatic cells per million normal bone marrow cells can be detected with cytological and histological methods whereas for a positive mIBG scan certain conditions must be fulfilled. Thus detection by mIBG scintigraphy is difficult in cases of non-secreting neuroblastoma (usually unable to take up mIBG), a minimum volume is required and contrast threshold for the detection of involved sites by the gamma camera is critical [8]. In addition, during the early phases of bone marrow infiltration, mIBG uptake may not be evident while bone marrow biopsy proves positive [21].

Another study [22] which was performed on the knee region (including tibia and distal femur) suggests that MRI is more sensitive than bone marrow cytology and mIBG scintigraphy in detecting marrow invasion by neuroblastoma; MRI may provide the first evidence of bone marrow involvement before positive mIBG and bone marrow aspiration biopsy findings appear. Some other recent studies have also demonstrated the high sensitivity of MRI for different kinds of tumoural infiltrations of bone/bone marrow [23–26]. Najean et al. [23] reported five cases of neuroblastoma with normal mIBG scans and reduced signal in the vertebral body on MR images, which may suggest that the mIBG scans were falsely negative. In three cases marrow infiltration was proven by biopsy; it is suggested that in the event of a negative mIBG scan and a positive MRI scan one may use ^{99m}Tc-MDP bone scintigraphy to complete the staging and in order to guide bone marrow biopsy.

A newly developed radiotracer (carbon-11 hydroxyephedrine) introduced by Shulkin et al. [27] for PET scanning of neuroblastoma shows significantly higher tumour/non-tumour ratios in comparison with mIBG and promises much better imaging quality and sensitivity for the primary tumour and probably for its metastases.

In our series no false-positive mIBG scans have been encountered. Jacobs et al. [28] have presented a case with skull metastasis, which was positive with mIBG during the follow-up. Following further chemotherapy, continuous regression was observed. A few months later the authors noticed a small but significant area of activity in the skull on the ^{123}I-mIBG scintigram whereas X-rays were normal and a biopsy performed at the same site did not reveal any tumour cells. The next mIBG scan was normal. The authors suggest that the mIBG scan performed at the time of the biopsy was false-positive. It has also been reported that positive mIBG foci may be found when no active neuroblastoma cells are discernible in the biopsy [21]. On the other hand, in a study concerning 115 scans it was reported that there were no false-positive mIBG scans for bony uptake [7]. The same observation was noted by Shulkin et al. in a group of 78 patients [29]. mIBG scans may return to normal after an interval of 6 weeks following chemotherapy [8]. Furthermore, it is generally accepted that roentgenography and X-ray computed tomography have a lower sensitivity than mIBG scintigraphy in detecting bone metastases for this particular disease [21, 30, 31].

mIBG examinations are of great value during the follow-up for detecting tumour relapse and bone marrow infiltration, especially before the onset of clinical symptoms and other indications like the production of catecholamines (vanillylmandelic acid, homovanillic acid or dopamine) [21].

It should be stressed that focal mIBG uptake due to mere bone marrow involvement without a bone lesion is also detectable. Bone metastases are generally regarded as starting in the bone marrow.

Although the primary aim of our study was to compare the bone marrow aspiration smears and mIBG scans, the available ^{99m}Tc-MDP bone scans of this group were also re-evaluated and correlated with matching ^{123}I-mIBG scans. Although ^{99m}Tc-MDP bone scans were positive in more than half of the patients with foci on their ^{123}I-mIBG scans, they were all negative in the patients with diffuse skeletal involvement on ^{123}I-mIBG scans. Bone scans were also negative in cases with negative ^{123}I-mIBG scans. No positive MDP scans were found if the ^{123}I-mIBG scintigram was normal. Our limited data suggest that the mIBG scintigram is more sensitive than the bone scintigram in the detection of bone/bone marrow metastases. The mIBG scan is able to show mere bone marrow localizations while the bone scan becomes positive at a further stage due to the reactive increased bone formation.

Most authors regard the mIBG scan as superior to the ^{99m}Tc-MDP bone scan in detecting small foci of bone metastases and/or diffuse bone marrow involvement [8, 21, 28, 32–35]. However, it is also reported that 10% of neuroblastomas fail to accumulate mIBG [36] and thus involved bony sites may escape detection, whereas MDP bone scan clearly demonstrates the lesions; this may cause an underestimation of the tumour dissemination [29, 32, 37–39].

For the clinician it is not essential to differentiate bone or bone marrow invasion in stage IV patients because in both situations staging, prognosis or therapeutic approaches are the same. However, for children less than 1 year old with a confined dissemination, the tumour is classified as stage IVs if bone marrow invasion exists whereas it is considered as stage IV in the case of bone involvement. This difference is important for the prognosis and the therapeutic approach. In cases

where the mIBG scans show positive foci which are not visible on the bone scan, one should conclude that there is merely bone marrow invasion and this is to be investigated further with MRI.

From our study the following conclusions can be drawn:

1. For the assessment of bone marrow infiltration by neuroblastoma, ^{123}I-mIBG scintigraphy is more sensitive than the conventional cytological examination of bone marrow smears which are routinely obtained from the iliac crest.
2. ^{123}I-mIBG has a high sensitivity in excluding bone marrow invasion.
3. ^{123}I-mIBG has a very high specificity for detecting bone marrow invasion.
4. ^{123}I-mIBG is able to detect early tumoural deposits in the bone marrow before osseous invasion occurs as shown on ^{99m}Tc-MDP bone scans.
5. ^{123}I-mIBG scintigraphy is superior to the ^{99m}Tc-MDP bone scan in detecting bone/bone marrow metastases of neuroblastomas.

The aim of the authors of this paper is not to suggest that bone marrow biopsy be replaced for the diagnosis and/or follow-up in neuroblastoma patients. In patients with a positive mIBG scan in the skeleton, however, bone marrow aspiration biopsy will not yield additional information. This is of practical importance during the follow-up procedure. Cases with a negative mIBG scintigram at the skeletal level should be further investigated by bone marrow biopsy.

Although in our study we have not detected any mIBG negative scan while the ^{99m}Tc-MDP bone scan was positive, it is reported in the literature that in some cases mIBG may fail to detect bone involvement which can be demonstrated by ^{99m}Tc-MDP bone scan [32, 37–39]. Therefore it may be advisable to use the ^{99m}Tc-MDP scan as a complementary method besides the mIBG scintigram and other laboratory techniques in order to avoid underestimation of tumour dissemination.

References

1. Behrman RE, Vaughan VC, Nelson WE. *Nelson textbook of pediatrics*. Philadelphia: Saunders; 1987: 1093–1095
2. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S Jr. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28: 1620–1624
3. Smets LA, Loesberg C, Janssen M, Ebtisam A, Metwally EA, Huiskamp R. Active uptake and extravesicular storage of *m*-iodobenzyl-guanidine in human neuroblastoma SK-N-SH cells. *Cancer Res* 1989;49: 2941–2944
4. Glowniak JV, Kilty JE, Amara SG, Hoffman BJ, Turner FE. Evaluation of metaiodobenzylguanidine uptake by the norepinephrine, dopamine and serotonin transporters. *J Nucl Med* 1993;34: 1140–1146
5. Geatti O, Shapiro B, Sisson JC, Hutchinson RJ, Malette S, Eyre P, Beierwaltes WH. Iodine-131 metaiodobenzylguanidine for the locating of neuroblastoma: preliminary experiences in ten cases. *J Nucl Med* 1985; 26: 736–742
6. Hoefnagel CA, Voûte PA, de Kraker J, Marcuse HR. Total body scintigraphy with 131 I-meta-iodobenzylguanidine for detection of neuroblastoma. *Diagn Imag Clin Med* 1985;54: 21–27
7. Hausegger KA, Fueger GF, Ebner F, Urban Ch. Indikationen zur mIBG-Szintigraphie in der Neuroblastomdiagnostik. *Nuklearmedizin* 1989;28: 34–40
8. Lumbroso JD, Guermazi F, Hartmann O, Coornaert S, Rabarison Y, Leclère JG, Counaet D, Bayle C, Caillaud JM, Lemerle J, Parmentier C. Meta-iodobenzylguanidine (mIBG) scan in neuroblastoma: sensitivity and specificity a review of 115 scans. *Prog Clin Biol Res* 1988;271: 689–705
9. Bostrom B, Nesbit ME, Brunning RD. The value of bone marrow trephine biopsy in the diagnosis of metastatic neuroblastoma. *Am J Pediatr Hematol Oncol* 1985;7: 303–305
10. Franklin IM, Pritchard J. Detection of bone marrow invasion by neuroblastoma is improved by sampling at two sites with both aspirates and trephine biopsies. *J Clin Pathol* 1983;36: 1215–1218
11. Widding A, Stilbo L, Hansen SW, Hansen HH, Rossing N. Scintigraphy with nanocolloid Tc 99m in patients with small cell lung cancer, with special reference to bone marrow and hepatic metastases. *Eur J Nucl Med* 1990;16: 717–719
12. Perrin-Resche I, Bizais Y, Buhe T, Fiche M. How does iliac crest bone marrow biopsy compare with imaging in the detection of bone metastases in small cell lung cancer? *Eur J Nucl Med* 1993;20: 420–425
13. Jonas M, Sciuk J, Dreyling M. 99m Tc-MAk-Knochenmarkszintigraphie und sondengezielte Punktion bei aplastischer Anämie. *Nucl Med* 1992;31: 202–204
14. Berthold F, Schneider A, Schumacher R, Bosslet K. Detection of minimal disease in bone marrow of neuroblastoma patients by immunoflorescence. *Pediatr Hematol Oncol* 1989;6: 73–83
15. Beck D, Maritazo, Gross N, Favrot M, Vultier N, Bailly C, Villa I, Gentilhomme O, Philip T. Immunocytochemical detection of neuroblastoma cells infiltrating clinical bone marrow samples. *Eur J Pediatr* 1988;147: 609–612
16. Moss TJ, Reynolds CP, Sather HN, Romansky SG, Hammond GD, Seeger RC. Prognostic value of immunocytologic detection of bone marrow metastases in neuroblastoma. *N Engl J Med* 1991;324: 219–226
17. Favrot MC, Frappaz D, Maritaz O, Philip I, Fontaniere B, Gentilhomme O, Bailly C, Zucker JM, Gentet JC, Kemshead J, Philip T. Histological, cytological and immunological analyses are complemetary for the detection of neuroblastoma cells in bone marrow. *Br J Cancer* 1986;54: 637–641
18. Combaret V, Favrot MC, Kremens B, Philip I, Bailly C, Fontaniere B, Gentilhomme O, Chauvin F, Zucker JM, Bernard JL, Philip T. Immunological detection of neuroblastoma cells in bone marrow harvested for autologous transplanation. *Br J Cancer* 1989;59: 844–847
19. Crary GS, Singleton TP, Neglia JP, Swanson PE, Strickler JG. Detection of metastatic neuroblastoma in bone marrow biopsy specimens with an antibody to neuron specific enolase. *Mod Pathol* 1992;5: 308–311
20. Boman F, Chastagner P, Floquet J, Sommelet D, Aymard B, Palau R, Kleinclaus I. Diagnostic histologique et immunohistochimique des métastases ostéomédullaires des neuroblastomes. *Bull Cancer* 1991;78: 943–951
21. Feine U, Mueller-Schauenburg W, Treuner J, Klingebiel Th. mIBG labeled with ^{123}I/^{131}I 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: 181–187

22. Benz-Bohm G, Gross-Fengels W, Widemann B, Linden A. Knochenmarkmetastasierung bei Neuroblastom: MRT im Vergleich zur Knochenmarkzytologie und mIBG-Szintigraphie. ROFO 1990;152: 523–527
23. Bourliere Najean B, Siles S, Panuel M, Cammileri S, Faure F, Devred P, Kaphan G. Value of MRI and mIBG-I 123 scintigraphy in the diagnosis of spinal bone marrow involvement in neuroblastoma in children. *Pediatr Radiol* 1992;22: 443–446
24. Kretschmer A, Dewes W, Graf N, Hau U, Kubale R, Kramann B, Sitzmann CF. MR-Tomographie der Unterschenkel bei Kindern mit Erkrankungen des hämatopoetischen Systems. *Nucl Med* 1992;31: 186–191
25. Algra PR, Postma T, van Groeningen CJ, van der Valk P, Bloem JL, Valk J. MR imaging of skeletal metastases from medulloblastoma. *Skeletal Radiol* 1992;21: 425–430
26. Layer G, Jarosch K. Magnetresonanztomographie des Knochenmarks zum Nachweis von Metastasen solider Tumoren. *Radiologe* 1992;32: 502–508
27. Shulkin BL, Wieland DM, Baro ME, Mitchell DS, Ungar DR, Dole MG, Hagen CA, Koeppe RA, Hutchinson RJ. PET studies of neuroblastoma with carbon 11-hydroxyephedrine. *J Nucl Med* 1993;34: 220P
28. Jacobs A, Delree M, Desprechins B, Otten J, Ferster A, Jonckheer MH, Mertens J, Ham HR, Piepsz A. Consolidating the role of I-mIBG scintigraphy in childhood neuroblastoma: five years of clinical experience. *Pediatr Radiol* 1990;20: 157–159
29. Shulkin BL, Shapiro B, Hutchinson RJ, Sisson JC, Mallette S, Mudgett EE. Comparison of bone and 131 I-mIBG scanning for the detection of skeletal and extraskeletal neuroblastoma. *Eur J Nucl Med* 1991;18: 553
30. Bomanji J, Conry BG, Britton KE, Reznek RH. Imaging neural crest tumours with 123 I-metaiodobenzylguanidine and X-ray computed tomography: a comparative study. *Clinic Radiol* 1988;39: 502–506
31. Mueller-Gaertner HW, Erttmann R, Helmke K. Metaiodobenzylguanidine scintigraphy in neuroblastoma: a comparison with conventional X-ray and ultrasound. *Pediatr Hematol Oncol* 1986;3: 97–109
32. Bouvier JF, Philp T, Chauvot P, Brunat Mentigny M, Ducrettet F, Maïassi N, Lahnèche BE. Pitfalls and solutions in neuroblastoma diagnosis using radioiodine mIBG: our experience about 50 cases. *Prog Clin Biol Res* 1988;271: 707–720
33. Shulkin BL, Shen SW, Sisson JC, Shapiro B. Iodine-131 mIBG scintigraphy of the extremities in metastatic pheochromocytoma and neuroblastoma. *J Nucl Med* 1987;28: 315–318
34. Hibi S, Todo S, Imashuku S, Miyazaki T. 131 I-metaiodobenzylguanidine scintigraphy in patients with neuroblastoma. *Pediatr Radiol* 1987;17: 308–313
35. Adolph J, Kimmig B. Diagnostik und Therapie neuroektodermaler Tumoren. *Radiologe* 1989;29: 32–42
36. Shulkin B, Shapiro B. Editorial. *J Nucl Med* 1993;34: 865
37. Gordon I, Peters AM, Gutman A, Morony S, Dicks-Mireaux C, Pritchard J. Skeletal assessment in neuroblastoma – the pitfalls of iodine-123-mIBG scans. *J Nucl Med* 1990;31: 129–134
38. Heyman S, Evans EA, D'Angio GJ. I-131 metaiodobenzylguanidine: diagnostic use in neuroblastoma patients in relapse. *Med Pediatr Oncol* 1988;16: 337–340
39. Sautter-Bihl ML, Bihl H, Heinze HG. Stellenwert der 99m Tc-MDP-Skelettszintigraphie beim Neuroblastom. Ist eine Neubewertung nötig? *Nuklearmedizin* 1991;30: 7–12