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A Systematic Literature Review of Imaging Definitions for Detection of Bone and Bone Marrow Metastases in Neuroblastoma Patients

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Abstract

Objective: The presence of bone and bone marrow (BM) metastases in neuroblastoma patients are independent adverse prognostic factors, so precise and consistent definitions of both categories on imaging are important. The objectives of this systematic review were to identify all definitions reported for detection of bone and bone marrow metastases on imaging in neuroblastoma to determine diagnostic accuracies of the most frequently used definitions for detection of bone and/or BM metastases on each imaging technique.

Methods: We searched MEDLINE/PubMed (1945 to April 2013) and EMBASE/Ovid (1980 to April 2013). Full-text original studies were included if they reported definitions of bone and/or BM metastases on diagnostic imaging of children with suspected metastatic neuroblastoma. As reference standard for bone metastases bone scintigraphy was used and for bone marrow metastases bone marrow biopsies/aspirates. Methodological quality was assessed.

Results: Of 403 identified studies (plus one relevant reference), 131 were assessed in full-text and 31 finally included, 23 described BM metastases and 18 bone metastases. No uniform definitions of bone and bone marrow metastases were reported for each imaging method. On MIBG scintigraphy bone metastases were mostly defined as "focal" and BM metastases as "diffuse" and on MRI both definitions were used for BM metastases. The diagnostic accuracy of different diagnostic methods to detect bone (reference test bone scintigraphy) or BM (reference test bone marrow biopsies/trephines) metastases varied widely.

Conclusion: No uniform definitions of bone and bone marrow metastases were reported for each imaging method and concerning the diagnostic accuracy no general conclusions could be drawn.

Keywords: Neuroblastoma; Bone metastases; Bone marrow metastases; Diagnostic imaging; MIBG scintigraphy; MRI

Introduction

Overall survival (OS) of high-risk neuroblastoma patients is about 40% despite intense multi-modality treatment [1-4], although the addition of anti-GD2 therapy might improve this outcome [5]. High-risk neuroblastoma is defined by the presence of distant metastases and/or the presence of biological factors like amplification of the MYCN gene (MNA). Because bone and bone marrow metastases are reported to be independent poor prognostic factors [6-10], it is necessary to have clear and uniform definitions of respectively bone metastases and bone marrow metastases, as well as a need of clear discrimination of both types of metastatic disease.

Ladenstein and co-workers reported an inferior outcome for patients with bone marrow metastases at initial diagnosis and furthermore an inferior, but not identical outcome for patients with bone and bone marrow metastases before mega-therapy [10]. In patients with metastatic disease younger than one year at diagnosis, the presence of bone metastases is reported to be associated with an inferior outcome [7]. According to the consensus paper of the International Neuroblastoma Risk Group (INRG), for the diagnosis of stage MS a maximum of 10% bone marrow invasion is allowed, and bone metastases are not [11,12]. In contrast to protocols for bone marrow involvement, no standardized protocols for the definition and differentiation of bone from bone marrow metastases on imaging are reported.

Because many studies report on the presence of both bone marrow and bone metastases detected on different imaging methods, such as metaiodobenzylguanidine (MIBG) scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, like Technetium-99m-methylene diphosphanate (^{99m}Tc-MDP) scintigraphy, and fluorine-18-fluorodeoxy-glucose positron emission tomography (^{18}F-FDG-PET) [7,13,14], we wondered what definitions were used in these papers.

So the objectives of this systematic review were to identify all published definitions of bone and bone marrow metastases on all different imaging modalities; and to determine the diagnostic accuracy to detect bone and bone marrow metastases, with these published definitions on the different imaging methods.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this review [15].

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Search strategy

We searched MEDLINE/PubMed (from 1945 to April 2013) with a combination of the following controlled vocabulary and text words:

((“Neuroblastoma”[Mesh:noexp] OR neuroblastoma[tiab] OR neuroblastomas[tiab]) AND (“Bone Neoplasms/secondary”[Mesh] OR bone metasta*[tiab] OR “Bone Marrow Neoplasms/secondary”[Mesh] OR bone marrow metasta*[tiab] OR skeletal metasta*[tiab]) AND (“Diagnostic Imaging”[Mesh] OR diagnostic imaging[tiab] OR radionuclide imaging[tiab] OR scintigraphy[tiab] OR SPECT[tiab] OR radiography[tiab] OR x-ray[tiab] OR *tomography[tiab] OR ultrasonography[tiab] OR magnetic resonance imaging[tiab] OR MRI[tiab]ORPET[tiab]ORMIBG[tiab]OR3-Iodobenzylguanidine[tw] OR technetium Tc 99m medronate[tw] OR fluorodeoxyglucose f18[tw] OR fdg[tiab] OR radiopharmaceuticals[pa]))

(Abbreviations: Mesh: Medical subject headings; Noexp: not exploded; Tiab: title and abstract; Tw: text word (=title and abstract); Pa: pharmacological.action; *: zero or more characters)

We also searched EMBASE/Ovid (from 1980 to April 2013) with a combination of the following controlled vocabulary and text words:

i. neuroblastoma/

ii. (neuroblastoma or neuroblastomas).ti,ab.

iii. 1 or 2

iv. bone metastasis/

v. bone marrow metastasis/

vi. (bone adj2 metastas*).ti,ab.

vii. (skeletal adj2 metastas*).ti,ab.

viii. or/4-7

ix. exp radiopharmaceutical agent/

x. exp diagnostic imaging/

xi. diagnostic imaging.ti,ab.

xii. radionuclide imaging.ti,ab.

xiii. scintigraphy.ti,ab.

xiv. SPECT.ti,ab.

xv. exp bone radiography/

xvi. radiography.ti,ab.

xvii. x-ray.ti,ab.

xviii. exp *tomography/

xix. *tomography/.ti,ab.

xx. ultrasonography.ti,ab.

xxi. magnetic resonance imaging.ti,ab.

xxii. MRI.ti,ab.

xxiii. PET.ti,ab.

xxiv. MIBG.ti,ab.

xxv. Iodobenzylguanidine.tw.

xxvi. Tc 99m.tw.

xxvii.fluorodeoxyglucose.tw.

xxviii. fdg.tw.

xxix. or/9-28

xxx. 3 and 8 and 29

(Abbreviations: Pa: pharmacological.action; /: word as subject heading (EMBASE); Ti.ab: title and abstract; Exp: explode; Tw: textword (=title and abstract); *: zero or more characters)

The resulting list of articles was supplemented through crosschecking of reference lists of relevant articles and review articles. If studies were reported in conference proceedings, we searched for full publications.

Eligibility criteria for study selection

Objective 1: Definitions of bone and bone marrow metastases: Studies were included if they reported on the use of diagnostic imaging in children (<18 years old) with neuroblastoma, English language was used, they described definitions of bone and/or bone marrow metastases, and if they were original reports (no reviews) and were reported as full-text studies. We clearly stated reasons for exclusion for any study considered for the review. In case of duplicate publications we used the most recent paper.

Objective 2: Diagnostic accuracy of all imaging techniques to detect bone and/or bone marrow metastases: From all studies that were included for objective 1, only studies that compared the results of an index test with a reference test, thus providing sensitivity and specificity, or data to calculate them, were included.

The literature was studied for bone and bone marrow metastases separately. Unless stated differently, in this review of the literature, we used bone marrow biopsies or aspirates as reference standard for bone marrow metastases [12] and bone scintigraphy for bone metastases. The results were described separately for bone and bone marrow metastases.

For both objective 1 and 2, two reviewers independently assessed all potentially eligible studies. First selection was performed on title and abstract. Next, the full text versions of the selected articles were reviewed to determine their eligibility for inclusion in the study. Disagreements were resolved by discussion.

Data collection

Objective 1: Definitions of bone and bone marrow metastases

The following items were scored for each included study:

a) Study population: age, sex, stage of neuroblastoma, primary or recurrent neuroblastoma, in- and exclusion criteria, number of subjects (including number eligible for the study, number enrolled in the study);

b) Description of diagnostic imaging method describing bone and/or bone marrow metastases;

c) Used definitions of bone and/or bone marrow metastases.

Objective 2: Diagnostic accuracy of all imaging techniques to detect bone and/or bone marrow metastases

We extracted data on the following additional items:

a) True positive, false negative, false positive and true negative

findings on diagnostic modalities for the detection of bone and/or bone marrow metastases (if not enough data were available to calculate sensitivity and/or specificity ourselves, we used the sensitivity and/or specificity as reported in the article);

b) The number of assessments (a patient could have more than one scan, e.g. at initial diagnosis and/or one or more during treatment or follow-up) and/or the number of lesions in the sensitivity/specificity analyses (out of the total number of eligible patients and/or lesions); and

c) The reference standards used in the sensitivity/specificity analyses.

For both objectives 1 and 2, two review authors performed data extraction independently, using standardized forms.

Methodological quality assessment

For each study eligible for objective 2, the risk of bias and concerns regarding applicability on four domains were scored namely patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard (flow and timing) according to a modified version of the QUADAS-2 tool (Table 1) [16]. Because studies could report on bone and/or bone marrow metastases, we scored them separately.

Two authors independently assessed methodological quality of the studies. Disagreements were resolved by discussion.

Statistical analyses

We calculated sensitivity and/or specificity using two-by-two tables (consisting of true positives, false negatives, false positives and true negatives) in MS-Excel. Unless stated differently, we used bone marrow biopsies or aspirates as reference standard for bone marrow metastases [12] and bone scintigraphy for bone metastases. Sensitivity was calculated as true positives divided by all positives (true positives + false negatives) and specificity as true negatives divided by all negatives (true negatives + false positives). Imaging could be performed at initial diagnosis and during treatment and follow-up. Therefore, analyses on diagnostic accuracy were performed on assessment level for all included studies. If data per lesion were available, we also calculated and reported the sensitivity and specificity at lesion level.

Pooled analysis only included studies that used the same index test, the same reference standard and the same definitions of bone and bone marrow metastases and if at least 10 patients (in total) were available. Data of ^{123}I- and ^{131}I-MIBG scans were not analysed separately, because it was reported in the literature that there is no significant difference in results by type of scan [17].

Results

Selection of articles

The search of the electronic databases of MEDLINE/PubMed and EMBASE/Ovid (in April 2013) yielded a total of 403 references (Figure 1). A total of 30 studies fulfilled the inclusion criteria of this review. Screening the reference lists of reviews and relevant articles identified one additional study, so a total of 31 studies were eligible for inclusion in this review.

The reasons for exclusion for 101 studies are provided in Supplementary Table 1.

Characteristics of included studies

Objective 1: Definitions of bone and bone marrow metastases: Of the 31 studies, 8 studies formulated a definition of bone metastases [8,18-24], 13 of bone marrow metastases [25-37] and 10 defined both types of metastases [38-47] (Table 2). The included studies used different imaging methods to detect bone or bone marrow metastases (per study often more than one imaging method was used). The most frequent reported imaging technique was MIBG scintigraphy (15 of 31 studies). 8 studies reported on ^{123}I-MIBG [27,31,36,38-40,44,45], 4 on ^{131}I-MIBG [23,29,33,46] and in 3 studies it was not clear [8,43,47].

12 studies reported on MRI, with a variety of MRI sequences: 1 reported on MRI with short TI inversion recovery (STIR), and MRI-gadolinium (gad)-T1, as well on MRI-T1 and MRI-T2 [41], 1 on MRI-STIR, MRI-gadolinium (gad)-T1 and MRI-T1 [32]; 1 on MRI-STIR only [24]; 7 on MRI-T1 or -T2 [22,26-28,30,34,35]. 2 studies did not define the type of MRI [31,36]. 10 studies reported on bone scintigraphy [21,23,24,38-40,42,44,45,47]; 8 on conventional radiographs [8,18-20,23,37,44,47]; 6 on computed tomography (CT) [18-20,24,37,44]; and 1 on ^{18}F-FDG PET (with or without CT) [43], ^{99m}Tc-sestamibi (MIBI) scintigraphy [52], ^{99m}Tc-sulphur colloid scintigraphy [26], ^{131}I-3F8

Domain	Patient Selection	Index Test	Reference Test	Flow and Timing
Description	Describe methods of patient selection.	Describe the index test and how it was conducted and interpreted.	Describe the reference standard and how it was conducted and interpreted.	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table.
Signalling Questions	– Consecutive or random sample? – Case-control design avoided? – Inappropriate exclusions avoided?	– Interpreted without knowledge of the reference test?	– Likely to correctly classify the target condition? – Interpreted without knowledge of the index test?	– Appropriate interval between index and reference test (< 2 weeks)? – Did all patients receive the reference standard? – Did all patients receive the same reference standard? – Were all patients included in the analysis (high risk bias if >10% missing data)?
Risk of Bias	Could the selection of patients have introduced bias?	Could the interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias
Concerns Applicability	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	
*According to a modified version of the QUADAS-2 tool				

Table 1: Methodological quality assessment [16]*.

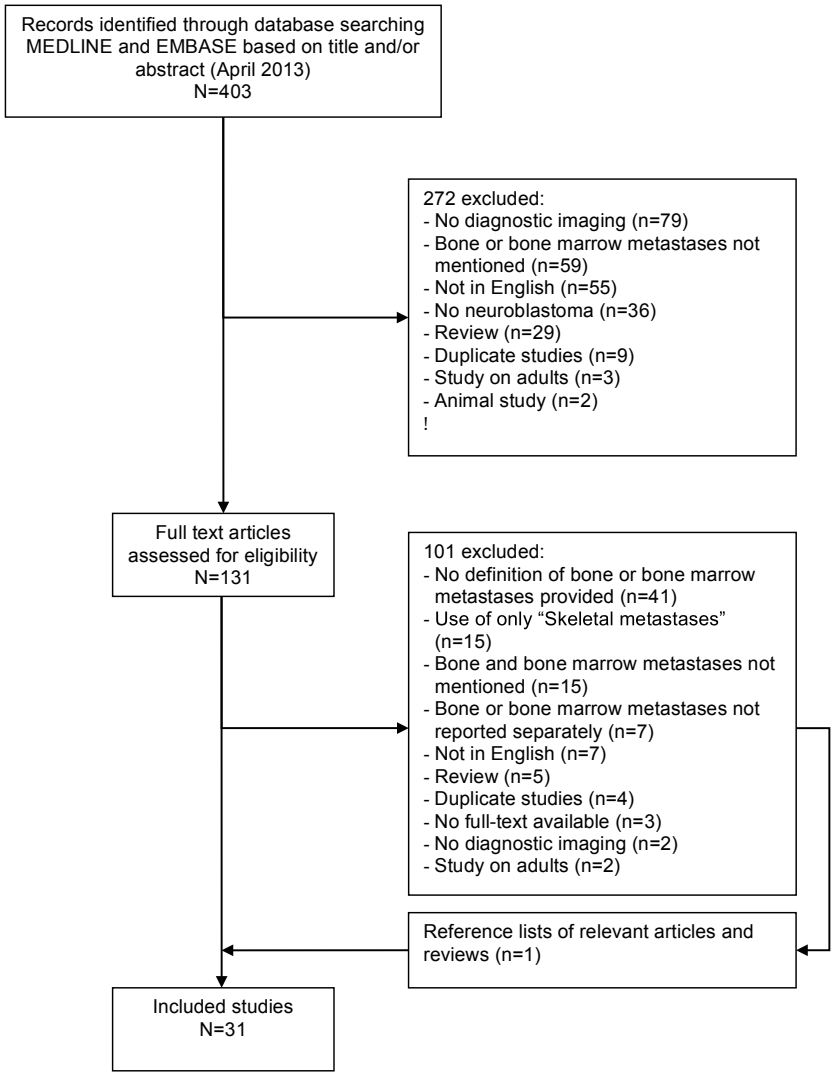

Figure 1: Flow chart Inclusion of studies.

Study	MIBG n=15		MRI n=12		BS n=10		RAD n=8		CT n=6		PET n=1		MIBI n=1		SC n=1		3F8 n=1		PEN n=1		TI n=1	
Type of Metastases	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**
Howman-Giles et al. [21]					+	-																
[a]Chirathivat et al. [18]							+	-	+	-												
[b]Cohen et al. [26]			-	+											-	+						
Shulkin et al. [33]	-	+																				
Fletcher et al. [28]			-	+													-	+				
Corbett et al. [27]	-	+	-	+																		
Hanna et al. [41]			-	+			+	-														
[d]Ruzal Shapiro et al. [22]							+	-	+	-												
[c]Haddad et al. [37]			-	+																		
Shulkin et al. [23]	+	-			+	-																
Osmanagoaglu et al. [45]	+	+			+	-																
Tanabe et al. [34]			-	+																		
Turba et al [47]	-	+			+	-	+	-														
Claudiani et al. [38]	+	+			+	-																
[e]Giammarile et al. [39]	+	+			+	-																
Hadj Djilani et al. [40]	+	+			+	+																

Study	MIBG n=15		MRI n=12		BS n=10		RAD n=8		CT n=6		PET n=1		MIBI n=1		SC n=1		3F8 n=1		PEN n=1		TI n=1	
Type of Metastases	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**	**B**	**BM**
Tanabe et al. [35]			-	+																		
[f]Lebtahi et al. [31]	-	+	-	+																		
Minard et al. [8]	+	-					+	-														
Kushner et al. [43]	+	+									+	+										
[g]Okuyama et al. [44]	+	+			+	-	+	-	+	-											+	+
Juweid et al. [42]					+	-													+	+		
Siegel et al. [24]			+	-	+	-			+	-												
[h]Ueno et al. [36]	-	+	-	+																		
[i]Grover et al [20]							+	-	+	-												
Frappaz et al. [29]	-	+																				
Shah Syed et al. [46]	+	+																				
Berberoglu et al. [25]													-	+								
Goo et al. [30]			-	+																		
Meyer et al. [32]			-	+																		
[i]Chu et al. [19]							+	-	+	-												
	9	13	1	11	10	1	8	0	6	0	1	1	0	1	0	1	0	1	1	1	1	1

MIBG: Metaiodobenzylguanidine Scintigraphy; MRI: Magnetic Resonance Imaging; BS: Bone Scintigraphy; RAD: Conventional Radiology; CT: Computed Tomography; PET: ^{18}F-FDG- Positron Emission Tomography; MIBI: ^{99m}Tc-Methoxyisobutylisonitrile Scintigraphy; SC: ^{99m}Tc-sulphur Colloid Scintigraphy; 3F8: ^{131}I-3F8 Monoclonal Anti-body Scintigraphy; PEN: ^{111}In Pentetreotide Scintigraphy; TI: ^{201}Tl Scintigraphy; B: Bone Metastases; BM: Bone Marrow Metastases.
[a]: Case series: two cases; [b]: One of seven patients had a neuroblastoma; [c]: Case series: three cases; [d]: Two of six patients had a neuroblastoma; [e]: Case report: one case; [f]: Case series: four cases; [g]: Eight patients + case series of three of these patients; [h]: Case report: one case; [i]: Case report: one case. Only contrast CT of head was performed; [j]: Case series: seven cases.

Table 2: Overview of all studies reporting a definition of bone and bone marrow metastases, detected on different imaging methods.

monoclonal anti-body scintigraphy [28], Indium (^{111}In) pentetreotide scintigraphy [42]; and Thallium (^{201}Tl) scintigraphy [44].

Reported definitions of bone metastases: In Table 3A, all the definitions of bone metastases per imaging technique for the 18 included studies, are listed. For reasons of clarity and interpretation, in the following text, similar definitions were grouped together in larger categories per imaging technique; however, these might not be identical to the exact definitions per study as reported in Table 3A.

In 9 out of 15 studies (60%) reporting on MIBG scintigraphy, a definition of bone metastases was given. Five studies gave clear definitions of bone metastases: "focal uptake" (n=3) [43,45,46] or "hotspots" (n=2) [40,44]. In 4 other studies the definition was more ambiguous: "any uptake" (n=3) [8,23,38] or "more intense uptake" (n=1) [39].

Of the 12 studies reporting on MRI, only 1 (8%) gave a definition of bone metastases i.e., "areas of cortical bone destruction" [24].

All studies reporting on bone scintigraphy (n=10) gave definitions of bone metastases. 5 studies gave clear definitions: "focal uptake" (n=3) [21,24,42] and "hotspots" (n=2) [40,45]. 5 other studies gave less clear definitions: "any uptake" (n=2) [23,47], "abnormal uptake" (n=2) [38,44], or "uptake throughout the skeleton with focal lesions that coalesce to produce a relatively diffuse image" (n=1) [39].

For conventional radiography, all 8 studies gave definitions of bone metastases: "osteolytic lesions", "periosteal reaction", "sunray spiculation", "pathological fractures" (n=6) [18-20,22,37,44]. Two studies defined bone metastases as "all abnormalities" on radiography [8,47].

For CT, all six studies reported on definitions of bone metastases: "sunray spiculation" (n=2) [18,20] and "bone destruction with characteristic periosteal reaction" (n=4) [18,24,37,44]. For the other nuclear imaging techniques, definitions, if available, are shown in Table 3A.

Reported definitions of bone marrow metastases: Table 3B reports on the definitions of bone marrow metastases provided in the 23 included studies. Again, for reasons of clarity and interpretation, in the following text, similar definitions were grouped together in larger categories per imaging technique; however, these might not be identical to the exact definitions per study as reported in Table 3B.

13 of the 15 studies (87%) reporting on MIBG scintigraphy gave a definition of bone marrow metastases. 11 studies [22,26-28,30-32,34-36,41] gave clear definitions: "diffuse uptake" (n=10, 77%) [31,33,38-40,43-47] or "hotspots" (n=1) [36]. Other, more ambiguous, definitions were "any uptake" (n=1) [29] or "abnormalities within the bone marrow compartment" (n=1) [27].

Of 12 studies reporting on MRI, 11 (92%) defined bone marrow metastases. Definitions were clear in 5: "focal areas" (n=1) [42], "diffuse and nodular type of lesions" (n=2) [28,35], or "diffuse abnormal uptake" (n=2) [26,31]. Furthermore, four studies (36%) reported "low intensity on T1 and high intensity on T2" [22,34,35,41]. Three studies gave a more ambiguous definition: "presence or absence of abnormalities" [27], "abnormal shadow" [36] and "hyper-intensity" [30].

Another study on MRI gave only specific definitions for vertebral metastases: "moderately heterogeneous or focal signal variations" or "greater signal than or equal to the signal intensity of cerebrospinal fluid" [32].

Of the 10 studies that reported on bone scintigraphy, 1 (10%) gave a definition of bone marrow metastases: "diffuse uptake" [40]. For the other nuclear imaging techniques, definitions, if available, are shown in Table 3B.

Objective 2: Diagnostic accuracy of all imaging techniques to detect bone and/or bone marrow metastases: 14 of the 31 included studies (45%) were included for objective 2 (Table 4A). They all reported definitions of bone and/or bone marrow metastases on an

MIBG Scintigraphy	
^{123}I-MIBG	
Osmanagoaglu et al. [45]	Focally increased uptake in the skeleton with or without diffuse uptake.
Claudiani et al. [38]	All other types of uptake than defined as bone marrow.
Giammarile et al. [39]	More intense uptake in a painful knee.
Hadj-Djilani et al. [40]	Hotspot.
Okuyama et al. [44]	Hotspot.
^{131}I-MIBG	
Shulkin et al. [23]	Any uptake.
Sha Syed et al. [46]	Focal uptake in bones.
^{123}I- / ^{131}I-MIBG	
Minard et al. [8]	Any uptake.
Kushner et al. [43]	Foci.
MRI	
MRI [STIR]	
Siegel et al. [24]	Areas of cortical bone destruction. Diffuse or focal changes in the bone marrow signal intensity.
Bone Scintigraphy	
Howman-Giles et al. [21]	Focal uptake or “cold” area of decreased uptake.
Shulkin et al. [23]	Any uptake.
Osmanagoaglu et al. [45]	Hotspot.
Turba et al. [47]	Any uptake
Claudiani et al. [38]	Abnormal uptake.
Giammarile et al. [39]	Uptake throughout the skeleton, focal lesions that are so extensive that they coalesce to produce a relatively diffuse image, resulting in a high bone-to-soft tissue ratio.
Hadj Djilani, et al. [40]	Hotspot
Okuyama, et al. [44]	Abnormal accumulations.
Juweid, et al. [42]	Predominantly focal in nature and quite asymmetric [in the extremities].
Siegel, et al. [24]	Two or more focal areas of either increased or decreased activity.
Conventional Radiography	
Chirathivat et al. [18]	Calvarium: widening of the sutures and indistinctness of their margins, localized thickening of the bony calvarium, multiple lytic defects, and subcutaneous scalp nodules. Other: hair-on-end appearance, small osteolytic lesions
Ruzal Shapiro et al. [22]	Metaphyseal demineralization, grey lines, or spotty areas of rarefaction. Faint periosteal reaction in some long bones.
Haddad, et al. [37]	Spiculate periosteal bone formation.
Turba, et al. [47]	All abnormalities.
Minard, et al. [8]	All abnormalities.
Okuyama et al. [44]	Osteolytic lesion with obvious cortical disruption and periosteal reaction in distal metaphysis.
Grover et al. [20]	Region of sunray spiculation in the parietal bone, underlying scalp swelling. Well-defined paravertebral shadow with a collapse.
Chu et al. [19]	Osteolytic focus with or without periosteal reaction, lucent horizontal metaphyseal lines or vertical linear radiolucent streaks in the metadiaphysis. Pathological fractures. Vertebral collapse in spinal metastases. Metastases to the cranium: widening of the cranial suture lines owing to subjacent dural metastases.
CT	
Chirathivat et al. [18]	Spiculation [new bony spicules]. Sunburst appearance.
Haddad et al. [37]	Focal bone destruction and spiculate periosteal calcification.
Okuyama et al. [44]	Focal osteolytic change with mild periosteal reaction.
Siegel et al. [24]	Areas of cortical bone destruction.
Grover et al. [20]	Sunray spiculation.
Chu et al. [19]	Bone destruction and characteristic periosteal reaction.
^{18}F-FDG-PET Scintigraphy	
Kushner et al. [43]	Foci.
^{111}In-Pentetreotide Scintigraphy	
Juweid et al. [42]	Predominantly focal and quite asymmetric [in the extremities].
^{201}Tl Scintigraphy	
Okuyama et al. [44]	Hotspot.
MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; ^{18}F-FDG-PET: Fluorine-18-fluorodeoxy-glucose Positron Emission Tomography; ^{111}In-Pentetreotide: Indium Pentetreotide; ^{201}T: Indium.	

Table 3A: Definitions of bone metastases as per imaging method.

MIBG Scintigraphy	
^{123}I-MIBG	
Corbett et al. [27]	Presence or absence of abnormalities in ten locations within the bone marrow compartment [thoracic and lumbar vertebral bodies, pelvis [left and right], and the upper, mid and lower shaft of each femur].
Osmanagoaglu et al. [45]	Diffuse and/or focal uptake in the skeleton.
Claudiani et al. [38]	Diffuse and symmetric uptake.
Giammarile et al. [39]	Diffuse uptake.
Hadj-Djilani et al. [40]	Diffuse uptake.
Lebtahi et al. [31]	Abnormal / diffuse uptake.
Okuyama et al. [44]	Diffuse uptake
Ueno et al. [36]	Hotspot.
^{131}I-MIBG	
Shulkin et al. [33]	– Diffuse uptake throughout the skeleton, in which cases bone scans may be normal. – Involvement at the distal metaphysis, in which cases bone scans are also abnormal.
Frappaz et al. [29]	Any uptake in metastatic sites [excluding distant lymph nodes].
Shah Syed et al. [46]	Diffuse uptake at the growing ends of the long bones or throughout the skeleton.
^{123}I- / ^{131}I-MIBG	
Turba et al. [47]	Diffuse uptake throughout the skeleton or involvement at the metaphysis of long bones.
Kushner et al. [43]	Diffuse uptake [not seen on bone scans] or both abnormal foci and diffuse uptake in skeletal structures not seen with bone scans.
MRI	
MRI [STIR]	
Hanna et al. [41]	Focal areas of marrow signal abnormalities in the form of high intensity.
Meyer et al. [32]	Vertebral bone marrow metastases: 1. Moderately heterogeneous or focal signal variations. 2. Homogeneous or minimally heterogeneous signal whose intensity is greater than or equal to the signal intensity of cerebrospinal fluid.
MRI [gad T1]	
Hanna et al. [41]	Focal areas of marrow signal abnormalities.
Meyer et al. [32]	Vertebral bone marrow metastases: 1. Moderately heterogeneous or focal signal variations. 2. Homogeneous or minimally heterogeneous signal whose intensity is greater than or equal to the signal intensity of cerebrospinal fluid.
MRI [T1]	
Hanna et al. [41]	Focal areas of marrow signal abnormalities.
Meyer et al. [32]	Vertebral bone marrow metastases: 1. Moderately heterogeneous or focal signal variations. 2. Homogeneous or minimally heterogeneous signal whose intensity is greater than or equal to the signal intensity of cerebrospinal fluid.
MRI [T2]	
Hanna et al. [41]	Focal areas of marrow signal abnormalities.
MRI [T1 and T2]	
Cohen et al. [26]	Diffuse abnormality [the marrow appears of the same intensity as adjacent muscle].
Fletcher et al. [28]	Diffuse or multifocal decrease of bone marrow signal.
Corbett et al. [27]	Presence or absence of abnormalities in ten locations within the bone marrow compartment [thoracic and lumbar vertebral bodies, pelvis [left and right], and the upper, mid and lower shaft of each femur].
Hanna et al. [41]	Focal areas of marrow signal abnormalities in the form of low intensity on T1 and high intensity on T2.
Ruzal Shapiro et al. [22]	Areas of hypo-intensity on T1-weighted images became hyper-intense on T2-weighted images and demonstrated diffuse, uniform distribution in the epiphyses, metaphysis, and diaphysis [termed the opposite of that observed in normal fatty marrow, the “flip-flop” sign].
Tanabe et al. [34]	Low and high intensity areas on T1- and T2-weighted images. Two types: 1. space-occupying lesions, visualized as low intensity areas. 2. speckled pattern of tissue in the medullary space with a signal intensity similar to that of bone marrow.
Tanabe et al. [35]	Low and high intensity areas on T1- and T2-weighted images. Two types: 1. Diffuse metastatic metastases [D type] segmentally occupying the medullary space. 2. Nodular metastasis [N type].
Goo et al. [30]	Hyper-intensity to muscle and normal bone marrow.
Lebtahi et al. [31]	Diffuse hypo-intense signal / pathological uptake.
Ueno et al. [36]	Abnormal shadow.
Bone Scintigraphy	
Hadj-Djilani et al. [40]	Diffuse uptake, especially in metaphyseal areas and axial skeleton
^{18}F-FDG-PET Scintigraphy	

Kushner et al. [43]	Diffuse uptake [not seen in bone scans]. Both abnormal foci and diffuse uptake in skeletal structures not seen with bone scans.
^{99}mTc-MIBI Scintigraphy	
Berberoglu et al. [25]	1. Diffuse pattern when diffuse bone marrow uptake was observed. 2. Diffuse + focal pattern when both patterns were observed.
^{99}mTc-Sulphur Colloid Scintigraphy	
Cohen et al. [26]	Extensive reduction of the marrow isotope uptake.
^{111}In-Pentetreotide Scintigraphy	
Juweid et al. [42]	More diffuse uptake.
^{131}I-3F8 Monoclonal Anti-body Scintigraphy	
Fletcher et al. [28]	Increased activity.
^{201}Tl scintigraphy	
Okuyama et al. [44]	Diffuse uptake

MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging; STIR: Short TI Inversion Recovery; gad-T1: Gadolinium-T1; CT: Computed Tomography; ^{18}F-FDG-PET: Fluorine-18-fluorodeoxy-glucose Positron Emission Tomography; ^{99m}Tc-MIBI: Technetium-99m-methyleen sestamibi [MIBI]; ^{99}mTc-Sulphur Colloid: Technetium-99m-Methylene Sulphur Colloid; ^{111}In-Pentetreotide: Indium Pentetreotide; ^{131}I-3F8 : Iodide-131 3F8 Monoclonal Antibody; ^{201}T: Indium.

Table 3B: Definitions of bone marrow metastases per imaging method.

Study	Total Patients Included In Study	Patients [N]		Lesions [N]		Assessments [N]		SENS		SPEC	
		B	BM	B	BM	B	BM	B	BM	B	BM
Index test MIBG Scintigraphy											
^{123}I-MIBG											
Corbett et al. [27]	19	-	19	-	-	-	30	-	1.00	-	0.41
Osmanagoaglu et al. [45]	26	?[1]	26	-	-	72	148	1.00	0.92	0.70	0.72
Hadj Djilani et al. [40]	27	26	27	-	-	26	27	0.83	1.00	1.00	1.00
	27	26	-	54	-	-	-	0.83	-	1.00	-
Okuyama et al. [44]	5	4	4	-	-	5	4	1.00	1.00	1.00	1.00
	5	4	-	22	-	-	-	0.17		0.20	
^{131}I-MIBG											
Frappaz et al. [29]	20	-	20	-	-	-	40	-	-	-	0.64
Shah Syed et al. [46]	18	12	18	-	-	12	18	0.86	0.71	1.00	1.00
^{123}I- / ^{131}I-MIBG											
Turba et al. [47]	22	22	22	-	-	27	41	-	0.56	-	0.91
Claudiani et al. [38]	97	12	34	-	-	12	34	0.73	0.26	0.00	-
Kushner et al. [43]	51	50	51	-	-	87	92	0.79	0.55	0.79	1.00
Index test MRI											
MRI [STIR]											
Hanna et al. [41]	6	-	6	-	-	-	8	-	1.00	-	0.20
Meyer et al.[2] [32]	91	-	91	-	-	-	-	-	0.74	-	0.73
MRI [gad T1]											
Hanna et al. [41]	6	-	3	-	-	-	5	-	-	-	1.00
Meyer et al.[2] [32]	91	-	91	-	-	-	-	-	0.67	-	0.97
MRI [T1]											
Hanna et al. [41]	6	-	6	-	-	-	9	-	-	-	0.00
Meyer et al.[2] [32]	91	-	91	-	-	-	-	-	0.96	-	0.58
MRI [T2]											
Hanna et al. [41]	6	-	3	-	-	-	4	-	-	-	1.00
MRI [T1/T2]											
Corbett et al. [27]	19	-	19	-	-	-	30	-	-	-	0.18
Tanabe et al. [34]	20	-	?[1]	-	-	-	21	-	1.00	-	n.a.
Index test ^{18}F-FDG-PET Scintigraphy											
Kushner et al. [43]	51	50	51	-	-	87	92	0.61	0.66	0.78	1.00
Index test ^{99}mTc-MIBI											
Berberoglu et al. [25]	9	-	9	-	-	-	10	-	-	-	0.83
Index test ^{111}In-Pentetreotide Scintigraphy											
Juweid et al. [42]	9	9	8	-	-	12	11	-	-	0.71	0.83
Index test ^{201}Tl Scintigraphy											
Okuyama et al. [44]	5	4	4	-	-	4	4	-	-	1.00	1.00
	5	-	4	22	-	-	-	0.17	-	0.30	-

SENS: Sensitivity; SPEC: Specificity; N: Number; B: Bone; BM: Bone marrow; MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging; STIR: Short TI Inversion Recovery; gad-T1: Gadolinium-T1; ^{18}F-FDG-PET: Fluorine-18-fluorodeoxy-glucose Positron Emission Tomography; ^{99}mTc-MIBI: Technetium-99m-methylene Sestamibi (MIBI); ^{111}In-pentetreotide: Indium Pentetreotide; ^{201}T: Indium.
-: no studies available; Lesions: number of lesions studied; Assessments: number of imaging-studies that were investigated; [1]: The number of assessments in the analysis is reported, but it is not clear how many patients were involved; [2]: Numbers from report, not able to calculate from text.

Table 4A: Diagnostic accuracy of different imaging methods for detecting bone (reference test bone scintigraphy) and bone marrow metastases (reference test bone marrow biopsies/aspirate).

Study	TP	FN	FP	TN	Total	SENS	SPEC
Osmanagaoglu et al. [45]	18	0	16	38	72	1.00	0.70
Hadj-Djilani et al. [40]	10	2	0	14	26	0.83	1.00
Kushner et al. [43]	19	5	13	50	87	0.79	0.79
Okuyama et al. [44]	4	0	0	1	5	1.00	1.00
Shah Syed et al. [46]	6	1	0	5	12	0.86	1.00
Pooled Result	**57**	**8**	**29**	**108**	**202**	**0.88**	**0.79**

MIBG: Metaiodobenzylguanidine; BS: Bone Scintigraphy; TP: True Positives; FN: False Negatives; FP: False Positives; TN: True Negatives; SENS: Sensitivity; SPEC: Specificity.
Bone metastases defined on MIBG scans as focal uptake and hot spots.

Table 4B: Pooled sensitivity and specificity analyses of bone metastases on MIBG scintigraphy with definition "focal lesions" with bone scintigraphy as reference test.

Study	TP	FN	FP	TN	Total	SENS	SPEC
Osmanagoaglu et al. [45]	23	2	34	89	148	0.92	0.72
Turba et al. [47]	10	8	2	21	41	0.56	0.91
Claudiani et al. [38]	9	25	NA	NA	34	0.26	-
Hadj-Djilani et al. [40]	8	0	0	19	27	1.00	1.00
Kushner et al. [43]	16	13	0	63	92	0.55	1.00
Okuyama et al. [44]	3	0	0	1	4	1.00	1.00
Shah Syed et al. [46]	5	2	0	11	18	0.71	1.00
Pooled result	**74**	**50**	**36**	**204**	**364**	**0.60**	**0.85**

MIBG: Metaiodobenzylguanidine; BS: Bone Scintigraphy; TP: True Positives; FN: False Negatives; FP: False Positives; TN: True Negatives; SENS: Sensitivity; SPEC: Specificity.
Bone marrow metastases defined on MIBG as diffuse uptake.

Table 4C: Pooled sensitivity and specificity analyses of bone marrow metastases on MIBG scintigraphy with definition "diffuse lesions" with bone marrow biopsy/aspirates as reference test.

index test (imaging technique). They all used bone scintigraphy as a reference test to detect bone metastases and bone marrow biopsies/aspirates as a reference test to detect bone marrow metastases. Patient characteristics of the included patients for this objective are shown in Supplementary Table 2.

Diagnostic accuracy for the detection of bone metastases: The sensitivities and specificities for the detection of bone metastases are given in Table 4A for all studies. The sensitivity and specificity on all reported imaging techniques and with different definitions, ranged widely, from 0.17 to 1.00 in 6 studies [38,40,43-46] and from 0.00 to 1.00 in 7 studies [38,40,42-46] respectively (Table 4A). For most imaging techniques, pooling was not possible, because of the small number of studies with the same techniques and definitions.

Only 5 studies that defined bone metastases on MIBG scintigraphy as "focal" or "hotspots" [40,43-46], could be pooled for their sensitivity and specificity, resulting in a sensitivity of 0.88 and specificity of 0.79 (MIBG with different radio-isotopes was used) (Table 4B).

Diagnostic accuracy for the detection of bone marrow metastases: The sensitivity and specificity for the detection of bone marrow metastases, on different imaging techniques and with different definitions, ranged from 0.26 to 1.00 in 11 studies [27,32,34,38,40,41,43-47], and 0.41 to 1.00 for 12 studies [25,27,29,32,40-47], respectively (Table 4A). For ^{18}F-FDG-PET scintigraphy, the sensitivity and specificity of the whole-body scans were shown. Because the brain is always ^{18}F-FDG positive, skull lesions are hard to visualize and therefore the diagnostic accuracy improved if skull lesions were excluded with a sensitivity of 0.63 [43].

The pooled sensitivity and specificity of the 7 studies that defined bone marrow metastases as "diffuse uptake" [38,40,43-47] was 0.60 and 0.85, respectively (Table 4C) (MIBG with different radio-isotopes was used).

Methodological quality of the studies evaluating the diagnostic test accuracy: Table 5 shows the overall quality of the 14 included studies for objective 2. Seven reported on bone metastases and all 14 on bone marrow metastases. Studies that reported on more than one index test were scored separately for each test, because they had the same scores on all QUADAS-items for each index test, only one QUADAS-score per study is shown in Table 5.

For the detection of bone metastases the risk of bias in patient selection was low in 2 (29%) [40-46] and unclear in 5 studies (71%) [38,42-45]. The concerns regarding applicability were low in 4 (57%) [40,42,45,46] and unclear in 3 (43%) [38,43,44]. In 2 of the 5 studies with an unclear risk of bias in patient selection, the applicability concerns were low [42,45] and in 3 unclear [38,43,44].

Concerning bone marrow metastases, the risk of bias in patient selection was low in 7 (50%) [29,32,34,40,45-47] and unclear in 7 studies (50%) [25,27,38,41-44]. The concerns regarding applicability were low in 9 (64%) [27,29,32,34,40,42,45-47] and unclear in 5 (36%) [25,38,41,43,44]. In 2 of the 7 studies with an unclear risk of bias in patient selection, the applicability concerns were low [27,42] and in 5 unclear [25,38,41,43,44].

Study	Risk of Bias								Applicability Concerns					
	Patient selection		Index test		Reference standard		Flow and timing		Patient selection		Index test		Reference standard	
	B	BM	B	BM	B	BM	B	BM	B	BM	B	BM	B	BM
Corbett et al. [27]	-	U	-	L	-	L	-	L	-	L	-	L	-	L
Hanna et al. [41]	-	U	-	L	-	L	-	H	-	U	-	L	-	L
Osmanagoaglu et al. [45]	U	L	U	U	L	L	H	L	L	L	L	L	L	L
Tanabe et al. [34]	-	L	-	L	-	L	-	U	-	L	-	L	-	L
Turba et al. [47]	-	L	-	U	-	U	-	L	-	L	-	L	-	L
Claudiani et al. [38]	U	U	U	U	L	L	H	H	U	U	U	U	L	L
Hadj Djilani et al. [40]	L	L	H	U	H	L	L	L	L	L	L	L	L	L
Kushner et al. [43]	U	U	L	L	L	L	L	L	U	U	L	L	L	L
Okuyama et al. [44]	U	U	U	U	L	L	H	H	U	U	L	L	L	L
Juweid et al. [42]	U	U	L	L	L	L	L	H	L	L	L	L	L	L
Frappaz et al. [29]	-	L	-	U	-	L	-	L	-	L	-	U	-	L
Shah Syed et al. [46]	L	L	L	L	L	L	H	L	L	L	L	L	L	L
Berberoglu et al. [25]	-	U	-	L	-	L	-	L	-	U	-	L	-	L
Meyer et al. [32]	-	L	-	L	-	L	-	L	-	L	-	L	-	L

B: Bone; BM: Bone marrow; U: unclear; L: low risk; H: high risk; -: no study available.

Table 5: Methodological quality assessment of studies assessing diagnostic test accuracy.

For the detection of bone metastases the risk of bias in the interpretation of the index test was high in 1 (14%) [40], because MIBG scans and bone scans were evaluated simultaneously. There are no applicability concerns for this study. The risk of bias was low in 3 (43%) [42,43,46] and unclear in 3 studies (43%) [38,44,45]. The applicability concerns were low in 6 (86%) [40,42-46] and unclear in 1 (14%) study [38]. Of the 4 studies with an unclear risk of bias, the applicability concerns were low in 2 [44,45] and unclear in 1 [38].

Concerning bone marrow metastases, the risk of bias in the interpretation of the index test was low in 8 (57%) [25,27,32,34,41-43,46] and unclear in 6 (43%) studies [29,38,40,44,45,47]. The applicability concerns were low in 12 (86%) [25,27,32,34,40-47] and unclear in 2 (14%) studies [29,38]. Of the 6 studies with an unclear risk of bias, the applicability concerns were low in 4 [40,44,45,47] and unclear in 2 [29,38].

For the detection of bone metastases the risk of bias in the interpretation of the reference test was high in 1 (14%), because MIBG scans and bone scans were evaluated simultaneously [40]. However, the applicability concerns were low for this study. The risk of bias was low in 6 (86%) [38,42-46]. The concerns regarding applicability were low for all 7 studies [38,40,42-46].

Concerning bone marrow metastases, the risk of bias on the reference standards was low in 13 (93%) [25,27,29,32,34,38,40-46] and unclear in one (7%) [47]. For all studies the concerns regarding applicability were low [25,27,29,32,34,38,40-47].

For the detection of bone metastases the risk of bias on flow and timing was low in 3 studies (43%) [40,42,43] and high in 4 studies (37%) [38,44,45,46]. Of the 97 patients included in one study bone metastases were reported in only 12 patients [38]. Of the 5 patients in the second study one was excluded from the analyses because of missing data (no bone scan was performed) [44]. In the third study only 12 of the 18 patients had bone scintigraphy [46]. Of one study the number of assessments was 72, but the number of patients was unclear [45].

Concerning bone marrow metastases the risk of bias on flow and timing was low in nine (64%) [25,27,29,32,40,43,45-47], unclear in 1 [34] and high in 4 (29%) studies. The reason for a high risk of bias was in the first study that three patients were not imaged with all possible MRI-sequences described in the study [41]. Of the 97 patients included in the second study bone marrow metastases were described in only 34 patients [38]. From 5 patients in the third study one was excluded from the analysis, because it was unknown whether the bone marrow was investigated [44]. In the last study, in 1 of 9 patients bone marrow biopsy was not performed [42].

Discussion

Because the presence of bone and bone marrow metastases are independent adverse prognostic factors, it is crucial to use consistent definitions of both bone and bone marrow metastases.

This systematic review showed that many studies did not provide a definition for bone and/or bone marrow metastases (n=41) or did not distinguish between both types of metastases (n=15). 31 studies did provide definitions (n=23 for bone marrow and n=18 for bone metastases), but these were not uniform. When focussing on the most used definitions for bone metastases, these were predominantly "focal uptake" on MIBG, bone scintigraphy and ^{18}F-FDG-PET-CT. For bone marrow metastases, these were mainly described as "diffuse lesions" on MIBG scintigraphy, but on MRI as both "diffuse" and "focal lesions".

So we conclude that, because of the wide variety of the definitions, results of different studies should be interpreted with caution, and international standards are needed. Along with the variable definitions for bone and bone marrow metastases, the sensitivity and specificity varied widely between the studies.

For MIBG scintigraphy pooling of data on diagnostic accuracy was possible for some of the studies. When using the definitions as "focal uptake" or "hotspots" to detect bone metastases, the sensitivity was 0.88, but the specificity was 0.79. The low specificity can be explained by the 29 of 202 (14%) lesions that were thought to be false positive (according to the bone scintigraphy), that might in fact be true positive, because bone remodelling was not yet present on bone scintigraphy.

To be able to define the diagnostic value of all different definitions on all different imaging techniques, ideally, uniform reference standards should be used.

Since the late 1970s, bone scintigraphy has been the main diagnostic

method for the detection of cortical skeletal metastases [48,49]. In this review, bone scintigraphy was therefore used as the reference standard to detect bone metastases. It portrays bone metastases of an osteoblastic type, while bone metastases of neuroblastomas are generally of the osteoclastic type [50]. As a result, bone metastases of neuroblastoma are depicted at a more advanced stage of the disease, when bone remodelling takes place and smaller lesions might be missed [51]. It has a reported sensitivity and specificity of 70-78% and 51%, respectively [52,53]. So false-negative as well as false-positive results are a problem when using this imaging technique as a reference standard. Nowadays, bone scintigraphy is usually not required, except in cases in which the primary tumor is not MIBG-avid or MIBG-positivity cannot be confirmed (i.e., if the primary tumor has been removed before examination). However, many studies in this review were published in an era where bone scintigraphy was mostly used as the reference standard.

Ideally, bone lesions should be confirmed by histology, but it is not common practice to biopsy bone metastases. Only in case of a single equivocal lesion on MIBG, the INRG recommends confirmation by another imaging modality (plain radiographs, and if negative, MRI and/or biopsy) [12,52]. 6 of the evaluated studies in this review described a case of a suspected bone lesion that was biopsied. Only 3 out of 6 were confirmed neuroblastoma bone metastases (Supplementary Table 3). Due to the small numbers no conclusions could be drawn from these studies.

The reference standard for bone marrow metastases, in this review, were bone marrow biopsies (trephines) or aspirates from iliac crests, as recommended by the INRG [11,12]. Generally, if one of these samples is positive, patients are considered to have bone marrow invasion. However, bone marrow can be infiltrated in other sites outside the pelvic area. Imaging techniques that show tumor infiltration in other localizations can be considered erroneously false positive compared to their reference standard bone marrow biopsies/aspirates. For example, in the study of Hanna et al. 4 MRI-T1 and STIR scans were judged false positive compared to the reference standard bone marrow biopsies/aspirates [41]. This might be caused by lesions on the MRI that are located outside the iliac crests. However, the study did not report on the localisation of the false-positive lesions. 1 of these 4 MRI's was false-positive during follow-up, and therefore post-therapy marrow signal alteration might also explain this false-positive result. Claudiani et al. reported a false positive MIBG scan [38], as stated above, if this was caused by a bone marrow metastasis located outside the iliac crest, this might in fact have been a true positive. The pooled MIBG scintigraphy data for the bone marrow metastases (definition "diffuse uptake") generated a low sensitivity of only 0.60, caused by a lot of false-negative results (50 of 364, 14%) on MIBG-scintigraphy. As bone marrow biopsies/aspirates were the golden standard, these results were really false-negative. One can imagine that a low level of infiltrating tumor cells can accumulate MIBG, but fail to be detected on whole body scans. In comparison with a sensitivity of 90-100% for the detection of neuroblastoma in general, the sensitivity to detect bone marrow metastases is rather low [48].

Despite the extensive use of MIBG scoring methods such as the Curie and SIOPEN method to assess response to therapy, MIBG avidity is not allocated to either bone or bone marrow [53-55]. The difficulty of MIBG scintigraphy to differentiate bone from bone marrow metastases is also a consequence of its two-dimensional nature. Routine use of SPECT-CT may overcome some of these limitations.

MRI has a unique soft tissue contrast, and therefore anatomical localization of lesions with MRI is very well possible. Furthermore MRI might provide early detection of bone marrow infiltration by the tumor before osseous destruction becomes apparent on radiography or CT or before metabolic changes occur on bone scintigraphy or PET-CT [56-58]. However, in children, in contrast to adults, it can be difficult to differentiate highly cellular hematopoietic marrow (red marrow) from metastatic disease [59]. ^{18}F-FDG-PET-CT can reveal early malignant bone marrow infiltration because of its increased glucose metabolism. In combination with CT, anatomical localization of abnormal signal is very well possible. However, the brain massively accumulates ^{18}F-FDG-PET and therefore metastatic lesions in the skull can be missed [48]. Also, accumulation in brown adipose tissue and cytokine-mediated diffusely hyper-metabolic bone marrow, as can be seen with the use of G-CSF, might result in false-positive images [60-63]. Data on ^{18}F-FDG-PET-CT in patients with neuroblastoma are still limited and it is mostly used in patients with neuroblastoma, when the tumor does not, or weakly accumulate MIBG [48].

Neuroblastoma is a unique tumor, because already at diagnosis 50% of patients present with metastatic disease. Therefore it is possible to study diagnostic imaging in these patients before any treatment. We do not know of any childhood or adult tumor with such an extensive number of patients with metastatic disease at diagnosis. Therefore, it was not possible to reliably compare our results with other types of cancer.

From the literature, we concluded that the distinction between bone and bone marrow metastases on imaging can be difficult. Furthermore, we concluded that for the detection of bone and bone marrow metastases on imaging, there are currently no unambiguous definitions, so the value of the prognostic significance as reported in the past should be interpreted with caution. Because of this problem, when using imaging modalities such as MIBG scans, the term skeletal might be more appropriate, where both bone and bone marrow lesions are combined. Brisse et al. described MIBG uptake using the term "skeletal metastases, in bone and bone marrow in a recent consensus paper on imaging of neuroblastoma [52]. In 15 of the 101 excluded studies in this review, this term was also used, but only 5 out of these 15 studies gave a definition of "skeletal metastases" (Supplementary Table 4).

The quality of the included studies in objective 2 was hard to assess. The scoring of QUADAS-items resulted mostly in an unclear risk of bias, because of the many missing items. We strongly recommend describing these items more precisely in future papers.

Future Perspectives

When focusing on MIBG scans, the use of SPECT-CT might enable this technique to better differentiate between localisations of the metastases. Because addition of CT increases the radiation burden, it is not recommendable to add this technique routinely for each lesion. However, the available MIBG-SPECT-CT's of body parts should be investigated for the possibility to differentiate bone and bone marrow metastases.

Another technique that shows promise is MRI imaging, especially combined with the high sensitivity of MIBG, this would be ideal to identify all involved skeletal lesions. Therefore, these two imaging techniques should be compared to see whether it is possible to differentiate between bone and bone marrow metastases on these imaging methods.

Implications for Clinical Practice

Up till now, MIBG scintigraphy is the most widely used imaging

method to diagnose neuroblastoma, but no uniform definitions of bone and bone marrow metastases are described for this technique. The role of ^{18}F-FDG-PET-CT and MRI in the detection of osteomedullary metastases in patients with neuroblastoma is still under investigation.

Because currently no uniform definitions are available to differentiate between bone and bone marrow, we suggest using the term "skeletal" or "osteomedullary" metastases until it is possible to discriminate these on imaging.

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