Neuroblastoma is an embryonic tumor of the peripheral sympathetic nervous system. It is the most common extracranial solid tumor of childhood and accounts for up to 15% of all pediatric cancer fatalities. The manifestation of neuroblastoma is variable depending on the location of the tumor and on the presence or absence of paraneoplastic syndromes. The prognosis of neuroblastoma is also highly variable, ranging from spontaneous regression to widespread metastatic disease that is unresponsive to treatment. The age of the patient, stage of disease, histopathologic results, and multiple biologic factors contribute to the presurgical and pretreatment risk stratification of a patient with neuroblastoma. Multimodality anatomic imaging with ultrasonography, computed tomography, and magnetic resonance imaging, as well as functional or metabolic nuclear imaging, are essential to determining the risk status of a patient with neuroblastoma. Patients at low risk of metastasis or death receive minimal intervention and those at high risk receive multimodality treatment. New immunotherapeutic techniques and nuclear medicine–targeted therapies have emerged and are demonstrating promising response rates for patients at high risk. This article reviews updates in the diagnosis, management, and treatment of neuroblastoma that have evolved over the past 2 decades, including emphasis on presurgical risk stratification, genetic evaluation of tumors, and the use of modern, high-quality, advanced imaging modalities.

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Abbreviations: FDG = fluorine 18 fluorodeoxyglucose, IDRF = image-defined risk factor, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, MIBG = metaiodobenzylguanidine

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ Recognize the role of different imaging modalities in the detection, diagnosis, treatment, and surveillance of neuroblastoma.

■ List factors associated with prognosis and risk stratification in patients diagnosed with neuroblastoma.

■ Describe the INRGSS staging system for neuroblastoma and recognize image-defined risk factors.

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Introduction

Neuroblastoma is a complex heterogeneous disease that arises from the embryonic cells that form the primitive neural crest, with a natural history ranging from a benign course to a terminal illness. In recent years, new imaging and molecular genetic techniques have been used to stratify patients according to risk of metastasis or death and to optimize treatment. In this article, we discuss the epidemiology and pathogenesis of neuroblastoma, with focus on modern practices in diagnosis, imaging, staging, and treatment of the disease.

Epidemiology

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma comprise a spectrum of tumors that arise from primitive sympathetic ganglion cells (neural crest cells). Overall, approximately 46% of neuroblastomas arise from the adrenal gland, 18% arise from an extra-adrenal abdominal location, 14% arise from the posterior mediastinum or thorax, and the remainder arise from the neck, pelvis,
TEACHING POINTS

- Clinical symptoms are diverse and vary depending on the anatomic location of the tumor. The majority of tumors (65%) occur in the abdomen, most of which arise from the adrenal gland.
- Genetic analysis of the tumor is an important component of risk stratification and determining the prognostic effect of neuroblastoma. Molecular classification of tumors is now routine due to the influence of genetic variations on outcome.
- The INRGSS was published in 2008 as a new way to stratify patients before surgical intervention. This system is now used in parallel with the older INSS. First, whereas the INSS was intended for postsurgical staging, the INRGSS places an emphasis on pretreatment risk stratification based on clinical criteria and IDRFs.
- Combining the INN/INRGSS stage with the age at diagnosis, the histologic results, and the biology and genetics of the tumor allows patients to be placed into a low-, intermediate- or high-risk group.
- US is often the first modality used to identify neuroblastic tumors. CT or MR imaging is then used to further characterize masses and evaluate for IDRFs. MIBG scintigraphy is now required for staging and to determine eligibility for potential MIBG therapy. In addition, nuclear medicine imaging, bone scanning, FDG PET/CT, whole-body MR imaging, and radiography may be used as adjuncts in evaluation of metastatic disease.

And other locations (1) (Fig 1). Neuroblastoma represents approximately 97% of all neuroblastic tumors and is the third most common childhood cancer (3,4). It is the most common extracranial solid tumor of childhood (4,5). Because of the aggressive nature and high likelihood of metastatic disease at diagnosis, neuroblastoma accounts for nearly 15% of all pediatric cancer fatalities (6,7).

Neuroblastoma is the most commonly diagnosed cancer in infancy, and 41% of patients with neuroblastoma receive the diagnosis within the first 3 months of life (4). The median age at diagnosis is 19 months (8). The prognosis of neuroblastoma varies with age. Children who are less than 1 year old at diagnosis of neuroblastoma have a significantly higher 5-year survival rate compared with those who receive the diagnosis at greater than 1 year of age (4,8). There are also racial and ethnic disparities in risk and survival in children with neuroblastoma. Analysis of 3539 patients enrolled in the Children’s Oncology Group neuroblastoma biology study demonstrated that black and Native American patients had a higher prevalence of high-risk disease, which was thought to be due to genetic differences (8).

Neuroblastomas can arise anywhere throughout the sympathetic nervous system. Clinical symptoms are diverse and vary depending on the anatomic location of the tumor. The majority of tumors (65%) occur in the abdomen, most of which arise from the adrenal gland (Fig 2) (6,7). Abdominal masses often manifest with constipation and abdominal distention that may be painful. Sometimes a palpable mass is found at routine physical examination (Fig 3). In other cases, compression of renal vessels can lead to hypertension. Some thoracic neuroblastomas can manifest with scoliosis or compression of the airway. If the tumor arises from the paravertebral sympathetic ganglia, it can invade the spinal canal and cause compression, leading to pain, motor sensory deficits, or Horner syndrome (Fig 4) (7,10). Common sites of metastasis include regional lymph nodes, bone marrow and cortex, and the liver (1). Infrequently, orbital metastasis can cause a “raccoon eyes” appearance and proptosis (Fig 5) (10,11). This is due to obstruction of ophthalmic and facial veins by metastatic tumor but could be misdiagnosed as nonaccidental trauma or coagulopathy. Most cases of disease recurrence occur in the bone marrow, cortex, or central nervous system (11).

Occasionally, the diagnosis is suspected on the basis of a bioactive molecular phenomenon in the form of a paraneoplastic syndrome. In 2%-3% of patients with neuroblastoma, opsoclonus-myoclonus syndrome occurs (12). This is believed to be an immune-mediated response that causes...
Figure 2. High-risk neuroblastoma in a 10-year-old girl. Coronal computed tomographic (CT) image shows a large heterogeneously enhancing mass. The primary mass is centered in the right adrenal gland (arrowheads). The left adrenal gland (circle) is normal.

Figure 3. Stage IV intermediate-risk neuroblastoma in a 5-month-old girl with hepatomegaly at physical examination. (a) Transverse ultrasonographic (US) view of the liver shows numerous hepatic masses replacing the normal hepatic tissue (arrowheads). (b) Subsequently acquired coronal CT image of the abdomen and pelvis with oral and intravenous contrast material shows innumerable hypoattenuating and heterogeneously enhancing metastatic lesions throughout the liver. The liver is markedly enlarged.

Figure 4. Biopsy-proven neuroblastoma in a 16-month-old girl with new-onset lower extremity weakness and inability to walk. Coronal (a) and axial (b) T2-weighted magnetic resonance (MR) images of the thoracic spine reveal a right lower thoracic paraspinal mass with extension through multiple neural foramina, invasion of the spinal canal (arrowheads), and compression of the spinal canal (arrow in b).
Neuroblastoma in a 22-month-old girl who presented with left-sided proptosis, facial swelling, and bruising. (a) Axial CT image of the face (bone window) shows an osseous lesion centered in the left lateral orbital wall (circle) with an extraosseous component exhibiting mass effect on the intraconal structures. (b) Axial postcontrast T1-weighted MR image reveals infiltration of the intraorbital extraconal space with associated mass effect and proptosis (arrowheads). There is extensive associated erosion of the pterygoid plates and invasion of the posterior paranasal sinuses. (c) Coronal CT image of the face (bone window) shows extensive tumor involvement of the skull base (arrowheads), with an additional lesion in the left mandibular ramus (circle).

Another paraneoplastic syndrome seen with neuroblastoma is associated with the secretion of vasoactive intestinal peptide. This is a less common phenomenon in which autonomous secretion of vasoactive intestinal peptide by the tumor causes profuse diarrhea and electrolyte abnormalities. This can be diagnosed by measuring serum vasoactive intestinal peptide levels. Symptoms usually subside after removal of the tumor (16).

Pathogenesis
Genetic analysis of the tumor is an important component of risk stratification and determining the prognostic effect of neuroblastoma. Molecular classification of tumors is now routine due to the influence of genetic variations on outcome. MYCN gene amplification and ploidy have been linked with neuroblastoma prognosis for more than 2 decades, and many more genetic abnormalities have been identified.

MYCN amplification occurs in approximately 20% of primary tumors and is associated with advanced stage and poor outcome. The detection of MYCN gene amplification can be performed with fluorescence in-situ hybridization (17). Although infants with neuroblastoma usually have a favorable prognosis, MYCN amplification has been shown to have significantly worse event-free and overall survival rates in both infants and young children. It is associated with advanced-stage disease, rapid tumor progression, and a poorer prognosis (18,19).
Tumor cell DNA content is also implicated in the pathogenesis of neuroblastoma. DNA content is measured and given a DNA index to compare the DNA content of the tumor cells to that of normal cells. Normal cells have a DNA index of 1. Neuroblastomas with a higher DNA content (DNA index > 1, hyperdiploid) are associated with lower tumor stage and improved outcomes in children younger than 18 months. In these younger patients, this increased DNA content is likely caused by defects in mitosis that lead to whole-chromosome gains, with no segmental aberration. In older patients, however, hyperploidy is often seen because of segmental chromosomal aberrations and is not as important for prognosis (20,21).

Chromosomal deletions are found in up to 50% of neuroblastomas. Segmental chromosomal aberrations associated with poor outcome include deletion of 1p36, unbalanced gain of 17q, and deletion of 11q (22,23). Unlike in adult tumors, somatic mutations are not common in the tumors of children. More frequently mutated genes in neuroblastomas include anaplastic lymphoma kinase (ALK), protein tyrosine phosphatase nonreceptor type 11 (PTPN11), α-thalassemia X-linked intellectual disability (ATRX), MYCN, and NRAS oncogenes (24). The majority of neuroblastomas are sporadic, with patients in whom they occur having no genetically inherited predisposition or additional congenital abnormality. Approximately 1% of cases are familial (17). Mutations in the ALK, PHOX2B, and KIF1B genes have been identified in patients with genetically inherited cases. Activating mutations in the tyrosine kinase domain of the ALK oncogene account for most cases of hereditary neuroblastoma (25). ALK mutations and amplification occur in approximately 15% of primary neuroblastoma tumors (26). Mutations in the tyrosine kinase region of this gene are involved in tumor development, and ALK inhibitors may be a therapeutic intervention in the future (27,28). Children with either sporadic or familial neuroblastoma in conjunction with congenital central hypoventilation syndrome, Hirschsprung disease, or both usually have loss-of-function mutations in the homeobox gene PHOX2B (18). Numerous other genetic abnormalities have been implicated in patients with neuroblastoma.

**Diagnosis**

Diagnosis of neuroblastoma is made on the basis of histologic confirmation combined with chemical profiling and imaging characteristics. Histologic confirmation is usually performed by acquiring an incisional biopsy of the primary tumor. For tumors that appear to be localized, the incisional biopsy may also include a sampling of nonadherent ipsilateral and contralateral lymph nodes. Bone marrow aspiration of two separate sites is necessary to evaluate fully the extent of disease.

Histologically, neuroblastoma falls into a category of malignant small round cell tumors. These tumors demonstrate small, round, relatively undifferentiated cells. They are sometimes called “blue” because they have large hyperchromatic nuclei and a thin rim of cytoplasm. Other malignancies that fall into this category include Ewing sarcoma, rhabdomyosarcoma, non-Hodgkin lymphoma, retinoblastoma, nephroblastoma, and hepatoblastoma. These malignant small round cell tumors can be difficult to diagnose when they are poorly differentiated. In neuroblastoma, small clusters of cells may be separated by a fibrillar matrix forming pseudorosettes (sometimes called Homer-Wright rosettes) (29). Immuno-histochemical stains for biologic markers such as neuron-specific enolase, S-100 protein, and chromogranin can be used to aid in the histologic diagnosis of neuroblastoma (29).

The International Neuroblastoma Pathology Committee (30) modified the previously used Shimada system as a prognostic classification system based on the morphologic features of neuroblastoma in 1999. Evaluation includes comment on the amount of Schwannian stroma, the degree of nodularity, the degree of neuroblastic differentiation, the mitosis-karyorrhexis index, and a note on the presence or absence of calcifications, among other descriptors. Two prognostic subgroups are possible: favorable and unfavorable histologic results. A favorable histologic result is assigned to children younger than 1.5 years with a low or intermediate mitosis-karyorrhexis index and a differentiating or partially differentiating tumor or
to children 1.5–5 years of age with a low mitosis-karyorrhexis index and a differentiating tumor. Results of genetic and molecular classifications can then be included in an integrated prognostic evaluation (30).

Since neuroblastoma is derived from neural crest cells, it often expresses the enzymes required for catecholamine metabolism. Degradation of norepinephrine, epinephrine, and dopamine by these enzymes leads to the final end products, vanillylmandelic acid and homovanillic acid. Detection of elevated serum and urine levels of vanillylmandelic acid and homovanillic acid can provide chemical evidence of disease. Although not specific for neuroblastoma, high vanillylmandelic acid and homovanillic acid levels are present in approximately 75% of patients with neuroblastoma (31). If pathologic examination is unequivocal for neuroblastoma, or tumor cells are detected in bone marrow, and there are elevated urinary vanillylmandelic acid and homovanillic acid levels, then a diagnosis can be made (32).

### Imaging of Neuroblastoma

#### Evaluation with US

US is usually the first examination performed when an abdominal mass is suspected in a child. At US, neuroblastoma appears as a solid heterogeneous mass that demonstrates calcification 30%–90% of the time (Fig 7) (1,33,34). If the mass arises from the adrenal gland, there may be inferior displacement of the adjacent kidney. Doppler evaluation can be performed in cases of suspected neuroblastoma to interrogate the regional vasculature. Neuroblastomas tend to encase the surrounding vessels or displace them rather than infiltrate them (33,35,36). A search for regional lymphadenopathy also can be performed during US evaluation. US is typically followed by CT or MR imaging to further evaluate the extent of disease and assist in staging.

The growing use of US during pregnancy is leading to an increasing number of prenatally diagnosed (congenital) neuroblastomas (Fig 8) (37–39). Congenital neuroblastoma should be considered in addition to adrenal hemorrhage and pulmonary sequestration when a solid or cystic adrenal mass is detected at prenatal imaging. Associated vascular flow and calcifications are common. More than 90% of congenital neuroblastomas arise from the adrenal gland compared with only 35% of postnatal cases (39,40). Most of these antenatal cases have favorable staging and histopathologic features, with spontaneous regression in the 1st year of life. Results of prior large-scale prospective studies have shown that screening for neuroblastoma in infancy does not reduce mortality, further supporting the notion that neuroblastoma in very young patients is a distinct disease that follows a different course than that in patients who are older at diagnosis (41–44).

#### CT and MR Imaging

There is no clear answer as to whether CT or MR imaging is superior for detection and evaluation of neuroblastoma. CT is rapidly performed and widely available, with superior detection of calcifications. MR imaging is better for evaluating spinal involvement and does not involve use of ionizing radiation. Often, both CT and MR imaging are performed at the initial evaluation, especially if the tumor is paraspinal. CT and MR imaging both demonstrate a heterogeneously enhancing solid mass that crosses the midline and encases or displaces vessels. Both modalities can also demonstrate metastasis to the liver, lymph nodes, bone, and skin (35,36).

Whole-body MR imaging can be a helpful diagnostic tool for imaging neuroblastomas in certain contexts. The entire body, from the vertex to the toes, is imaged in one or more planes, usually with multiple sequences (Fig 9). This method is radiation free and allows a complete workup for disease staging in a single session of sedation or anesthesia. For evaluation of all solid tumors in children, whole-body MR imaging has consistently shown sensitivity comparable to or greater than that of skeletal scintigraphy with technetium 99m \( ^{99m} \text{Tc} \) diphosphonates for detecting skeletal metastases to bone (45). When evaluating neuroblastoma, authors of previous studies showed that MR imaging demonstrates higher sensitivity than that with MIBG, whereas MIBG scintigraphy demonstrates higher specificity (46,47). MR imaging also demonstrates superior sensitivity to that with CT alone. The increased sensitivity of MR imaging is due to superior detection of osseous metastases (48).
However, the specificity of whole-body MR imaging remains low, because it is difficult to distinguish treated from active disease. MIBG and fluorine 18 ($^{18}$F) fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT are more helpful in determining tumor viability (Fig 10). Owing to the increased number of sequences and length of imaging required, whole-body MR imaging is less likely to be used for staging and more likely to be used for surveillance and for evaluation of osseous metastatic disease that may be less conspicuous at CT.

### Nuclear Medicine

Iodine 123 ($^{123}$I) and 131 ($^{131}$I)–labeled MIBG are functional agents ideal for use in imaging of neuroendocrine tumors, primarily neuroblastomas in children. As an analog of norepinephrine, MIBG is taken up by norepinephrine transporters. This is demonstrated in up to 90% of neuroblastomas (49). Although $^{123}$I MIBG is now the agent of choice for diagnostic imaging, there are some centers that still use $^{131}$I MIBG because of availability and/or decreased cost. In a study by Yanik et al (50), in approximately 27% of their centrally reviewed examinations, $^{131}$I was used instead of $^{123}$I. They did not report any notable difference in the mean Curie score based on isotope type. The addition of SPECT and SPECT/CT improves the accuracy of identification of specific sites of uptake (Fig 11) (49). The high specificity and improved accuracy of localization make MIBG imaging the test of choice for identification of metastatic disease. Imaging is qualitative, with any uptake be-
The body is divided into nine skeletal segments with an additional segment for soft-tissue involvement. Each segment is assigned a score of 0–3 depending on the extent of disease involvement: (a) If there is no disease involvement, the segment is given a score of 0. (b) If there is a single site of disease, the segment is given a score of 1. (c) If there are two or more sites of disease but less than 50% involvement of the segment, it is given a score of 2. (d) If more than 50% of the segment has disease involvement, it is given a score of 3. (e) The maximum score is 30.

Assessment of MIBG avidity at follow-up may be a useful surrogate marker for evaluating response to therapy over time. In a study by Yanik et al (50) conducted through the Children’s Oncology Group, children with stage 4 high-risk neuroblastoma were evaluated. A Curie score of greater than or equal to 2 at the end of induction was associated with an inferior outcome to those with Curie scores less than 2. The event-free survival rate was approximately 15% for patients who had more than minimal residual disease compared with 46% for those who had an absolute Curie score of less than 2. Furthermore, they showed that the presence of more than minimal residual disease was more predictive than the percentage of response from diagnosis to end induction (50, 51).

Indium 111 ($^{111}$In) pentetreotide has been shown to be taken up by somatostatin receptor–positive neuroblastomas. With preferential affinity for somatostatin type-2 receptors, it was shown in studies in the 1990s to have a complementary role to that of $^{123}$I MIBG. However, the high specificity of MIBG outmatched the added value of pentetreotide in these patients. Furthermore, the imaging protocol and radiation exposure of $^{111}$In required patients to be imaged at 48–72 hours, whereas MIBG imaging typically is completed at 24 hours. In MIBG-nonavid neuroblastomas, the addition of another metabolic imaging study may be more pertinent (52).

When neuroblastoma tumors are not MIBG avid, or when MIBG imaging and anatomic imaging do not correlate, FDG PET/CT is a useful diagnostic tool (Fig 13). Although MIBG is thought to be more sensitive for detection of individual lesions in patients with relapse of neuroblastoma, FDG PET/CT, and even FDG PET/MR imaging, can have a complementary role, particularly in soft-tissue lesions. The complete FDG response does not always correlate with the MIBG response (47).

Newer agents for use in PET/CT that have higher image resolution than agents imaged with gamma cameras (even with the addition of SPECT/CT) are gaining interest in the community.

**Figure 9.** Newly diagnosed neuroblastoma in a 3-year-old boy. Coronal T2-weighted short inversion time inversion-recovery whole-body MR image shows a large soft-tissue mass in the left superior mediastinum (asterisk) and osseous metastases to the proximal humeri, right femur, and right tibia (arrowheads). Left cervical lymphadenopathy is also partially included.
Figure 10. Neuroblastoma refractory to treatment with unfavorable histologic features in a 3.5-year-old boy. (a) Whole-body MIBG maximum intensity projection image shows several sites of osseous metastatic disease (arrowheads). (b, c) Whole-body MR images show multifocal osseous lesions with sagittal T1-weighted (b) and coronal short inversion time inversion-recovery (c) sequences (arrowheads). (d, e) FDG PET/CT (d) and PET maximum intensity projection (e) images confirm active disease at some metastatic sites (arrowheads), while others had no FDG avidity, indicating treated disease.

of physicians who study and treat neuroblastomas. Gallium 68 ($^{68}$Ga)-[tetraxetan-D-Phe1, Tyr3]-octreotate ($^{68}$Ga DOTATATE) and $^{68}$Ga-[tetraxetan-D-Phe1, Tyr3]-octreotide ($^{68}$Ga DOTATOC) are somatostatin analogs suited for use with PET/CT. A third somatostatin receptor analog specific to somatostatin receptor 3 ($^{68}$Ga DOTANOC) has also been studied but has not been as widely investigated in neuroblastomas, which more commonly express somatostatin receptor 2. As recently as late 2016, $^{68}$Ga DOTATATE received U.S. Food and Drug Administration approval and is now commercially available for detection of somatostatin receptor–positive neuroendocrine tumors. The advantage of this agent over $^{111}$In pentetreotide is twofold: not only do the images show higher resolution with clearer definition than those with $^{111}$In pentetreotide or $^{123}$I MIBG, but the imaging protocol allows injection and imaging during the same single-day visit (53–57).

$^{99m}$Tc bone scans are an additional tool in the diagnosis and staging of neuroblastoma. A bone scan is performed if the primary tumor is not MIBG avid or if the tumor has been excised. In some instances, where MIBG may not be readily available, a bone scan is still routinely used. Isolated bone uptake of $^{99m}$Tc should be confirmed with another imaging modality or biopsy.

Figure 11. Newly diagnosed neuroblastoma in a 4-year-old girl. (a) Anterior whole-body planar image from a 24-hour $^{123}$I MIBG study shows increased radiotracer uptake in a left adrenal mass (●) as well as diffuse osseous metastatic disease (arrowheads). (b) SPECT/CT image shows superior anatomic detail for characterization of sites of tumor involvement (●, arrowheads). Physiologic activity is present within the salivary glands, oropharynx, liver, heart, and urinary bladder.
Figure 12. The Curie score provides prognostic information in evaluation of patients with neuroblastoma based on the number of involved segments and extent of disease on MIBG images. (a) Anatomic drawing shows regions used to determine the Curie score. (b) Anterior whole-body planar image from a 24-hour $^{123}$I MIBG study in a 14-month-old girl with opsoclonus-myoclonus syndrome shows isolated uptake in a left paraspinal mass (arrowhead), compatible with a Curie score of 1. (c) Anterior whole-body planar image from a 24-hour $^{123}$I MIBG study in a 22-month-old girl with newly diagnosed neuroblastoma shows extensive abnormal uptake (arrowheads), including the right frontal calvaria, sphenoid bone, left mandible, bilateral proximal femora, distal left femur, and abdominal and pelvic soft tissue. The Curie score was 12.

Figure 13. MIBG-nonavid neuroblastoma. (a) Anterior whole-body planar image from a 24-hour $^{123}$I MIBG study shows no abnormal foci of MIBG uptake. (b) Image from subsequent $^{99m}$Tc bone scan shows physiologic uptake with subtle findings of diffusely increased metaphyseal uptake (arrowheads), most noticeable in the proximal femora and humeri. This pattern can be difficult to recognize. (c) FDG PET/CT image reveals abnormally increased metabolic activity within a large left retroperitoneal mass (*) and extensive liver metastases (arrowheads), and a metastatic focus within the left lamina of the T4 vertebral body (arrow), compatible with viable tumor.
Staging
The International Neuroblastoma Risk Group Staging System (INRGSS) was published in 2008 as a new way to stratify patients before surgical intervention (58). This system is now used in parallel with the older International Neuroblastoma Staging System (INSS). There are several key differences between the INRGSS and the INSS. First, whereas the INSS was intended for postsurgical staging, the INRGSS emphasizes pretreatment risk stratification based on clinical criteria and image-defined risk factors (IDRFs) (Table 1, Fig 14). These IDRFs are focused on evaluation of tumor extent to nearby vessels and adjacent structures. Brisse et al (59) further clarified the terminology to describe a primary tumor in the INRGSS:

(a) “Encasement” of a vessel means that more than 50% of the vessel circumference is in contact with the tumor,

(b) “contact” means that less than 50% of the vessel’s circumference is in contact with the tumor, and

(c) “flattened” is used to describe a vessel that has a reduced diameter with a partially visible lumen. Of these, only encasement constitutes an IDRF. Infiltration is used to describe a tumor that has no well-defined layer (usually fat) between the tumor and a neighboring structure, and also represents an IDRF. CT and/or MR imaging of the primary tumor is required to determine IDRFs, and MIBG imaging is mandatory in this new system. If one unequivocal MIBG-positive lesion is shown at a distant site, that is considered metastatic disease. If one positive lesion is found at a distant site at MIBG imaging, it is considered metastatic disease (60).

With the addition of the IDRFs, several other modifications have been made to the INSS. Now, local-regional disease is divided into two instead of three stages, with no importance given to tumor extension across the midline. Lymph nodes are now classified as regional or nonregional rather than ipsilateral, contralateral, or distant. Also, stage MS, which includes metastatic disease confined to the liver, marrow, and/or skin only, has an upper age limit of 18 months. The previous corresponding stage of 4S disease had an upper age limit of 12 months (Table 2) (60).

<table>
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<th>Table 1: IDRFs in Neuroblastoma</th>
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<tr>
<td>Ipsilateral tumor extension within two body compartments</td>
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<tr>
<td>Neck</td>
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<tr>
<td>Tumor encasing carotid and/or vertebral body and/or internal jugular vein</td>
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<tr>
<td>Tumor extending to base of skull</td>
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<td>Tumor compressing the trachea</td>
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<td>Cervicothoracic junction</td>
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<td>Tumor encasing brachial plexus roots</td>
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<tr>
<td>Tumor encasing subclavian vessels and/or vertebral and/or carotid artery</td>
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<tr>
<td>Tumor compressing the trachea</td>
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<tr>
<td>Thorax</td>
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<tr>
<td>Tumor encasing the aorta and/or major branches</td>
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<tr>
<td>Tumor compressing the trachea and/or principal bronchi</td>
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<tr>
<td>Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12</td>
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<tr>
<td>Thoracoabdominal tumor encasing the aorta and/or vena cava</td>
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<td>Abdomen and/or pelvis</td>
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<tr>
<td>Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament</td>
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<tr>
<td>Tumor encasing branches of the superior mesenteric artery at the mesenteric root</td>
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<tr>
<td>Tumor encasing the origin of the celiac axis and/or of the superior mesenteric artery</td>
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<td>Tumor invading one or both renal pedicles</td>
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<td>Tumor encasing the aorta and/or vena cava</td>
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<td>Tumor encasing the iliac vessels</td>
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<tr>
<td>Pelvic tumor crossing the sciatic notch</td>
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<td>Intraspinal tumor extension whatever the location provided that more than one-third of the spinal canal in the axial plane is invaded, and/or the perimedullary leptomeningeal spaces are not visible, and/or the spinal cord signal intensity is abnormal</td>
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<tr>
<td>Infiltration of adjacent organs and structures: pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery</td>
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<tr>
<td>Conditions to be recorded, but not considered IDRFs</td>
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<tr>
<td>Multifocal primary tumors</td>
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<td>Pleural effusion, with or without malignant cells</td>
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<td>Ascites, with or without malignant cells</td>
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Note.—Reprinted, with permission, from reference 58.

Treatment
In North America, most patients are treated under protocols designed by the National Cancer Institute–funded cooperative group, the Children’s Oncology Group. To determine the appropriate treatment strategy, the Children’s Oncology Group risk group stratification has been developed from more than 20 years of clinical trials. Combining the INSS/INRGSS stage with the age at diagnosis, the histologic results, and the biology and genetics of the tumor allows the patient to be placed into a low-, intermediate-, or high-risk group. The intensity and duration of treatment are then determined. The most important imaging factors for determining induction and consolidation therapy include the presence or absence of localized disease
Figure 14. Examples of IDRFs in neuroblastomas. (a) Coronal T2-weighted MR image shows tumor extending to the skull base (arrowheads) and encasing the left carotid artery (arrow), both IDRFs, in the same patient as in Figure 5. (b) Axial T2-weighted MR image reveals tumor encasement (arrowheads) of the thoracic aorta (white *). There is a small right pleural effusion (black *), which should be recorded but does not qualify as an IDRF. (c) Axial contrast-enhanced chest CT image in a child with newly diagnosed neuroblastoma shows tumor encasing and compressing the main bronchi (arrowheads), an IDRF. (d) Axial CT image of the abdomen with intravenous and oral contrast material shows tumor encasement (arrowheads) of the superior mesenteric artery (arrows). * = aorta. (e, f) Axial (e) and coronal (f) CT images of the abdomen with intravenous contrast material show a large heterogeneous mass in the right upper quadrant that encases the right renal artery (arrows), inferior vena cava (+), and aorta (arrowhead in e) and also infiltrates the liver (arrowheads in f), which are all IDRFs in the INRGSS.
at the original tumor site, confined unilateral disease, contralateral disease, and metastatic disease. IDRFs have an increasingly important role in determining a treatment approach.

Once a diagnosis of neuroblastoma is established, there are various surgical approaches according to risk classification and Children’s Oncology Group guidelines. Surgical removal of the tumor may be all that is necessary for children with low-risk disease that is localized. Authors of recent studies (61–63) in North America and Europe suggest that complete surgical resection is often not necessary for low- to intermediate-risk tumors. Patients with intermediate-risk tumors may receive chemotherapy to shrink the tumor before surgical removal. In patients at higher risk, surgery may be performed to remove as much tumor as possible after the induction of chemotherapy.

If there is a congenital neuroblastoma, observation may be the most appropriate management (39,62). For other low-risk tumors, surgery is the mainstay of treatment. Chemotherapy is added for tumors that cannot be resected or for tumors that may cause spinal cord compression or respiratory compromise from hepatic involvement. Patients at intermediate risk usually receive chemotherapy in combination with surgical resection when possible. Radiation therapy is rarely indicated for patients at intermediate risk but should be considered for those with tumor progression or life-threatening complications from chemotherapy. Outcomes for patients at low risk (event-free survival, >95%) and intermediate risk (event-free survival, 80%–95%) are excellent (64).

For patients at high risk, an aggressive multimodality approach is used, including neoadjuvant chemotherapy, surgical resection, adjuvant high-dose chemotherapy with hematopoietic stem cell rescue, and radiation therapy (65). Maintenance therapy is directed at eradication of residual disease. Anti-GD2 immunotherapy with dinutuximab is the standard of care (66). Historically, event-free survival for patients at high risk was less than 50%. The addition of anti-GD2 immunotherapy with dinutuximab improved 2-year event-free survival to 66% (66). Now, emerging therapy of $^{131}$I MIBG imaging followed by autologous stem cell rescue has shown promising response rates.

MIBG labeled with $^{131}$I allows for targeted therapy of neuroblastoma. $^{131}$I MIBG therapy is a new and emerging technique. Patients tolerate it better than they do many other treatments, largely because it does not cause adverse effects such as nausea and pain, and it has been shown to provide palliative relief of pain from metastatic bone disease in patients with other neuroendocrine tumors (67). Clinical trials are underway to investigate its use as a primary and adjunctive therapy. Studies have shown response rates of up to 66% in patients newly diagnosed with high-risk disease (68). Response rates of 37% have been demonstrated in cases of relapsed neuroblastoma (69). Potential adverse effects of therapeutic $^{131}$I MIBG include myelosuppression, transient hypertension, and thyroid disorders (51). In addition, on the basis of the avidity of this agent for neuroblastoma, as with MIBG, an agent currently in clinical trials for therapy for refractory neuroblastoma, lutetium 177-DOTATATE, that shows promise in select patients has been developed (70).

### Conclusion

Neuroblastoma is a heterogeneous disease with a broad range of clinical presentations. The prognosis varies depending on the age of the patient and the histologic and biologic characteristics of the tumor. US is often the first modality used to identify neuroblastic tumors. CT or MR imaging is then used to further characterize masses and evaluate for IDRFs. MIBG scintigraphy is now required for staging and to determine eligibility for potential MIBG therapy. In addition, nuclear medicine imaging, bone scanning, FDG PET/CT, whole-body MR imaging, and radiography may be used as adjuncts in evaluation of metastatic disease. The INRGSS emphasizes pretreatment image-defined risk classifications. New immunotherapy techniques and $^{131}$I MIBG

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**Table 2: INRGSS Stages**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>L1</td>
<td>Localized tumor not involving vital structures as defined by the list of IDRFs and confined to one body compartment</td>
</tr>
<tr>
<td>L2</td>
<td>Local-regional tumor with presence of one or more IDRFs</td>
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<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>
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Note.—Patients with multifocal primary tumors should be staged according to the greatest extent of disease. Reprinted, with permission, from reference 58.
targeted therapy have shown promising results in high-risk patients. Although our understanding of neuroblastoma will continue to evolve, it is important for radiologists to understand the updated guidelines to optimize disease evaluation and treatment course.

References

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