The use of both diagnostic and therapeutic MIBG in neuroblastoma patients
Bleeker, G.

Citation for published version (APA):
Bleeker, G. (2014). The use of both diagnostic and therapeutic MIBG in neuroblastoma patients

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 2

$^{123}$I-MIBG scintigraphy and $^{18}$F-FDG-PET imaging for diagnosing neuroblastoma: a Cochrane systematic review of diagnostic test accuracy

Gitta Bleeker$^1$, Godelieve AM Tytgat$^1$, Judit A Adam$^2$, Huib N Caron$^1$, Leontien CM Kremer$^1$, Lotty Hooft$^3$, Elvira C van Dalen$^1$

$^1$Department of Paediatric Oncology, Emma Children’s Hospital / Academic Medical Center, Amsterdam, Netherlands
$^2$Nuclear Medicine and Radiology, Academic Medical Center, Amsterdam, Netherlands
$^3$Dutch Cochrane Centre, University Medical Center Utrecht, Utrecht, Netherlands

Manuscript submitted.
Abstract

Background
Neuroblastoma is an embryonic tumour of childhood that originates in the neural crest. It is the second most common extracranial malignant solid tumour of childhood. A lot of studies have been published on the diagnostic accuracy of $^{123}$I-MIBG scintigraphy, but studies are very heterogeneous in number of patients and performance of the imaging methods. Prognosis, treatment and response of patients with neuroblastoma are yet based on extension scoring of $^{123}$I-MIBG scans. Therefore, it is important to have a good overview of the sensitivity and specificity of this diagnostic test to detect neuroblastoma. A promising add-on test is Fluorine-18-fluorodeoxy-glucose ($^{18}$F-FDG) positron emission tomography (PET) in case of $^{123}$I-MIBG negative neuroblastomas.

Objectives
Our primary objective was to determine the diagnostic accuracy of index test $^{123}$I-MIBG scintigraphy (with or without SPECT-CT) for detecting a neuroblastoma tumour and its metastases measured by a reference standard at first diagnosis or at recurrence in children from 0 to 18 years old (objective 1.1). In case of a negative $^{123}$I-MIBG scintigraphy, the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging was determined (add-on test) (objective 1.2). Secondary objectives were to determine the diagnostic accuracy of index test $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma tumour and its metastases (objective 2.1), and to compare this to comparator test $^{123}$I-MIBG (SPECT-CT) scintigraphy (objective 2.2), in the above mentioned patient groups.

Search methods
We searched the databases of MEDLINE/PubMed (from 1945 to September 2012) and EMBASE/Ovid (from 1980 to September 2012) for potentially relevant articles. We additionally searched reference lists of relevant articles and review articles, scanned conference proceedings and searched for unpublished studies by contacting researchers involved in this area.

Selection criteria
Cross-sectional studies, either retrospective or prospective, were included if they compared the results of $^{123}$I-MIBG (SPECT-CT) scintigraphy, $^{18}$F-FDG-PET(-CT) imaging, or both with the reference standards or with each other. Studies had to be primary diagnostic and had to report on children 0-18 years old with a neuroblastoma of any stage at first diagnosis or at recurrence.
Data collection and analysis
One review author performed the initial screening of identified references, then two review authors independently performed the study selection, extracted data and assessed the methodological quality. We used data from two-by-two tables, describing the number of patients with a true or false positive test and the number of patients with a true or false negative test, to calculate sensitivity and/or specificity for each study. If possible, we generated forest plots showing estimates of sensitivity and specificity together with 95% confidence intervals. For the pooled estimate of sensitivity for objective 1.1 we also calculated the 95% prediction interval.

Results
The sensitivity of $^{123}$I-MIBG (SPECT-CT) scintigraphy (objective 1.1), determined in 608 of 621 eligible patients included in the 11 studies, varied from 67% to 100%, with a pooled mean value of 92.4%, a 95% confidence interval of 84.5% to 96.4% and a 95% prediction interval of 62.5 to 98.9%. The specificity was 85% in 115 lesions in 22 patients, described in one study. The mean sensitivity of $^{123}$I-MIBG scintigraphy for detecting metastases separately from the primary tumour in patients with all neuroblastoma stages was 91% (range 79%-100%) in three studies and the mean specificity could be calculated for two of these studies and was 67% (range 33%-89%). Only one study reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging (add-on test) in patients with negative $^{123}$I-MIBG scintigraphy (objective 1.2). Two of the 24 eligible patients with proven neuroblastoma had a negative $^{123}$I-MIBG scan and a positive $^{18}$F-FDG-PET(-CT) scan. The sensitivity of $^{18}$F-FDG-PET(-CT) imaging as a single diagnostic test (objective 2.1) and compared to $^{123}$I-MIBG (SPECT-CT) (objective 2.2) was only reported in one study. The sensitivity of $^{18}$F-FDG-PET(-CT) imaging was 100% versus 92% of $^{123}$I-MIBG (SPECT-CT) scintigraphy. The specificity could not be calculated for both modalities.

Authors’ conclusions
We found a pooled mean sensitivity of 92.4% with a 95% confidence interval of 84.5% to 96.4% and a 95% prediction interval of 62.5 to 98.9%. Only one study in this review reported on false positive findings. It is important to keep in mind that false positive findings can occur. For example, physiological uptake should be ruled out, by using SPECT-CT scans, although more research is needed before definitive conclusions can be made. As described both in the literature and in this study, around 10% of the $^{123}$I-MIBG scans give false negative results. However to stage these patients properly and to assess response, it is advisable to perform an additional test in patients that are suspected of having a neuroblastoma. Although not enough evidence is available, a possible add-on test could be $^{18}$F-FDG-PET scintigraphy. More research is needed to support this for clinical practice.
BACKGROUND

Target condition being diagnosed

Neuroblastoma is an embryonic tumour of childhood that originates in the neural crest. It is the second most common extracranial malignant solid tumour of childhood and the most common solid tumour of infancy (Brodeur 2003; Castleberry 1997; Park 2008). It accounts for 7% of all childhood cancers and for approximately 15% of cancer deaths in children (Castleberry 1997; Maris 2007; Park 2008; Spix 2006). Neuroblastomas may arise anywhere along the sympathetic nervous system (side chain), but are found most frequently in the abdomen (65%). Half of them arise from the adrenal glands. Other common sites are the neck, chest and pelvis (Maris 2007; Maris 2010; Park 2008). They particularly occur in children at a young age, with a median age at diagnosis of 17 months (Maris 2010). Around 50% of patients present with disseminated disease at the time of diagnosis (Maris 2007; Maris 2010). Dissemination occurs through lymphatic and hematogenous routes, with involvement of bone, bone marrow and liver (Maris 2007; Maris 2010).

Neuroblastomas are staged according to the International Neuroblastoma Staging System (INSS) (Table 1) (Brodeur 1988; Brodeur 1993). Stage 1 to 2 neuroblastomas are localised, stage 3 neuroblastomas consist of regional disease and stage 4 neuroblastomas are marked by distant metastases. A unique pattern of dissemination, limited to the liver, skin and less than 10% of bone marrow in children younger than one year is defined as stage 4S, which has a potential for spontaneous regression (Brodeur 1988; Brodeur 1993). The INSS system is a postsurgical staging system and therefore the International Neuroblastoma Risk Group (INRG) published a new clinical staging system in 2008: the INRG classification system (Table 2) (Monclair 2009).

The clinical course in patients with a neuroblastoma varies enormously, ranging from spontaneous regression to rapid and fatal tumour progression despite extensive treatment (Brodeur 2003; Castleberry 1997; Park 2008). Known predictors of poor prognosis are stage, age at diagnosis, chromosomal aberrations such as MYCN-amplification and chromosomal loss of 1p36 (Brodeur 1984; Brodeur 1988; Brodeur 1988a; Brodeur 1993; Cohn 2009).

Children with metastatic disease are quite ill at presentation. As the tumour disseminates to the bone, patients often present with bone pain, limping or both. Metastases in the orbits can cause periorbital ecchymoses (raccoon eyes), sometimes accompanied by proptosis. Another symptom is abdominal distension caused by a large tumour. Paraspinal tumours may cause myelum compression, resulting in neurological symptoms, such as motor weakness, pain and sensory loss, which can be medical emergencies (Maris 2010; Park 2008).
The treatment of neuroblastoma patients generally consists of induction chemotherapy, surgery, myeloablative chemotherapy with stem cell rescue, radiotherapy and/or ¹³¹Iodide-metaiodobenzylguanidine (¹³¹I-MIBG) therapy (Maris 2007; Maris 2010; Park 2008; Yalcin 2010).

A single reference test for the diagnosis of neuroblastoma does not exist. In clinical practice, the most comprehensive diagnosis is obtained by a combination of clinical examination, urinary catecholamine tests, imaging procedures and histopathology. These tests are performed in all patients suspected of neuroblastoma.

Table 1: International Neuroblastoma Staging System (INSS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localised tumour with complete gross excision with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive).</td>
</tr>
<tr>
<td>2A</td>
<td>Localised tumour with incomplete gross resection; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localised tumour with or without complete gross excision with ipsilateral non-adherent lymph nodes positive for tumour; enlarged contralateral lymph nodes must be negative microscopically.</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumour infiltrating across the midline a with or without regional lymph node involvement, localised unilateral tumour with contralateral regional lymph node involvement, or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin or other organs (except as defined for stage 4S).</td>
</tr>
<tr>
<td>4S</td>
<td>Localised primary tumour (as defined for stage 1, 2A or 2B) with dissemination limited to skin, liver or &lt; 10% of bone marrow (limited to infants &lt; 1 year of age). b</td>
</tr>
</tbody>
</table>

Multifocal primary tumours (e.g. bilateral adrenal primary tumours) should be staged according to the greatest extent of disease, as defined in the table, and followed by a subscript “M” (e.g. 3M).

a The midline is defined as the vertebral column. Tumours originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
b Marrow involvement in stage 4S should be minimal (i.e. < 10% of total nucleated cells identified as malignant on bone marrow biopsy or marrow aspirate). More extensive marrow involvement would be considered to be stage 4. The metaiodobenzylguanidine scan (if performed) should be negative in the marrow (Brodeur 1988; Brodeur 1993).

Table 2: International Neuroblastoma Risk Group Staging System (INRG)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localised tumour not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment.</td>
</tr>
<tr>
<td>L2</td>
<td>Locoregional tumour with presence of one or more image-defined risk factors.</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS).</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease in children younger than 18 months with metastases confined to skin, liver and/or bone marrow.</td>
</tr>
</tbody>
</table>

Patients with multifocal primary tumours should be staged according to the greatest extent of disease as defined in the table (Monclair 2009).

The treatment of neuroblastoma patients generally consists of induction chemotherapy, surgery, myeloablative chemotherapy with stem cell rescue, radiotherapy and/or ¹³¹Iodide-metaiodobenzylguanidine (¹³¹I-MIBG) therapy (Maris 2007; Maris 2010; Park 2008; Yalcin 2010).

A single reference test for the diagnosis of neuroblastoma does not exist. In clinical practice, the most comprehensive diagnosis is obtained by a combination of clinical examination, urinary catecholamine tests, imaging procedures and histopathology. These tests are performed in all patients suspected of neuroblastoma.
chapter 2

Index test(s)

This review assessed the diagnostic use of Iodine-123-metaiodobenzylguanidine (\(^{123}\)I-MIBG) scintigraphy and fluorine-18-fluorodeoxy-glucose (\(^{18}\)F-FDG) positron emission tomography (PET) in the detection of a neuroblastoma and its metastases at first diagnosis or at recurrence. \(^{123}\)I-MIBG scintigraphy can be performed as a twodimensional whole-body (WB) scan or a threedimensional single photon emission computed tomography (SPECT) scan, with or without computed tomography (CT) for localisation of neuroblastoma lesions.

MIBG, a compound that is structural analogous to the neurotransmitter norepinephrine, is actively taken up in neuroendocrine cells via the norepinephrine transporter (NET) and is stored in the neurosecretory granules, resulting in a specific concentration in the tumour in contrast to cells of other tissue (Taggart 2008; Vaidyanathan 2008). Once labelled with radioactive iodine (\(^{123}\)I or \(^{131}\)I), MIBG scintigraphy can be used for imaging of tumours of neuroendocrine origin, such as neuroblastomas, paragangliomas and phaeochromocytomas (Boubaker 2008; Taggart 2008; Vaidyanathan 2008). In the past, both \(^{123}\)I-MIBG and \(^{131}\)I-MIBG were used for diagnostic purposes. However, \(^{123}\)I-MIBG is considered first choice for imaging because it has a more favourable dosimetry and it was assumed that it provided a better image quality than \(^{131}\)I-MIBG (Bombardieri 2003a; Boubaker 2008; Taggart 2008). Consequently, \(^{123}\)I-MIBG is mainly used for diagnostic purposes in international protocols. \(^{123}\)I-MIBG whole-body or static scans visualise the primary tumour and its metastases twodimensional. SPECT enables threedimensional imaging of the primary tumour. However, in practice this imaging modality cannot replace whole-body imaging, because SPECT often does not fully visualise the whole-body, but only a selected part of the body (Rufini 1996). MIBG-SPECT can be combined with CT to determine the exact localisation of the primary tumour and its relation to other organ structures (Rufini 1996; Taggart 2008).

Physiological distribution of \(^{123}\)I-MIBG can be found in structures that excrete catecholamines, like the bladder, urinary tract and gastrointestinal system. MIBG usually accumulates in the liver, myocardium, salivary glands and thyroid, and less frequently in the spleen, lungs, brown adipose tissue and skeletal muscles. It is essential to recognise this normal distribution to avoid false positive interpretation of MIBG scans (Bombardieri 2003a; Boubaker 2008).

Many drugs can interfere with the uptake or vesicular storage of \(^{123}\)I-MIBG (or both) (Table 3) (Bombardieri 2003a). Therefore, it is important to stop these medications before the procedure to prevent negative results of \(^{123}\)I-MIBG scans. In cases of severe hypertension, antihypertensive medication is necessary and cannot be stopped. Consequently, the \(^{123}\)I-MIBG scan may not be reliable, if the patient is treated with an antihypertensive agent that interferes with \(^{123}\)I-MIBG. On the other hand, \(^{123}\)I-MIBG scan test results
can be negative because of low expression of the NET (Boubaker 2008; Taggart 2008). Therefore, it is important to perform an additional test in case of a negative $^{123}$I-MIBG scan.

Another imaging modality to diagnose neuroblastoma is PET(-CT) imaging, which uses the glucose metabolism to visualise the primary tumour and metastases with $^{18}$F-FDG. In contrast to normal cells, cancer cells avidly take up glucose and metabolise it to lactate even when oxygen is abundantly present. This glucose metabolism in cancer cells enables specific detection by PET with the glucose analogue FDG. Although in contrast to $^{123}$I-MIBG imaging, $^{18}$F-FDG PET(-CT) imaging is not specific for neuroblastoma tumours, it may be a useful additional imaging modality for diagnosing neuroblastoma (Bombardieri 2003b; Murphy 2008; Shore 2008). This imaging modality might have additional value in patients with (false) negative $^{123}$I-MIBG scans. In this case $^{123}$I-MIBG would be the comparator test.

### Table 3: Medication interfering with MIBG uptake

<table>
<thead>
<tr>
<th>Opioids</th>
<th>amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, doxepine, dothiepin, imipramine, iprindole, lofepramine, loxapine, maprotiline, mazindol, protriptyline, salbutamol, trimipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants:</td>
<td>amphetamine, dopamine, dobutamine, ephedrine, fenoterol, guanethidine, isoetharine, isoprenaline, isoproterenol, metaramimol, metylephedrine, metoserpipidine, methoxamine, noradrenaline, nortriptyline, orciprenaline, oxymethazoline, phenoterol, phenilephrine, phenylpropanolamine, pibuterol, pseudoephedrine, rimiterol, reproterol, salbutamol, terbutaline, tramazoline, xylometazoline</td>
</tr>
<tr>
<td>Sympathomimetics (components of bronchodilators, decongestants and diet aids):</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive/ cardiovascular agents:</td>
<td>amiodarone, bretylium, debrisoquin, guanethidine, labetalol, methoserpipidine, metoprolol, reserpine calcium channel blockers: amlodipine, diltiazem, isradipine, lidoflazine, nicardipine, nifedipine, nimodipine, verapamil. ACE inhibitors: captopril, enalapril</td>
</tr>
<tr>
<td>Antipsychotics (frequent components of anti-emetic and anti-allergic agents):</td>
<td>phenothiazines: chlorpromazine, fluphenazine, loxapine, methotrimiprazine, pericyazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, thioridazine, trifluoperazine thioxanthenes: flupenthixol, maprotiline, trazodone, zuclopenthixol butyrophenones: benperidol, droperidol, haloperidol, trifluperidol</td>
</tr>
</tbody>
</table>

Bombardieri 2003a; Solanki 1992
Alternative test(s)

All patients suspected of neuroblastoma have a diagnostic work-up consisting of: clinical examination, urinary catecholamines, imaging modalities and histopathology. The reference standard for the diagnosis neuroblastoma is a histopathological diagnosis (Brodeur 1993), either by tumour biopsy, trephines or bone marrow aspirates. A tumour biopsy can be an invasive procedure and sometimes it is contra-indicated at the time of diagnosis. For example, if the patient is seriously ill or if such a procedure is life-threatening because of tumour localisation. However, all patients suspected of neuroblastoma have bone marrow aspirates and trephines. Only in stage 4 or 4S neuroblastomas, these bone marrow aspirates and trephines can reveal neuroblastoma cells. If histopathological examination is not able to confirm the diagnosis neuroblastoma, another diagnostic test is required. Increased excretion of urinary catecholamines indicates a neuroblastoma, but this test is not specific (Strenger 2007). Ultrasound is often applied to evaluate the primary tumour and is used for follow-up, but it does not give detailed images and it is not specific for neuroblastomas. CT and magnetic resonance imaging (MRI) give detailed images that enable anatomic localisation, measurement of tumour size and visualisation of metastases. However, these imaging modalities are also not specific for neuroblastomas (Kaste 2008a).

Rationale

$^{123}$I-MIBG (SPECT-CT) scintigraphy is a non-invasive imaging modality that is thought to be specific for neuroendocrine tumours such as neuroblastomas. Diagnostic accuracies vary within published studies. With this Cochrane systematic review we evaluated the diagnostic accuracy of this test in children with suspected neuroblastoma. $^{18}$F-FDG-PET(-CT) imaging might be a useful additional test for diagnosing $^{123}$I-MIBG-negative neuroblastomas, metastases or both. With this Cochrane systematic review we also evaluated the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) as an add-on test in children with suspected neuroblastoma, as well as the diagnostic accuracy of this test as a single diagnostic test and in comparison with the diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy.

In clinical practice, $^{123}$I-MIBG and $^{18}$F-FDG-PET scintigraphy are performed if a neuroblastoma is strongly suspected and other tests like urinary catecholamines are positive and suggestive for a neuroblastoma. Therefore, only few studies report on false positive and true negative results of $^{123}$I-MIBG and $^{18}$F-FDG-PET scintigraphy. There will be no adverse clinical consequences of false positive or false negative test results: a false positive $^{123}$I-MIBG scan will have no consequences in practice, because the histopathology or urinary catecholamines will be negative and additional imaging tests, like ultrasound will be performed. In this case the patient will not be treated unnecessarily. If a $^{123}$I-MIBG
scan is false negative, the histopathology or urinary catecholamines will turn out positive and an additional imaging test like \(^{18}\text{FDG-PET(-CT)}\) will be performed. This patient will be treated for neuroblastoma.

**OBJECTIVES**

Three index test combinations are reviewed: 1. \(^{123}\text{I-MIBG}\) scintigraphy, 2. \(^{18}\text{F-FDG-PET(-CT)}\), \(^{123}\text{I-MIBG}\) scintigraphy plus \(^{18}\text{F-FDG-PET(-CT)}\). See Figure 1: flowchart of index tests.

**Figure 1:** Flow chart index tests in patients with suspected neuroblastoma

![Flowchart Index Tests](image)

NBL: neuroblastoma; +: positive test result; -: negative test result.; 1.1: primary objective 1; 1.2: primary objective 2; 2.1: secondary objective 1; 2.2: secondary objective 2.

**Primary objective**

1.1 To determine the diagnostic accuracy of \(^{123}\text{I-MIBG}\) (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

1.2 To determine the diagnostic accuracy of negative \(^{123}\text{I-MIBG}\) scintigraphy in combination with \(^{18}\text{F-FDG-PET(-CT)}\) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old. In this case \(^{18}\text{F-FDG-PET(-CT)}\) is an add-on test.
Secondary objectives

2.1 To determine the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

2.2 To compare the diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy and of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old. This will be performed within and between (objective 1.1 compared to objective 2.1) included studies. $^{123}$I-MIBG (SPECT-CT) scintigraphy is the comparator test in this case.

Investigation of sources of heterogeneity

When assessing study results, we considered methodological and clinical sources of heterogeneity as well as variation in the criteria used to define a positive test result. Several factors may contribute to heterogeneity in diagnostic performance across studies. We investigated, where possible, the potential influence of differences in the following items:

**Study population:**
- Newly diagnosed versus recurrent neuroblastoma.
- Stage of disease (1 to 4 and 4S) as an ordinal variable. We reported stage 1 and 2 combined and stage 3, 4 and 4S separately.

**Index test radio labelled MIBG (SPECT-CT) scintigraphy:**
- Time span between injection and scanning (24 or 48 hours) (acquisition time).
- Whole-body scan versus SPECT-CT.
- Interfering medication (Table 3).

**Reference standard:**
- Type of test: histopathology (reference test 1) versus bone marrow aspirate or trephine biopsy (reference test 2) versus histopathology in combination with urinary catecholamines and additional imaging modalities (reference test 3).
CHAPTER 2

METHODS

Criteria for considering studies for this review

Types of studies
Primary diagnostic studies were eligible for inclusion if they compared the results of 123I-MIBG (SPECT-CT) scintigraphy, 18F-FDG-PET(-CT) imaging, or both, with the tests described as reference standards (as defined below) and if they compared the results of both tests with each other. Studies needed to be of a cross-sectional design and could be retrospective or prospective. We excluded case reports, studies that described less than ten patients suspected for neuroblastoma and diagnostic case-control studies. Studies had to report sufficient data to construct (part of) a two-by-two table, i.e. the absolute number of true positives, false positives, false negatives and/or true negatives had to be available from the data reported in the primary studies or obtainable from the authors. Considering the nature of the disease it is expected that mainly proven neuroblastomas will be reported and that thus often only sensitivity can be analysed.

Participants
Children from 0 to 18 years old with suspected neuroblastoma and its metastases of any stage at first diagnosis or at recurrence in a tertiary care centre of paediatric oncology. We excluded studies on animals, studies not performed in children with suspected neuroblastoma, studies performed in children with esthesioneuroblastoma and olfactory neuroblastoma and studies on the therapeutic use of MIBG.

Index tests
- 123I-MIBG scintigraphy (whole-body, SPECT or SPECT-CT) of a neuroblastoma and its metastases at first diagnosis or at recurrence.
- 18F-FDG-PET(-CT) scans of a neuroblastoma and its metastases at first diagnosis or at recurrence.
- 123I-MIBG scintigraphy plus 18F-FDG-PET(-CT).

Comparator tests
When 18F-FDG-PET(-CT) imaging was the index test:
- 123I-MIBG scintigraphy (whole-body, SPECT or SPECT-CT) of a neuroblastoma and its metastases at first diagnosis or at recurrence.

Target conditions
Neuroblastoma at first diagnosis or at recurrence.
Reference standards

The most optimal combination of reference tests is described below. However, studies that did not use the optimal combination of reference tests, were not excluded.

The reference tests for the diagnosis of the primary neuroblastoma tumour were as follows.

1. An unequivocal pathological diagnosis according to the Shimada classification or the International Neuroblastoma Pathology Classification (INPC) (Brodeur 1984; Joshi 2000; Peuchmaur 2003; Shimada 1984; Shimada 1993; Shimada 1999a; Shimada 1999b; Shimada 2003). Tumour tissue was examined by use of light or electron microscopy with immunohistochemistry. At least two of the following antigens had to be positive: neuron-specific enolase (NSE), synaptophysin or chromogranin A (CGA). Tissue had to be preferably obtained by the use of Trucut, core-needle biopsy. However, if this approach was contra-indicated, fine-needle aspiration could be used (Brodeur 1993).

2. A bone marrow aspirate or trephine biopsy containing unequivocal tumour cells. These are immunocytologically positive clumps of cells, containing antibodies against at least two of the following antigens: NSE, synaptophysin or CGA (Brodeur 1993).

3. Histopathology during or after treatment (e.g. tissue obtained during surgery), if excretion of urinary catecholamines was elevated at diagnosis and additional imaging modalities (e.g. ultrasound, CT scan, MRI scan) suggested a neuroblastoma at diagnosis.

Three different tests were used as possible reference standards. If only one of the three reference standards had a positive result, the diagnosis neuroblastoma could be confirmed. However, to reject the diagnosis neuroblastoma all three had to give a negative result.

The reference tests for the diagnosis of neuroblastoma metastases were as follows.

Bone marrow metastases: bone marrow aspirates from at least four different puncture sites (bilateral posterior iliac crest, two left and two right) with at least one single positive site. If the aspirates were not representative, two bone marrow aspirates and two trephine biopsies were sufficient instead.

- Bone metastases: positive lesions on a $^{99m}$Tc skeleton scintigraphy, MRI and/or CT scan.
- Lymph node metastases: histologically proven palpable nodes and/or ultrasound, MRI or CT scan for non-palpable nodes.
- Liver metastases: ultrasound, MRI and/or CT scan.

Diagnosis of neuroblastoma metastases resulted from at least one positive result of these reference tests. The result was assumed negative if all reference tests were negative. There are no inadequate reference standards in the diagnostic process of neuroblastoma.
Search methods for identification of studies

Electronic searches
We searched the databases of MEDLINE/PubMed (from 1945 to September 2012) and EMBASE/Ovid (from 1980 to September 2012). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in the appendices (Appendix 1; Appendix 2). We did not impose language restrictions.

Searching other resources
We located information about studies not registered in MEDLINE and EMBASE, either published or unpublished, by screening the reference lists of relevant articles and review articles. We also scanned the conference proceedings of the International Society for Paediatric Oncology (SIOP), the American Society of Clinical Oncology (ASCO), Advances in Neuroblastoma Research (ANR) and the Society of Nuclear Medicine (SNM) from 2006 to 2012. If studies were reported in abstracts or conference proceedings we searched for full publications. We searched for unpublished studies by contacting researchers involved in this area.

Data collection and analysis
Selection of studies
After employing the search strategy described previously, one review author performed the initial screening of identified references, excluding studies on animals, studies not performed in children with suspected neuroblastoma, studies performed in children with esthesioneuroblastoma and olfactory neuroblastoma, studies on the therapeutic use of MIBG, case reports and studies that described less than ten patients that were suspected of neuroblastoma. Next, two review authors independently identified studies from the remaining references that seemed to meet the inclusion criteria based on title, abstract, or both and screened these full-text studies. Only full-text studies that fulfilled all inclusion criteria for this review were eligible for inclusion. We clearly stated reasons for exclusion of any study considered for the review. Both initial and definite selection needed consensus of both reviewers. In case of disagreement, final resolution was achieved by a third-party arbitrator.

Data extraction and management
Two review authors performed data extraction independently using standardised forms. We extracted data on the following items.

- Article: author, year of publication, journal.
- Study population: age, sex, neuroblastoma at first diagnosis or at recurrence, stage, inclusion and exclusion criteria, number of subjects (including number eligible for the study, number enrolled in the study, number subjected to the index test and reference standard, number for whom results were reported in the two-by-two-table, reasons for withdrawal).
- Index tests: $^{123}$I-MIBG scintigraphy, $^{18}$F-FDG-PET(-CT) imaging or both.
- Comparator test: $^{123}$I-MIBG scintigraphy, if $^{18}$F-FDG-PET(-CT) imaging was the index test.
- Interfering medication in case of $^{123}$I-MIBG scintigraphy (Table 3).
- Reference test: type of test.
- Study methods: basic design of the study (prospective cohort or historical cohort with data collection based on medical records or case-control study), time span between index test and reference test, treatment between index test and reference test.
- Data for the two-by-two table: true positive, false positive, true negative and false negative rates or, if not available, relevant parameters (sensitivity, specificity or predictive values) to reconstruct the two-by-two table.
- Data extraction was successfully pilotted for two studies.
- When data were missing in a published report, we attempted to contact the authors for the missing information. In cases of disagreement, we re-examined the abstracts and articles and undertook discussion until consensus was achieved. If this was impossible, we achieved final resolution using a third-party arbitrator.

Assessment of methodological quality
Two of the authors independently assessed the methodological quality of each included study using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS) items (Additional Table 1) developed by the NHS Centre for Reviews and Dissemination at the University of York, UK (Whiting 2003). We scored each item as ‘yes’, ‘no’ or ‘unclear’. The items of the QUADAS tool and our scoring interpretations for each item are presented in additional Table 1. We resolved discrepancies between review authors by consensus. If this was impossible, we sought final resolution using a third-party arbitrator. We did not calculate a summary score estimating the overall quality of an article since the interpretation of such summary scores is problematic and potentially misleading (Jüni 1999; Whiting 2003). We presented results in the text, in a graph and in a table. We piloted three studies to test the QUADAS tool and this was successful.

Statistical analysis and data synthesis
We analysed data at patient and lesion level.
Our aim was to extract from each included study the two-by-two tables (consisting of true positives, false positives, true negatives and false negatives) to calculate sensitivity and specificity. We generated a paired forest plot showing estimates of sensitivity and specificity. The forest plot provides a visual impression of the precision by which sensitivity and specificity have been measured in each study as well as an indication of the amount of variability in these parameters across studies. We did not plot pairs of sensitivity and specificity from each study in receiver operating characteristic (ROC), because only one study provided data to calculate specificity for diagnosing neuroblastoma in general and only three studies provided data on both sensitivity and specificity for diagnosing metastases. For this reason also the bivariate random-effects approach was not possible.

For the diagnosis of neuroblastoma, we performed a random effects meta-analysis of sensitivity of all included studies. The logit transformed value of sensitivity were meta-analysed using a random effects model to estimate the amount of between-study variance across studies and the “exact” binomial distribution was used to account for the within-study variance of each study (i.e. the precision by which sensitivity has been measured). These analyses were done in SAS 9.1 using the non-linear mixed effect module (PROC NLMIXED).

Investigations of heterogeneity
In first instance, we investigated heterogeneity through visual inspection of the forest plots. We planned to more formally examine the effects of covariates on sensitivity, specificity or both in the bivariate model, if sufficient data in the individual studies were available (data in at least four studies for each level of a covariate) to investigate heterogeneity. However, this was not possible.

Sensitivity analyses
To assess whether methodological quality influenced the results we planned to perform sensitivity analyses for the following individual quality items of QUADAS (Additional Table 1). However, due to a lack of discrimination within these items, it was not possible to do this.

- Item 1: different stages of the disease and newly diagnosed versus recurrent neuroblastoma may result in different groups.
- Item 4: partial verification bias.
- Item 5: differential verification bias.
- Item 11: withdrawals from the study may differ systematically from those who remain.
- Item 13: the execution of the index test may differ between clinical centres and may consequently lead to various results.
RESULTS

Results of the search

The searches, performed in the electronic databases of MEDLINE/PubMed and EMBASE/Ovid (September 2012) yielded a total of 4693 references. Initial screening of titles excluded 3204 references based on the finding that these studies described less than ten patients, were case reports, studies on animals, studies not performed in children with suspected neuroblastoma, or were not written in English. Thereafter, 1489 references were excluded based on the abstracts. A total of 246 full-text articles were assessed for eligibility, of which 201 were excluded (for reasons see Table Characteristics of excluded studies). The reference lists of included studies and relevant reviews yielded 1 additional conference proceeding. Conference proceedings of the International Society for Paediatric Oncology (SIOP), the American Society of Clinical Oncology (ASCO), Advances in Neuroblastoma Research (ANR) and the Society of Nuclear Medicine (SNM) from 2006 to 2012 yielded 4 additional conference proceedings. Consultation of researchers in the field yielded no ongoing studies. A total of 11 studies were included.

Figure 2: Flow chart inclusion of studies
neuroblastoma, studies performed in children with esthesioneuroblastoma and olfactory neuroblastoma or studies on the therapeutic use of MIBG (see Figure 2). Screening of title and abstract of the 1489 remaining references resulted in 246 studies that were assessed in full-text; 1243 studies were excluded because they did not meet the inclusion criteria, i.e. studies reporting less than ten patients, case reports, studies on animals, studies not performed in children with suspected neuroblastoma, studies performed in children with esthesioneuroblastoma and olfactory neuroblastoma, studies on the therapeutic use of MIBG and duplicate studies. Of the 246 full-text studies we included a total of 11 which fulfilled all the inclusion criteria for this review (see Additional Table 2A the Characteristics of included studies table). Of 22 studies we need additional information to assess whether they could be included and are awaiting further assessment (see Additional Table 2B the Characteristics of studies awaiting classification table). Six studies were not in English and are waiting to be translated (see Additional Table 2B Characteristics of studies awaiting classification table). Six studies appeared to be conference proceedings that were not published as full-text yet and are awaiting further assessment (see Additional Table 2B Characteristics of studies awaiting classification table). A total of 201 studies were excluded after assessing the full-text study for reasons described in Additional Table 2C Characteristics of excluded studies table.

Additionally, scanning the reference lists of relevant articles and reviews identified one conference proceeding (see Additional Table 2B Characteristics of studies awaiting classification table). Consultation of researchers in the field did not identify any ongoing studies. Scanning the conference proceedings of SIOP, ANR and SNM, resulted in four additional conference proceedings that have not been published as full-text yet and are awaiting further assessment (see Additional Table 2B Characteristics of studies awaiting classification table). Scanning the conference proceedings of ASCO did not identify relevant conference proceedings.

In summary, the total number of included studies was 11 (see Additional Table 2A Characteristics of included studies table). We also identified 22 studies from which we need additional information, six studies that are waiting to be translated and 11 studies that have not been published in full-text yet and are also awaiting further assessment (see Additional Table 2B Characteristics of studies awaiting classification table).

Included studies:
Characteristics of the included studies are summarised below. For more detailed information see Additional Table 2A Characteristics of included studies table.
The total number of patients that was reported in the eleven identified studies was 844. In this review we report only on 621 eligible patients that fulfilled the inclusion criteria for this review, being children younger than 18 years old with a neuroblastoma and a \textsuperscript{123}I-MIBG and/or \textsuperscript{18}F-FDG-PET(-CT) scan at first diagnosis or at recurrence. We excluded
patients from four studies that included both diagnostic and follow-up scans (Gordon 1990; Neuenschwander 1987; Pfluger 2003; Sharp 2009), from one study that included both $^{123}$I- and $^{131}$I-MIBG scans (Naranjo 2011a), from one study that included two adults (Piccardo 2012) and from one study that reported on neuroblastoma patients with and without MIBG scintigraphy (Hugosson 1999).

Five studies did not report on the median age of eligible patients for this review (Gordon 1990; Hugosson 1999; Neuenschwander 1987; Pfluger 2003; Sharp 2009). Four studies reported an age range from 0 to 15.2 years (Biasotti 2000; Hashimoto 2003; Naranjo 2011a; Piccardo 2012). One study reported a median age of 4 years (Lvanova 2008) and one a median of 0.4 years (Labreveux 1994).

The sex distribution was often not reported for the 621 eligible patients separately from the other patients in the studies. Six studies did not report on the sex distribution of eligible patients for this review (Biasotti 2000; Gordon 1990; Hugosson 1999; Neuenschwander 1987; Pfluger 2003; Sharp 2009) and five studies did: Hashimoto 2003 reported 20 boys (61%) and 13 girls (39%); Labreveux 1994 reported 10 boys (37%) and 17 girls (63%); Lvanova 2008 reported 14 boys (64%) and 8 girls (36%); Naranjo 2011a reported 124 boys (57%) and 94 girls (43%); and Piccardo 2012 reported 4 boys (24%) and 13 girls (76%).

The INSS stage distribution was also frequently not reported separately for the 621 eligible patients from the other patients in the studies. Five studies did not report on the INSS stage distribution of patients eligible for this review (Hugosson 1999; Labreveux 1994; Lvanova 2008; Neuenschwander 1987; Pfluger 2003). Two studies reported on patients with stage 1, 2, 3 and 4 neuroblastomas (Gordon 1990; Sharp 2009); two reported on patients with stage 1, 2, 3, 4 and 4S neuroblastomas (Biasotti 2000; Hashimoto 2003); one reported on patients with stage 3 and 4 neuroblastomas (Piccardo 2012); and one reported on patients with stage 4 neuroblastomas only (Naranjo 2011a). Three of these studies (Hashimoto 2003; Naranjo 2011a; Piccardo 2012) reported the exact number per INSS stage: 16 patients with stage 1, five with stage 2, six with stage 3, 239 patients with stage 4 and two patients with stage 4S neuroblastomas.

Four studies were retrospective cohort studies (Hashimoto 2003; Labreveux 1994; Pfluger 2003; Sharp 2009), two were prospective cohort studies (Naranjo 2011a; Piccardo 2012), one was a retrospective cross-sectional study (Lvanova 2008) and of four the type of study was not reported (Biasotti 2000; Gordon 1990; Hugosson 1999; Neuenschwander 1987). The diagnosis neuroblastoma was confirmed by histopathology in all 11 studies. In three studies both histopathology and bone marrow biopsies were used (Hugosson 1999; Naranjo 2011a; Sharp 2009) for the diagnosis neuroblastoma. In one study 11 patients had bone marrow biopsies and contrast-enhanced CT or MRI, one patient had histopathology of the primary tumour and contrast-enhanced CT or MRI and five patients had histopathology of the primary tumour, bone marrow biopsies and contrast-enhanced CT or MRI (Piccardo 2012). To evaluate metastatic disease on $^{123}$I-MIBG
scans, bone marrow biopsies were used as golden standard in three studies (Gordon 1990; Hashimoto 2003; Piccardo 2012). One study reported on a lesion level and used histologic verification as a reference standard for most lesions (Pfluger 2003). However, for stage 4 patients histologic verification of all metastases was impossible. Therefore, another reference standard was used: a minimum of six months was used for verification of lesions on follow-up control examinations. A lesion was classified as a false positive finding if it disappeared without tumour therapy during the observation period. A lesion was classified as a true positive finding if it persisted or progressed during follow-up or if it showed clear regression under specific therapy.

$^{123}$I-MIBG or $^{18}$F-FDG-PET scintigraphy was performed for 608 patients at the time of first diagnosis and for 13 patients at the time of a recurrence. Just one study reported on the 13 patients with a recurrent neuroblastoma (Piccardo 2012). All studies reported on $^{123}$I-MIBG scintigraphy as an index test; one study also reported on $^{123}$I-MIBG scintigraphy as a comparator test and $^{18}$F-FDG-PET scintigraphy as an index test (Sharp 2009). The administered activity of $^{123}$I-MIBG varied from 3.7 to 5.18 MBq/kg (Labreveux 1994; Lvanova 2008; Neuenschwander 1987; Pfluger 2003; Piccardo 2012; Sharp 2009), 185 to 370 MBq/1.73m² body surface (Hugosson 1999; Naranjo 2011a; Sharp 2009) or was in total 111 to 370 MBq (Gordon 1990; Hashimoto 2003; Sharp 2009). One study did not report on the administered activity of $^{123}$I-MIBG (Biasotti 2000).

$^{123}$I-MIB scintigraphy was performed 24 hours after administration of $^{123}$I-MIBG in six studies (Hashimoto 2003; Labreveux 1994; Naranjo 2011a; Neuenschwander 1987; Pfluger 2003; Piccardo 2012). One study reported an acquisition time of 24 or 48 hours (Hugosson 1999) and one study of 18 to 24 hours (Gordon 1990). In three studies the acquisition time was not reported (Biasotti 2000; Lvanova 2008; Sharp 2009).

In 91 patients only a whole-body $^{123}$I-MIBG scan was performed (Gordon 1990; Hashimoto 2003; Hugosson 1999; Pfluger 2003; Piccardo 2012), in 27 patients a $^{123}$I-MIBG whole-body scan with SPECT (Hashimoto 2003; Piccardo 2012) was performed, in 264 patients it was unclear whether a $^{123}$I-MIBG whole-body scan was performed with or without SPECT (Lvanova 2008; Naranjo 2011a; Sharp 2009) and of 239 patients it was not reported (Biasotti 2000; Labreveux 1994; Neuenschwander 1987). The one study that reported on $^{18}$F-FDG-PET scintigraphy described whole-body scans (Sharp 2009). However, it is known that in studies concerning PET-scintigraphy the definition of whole-body may indicate from cranium to toe, but sometimes also from base of skull to knees. This information was not provided by any of the studies.

Four studies reported that interpretation of the $^{123}$I-MIBG or $^{18}$F-FDG-PET scans was performed by two or more experienced observers (Hashimoto 2003; Naranjo 2011a; Pfluger 2003; Piccardo 2012), two studies reported one observer (Gordon 1990; Hugosson 1999) and five did not report on observers (Biasotti 2000; Labreveux 1994; Lvanova 2008; Neuenschwander 1987; Sharp 2009).
None of the included studies reported on treatment between index test and reference standard.

**Excluded studies:**
Two-hundred-one studies were excluded (see Additional Table 2C Characteristics of excluded studies table): 85 studies did not report on original research; 54 studies reported on less than ten children with a $^{123}$I-MIBG scan at diagnosis; 19 studies reported on patients that were not suspected of having a neuroblastoma but another tumour; 18 studies were no primary diagnostic investigations; 13 studies reported on $^{131}$I-MIBG scintigraphy and one on bone scintigraphy, instead of $^{123}$I-MIBG scintigraphy; the selection criteria were unclear in five studies and authors were unable to clarify these; two studies reported on patients older than 18 years; one study did not report on humans; three studies were duplicates.

**Figure 3:** Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.
The quality assessment results for the individual studies can be found in Additional Table 2A Characteristics of included studies Table. Figure 3 and Figure 4 give an overview of all quality assessment items.

In summary, in 55% of the studies the patients were representative for the patients that will be subjected to the index test in practice, in 18% of the studies patients were not representative and it was unclear in 27% of the studies. All studies used an acceptable reference standard. The time between the index and the reference test, the index and the comparator test, the comparator and the reference test was not reported in any of the studies. Although only one study provided data on specificity, partial verification bias was avoided in 64% of the studies. These studies only reported on patients with proven neuroblastoma and they all received the same reference standard. Partial verification bias might have played a role in 9% of the studies and it was unclear in 27%. Differential verification bias was avoided in 46% and might have been present in 27% of the included studies.

**Figure 4:** Methodological quality summary: review authors’ judgements about each methodological quality item for each included study.

Methodological quality of included studies

The quality assessment results for the individual studies can be found in Additional Table 2A Characteristics of included studies Table. Figure 3 and Figure 4 give an overview of all quality assessment items.

In summary, in 55% of the studies the patients were representative for the patients that will be subjected to the index test in practice, in 18% of the studies patients were not representative and it was unclear in 27% of the studies. All studies used an acceptable reference standard. The time between the index and the reference test, the index and the comparator test, the comparator and the reference test was not reported in any of the studies. Although only one study provided data on specificity, partial verification bias was avoided in 64% of the studies. These studies only reported on patients with proven neuroblastoma and they all received the same reference standard. Partial verification bias might have played a role in 9% of the studies and it was unclear in 27%. Differential verification bias was avoided in 46% and might have been present in 27% of the included studies.
studies; for 27% of the studies this was unclear. Incorporation bias was avoided in 91% and in 9% it was unclear.

It was unclear if the reference test results were blinded in all of the studies. The index test results were blinded in 9% of the studies. Observers were blinded for clinical data in 18%, in 18% of the studies clinical data were available to observers, and in 64% of studies it was unclear whether observers were blinded for clinical data.

Uninterpretable results were reported in 18% and in 82% this item was unclear. Withdrawals were reported in 36% of the studies and were not reported in 64%. The selection criteria were provided in 73% of the studies and they were not reported in 27%.

In 55% of the studies the index test was described in sufficient detail to replicate the test and in 45% this was not the case. The reference test was described in sufficient detail to replicate the test in just 9% of the studies, 82% of the studies did not report on this item and in 9% this item was unclear. A definition of a positive test result was reported in 46% of the studies, it was not reported in 36% of the studies, and in 18% there was no sufficient information about this item.

Interobserver variation was not reported in any of the eleven studies.

Findings

The sensitivity and specificity of the diagnosis neuroblastoma could be analysed for 608 of the 621 eligible patients. The remaining 13 patients were reported in two studies and had false positive or true negative results for neuroblastoma based just on negative bone marrow biopsies which is not a valid method to detect neuroblastoma, but only to detect metastases (Gordon 1990; Piccardo 2012). Of these 13 patients, twelve had a stage 4 neuroblastoma and could therefore be analysed for diagnostic accuracy of the presence of metastases (Gordon 1990; Piccardo 2012). One of the 13 patients had a stage 3 neuroblastoma and therefore could not be analysed for any of the diagnostic accuracies (Piccardo 2012).

One study did not report results on a patient level, but on a lesion level (115 lesions in 22 patients) (Pfluger 2003).

The true positive fractions per study are represented in Figure 5 and the true negative fraction of one study (Pfluger 2003) is represented in Figure 6.
Objective 1.1 Diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old

For the diagnostic accuracy of detecting a neuroblastoma at first diagnosis or at recurrence with $^{123}$I-MIBG scintigraphy, we analysed data of 608 patients out of 621 eligible patients. The sensitivity of the separate studies varied from 67% to 100% with a pooled mean value of 92.4%, a 95% confidence interval of 84.5% to 96.4%, and a 95% prediction interval of 62.5 to 98.9% (see Figure 5). The total false negative rate was 11%. Only one study described patients with both suspected and already proven neuroblastoma (Pfluger 2003) and therefore specificity could only be evaluated in this study. It was 85% in 22 patients with 115 lesions (see Figure 6). The findings of this study were determined for each lesion (on a lesion level), while in all other studies they were determined per patient (on a patient level).

The false positive findings of the $^{123}$I-MIBG scans at diagnosis (n=8 lesions), in the study of Pfluger 2003 were due to: ganglioneuromas (n=2), hemangioma of the liver (n=1), focal nodular hyperplasia of the liver (n=1), normal liver (n=1), renal pelvis (n=1) and physiological activity in a normal adrenal gland, bowel or musculature (n=2). Most of these findings are known as physiological activity of $^{123}$I-MIBG and should be distinguished from pathological uptake by a nuclear medicine expert, i.e. normal liver, renal pelvis, and physiological activity in a normal adrenal gland, bowel or musculature. Therefore we adjusted the number of false positive findings of this study from eight to four. The specificity was 85% with these four positive findings instead of the 68% if the physiological uptake was taken into account as false positive results (as done in the study by the authors).

The diagnostic accuracy of detecting metastases (osteomedullary and soft tissue) of neuroblastoma was analysed in three studies (Gordon 1990; Labreveux 1994; Piccardo 2012) with all 72 eligible patients. In contrast to the diagnosis of the primary tumour, analyses for the diagnostic accuracy of metastases did include false positive and true negative findings in all three studies and therefore sensitivity as well as specificity could be calculated. The mean sensitivity of $^{123}$I-MIBG scintigraphy for detecting neuroblastoma metastases in these three studies was 91% (range 79% to 100%). The the mean specificity could be calculated for two of these studies with 45 patients and was 67% (range 33% to 89%). Of the 72 patients 72% had true positive metastases on the $^{123}$I-MIBG scan, 7% false negative, 7% false positive and 14% true negative. Because sensitivity and specificity for the detection of metastases were described in less than four studies, no forest plots were generated.

The detection of metastases was also analysed for osteomedullary, lymph node and liver metastases separately. The detection of osteomedullary metastases was reported in four studies with 105 eligible patients (Gordon 1990; Hashimoto 2003; Labreveux 1994; Piccardo 2012). The mean sensitivity of these four studies was 88% (range 33% to 100%)
and the mean specificity 91% (range 57% to 100%). The detection of lymph node and liver metastases was reported in one study with 33 eligible patients (Hashimoto 2003). For the detection of liver metastases the sensitivity for 33 patients was 80% and the specificity 93%. For the detection of lymph node metastases this was 23% and 100%, respectively.

**Subgroup analyses**

For some items subgroup analyses were not possible at all (acquisition time and interfering medication), because no sufficient data were given to identify subgroups.
Stage of disease:

Two studies reported data on diagnostic accuracy of $^{123}$I-MIBG scintigraphy in all 43 eligible patients with stage 1 or 2 neuroblastoma (Biasotti 2000; Sharp 2009). The mean sensitivity of these studies was 74% (range 60% to 76%).

Three studies reported data on diagnostic accuracy of $^{123}$I-MIBG scintigraphy in 54 of all 55 eligible patients with stage 3 neuroblastoma (Biasotti 2000; Piccardo 2012; Sharp 2009). The mean sensitivity of these studies was 94% (0% to 100%).

Four studies reported data on diagnostic accuracy of $^{123}$I-MIBG scintigraphy in all 344 eligible patients with stage 4 neuroblastoma (Biasotti 2000; Naranjo 2011a; Piccardo 2012; Sharp 2009). The mean sensitivity of these studies was 92% (range 80% to 100%).
Only one study reported data on diagnostic accuracy of \(^{123}\)I-MIBG scintigraphy in all 13 eligible patients with stage 4S neuroblastoma (Biasotti 2000). The sensitivity was 100%. Two studies reported on diagnostic accuracy of \(^{123}\)I-MIBG scintigraphy for detecting osteomedullary metastases of stage 4 neuroblastoma separately from the other stages (Gordon 1990; Piccardo 2012). For the 37 eligible patients with stage 4 disease described in these two studies, the mean sensitivity was 83% (range 79% to 90%) and the mean specificity 50% (range 40% to 67%).

Newly diagnosed versus recurrent neuroblastoma:
Data on the diagnostic accuracy of \(^{123}\)I-MIBG scintigraphy for detecting neuroblastoma in children from 0 to 18 years for patients with a newly diagnosed versus a recurrent neuroblastoma were only available for 13 eligible patients in one study (Piccardo 2012). Of the four patients with a \(^{123}\)I-MIBG at first diagnosis two had true positive and two had false negative findings (sensitivity 50%). Of the 9 patients with a \(^{123}\)I-MIBG at recurrence eight had true positive and one had false negative findings (sensitivity 89%).

Type of reference standard:
Diagnostic accuracy of \(^{123}\)I-MIBG scintigraphy for detecting neuroblastoma in children from 0 to 18 years old per reference standard (histopathology versus bone marrow biopsies) could be analysed with the data of one study with 17 eligible patients (Piccardo 2012). In six children histopathology as the reference standard gave three true positive and three true negative results (sensitivity 50%). Bone marrow biopsies in all 17 children gave nine true positive, two false positive, two false negative and four true negative findings (sensitivity of 82% and specificity of 67%).

Plane whole-body versus whole-body SPECT/CT \(^{123}\)I-MIBG scintigraphy:
The sensitivity of \(^{123}\)I-MIBG scintigraphy for detecting neuroblastoma in children from 0 to 18 years for patients with whole-body \(^{123}\)I-MIBG scintigraphy could be analysed with the data of four studies with 62 of 85 eligible patients (Gordon 1990; Hugosson 1999; Pfluger 2003; Piccardo 2012). The mean sensitivity was 73% (range 67% to 100%). The specificity was only provided in one study for all 115 lesions of 22 eligible patients (Pfluger 2003) and was 68%.
The sensitivity of whole-body \(^{123}\)I-MIBG scans with SPECT/CT separately from those without was only reported in one study for 11 of 17 eligible patients (Piccardo 2012) and was 73%.
Objective 1.2 Diagnostic accuracy of negative $^{123}$I-MIBG scintigraphy in combination with $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old

Only one study reported on the diagnostic accuracy of negative $^{123}$I-MIBG scintigraphy in combination with $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children 0 to 18 years (Sharp 2009). Two of the 24 eligible patients with proven neuroblastoma had a negative $^{123}$I-MIBG scan and a positive $^{18}$F-FDG-PET(-CT) scan.

Objective 2.1 Diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old

Only one study reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis in children from 0 to 18 years (Sharp 2009). This study described data on $^{18}$F-FDG-PET(-CT) scans of all 24 eligible patients with proven neuroblastoma with a sensitivity of 100%. Because all patients had already proven neuroblastoma, false positive and true negative findings did not occur in this study and therefore specificity could not be analysed.

Subgroup analyses

Pooled analyses were not possible, because only one study reported on this objective. However, data on diagnostic accuracy for subgroups of INSS stage within this study were available. For the other subgroups these data were not provided (newly diagnosed versus recurrent neuroblastoma, plane whole-body versus whole-body SPECT/CT $^{123}$I-MIBG scintigraphy, type of reference standard, acquisition time and interfering medication).

Stage of disease:

The one study with 24 eligible patients that reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a primary neuroblastoma tumour and its metastases in children from 0 to 18 years old (Sharp 2009), described only true positive findings for 5 patients with stage 1 or 2 disease, 3 patients with stage 3 disease and 16 patients with stage 4 tumours, so a sensitivity of 100%.

Objective 2.2 Comparison of diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy and of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old

Only one study reported on the diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy versus $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years (Sharp 2009). This study
described data on all 24 eligible patients with proven neuroblastoma. The sensitivity of \(^{123}\)I-MIBG scintigraphy was 92% with two false positive results. The sensitivity of \(^{18}\)F-FDG-PET(-CT) imaging was 100%. The specificity could not be calculated, because only proven neuroblastoma patients were included. So, \(^{18}\)F-FDG-PET(-CT) imaging had a better sensitivity than \(^{123}\)I-MIBG scintigraphy. The two \(^{123}\)I-MIBG negative neuroblastomas were positive on \(^{18}\)F-FDG-PET(-CT) imaging.

Subgroup analyses
Pooled analyses were not possible, because only one study reported on this objective. However, data on diagnostic accuracy for subgroups of INSS stage within this study were available. For the other subgroups these data were not provided (newly diagnosed versus recurrent neuroblastoma, plane whole-body versus whole-body SPECT/CT \(^{123}\)I-MIBG scintigraphy, type of reference standard, acquisition time and interfering medication).

Stage of disease:
The one study with 24 eligible patients that compared the diagnostic accuracy of \(^{123}\)I-MIBG and \(^{18}\)F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis in children from 0 to 18 years old (Sharp 2009), described two false negative findings on \(^{123}\)I-MIBG scintigraphy of 5 patients with stage 1 or 2 disease, resulting in a sensitivity of 60%. \(^{18}\)F-FDG-PET(-CT) imaging was positive for all 5 patients with a sensitivity of 100%. Three patients with stage 3 disease and 16 patients with stage 4 tumour had all true positive findings on the \(^{123}\)I-MIBG scintigraphy and the \(^{18}\)F-FDG-PET(-CT) imaging, with sensitivities of 100%. Specificity could not be calculated, because only proven neuroblastomas were described.

DISCUSSION

Summary of main results
Many studies have been published on the diagnostic accuracy of \(^{123}\)I-MIBG (SPECT-CT) scintigraphy, but studies report variable numbers of patients and variable results of the imaging methods. Many studies only describe a small number of patients and the specificity is not even clearly reported in most studies. Still, prognosis, treatment and response of patients with neuroblastoma are yet based on extension scoring of \(^{123}\)I-MIBG scans (Decarolis 2013; Matthay 2010; Naranjo 2011; Yanik 2013). Therefore, it is important to have a good overview of the sensitivity and specificity of this diagnostic test. In this review we evaluated the diagnostic accuracy of \(^{123}\)I-MIBG (SPECT-CT) scintigraphy and \(^{18}\)F-FDG-PET(-CT) imaging for the detection of a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old, described in 11 studies that met the inclusion criteria.
Table 4A: Summary of results table of objective 1.1 123I-MIBG scintigraphy for diagnosing a neuroblastoma and its metastases at first diagnosis or at recurrence

**Objective 1.1** 123I-MIBG scintigraphy for diagnosing a neuroblastoma and its metastases at first diagnosis or at recurrence.

**Patients/population:** children from 0 to 18 years old with a suspected neuroblastoma of any stage at first diagnosis or at recurrence.

**Setting:** tertiary care centres of paediatric oncology.

**Index test:** 123I-MIBG scintigraphy (whole-body, SPECT or SPECT-CT).

**Reference test:** golden standard is histopathology and or bone marrow biopsies/trephine biopsies, but that was not always performed; so also: histopathology during or after treatment (e.g. tissue obtained during surgery), if urinary metabolites were elevated at diagnosis and additional imaging modalities (e.g. ultrasound, CT scan, MRI scan) suggested a neuroblastoma at diagnosis.

**Studies:** primary diagnostic cohort studies (retrospective and prospective), cross-sectional study.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Second covariate</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Number of participants (studies) unless otherwise stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma at first diagnosis or at recurrence (all stages)</td>
<td>-</td>
<td>pooled mean 0.92 (95%CI 0.85 - 0.96) (95% PI 0.63 - 0.99)</td>
<td>0.85* (one study)</td>
<td>608 (11 studies)</td>
</tr>
<tr>
<td>Metastases (osteomedullary and soft tissue)</td>
<td>-</td>
<td>mean 0.91 (range: 0.79-1.00)</td>
<td>mean 0.67 (range: 0.33-0.89) (two studies, 45 patients)</td>
<td>72 (3 studies)</td>
</tr>
<tr>
<td>Stage 1 and 2</td>
<td>-</td>
<td>mean 0.74 (range: 0.60-0.76)</td>
<td>**</td>
<td>43 (2 studies)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>-</td>
<td>mean 0.94 (range: 0.00 - 1.00)</td>
<td>**</td>
<td>54 (3 studies)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>-</td>
<td>mean 0.92 (range: 0.80 - 1.00)</td>
<td>**</td>
<td>344 (4 studies)</td>
</tr>
<tr>
<td>Stage 4S</td>
<td>Osteomedullary metastases</td>
<td>mean 0.83 (range: 0.79 - 0.90)</td>
<td>mean 0.50 (range: 0.40-0.67)</td>
<td>37 (2 studies)</td>
</tr>
<tr>
<td>Stage 4S</td>
<td>-</td>
<td>1.00</td>
<td>**</td>
<td>13 (1 study)</td>
</tr>
</tbody>
</table>

* Because only one study (Pfluger 2003) reported on diseases, other than neuroblastoma, the specificity could be calculated for only this one study. This should be kept in mind. Besides, this study is the only one reporting at lesion level instead of patient level. ** Because none of the studies, that distinguished stages of neuroblastoma, reported on diseases other than neuroblastoma, the specificity could not be calculated for any of these studies. CI: confidence interval PI: prediction interval

The sensitivity of 123I-MIBG (SPECT-CT) scintigraphy (objective 1.1), determined in 608 of 621 eligible patients included in the 11 studies, varied from 67% to 100%, with a pooled mean value of 92.4%, a 95% confidence interval of 84.5% to 96.4% and a 95% prediction interval of 62.5 to 98.9% (see Figure 5 and table 4A Summary of results table). The specificity was 85% in 115 lesions in 22 patients, described in one study (see Figure 6).
We pooled results of studies at patient level and at lesion level. Only one study provided data at lesion level. We included this study because data at lesion level are important for staging and treatment allocation.

The sensitivity for the detection of stage 1 and 2 neuroblastomas with $^{123}$I-MIBG scintigraphy varied from 60 to 76% with a mean of 74% (two studies), for stage 3 neuroblastomas from 0% to 100% with a mean of 94% (three studies), for stage 4 neuroblastomas 80% to 100% with a mean of 92% (four studies), and for stage 4S neuroblastomas the sensitivity was 100% (one study) (see table 4A Summary of results table). The range of the sensitivity of stage 3 tumours was quite broad in comparison to that for all tumours. An explanation might be that of the three studies included in this subgroup analysis, one study (Piccardo 2012) reported on just one patient with a false negative scan, resulting in a sensitivity of 0%. The sensitivity of 100% for stage 4S tumours might also be explained by the small number of included patients, being 13 patients from only one study with all true positive investigations.

---

**Table 4B: Summary of results table of objective 2.1 Diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence**

<table>
<thead>
<tr>
<th>Objective 2.1 Diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients/population:</strong> children from 0 to 18 years old with a neuroblastoma of any stage at first diagnosis or at recurrence.</td>
</tr>
<tr>
<td><strong>Setting:</strong> tertiary care centres of paediatric oncology.</td>
</tr>
<tr>
<td><strong>Index test:</strong> $^{18}$F-FDG-PET(-CT) imaging.</td>
</tr>
<tr>
<td><strong>Reference test:</strong> golden standard is histopathology and or bone marrow biopsies/trephine biopsies, but that was not always performed; so also: histopathology during or after treatment (e.g. tissue obtained during surgery), if urinary metabolites were elevated at diagnosis and additional imaging modalities (e.g. ultrasound, CT scan, MRI scan) suggested a neuroblastoma at diagnosis.</td>
</tr>
<tr>
<td><strong>Studies:</strong> retrospective cohort study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Second covariate</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Number of participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma (all stages) at first diagnosis</td>
<td>-</td>
<td>1.00</td>
<td>*</td>
<td>24 (1 study)</td>
</tr>
<tr>
<td>Stage 1 and 2</td>
<td>-</td>
<td>1.00</td>
<td>*</td>
<td>5 (1 study)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>-</td>
<td>1.00</td>
<td>*</td>
<td>3 (1 study)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>-</td>
<td>1.00</td>
<td>*</td>
<td>16 (1 study)</td>
</tr>
</tbody>
</table>

* Only one study reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma tumour and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old (Sharp 2009). Because all patients had already proven neuroblastoma, true negative findings did not occur in this study and therefore specificity could not be analysed. The study did not demonstrate false negative findings at diagnosis, which suggests that patients might be selected based on uptake on their scan. CI: confidence interval.
The diagnostic accuracy of $^{123}$I-MIBG (SPECT-CT) scintigraphy for detecting metastases (soft tissue and osteomedullary) separately from the primary tumour in patients with all neuroblastoma stages, was described in three of the 11 studies with in total 72 patients (see table 4A Summary of results table). The sensitivity ranged from 79% to 100% with a mean of 91% (3 studies) and the specificity from 33% to 89% with a mean of 67% (2 studies). For lymph node metastases the sensitivity was 23% and the specificity 100%; and for liver metastases this was 80% and 93%. Both types of metastases were reported in one study with 33 patients. Osteomedullary metastases were described in four studies with 105 patients. The sensitivity varied from 33% to 100% with a mean of 88% and the specificity from 57% to 100% with a mean of 91%. The sensitivity for osteomedullary metastases in only stage 4 neuroblastomas varied from 79% to 90% with a mean of 83% and a specificity from 40% to 67% with a mean of 50% (two studies) (see table 4A Summary of results table).

Only one study reported on the diagnostic accuracy of negative $^{123}$I-MIBG scintigraphy in combination with $^{18}$F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children 0 to 18 years (objective 1.2). For two of the 24 eligible patients with proven neuroblastoma $^{18}$F-FDG-PET(-CT) imaging had additional value. Two patients with a negative $^{123}$I-MIBG scan, had a positive $^{18}$F-FDG-PET(-CT) scan.

One study reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging for detecting both the primary tumour and its metastases compared to the reference standards (objective 2.1) and compared to $^{123}$I-MIBG (SPECT-CT) scintigraphy (objective 2.2). The sensitivity of $^{123}$I-MIBG scintigraphy was 92% and of $^{18}$F-FDG-PET(-CT) imaging was 100%. The specificity could not be analysed because all patients had already proven neuroblastomas (table 4B Summary of results table). So, for the 24 eligible patients in this study, $^{18}$F-FDG-PET(-CT) imaging had a better sensitivity than $^{123}$I-MIBG (SPECT-CT) scintigraphy.

Summarising, $^{123}$I-MIBG scintigraphy is a sensitive method for detecting a neuroblastoma at first diagnosis or at recurrence with a pooled mean sensitivity of 92.4% (95% CI 84.5 to 96.4%; 95% PI 62.5 to 98.9%). Analysis of the specificity was difficult, because only one study provided data on false positive and true negative results. The sensitivity of $^{18}$F-FDG-PET(-CT) imaging as a single diagnostic test and compared to $^{123}$I-MIBG (SPECT-CT) was only reported in one study as 100% (compared to 92% of $^{123}$I-MIBG scintigraphy in this study) and the specificity could not be calculated. In case of two negative $^{123}$I-MIBG scans, the $^{18}$F-FDG-PET(-CT) scan had added value and was positive.
Strengths and weaknesses of the review

*Insufficient data for subgroup analyses and specificity determination*

One of the most important weaknesses in this review is the small number of patients from the included studies that could be analysed for specificity of $^{123}$I-MIBG (SPECT-CT) scintigraphy (objective 1.1). Only one study provided data to calculate the specificity of $^{123}$I-MIBG scintigraphy and reported on 22 eligible patients with 115 lesions in total of which eight false positive and 17 true negative (Pfluger 2003).

In clinical practice, $^{123}$I-MIBG and $^{18}$F-FDG scintigraphy are only performed if a neuroblastoma is already strongly suspected and other tests like urinary catecholamines are already proven positive. Therefore, only few studies on diagnostic accuracy $^{123}$I-MIBG and $^{18}$F-FDG-PET(-CT) scintigraphy report on false positive results and as a result specificity of these tests is difficult to assess.

The inclusion of a small number of patients in the studies of Gordon 1990 and Piccardo 2012 (19 and 13, respectively) might explain the minor sensitivity in comparison to the other studies. Because of small numbers, one scan more or less scored as false negative, might have a great effect on the sensitivity. For the study of Pfluger 2003 the minor sensitivity might be explained by the fact that the study results were based on a lesion level and not on a patient level. Just one positive lesion is enough for the diagnosis neuroblastoma and just one positive metastatic site is enough to define stage 4 disease. However, probably, patients were included in this study with more than one positive lesion. Therefore, sensitivity may be overestimated.

Moreover, only one study with 24 eligible patients (Sharp 2009) reported on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging as a single diagnostic test (objective 2.1) and compared to $^{123}$I-MIBG scintigraphy (objective 2.2). Therefore, it is difficult to draw reliable conclusions from analyses on this study. In this study only two patients with negative $^{123}$I-MIBG scans were reported that were positive on $^{18}$F-FDG-PET(-CT) scans (objective 1.2). $^{18}$F-FDG-PET(-CT) imaging is an upcoming diagnostic imaging method for the detection of neuroblastoma and its metastases. It is already considered as an important additional diagnostic method if $^{123}$I-MIBG scintigraphy is negative (Piccardo 2013). We hope that in an update of this Cochrane diagnostic test accuracy systematic review we can include more studies on this objective and provide more reliable information on the diagnostic accuracy of $^{18}$F-FDG-PET(-CT) imaging.

*Subgroup analyses*

For some items subgroup analyses were not possible at all (acquisition time and interfering medication), because no sufficient data were given to identify subgroups. In this review, the type of the $^{123}$I-MIBG scans (whole-body, SPECT-CT, or a combination) varied between the studies and not all studies did report on the distinction between these types of scans. The sensitivity of $^{123}$I-MIBG whole-body scintigraphy (Gordon 2013).
as well as of $^{123}\text{I}}$-MIBG whole-body SPECT-CT scintigraphy (Piccardo 2012) was 73%. So, no difference in sensitivity for whole-body versus whole-body SPECT-CT scans. However, only one study described whole-body SPECT-CT scans of only 11 of 17 eligible patients. In the literature, the addition of SPECT-CT might change the diagnostic accuracy of $^{123}\text{I}}$-MIBG scintigraphy (Gelfand 1994 Rozovsky 2008; Rufini 1995; Rufini 1996). Usually it improves the detection of neuroblastoma lesions and it is better possible to differentiate pathological from physiological uptake. Therefore, although the sensitivity of both modalities were not different in this review, it is still important to make a distinction between studies that used whole-body scintigraphy only and those that added SPECT-CT.

**Reference standards**

Three different tests were used as possible reference standards. If only one of the three reference standards had a positive result, the diagnosis neuroblastoma could be confirmed. However, to reject the diagnosis neuroblastoma all three had to give a negative result. For some of the studies, only bone marrow biopsies, but not histopathology was reported for some patients. However, because of sampling error, a negative result of bone marrow aspirates or trephine biopsies does not exclude a primary neuroblastoma tumour or metastatic disease. Because no reliable conclusions could be drawn, these patients were excluded from sensitivity and specificity analyses.

One study reported on a lesion level (Pfluger 2003). Histologic verification of all lesions in stage 4 patients with metastases is impossible. Therefore, another reference standard was used: a minimum of six months was used for verification of lesions on follow-up control examinations. A lesion was classified as a false-positive finding if it disappeared without tumour therapy during the observation period. A lesion was classified as a true positive finding if it persisted or progressed during follow-up or if it showed clear regression under specific therapy. This might explain the fact that this study found more false positive and false negative results than the other studies. The other studies did not report on a lesion level, but on a patient level. Only one positive lesion is then enough to diagnose a neuroblastoma and only one metastatic lesion is enough to classify the patient as stage 4 or 4S. So for the diagnosis of neuroblastoma in general, sensitivity and specificity on a lesion level is less important.

**Applicability of findings to clinical practice and policy**

In the literature it is often stated that 90% of neuroblastoma tumours take up MIBG (MIBG-avid) and that around 10% do not (Boubaker 2008). In concordance with the literature, this review reported 11% of the 608 patients in the 11 included studies with MIBG-non-avid neuroblastomas. The reasons for these MIBG-non-avid tumours are not entirely clear. Possible modifications in the uptake mechanism or interfering medication
may play a role (Boubaker 2008), but most studies do not report on the reasons of MIBG-non-avid neuroblastoma lesions. Also intense radiotracer uptake in normal liver, myocardium, salivary glands and gut may blur the picture and small pathological lesions can be less visible. SPECT-CT might improve the detection of these lesions, but more research is needed before a definitive conclusion can be made.

The analyses in this review showed a false negative rate of around 7% for all types of metastases and for osteomedullary metastases specifically. So, investigation of bone marrow aspirates or trephine biopsies, as described in current protocols (Monclair 2009), are justified in all patients at diagnosis. However, these aspirates and biopsies are taken from the iliac crest, so distant metastases might still be missed. Therefore it is worthwhile to perform an additional test, in case of a negative result of whole-body ¹²³I-MIBG scintigraphy. For metastases this is of great importance, because the presence of metastases classifies the patient as stage 4 or 4S and this has severe consequences for the prognosis and treatment. A possible candidate as add-on test might be ¹⁸F-FDG-PET(-CT) or MRI (Corbett 1991a; Siegel 2013). In this diagnostic test accuracy review we reviewed the diagnostic accuracy of ¹⁸F-FDG-PET(-CT). When comparing ¹⁸F-FDG-PET(CT) imaging to ¹²³I-MIBG scintigraphy, the sensitivity of ¹⁸F-FDG-PET(CT) was better and it had additional value if ¹²³I-MIBG scintigraphy was negative (all in one study). So, it is worthwhile to study this imaging method as a promising add-on test.

Although the specificity of ¹²³I-MIBG scintigraphy was analysed in just one study, analyses were performed for 115 lesions in 22 patients (Pfluger 2003). The general assumption is that MIBG activity on an ¹²³I-MIBG scan, that is not explained by physiological uptake, is most likely neuroblastoma tumour. In contrast, this one study reported false positive findings (Pfluger 2003). We, however, believe that not all of these false positive results were justified, because some of them could also be considered as physiological uptake, like normal liver, renal pelvis, physiological activity in a normal adrenal gland, bowel or musculature.

**AUTHOR’S CONCLUSIONS**

Implications for practice

With this Cochrane diagnostic test accuracy review we included 11 studies and we found a pooled mean sensitivity of 92.4% with a 95% confidence interval of 84.5% to 96.4% and a 95% prediction interval of 62.5 to 98.9%. Although only one study in this review reported on false positive findings, it is important to keep in mind that false positive findings occur. Most reported false positive findings in this one study seemed to be physiological uptake. However, this implies that ¹²³I-MIBG scans may not be evaluated as easy as is generally thought and that it is important to rule out physiological uptake,
for example by using SPECT-CT scans, although more research is needed before definitive conclusions can be made.

As described in the literature around 10% of the $^{123}$I-MIBG scans gave false negative results. Usually these patients with MIBG-non-avid neuroblastoma will eventually be detected by histopathology. However to stage these patients properly and to assess response, it is advisable to perform an additional test in patients that are suspected of having a neuroblastoma, but have a negative result of their $^{123}$I-MIBG scan. This is also important for patients with a positive result of the histopathology, because the presence of distant metastases is important for staging and response which has consequences for prognosis and treatment. Although not enough evidence is available, a possible add-on test could be $^{18}$F-FDG-PET(-CT). Further research is required to support this for clinical practice.

Implications for research

In this Cochrane systematic diagnostic test accuracy review, only one study reported on the specificity of $^{123}$I-MIBG scintigraphy (Pfluger 2003). The other ten studies reported on patients with already proven neuroblastoma. Although the general assumption is that $^{123}$I-MIBG uptake outside the physiological areas proves neuroblastoma, this one study reported on 7% false positive findings or 3% if cases with physiological uptake were excluded. It would be worthwhile to further and better assess the specificity in future studies. Furthermore, it is important to study the possibilities of other additional diagnostic tests in case of negative results of $^{123}$I-MIBG scans in patients suspected of neuroblastoma or already diagnosed with neuroblastoma according to histopathology. One possible additional test is $^{18}$F-FDG-PET(-CT). Only one study concerning $^{18}$F-FDG-PET imaging was included. Because more and more studies are performed with this diagnostic test for patients with neuroblastoma, we think that with the update of this review more studies on $^{18}$F-FDG PET(-CT) can be analysed and more robust conclusions can be drawn.

In this Cochrane systematic diagnostic test accuracy review some subgroup analyses were not possible, because studies did not report the data in sufficient detail to assign all patients to subgroups.

Only eleven studies were included in this diagnostic test accuracy review. The first reason for the small number of included studies is that we excluded studies that performed $^{131}$I-MIBG instead of $^{123}$I-MIBG scintigraphy. However, a recent publication (Naranjo 2011) reported no evidence of a statistically significant difference in outcome by type of scan. Therefore, for an update of this review it would advisable to take these $^{131}$I-MIBG scans also into account. A second reason for the small number of included studies was that many studies reported on $^{123}$I-MIBG scintigraphy of less than ten patients which was an exclusion criteria for our review, assuming that less than ten patients could not give robust results. However, if reported clearly, studies with less than ten patients might be able to
give reliable data and pooling them would be an opportunity for an update of this review. A last reason is that in the past, many studies reported patients per centre, resulting in a small number of patients per study. Nowadays, more and more centres collaborate to publish results of their patients together, resulting in more robust data. For an update of this review, we hope that these kind of collaborations will result in many studies with a large number of patients and with robust results, so we can include more patients and do more reliable analyses.

ACKNOWLEDGEMENTS

The authors would like to thank Edith Leclercq, the Trials Search Co-ordinator of the Cochrane Childhood Cancer Group, for helping to design the search strategy and running the searches.

The authors would like to thank E.M.C. Michiels, MD, PhD; A. Seniukovich, MD; P. Alonso-Coello, MD; and K. Hayashi for their help with translating non-English studies.

The authors would like to thank A.F. Jacobson, MD, PhD, and A. Naranjo, PhD for their additional information on studies that we had to asses.

The authors would like to thank K. Matthay, MD, and B.L. Shulkin, MD for their information on ongoing studies.

The authors would like to thank H. Reitsma for performing analyses of data.

The editorial base of the Cochrane Childhood Cancer Group is funded by Kinderen Kankervrij (KiKa).

DECLARATIONS OF INTEREST

None known.

Sources of support

Internal sources: Dutch Cochrane Centre, Netherlands

External sources: Stichting Kinderen Kankervrij (KiKA), Netherlands
### Additional Table 1: Items of the QUADAS tool and their interpretation

**1. Was the spectrum of patients representative of the patients who will receive the test in practice? Is it a selective sample of patients?**

Differences in demographic or clinical features between the study population and the source population may lead to selection bias or spectrum variation. In this item we will focus on selection bias: is a selective sample of patients included? The age group and method of patient recruitment will be assessed.

- Classify as ‘yes’ if the study describes a cohort of children 0 to 18 years old; if the study describes whether a suspected primary or relapsed neuroblastoma is concerned; if the study describes stage of the disease (1 to 4 and 4S).
- Classify as ‘no’ if the study describes patients older than 18 years old; if the study does not describe stage of the disease (1 to 4 and 4S); if the study recruited a group of healthy controls and a group known to have the target disorder.
- Classify as ‘unclear’ if there is insufficient information on these items.

**2. Is the reference standard likely to classify the target condition correctly?**

Estimates of test performance are based on the assumption that the reference standard will identify neuroblastoma with 100% sensitivity and 100% specificity. Such reference standards are rare. Errors due to an imperfect reference standard may bias the estimation of diagnostic performance. For this review acceptable reference standards are: 1) histopathology of primary tumour; or 2) bone marrow aspirates or trephine biopsies; or 3) histopathology during or after treatment, if urinary metabolites are elevated at diagnosis and additional imaging modalities suggest neuroblastoma at diagnosis (Brodeur 1993).

- Classify as ‘yes’ if one of these tests is described as the reference test.
- Classify as ‘no’ if one or more reference standards used do not meet the pre-stated criteria.
- Classify as ‘unclear’ if there is insufficient information on the reference standard.

**3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?**

Ideally the index test and the reference standard should be performed at the same time. If there is a considerable delay, misclassification due to treatment, spontaneous recovery or progression to a more advanced stage of disease may occur.

- Classify as ‘yes’ if the time period between index test and reference standard is two weeks or less and no treatment was given in between.
- Classify as ‘no’ if the time period between index test and reference standard is longer than two weeks or if treatment was given in between.
- Classify as ‘unclear’ if there is insufficient information on the time period between index test and reference standard.

**4. Did the whole sample or a random selection of the sample receive verification using a reference standard?**

Partial verification bias occurs when not all of the study group receive confirmation of the diagnosis by the reference standard. Partial verification bias is very likely if the results of the index test influence the decision to perform the reference standard.

- Classify as ‘yes’ if it is clear that all patients or a random selection of patients, that received the index test, went on to the reference standard, even if the reference standard is not the same for all patients.
- Classify as ‘no’ if not all patients, that received the index test, went on to the reference standard or if the selection of patients receiving the reference standard was not random.
- Classify as ‘unclear’ if there is insufficient information on this item.
### 5. Did patients receive the same reference standard regardless of the index test result?

Differential verification bias occurs when some of the index test results are verified by different reference standards. This is not unlikely in this review.

- Classify as 'yes' if the same reference standard is used to verify the true disease status in ≥ 90% of the patients.
- Classify as 'no' if different reference standards are used to verify the true disease status in ≥ 10% of the patients.
- Classify as 'unclear' if there is insufficient information on this item.

### 6. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

Incorporation bias occurs when the result of the index test is used in establishing the final diagnosis. This will probably increase the amount of agreement between index test result and the outcome of the reference standard, and hence overestimate the various measures of diagnostic accuracy.

- Score 'yes' if the index test is no part of the reference standard.
- Score 'no' if the index test is part of the reference standard.
- Score 'unclear' if there is insufficient information on this item.

### 7. Were the reference standard results interpreted without knowledge of the results of the index test?

Review bias occurs when interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This may lead to inflated measures of diagnostic accuracy.

- Classify as 'yes' if the reference test results were interpreted blind to the results of the index test or blinding is dictated by the test order.
- Classify as 'no' if reference test results were interpreted with knowledge of the index test results.
- Classify as 'unclear' if there is insufficient information on this item.

### 8. Were the index test results interpreted without knowledge of the results of the reference standard?

Review bias occurs when interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This may lead to inflated measures of diagnostic accuracy.

- Classify as 'yes' if the test index test results are interpreted blind to the results of the reference test or blinding is dictated by the test order.
- Classify as 'no' if the index test results were interpreted with knowledge of reference test results.
- Classify as 'unclear' if there is insufficient information on this item.

### 9. Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice?

The availability of clinical data during interpretation of test results may affect estimates of test performance.

- Classify as 'yes' if clinical data, like demographic factors (sex and age); patient history and physical examination (e.g. abdominal extension, bone pains, respiratory distress); additional tests (urine catecholamines, ferritin, lactate dehydrogenase (LDH), other imaging modalities) are available when the test results are interpreted.
- Classify as 'no' if clinical data, like demographic factors (sex and age), patient history and physical examination (e.g. abdominal extension, bone pains, respiratory distress); additional tests (urine catecholamines, ferritin, LDH, other imaging modalities) are not available when the test results are interpreted.
10. Were uninterpretable/intermediate test results reported?

Uninterpretable or intermediate test results are often not reported in diagnostic accuracy studies. These uninterpretable or intermediate results are simply removed from the analysis. This may lead to biased assessment of test characteristics. If uninterpretable or intermediate test results occur randomly and are not related to disease status, bias is unlikely. Whatever the cause of uninterpretable results they should be reported in order to estimate their potential influence on diagnostic performance.

- Classify as ‘yes’ if all test results are reported for all patients, including uninterpretable, indeterminate or intermediate results.
- Classify as ‘no’ if not all test results are reported for all patients, including uninterpretable, indeterminate or intermediate results.
- Classify as ‘unclear’ if it is unclear whether all results have been reported.

11. Were withdrawals from the study explained?

If patients lost to follow up differ systematically from those who remain, for whatever reason, estimates of test performance may be biased.

- Classify as ‘yes’ if it is clear what happened to all patients who entered the study (e.g. if a flow diagram is reported).
- Classify as ‘no’ if it is clear that not all patients completed the study (did not receive both index test and reference standard).
- Classify as ‘unclear’ if it is not clear whether all patients who entered the study received both index test and reference standard.

12. Were selection criteria clearly described?

This refers to whether studies have provided a clear definition of the criteria used as inclusion (0 to 18 years, primary or relapsed neuroblastoma of any stage) or exclusion criteria (> 18 years, phaeochromocytoma, ganglioneuroma only) for entry into the study.

- Classify as ‘yes’ if there is a description of how patients were selected for the study.
- Classify as ‘no’ if study selection criteria are not reported.
- Classify as ‘unclear’ if selection criteria are partially reported and there is not enough information to score this item.

13. Was the execution of the index test described in sufficient detail to permit its replication?

If tests are executed in different ways, this would be expected to impact on test performance. Details that should be described are: 123I radioactive labelling, 18F radioactive labelling, dosage, time between infusion and scanning.

- Score ‘yes’ if sufficient details or citations to permit replication of the index test are described or if this is done according to protocol.
- Score ‘no’ if sufficient details or citations to permit replication of the index test are not described.
- Score ‘unclear’ if there is insufficient information on this item.

14. Was the execution of the reference standard described in sufficient detail to permit its replication?

If tests are executed in different ways, this would be expected to impact on test performance. Details that should be described for diagnosing the primary tumour are: pathologic diagnosis by a biopsy OR bone marrow aspirate or trephine biopsy; Shimada or INPCC classification.
Details that should be described for diagnosing metastases are: positive bone marrow or trephine aspirates; OR positive lesions on 99m-Tc skeleton scintigraphy, MRI and/or CT scan; OR histologically proven palpable nodes and/or positive lesions on ultrasound, MRI or CT scan for non-palpable nodes; OR positive liver lesions on ultrasound, MRI and/or CT scan.

- Score ‘yes’ if sufficient details or citations to permit replication of the reference standard are described or if this is done according to protocol.
- Score ‘no’ if sufficient details or citations to permit replication of the reference standard are not described.
- Score ‘unclear’ if there is insufficient information on this item.

15. **Did the study provide a clear definition of what was considered to be a ‘positive’ result of the index test?**

- Classify as ‘yes’ if the study describes what a positive and/or a negative result is.
- Classify as ‘no’ if the study does not describe what a positive and/or a negative result is.
- Classify as ‘unclear’ if there is insufficient information on this item.

16. **Were data on inter-observer variation reported and within acceptable range?**

There may be considerable interobserver variation in scoring a MIBG scan. This may influence the diagnostic performance of the index test. It is difficult to give minimal cut-off scores for inter-observer agreement. A kappa or intra-class correlation coefficient (ICC) of 0.70 is considered to be acceptable.

- Classify as ‘yes’ if information on inter-observer variation is given, and the results are acceptable.
- Classify as ‘no’ if information on inter-observer variation is given, and the results demonstrate poor agreement.
- Classify as ‘unclear’ if there is insufficient information on inter-observer variation.
### Additional Table 2A: Characteristics of included studies

#### BIASSOTTI 2000

**Study characteristics table Biasotti 2000**

Patient population: 196 children with suspected neuroblastoma  
prior to chemotherapy and surgery were included.  
Consecutive series: not reported.  
Diagnostic work-up: CT and/or MRI, 123I-MIBG and/or 99mTc- 
MDP scans, one to four bone marrow aspirations and at least one  
bone marrow biopsy (limited to children 1 year of age or older),  
urinary catecholamines, serum ferritin, neuro specific enolase and  
lactate dehydrogenase.  
Time spans symptoms-index test, symptoms-reference standard  
and index test-reference standard: n.r.  
Treatment between index test-reference standard: n.r. |
|---|---|
| Participants | Included patients: 196 children with a neuroblastoma and  
123I-MIBG scan at first diagnosis.  
Median age at diagnosis: 31 months (range 8 to 65 months).  
Sex distribution: not reported.  
INSS stage: 38 stage 1 or 2, 50 stage 3, 95 stage 4 and 13 stage  
4S. |
| Study design | n.r. |
| Target condition and reference standard(s) | Target condition: newly diagnosed neuroblastoma.  
Reference standard: histopathology according to Joshi  
nomenclature. |
| Index and comparator tests | Assessed primary objective 1.1: to determine the diagnostic  
accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting  
a neuroblastoma and its metastases at first diagnosis or at  
recurrence in children from 0 to 18 years old.  
Index test: 123I-MIBG scintigraphy.  
Radiofarmacon: 123I-MIBG.  
Dose: n.r.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: n.r.  
Acquisition time: n.r.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: n.r.  
Positive test result: pathologic 123I-MIBG uptake.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | Median follow-up: n.r; for some patients: up to five years. |
| Notes |  |

**Risk of bias table Biasotti 2000**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Representative spectrum? | Yes | Patients with a neuroblastoma at first diagnosis,  
age 8 to 65 months and stage distribution is reported. |
| Acceptable reference standard? | Yes | Histopathology according to the Joshi nomenclature. |
### Acceptable delay between tests?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Partial verification avoided?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Differential verification avoided?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Incorporation avoided?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Reference standard results blinded?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Index test results blinded?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Relevant clinical information?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Uninterpretable results reported?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Withdrawals explained?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Selection criteria clearly described?
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Sufficient detail for replication index test?
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Performance and equipment of 123I-MIBG scintigraphy: n.r. Radiofarmacon, dose, collimator, matrix, acquisition protocol, acquisition time and acquisition duration were n.r.</th>
</tr>
</thead>
</table>

### Sufficient detail for replication reference test?
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>n.r.</th>
</tr>
</thead>
</table>

### Clear definition of positive result index test?
<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Pathologic isotope accumulation of 123I-MIBG.</th>
</tr>
</thead>
</table>

### Interobserver variation reported and acceptable?
<table>
<thead>
<tr>
<th></th>
<th>Unclear</th>
<th>n.r.</th>
</tr>
</thead>
</table>

---

### GORDON 1990

#### Study characteristics table Gordon 1990

**Clinical features and settings**
- **Inclusion period:** January 1986 to March 1988.
- **Patient population:** 44 unselected eligible patients with histologically proven neuroblastoma and with a 123I-MIBG scan; 9mTc-MDP and 123I-MIBG scans were completed within four weeks of each other. Three patients were excluded due to incorrect timing of the studies and another five because the images were missing from the file. So 36 of 44 patients were included, of which 28 had a 123I-MIBG scan at diagnosis and thus could be included in this review.
- **Consecutive series:** n.r.
- **Diagnostic work-up:** n.r.
- **Time spans symptoms-index test, symptoms-reference standard and index test-reference standard:** n.r.
- **Treatment between index test-reference standard:** n.r.

**Participants**
- **Included patients:** 28 children with a neuroblastoma and a 123I-MIBG scan at first diagnosis.
- **Median age at diagnosis:** n.r. for these 28 included patients; for all 36 patients: 3.0 years (range 1 week to 11.5 years).
- **Sex distribution:** n.r. for these 28 included patients; for all 36 patients: 23 boys (62%) - 13 girls (38%).
- **INSS stage:** six stage 1 to 3 and 22 stage 4.
### Study design

<table>
<thead>
<tr>
<th>Target condition and reference standard(s)</th>
<th>Target condition: Newly diagnosed neuroblastoma. Reference standard: histopathology or bilateral aspirates of bone marrow and trephine biopsy.</th>
</tr>
</thead>
</table>

### Index and comparator tests

- **Assessed primary objective**: 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.
- **Index test**: 123I-MIBG scintigraphy.
- **Radiofarmacon**: 123I-MIBG.
- **Dose**: 120 MBq for children aged under two years and 160 MBq for those over two years.
- **Collimator**: n.r.
- **Matrix**: n.r.
- **Acquisition protocol**: whole-body scans. The children were sedated, if necessary.
- **Acquisition time**: 18 to 24 hours after injection.
- **Acquisition duration**: 5 minutes for whole-body scans.
- **Interfering medication**: n.r.; parents received a list of drugs known to inhibit 123I-MIBG uptake.
- **Thyroid prophylaxis**: oral potassium iodide three days before the examination.
- **Positive test result**: n.r.
- **Number of observers**: one author blinded for the results of the 99mTc-MDP scan.
- **Expertise of observers**: n.r.
- **Interobserver concordance**: n.r.

### Follow-up

- **n.r.; some patients were followed up to 64 months.**

### Notes

- The sensitivity and specificity of the diagnosis neuroblastoma could be analysed for 19 of the 28 eligible patients. The remaining nine patients could be analysed concerning sensitivity and specificity of metastases only. These patients had false positive results for neuroblastoma based just on negative bone marrow biopsies which is not a valid method to detect neuroblastoma, but only to detect metastases. As stated in the methods, neuroblastoma was assumed not present if all three reference tests were negative.

### Risk of bias table Gordon 1990

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Patients with a neuroblastoma at first diagnosis, age 1 week to 11.5 years and stage distribution is reported.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Description</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HASHIMOTO 2003**

**Study characteristics table Hashimoto 2003**

**Clinical features and settings**
- Inclusion period: n.r.
- Patient population: 33 patients younger than one year of age suspected of having a first neuroblastoma by mass screening of urinary VMA and HVA in their sixth month after birth with a 123I-MIBG scan.
- Consecutive series: n.r.
- Diagnostic work-up: abdominal US, abdominal CT and/or MRI, 123I-MIBG scintigraphy and final confirmation of the diagnosis by surgery.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.
- The flow chart did not show treatment between index test and reference standard, but this was not reported in the text.

**Participants**
- Included patients: thirty-three children younger than one year of age with a neuroblastoma and a 123I-MIBG scan at first diagnosis.
- Median age at diagnosis: 6 months and 27 days (range 6 months and 12 days to 10 months and three days).
- Sex distribution: 20 boys (61%) - 13 girls (39%).
- INSS stage: 16 patients stage 1, five stage 2, four stage 3, six stage 4 and two stage 4S.

**Study design**
- Retrospective cohort study.
## Target condition and reference standard(s)

Target condition: newly diagnosed neuroblastoma.
Reference standard: histopathology.
Primary and metastatic foci in the liver, lymph nodes and bone marrow were confirmed by histopathology (surgery or biopsy) or other imaging modalities; Bone marrow infiltration was defined as positive if there were tumour cells in the specimen from the ilium and negative bone scintigraphy and bone X-ray pictures; Liver metastases were confirmed by abdominal CT and/or MRI; Lymph node metastases were confirmed by histopathology (surgery).

## Index and comparator tests

Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

Index test: 123I-MIBG scintigraphy.
Radiofarmacon: 123I-MIBG.
Dose: 111 MBq, without changing the dose according to the body size.
Collimator: low-energy, high-resolution.
Matrix: n.r.
Acquisition protocol: whole-body scans and SPECT of chest and abdomen or abdomen and pelvis.
SPECT: low-energy, high-resolution collimator in a 128x128 matrix, rotated through 120 degrees in 30 steps of 10 to 30 seconds.
Acquisition time: 24 hours after injection.
Acquisition duration: 15 minutes for whole-body scans.
Interfering medication: n.r.
Thyroid prophylaxis: n.r.
Positive test result: abnormal 123I-MIBG uptake.
Number and expertise of observers: two radiologists familiar with these nuclear medicine procedures judged independently if supplemental SPECT images provided additional information compared with planar whole-body 123I-MIBG scans; it was not reported whether these two radiologists evaluated all 123I-MIBG scans for diagnosing neuroblastoma.
Interobserver concordance: n.r.

## Follow-up

n.r.

## Notes

Risk of bias table Hashimoto 2003

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>No</td>
<td>Patients younger than one year of age.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Details</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Yes</td>
<td>In the flow chart it is clear that urinary catecholamines and CT were performed before 123I-MIBG scintigraphy and it is stated that everyone was examined by abdominal US and chest and abdominal X-ray before 123I-MIBG scintigraphy.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>Unclear whether all results were reported.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Yes</td>
<td>All 33 patients had an index and a reference test.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Patients younger than one year that were suspected of having a first neuroblastoma after the mass screening of urinary VMA and HVA in their sixth month after birth.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>Yes</td>
<td>Radiofarmacon, dose, collimator, matrix, acquisition protocol, acquisition time and acquisition duration were reported.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>Unclear</td>
<td>Primary tumour: n.r. Metastasis: Primary and metastatic foci in the liver, lymph nodes and bone marrow were confirmed by histopathology (surgery or biopsy) or other imaging modalities. Bone marrow infiltration was defined as positive if there were tumour cells in the specimen from the ilium and negative bone scintigraphy and bone X-ray pictures. Liver metastases were confirmed by abdominal CT and/or MRI. Lymph node metastases were confirmed by histopathology (surgery).</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>Yes</td>
<td>Abnormal 123I-MIBG accumulation.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

**HUGOSSON 1999**

**Study characteristics table Hugosson 1999**

- **Clinical features and settings**
  - Patient population: 31 patients suspected for a primary abdominal neuroblastoma in one hospital.
  - Consecutive series: yes.
  - Diagnostic work-up: US of the abdomen, CT of the thorax and abdomen, MRI of the abdomen and sometimes the spine, skeletal survey, chest radiography, bone scintigraphy and 123I-MIBG scintigraphy.
  - Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
  - Treatment between index test-reference standard: n.r.
Participants

Included patients: eighteen children with an abdominal neuroblastoma and a 123I-MIBG scan at first diagnosis; Thoraco-abdominal and pelvic tumours were excluded. Median age at diagnosis: n.r. for these eighteen included patients; for all 31 patients: 2 years (range 1 month to 9 years). Sex distribution: n.r. for these eighteen included patients; for all 31 patients: 17 boys (55%) - 14 girls (38%). INSS stage: n.r. for these eighteen included patients; for all 31 patients: five with stage 1/2, three stage 3 and 16 stage 4.

Study design

n.r.

Target condition and reference standard(s)

Target condition: newly diagnosed abdominal neuroblastoma. Reference standard: cytology, using fine-needle aspiration of the tumour, in 23 patients; histopathological examination of a surgical biopsy specimen in seven patients; and bone marrow aspirates with cytology in one patient. It is not clear which reference test the eighteen included patients received.

Index and comparator tests

Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old. Index test: 123I-MIBG scintigraphy.

- Radiofarmacon: 123I-MIBG,
- Dose: 185 MBq per 1.73 m² and this adult dose was adjusted in proportion to the body area.
- Collimator: medium energy.
- Matrix: n.r.
- Acquisition protocol: whole-body scans.
- Acquisition time: 24 and sometimes 48 hours after injection.
- Acquisition duration: n.r.
- Interfering medication: n.r.
- Thyroid prophylaxis: Lugol solution one day before until three days after the examination.
- Positive test result: in general n.r.; for metastases: an area of increased uptake outside the primary tumour.
- Number and expertise of observers: 123I-MIBG scans were interpreted by a radiologist without knowledge of previous examinations.
- Interobserver concordance: n.r.

Follow-up

n.r.; some patients were followed up to five years.

Notes

Risk of bias table Hugosson 1999

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Patients with a neuroblastoma at first diagnosis, age 1 month to 9 years and stage distribution is reported.</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>Yes</td>
<td>Histopathology and cytology.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology/cytology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology/cytology in all patients.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Yes</td>
<td>Radiologist blinded for results of previous examinations.</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Unclear</td>
<td>n.r., but blinded for previous examinations.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Yes</td>
<td>Faint uptake of 123I-MIBG was reported.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Children with primary abdominal neuroblastoma were included and patients with thoraco-abdominal or pelvic tumours excluded.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>Yes</td>
<td>Radiofarmacon, dose, collimator, matrix, acquisition protocol and acquisition time.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>Yes</td>
<td>Cytology on fine-needle aspiration or bone marrow aspirates of the tumour and histopathology of a surgical biopsy specimen.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>Unclear</td>
<td>In general: n.r.. For metastases: an area of increased uptake outside the primary tumour.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

**LABREVEUX 1994**

**Study characteristics table Labreveux 1994**

<table>
<thead>
<tr>
<th>Clinical features and settings</th>
<th>Inclusion period: 1984 to 1991. Patient population: 41 patients younger than one year with a histologically proven neuroblastoma at first diagnosis. Consecutive series: yes. Diagnostic work-up: urinary catecholamines (VMA, HVA, dopamine), US of abdomen, CT of thorax or abdomen, extensive bone marrow examination (ten bone marrow aspirates and two trephine biopsies), complete evaluation of the skeleton by skeletal X-ray and 123I-MIBG scintigraphy and when necessary a CT of the skull if bone lesions of the skull were difficult to appreciate on standard X-ray Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r. Treatment between index test-reference standard: n.r.</th>
</tr>
</thead>
</table>
Participants
Included patients: twenty-seven children with a neuroblastoma and metastatic abnormalities on one or several imaging methods and a 123I-MIBG scan at first diagnosis; these patients were divided in three groups: Group I. eight patients with bone lesions by X-ray and an abnormal 123I-MIBG scan; Group II. thirteen patients with bone lesions not detected by X-ray or 123I-MIBG scan; Group III. six patients with normal X-ray and an abnormal 123I-MIBG scan.
Median age at diagnosis: 0.4 years (range 0-0.8 years). Group I: 10 months (range of 4 to 11 months); Group II: 3 months (range 0 to 8 months); Group III: 7.5 months (range 0 to 10 months).
Sex distribution: 10 boys (37%) - 17 girls (63%). Group I: 2 boys (25%) - 6 girls (75%); Group II: 5 boys (38%) - 8 girls (62%); Group III: 3 boys (50%) - 3 girls (50%).
INTS stage: n.r.; all patients had either stage 4 or stage 4S.

Study design
Retrospective cohort study.

Target condition and reference standard(s)
Target condition: newly diagnosed neuroblastoma. Reference standard: histology or cytology.

Index and comparator tests
Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old. Index test: 123I-MIBG scintigraphy. Radiofarmacon: 123I-MIBG. Dose: 3.7 MBq/kg. Collimator: n.r. Matrix: n.r. Acquisition protocol: whole-body scans. Acquisition time: 24 hours after injection. Acquisition duration: n.r. Interfering medication: n.r. Thyroid prophylaxis: Lugol administered three days before and five days after the examination. Positive test result: in general n.r.; For metastases: osteo medullary uptake. Number and expertise of investigators: n.r. Interobserver concordance: n.r.

Follow-up
n.r.; In Group I some patients were followed up to five years; in Group II up to eight years; and in Group III up to six years.

Notes

Risk of bias table Labreveux 1994

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgment</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>No</td>
<td>Patients younger than one year old with a stage 4 or 4S neuroblastoma at first diagnosis.</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>Yes</td>
<td>Histopathology or cytology.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>No</td>
<td>Diagnosis confirmed by histopathology and/or cytology.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
</tbody>
</table>
### Reference standard results blinded?

Unclear n.r.

### Index test results blinded?

Unclear n.r.

### Relevant clinical information?

Unclear n.r.

### Uninterpretable results reported?

Unclear n.r.

### Withdrawals explained?

Yes

Fourteen patients excluded because of no osteomedullary uptake.

### Selection criteria clearly described?

No n.r.

### Sufficient detail for replication index test?

No

Equipment was not reported. Acquisition protocol was not completely reported (dimensions).

### Sufficient detail for replication reference test?

No n.r.

### Clear definition of positive result index test?

Unclear

Description of a positive test result for metastases was reported: osteomedullary uptake. A description of a positive test result in general: n.r..

### Interobserver variation reported and acceptable?

Unclear n.r.

## LVANOVA 2008

### Study characteristics table LVanova 2008

#### Clinical features and settings

- Inclusion period: n.r.
- Patient population: 22 patients with histologically proven neuroblastoma at first diagnosis and 22 123I-MIBG scans.
- Consecutive series: yes.
- Diagnostic work-up: pathology, blood chemistry, US, abdominal CT or MRI.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.

#### Participants

- Included patients: 22 children with neuroblastoma and a 123I-MIBG scan at first diagnosis.
- Median age at diagnosis: 48 months (+/- 42 months).
- Sex distribution: 14 boys (64%) - 8 girls (36%).
- INSS stage: n.r.

#### Study design

- Retrospective cross-sectional study.

#### Target condition and reference standard(s)

- Target condition: newly diagnosed neuroblastoma.
- Reference standard: histopathology obtained prior to the index test.
Index and comparator tests
Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

Index test: 123I-MIBG scintigraphy.
Radiofarmacon: 123I-MIBG.
Dose: 4 MBq/kg.
Collimator: n.r.
Matrix: n.r.
Acquisition protocol: whole-body scans with or without SPECT.
Acquisition time: n.r.
Acquisition duration: n.r.
Interfering medication: n.r.
Thyroid prophylaxis: n.r.
A description of a positive test result for 123I-MIBG scans was not reported.
Number and expertise of investigators: n.r.
Interobserver concordance: n.r.

Follow-up
n.r.

Notes
Data-extraction performed by a translator.

Risk of bias table Lvanova 2008

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Unclear</td>
<td>INSS stage not reported.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>Histopathology obtained prior to Index test.</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>No</td>
<td>In- and exclusion criteria n.r.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>No</td>
<td>Eexecution of the index test n.r.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>
### NARANJO 2011a

#### Study characteristics table Naranjo 2011a

Patient population: 350 patients with newly diagnosed histologically proven stage 4 neuroblastoma and with 926 123I-MIBG scans of which 218 with a 123I-MIBG scan at first diagnosis. Patients were enrolled on COG protocol A3973 and had completed 123I-MIBG or 131I-MIBG scans at one or more of the following time points: diagnosis, post-induction, post-transplant, or post biotherapy. To be eligible for COG A3973, patients with stage 4 neuroblastoma had to be aged 30 years or younger at the time of initial diagnosis. If younger than 12 months, MYCN amplification (>10 copies) was required; if between 12 and 18 months of age, any unfavourable (MYCN amplification, unfavourable histology, and diploid) or unknown biologic feature was required. Patients were excluded when pregnant or lactating. Patients of childbearing potential had to practice an effective method of birth control while participating on this study. Normal renal, cardiac, hepatic, and hematopoietic function was required, as well as no prior systemic therapy.  
Consecutive series: n.r.  
Diagnostic work-up: 123I-MIBG or 131I-MIBG scans, histopathology.  
Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.  
Treatement between index test-reference standard: n.r. |
| Participants | Included patients: 218 children with stage 4 neuroblastoma and with a 123I-MIBG scan at first diagnosis.  
Median age at diagnosis: 3.1 years (range 6.8 months to 15.2 years).  
Sex distribution: 124 boys (57%) - 94 girls (43%).  
INSS stage: all stage 4. |
| Study design | Prospective cohort study. |
| Target condition and reference standard(s) | Target condition: newly diagnosed stage 4 neuroblastoma.  
Reference standard: histopathology (biopsy of soft tissue or bone marrow). |
| Index and comparator tests | Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.  
Index test: 123I-MIBG scintigraphy.  
Radiofarmacon: 123I-MIBG.  
Dose: 370 MBq/1.7 m2 of body surface area.  
Collimator: low-energy.  
Matrix: n.r.  
Acquisition protocol: overlapping anterior and posterior spot views for planar imaging or whole-body scans.  
The exact number of patients per dimension: n.r. |
SPECT: a low-energy collimator, rotated 360° with 120 projections at 20 seconds per stop; filtered back-projection with a Butterworth filter and a cut-off frequency of 0.2–0.5 to reconstruct the images. 

Acquisition time: 24 hours after injection. 
Acquisition duration: 10 minutes per spot view and low-speed for whole-body scans. 
Interfering medication: n.r. 
Thyroid prophylaxis: supersaturated potassium iodide generally 24 hours prior to the diagnostic 123I-MIBG injection and for three to seven days following the injection. 
Description of positive test result: Skeletal sites were individually scored: 0=no MIBG involvement; 1=one MIBG-avid lesion present; 2=greater than one MIBG-avid lesion present; and 3=MIBG-avidity present in >50% of an individual site. Soft tissue lesions were scored: 0=no MIBG involvement; 1=one MIBG-avid soft tissue lesion present; 2=greater than one MIBG-avid soft tissue lesion present; and 3=MIBG-avidity in a soft tissue lesion occupying >50% of the chest or abdomen. A patient’s Curie score at each time point was calculated as the sum of his/her scores over all individual sites. 
Number and expertise of observers: 123I-MIBG scans were centrally reviewed by two nuclear medicine physicians without knowledge of the original scan reports or other clinical or imaging information. 

Follow-up: n.r.; some patients were followed for approximately seven years. 
Notes: We received additional data from the author to fill in the two-by-two-table of objective 1.1. 

### Risk of bias table Naranjo 2011a

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Children with stage 4 neuroblastoma at first diagnosis.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Yes</td>
<td>123I-MIBG scans were centrally reviewed by two nuclear medicine physicians without knowledge of other clinical information (like histopathology).</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>No</td>
<td>Clinical data, like demographic factors (sex and age), patient history and physical examination (e.g. abdominal extension, bone pains, respiratory distress); additional tests (urinary catecholamines, ferritin, LDH, other imaging modalities) were not available when the test results were interpreted.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Newly diagnosed high-risk patients with INSS stage 4 neuroblastoma enrolled on COG protocol A3973 who had completed 123I-MIBG or 131I-MIBG scans at one or more of the following time points: diagnosis, post-induction, post-transplant, or post biotherapy. To be eligible for COG A3973, patients with stage 4 disease had to be aged 30 years or younger at the time of initial diagnosis. If younger than 12 months, MYCN amplification (&gt;10 copies) was required; if between 12 and 18 months of age, any unfavourable (MYCN amplification, unfavourable histology, and diploid) or unknown biologic feature was required. Normal renal, cardiac, hepatic, and hematopoietic function was required, as well as no prior systemic therapy.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>Yes</td>
<td>Radiofarmacon, dose, collimator, matrix, acquisition protocol, acquisition time and acquisition duration were reported.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>Yes</td>
<td>Skeletal sites: 0=no MIBG involvement; 1=one MIBG-avid lesion present; 2=greater than one MIBG-avid lesion present; and 3=MIBG-avidity present in &gt;50% of an individual site. Soft tissue lesions: 0=no MIBG involvement; 1=one MIBG-avid soft tissue lesion present; 2=greater than one MIBG-avid soft tissue lesion present; and 3=MIBG-avidity in a soft tissue lesion occupying &gt;50% of the chest or abdomen. A patient’s Curie score at each time point was calculated as the sum of his/her scores over all individual sites.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

**NEUENSCHWANDER 1987**

Study characteristics table Neuenschwander 1987


86
Participants

Included patients: 16 children with primary advanced abdominal neuroblastoma and a 123I-MIBG scan at first diagnosis. Median age at diagnosis: n.r. for these 16 included patients; for all 20 patients mean age: 42 months (range 15 to 77 months). Sex distribution: n.r. for these 16 included patients; for all 20 patients: 12 boys (60%) - 8 girls (40%). INSS stage: n.r. for these 16 included patients; for all 20 patients: four stage 3 and 16 stage 4.

Study design

n.r.

Target condition and reference standard(s)

Target condition: newly diagnosed neuroblastoma. Reference standard: histopathology (biopsy or surgical resection).

Index and comparator tests

Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

Index test: 123I-MIBG scintigraphy.

Radiofarmacon: 123I-MIBG.

Dose: 3.7 MBq/kg.

Collimator: n.r.

Matrix: n.r.

Acquisition protocol: n.r.

Acquisition time: 24 hours after injection.

Acquisition duration: n.r.

The exact number of patients per dimension: n.r.

Interfering medication: n.r.

Thyroid prophylaxis: n.r.

Positive test result: n.r.

Number and expertise of investigators: n.r.

Interobserver concordance: n.r.

Follow-up

n.r.

Notes

Risk of bias table Neuenschwander 1987

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Age, stage and primary disease were described. Stage 4S excluded.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology in all patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Diagnosis confirmed by histopathology.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Question</td>
<td>Response</td>
<td>Additional Information</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Unclear</td>
<td>Urinary catecholamines available. Further information n.r.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Patients with advanced abdominal neuroblastoma; stage 4S neuroblastoma excluded.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>No</td>
<td>Dimensions and imaged body parts: n.r. Equipment was not reported.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiofarmacon, dose and acquisition time reported. Equipment, acquisition protocol and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acquisition n.r.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

**PFLUGER 2003**

**Study characteristics table Pfluger 2003**

| Clinical features and settings | Inclusion period: five years and nine months for all studies (including follow-up and MRI). |
|                               | Patient population: 28 patients with suspected or histologically proven neuroblastoma and a total of 50 123I-MIBG scans and 50 MRI examinations |
|                               | Inclusion criteria: suspected or histologically proven neuroblastoma and a maximum time frame of 30 days between 123I-MIBG scintigraphy and MRI. Suspect tumour lesions were included only if they were in the field of view on images from both modalities. Exclusion criteria were not reported. Image analyses were performed on a lesion-related basis. A total of 115 lesions were evaluated. |
|                               | Consecutive series: n.r. |
|                               | Diagnostic work-up: 123I-MIBG scintigraphy and MRI examinations |
|                               | Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r. |
|                               | Treatment between index test-reference standard: n.r. |

| Participants                  | Included patients: 22 children with neuroblastoma and a 123I-MIBG scan at first diagnosis. |
|                               | Median age at diagnosis: n.r. for these 22 included patients; for all 28 patients: mean age of 3.2 years (range 1 week to 11 years). |
|                               | Sex distribution: n.r. for these 22 included patients; for all 28 patients: 18 boys (64%) - 10 girls (36%). |
|                               | INSS stage: n.r. |

| Study design                  | Retrospective cohort study. |
Target condition and reference standard(s)

Target condition: newly diagnosed neuroblastoma. Reference standard: histopathology. For patients with stage 4 neuroblastoma, histologic verification of all metastases is impossible. Therefore, on follow-up control examinations, a minimum of six months was used for verification of lesions. In these cases, a lesion was classified as a false-positive finding if it disappeared without tumour therapy during the observation period. A lesion was classified as a true-positive finding if it persisted or progressed during follow-up or if it showed clear regression under specific therapy.

Index and comparator tests

Assessed primary objective 1.1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

Index test: 123I-MIBG scintigraphy.
Radiofarmacon: 123I-MIBG.
Dose: 3.7 MBq/kg.
Collimator: medium energy.
Matrix: 256x256.
Acquisition protocol: anterior and posterior images of the whole-body and SPECT.
Acquisition time: 24 hours after injection.
Interfering medication: n.r.
Thyroid prophylaxis: supersaturated potassium iodide one day before the examination and for three days.
Positive test result: non-physiologic focal uptake.
Number and expertise of observers: 123I-MIBG scans were interpreted by two experienced observers with knowledge of clinical data, but blinded for the results on the MRI.

Notes

Follow-up n.r.; follow-up of a minimum of six months was used for verification of lesions.

Risk of bias table Pfluger 2003

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Unclear</td>
<td>Distribution of stage n.r.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>No</td>
<td>For patients with stage 4 neuroblastoma, histologic verification of all metastases is impossible. Therefore, on follow-up control examinations, a minimum of six months was used for verification of lesions. In these cases, a lesion was classified as a false-positive finding if it disappeared without tumour therapy during the observation period.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>No</td>
<td>For patients with stage 4 neuroblastoma, histologic verification of all metastases is impossible. Therefore, on follow-up control examinations, a minimum of six months was used for verification of lesions. In these cases, a lesion was classified as a false-positive finding if it disappeared without tumour therapy during the observation period.</td>
</tr>
</tbody>
</table>
Incorporation avoided? | Yes | Index test was not a part of the reference test.
---|---|---
Reference standard results blinded? | Unclear | n.r.
Index test results blinded? | Unclear | n.r.
Relevant clinical information? | Yes | Analysis was performed with knowledge of clinical data.
Uninterpretable results reported? | Yes | For observers to reach a decision about lesions with discrepant results on both modalities, a diagnostic confidence score of three levels was established for each modality: 1. both observers were uncertain about a positive or negative finding; 2. one observer was uncertain and one observer was certain; and 3. both observers were certain. This diagnostic confidence score was assigned to each suspect lesion on MIBG scintigraphy separately.
Withdrawals explained? | Unclear | n.r.
Selection criteria clearly described? | Yes | Inclusion criteria: suspected or proven neuroblastoma; maximum time frame of 10 days between 123I-MIBG scan and MRI scan.
Sufficient detail for replication index test? | Yes | 123I-MIBG scans were acquired 24 hours after injection of tracer with an administered activity of 3.7 MBq/kg. SPECT images were acquired at intervals of 24 hours only. The dual-headed gamma camera was equipped with a medium-energy collimator, 256 × 256 matrix. MIBG scans were reviewed on a Hermes workstation.
Sufficient detail for replication reference test? | No | n.r.
Clear definition of positive result index test? | Yes | Non physiological focal uptake.
Interobserver variation reported and acceptable? | Unclear | n.r.

**PICCARDO 2012**

**Study characteristics table Piccardo 2012**

**Clinical features and settings**
Inclusion period: n.r.
Patient population: 19 patients with stage 3 and 4 neuroblastoma and a total of 28 paired 123I-MIBG and 18F-dopa-PET/CT scans.
Consecutive series: yes.
Diagnostic work-up: urinary catecholamines, 123I-MIBG scans, CT, MRI and dopa-PET scans, histopathology and bone marrow biopsies.
Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
Treatment between index test-reference standard: n.r.

**Participants**
Included patients: 17 children with a stage 3 or 4 neuroblastoma and a 123I-MIBG scan at first diagnosis or at recurrence. Four had their first diagnosis and 13 a recurrence.
Median age at diagnosis: 6 years (range 1 to 9 years).
Sex distribution: 4 boys (24%) - 13 girls (76%).
INSS stage: two stage 3 and 15 stage 4.
## Study design
Prospective cohort study.

### Target condition and reference standard(s)
Target condition: newly diagnosed and recurrent neuroblastoma. Reference standard: all patients had histopathology and/or bone marrow biopsies with contrast-enhanced CT or MRI (one patient had histopathology of the primary tumour and contrast-enhanced CT or MRI and five patients had histopathology of the primary tumour, bone marrow biopsies and contrast-enhanced CT or MRI).

### Index and comparator tests
Assessed primary objective 1: to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.

- **Index test**: 123I-MIBG scintigraphy.
- **Radiofarmacon**: 123I-MIBG.
- **Dose**: 5.18 MBq/kg.
- **Collimator**: low-energy high-resolution parallel-hole collimator.
- **Matrix**: n.r.
- **Acquisition protocol**: whole-body scans and SPECT.
- **SPECT**: 64 projections, 128x128 matrix, 40 seconds acquisition time per projection; standard filtered backprojection using a Butterworth filter.
- **Acquisition time**: 24 hours after injection.
- **Acquisition duration**: 6 cm/min for whole-body scans.
- **Interfering medication**: n.r.
- **Thyroid prophylaxis**: n.r.
- **Positive test result**: n.r.
- **Number and expertise of observers**: 123I-MIBG scans were interpreted after a consensus reading by two nuclear medicine physicians in each institute with knowledge of the patient’s clinical history but blinded to any results of the anatomical imaging modalities.

### Follow-up
n.r; at least four months of clinical and imaging follow-up data were available for all patients.

### Notes
The sensitivity and specificity of the diagnosis neuroblastoma could be analysed for 13 of the 17 eligible patients. The remaining four patients had false positive results for neuroblastoma based just on negative bone marrow biopsies which is not a valid method to detect neuroblastoma, but only to detect metastases. Of these four patients, three had a stage 4 neuroblastoma and could therefore be analysed for diagnostic accuracy of the presence of metastases. One of the four patients had a stage 3 neuroblastoma and therefore could not be analysed for any of the diagnostic accuracies.

### Risk of bias table Piccardo 2012

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Age, stage and disease at first diagnosis or at recurrence were reported.</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>Yes</td>
<td>Tumour at first diagnosis or at recurrence and locoregional soft tissue recurrence/metastases: histopathology and/or diagnostic contrast-enhanced CT and/or MRI findings. Bone and bone marrow metastases: bone marrow biopsy and/or MRI when available.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Histopathology and bone marrow biopsy in four patients and bone marrow biopsy only in 13 patients.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>No</td>
<td>Histopathology and bone marrow biopsy in four patients and bone marrow biopsy only in 13 patients.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>Investigators blinded for any results of the anatomical imaging modalities (MRI/CT). The other parts of the reference standard (histopathology and bone marrow biopsy) were n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>No</td>
<td>Investigators blinded for any results of the anatomical imaging modalities (MRI/CT).</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Yes</td>
<td>One patient was reported as lost to follow-up.</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Patients older than one year with a stage 3 or 4 neuroblastoma at first diagnosis or at recurrence were included.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>Yes</td>
<td>123I-MIBG scans were acquired 24 hours after injection of tracer with an administered activity of 5.18 MBq/kg. SPECT images were acquired at intervals of 24 hours only. The scan speed for whole-body imaging was 6 cm/min. The dual-head gamma scintillation camera was equipped with a low-energy high-resolution parallel-hole collimator. For SPECT acquisitions the following parameters were used: 64 projections, 128x128 matrix, 40 seconds acquisition time per projection. SPECT data were reconstructed by standard filtered backprojection using a Butterworth filter. Radiofarmacon, dose, collimator, acquisition protocol, acquisition time and acquisition duration were reported.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>
SHARP 2009

Study characteristics table Sharp 2009

Clinical features and settings

Patient population: 60 patients with histologically proven neuroblastoma and a total of 113 paired 123I-MIBG and 18F-FDG-PET scans.
Consecutive series: no; paired scans at one hospital were acquired for research purposes after informed consent was obtained; paired scans at the second hospital were obtained when requested by the oncology service for clinical reasons.
Diagnostic work-up: n.r.
Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
Treatment between index test-reference standard: n.r.

Participants

Included patients: 24 children with a neuroblastoma and a 123I-MIBG scan at first diagnosis.
Median age at diagnosis: n.r. for these 24 included patients; for all 60 patients: 3.1 years.
Sex distribution: n.r. for these 24 included patients; for all 60 patients: 37 boys (62%) - 23 girls (38%).
INSS stage: five stage 1/2, three stage 3 and 16 stage 4.

Study design

Retrospective cohort study.

Target condition and reference standard(s)

Target condition: newly diagnosed neuroblastoma.
Reference standard: histopathology. If both 123I-MIBG and 18F-FDG-PET scans were negative: information concerning bone marrow biopsies and urinary catecholamines were provided.

Index and comparator tests

Assessed primary objectives:
1.1 to determine the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old;
1.2 to determine the diagnostic accuracy of negative 123I-MIBG scintigraphy in combination with 18F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old. In this case 18F-FDG-PET(-CT) is an add-on test.
Assessed secondary objectives:
2.1 to determine the diagnostic accuracy of 18F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.
2.2 To compare the diagnostic accuracy of 123I-MIBG (SPECT-CT) scintigraphy and of 18F-FDG-PET(-CT) imaging for detecting a neuroblastoma and its metastases at first diagnosis or at recurrence in children from 0 to 18 years old.
Positive test result for both 123I-MIBG and 18F-FDG-PET scans: uptake in primary and residual tumour, local and regional soft-tissue (local/regional) metastases, and bone and bone marrow (bone/marrow) metastases.
1. 123I-MIBG scintigraphy:
Three 123I-MIBG whole-body scans without SPECT and 110 123I-MIBG whole-body scans with SPECT. The number of each dimension was n.r for the 24 included patients only.
Radiofarmacon: 123I-MIBG.
Dose: 5.18 MBq/kg or 370 MBq/1.7 m2 body surface area, depending on the institution, with a maximum dose of 370 MBq.
Collimator: n.r.
Matrix: 256x256.
Acquisition protocol: whole-body scans and SPECT.
SPECT: n.r.
Acquisition time: n.r.
Acquisition duration: n.r.
Interfering medication: n.r.
Thyroid prophylaxis: n.r.
Number and expertise of investigators: n.r.
Interobserver concordance: n.r.

18F-FDG-PET scintigraphy:
Thirteen 18F-FDG-PET only scans and 100 18F-FDG-PET scans with CT. The number of each dimension was n.r for the 24 included patients only.
Radiofarmacon: 18F-FDG-PET.
Dose: 5.18 or 5.55 MBq/kg, depending on the institution, with a maximum dosage of 444 MBq.
Equipment: LS Discovery PET/CT scanner (GE Healthcare), Siemens Exact or Accel PET scanners, DSTe PET/CT scanner (GE Healthcare) or not reported.
Acquisition protocol: n.r.
Acquisition time: n.r.
Acquisition duration: n.r.
Number and expertise of investigators: n.r.
Interobserver concordance: n.r.
Blood glucose levels: n.r.

Follow-up
n.a.

Notes
We received additional data from the author to fill in the two-by-two-table of objective 1.1, 1.2, 2.1 and 2.2.

Risk of bias table Sharp 2009

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Unclear</td>
<td>Patients with proven stage 1-4 neuroblastoma were included, but age range n.r.</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Unclear</td>
<td>Insufficient information regarding the different reference tests.</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Index test was not a part of the reference test.</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Yes</td>
<td>Results of all patients reported.</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Selection criteria clearly described?</td>
<td>Yes</td>
<td>Relevant information reported.</td>
</tr>
<tr>
<td>Sufficient detail for replication index test?</td>
<td>No</td>
<td>SPECT, acquisition time and acquisition duration of 123I-MIBG scintigraphy n.r. Acquisition protocol, acquisition time and acquisition duration of 18F-FDG-PET scintigraphy n.r.</td>
</tr>
<tr>
<td>Sufficient detail for replication reference test?</td>
<td>No</td>
<td>n.r.</td>
</tr>
<tr>
<td>Clear definition of positive result index test?</td>
<td>Yes</td>
<td>Uptake in primary and residual tumour, local and regional soft-tissue (local/regional) metastases, and bone and bone marrow (bone/marrow) metastases.</td>
</tr>
<tr>
<td>Interobserver variation reported and acceptable?</td>
<td>Unclear</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- 123I-MIBG: Iodine-123-metaiodobenzylguanidine;
- 131I-MIBG: Iodine-131-metaiodobenzylguanidine;
- 18F-FDG-PET: fluorine-18-fluorodeoxy-glucose positron emission tomography;
- 18F-dopa PET: fluorine-18-dihydroxyphenylalanine positron emission tomography;
- 99mTc-MDP: metastable-technetium-99-methylidiphosphanate;
- cm: centimetre;
- COG: children’s oncology group;
- CT: computed tomography;
- dopa PET: dihydroxyphenylalanine positron emission tomography;
- HVA: homovanillic acid;
- INSS: international neuroblastoma staging system;
- keV: kilo-electron volt;
- kg: kilogram;
- m2: square metre;
- MBq: mega becquerel;
- MIBG: metaiodobenzylguanidine;
- min: minute;
- mm: millimetre;
- MRI: magnetic resonance imaging;
- n.a.: not applicable;
- n.r.: not reported;
- SD: standard deviation;
- SPECT: single photon emission computed tomography;
- US: ultrasound
- VMA: vanillylmandelic acid.
### Additional Table 2B: Characteristics of studies awaiting classification

#### Abrahamsen 1995

| Clinical features and settings | Inclusion period: September 1984 to December 1993.  
Patient population: 36 patients with suspected neuroblastoma and 125 123I- and 131I-MIBG scans  
Consecutive series: yes.  
Diagnostic work-up: standard investigations like CT and US.  
Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.  
Treatment between index test-reference standard: n.r. |
|---|---|
| Participants | Included patients: 36 children with suspected neuroblastoma and a 123I- or 131I-MIBG scan at diagnosis; in 19 patients the diagnosis was confirmed by histopathology, in 17 patients it was not.  
Median age at diagnosis: n.r. for patients with 123I-MIBG scans separate from those with 131I-MIBG scans; for all 36 patients: 2 years and 10 months (range 1 month to 14 years and 10 months); for the 19 patients with confirmed neuroblastoma at first diagnosis: 2 years and 9 months (range 1 to 10 years and 10 months); for the 17 patients without neuroblastoma: 2 years and 10.5 months (range 9 months to 14 years and 10 months).  
Sex distribution: 20 boys (56%) - 16 girls (44%); for the 19 patients with confirmed neuroblastoma at first diagnosis: 9 boys (47%) - 10 girls (53%); for the 17 patients without neuroblastoma: 11 boys (65%) - 6 girls (35%).  
INSS stage for the 19 patients with confirmed neuroblastoma: one stage 1, seven stage 3, eight stage 4 and three stage 4S. |
| Study design | Retrospective cohort study. |
| Target condition and reference standard(s) | Target condition: newly diagnosed neuroblastoma.  
Reference standard: histopathology in 19 patients. |
| Index and comparator tests | Index test: 123I-MIBG and 131I-scintigraphy.  
Radiofarmacon: 123I- and 131I-MIBG.  
Dose: 74 MBq for children weighing less than 8 kg, 111 MBq for children weighing more than 20 kg and 185 MBq for children weighing more than 20 kg.  
Collimator: n.r.  
Matrix: 64x64.  
Acquisition protocol: anterior and posterior images of the head and the whole truncus.  
Acquisition time: 4, 24 and 48 hours after injection.  
Acquisition duration: 300 seconds, 300-400.000 counts.  
Interfering medication: n.r.  
Thyroid prophylaxis: supersaturated potassium iodide twice daily starting one day before the examination and for three days.  
Positive test result: the level of tumour uptake similar to or higher than that in the salivary glands, myocardium and liver.  
Number of observers: 123I-MIBG scans were interpreted by one specialist, without knowledge of the diagnosis at the time of the first 123I-MIBG scan.  
Expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | n.r. |
| Notes | Results not reported for 123I-MIBG scans separately from the 131I-MIBG scans.  
Contact information of the authors: not available. |
### Ady 1995

**Clinical features and settings**
- Patient population: 37 patients with newly diagnosed stage 4 neuroblastoma of which 27 were included in this study; nine children were excluded because of unavailable data at mid-course and one other for lack of 123I-MIBG uptake (negative scan).
- Consecutive series: yes.
- Diagnostic work-up: clinical examination, bone marrow status and all imaging data: at least CT scan and 123I-MIBG scan, and in certain cases bone scan, X-rays and MRI scan to explore metastases to bone and bone marrow, liver, distant lymph nodes, skin, lungs and central nervous system.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.

**Participants**
- Included patients: 27 children with neuroblastoma at first diagnosis.
- Median age at diagnosis: n.r.; mean age at diagnosis: 37 months (range 10 to 97 months).
- Sex distribution: 19 boys (70%) - 8 girls (30%).
- INSS stage: all stage 4 neuroblastoma.

**Study design**
- Cohort study. N.r. whether the study was retrospective or prospective.

**Target condition and reference standard(s)**
- Target condition: newly diagnosed neuroblastoma.
- Reference standard: n.r. for the primary tumour. For metastases: bone marrow status by bone marrow cytology, bone histology (at least four samples) and immunocytoLOGY. In case of discrepant results from different methods, the most abnormal data were considered as definitive.

**Index and comparator tests**
- Index test: 123I-MIBG scintigraphy.
- Radiofarmacon: 123I-MIBG.
- Dose: 3.7 MBq/kg, with a maximum of 110 MBq
- Collimator: low energy, high definition.
- Matrix: 256x1024 for whole-body scans and 256x256 for lateral views (4 mid frame).
- Acquisition protocol: anterior and posterior whole-body scans and lateral views of the head.
- Acquisition time: 2.2 to 26 hours after injection.
- Acquisition duration: 12 min/m for whole-body scans.
- Interfering medication: not reported.
- Thyroid prophylaxis: not reported.
- Positive test result: n.r.
- Number of observers: two independent specialists; to assess reproducibility of the method, images of 16/27 patients were interpreted independently by four investigators (including the previous two specialists).
- Expertise of investigators: n.r.
- Interobserver concordance: n.r.

**Follow-up**
- Median follow-up: 18 months (range 1 to 52 months) after diagnosis.

**Notes**
- Results were n.r. for 123I-MIBG scans at first diagnosis separately from 123I-MIBG scans during follow-up.
- Contact information of the authors: not available.

### Boubaker 2012

**Clinical features and settings**
- Inclusion period: n.r.
- Patient population: 357 patients with newly diagnosed high risk stage 4 neuroblastoma (HR-NBL1/SIOPEN trial).
- Consecutive series: n.r.
- Diagnostic work-up: n.r.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.
### Participants

- **Participants**: Included patients: 357 patients with newly diagnosed high risk stage 4 neuroblastoma.  
  Median age at first diagnosis: n.r.  
  Sex distribution: n.r.  
  INSS stage: n.r.

### Study design

- **Study design**: Cohort study with patients from the (HR-NBL1/SIOPEN trial). N.r. whether the study was retrospective or prospective.

### Target condition and reference standard(s)

- **Target condition and reference standard(s)**: Target condition: newly diagnosed high risk stage 4 neuroblastoma.  
  Reference standard: n.r.

### Index and comparator tests

- **Index and comparator tests**:
  - Index test: 123I-MIBG scintigraphy.  
  - Radiofarmacon: 123I-MIBG.  
  - Dose: n.r.  
  - Collimator: n.r.  
  - Matrix: n.r.  
  - Acquisition protocol: n.r.  
  - Acquisition time: n.r.  
  - Acquisition duration: n.r.  
  - Interfering medication: not reported.  
  - Thyroid prophylaxis: not reported.  
  - Positive test result: skeletal 123I-MIBG uptake.  
  - Number and expertise of observers: eight nuclear medicine experts in four groups.  
  - Interobserver concordance: n.r.

### Follow-up

- **Follow-up**: n.r.; some patients were followed for approximately five years.

### Notes

- **Notes**: This study has not been published in full-text (as of December 2012), but has been presented at the ANR conference 2012.  
  Results not reported for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up.  
  We did not contact the authors.

### Claudiani 1995

#### Clinical features and settings

- **Clinical features and settings**: Study period: beginning of 1985 to the middle of 1993.  
  Patient population: 97 patients with suspected or histologically proven neural crest tumours of which 46 with a 123I-MIBG scan.  
  Consecutive series: n.r.  
  Diagnostic work-up: US, X-ray, CT and/or MRI within a short period before or after 123I-MIBG scintigraphy.  
  Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.  
  Treatment between index test-reference standard: n.r.

#### Participants

- **Participants**: Included patients: 46 of 97 children with suspected or histologically proven neural crest tumours had a 123I-MIBG scan.  
  Median age: n.r. for these 46 included patients: for all 97 patients the range: 6 months to 12 years.  
  Sex distribution: n.r. for these 46 included patients: for all 97 patients: 50 boys (52%) - 47 girls (48%).  
  INSS stage: n.r. According to the Italian Association of Paediatric Hematology and Oncology (AIEOP) staging criteria and on the basis of the biopsy results staging for all 97 patients was: three group 1 neuroblastoma, 12 group 2 neuroblastoma, 25 group 3 neuroblastoma, 45 group 4 neuroblastoma, 2 group 5 neuroblastoma, 5 group 2 to 4 ganglioneuroblastomas and 5 ganglieneuromas.

#### Study design

- **Study design**: Cohort study with patients from the HR-NBL1/SIOPEN trial. N.r. whether the study was retrospective or prospective.
### Target condition and reference standard(s)

**Target condition:** newly diagnosed neuroblastoma.  
**Reference standard:** histopathology (tumour biopsy with cytological and histological examination).

### Index and comparator tests

**Index test:** 123I-MIBG and 131I-MIBG scintigraphy.  
**Radiofarmacon:** 123I-MIBG.  
**Dose:** 1.85 MBq/kg.  
**Collimator:** low-energy, all-purpose.  
**Matrix:** not reported.  
**Acquisition protocol:** n.r.  
**Acquisition time:** 24 hours after injection.  
**Acquisition duration:** n.r.  
**Interfering medication:** not reported.  
**Thyroid prophylaxis:** not reported.  
**Positive test result:** n.r.  
**Number and expertise of observers:** n.r.  
**Interobserver concordance:** n.r.

### Follow-up

n.r.

### Notes

Results n.r. for 123I-MIBG scans separately from the 131I-MIBG scans.  
Contact information of the authors: not available.

### Fania 2011

#### Clinical features and settings

**Study period:** n.r.  
**Patient population:** 11 patients with recurrent INSS stage 4 neuroblastoma previously treated with first line therapy according European protocol NB-HR 01.  
**Consecutive series:** n.r.  
**Diagnostic work-up:** n.r.  
**Time spans symptoms-index test, symptoms-reference standard and index test-reference standard:** n.r.  
**Treatment between index test-reference standard:** n.r.

#### Participants

Included patients: eleven patients with recurrent neuroblastoma.  
**Median age:** n.r.; mean age was 10.8 years (range 3 to 15 years).  
**Sex distribution:** 7 boys (64%) - 4 girls (36%).  
**INSS stage:** all stage 4.

#### Study design

Cohort study. N.r. whether the study was retrospective or prospective.

#### Target condition and reference standard(s)

**Target condition:** recurrent INSS stage 4 neuroblastoma.  
**Reference standard of the primary tumour:** n.r.  
**Reference standard of metastases:** histopathology (bone marrow aspirates and trephine biopsies) and/or clinical imaging.  

#### Index and comparator tests

**Index test:** FDG-PET scintigraphy.  
**Comparator test:** MIBG scintigraphy.  
**Radiofarmacon:** FDG-PET and MIBG.  
**Dose:** n.r.  
**Equipment:** n.r.  
**Acquisition protocol:** n.r.  
**Acquisition time:** n.r.  
**Acquisition duration:** n.r.  
**Interfering medication:** n.r.  
**Thyroid prophylaxis:** n.r.  
**Positive test result:** n.r.  
**Number and expertise of observers:** n.r.  
**Interobserver concordance:** n.r.

#### Follow-up

n.r.

#### Notes

Not published in full-text (as of December 2012), but presented at the EANM 2011.  
It was n.r. which tracers were used for MIBG- and FDG-PET scintigraphy.  
We did not contact the authors.
### Feine 1987

| Clinical features and settings | Study period: n.r.  
Patient population: 37 patients with suspected or histologically proven neuroblastomas with 121 131I- (n=49) and 131I-MIBG scans (n=66).  
Consecutive series: no; multicenter study, nu further information reported.  
Diagnostic work-up: n.r.  
Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.  
Treatment between index test-reference standard: n.r. |
|-----------------------------|---------------------------------------------------------------|
| Participants | Included patients; 37 patients with suspected or histologically proven neuroblastoma.  
Median age: n.r.  
Sex distribution: n.r.  
INSS stage: n.r. |
| Study design | Multicenter study. No further information reported. |
| Target condition and reference standard(s) | Target condition: newly diagnosed or recurrent neuroblastoma.  
Reference standard: histopathology. |
| Index and comparator tests | Index test: MIBG scintigraphy.  
Radiofarmacon: MIBG.  
Dose: n.r.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: n.r.  
Acquisition time: n.r.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: n.r.  
Positive test result: n.r.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | Length of follow-up: n.r. |
| Notes | Results were n.r. for 123I-MIBG scans separately from the 131I-MIBG scans.  
Contact information: not available. |

### Ferris 1992

| Clinical features and settings | Currently unclear. |
| Participants | Currently unclear. |
| Study design | Currently unclear. |
| Target condition and reference standard(s) | Currently unclear. |
| Index and comparator tests | Currently unclear. |
| Follow-up | Currently unclear. |
| Notes | Study in Spanish. We did not find a translator yet. Based on currently available information unclear whether this study fulfils the inclusion criteria. |
### Fischer 1989

**Clinical features and settings**

- Study period: since 1981.
- Patient population: 300 patients suspected for having a catecholamine producing tumour of which 21 patients with suspected neuroblastoma after elevated urinary catecholamines.
- Consecutive series: yes.
- Diagnostic work-up: n.r.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.

**Participants**

- Included patients: 21 children with suspected neuroblastoma.
- Median age: n.r.
- Sex distribution: n.r.
- INSS stage: n.r; all stage 3 or 4.

**Study design**

- n.r.

**Target condition and reference standard(s)**

- Target condition: newly diagnosed neuroblastoma.
- Reference standard: n.r.

**Index and comparator tests**

- Index test: 123I-MIBG and 131I-scintigraphy.
- Radiofarmacon: 123I-MIBG.
- Dose: 185 MBq.
- Collimator: n.r.
- Matrix: n.r.
- Acquisition protocol: posterior scans of the head, neck, thorax and abdomen; anterior scans of the pelvis; images of the upper en lower extremities in children suspected of neuroblastoma.
- Acquisition time: 2 to 24 hours after injection.
- Acquisition duration: n.r.
- Interfering medication: n.r.
- Thyroid prophylaxis: n.r.
- Positive test result: n.r.
- Number and expertise of observers: n.r.
- Interobserver concordance: n.r.

**Follow-up**

- n.r.

**Notes**

- Results n.r. for 123I-MIBG scans separately from the 131I-MIBG scans.
- Contact information of the authors: not available.

### Gelfand 1994

**Clinical features and settings**

- Study period: n.r.
- Patient population: 25 patients with neural crest tumours of which 20 with neuroblastoma.
- Consecutive series: n.r.
- Diagnostic work-up: n.r.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.

**Participants**

- Included patients: children with suspected neuroblastoma and a 123I-MIBG scan at diagnosis.
- Median age: n.r.
- Sex distribution: n.r.
- INSS stage: n.r.

**Study design**

- Retrospective cohort study.

**Target condition and reference standard(s)**

- Target condition: newly diagnosed neuroblastoma.
- Reference standard: n.r.
Index and comparator tests

Index test: 123I-MIBG scintigraphy. The diagnostic utility of 123I-MIBG SPECT was evaluated as a supplement to planar imaging.

Radiofarmacon: 123I-MIBG.
Dose: 0.140 mCi/kg.
Collimator: high-resolution.
Matrix: n.r.

Acquisition protocol: whole-body planar and SPECT scans; and for the 48 hours post injection images: 10-minutes images of the abdomen, chest (particularly if the primary tumour arose in the chest) and any other locations where the findings on the planar study at 24 hours were difficult to interpret.

Acquisition time: 24 hours after injection and 48 hours after injection in all patients who were able to return for repeat imaging.

Acquisition duration: 300,000 counts/image or 7.2 cm/min.

SPECT: Triad triple-detector SPECT camera, 40 increments, 40 sec/frame (24.5 cm axial field of view) or 30 sec/frame (49 cm axial field of view), body contouring, 20% window around 159 keV and low-energy, ultrahigh-resolution collimator.

Processing parameters of SPECT imaging: Hanning filter, 0.70-0.80 cycles/cm cutoff, coronal, sagittal and transaxial displays and cine and static displays of volume-rendered images.

Interfering medication: n.r.
Thyroid prophylaxis: n.r.

A description of a positive test result was not reported.

Number of observers: two experienced readers enumerated the number of abnormal sites on the planar and SPECT studies and rated the certainty of interpretation for each study on a scale from 0.1 (low certainty) to 1.0 (high).

Expertise of observers: n.r.
Interobserver concordance: n.r.

Follow-up
n.r.

Notes
Results n.r. for 20 patients with neuroblastoma separately for those with other tumours. Results n.r. for 123I-MIBG scans at first diagnosis separately from 123I-MIBG scans during follow-up.

We could not get into contact with the authors.

### Ginsburg 2012

**Clinical features and settings**

- Study period: n.r.
- Patient population: 49 patients with neuroblastoma and 86 123I-MIBG scans.
- Consecutive series: yes.
- Diagnostic work-up: n.r.
- Time spans symptoms-index test, symptoms-reference standard and index test-reference standard: n.r.
- Treatment between index test-reference standard: n.r.

**Participants**

- Included patients: children with neuroblastoma at first diagnosis.
- Median age: n.r.
- Sex distribution: n.r.
- INSS stage: n.r.

**Study design**

- Retrospective cohort study.

**Target condition and reference standard(s)**

- Target condition: newly diagnosed neuroblastoma.
- Reference standard: n.r.
### Index and comparator tests

| Index test: 123I-MIBG scintigraphy. | Radiofarmacon: 123I-MIBG. |
| Dose: 0.140 mCi/kg. | Collimator: n.r. |
| Matrix: n.r. | Acquisition protocol: whole-body and SPECT scans. |
| Acquisition time: 24 hours after injection. | Acquisition duration: n.r. |
| SPECT: n.r. | Interfering medication: n.r. |
| Thyroid prophylaxis: n.r. | Positive test result: n.r. |
| Number and expertise of observers: two radiologists visually compared the tumour detectability on four and 24 hours delayed planar images for bony and soft tissue lesions, as well as the detectability of soft tissue tumour on four and 24 hours delayed SPECT images. | Interobserver concordance: the agreement between the two radiologists was moderate for the detection of bony (kappa = 0.49) and soft tissue tumours (kappa = 0.50) on planar images as well as for the detection of soft tissue tumour with SPECT (kappa = 0.49). |

### Follow-up

| n.r. |

### Notes

| Not published in full-text (as of December 2012), but presented at the WMIC conference 2011. Results n.r. for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up. We did not contact the authors. |

### Goo 2005

| Clinical features and settings | Study period: May 2003 to September 2004. |
| Patient population: 41 children with a whole-body MRI scan of which thirty-six had conventional oncological imaging within 15 days (26 123I MIBG scans) | Consecutive series: n.r. |

| Participants | Included patients: eleven children with a neuroblastoma and a 123I-MIBG scan at first diagnosis. |
| Median age: n.r. for these eleven included patients; for all 36 patients: 3.5 years (range 4 months to 12 years). | Sex distribution: n.r. for these eleven included patients; for all 36 patients: 21 boys (58%) - 15 girls (42%). |
| INSS stage: n.r. |

| Study design | n.r. |

| Target condition and reference standard(s) | Target condition: newly diagnosed neuroblastoma. Reference standard: n.r. |
| **Index and comparator tests** | Index test: 123I-MIBG scintigraphy.  
Radiofarmacon: 123I-MIBG.  
Dose: n.r.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: standard protocols of the Asian Medical Centre in Seoul.  
Acquisition time: n.r.  
Acquisition duration: n.r.  
Interfering medication: not reported.  
Thyroid prophylaxis: not reported.  
Positive test result: n.r.  
Number and expertise of observers: one paediatric radiologist.  
Interobserver concordance: n.r. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up</strong></td>
<td>n.r.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Results n.r. for eleven patients with neuroblastoma separately for those with other tumours. We could not get into contact with the authors.</td>
</tr>
</tbody>
</table>

**Hervas 2001**

- **Clinical features and settings**
  - Study period: n.r.
  - Patient population: 20 patients with neuroblastoma with 47 123I-MIBG scans.  
  - Consecutive series: n.r.
  - Further information currently unclear.

- **Participants**
  - Included patients: children with newly diagnosed neuroblastoma.  
  - Median age: n.r.; mean age: 2.6 years (range 2 months to 9 years).  
  - Further information currently unclear.

- **Study design**
  - Currently unclear.

- **Target condition and reference standard(s)**
  - Currently unclear.

- **Index and comparator tests**
  - Currently unclear.

- **Follow-up**
  - Currently unclear.

- **Notes**
  - Study in Spanish. We did not find a translator yet. Based on currently available information unclear whether this study fulfils the inclusion criteria.

**Ishii 2000**

- **Clinical features and settings**
  - Currently unclear.

- **Participants**
  - Currently unclear.

- **Study design**
  - Currently unclear.

- **Target condition and reference standard(s)**
  - Currently unclear.

- **Index and comparator tests**
  - Currently unclear.

- **Follow-up**
  - Currently unclear.

- **Notes**
  - Study in Japanese. We did not find a translator yet. Based on currently available information unclear whether this study fulfils the inclusion criteria.

**Jacobs 1990a**

- **Currently unclear.**
| Clinical features and settings | Study period: n.r.  
Patient population: 16 patients with neuroblastoma, three with retinoblastoma and one with a malignant paraganglioma; with 30 123I- (n=17) and 131I- (n=13) MIBG scans.  
Consecutive series: n.r.  
Diagnostic work-up: n.r.  
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.  
Treatment between index test and reference standard: n.r. |
|-------------------------------|---------------------------------------------------------------|
| Participants                  | Included patients: twelve children with a neuroblastoma and a 123I-MIBG scan at first diagnosis.  
Median age: n.r. for these twelve included patients; for all 16 patients: 17.5 months (range 1 to 72 months).  
Sex distribution: n.r. for these twelve included patients; for all 16 patients: 13 boys (81%) – 3 girls (19%).  
INSS stage: n.r. for these twelve included patients; all 16 patients with neuroblastoma: two stage 1, two stage 2, four stage 3, five stage 4 and three stage 4S. |
| Study design                  | Cohort study. N.r. whether the study was retrospective or prospective. |
| Target condition and reference standard(s) | n.r. |
| Index and comparator tests    | Index test: 123I- and 131I-MIBG scintigraphy.  
Radiofarmacon: 123I- and 131I-MIBG.  
Dose: around 2 mCi.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: whole-body planar scans.  
Acquisition time: 24 hours after injection and 48 hours after injection in case of doubtful cases.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: potassium perchlorate or lugol solution before and after 123I-MIBG injection.  
Positive test result: n.r.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up                     | n.r. |
| Notes                         | Results n.r. for 123I-MIBG scans separately from 131I-MIBG scans.  
Contact information of the authors: not available. |

**Kurkure 2012**

| Clinical features and settings | Study period: n.r.  
Patient population: 22 patients with neuroblastoma and 18F-FDG-PET scans and 131I-MIBG scans within a time span of three days.  
Consecutive series: n.r.  
Diagnostic work-up: n.r.  
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.  
Treatment between index test and reference standard: n.r. |
|-------------------------------|---------------------------------------------------------------|
| Participants                  | Included patients: 22 children with neuroblastoma and a 18F-FDG-PET scan at first diagnosis.  
Median age: n.r.  
Sex distribution: n.r.  
INSS stage: n.r. |
| Study design                  | n.r. |
### Target condition and reference standard(s)

- **Target condition:** newly diagnosed neuroblastoma.
- **Reference standard:** n.r.

### Index and comparator tests

- **Index test:** 18F-FDG-PET scintigraphy.
  - **Radiofarmacon:** 18F-FDG-PET.
  - **Dose:** n.r.
  - **Equipment:** n.r.
  - **Acquisition protocol:** n.r.
  - **Acquisition time:** n.r.
  - **Acquisition duration:** n.r.
  - **Interfering medication:** n.r.
  - **Thyroid prophylaxis:** n.r.
  - **Positive test result:** n.r.
  - **Number and expertise of observers:** n.r.
  - **Interobserver concordance:** n.r.

### Follow-up

- **n.r.

### Notes

- Not published in full-text (as of December 2012), but presented at the SIOP conference 2012.
- The abstract did not contain relevant results for this review and based on the currently available information it is unclear whether this study fullfills the inclusion criteria for this review.
- We did not contact the authors.

### Lebtahi 1995

#### Clinical features and settings

- **Study period:** n.r.
- **Patient population:** 27 patients with neuroblastoma.
  - Consecutive series: n.r.
  - Diagnostic work-up: physical examinations, urinary catecholamines, bone marrow biopsies and smears and radiological studies.
  - Time span between 123I-MIBG scintigraphy and bone marrow biopsy: two to 15 days. Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
  - Treatment between index test and reference standard: n.r.

#### Participants

- Included patients: 24 children with neuroblastoma and a 123I-MIBG scan at first diagnosis.
- Median age: n.r. for these 24 included patients; for all 27 patients the mean age: 3.5 years (range ten days to 24 years).
- Sex distribution: n.r. for these 24 included patients; for all 27 patients: 19 boys (70%) - eight girls (30%).
- INSS stage: n.r. for these 24 included patients; for all 27 patients: two stage 1, six stage 2, seven stage 3, nine stage 4 and three stage 4.

#### Study design

- Retrospective cohort study.

#### Target condition and reference standard(s)

- **Target condition:** newly diagnosed neuroblastoma.
- **Reference standard of primary tumour:** histopathology.
- **Reference standard of metastases:** bone marrow biopsy or aspiration.
Index and comparator tests

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test: 123I-MIBG scintigraphy.</td>
<td>Radiofarmacon: 123I-MIBG.</td>
</tr>
<tr>
<td>Dose: 3.7 MBq/kg.</td>
<td>Collimator: n.r.</td>
</tr>
<tr>
<td>Matrix: n.r.</td>
<td>Acquisition protocol: whole-body planar scans. Anterior and posterior images of the whole-body and spot images were recorded with a dual-head gamma camera (both heads had a 3/4 inch thick crystal, 37 photo multipliers (PM) and low-energy all-purpose collimators). Average acquisition counts were 300 kcounts for the head (anterior, posterior and left and right lateral views), 500 kcounts for the anterior and posterior thorax, abdomen and pelvis, and 200 kcounts for the lower extremities. In the case of insufficient count rates, a minimum acquisition time of 20 minutes was preset for the views of the trunk, and of 10 minutes for the head and lower extremities. In some cases, single-photon emission tomography (SPET) of a given area was performed 24 hours post injection.</td>
</tr>
<tr>
<td>Acquisition time: 6, 24 and 48 hours after injection.</td>
<td>Acquisition duration: n.r.</td>
</tr>
<tr>
<td>Interfering medication: n.r.</td>
<td>Thyroid prophylaxis: lugol solution one day before and three days after 123I-MIBG injection.</td>
</tr>
<tr>
<td>Positive test result: n.r.</td>
<td>Number and expertise of observers: n.r.</td>
</tr>
<tr>
<td>Interobserver concordance: n.r.</td>
<td>Follow-up: n.r.</td>
</tr>
</tbody>
</table>

Notes

Results n.r. for children between younger than 18 years separately from two adults. Results n.r. for 123I-MIBG scans separately from 131I-MIBG scans. Contact information of the authors: not available.

Lumbroso 1988a

Clinical features and settings

| Study period: n.r. | Patient population: 70 patients with neuroblastoma or ganglioneuroblastoma and with 83 123I-MIBG and 32 131I-MIBG scans. |
| Consecutive series: n.r. | Diagnostic work-up: urinary catecholamines, 99mTc-MDP bone scans, US, CT, surgery, bone marrow aspirates and/or biopsies. |
| Time spans between symptoms and index test and between symptoms and reference standard: n.r. | Time span between index test and reference standard: less than 14 days. |
| Treatment between index test and reference standard: n.r. | Participants: included patients: children with confirmed neuroblastoma with 123I-MIBG scintigraphy at first diagnosis. Median age: n.r. for the included patients with confirmed neuroblastoma; for all 70 patients: range of 3.7 +/- 3.3 years. Further information currently unclear. |

Study design

Prospective cohort study.

Target condition and reference standard(s)

### Index and comparator tests

- **Index test:** 123I-MIBG scintigraphy.
- **Radiofarmacon:** 123I-MIBG.
- **Dose:** 3.7 MBq/kg.
- **Collimator:** n.r.
- **Matrix:** n.r.
- **Acquisition protocol:** n.r.
- **Acquisition time:** 24 hours after injection.
- **Acquisition duration:** n.r.
- **Interfering medication:** n.r.
- **Thyroid prophylaxis:** stable iodide.
- **Positive test result:** non-physiological uptake area or any bone uptake of 123I-MIBG, even in the metaphyseal complex.
- **Number and expertise of observers:** two independent observers that were trained for six months.
- **Interobserver concordance:** n.r.

### Follow-up

n.r.

### Notes

- Results n.r. for 123I-MIBG scans separately from the 131I-MIBG scans.
- Contact information of the authors: not available.

### Moschogiannis 2011

#### Clinical features and settings

- **Study period:** 2009 to 2010.
- **Patient population:** 99 patients with suspected neuroblastoma with 123I-MIBG scans.
- **Consecutive series:** n.r.
- **Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard:** n.r.
- **Treatment between index test and reference standard:** n.r.

#### Participants

- **Included patients:** 32 children with suspected neuroblastoma and a 123I-MIBG scan at diagnosis.
- **Median age:** n.r. for these 32 included patients; for all 99 patients: range of 1 month to 8 years.
- **Sex distribution:** n.r. for these 32 included patients; for all 99 patients: 52 boys (53%) - 47 girls (47%).
- **INSS stage:** n.r.

#### Study design

- **Cohort study.** N.r. whether the study was retrospective or prospective.

#### Target condition and reference standard(s)

- **Target condition:** newly diagnosed neuroblastoma.
- **Reference standard:** n.r.

#### Index and comparator tests

- **Index test:** 123I-MIBG scintigraphy.
- **Radiofarmacon:** 123I-MIBG.
- **Dose:** n.r.
- **Collimator:** n.r.
- **Matrix:** n.r.
- **Acquisition protocol:** planar and SPECT images; a subtraction technique was applied (a kidney’s image using 99mTc-DMSA subtracted from the 123I-MIBG scan, achieving a better localization of the adrenal medulla as well as a more exact determination of adrenal uptake).
- **Acquisition time:** 24 hours after injection.
- **Acquisition duration:** n.r.
- **SPECT:** n.r.
- **Interfering medication:** n.r.
- **Thyroid prophylaxis:** stable iodide.
- **Positive test result:** pathological uptake.
- **Number and expertise of observers:** n.r.
- **Interobserver concordance:** n.r.

#### Follow-up

n.r.
## Notes

Not published in full-text (as of December 2012), but presented at the EANM conference 2011.
Results n.r. for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up.
We did not contact the authors.

### Muckle 2012

**Clinical features and settings**
- Study period: n.r.
- Patient population: 18 patients with neuroblastoma with 44 123I-MIBG scans
- Consecutive series: n.r.
- Diagnostic work-up: n.r.
- Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
- Treatment between index test and reference standard: n.r.

**Participants**
- Included patients: children with newly diagnosed neuroblastoma and 123I-MIBG scintigraphy at diagnosis.
- Median age: n.r. for these included patient with newly diagnosed neuroblastoma; for all 18 patients: a range of 1 month to 15 years.
- Sex distribution: n.r.
- INSS stage: n.r.

**Study design**
- n.r.

**Target condition and reference standard(s)**
- Target condition: newly diagnosed neuroblastoma.
- Reference standard: histopathology, follow-up of the patients and conventional radiological imaging, especially MRI served as reference standard. For clarification of suspected MRI findings SPECT and MRI images were fused using CT anatomical landmarks.

**Index and comparator tests**
- Index test: 123I-MIBG scintigraphy.
- Radiofarmacon: 123I-MIBG.
- Dose: n.r.
- Collimator: n.r.
- Matrix: n.r.
- Acquisition protocol: n.r.
- Acquisition time: n.r.
- Acquisition duration: n.r.
- Interfering medication: n.r.
- Thyroid prophylaxis: n.r.
- Positive test result: n.r.
- Number and expertise of observers: n.r.
- Interobserver concordance: n.r.

**Follow-up**
- n.r.

**Notes**
- Not published in full-text (as of December 2012), but presented at the SNM conference 2012.
- Results n.r. for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up.
- We did not contact the authors.

### Muller-Gartner 1985

**Clinical features and settings**
- Study period: July 1984 to August 1985.
- Patient population: 19 patients with confirmed (n=18) or suspected neuroblastoma (n=1) with 35 123I-MIBG and 131I-MIBG scans.
- Consecutive series: n.r.
- Diagnostic work-up: n.r.
- Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
- Treatment between index test and reference standard: n.r.
### Muller-Gartner 1986

| Participants | Included patients: 15 children with newly diagnosed neuroblastoma at 123I-MIBG scintigraphy at diagnosis.  
Median age: 3 years (range 0.2 to 14 years).  
Sex distribution: n.r.  
INSS stage: three stage 2, two stage 3, nine stage 4 and one stage 4S. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Cohort study. N.r. whether the study was retrospective or prospective.</td>
</tr>
</tbody>
</table>
| Target condition and reference standard(s) | Target condition: newly diagnosed neuroblastoma.  
Reference standard of primary tumour: histopathology.  
If neuroblastoma could be excluded by US, radiological examinations, urinary catecholamines and bone marrow biopsy, a pathological 123I-MIBG uptake was deemed to be false-positive and a physiological 123I-MIBG distribution right-negative. |
| Index and comparator tests | Index test: 123I-MIBG and 131I-MIBG scintigraphy.  
Radiofarmacn: 123I- and 131I-MIBG.  
Dose: 111 to 185 MBq.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: anterior and posterior spot images of head; thorax, neck and upper arms; abdomen; upper legs and proximal tibiae.  
Acquisition time: 24 and 48 hours after injection.  
Acquisition duration: 200 kcounts for the head (lateral views); 400 to 1000 kcounts for the thorax, neck and upper arms (anterior and posterior views); 400 to 1000 kcounts for the abdomen (anterior and posterior views); 100 to 200 kcounts for the upper legs and proximal tibiae (anterior or posterior views).  
Interfering medication: n.r.  
Thyroid prophylaxis: 200 μg iodide.  
Positive test: non-physiological 123I-MIBG uptake.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | n.r. |
| Notes | Results n.r. for 123I-MIBG scans separately from 131I-MIBG scans. And results n.r. for 123I-MIBG scans at first diagnosis separately from 123I-MIBG scans during follow-up.  
Contact information of the authors: not available. |
## Chapter 2

### Index and comparator tests

| Index test: 123I-MIBG and 131I-MIBG scintigraphy. Radiofarmaceuticals: 123I- and 131I-MIBG. Dose: 111 to 185 MBq. Collimator: n.r. Matrix: n.r. Acquisition protocol: anterior and posterior spot images of head; thorax, neck and upper arms; abdomen; upper legs and proximal tibiae; and SPECT scans. Acquisition time: 24 and 48 hours after injection. Acquisition duration: 200 kcounts for the head (lateral views); 400 to 1000 kcounts for the thorax, neck and upper arms (anterior and posterior views); 400 to 1000 kcounts for the abdomen (anterior and posterior views); 100 to 200 kcounts for the upper legs and proximal tibiae (anterior or posterior views). SPECT: n.r. Interfering medication: n.r. Thyroid prophylaxis: 200 μg Iodide one day before and three days after tracer injection. Positive test: pathological 123I-MIBG uptake. Number and expertise of observers: n.r. Interobserver concordance: n.r. |
| Follow-up: n.r. |
| Notes: Results n.r. for 123I-MIBG scans separately from the 131I-MIBG scans. And results n.r. for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up. Contact information of the authors: not available. |

### Nikolaos 2011

| Clinical features and settings: Study period: November 2004 to October 2008. Patient population: 28 patients with refractory or relapsed high-risk neuroblastoma. Consecutive series: n.r. Diagnostic work-up: each patient underwent a pair of 18F-FDG and 123I-MIBG scans, performed within two weeks before treatment. Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: Treatment between index test and reference standard: |
| Participants: Included patients: 28 patients with refractory or relapsed high-risk neuroblastoma. Median age: 7.5 years (range 2 to 45 years). Sex distribution: 16 boys (57%) - 12 girls (43%). INSS stage: all stage 4. |
| Study design: Prospective cohort study. |
| Target condition and reference standard(s): Target condition: recurrent neuroblastoma. Reference standard: histopathology. |
| Index and comparator tests | Index test: 18F-FDG PET scintigraphy; comparator test: 123I-MIBG scintigraphy. Paired scans obtained within 14 days before treatment. When necessary, sedation was used in accordance with guidelines before 18F-FDG-PET/CT or 123I-MIBG scintigraphy to ensure patient immobilization and adequate image quality. 18F-FDG-PET scintigraphy: Radiofarmaco: 18F-FDG-PET. Dose: 5.5 to 7.7 MBq/kg (maximum 440 MBq). Equipment: CT data were acquired using four 3.75-mm detectors, a pitch of 1.5-, and 5-mm collimation (5 minutes per bed position). The CT exposure factors were 120–140 kVp and 80 mA. Acquisition protocol: PET images were reconstructed using CT data for attenuation correction. Transaxial PET emission images of 4.3x4.3x4.25 mm were reconstructed using ordered subsets expectation maximization, with two iterations and 28 subsets. Acquisition time: 50 to 75 minutes after injection. Acquisition duration: not reported. Positive test: any focal, superior-to-background 18F-FDG uptake in the primary mass, lymph nodes, liver, or skeleton and inhomogeneous 18F-FDG uptake in the bone marrow, especially in the absence of recent chemotherapy or hematopoietic stimulating factors. 123I-MIBG scintigraphy: Radiofarmaco: 123I-MiBG. Dose: 5.20 MBq/kg (maximum 370 MBq). Collimator: n.r. Matrix: n.r. Acquisition protocol: planar whole-body images were supplemented with spot views or 123I-MiBG SPECT-CT of the chest and abdomen, if deemed necessary for anatomic localization of the lesion or clarification of equivocal findings. Acquisition time: 24 and 48 hours after injection. Acquisition duration: SPECT: n.r. Interfering medication: n.r. Thyroid prophylaxis: potassium perchlorate or potassium iodide before and two days after 123I-MiBG injection. Positive test: n.r. Number and expertise of observers: n.r. Interobserver concordance: n.r. |
| Follow-up | Median observation time from imaging: 1.03 years (range 0.27 to 3.5 years). |
| Notes | Results not reported for children separately from adults. We could not get in contact with the authors. |

**Okuyama 1998**

**Clinical features and settings**

| Participants | Patient population: 19 patients with neuroblastoma and with 123I-MiBG scans. Further information currently unclear. Included patients: 19 children with neuroblastoma and a 123I-MiBG scan at first diagnosis. Median age: 8 months (range 2 weeks to 7 years). Sex distribution: 10 boys (53%) - 9 girls (47%). INSS stage: six stage 1, one stage 2, five stage 3, four stage 4 and three stage 4S. |

| Study design | Currently unclear. |

<p>| Target condition and reference standard(s) | Target condition: newly diagnosed neuroblastoma. Further information currently unclear. |</p>
<table>
<thead>
<tr>
<th>Study design</th>
<th>Clinical features and settings</th>
<th>Index and comparator tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient population: 23 patients with neuroblastoma at first diagnosis and with 123I-MIBG scans.</td>
<td>Index test: 123I-MIBG scintigraphy.</td>
</tr>
<tr>
<td></td>
<td>Further information currently unclear.</td>
<td>Radiofarmacon: 123I-MIBG.</td>
</tr>
<tr>
<td></td>
<td>Further information currently unclear.</td>
<td>Acquisition protocol: whole-body, truncal and SPECT scans.</td>
</tr>
<tr>
<td></td>
<td>Further information currently unclear.</td>
<td>Acquisition time: six and 24 hours after injection.</td>
</tr>
<tr>
<td></td>
<td>123I-MIBG scintigraphy was compared to CT or MRI and bone scintigraphy to investigate which imaging modality could demonstrate the extent of disease most exactly.</td>
<td>123I-MIBG scintigraphy was compared to CT or MRI and bone scintigraphy to investigate which imaging modality could demonstrate the extent of disease most exactly.</td>
</tr>
<tr>
<td>Notes</td>
<td>Study in Japanese. We did not find a translator yet. Based on currently available information unclear whether this study fulfills the inclusion criteria.</td>
<td>Further information currently unclear.</td>
</tr>
</tbody>
</table>

**Okuyama 1999**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Included patients: 22 children with newly diagnosed neuroblastoma and with 123I-MIBG scintigraphy at first diagnosis.</th>
<th>Further information currently unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median age: 9 months (range 0.5 month to 86 months).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex distribution: 12 boys (55%) - 10 girls (45%).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INSS stage: four stage 1, five stage 2, seven stage 3 and six stage 4.</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Currently unclear.</td>
<td></td>
</tr>
<tr>
<td>Target condition and reference standard(s)</td>
<td>Target condition: newly diagnosed neuroblastoma. Reference standard: histopathology.</td>
<td></td>
</tr>
<tr>
<td>Index and comparator tests</td>
<td>Index test: 123I-MIBG scintigraphy. Further information currently unclear.</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Currently unclear.</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Study was in Japanese. We did not find a translator yet. Based on currently available information unclear whether this study fulfills the inclusion criteria.</td>
<td></td>
</tr>
</tbody>
</table>

**Osmanagaoglu 1993**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Included patients: 26 children with newly diagnosed neuroblastoma and with a 123I-MIBG scan at diagnosis.</th>
<th>Further information currently unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median age: n.r.; mean age: 3.3 years (range 1 month to 13 years).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex distribution: 14 boys (54%) - 12 girls (46%).</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective cohort study.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient population: 26 patients with neuroblastoma and with 148 123I-MIBG scans.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consecutive series: n.r.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnostic work-up: urinary catecholamines, US, CT, MRI, 123I-MIBG scintigraphy, 99mTc-MDP-bone scintigraphy and cytological examination of bone marrow aspiration biopsy specimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time span between 123I-MIBG scintigraphy and routine cytological bone marrow aspiration: four weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time spans between symptoms and index test and between symptoms and reference standard: n.r.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment between index test and reference standard: n.r.</td>
<td></td>
</tr>
</tbody>
</table>
### Target condition and reference standard(s)

Target condition: newly diagnosed neuroblastoma.
Reference standard of primary tumour: histopathology.
Reference standard of metastases: unguided, unilateral bone marrow aspiration biopsies at the anterior iliac crest and various smear samples from the aspiration material; cytologically analysed by an experienced haemato-oncologist. May-Grinwald-Giemsa staining was employed for morphological evaluation of the cells.

### Index and comparator tests

- **Index test:** 123I-MIBG scintigraphy.
- **Radiofarmacon:** 123I-MIBG.
- **Dose:** 111 MBq.
- **Collimator:** n.r.
- **Matrix:** n.r.
- **Acquisition protocol:** whole-body scans and additional spot views if necessary.
- **Acquisition time:** six and 24 hours after injection.
- **Interfering medication:** n.r.
- **Thyroid prophylaxis:** potassium iodide (30 mg/day) three days before 123I-MIBG injection.
- **Positive test:** 123I-MIBG uptake in skeleton and bone marrow.
- **Number and expertise of observers:** two residents and two experienced nuclear medicine physicians; interpretations were compared in order to reach a consensus.
- **Interobserver concordance:** n.r.

### Follow-up

- **Follow-up time:** minimally two years.

### Notes

Results not reported for 123I-MIBG scans at first diagnosis separately from 123I-MIBG scans during follow-up.

Contact information of the authors: not available.

---

### Paltiel 1994

#### Clinical features and settings

- **Study period:** March 1991 to February 1992.
- **Patient population:** 33 patients with a suspected neural crest tumour and with 77 consecutive 123I-MIBG scans.
- **Consecutive series:** yes.
- **Diagnostic work-up:** US, CT, MRI, 99mTc-bone scintigraphy, skeletal surveys, bone marrow aspiration/biopsy or histopathology.
- **Results of the 123I-MIBG scans** were compared with those of other imaging studies and any biopsy studies performed in the three months before and after each 123I-MIBG scan.
- **Time spans between symptoms and index test** and between symptoms and reference standard: n.r.
- **Treatment between index test and reference standard:** n.r.

#### Participants

- **Included patients:** 28 children with newly diagnosed neuroblastoma and with a 123I-MIBG scan at first diagnosis.
- **Median age:** n.r. for these included patients; for all 33 patients the mean age: 5.6 years (range 2 weeks to 14.8 years).
- **Sex distribution:** n.r. for these included patients; for all 33 patients: 18 boys (55%) - 15 girls (45%).
- **INSS stage:** n.r. for these included patients; for all 33 patients: two stage 1, four stage 3, 17 stage 4 and three stage 4S.

#### Study design

- **Cohort study.** N.r. whether the study was retrospective or prospective.

#### Target condition and reference standard(s)

- **Target condition:** newly diagnosed neuroblastoma.
- **Reference standard:** histopathology.
### Index and comparator tests

**Index test:** 123I-MIBG scintigraphy.

**Radiofarmacan:** 123I-MIBG.

**Dose:** 0.07 mCi/kg for patients with stage 1 or 2 neuroblastoma, 0.14 mCi/kg for patients with stage 3 or 4 neuroblastoma and 0.07 mCi/kg for patients with other proved or suspected neural crest tumours; with a maximum of 5.0 mCi.

**Collimator:** general-purpose.

**Matrix:** n.r.

**Acquisition protocol:** anterior and posterior planar scans.

**Acquisition time:** 24 and 48 hours after injection.

**Acquisition duration:** 300 kcount for images over the torso; the same time per image (usually 2 to 2.5 minutes) for whole-body scans in anterior and posterior projections; and 6-minute images of the torso, shoulders, and hips in anterior and posterior projections; the skull and extremity sites were re-imaged only if equivocal lesions were seen at 24 hours.

**Interfering medication:** n.r.

**Thyroid prophylaxis:** saturated potassium iodide solution (30 mg/day) prior to until two days after 123I-MIBG injection.

**Positive test:** abnormally increased 123I-MIBG uptake.

**Number and expertise of observers:** all scans were retrospectively and separately interpreted by three nuclear medicine specialists with two serving as primary reviewers of each study and the third as a “tie breaker,” when needed.

**Interobserver concordance:** n.r.

---

### Follow-up

**Follow-up time:** up to two years.

### Notes

Results not reported for patients with neuroblastoma separately from patients with other neural crest tumours.

Contact information of the authors: not available.

---

### Parisi 1992

**Clinical features and settings**

**Study period:** 1983 through April 1991.

**Patient population:** 20 patients with known or suspected neuroblastoma and with 26 paired 123I-MIBG (n=20), 131I-MIBG (n=6) and 99mTc-MDP bone scans less than four weeks apart.

**Consecutive series:** no, the pairs were randomly chosen from a pool of over 86 similar pairs representing all the paired studies performed in neuroblastoma patients.

**Diagnostic work-up:** n.r.

**Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard:** n.r.

**Treatment between index test and reference standard:** n.r.

**Participants**

Included patients: 14 patients with neuroblastoma and with a 123I-MIBG scan.

**Median age:** n.r.

**Sex distribution:** n.r.

**INSS stage:** n.r.; for all 20 patients: three stage 2, one stage 3, 15 stage 4 and one not specified.

**Study design**

Cohort study. N.r. whether the study was retrospective or prospective.

**Target condition and reference standard(s)**

**Target condition:** newly diagnosed neuroblastoma.

**Reference standard:** For the purposes of statistical analysis, the scores of the experienced observers were considered the "gold standard," as occurs in clinical practice. However, experienced observer scores were 100% correlated with concomitant available bone marrow aspirates as well as other clinical, biochemical, and radiographic indicators of disease status.
Chapter 2

Index and comparator tests

Index test: 123I-MIBG scintigraphy.
Radiofarmacon: 123I-MIBG.
Dose: n.r.
Collimator: n.r.
Matrix: n.r.
Acquisition protocol: n.r.
Acquisition time: n.r.
Acquisition duration: n.r.
Interfering medication: n.r.
Thyroid prophylaxis: n.r.
Positive test: n.r.

Number and expertise of observers: each study was evaluated independently of its counterpart by six separate observers (three experienced and three inexperienced in MIBG scintigraphy) to determine the presence or absence of disease and the tumour burden.

Finally, inexperienced observers submitted level of confidence scores (1 = true-negative; 5 = true-positive) for each study evaluated. Analysis of confidence levels using a paired Student’s test confirmed that the residents were significantly more confident using, and more confident of, their interpretations on 99mTc-MDP bone scans. However, despite their familiarity and confidence with 99mTc-MDP scans, inexperienced observers identified only 52% and 57% of the lesions and regions of disease involvement, respectively, found by the experienced observers on the radionuclide bone scans.

Interobserver concordance: identifying lesions and regions of disease extent between inexperienced and experienced observers increased appreciably on MIBG scans to 66% and 83%, respectively.

Follow-up
n.r.; some patients were followed for approximately 33 months.

Notes
Results not reported for 123I-MIBG scans separately from 131I-MIBG scans.
Unclear whether 123I-MIBG scans were performed at first diagnosis, recurrence or refractory neuroblastoma.
Contact information of the authors: not available.

Rathore 2011

Clinical features and settings

Patient population: 168 patients with neuroendocrine tumours and with 100 MIBG scans.
Consecutive series: n.r.
Diagnostic work-up: CT, MRI and histopathology.
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
Treatment between index test and reference standard: n.r.

Participants
Included patients: 168 patients with neuroendocrine tumours.
Median age: n.r.
Sex distribution: n.r.
INSS stage: n.r.

Study design
Cohort study. N.r. whether the study was retrospective or prospective.

Target condition and reference standard(s)
Target condition: neuroblastoma.
Reference standard: histopathology.
### Index and comparator tests

| Index test | 123I-MIBG. |
| Radiofarmacon | 123I-MIBG. |
| Dose | n.r. |
| Collimator | n.r. |
| Matrix | n.r. |
| Acquisition protocol | planar and SPECT scans. |
| Acquisition time | n.r. |
| Acquisition duration | n.r. |
| SPECT | n.r. |
| Interfering medication | n.r. |
| Thyroid prophylaxis | n.r. |
| Positive test | n.r. |
| Number and expertise of observers | n.r. |
| Interobserver concordance | n.r. |

### Follow-up

| n.r. |

### Notes

Not published in full-text (as of December 2012), but presented at the ACNM conference 2011. Unclear how many patients were diagnosed with neuroblastoma, whether 123I- or 131I-MIBG scintigraphy was performed and whether MIBG scintigraphy was performed at first diagnosis or at follow-up. We did not contact the authors.

---

### Sarkadi 2011

**Clinical features and settings**

- Currently unclear.

**Participants**

- Currently unclear.

**Study design**

- Currently unclear.

**Target condition and reference standard(s)**

- Currently unclear.

**Index and comparator tests**

- Currently unclear.

**Follow-up**

- Currently unclear.

**Notes**

Not published in full-text (as of December 2012), but presented at a Hungarian conference. We could not find the abstract, so we were not able to evaluate the eligibility of this study.

---

### Schilling 2000

**Clinical features and settings**

- Study period: n.r.
- Patient population: 88 patients with histologically proven neuroblastoma at first diagnosis or recurrence and with 123I-MIBG scans.
- Consecutive series: n.r.
- Diagnostic work-up: urinary catecholamines, US, CT, MRI, 123I-MIBG scintigraphy and multiple bone marrow biopsies.
- Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
- Treatment between index test and reference standard: n.r.

**Participants**

- Included patients: children with newly diagnosed or recurrent neuroblastoma and with a 123I-MIBG scan at first diagnosis.
- Median age: n.r. for these included patients; for all 88 patients: 14 months (range 0 to 290 months).
- Sex distribution: n.r. for these included patients; for all 88 patients: 48 boys (55%) - 40 girls (45%).
- INSS stage: n.r. for these included patients; for all 88 patients: 58 stage 1,2,3 or 45 and 30 stage 4.
**Study design**  
Cohort study. N.r. whether the study was retrospective or prospective.

**Target condition and reference standard(s)**  
Target condition: newly diagnosed or recurrent neuroblastoma.  
Reference standard: histopathology.

**Index and comparator tests**  
Index test: 123I-MIBG scintigraphy.  
Radiofarmacon: 123I-MIBG.  
Dose: 110 MBq.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: n.r.  
Acquisition time: 24 hours after injection.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: n.r.  
Positive test: n.r.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r.

**Follow-up**  
Median follow-up: 35 months (range 1 to 88 months).

**Notes**  
Results not reported for children separately from adults.  
We could not get contact with the authors.

**Schmiegelow 1989**

**Clinical features and settings**  
Study period: n.r.  
Patient population: 96 patients with confirmed neuroblastoma (n=71) or suspected neuroblastoma (n=25) and with 123I- and 131I-MIBG scans.  
Consecutive series: n.r.  
Diagnostic work-up: urinary catecholamines, US, CT, radiological examinations, 99mTc-MDP-bone scan.  
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.  
Treatment between index test and reference standard: n.r.

**Participants**  
Included patients: 31 children younger than 15 years old with neuroblastoma and with a 123I-MIBG scan at first diagnosis.  
Median age: n.r. for these 31 included patients; for all 71 patients with a neuroblastoma: 2 years (range 0 to 15 years).  
Sex distribution: n.r. for these 31 included patients; for all 71 patients with a neuroblastoma: 42 boys (59%) - 29 girls (41%).  
INSS stage: n.r. for these 31 included patients; for all 71 patients: seven stage 1, nine stage 2, 13 stage 3 and 42 stage 4.

**Study design**  
Cohort study. N.r. whether the study was retrospective or prospective.

**Target condition and reference standard(s)**  
Target condition: newly diagnosed neuroblastoma.  
Reference standard: histopathology (and US, CT, radiological examinations, 99mTc-bone scan, urinary catecholamines).

**Index and comparator tests**  
Index test: 123I-MIBG scintigraphy.
| comparator tests | Radiofarmacon: 123I-MIBG.  
Dose: 30(+10*age in years) MBq in children younger than eight years and 70 to 80 MBq in two adolescents of 16 years.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: n.r.  
Acquisition time: 24 hours after injection.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: Lugol’s solution, potassium iodide or perchlorate less than 24 hours before injection of 123I-MIBG.  
Positive test: pathological 123I-MIBG uptake.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>n.r.; some patients were followed for approximately 44 months.</td>
</tr>
</tbody>
</table>
| Notes | Results not reported for 123I-MIBG scans separately from 131I-MIBG scans.  
We could not get contact with the authors. |

**Sharp 2009a**

| Clinical features and settings | Study period: n.r.  
Patient population: 23 patients with neuroblastoma.  
Consecutive series: n.r.  
Diagnostic work-up: n.r.  
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.  
Treatment between index test and reference standard: n.r. |
|---|---|
| Participants | Included patients: 23 patients with neuroblastoma.  
Median age: n.r.  
Sex distribution: n.r.  
INSS stage: n.r. |
| Study design | n.r. |
| Target condition and reference standard(s) | Target condition: n.r.  
Reference standard: n.r. |
| Index and comparator tests | Index test: 123I-MIBG SPECT/CT.  
Radiofarmacon: 123I-MIBG.  
Dose: 0.14 mCi/kg.  
Equipment: two different SPECT/CT scanners A and B (with diagnostic CT unit), details n.r.  
Acquisition protocol: whole-body planar MIBG scintigraphy, SPECT, and co-registered low-dose CT imaging  
Acquisition time: n.r.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: n.r.  
Positive test result: foci of uptake.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | n.r. |
| Notes | Not published in full-text (as of 2009), but presented at the SIOP conference 2012.  
Results n.r. for 123I-MIBG scans at first diagnosis separately from the 123I-MIBG scans during follow-up.  
We did not contact the authors. |
<table>
<thead>
<tr>
<th><strong>Suc 1996</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features and settings</strong></td>
</tr>
<tr>
<td>Patient population: 129 consecutive patients with neuroblastoma; thirty-two not enrolled in the study because MIBG scans were unavailable (n=26) or because patients were treated before their first MIBG scan (n=6); of the remaining 97 children 86 had a positive MIBG scan and were included in this study; eleven were excluded, because their first MIBG scan did not show any skeletal metastases. Five-hundred-twenty-two MIBG scans were performed in these patients; 519 with 123I-MIG and three with 131I-MIBG.</td>
</tr>
<tr>
<td>Diagnostic work-up: urinary catecholamines, CT, MRI, MIBG scintigraphy, two trephine biopsies and ten bone marrow aspirates.</td>
</tr>
<tr>
<td>Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.</td>
</tr>
<tr>
<td>Treatment between index test and reference standard: n.r.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td>Included patients: 86 children with newly diagnosed neuroblastoma and with a 123I-MIBG scan at first diagnosis.</td>
</tr>
<tr>
<td>Median age: 3 years (range 1 to 14 years).</td>
</tr>
<tr>
<td>Sex distribution: 54 boys (63%) and 32 girls (37%).</td>
</tr>
<tr>
<td>INSS stage: all stage 4.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td>Retrospective cohort study.</td>
</tr>
<tr>
<td><strong>Target condition and reference standard(s)</strong></td>
</tr>
<tr>
<td>Target condition: primary neuroblastoma.</td>
</tr>
<tr>
<td>Reference standard of primary tumour: histopathology.</td>
</tr>
<tr>
<td>Reference standard of metastases: two trephine biopsies and ten bone marrow aspirates; examination of spread films of aspirated material and stained by May-Grunwald-Giemsa stain (all slides were examined for evidence of gross disease or for small clumps of tumour cells); sections of formalin fixed trephine biopsies obtained with a Jamshidi needle were examined systematically at low and high magnifications. Bone marrow involvement was defined by any positive cytologic and/or histologic findings.</td>
</tr>
<tr>
<td><strong>Index and comparator tests</strong></td>
</tr>
<tr>
<td>Index test: 123I-MIBG scintigraphy.</td>
</tr>
<tr>
<td>Radiofarmacon: 123I-MIBG.</td>
</tr>
<tr>
<td>Dose: 4 MBq/kg.</td>
</tr>
<tr>
<td>Collimator: n.r.</td>
</tr>
<tr>
<td>Matrix: n.r.</td>
</tr>
<tr>
<td>Acquisition protocol: n.r.</td>
</tr>
<tr>
<td>Acquisition time: 24 hours after injection.</td>
</tr>
<tr>
<td>Acquisition duration: n.r.</td>
</tr>
<tr>
<td>Interfering medication: n.r.</td>
</tr>
<tr>
<td>Thyroid prophylaxis: potassium iodide four days before the injection of 123I-MIBG and for the next three days.</td>
</tr>
<tr>
<td>Positive test: focal 123I-MIBG uptake or diffuse 123I-MIBG uptake throughout the skeleton, including the metaphyseal complex.</td>
</tr>
<tr>
<td>Number of observers: two independent observers.</td>
</tr>
<tr>
<td>Expertise of observers: n.r.</td>
</tr>
<tr>
<td>Interobserver concordance: n.r.</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
</tr>
<tr>
<td>n.r.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
<tr>
<td>Results not reported for 123I-MIBG scans separately from 131I-MIBG scans.</td>
</tr>
<tr>
<td>Contact information of the authors: not available.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Tahir 2011</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features and settings</strong></td>
</tr>
<tr>
<td>Study period: five-year period.</td>
</tr>
<tr>
<td>Patient population: 23 patients with MIBG and bone scans.</td>
</tr>
<tr>
<td>Further information n.r.</td>
</tr>
<tr>
<td>Included patients: 23 patients with neuroblastoma.</td>
</tr>
<tr>
<td>Median age: n.r.</td>
</tr>
<tr>
<td>Sex distribution: 13 boys (57%) - 10 girls (43%).</td>
</tr>
<tr>
<td>INSS stage: n.r.</td>
</tr>
</tbody>
</table>
### Study design

Prospective cohort study.

### Target condition and reference standard(s)

**Target condition:** patients with neuroblastoma.
**Reference standard:** n.r.

### Index and comparator tests

**Index test:** MIBG scintigraphy.
**Further information:** n.r.

### Follow-up

n.r.

### Notes

Not published in full-text (as of December 2012), but presented at the RSNA conference 2012.
Unclear whether patients were younger than 18 years, whether 123I- or 131I-MIBG scintigraphy was performed and whether MIBG scintigraphy was performed at first diagnosis or at follow-up.
We did not contact the authors.

---

### Turba 1993

#### Clinical features and settings

**Study period:** April 1986 to November 1991.
**Study population:** 22 consecutive patients with histopathologically confirmed stage 4 neuroblastoma and with 123I-MIBG and 131I-MIBG scans at first diagnosis.
**Diagnostic work-up:** urinary catecholamines, other imaging modalities, bone marrow aspirates and bone biopsies.
**Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard:** n.r.
**Treatment between index test and reference standard:** n.r.

#### Participants

**Included patients:** 14 children with newly diagnosed stage 4 neuroblastoma and with a 123I-MIBG scan at first diagnosis.
**Median age:** n.r. for these 14 included patients; for all 22 patients: 2.9 years (range 8 months to 8 years).
**Sex distribution:** n.r. for these 14 included patients; for all 22 patients: 11 boys (50%) - 11 girls (50%).
**INSS stage:** all stage 4.

#### Study design

Cohort study. N.r. whether the study was retrospective or prospective.

#### Target condition and reference standard(s)

**Target condition:** newly diagnosed stage 4 neuroblastoma.
**Reference standard:** histopathology (bone marrow aspirate and/or trephine biopsy) and urinary catecholamines.

#### Index and comparator tests

**Index test:** 123I-MIBG scintigraphy.
**Radiofarmacon:** 123I-MIBG.
**Dose:** 120 to 160 MBq/kg.
**Collimator:** medium-energy.
**Matrix:** 256x256.
**Acquisition protocol:** whole-body scans.
**Acquisition time:** 24 hours after injection; in selected cases also 48 hours after injection.
**Acquisition duration:** 20 min/view or 500 kcounts.
**Interfering medication:** n.r.
**Thyroid prophylaxis:** Lugol’s solution and potassium perchlorate.
**Positive test:** n.r.
**Number of observers:** two independent observers.
**Expertise of observers:** n.r.
**Interobserver concordance:** n.r.

#### Follow-up

Mean follow-up time: 26 months from diagnosis (range 11 to 42 months).
**Notes**
Results not reported for 123I-MIBG scans separately from 131I-MIBG scans. Contact information of the authors: not available.

**Vik 2009**

### Clinical features and settings
- **Study period:** n.r.
- **Patient population:** 100 patients with known or suspected neuroblastoma with 123I-MIBG scans at first diagnosis.
- **Consecutive series of patients:** no, patients from ten centres in the US and seven in Europe participated.
- **Diagnostic work-up:** urinary catecholamines, other imaging modalities, bone marrow aspirates and bone biopsies.
- **Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard:** n.r.
- **Treatment between index test and reference standard:** n.r.

### Participants
- **Included patients:** 62 children with newly diagnosed neuroblastoma and with a 123I-MIBG scan at first diagnosis.
- **Median age:** n.r. for these 62 included patients; for all 100 patients the mean age: 4.7 years (range 0.08 years to 58 years).
- **Sex distribution:** n.r. for these 62 included patients; for all 100 patients: 57 boys (57%) - 43 girls (43%).
- **INSS stage:** all stage 4.

### Study design
- **Prospective trial:** open-label phase 3 scintigraphy study designed to document that 123I-mIBG was effective for imaging of subjects being evaluated for known or suspected neuroblastoma.

### Target condition and reference standard(s)
- **Target condition:** newly diagnosed stage 4 neuroblastoma.
- **Reference standard:** histopathology from biopsy or surgical specimens. For patients with no definitive histopathology, the final diagnosis was based upon the combination of data from available histopathology (e.g. bone marrow biopsy, surgery following chemotherapy), results of recent imaging procedures (CT, MRI, scintigraphy), urinary and blood catecholamines and clinical follow-up.
- **The final diagnosis for neuroblastoma was confirmed in 64 patients (62 children), not confirmed in 30 patients and indeterminate in six patients.**

### Index and comparator tests
- **Index test:** 123I-MIBG scintigraphy.
- **Radiofarmacon:** 123I-MIBG.
- **Dose:** 37 MBq for a 3 kg infant to 185 MBq for a 22 kg child and 370 MBq for a 70 kg adolescent.
- **Collimator:** n.r.
- **Matrix:** n.r.
- **Acquisition protocol:** anterior and posterior whole-body or multiple overlapping spot images from the head to below the knees; supplemental spot images as deemed appropriate by the investigator.
- **Acquisition time:** 24 hours after injection. SPECT imaging of the thorax and abdomen was acquired unless the investigator determined that either the subject could not tolerate the procedure or the information that might be obtained would be of negligible clinical value.
- **Acquisition duration:** n.r.
- **SPECT:** n.r.
- 123I-MIBG whole-body scans were acquired for 93 patients and 123I-MIBG SPECT scans for 45 patients (of 94 patients with a confirmed diagnosis).
- **Interfering medication:** n.r.
- **Thyroid prophylaxis:** n.r.
- **Positive test:** n.r.
CHAPTER 2

Number and expertise of observers: three blinded readers that were experienced nuclear imagers. The readers were blinded to the protocol and to all clinical data except for the diagnostic purpose of the imaging examination. All evaluations were performed independently (all planar images first, followed by SPECT if that procedure had been performed). Based upon the independent results for each reader, a derived consensus regarding presence or absence of neuroblastoma (agreement of at least two readers) was obtained for the planar and planar+SPECT interpretations.

Interobserver concordance: all three observers agreed on the diagnosis in 64 of the 94 subjects (67%) with confirmed diagnosis. The kappa statistic among each pair of readers: >0.60. With regard to the contribution of SPECT, the readers indicated that this study clarified the location of findings on planar images in 49 to 65% of patients and provided additional diagnostic value in 31 to 59% of studies examined.

Follow-up n.r.

Notes Results not reported for children younger than 18 years separately from adults. We did not get additional information on age from the authors yet.

Yang 2012

Clinical features and settings Study period: January 2006 to December 2011.
Patient population: 126 paediatric patients with malignant neuroblastoma and with pre-therapy 123I-MIBG and post-therapy 131I-MIBG scans.
Diagnostic work-up: n.r.
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.
For every patient, the 123I-MIBG and 131I-MIBG scans were acquired within two weeks.
Treatment between index test and reference standard: n.r.

Participants Included patients: 126 patients with malignant neuroblastoma and with a 123I-MIBG scan before 131I-MIBG therapy.
Median age: n.r. mean age: 8.8 years (range 2 years to 25 years).
Sex distribution: n.r.
INSS stage: n.r.

Study design Retrospective cohort study.

Target condition and reference standard(s) Target condition: malignant neuroblastoma.
Reference standard: n.r.

Index and comparator tests Index test: 123I-MIBG scintigraphy.
Radiofarmacon: 123I-MIBG.
Dose: n.r.
Collimator: n.r.
Matrix: n.r.
Acquisition protocol: n.r.
Acquisition time: n.r.
Acquisition duration: n.r.
Interfering medication: n.r.
Thyroid prophylaxis: not reported.
Positive test: n.r.
Number and expertise of observers: n.r.
Interobserver concordance: n.r.

Follow-up n.r.

Notes Results not reported for children younger than 18 years separately from adults. Unclear whether all 123I-MIBG scans were performed at first diagnosis. We did not get contact with the authors.
### Young-Seok 2006

| Clinical features and settings | Study period: n.r.  
Patient population: 19 patients older than one year with stage 4 neuroblastoma and with 123I-MIBG and 131I-MIBG scans.  
Consecutive series: n.r.  
Time spans between symptoms and index test, between symptoms and reference standard and between index test and reference standard: n.r.  
Treatment between index test and reference standard: n.r. |
| --- | --- |
| Participants | Included patients: 13 patients with neuroblastoma and with a 123I-MIBG scan.  
Median age: n.r. for these 13 included patients; for all 19 patients mean age: 45.9 months.  
Sex distribution: n.r. for these 13 included patients; for all 19 patients: 12 boys (63%) - 7 girls (37%).  
INSS stage: all stage 4. |
| Study design | n.r. |
| Target condition and reference standard(s) | Target condition: stage 4 neuroblastoma.  
Reference standard: n.r. |
| Index and comparator tests | Index test: 123I-MIBG scintigraphy.  
Radiofarmacon: 123I-MIBG.  
Dose: n.r.  
Collimator: n.r.  
Matrix: n.r.  
Acquisition protocol: n.r.  
Acquisition time: n.r.  
Acquisition duration: n.r.  
Interfering medication: n.r.  
Thyroid prophylaxis: n.r.  
Positive test: n.r.  
Number and expertise of observers: n.r.  
Interobserver concordance: n.r. |
| Follow-up | n.r. |
| Notes | Not published in full-text (as of December 2012), but presented at the SNM conference 2006.  
Results not reported for 123I-MIBG scans separately from 131I-MIBG scans.  
We did not contact the authors |

### Ythier 1987

| Clinical features and settings | Study period: n.r.  
Patient population: 33 patients with suspected neuroblastoma and with 46123I-MIBG (26 at first diagnosis).  
Consecutive series: n.r.  
Further information currently unclear. |
| --- | --- |
| Participants | Included patients: 23 children with suspected neuroblastoma and with a 123I-MIBG scan at first diagnosis of which five had confirmed neuroblastoma.  
Median age: n.r. for these 23 included patients; for all 33 patients the range: 1 month to 14 years.  
Sex distribution: n.r.  
INSS stage: one stage 2, one stage 3, two stage 4 and one stage 4S. |
| Study design | Currently unclear. |
| Target condition and reference standard(s) | Target condition: neuroblastoma.  
Reference standard: currently unclear. |
## Chapter 2

### Index and comparator tests

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>123I-MIBG scintigraphy. Radiofarmacon: 123I-MIBG.</td>
</tr>
<tr>
<td>Dose</td>
<td>1.8 MBq/kg.</td>
</tr>
<tr>
<td>Acquisition time</td>
<td>six and 24 hours after injection.</td>
</tr>
<tr>
<td>Thyroid prophylaxis</td>
<td>Lugol's solution and potassium perchlorate administered before injection of 123I-MIBG.</td>
</tr>
<tr>
<td>Further information</td>
<td>Currently unclear.</td>
</tr>
</tbody>
</table>

### Follow-up

Currently unclear.

### Notes

Study in French. Not enough information from translator. Based on currently available information unclear whether this study fulfils the inclusion criteria.

### Abbreviations:

- **123I-MIBG**: Iodine-123-metaiodobenzylguanidine;
- **131I-MIBG**: Iodine-131-metaiodobenzylguanidine;
- **18F-FDG-PET**: Fluorine-18-fluorodeoxy-glucose positron emission tomography;
- **99mTc-DMSA**: metastable-technetium-99-dimercaptosuccinic acid;
- **99mTc-MDP**: metastable-technetium-99-methyldiphosphonate;
- **AIEOP**: Italian Association of Paediatric Hematology and Oncology;
- **ANR**: advances in neuroblastoma research;
- **cm**: centimetre;
- **CT**: computed tomography;
- **EANM**: European association of nuclear medicine;
- **e.g.**: exempli gratia;
- **FDG-PET**: Fluoro-deoxy-glucose positron emission tomography;
- **HR-NBL1**: High risk-neuroblastoma 1;
- **INSS**: international neuroblastoma staging system;
- **kcount**: kilo count;
- **keV**: kilo-electron volt;
- **kg**: kilogram;
- **kVp**: kilovolt peak;
- **mA**: milli Ampère;
- **m**: metre;
- **μg**: micro gram;
- **mCi**: milli Curie;
- **mg**: milligram;
- **MBq**: mega becquerel;
- **MIBG**: metaiodobenzylguanidine;
- **min**: minute;
- **MRI**: magnetic resonance imaging;
- **NB-HR 01**: neuroblastoma-high risk 01;
- **n.r.**: not reported;
- **PET**: positron emission tomography;
- **RSNA**: radiological society of North America;
- **sec**: second;
- **SIOP**: société internationale d’oncologie pédiatrique;
- **SIOPEN**: Society of Paediatric Oncology European Neuroblastoma Group;
- **SNM**: society of nuclear medicine;
- **SPECT**: single photon emission computed tomography;
- **SPECT-CT**: single photon emission tomography - computed tomography;
- **US**: ultrasound;
- **WMIC**: World Molecular Imaging Congress.
### Additional Table 2C: Characteristics of included studies

<table>
<thead>
<tr>
<th>Study:</th>
<th>Reason for exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramowsky 2009</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Adam 2008</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Adolph 1989</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Alessio 2011</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Andersen 2011</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Angelini 2007</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Arceci 1999</td>
<td>No original research: comments from the editor-in-chief.</td>
</tr>
<tr>
<td>Arceci 2003</td>
<td>No original research: comments from the editor-in-chief.</td>
</tr>
<tr>
<td>Arora 2010</td>
<td>No original research: guest editorial / review.</td>
</tr>
<tr>
<td>Balagué 2008</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Bardi 2009</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Barliev 1988</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Baulieu 1984</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Beierwaltes 1991</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Benz-Bohm 1990</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Berthold 1990</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Bian 2009</td>
<td>Bone scintigraphy.</td>
</tr>
<tr>
<td>Biersack 2010</td>
<td>No original research: guest editorial.</td>
</tr>
<tr>
<td>Binderup 2010</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Bomanji 1987</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Bomanji 1988</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Bomanji 1991</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Bombardieri 2003</td>
<td>No original research: foreword.</td>
</tr>
<tr>
<td>Bonisch 1994</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Bonnin 1994</td>
<td>Not primary diagnostic.</td>
</tr>
<tr>
<td>Bourliere 1992</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Brandon 2011</td>
<td>No original research: review (no eligible studies identified).</td>
</tr>
<tr>
<td>Brendel 1986</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Brisse 2009</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Britton 1997</td>
<td>Letter to the editor (comment).</td>
</tr>
<tr>
<td>Brodeur 1993</td>
<td>No original research: guideline.</td>
</tr>
<tr>
<td>Brunklaus 2012</td>
<td>Unclear which MIBG-scans were 123I-labelled; upon consultation the authors were unable to clarify this.</td>
</tr>
<tr>
<td>Brunklaus 2012a</td>
<td>Same publication as Brunklaus 2012.</td>
</tr>
<tr>
<td>Buck 2008</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Calisti 2012</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Carachi 2002</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Caravel 2001</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Author</td>
<td>Publication Year</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Castel</td>
<td>2006</td>
</tr>
<tr>
<td>Cedenkayevna</td>
<td>2011</td>
</tr>
<tr>
<td>Chan</td>
<td>2001</td>
</tr>
<tr>
<td>Chan</td>
<td>2001a</td>
</tr>
<tr>
<td>Chatal</td>
<td>1984</td>
</tr>
<tr>
<td>Chu</td>
<td>2011</td>
</tr>
<tr>
<td>Clarke</td>
<td>2001</td>
</tr>
<tr>
<td>Corbett</td>
<td>1991</td>
</tr>
<tr>
<td>Corbett</td>
<td>1991a</td>
</tr>
<tr>
<td>Dabasi</td>
<td>1989</td>
</tr>
<tr>
<td>Dalmau</td>
<td>2008</td>
</tr>
<tr>
<td>Dessner</td>
<td>1993</td>
</tr>
<tr>
<td>Dhir</td>
<td>2010</td>
</tr>
<tr>
<td>Diez</td>
<td>2006</td>
</tr>
<tr>
<td>Dirisamer</td>
<td>2008</td>
</tr>
<tr>
<td>Durak</td>
<td>2002</td>
</tr>
<tr>
<td>Eckelman</td>
<td>2007</td>
</tr>
<tr>
<td>Edeling</td>
<td>1987</td>
</tr>
<tr>
<td>Ell</td>
<td>2006</td>
</tr>
<tr>
<td>Fischer</td>
<td>1993</td>
</tr>
<tr>
<td>Franzius</td>
<td>2006</td>
</tr>
<tr>
<td>Franzius</td>
<td>2009</td>
</tr>
<tr>
<td>Frappaz</td>
<td>2000</td>
</tr>
<tr>
<td>Frappaz</td>
<td>2004</td>
</tr>
<tr>
<td>Freeman</td>
<td>2007</td>
</tr>
<tr>
<td>Freeman</td>
<td>2011</td>
</tr>
<tr>
<td>Fukuoka</td>
<td>2011</td>
</tr>
<tr>
<td>Fukuoka</td>
<td>2011a</td>
</tr>
<tr>
<td>Garaventa</td>
<td>2001</td>
</tr>
<tr>
<td>Garaventa</td>
<td>2008</td>
</tr>
<tr>
<td>Garcoa-Pena</td>
<td>2010</td>
</tr>
<tr>
<td>Giammarile</td>
<td>1998</td>
</tr>
<tr>
<td>Giammarile</td>
<td>2000</td>
</tr>
<tr>
<td>Gilday</td>
<td>1990</td>
</tr>
<tr>
<td>Goo</td>
<td>2006</td>
</tr>
<tr>
<td>Gruner</td>
<td>1990</td>
</tr>
<tr>
<td>Guerra</td>
<td>1990</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hahn 2003</td>
<td>Letter to the editor (comment on a study not reporting on 123I-MIBG).</td>
</tr>
<tr>
<td>Hahn 2004</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Hammami 2007</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Han 2007</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Hattner 1988</td>
<td>No original research: review (no eligible studies identified).</td>
</tr>
<tr>
<td>Hausegger 1989</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Haynie 1993</td>
<td>No original research: editorial.</td>
</tr>
<tr>
<td>Hero 2001</td>
<td>Unclear which MIBG-scans were 123I-labelled; upon consultation the authors were unable to clarify this.</td>
</tr>
<tr>
<td>Heston 2010</td>
<td>Letter to the editor (comment on a study already assessed in this review (Sharp 2009).</td>
</tr>
<tr>
<td>Hildebrand 2007</td>
<td>No original research: editorial.</td>
</tr>
<tr>
<td>Hoefnagel 1995</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Ikekubo 1994</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Jacobs 1990</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Jadvar 2005</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Jofre 2007</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Kairemo 1998</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Kaste 2008</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Kaste 2008a</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Keidar 2003</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Kim 2006</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Kimmig 1984</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Kimmig 1985</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kimmig 1985a</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kimmig 1985b</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kleis 2009</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Klingebiel 1992</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Knight 1996</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Koizumi 1994</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Krausz 2006</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Kroiss 2011</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kroiss 2012</td>
<td>Letter to the editor (comment on a study already assessed in this review (Kroiss 2011).</td>
</tr>
<tr>
<td>Kumar 1988</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Kumar 2008</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kumar 2010</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Kumar 2011</td>
<td>Patients older than 18 years old.</td>
</tr>
<tr>
<td>Kushner 2001</td>
<td>Less than 10 patients with a MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Kushner 2006</td>
<td>No original research: highlight.</td>
</tr>
<tr>
<td>Kushner 2009</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kushner 2009a</td>
<td>No original research: reply.</td>
</tr>
<tr>
<td>Ladenstein 1993</td>
<td>Study was not primary diagnostic (therapy).</td>
</tr>
<tr>
<td>Ladenstein 2011</td>
<td>The same study as Lewington 2011.</td>
</tr>
<tr>
<td>Ladenstein 2012</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Larcos 1996</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Lastoria 1993</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Le Neel 1991</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Lesslie 2007</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Leung 1997</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Lewington 2009</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Lewington 2011</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Ley 2011</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Limouris 1997</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Lucignani 2011</td>
<td>No original research: review (no eligible studies identified).</td>
</tr>
<tr>
<td>Lumbroso 1990</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Ma 2007</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Mastrangelo 1987</td>
<td>No original research: summary MIBG symposium.</td>
</tr>
<tr>
<td>Matheja 2001</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Matthay 2003</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Matthay 2003a</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>McCloskey 2010</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>McEwan 1986</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Melzer 2011</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Mena Bares 2009</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Messina 1992</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Messina 2006</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Miceli 1986</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Mitjavila 1991</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Mitjavila 2002</td>
<td>No original research: editorial.</td>
</tr>
<tr>
<td>Mitty 1985</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Montravers 1993</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Murphy 2008</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Nakai 1997</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Ng 1993</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Nguyen 2010</td>
<td>Letter to the editor (comment on a study already assessed in this review (Sharp 2009)).</td>
</tr>
<tr>
<td>O’Hara 1999</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Okuyama 2001</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Author</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Okuyama 2002</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Okuyama 2003</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Pein 1995</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Peng 2010</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Perel 1999</td>
<td>Unclear which MIBG-scans were 123I-labelled; upon consultation the authors were unable to clarify this.</td>
</tr>
<tr>
<td>Petjak 1997</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Pinto 2010</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Plowman 1997</td>
<td>Letter to the editor (comment).</td>
</tr>
<tr>
<td>Priestley 1993</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Pritchard 1988</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Pritchard 2002</td>
<td>Letter to the editor (comment on a study already assessed in this review (Brodeur 1993)).</td>
</tr>
<tr>
<td>Quigley 2005</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Reavey 2010</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Regelink 2002</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Reuland 2001</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Robbins 2000</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Roh 2008</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Rozovsky 2008</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Rubello 2007</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Rufini 1995</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Rufini 1996</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Saadullah 2009</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Sano 2012</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Sasajima 2006</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Satharasinghe 2009</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Sauer 1985</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Sautter-Bihl 1991</td>
<td>Unclear which MIBG-scans were 123I-labelled; upon consultation the authors were unable to clarify this.</td>
</tr>
<tr>
<td>Scanga 2004</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Schaffer 1991</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Shammas 2009</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Shapiro 1990</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Shapiro 1993</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Shapiro 1994</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Sharp 2008</td>
<td>No original research: review (no eligible studies identified).</td>
</tr>
<tr>
<td>Shulkin 1995</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Shulkin 1996</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Sisson 1986</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Sutton 1982</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Taggart 2009</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Tahir 2009</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Troncone 1990</td>
<td>131I-MIBG.</td>
</tr>
<tr>
<td>Vanchieri 1993</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Vatankulu 2011</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Volchenbourn 2009</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>Less than 10 patients with a 123I-MIBG scan at diagnosis.</td>
</tr>
<tr>
<td>Weckesser 2009</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Yang 2003</td>
<td>Included patients not suspected for neuroblastoma.</td>
</tr>
<tr>
<td>Yanik 2010</td>
<td>Study was not primary diagnostic.</td>
</tr>
<tr>
<td>Zerva 2005</td>
<td>No original research: review.</td>
</tr>
<tr>
<td>Zhang 2009</td>
<td>No original research: review.</td>
</tr>
</tbody>
</table>
Chapter 2

Appendix 1: Search strategy used in PubMed

1. For neuroblastoma the following MeSH headings and text words were used:

   (((neuroblastoma) OR (neuroblastos) OR (neuroblast*)) OR (ganglioneuroblastoma) OR (ganglioneuroblastomas) OR (ganglioneuroblast*)) OR ((neuroepithelioma) OR (neuroepitheliomas) OR (neuroepitheliom*)) OR ((esthesioneuroblastoma) OR (esthesioneuroblastomas) OR (esthesioneuroblastom*)) OR (Peripheral Primitive Neuroectodermal Tumors OR Peripheral Primitive Neuroectodermal Neoplasm OR Primitive Neuroectodermal Tumor, Extracranial OR Neuroectodermal Tumor, Peripheral OR Neuroectodermal Tumors, Peripheral OR Peripheral Neuroectodermal Tumor OR Peripheral Neuroectodermal Tumors OR Tumor, Peripheral Neuroectodermal OR Tumors, Peripheral Neuroectodermal OR (pPNET OR PNET OR PNET*) OR Peripheral Primitive Neuroectodermal Tumor OR Peripheral Primitive Neuroectodermal Tumour OR Extracranial Primitive Neuroectodermal Tumor OR Extracranial Primitive Neuroectodermal Tumour OR Extracranial Primitive Neuroectodermal Tumors OR Extracranial Primitive Neuroectodermal Tumours OR Neuroectodermal Neoplasm, Peripheral Primitive OR Neuroectodermal Tumor, Peripheral Primitive) OR (Esthesioneuroblastomas, Olfactory OR Olfactory Esthesioneuroblastoma OR Olfactory Esthesioneuroblastomas OR Esthesioneuroblastoma, Paranasal Sinus-Nasal Cavity OR Esthesioneuroblastoma, Paranasal Sinus Nasal Cavity OR Neuroblastoma, Olfactory OR Neuroblastomas, Olfactory OR Olfactory Neuroblastomas OR Paranasal Sinus-Nasal Cavity Esthesioneuroblastoma OR Paranasal Sinus Nasal Cavity Esthesioneuroblastoma OR Aesthesioneuroblastoma OR Aesthesioneuroblastomas OR Olfactory Neuroblastoma)

2. For MIBG scintigraphy or PET imaging the following MeSH headings and text words were used:

   (MIBG OR Iodine-123 Metaiodobenzylguanidine Imaging OR Iodine 123 Metaiodobenzylguanidine Imaging* OR Metaiodobenzylguanidine Metabolites OR Metaiodobenzylguanidine (ketone) OR Metaiodobenzylguanidine OR Metaiodobenzylguanidine scintigraphy OR Metaiodobenzylguanidine scintigraphy*) OR

   (123I-mIBG) OR (3 Iodobenzylguanidine OR meta-Iodobenzylguanidine OR meta Iodobenzylguanidine OR meta-Iodobenzylguanidine OR m-Iodobenzylguanidine OR m-Iodobenzylguanidine OR (Iobenguane AND (131I) OR (3-Iodo- AND (131I) AND benzyl) AND guanidine) OR 3-Iodobenzylguanidine, 123I Labeled OR 123I Labeled 3-Iodobenzylguanidine OR 3 Iodobenzylguanidine, 123I Labeled OR meta-Iodobenzylguanidine OR meta Iodobenzylguanidine OR m-Iodobenzylguanidine OR m-Iodobenzylguanidine OR m-Iodobenzylguanidine OR m-Iodobenzylguanidine OR Iobenguane (131I) OR (3-Iodo-(131I)benzyl)guanidine) OR (77679-27-7[rn])

   OR
(Positron Emission Tomography OR Positron Emission Tomograph* OR Tomography, Positron-Emission OR Tomography, Positron Emission OR PET Scan OR PET Scans OR Scan, PET OR Scans, PET OR PET Scan* OR PET)
OR
(SPECT OR SPECT-CT OR 18F-FDG-PET-CT OR Single Photon Emission Computed Tomography OR Single photon emission computerized tomography OR Single photon emission computerised tomography OR Tomography, Emission-Computed, Single-Photon)
OR

3. (1 AND 2) NOT case reports [pt]
* = zero or more characters
Appendix 2: Search strategy used in EMBASE

1. For **neuroblastoma** the following Emtree terms and text words were used:
   1. exp neuroblastoma/
   2. (neuroblastoma or neuroblastomas or neuroblast$).mp.
   3. (ganglioneuroblastoma or ganglioneuroblastomas or ganglioneuroblast$).mp.
   4. exp olfactory neuroepithelioma/ or exp neuroepithelioma/
   5. (neuroepithelioma or neuroepitheliomas or neuroepitheliom$).mp.
   6. exp esthesioneuroblastoma/
   7. (esthesioneuroblastoma or esthesioneuroblastomas or esthesioneuroblastom$).mp.
   8. exp neuroectoderm tumor/ or (peripheral primitive neuroectodermal tumors or peripheral primitive neuroectodermal tumours).mp.
   9. (peripheral primitive neuroectodermal neoplasm or peripheral primitive neuroectodermal neoplasms).mp.
   10. (peripheral neuroectodermal tumor or peripheral neuroectodermal tumors or peripheral neuroectodermal tumour or peripheral neuroectodermal tumours).mp.
   11. (pPNET or PNET or PNET$).mp.
   12. (peripheral primitive neuroectodermal tumor or peripheral primitive neuroectodermal tumour).mp.
   13. (extracranial primitive neuroectodermal tumor or extracranial primitive neuroectodermal tumors or extracranial primitive neuroectodermal tumour or extracranial primitive neuroectodermal tumours).mp.
   14. (olfactory esthesioneuroblastoma or olfactory esthesioneuroblastomas).mp.
   15. (olfactory neuroblastoma or olfactory neuroblastomas).mp.
   16. (paranasal sinus-nasal cavity esthesioneuroblastoma or paranasal sinus nasal cavity esthesioneuroblastoma).mp.
   17. (esthesioneuroblastoma or esthesioneuroblastomas).mp.
   18. or/1-17

2. For **MIBG scintigraphy** or **PET** imaging the following Emtree terms and text words were used:
   1. exp “(3 iodobenzyl)guanidine i 123”/ or exp “(3 iodobenzyl)guanidine”/ or exp “(3 iodobenzyl)guanidine i 131”/
   2. MIBG.mp.
   3. (Iodine-123 Metaiodobenzylguanidine Imaging or Iodine-123 Metaiodobenzylguanidine Imag$).mp.
   4. (Metaiodobenzylguanidine or Metaiodobenzylguanidin$).mp.
   5. (Metaiodobenzylguanidine scintigraphy or Metaiodobenzylguanidine scintigraph$).mp.
   6. 123I-mlBG.mp.
7. 3 Iodobenzylguanidine.mp.
8. (meta-Iodobenzylguanidine or meta lodo benzylguanidine).mp.
9. Iobenguane.mp.
10. (m-Iodobenzylguanidine or m lodo benzylguanidine).mp.
11. (3-Iodo- and 131I and benzyl and guanidine).mp.
12. 123I Labeled 3-Iodobenzylguanidine.mp.
13. (meta-Iodobenzylguanidine or meta lodo benzylguanidine).mp.
14. (m lodo benzylguanidine or m-lodobenzylguanidine).mp.
15. 77679-27-7.rn.
16. or/1-15
17. exp positron emission tomography/ or exp fluorodeoxyglucose f18/
18. (positron emission tomography or positron emission tomograph$).mp.
19. (PET scan or PET scans or PET scan$ or PET).mp.
20. (SPECT or SPECT-CT or 18F-FDG-PET-CT).mp.
21. exp single photon emission computer tomography/
22. (single photon emission computed tomography or single photon emission computerized tomography or single photon emission computerised tomography).mp.
23. single photon emission computed radionuclide tomography.mp.
24. (Single Photon Emission CT Scan or Single Photon Emission CT Scan$).mp.
27. 18 F-FDG-PET or 18-fluorodeoxy$ or 18fluorodeoxy$ or fdgpet or fdg pet or 18f fdg$).mp.
30. (Single photon emission computerized tomograph$ or Single photon emission computerised tomograph$).mp.
32. or/17-30
33. 16 or 31

3. (1 AND 2) not (case report or case reports)
REFERENCES TO STUDIES

Included studies

**Biasotti 2000**

**Gordon 1990**

**Hashimoto 2003**

**Hugosson 1999**

**Labreveux 1994**

**Lvanova 2008**

**Naranjo 2011a**

**Neuenschwander 1987**

**Pfluger 2003**

**Piccardo 2012**

**Sharp 2009**

Excluded studies

**Abramowsky 2009**

**Adam 2008**

**Adolph 1989**
**Alessio 2011**

**Andersen 2011**

**Angelini 2007**

**Arceci 1999**

**Arceci 2003**

**Arora 2010**

**Balaguer 2008**

**Bardi 2009**

**Barliev 1988**

**Baulieu 1984**

**Beierwaltes 1991**

**Benz-Bohm 1990**

**Berthold 1990**

**Bian 2009**

**Biersack 2010**

**Binderup 2010**

**Bomanji 1987**
Bomanji 1988

Bomanji 1991

Bombardieri 2003

Bonisch 1994

Bonnin 1994

Bourliere 1992

Brandon 2011

Brendel 1986

Brisse 2009

Britton 1997
Britton KE. Positive MIBG scanning at the time of relapse in neuroblastoma which was MIBG negative at diagnosis. British Journal of Radiology 1997;70:969.

Brodeur 1993

Brunklaus 2012

Brunklaus 2012a

Buck 2008

Carachi 2002

Caravel 2001

Castel 2006

Cedenkayevna 2011
**Chan 2001**

**Chan 2001a**

**Chatal 1984**
Chatal JF, Coornaert S, Rialland X. Diagnostic scintigraphy of neuroblastomas with $^{123}$I-labeled (3-iodobenzyl)guanidine. Journal de Biophysique et Medecine Nucleaire 1984;8:156-7.

**Chu 2011**

**Clarke 2001**

**Corbett 1991**

**Corbett 1991a**

**Dabasi 1989**

**Dalmau 2008**

**Dessner 1993**

**Dhir 2010**

**Diez 2006**

**Dirisamer 2008**

**Durak 2002**

**Eckelman 2007**

**Edeling 1987**

**Ell 2006**

**Fischer 1993**

**Franzius 2006**
Franzius 2009

Frappaz 2000

Frappaz 2004

Freeman 2007

Franzius 2009

Giammarile 1998

Giammarile 2000

Gilday 1990

Garaventa 2008
Han 2007

Hattner 1988

Hausegger 1989

Haynie 1993

Hero 2001
Hero B, Hunneman DH, Gahr M, Berthold F. Evaluation of catecholamine metabolites, mIBG scan, and bone marrow cytology as response markers in stage 4 neuroblastoma. Medical and Pediatric Oncology 2001;36(1):220-3.

Heston 2010
Heston TF. 123I-MIBG versus 18F-FDG: which is better, or which can be eliminated? Journal of Nuclear Medicine 2010;51:330.

Hildebrand 2007

Hoefnagel 1995

Ikekubo 1994

Jacobs 1990

Jadvar 2005

Jofre 2007

Kairemo 1998

Kaste 2008

Kaste 2008a

Keidar 2003

Kim 2006

Kimmig 1984

Kimmig 1985

Kimmig 1985a
Kimmig 1985b

Kleis 2009

Klingebiel 1992

Knight 1996

Koizumi 1994

Krausz 2006

Kroiss 2011

Kroiss 2012

Kumar 1988

Kumar 2008

Kumar 2010

Kumar 2011

Kushner 2001

Kushner 2006

Kushner 2009

Kushner 2009a
MIBG and PET for diagnosing neuroblastoma- a DTA Cochrane systematic review

Ladenstein 1993

Ladenstein 2011

Ladenstein 2012

Larcos 1996

Lastoria 1993

Le Neel 1991

Lesslie 2007

Leung 1997

Lewington 2009

Lewington 2011

Ley 2011

Limouris 1997

Lucignani 2011

Lumbroso 1988

Lumbroso 1990
Ma 2007

Mastrangelo 1987

Matheja 2001

Matthay 2003

Matthay 2003a

McCloskey 2010

McEwan 1986

Melino 1989

Melzer 2011

Mena Bares 2009

Messa 1992

Messina 2006

Miceli 1986

Mitjavila 1991

Mitjavila 2002

Mitty 1985

Montravers 1993
Murphy 2008

Nakai 1997

Ng 1993

Nguyen 2010

O’Hara 1999

Okuyama 2001

Okuyama 2002

Okuyama 2003

Pein 1995

Peng 2010

Perel 1999

Petjak 1997

Pinto 2010

Plowman 1997
Plowman PN. Positive MIBG scanning at the time of relapse in neuroblastoma which was MIBG negative at diagnosis. British Journal of Radiology 1997;70:969.

Priestley 1993

Pritchard 1988

Pritchard 2002
Pritchard J. Re: Commentary by G.J. D’Angio to the article by S. Biasotti et al. Medical and Pediatric Oncology 2002;38:152.
Quigley 2005

Reavey 2010

Regelink 2002

Reuland 2001

Robbins 2000

Roh 2008

Rozovsky 2008

Rubello 2007

Rufini 1995

Rufini 1996

Saadullah 2009

Sano 2012

Sasajima 2006

Satharasinghe 2009

Sauer 1985
CHAPTER 2

Sautter-Bihl 1991

Scanga 2004

Schaffer 1991

Shammas 2009

Shapiro 1990

Shapiro 1993

Shapiro 1994

Sharp 2008

Shulkin 1995

Shulkin 1996

Sisson 1986

Sutton 1982

Taggart 2009

Tahir 2009

Troncone 1990

Vanchieri 1993
Vanchieri C. European cancer center links basic and clinical science. Journal of the National Cancer Institute 1993;85:1370-1.

Vatankulu 2011
Studies awaiting classification

**Abrahamsen 1995**

**Ady 1995**

**Boubaker 2012**

**Claudiani 1995**

**Fania 2011**

**Feine 1987**
CHAPTER 2

Ferris 1992

Fischer 1989

Gelfand 1994

Ginsburg 2012

Goo 2005

Hervas 2001

Ishii 2000

Jacobs 1990a

Kurkure 2012

Lebtahi 1995

Lumbroso 1988a

Moschogiannis 2011

Muckle 2012

Muller-Gartner 1985
Muller-Gartner 1986

Nikolaos 2011

Okuyama 1998

Okuyama 1999

Osmanagaoglu 1993

Paltiel 1994

Parisi 1992

Rathore 2011

Sarkadi 2011

Schilling 2000

Schmiegelow 1989

Sharp 2009a

Suc 1996
**Tahir 2011**


**Turba 1993**


**Vik 2009**


**Yang 2012**


**Young-Seok 2006**


**Ythier 1987**


**OTHER REFERENCES**

**Additional references**

**Bombardieri 2003a**


**Bombardieri 2003b**


**Boubaker 2008**


**Brodeur 1984**


**Brodeur 1988**


**Brodeur 1988a**


**Brodeur 2003**


**Castleberry 1997**

Cohn 2009

Decarolis 2013

Joshi 2000

Jüni 1999

Maris 2007

Maris 2010

Matthay 2010

Monclair 2009

Naranjo 2011

Park 2008

Peuchmaur 2003

Piccardo 2013

RevMan 2011

Shimada 1984

Shimada 1993

Shimada 1999a

Shimada 1999b
MIBG and PET for diagnosing neuroblastoma- a DTA Cochrane systematic review

Shimada 2003

Shore 2008

Siegel 2013

Solanki 1992

Spix 2006

Strenger 2007

Taggart 2008

Vaidyanathan 2008

Whiting 2003

Yalcin 2010

Yanik 2013