The use of both diagnostic and therapeutic MIBG in neuroblastoma patients
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Chapter 4

MRI-STIR and $^{123}$I-MIBG scintigraphy detection of osteomedullary lesions in metastatic neuroblastoma at diagnosis

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ABSTRACT

Purpose
Metaiodobenzylguanidine (MIBG) scintigraphy is highly sensitive and specific for staging of patients with neuroblastoma. About 10% of neuroblastomas are not MIBG-avid and, if MIBG-avid, differentiation between bone and bone marrow metastases is difficult. Short TI inversion recovery (STIR) magnetic resonance imaging (MRI) is highly sensitive for the detection of osteomedullary metastases. We retrospectively investigated detection of osteomedullary metastases by $^{123}$I-MIBG scintigraphy and MRI-STIR.

Methods
Diagnostic iodine-123 ($^{123}$I)-MIBG scans and MRI-STIR images from 10 patients with stage 4 neuroblastoma were evaluated for osteomedullary metastases in 14 different skeletal segments. Morphological characteristics were qualified as “focal”, “diffuse” or both types co-occurring.

Results
Of the in total 140 body segments, both MRI-STIR and $^{123}$I-MIBG imaging were available for 58 body segments. MRI-STIR showed more osteomedullary lesions than $^{123}$I-MIBG imaging ($p<0.01$). All 16 MIBG+/MRI⁺ lesions were focal on MRI-STIR (12 focal and 4 both types co-occurring) and all MIBG⁺/MRI⁻ lesions (n=3, 5%) were diffuse on $^{123}$I-MIBG imaging. For the body segments that had metastatic disease on both imaging modalities, discrepancy on characteristics of lesions were seen in seven focal lesions on $^{123}$I-MIBG, being diffuse (n=2) and both types co-occurring (n=5) on MRI-STIR and 13 $^{123}$I-MIBG diffuse lesions were focal (n=2) and both types co-occurring (n=11) on MRI-STIR.

Conclusion
MRI-STIR showed more osteomedullary lesions than $^{123}$I-MIBG scintigraphy and more often with a focal or a co-occurring focal + diffuse pattern.
INTRODUCTION

In 50% of patients with neuroblastoma distant metastases are present at the time of diagnosis, classifying these patients as stage 4, according to the International Neuroblastoma Staging System (INSS), or stage M, according to the international neuroblastoma risk group system (INRG) (1-3). To assess distant metastases the INRG recommends bilateral bone marrow biopsies/aspirates from the iliac crest and metaiodobenzylguanidine (MIBG) scintigraphy. Since there is no physiologic uptake of MIBG in bone or bone marrow, MIBG imaging is an accurate method for detecting osteomedullary metastases. The routine use of SPECT-CT to assign MIBG-positive lesions to a specific anatomic site is not proposed in these guidelines (3, 4). One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. However, a single equivocal lesion on MIBG scans requires confirmation with another imaging modality, namely, conventional radiography, and magnetic resonance imaging (MRI) or computed tomography (CT) if the radiographic findings are negative, or with biopsy (5). Technetium-99 (99mTc) bone scintigraphy is usually not required, except in cases in which the primary tumour is not MIBG-avid or MIBG-positivity cannot be confirmed (if the primary tumour is removed or is not MIBG-avid) (5). In current international neuroblastoma protocols 18F-FDG-PET-CT is being added to MIBG scintigraphy in case of MIBG-negative neuroblastoma. Although both bone and bone marrow metastases are independent prognostic factors (3-6), recent guidelines of the INRG do not require differentiation between bone and bone marrow metastases (3, 4). Because bone marrow metastases are assessed by bilateral bone marrow biopsies/aspirates from the iliac crest, focal bone marrow lesions outside the pelvis can be missed. MIBG scintigraphy can detect distant bone and bone marrow (osteomedullary) metastases. It has a sensitivity and a specificity to detect both the primary neuroblastoma and its distant metastases of 90% and 100% respectively, but no golden standards were used to detect bone metastases (4, 6). Different characteristics of MIBG-avid osteomedullary metastases on MIBG scintigraphy have been reported, such as “focal” and “diffuse”, possibly indicating bone and bone marrow metastases, respectively (7-12).

Short TI inversion recovery (STIR) is a highly sensitive MRI sequence for the early detection of bone marrow disease, but it is not specific for malignancy and hence less specific than MIBG scintigraphy for the detection of bone and bone marrow metastases in children with neuroblastoma (13). The exact role of this imaging technique for the detection of osteomedullary metastases in staging of patients with neuroblastoma still has to be determined (14, 15).

We hypothesise that because neuroblastoma metastases can be non-avid on MIBG, MRI can play a complementary role in the detection of osteomedullary metastases and MRI can help differentiate between bone from bone marrow metastasis with both imaging techniques. Therefore, we retrospectively compared the total number of lesions on...
123I-MIBG scintigraphy and MRI-STIR images in metastatic neuroblastoma patients and analysed and compared the different characteristics of lesions on MRI-STIR and 123I-MIBG scintigraphy (focal and diffuse lesions).

**METHODS**

**Patients**

Patients were included if they were diagnosed with histologically proven stage 4 neuroblastoma between March 2009 and June 2012 at the Emma Children’s Hospital – Academic Medical Centre (EKZ-AMC) and if a 123I-MIBG scan and a MRI-STIR scan at diagnosis were available.

This study was a retrospective analysis of 123I-MIBG and MRI-STIR images and was conducted in accordance with the principles of the Declaration of Helsinki and rules of the Good Clinical Practice. All patients and/or parents signed informed consent.

**Imaging techniques**

Diagnostic high-quality whole-body 123I-MIBG scans were selected, acquired according to protocols corresponding with European guidelines and INRG taskforce recommendations (14-16). Scans were excluded if all neuroblastoma lesions were MIBG-negative.

Concerning MRI-STIR, all patients were scanned on a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany). Only body segments, for which STIR sequences were performed in at least one plane, were evaluated. Slice thickness was 4 mm or less.

The observers were blinded to all other sequences.

Both MIBG and MRI-STIR imaging were performed within a time frame of maximal 6 days for each individual patient.

On both imaging modalities, metastatic spread was assessed in 14 skeletal segments if visualised by the technique (Figure 1). For both MIBG and MRI-STIR the morphological definition of a focal lesion was: sharply demarcated lesions, distinguishable from the background. For diffuse lesions this was on MIBG scintigraphy: indistinct margins, dispersed throughout the skeletal segment. For MRI-STIR this was identical, but with spread in at least 50% of the segment. Each body segment was scored as “focal”, “diffuse” or “co-occurrence of focal and diffuse” (when both types of lesions were present in one body segment).

On MRI-STIR hyper-intense lesions in the skeleton were numerically quantified and measured. Cortical destruction was recorded and if present this was considered to be bone metastases. All other skeletal lesions were considered bone marrow metastases.

Each 123I-MIBG scan was reviewed independently by a paediatrician and a medical doctor trained by a nuclear medicine physician specialised in the assessment of MIBG-scans. Each
MRI-study was reviewed independently by two paediatric radiologists with respectively 23 and 5 years of experience. Discrepancies were resolved by consensus.

Analyses

Because all $^{123}$I-MIBG scans were whole-body scans, all 14 body segments were depicted for all 10 patients (total 140). Whole-body MRI-STIR was not carried out systematically in every patient with neuroblastoma. Therefore in most patients only selected body parts were imaged with STIR sequences, mostly the trunk and the extremities. If a body segment was imaged on MRI-STIR for less than three patients, it was excluded for further analyses, because there were more than 60% missing studies. Both $^{123}$I-MIBG and MRI-STIR imaging could be positive (MIBG+/MRI+), both could be negative (MIBG-/MRI-), one of both types of imaging modalities could be positive and the other negative (MIBG-/MRI+ an MIBG+/MRI-). Differences between the results of both imaging modalities were assessed using McNemar’s test and Wilcoxon signed rank test. Moreover, the concordance of the characteristics of the lesions (“focal”, “diffuse” or “co-occurrence of focal and diffuse”) between $^{123}$I-MIBG and MRI-STIR imaging was assessed. When focal and diffuse lesions co-occurred in a body segment, it could be

![Figure 1: Body segments in scoring system](image)
present in the concordant and discordant groups, because one of the lesions was in agreement and one was not (focal co-occurrence, diffuse co-occurrence).

RESULTS

Ten patients were included in this study. In all patients bone marrow involvement was confirmed by bilateral bone marrow biopsies/aspirates from the iliac crest. Patient characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics</th>
<th>Number of patients: (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSS Stage 4:</td>
<td>10</td>
</tr>
<tr>
<td>Age (median (range)):</td>
<td>2.5 (0-6.6)</td>
</tr>
<tr>
<td>Sex ratio (M:F):</td>
<td>08:02</td>
</tr>
<tr>
<td>MYCN status:</td>
<td></td>
</tr>
<tr>
<td>MNA:</td>
<td>2</td>
</tr>
<tr>
<td>MYCNsc:</td>
<td>7</td>
</tr>
<tr>
<td>Unknown:</td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow involvement¹:</td>
<td>10</td>
</tr>
</tbody>
</table>

INSS: international neuroblastoma staging system; M: male; F: female; MNA: MYCN amplification; MYCNsc: MYCN single copy. ¹ bone marrow involvement tested with bilateral biopsies/aspirates from the iliac crest.

MRI-STIR images displayed more lesions than $^{123}$I-MIBG scintigraphy

On the $^{123}$I-MIBG scans, all 140 body segments of the ten patients were available and scored. On MRI-STIR images of these 10 patients 51 body segments were not depicted. In Table 2 an overview of the lesions scored in all available combinations of MIBG and MRI-STIR images is shown. For further statistical analyses, a body segment needed to be available on both scans for more than three patients. Therefore, seven body segments were excluded (total 31 segments) (Table 2, grey bars). For the other body segments (trunk, vertebral column, pelvis, left and right upper arm; left and right upper leg) further statistical analyses were performed (total 58 body segments).

MRI-STIR showed lesions in 44 of the 58 imaged body segments (76%), compared to 31 of 58 (53%) on $^{123}$I-MIBG imaging ($p<0.01$). Overall, $^{123}$I-MIBG and MRI-STIR image findings were concordant, concerning the presence and localisation of the lesions, in 39 of the 58 imaged body segments (67%). They were both positive (MIBG$^+/\text{MRI}^+$) in 28 (48%) and both negative (MIBG$^-/\text{MRI}^-$) in 11 (19%) of the 58 body segments available. In 16 of the 58 available body segments (28%) MRI-STIR showed lesions that were MIBG-non-avid (MIBG$^-/\text{MRI}^+$). In contrast, only three body segments (5%) were MIBG$^+/\text{MRI}^-$.
MRI-STIR images and $^{123}$I-MIBG scintigraphy differ in the characteristics of detected lesions

MRI-STIR and $^{123}$I-MIBG scans were both negative in 11 body segments (Table 2). Therefore, concordance between the characteristics of metastases was analysed in the remaining 47 body segments that showed a lesion on either of the two imaging types. MRI-STIR showed co-occurrence of focal and diffuse lesions in a body segment more often than $^{123}$I-MIBG imaging (21 vs. 1 segments) ($p<0.05$). Exclusively focal lesions in a body segment were more often visualised on MRI-STIR (17 versus 10 segments) (not significant). In contrast, exclusively diffuse lesions in a body segment were more often visualised on $^{123}$I-MIBG than on MRI-STIR imaging: 20 versus 6 segments (not significant).

In Figure 3A the concordant findings for characteristics of metastases per body segment between $^{123}$I-MIBG and MRI-STIR images are shown (example in Figure 4A). In 15 body segments $^{123}$I-MIBG and MRI-STIR images agreed on the presence of diffuse lesions (see Figure 3A for details), being exclusively diffuse on both imaging types in four body

Table 2: presence of metastases on $^{123}$I-MIBG v MRI-STIR imaging

<table>
<thead>
<tr>
<th>Body segments</th>
<th>MIBG+/MRI+/</th>
<th>MIBG-/MRI-/</th>
<th>MIBG-/MRI+</th>
<th>MIBG+/MRI-</th>
<th>No. patients with both MIBG and MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dome of skull</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Base of skull</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Facial bones and orbits</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Thoracic cage</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Pelvis</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Vertebral column</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Upper arm left</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Upper arm right</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Fore arm and hand left</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Fore arm and hand right</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Upper leg left</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Upper leg right</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Lower leg and foot left</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Lower leg and foot right</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>36</strong></td>
<td><strong>20</strong></td>
<td><strong>26</strong></td>
<td><strong>7</strong></td>
<td><strong>89</strong></td>
</tr>
<tr>
<td><strong>Included</strong></td>
<td><strong>28</strong></td>
<td><strong>11</strong></td>
<td><strong>16</strong></td>
<td><strong>3</strong></td>
<td><strong>58</strong></td>
</tr>
</tbody>
</table>

MIBG: Iodine-123-metaiodobenzylguanidine; MRI-STIR: magnetic resonance imaging - short TI inversion recovery; +: positive on imaging; -: negative on imaging; no.: number of. TOTAL: all body segments depicted. Included: the body segments for which analysis were performed (58 in total). Dark grey shading: body segments with less than 3 (out of 10) MRI-STIR images (excluded).
segments and with additional focal lesions on MRI-STIR in 11. In only eight of the 47 body segments $^{123}$I-MIBG and MRI-STIR imaging agreed on focal lesions, being exclusively focal on $^{123}$I-MIBG imaging in all eight segments and on MRI-STIR additional diffuse lesions were detected in five segments.

Overall, full concordance was only present in eight body segments (17%) of all 47 body: three segments with exclusively focal lesions, four with exclusively diffuse lesions and one segment with co-occurring focal and diffuse lesions.

Discrepant findings were observed in 39 out of 47 body segments. Two types of discordance could be discriminated: 1. negative findings on one imaging technique and positive on the other in 19 body segments (Table 2 and Figure 4B); and 2. positive findings on both imaging types, but different characteristics of lesions in 20 body segments. In the 16 MIBG-negative body segments MRI-STIR detected focal lesions in 12 segments and co-occurrence of focal and diffuse lesions in 4 body segments. The 3 MRI-STIR-negative body segments (6%) all had diffuse lesions on $^{123}$I-MIBG imaging.

Concerning the second type of discordance, 7 body segments with exclusively focal lesions on $^{123}$I-MIBG imaging, were depicted as diffuse lesions in 2 body segments on MRI-STIR imaging and with both types of lesions co-occurring in 5. Of the 13 diffuse lesions on $^{123}$I-MIBG imaging, two were exclusively focal on MRI-STIR (see Figure 4C for example) and 11 showed co-occurrence of focal and diffuse lesions on MRI-STIR.

**Figure 2:** Number of focal, diffuse and co-occurrence of both types of metastases on $^{123}$I-MIBG and MRI-STIR

MIBG: Iodine-123 ($^{123}$I) -metaiodobenzylguanidine; MRI-STIR: magnetic resonance imaging – short TI inversion recovery. F+D: co-occurrence of focal and diffuse lesions.

On MRI-STIR significantly more focal and diffuse lesions co-occurred than on $^{123}$I-MIBG imaging (p<0.05).
Bone versus bone marrow metastases

Bone metastases were defined as lesions showing cortical destruction on MRI-STIR. We documented 3 body segments (three different patients) with cortical destruction (see Table 3) and compared these body segments with the characteristics of the lesions on both imaging modalities. Two patients (nr 1 and 3) with cortical destruction in the upper legs on MRI-STIR showed exclusively diffuse lesions in this body segment on both the MRI-STIR and $^{123}$I-MIBG images. One patient (nr 2) with cortical destruction in the trunk
Table 3: Cortical destruction on MRI-STIR and the characteristics of metastases on MIBG imaging

<table>
<thead>
<tr>
<th>Body segments:</th>
<th>Characteristics</th>
<th>MRI-STIR:</th>
<th>MIBG:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 Upper leg left</td>
<td></td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Patient 2 Trunk</td>
<td></td>
<td>F</td>
<td>-</td>
</tr>
<tr>
<td>Patient 3 Upper leg right</td>
<td></td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

Cortical destruction was displayed in three body segments in three patients. F: focal; D: diffuse; MRI-STIR: magnetic resonance imaging – short TI inversion recovery; MIBG: Iodine-123-metaiodobenzylguanidine scintigraphy.

Figure 4A: Concordant findings on $^{123}$I-MIBG and MRI-STIR

The focal lesion in the left femur on $^{123}$I-MIBG imaging was shown as a focal lesion at the exact same localization on MRI-STIR.

Figure 4B: Discordant findings on $^{123}$I-MIBG v MRI-STIR

The focal and diffuse lesions in the femora and tibiae were not visible on $^{123}$I-MIBG imaging.
(a rib) on MRI-STIR had a focal lesion in this body segment on MRI-STIR, but the $^{123}$I-MIBG image was negative for this body segment.

**DISCUSSION**

In this small patient group ($n=10$) we found that 48% of the 58 available body segments showed lesions positive for both $^{123}$I-MIBG and MRI-STIR (MIBG+/MRI+), 19% were negative for both techniques (MIBG-/MRI-), in 29% the lesions were MIBG-/MRI+ and in only 5% MIBG+/MRI-.

An explanation for the fact that MRI-STIR showed a higher number of lesions than $^{123}$I-MIBG scintigraphy, may be that MRI is a high resolution imaging technique enabling sensitive detection of bone marrow reaction (14, 15). However, hyper-intense signal changes in bone marrow on MRI-STIR are not specific for bone marrow metastases; all abnormalities with an increased water content will show as hyper-intense lesions, such as oedema, inflammation or infection, cysts and haemangioma (16).

Due to the characteristics of the radiopharmaceutical, $^{123}$I-MIBG imaging is a highly specific imaging modality, but the mostly used two-dimensional planar imaging technique and physiological uptake in soft tissue hampers contrast resolution, and therefore sensitivity. Routine use of SPECT-CT with $^{123}$I-MIBG scintigraphy could partly solve this problem (6). So one can imagine that early tumour infiltration, can lead to changes in the bone marrow that are already visible on MRI-STIR before these lesions are large enough to be visible on MIBG scintigraphy.

The discrepancy concerning diffuse lesions on $^{123}$I-MIBG imaging being either exclusively focal (diffuse/focal) or with additional focal lesions on MRI-STIR may be explained by the
lower spatial resolution of MIBG, merging multiple focal lesions into a diffuse lesion (see the example in Figure 4B). Diffuse reactive alterations (e.g. oedema, bruises, inflammation) on MRI may be another explanation for this discrepancy (15).

Surprisingly, ¹²³I-MIBG imaging displayed diffuse lesions in three body segments when the MRI-STIR did not show any lesion. One of these diffuse lesions was present in the thoracic cage and was located in the soft tissue on MRI-STIR. Abnormal MIBG uptake in the thoracic cage is difficult to assess, because the skeletal structures (like the ribs and the clavicles) are small and physiological uptake in the myocardium and the liver may obscure the skeletal lesions on two-dimensional scans or falsely overestimate uptake in the ribs, risking false-positive results. The two other lesions were located in the upper arms. Although, physiological uptake in surrounding tissue does not play a major role, one of these lesions located in the upper arms, was located in the soft tissue on MRI-STIR. In this study we investigated only patients with metastatic MIBG-avid disease and found a discrepancy of 28% in number of detected osteomedullary lesions between ¹²³I-MIBG and MRI, in favour of MRI. One can wonder if in patients classified with lower stages based on absence of MIBG-avid metastases and negative bone marrow smears, this might also be the case. At diagnosis, all patients routinely undergo bone marrow biopsies/aspirates from the iliac crest, hence bone marrow disease is investigated. On the MRI-STIR images, more often focal than diffuse abnormalities were detected, so sites outside the pelvic crest, particularly the focal ones, might have been missed by bone marrow investigations restricted to the iliac crest. However, the patients in this study all had bone marrow involvement confirmed by bilateral bone marrow biopsies/aspirates from the iliac crest.

We were not able to differentiate bone from bone marrow metastases on whole-body ¹²³I-MIBG scintigraphy, partly because of its two-dimensional nature (4, 6, 9, 17, 18). It has been reported that MRI has a sensitivity of 82% for the detection of stage 4 neuroblastoma, but this accounts rather for regional than for whole-body imaging, and for the detection of bone metastases particularly (14, 19). In a comparative study in 13 children with neuroblastoma, sensitivity for the detection of bone metastases was substantially higher for whole-body MRI (100%) than for ¹²³I-MIBG scintigraphy (25%) (20, 21). However, low specificity is a disadvantage and therefore additional ¹²³I-MIBG imaging is required for the definite diagnosis of neuroblastoma (21). Another limitation of MRI-STIR is that it can be difficult to differentiate highly cellular hematopoietic marrow (red marrow) from metastatic disease in children (15). The main disadvantage of whole-body MRI is that it is a long procedure and young children need to be sedated. However, the high diagnostic accuracy in staging neuroblastomas and its lack of ionizing radiation make it an excellent tool in paediatric patients (21). Hence, whole-body MRI-STIR could be a promising technique for the detection of bone and bone marrow metastases and for staging children with neuroblastoma.

Because most lesions in our study were confined to the bone marrow on MRI-STIR and did not show any cortical destruction, we assumed these to be bone marrow lesions. They
presented on MRI-STIR as diffuse, focal, or with both types of lesions co-occurring. This might imply that different types of bone marrow metastases exist, possibly correlating with different biological processes. Another more plausible explanation might be that all lesions start as small focal sites of bone marrow infiltration, which may grow and become diffuse lesions within the bone marrow and may eventually affect the cortical bone. Therefore, instead of differentiating between bone and bone marrow metastases, the term “skeletal” or “osteomedullary” metastases might be more appropriate.

**Study limitations**

A first limitation is the small number of patients that could be included because MRI-STIR was not routinely performed at initial diagnosis. We selected only MRI-STIR and not other MRI-sequences, because STIR-sequence is known to be a robust sequence for the detection of changes in the hypercellular bone marrow in children (15, 21). Moreover, MRI-STIR images frequently were performed for selected body parts, mostly the trunk and extremities. To be included, a body segment needed to be available on both scans for more than three patients and consequently seven body segments were excluded. Thus, inclusion bias cannot be excluded.

Furthermore, we defined bone metastases when cortical destruction was visible, because in that case it was clear that the bone was involved. However, before the cortex is destructed it might be invaded with tumour cells, and this cannot be detected with MRI-STIR.

Lastly, a golden standard for bone as well as for bone marrow metastases was lacking in this study. We assumed MRI-STIR to detect and differentiate bone from bone marrow metastases. We did not use bone scintigraphy to detect bone metastases, because it was not performed in most patients and because bone metastases on bone scintigraphy are commonly only visible at an advanced stage of the disease (16).

**Future perspectives**

We know that 10% of all neuroblastomas are MIBG-non-avid, but neuroblastoma metastases can be both MIBG-avid and -non-avid in the same patient at the same time. This raises the question how many of these MIBG-non-avid lesions exist in each patient. Furthermore, these lesions will not be assessed in currently used MIBG scoring methods, possibly underscoring tumour burden, and we do not know if these MIBG non-avid lesions will become MIBG avid in time. So ideally, a prospective study should be undertaken to investigate the clinical relevance of whole-body MRI with STIR sequence or a combination of sequences, to increase the specificity, and MIBG imaging at initial diagnosis and during therapy in patients with all stages of neuroblastoma.
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