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Imaging of Pediatric Neuroblastoma: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper

Hollie A. Lai, MD[1], **Susan E. Sharp, MD**[2], **Aashim Bhatia, MD, MS**[3], **Kelly R. Dietz, MD**[4], **Beth McCarville, MD**[5], **Dhanashree Rajderkar, MD**[6], **Sabah Servaes, MD**[7], **Barry L. Shulkin, MD MBA**[8], **Sudha Singh, MB BS, MD**[9], **Andrew T. Trout, MD**[10], **Pankaj Watal, MD**[11], **Marguerite T. Parisi, MD, MS**[12]

[1.]Department of Radiology, Children's Health Orange County, Orange, CA

[2.]Department of Radiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH

[3.]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA

[4.]Department of Radiology, University of Minnesota, Minneapolis, MN

[5.]Department of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN

[6.]Department of Radiology, University of Florida, Gainesville, FL

[7.]Department of Radiology, West Virginia University Children's Hospital, Morgantown, WV

[8.]Department of Diagnostic Imaging, University of TN Health Science Center, St. Jude Children's Research Hospital, Memphis, TN

[9.]Department of Radiology, Monroe Carrell Jr Children's Hospital, Vanderbilt University, Nashville, TN

[10.]Department of Radiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH

[11.]Department of Radiology, Nemours Children's Hospital, Florida and University of Central Florida College of Medicine, Orlando, FL

[12.]Departments of Radiology and Pediatrics, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, WA

Abstract

CORRESPONDING AUTHOR: Hollie A. Lai, MD, Children's Health Orange County, Department of Radiology, 1201 W. La Veta Ave., Orange, CA 92868, 714) 509-9160 (phone), 714) 509-9078 (fax), hlai@choc.org.

CONFLICT OF INTERESTS:
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Neuroblastoma is the most common extracranial solid neoplasm in children. This manuscript provides consensus-based imaging recommendations for pediatric neuroblastoma patients at diagnosis and during follow-up.

Keywords

Neuroblastoma; Imaging; Staging; Response

INTRODUCTION

Neuroblastoma (NB), the most common extracranial solid neoplasm in children, accounts for approximately 6-8% (1, 2) of all pediatric tumors and 15% of pediatric oncologic deaths (3). The majority (90%) of cases present before 5 years of age (2). Although 65% of NB arise in the abdomen, typically in the adrenal gland, NB can arise anywhere along the sympathetic nervous system (3).

Presenting signs and symptoms are highly variable, ranging from an asymptomatic mass to critical illness. Clinical manifestations may arise secondary to tumor growth, invasion of or mass effect on surrounding structures, the presence of metastatic disease, paraneoplastic syndromes, or autoimmune response (4). Metastatic disease to lymph nodes, bone, bone marrow, or skin is present in approximately 50% of patients at presentation (5).

Prognosis of NB varies widely. Patient age, stage, and various biologic factors present at diagnosis are among the most important prognostic factors in overall survival. Both anatomic and functional imaging are crucial to accurately determine patient stage prior to biopsy or surgery.

IMAGING IN TUMOR STAGING

The International Neuroblastoma Risk Group (INRG) Task Force was formed in 2004 to develop a pre-treatment risk stratification system as well as a new image-based staging system, the International Neuroblastoma Risk Group Staging System (INRGSS), which could then be used to identify homogenous pre-treatment groups for risk-based clinical trials (6,7). The INRG Staging System, which accounts for stage, age, histologic category, grade of tumor differentiation, the status of the MYCN oncogene, chromosome 11q status, and DNA ploidy as well as an image based staging system, is not intended to replace, but rather to be used in conjunction with the International Neuroblastoma Staging System (INSS), the former system where NB staging was based on the extent of surgical tumor excision (6,7).

The INRGSS is a pretreatment staging system based on imaging findings, particularly the presence or absence of image-defined risk factors (IDRFs) and distant metastatic disease (8). 20 IDRFs that make safe, total tumor resection impractical at diagnosis were identified. IDRFs were based on the International Society of Pediatric Oncology European Neuroblastoma Research Network (SIOPEN) “surgical risk factors” which were demonstrated to be highly predictive of event free survival (8, 9). The INRG image-based staging system (INRGSS), modified from Brisse, et al. (10) is categorized in Table 1.

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In the INRGSS, localized disease (L1) or the presence of one or more IDRFs (L2) at diagnosis is the most statistically significant prognostic factor (7). In one study of 661 patients, those with INRGSS stage L2 disease had significantly lower 5-year event-free survival than those with INRGSS stage L1 disease (78% ± 4% versus 90% ± 3%; P .0010) (8).

Combinations of INRGSS stage, tumor histology and biology (MYCN oncogene status, chromosome 11q status, DNA ploidy) and patient age are used to stratify NB patients into low, intermediate, and high-risk groups that determine treatment options (11).

IMAGING AT DIAGNOSIS AND STAGING

According to the current INRG recommendations, diagnostic and staging evaluations of NB must include anatomic imaging with contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI), depending on the primary site of disease (10), and functional imaging with ^{123}I-metaiodobenzylguanidine (^{123}I-mIBG). 18Fluorine-Fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET-CT) is currently recommended for non-mIBG avid tumors (12). (Grade A; SOR: 1.08)

CT or MRI of the primary tumor and adjacent structures is mandatory to identify IDRF's (10). Both CT and MR can adequately identify IDRFs, though the greater soft tissue contrast of MR may provide better characterization of some (10). If not included in imaging of the primary tumor site and adjacent structures, CT of the chest is recommended to define the presence of pulmonary metastatic disease while CT or MRI of the abdomen is recommended to define the presence of hepatic metastases (10). **High B value diffusion weighted imaging may be included in diagnostic MR imaging protocols as it has shown value in differentiating malignant (NB and ganglioneuroblastoma [GNB]) from benign (ganglioneuroma) neuroblastic tumors (13,14). (Grade B; SOR 2.25)** Diffusion imaging may also be useful in detecting small metastases in solid viscera, especially the liver (13,14).

While ultrasound may be initially used to evaluate a suspected mass, it is not useful in tumor staging [10]. (Grade A; SOR 1.0)

^{123}I-mIBG scintigraphy is highly specific (83-100%) and sensitive (88-93%) for NB (15–17); and is recommended by international consensus guidelines for staging, therapeutic response monitoring, prognostication, and determining eligibility for ^{131}I-mIBG therapy (18**). Single-photon emission computed tomography (SPECT) or SPECT/CT should be performed, where available, due to superior sensitivity and improved anatomic localization, allowing for the differentiation of physiologic from pathologic uptake** (12, 19). **(Grade A; SOR: 1.08) In addition to a qualitative interpretation, a semiquantitative score using either the Curie or SIOPEN method based on planar imaging, should be included in the final report** (12,18). **The mIBG-avid or non-avid nature of the tumor and the extent of mIBG-avid disease based on the semiquantitative score at initial diagnosis have significant prognostic value in high-risk patients** (12, 20, 21, 22). **(Grade A; SOR 1.42)**

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Approximately 10% of NB lack, or have poor, mIBG avidity (16,18). In such cases, a ^{99m}Technetium methylene diphosphonate (^{99m}Tc-MDP) bone scan can be performed if time-critical and ^{18}F-FDG, the recommended functional imaging alternative, is not available. When ^{18}F-FDG is performed, true whole body (vertex to toes) imaging should be performed.

FDG PET/CT should not be used in place of mIBG when there is mIBG avid disease because it has a lower sensitivity and specificity for neuroblastoma (23–27) and can result in the misinterpretation of disease burden when FDG accumulates in non-malignant lesions. Identification of marrow involvement by NB, usually apparent on ^{123}I-mIBG scans, can be difficult on FDG scans due to physiologic marrow uptake and marrow changes that can occur as a result of chemotherapy or granulocyte colony stimulating factor (24). Furthermore, FDG PET/CT cannot be used to identify candidates for ^{131}I-mIBG therapy. See tables 2, 3, 4, and 5.

IMAGING AT FOLLOW-UP

The schedule for follow-up imaging will depend on individual treatment regimens and whether patients have low, intermediate, or high-risk disease (18).

Anatomic imaging is used to determine the size of measurable lesions (i.e., the primary tumor and sites of soft tissue disease) (28). 3D measurements on anatomic imaging are more accurate, with underestimation of response on 1D and 2D measurements (29).

The same modality used at diagnosis should be used at all follow-up time points. If MRI is utilized, the inclusion of high B-value diffusion weighted imaging is suggested on all follow-up scans (13). Anatomic imaging is not used to evaluate bone disease, as bone lesions may not decrease in size when assessed by CT or MRI, even when there is no remaining viable tumor. Bone lesions without an associated soft tissue mass are non-measurable while extramedullary soft tissue components of bone lesions are measurable using the same criteria as soft tissue lesions (28).

Functional imaging is used to evaluate therapeutic response in both the primary tumor and sites of soft tissue and osteomedullary metastatic disease (6, 12, 18, 28). Functional imaging is key in differentiating postoperative changes from residual tumor at sites of resected soft tissue disease (25). The semiquantitative scoring method (Curie or SIOPEN) used at baseline should be used at follow-up (21, 28). Additionally, a “relative” Curie or SIOPEN osteomedullary score should be reported. The “relative bone score” is the ratio of the Curie or SIOPEN scores at response assessment to those at diagnosis, without the soft tissue component. If FDG PET/CT is being used, a tissue biopsy of at least one FDG avid may be needed to confirm that the lesion is NB or GNB (28).

TUMOR RESPONSE ASSESSMENT

Utilizing the International Neuroblastoma Response Criteria (6 28) response of the primary tumor and metastatic deposits is determined using both anatomic imaging with CT or MR

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as well as functional imaging with mIBG or FDG if the tumor is non-mIBG avid (28) in addition to bone marrow aspirate and biopsy (Table 6). (Grade A; SOR 1.17)

Response to treatment is strongly associated with outcome. In the COG ANBL0531 (NCT00499616) study, 6 of 20 intermediate-risk patients with a poor response to initial therapy subsequently developed progressive or recurrent disease, and one died of disease (30). A Curie or SIOPEN score greater than 2 or 3, respectively, after completion of induction therapy predicts a poor prognosis for patients with MYCN-nonamplified high-risk tumors while a Curie score greater than 0 is associated with a worse outcome in those with MYCN-amplified disease (21, 22, 31).

Surveillance imaging

There is no uniform consensus for timing of surveillance imaging. It is typically based on risk group and often protocol driven.

Anatomic Imaging:

Low-risk, congenital or localized, abdominal, or pelvic NB without risk of epidural extension can be followed by ultrasound every 1-2 months for one year and then yearly for 3 years (32, 33).

Intermediate risk NB with favorable biology and without risk of epidural extension can be followed with ultrasound every 3 months for the first year, every 4 months for one year, then yearly for 3 years. (32)

Contrast enhanced CT (CECT), when used, should include the primary site in addition to adjacent areas of the body. Intermediate risk NB with unfavorable biology, or any tumor with risk for epidural extension, should be followed by MRI. In intermediate risk patients, MR and CT should be performed in conjunction with scintigraphic studies every 3 months for one year, every 6 months for one year, then yearly for 3 years. In high-risk patients, anatomic and functional imaging should be performed every 3 months for 2 years, every 4 months for a year, then yearly for 3 years. (32)

Scintigraphic studies:

Due to its lower sensitivity for detecting relapse compared with ^{123}I-mIBG, whole-body ^{99m}Tc-MDP bone scan is not indicated for routine surveillance (34). (Grade A; SOR 1.17)

In high-risk NB, ^{123}I-mIBG with SPECT/CT has been shown to improve detection of disease, particularly after relapse. In patients with a history of non-mIBG avid disease, ^{18}F-FDG PET/CT is currently recommended for surveillance.

The timing of surveillance studies should be customized for each patient's risk for relapse as described above. Surveillance is typically initiated 3 years from the start of treatment in the setting of remission (34).

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Imaging late effects:

Surgery, chemotherapy, radiation therapy, bone marrow transplantation, and ^{131}I-mIBG therapy in patients with high-risk NB- have known consequences. Recognizing the sequela of therapy is critical for both the quality and duration of life of the cancer survivor. Imaging can identify some late treatment effects not evident by physical exam or laboratory studies.

Many chronic health conditions that develop because of treatment are related to the location of the primary tumor or metastatic disease and the type of surgery or chemotherapy the patient received. A well-known late effect of treatment for NB is the development of scoliosis secondary to radiation therapy to the paraspinal region. ^{131}I-mIBG therapy alone or in conjunction with bone marrow transplant can cause hepatotoxicity. Hypothyroidism occurs in up to 10% of patients by one year after ^{131}I-mIBG therapy, despite the use of thyroid blockade (35).

Perhaps the most devastating late effect is the development of secondary malignancy, which occurs in 3-12% of survivors of childhood cancers (36, 37). The risk of second malignancies in patients treated for NB increases with exposure to radiation therapy. In NB patients treated with ^{131}I-mIBG therapy, the incidence of secondary malignancy, typically acute myelogenous leukemia or myelodysplastic syndrome is as high as 3% by 3 years post treatment (35). Surveillance imaging for second primary malignancies should be tailored to the patient's risk level (38).

Future Directions in Imaging Neuroblastoma

CT, MRI, and ^{123}I-mIBG planar and SPECT/CT imaging will remain essential imaging tools for the diagnosis, staging, therapeutic response monitoring and surveillance of patients with neuroblastoma. ^{123}I-mIBG imaging provides prognostic information and is used to select patients appropriate for ^{131}I-mIBG therapy.

Newer PET agents may provide several advantages to ^{123}I-mIBG planar and SPECT/CT imaging including higher spatial resolution, improved tumor-to- background ratios, same day administration and imaging, quantification of tracer uptake, and much shorter imaging times, which should decrease motion artifacts and the length of sedation (27). The increased sensitivity afforded by their use may more accurately quantify disease burden, leading to improvements in staging, prognostication, and treatment management.

^{68}-Gallium DOTATATE and other DOTA peptides

^{68}Ga-DOTATATE, ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC, are somatostatin analogues suitable for PET imaging. Most neuroblastomas and other neuroendocrine tumors such as pheochromocytoma express somatostatin receptor type 2 (SSRT2) (39–41). In limited studies to date, ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC appeared to be more sensitive that ^{123}I-mIBG in the detection of NB lesions (42–45). Physiologic radiotracer uptake in the spleen, adrenal glands, liver, pancreas, particularly the uncinate process, gut and urinary tract may hinder identification of small volume disease (27). ^{68}Ga-DOTA peptide imaging may be negative in tumors with low SSRT expression as can occur in poorly differentiated

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tumors (45). False positives findings can occur when benign processes, including infection, inflammation, or sites of osteoblastic activity, mimic focal metastatic lesions. (27, 46)

Initial reports suggested that ^{68}Ga-DOTA peptides may be safe and feasible for use in children. Their short half-life allows for 1-day imaging protocols and results in a lower radiation dose than either ^{123}I- or ^{18}F-labeled tracers (27). Further, ^{68}Ga-DOTA positive patients can be considered for treatment with peptide receptor radionuclide therapy with Lutetium-177 DOTATATE whose safety and efficacy were demonstrated in small groups of neuroblastoma patients with relapsed or refractory disease (42, 47, 48). Despite several apparent advantages, as well as the increasing, off-label use of these agents in the evaluation of non-mIBG-avid neuroblastoma patients, there is not yet an established role for ^{68}Ga-DOTA peptide imaging in the current NB imaging guidelines (27).

^{18}F Fluorodihydroxyphenylalanine (^{18}F-FDOPA)

When labeled with ^{18}F, FDOPA, the precursor of dopamine, norepinephrine and epinephrine, localizes in sites of increased catecholamine metabolism (49). This agent is used to image neuroendocrine tumors including NB, often as an alternative to ^{68}Ga-DOTA peptide imaging (50). Early, prospective studies in NB reported increased lesion detection with ^{18}F-FDOPA compared to ^{123}I-mIBG planar imaging (51, 52). A more recent study comparing ^{18}F-FDOPA to ^{123}I-mIBG imaging with planar and SPECT/CT imaging for NB confirmed the increased sensitivity of ^{18}F-FDOPA in the detection of soft tissue as well as small osseous lesions, both at diagnosis and after chemotherapy (53). These same authors (53) as well as Lu, et al (51) also demonstrated that ^{18}F-FDOPA may reveal persistent disease in the face of a negative ^{123}I-mIBG scan. Currently ^{18}F-FDOPA does not have a role in neuroblastoma imaging guidelines.

^{124}I-mIBG

mIBG labeled with ^{124}I, has a similar uptake mechanism and biodistribution to ^{123}I-mIBG but demonstrates increased sensitivity in disease detection (54, 55). The routine use of ^{124}I-mIBG in children with NB is problematic as, even with dose modifications (56), it delivers a high patient radiation dose compared to ^{123}I-mIBG. Other issues with ^{124}I-mIBG include poorer image quality compared to ^{18}F or ^{68}Ga; 2-day imaging protocol, limited availability, and high cost (27). However, given its' long half-life, ^{124}I-mIBG could prove useful in personalized dosimetry estimation for ^{131}I-mIBG therapy (57).

^{18}F-mFBG

Meta [^{18}F] Fluorobenzylguanidine (^{18}F-mFBG), a fluorinated mIBG analog labeled with ^{18}F, has a similar uptake mechanism and biodistribution to that of ^{123}I-mIBG with the added benefits of fast pharmacokinetics and faster renal clearance, resulting in a 3-fold higher tumor uptake of the tracer compared to ^{123}I-mIBG (58). While human experience with this tracer is limited, advantages of its use include a same day imaging protocol and patient radiation exposures similar or lower than ^{123}I-mIBG (58). An early report by Pandit-Tasker et al (59) showed that ^{18}F-mFBG PET/CT was superior to ^{123}I-mIBG, demonstrating all lesions detected on ^{123}I-mIBG scans in addition to 59 additional lesions in 5 patients with neuroblastoma and 5 patients with pheochromocytoma. A single case reported by Pauwels et

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al (60), also suggested improved sensitivity and image resolution of ^{18}F-mFBG compared to ^{123}I-mIBG.

More data is needed to clarify the respective roles of ^{123}I-mIBG, ^{18}F-FDG, and the non-FDG PET agents in the management of patients with NB.

Finally, we can anticipate the increased use of theranostic agents such as ^{131}I-mIBG and potentially, ^{177}Lu-Dotatate in the treatment of high-risk NB patients in future clinical trials.

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ABBREVIATONS

NB	Neuroblastoma
INRG	International Neuroblastoma Risk Group
INRGSS	International Neuroblastoma Risk Group Staging System
INSS	International Neuroblastoma Staging System
IDRFs	Image-Defined Risk Factors
SIOPEN	Society of Pediatric Oncology EuropeanNeuroblastoma Research Network
CECT	Contrast-Enhanced Computed Tomography
MRI	Magnetic Resonance Imaging
^{123}I-mIBG	^{123}I-metaiodobenzylguanidine
^{18}F-FDG PET-CT	18Fluorine-Fluorodeoxyglucose Positron Emission Tomography/CT
GNB	Ganglioneuroblastoma
SPECT	Single-Photon Emission Computed Tomography
^{99m}Tc-MDP	^{99m}Technetium methylene diphosphonate
^{18}F-FDOPA	^{18}F Fluorodihydroxyphenylalanine
^{18}F-mFBG	Meta [^{18}F] Fluorobenzylguanidine

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Table 1

International Neuroblastoma Risk Group Staging System (INRGSS)

Tumor Stage	Description
L1	Localized tumor not involving vital structures (no IDRFs present) and confined to one body compartment.
L2	Local-regional tumor (may be ipsilaterally contiguous within body compartments) with one or more IDRFs.
M	Distant metastatic disease (except stage MS).
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow (involving less than 10% of all nucleated cells in culture smears or biopsy samples).

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Table 2:

Advantages and disadvantages of each modality for the evaluation of the primary tumor.

Procedure Name	Timepoint(s)	Advantage(s)	Disadvantage(s)
Ultrasound	• Diagnosis	• Readily available • Portable • No ionizing radiation	• Cannot be used for staging
Computed Tomography	• Diagnosis • Staging • Therapeutic response monitoring • Surveillance	• Accessible • Rapid image acquisition • Excellent spatial resolution • Multiplanar capabilities • Assess relationship between mass and adjacent vessels as well as vessel patency • Necessary for detection of lung lesions • Frequent surgeon preference	• Exposure to ionizing radiation • Risk of IV contrast
Magnetic Resonance Imaging	• Diagnosis • Staging • Therapeutic response monitoring • Surveillance	• Exceptional contrast resolution • Multiplanar capabilities • No ionizing radiation • Excellent lesion detection and characterization • Valuable for intraspinal extension	• Motion sensitive • Frequent need for sedation • Frequent artifacts • Difficult to detect small calcified lesions • Risk of IV contrast
^{18}F FDG PET	• Diagnosis • Staging • Therapeutic response monitoring • Surveillance	• Useful for non- or poorly mIBG avid NB	• Exposure to ionizing radiation • Frequent need for sedation
^{123}I mIBG	• Diagnosis • Staging • Therapeutic response monitoring • Prognostication in high-risk groups • Determination of eligibility for ^{131}I mIBG therapy • Surveillance	• Highly specific (83-100%) and sensitive (88-93%).	• Exposure to ionizing radiation • Frequent need for sedation (with use of SPECT or SPECT/CT)

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Table 3a:

Suggested MR protocol for evaluation of a primary tumor located in the chest, abdomen, and/or pelvis.

Plane	Sequence	Contrast phase	Coverage	Required/ Optional	Comment
Coronal	T1	Noncontrast	Site of primary tumorin the chest and/ orabdomen/pelvis)	Required	Slicethickness/Gap 5 skip 1
Coronal	T2 RTr FS	Noncontrast	“	Required	Consider STIR if fat saturation is inhomogeneous
Axial	SSFSE No FS	Noncontrast	“	Required	Slicethickness/Gap 5 skip 1
Axial	T2 RTr FS	Noncontrast	“	Required	
Axial	DWI	Noncontrast	“	Required	3 b values: 10, 100, 800. Diffusion direction = ALL.
Axial	T1 FS	Pre-contrast	“	Required	Free breathingor breath hold
Axial	T1 FS	Post-contrast	“	Required	Free breathing or breath hold
Coronal	T1 FS	Post-contrast	“	Required	Free breathing or breath hold

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Table 3b:

Suggested MR protocol for evaluation of a primary tumor located in the neck.

Plane	Sequence	Contrast phase	Coverage	Required/Optional	Comment
Sagittal	T2	Noncontrast	Site of primary tumorin the neck	Required	Slicethickness/Gap 5 skip 1
Coronal	IR	Noncontrast	“	Required	Slicethickness/Gap 5 skip 1-2
Axial	IR	Noncontrast	“	Required	Slicethickness/Gap 5 skip 1-2
Axial	T1	Pre-contrast	“	Required	Slicethickness/Gap 5 skip 1-1.5
Axial	DWI	Pre-contrast	“	Required	2 b values: 0 and 1000.
Axial	T1 FS	Post-contrast	“	Required	Slice thickness/Gap 5 skip 1-2
Coronal	T1 FS	Post-contrast	“	Required	Slicethickness/Gap 5 skip 1-2

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Table 4:

Suggested CT protocol for evaluation of the primary tumor and image-defined risk factors.

Name	Coverage	Slice thickness	Contrast phase	Reformat planes/types/ reconstruction kernel	Comment
CT	Site of primary tumor (ie neck, chest, and/or abdomen/pelvis) and chest if not site of primary tumor	3 – 5 mm (based on body region and patient size)	Post contrast	Coronal & sagittal MPR	

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Table 5:

Suggested nuclear medicine protocols for evaluation of neuroblastoma

Study name	Patient prep	Radiopharmaceutical	Dose range	Delivery	Time from dose to imaging	Imaging acquisition	Comment
^{123}I mIBG	Pretreatment with saturated solution of potassium iodide or potassium iodate tablets for thyroid blockade (dosing varies by local practice) The EANM Paediatric Committee guidelines recommend the following: Beginning on the day before tracer injection until the day after injection, children from one month to three years should receive 32 mg potassium iodide daily, from three to thirteen years 65 mg, and over this age 130 mg daily. Newborns receive 16 mg potassium iodide only on the day before tracer injection (61).	^{123} I-MIBG (Meta-iodobenzylguanindine)	0.14 mCi/kg (Minimum dose 1 mCi Maximum dose 10 mCi) (62)	Intravenous	24 hours and possibly 48 hours (if needed)	Planar: Anterior and posterior whole body images are obtained (can be spot images of overlapping body segments if needed). Lateral views of the skull (if needed). SPECT or SPECT/CT: Centered on areas where further information is needed 120 projections, 3 degree steps, continuous or step-and-shoot mode, 25–35 seconds/step, 128 × 128 matrix. CT performed as a non-contrast localization CT or as a contrast enhanced diagnostic CT with appropriate pediatric CT settings.	Medium energy collimators may be used to improve image quality.
F-18-FDG	NPO for 4-6 hours to decrease serum glucose and insulin levels. Warm the patient for 30 – 60 minutes prior to FDG injection to minimize uptake in brown adipose tissue.	F-18-Fluorodeoxyglucose (FDG)	0.10-0.14 mCi/kg Minimum dose 0.7 mCi (62)	Intravenous	~60 minutes	PET/CT or PET/MR acquisition (depending on availability and local practice) CT can be performed as a non-contrast localization CT or as a contrast enhanced diagnostic CT with appropriate pediatric CT settings.	True whole body field of view (skull vertex to feet)

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Table 6:

Treatment Response Criteria (Anatomic & Functional Response) (25)

PRIMARY SOFT TISSUE TUMOR RESPONSE	
Complete Response (CR):	• < 10 mm residual soft tissue at primary site AND • Complete resolution of mIBG or FDG uptake (for MIBG-non-avid tumors) at primary site
Partial Response (PR)	• ≥ 30% decrease in longest diameter of primary site AND • mIBG or FDG uptake at primary site stable, improved, or resolved
Progressive Disease (PD)	• > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND • Minimum absolute increase of 5 mm in longest dimension
Stable Disease (SD)	• Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site
SOFT TISSUE AND OSTEOMEDULLARY METASTATIC TUMOR RESPONSE	
Complete Response (CR):	Resolution of all sites of disease, defined as: • Nonprimary target and nontarget lesions measure, 10 mm AND • Lymph nodes identified as target lesions decrease to a short axis < 10 mm AND • mIBG uptake or FDG uptake (for non mIBG avid tumors) of nonprimary lesions resolves completely
Partial Response (PR)	> 30% decrease in sum of diameters of nonprimary target lesions compared with baseline AND all of the following: • Nontarget lesions may be stable or smaller in size AND • No new lesions AND ≥ 50% reduction in mIBG absolute bone score (relative mIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG avid bone lesions
Progressive Disease (PD)	Any of the following: • Any new soft tissue lesion detected by CT/MRI that is also mIBG avid or FDG avid • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma • Any new bone site that is mIBG avid • A new bone site that is FDG avid (for mIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions • Relative mIBG score ≥ 1.2
Stable Disease (SD)	• Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site