Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project

Neuroblastoma is an enigmatic disease entity; some tumors disappear spontaneously without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy. However, strong prognostic factors can accurately predict whether children have “good” or “bad” disease at diagnosis, and the clinical stage is currently the most significant and clinically relevant prognostic factor. Therefore, for an individual patient, proper staging is of paramount importance for risk assessment and selection of optimal treatment. In 2009, the International Neuroblastoma Risk Group (INRG) Project proposed a new staging system designed for tumor staging before any treatment, including surgery. Compared with the focus of the International Neuroblastoma Staging System, which is currently the most used, the focus has now shifted from surgicopathologic findings to imaging findings. The new INRG Staging System includes two stages of localized disease, which are dependent on whether image-defined risk factors (IDRFs) are or are not present. IDRFs are features detected with imaging at the time of diagnosis. The present consensus report was written by the INRG Imaging Committee to optimize imaging and staging and reduce interobserver variability. The rationales for using imaging methods (ultrasonography, magnetic resonance imaging, computed tomography, and scintigraphy), as well as technical guidelines, are described. Definitions of the terms recommended for assessing IDRFs are provided with examples. It is anticipated that the use of standardized nomenclature will contribute substantially to more uniform staging and thereby facilitate comparisons of clinical trials conducted in different parts of the world.


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Neuroblastomas (ie, neuroblastoma, ganglioneuroblastoma, ganglioneuroma) are the most common extracranial solid tumors occurring in children (1). The median age at diagnosis is about 16 months, and 95% of cases are diagnosed by 7 years of age (2,3). The most common sites of origin of neuroblastomas are the adrenal region (48%), extraadrenal retroperitoneum (25%), and chest (16%). Less common sites are the neck (3%) and the pelvis (3%) (2). Forty-eight percent of patients have metastatic disease at diagnosis (2).

The enigmatic nature of this tumor group has long been recognized: Some tumors undergo spontaneous involution without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy (3). Fortunately, strong prognostic factors can be used to accurately predict whether children have “good” or “bad” disease at diagnosis (4). Clinical stage is currently the most statistically significant and clinically relevant prognostic factor (2). Other factors include patient age, serum lactate dehydrogenase level, histologic category and grade of tumor differentiation (5), status of the MYCN oncogene, DNA ploidy, aberrations of chromosomes 1p and 11q, and genomic profile (5). Combinations of biologic factors with age and clinical stage have been used as stratifying criteria to define risk groups (2), and current treatment protocols are stratified according to risk. Thus, accurate staging at the time of diagnosis is of paramount importance.

The International Neuroblastoma Staging System (INSS) (Table 1), developed in 1988 (7) and modified in 1993 (6), is still used by most cooperative groups. However, the INSS is not suitable for the pretreatment risk classification of patients with localized disease as this staging is based on the extent of tumor removal (8). Actually, the same tumor can be classified as INSS stage 1 or 3 disease depending on the extent of surgical excision (9), making direct comparisons of clinical trials based on the INSS difficult. Furthermore, the localized disease of patients whose “treatment” is observation because spontaneous tumor regression is anticipated cannot be properly staged by using the INSS. Assessment of lymph node involvement is also difficult to apply uniformly (8).

In 2004, investigators from the major cooperative groups—the Children’s Oncology Group (COG) from North America and Australia–New Zealand, the German Pediatric Oncology and Hematology Group (GPOH), the Japanese Neuroblastoma Study Group (JNBSG), and the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) Group—and China formed the International Neuroblastoma Risk Group (INRG) Task Force, which developed the INRG Staging System (INRGSS) and the INRG Risk Classification System for neuroblastoma (2,8). The INRGSS, published in 2009, is designed for tumor staging before surgery or any other treatment (Table 2) (8). Localized tumors are classified as stage L1 or L2 disease on the basis of whether one or more of 20 IDRFs are present (Table 3) (8). IDRFs are surgical risk factors, detected on images, that make total tumor excision risky or difficult at the time of diagnosis (9,10). Stage M indicates disseminated disease (comparable to the INSS stage 4), and stage MS indicates metastatic disease similar to INSS stage 4S disease (with exception of primary tumor size and patient age range). Compared with the focus on surgicopathologic findings in the INSS, the focus has now shifted to imaging. Since imaging data can be retrospectively reviewed, a system based on preoperative diagnostic image findings will be more robust and reproducible than one based on surgical findings. In addition, because the digital imaging data can be reviewed centrally by expert radiologists, the likelihood of uniform evaluation will be increased. This new staging system is not intended to be a substitute for the INSS, and it is recommended that both systems be used in parallel.

Stage L1 tumors are localized tumors that do not involve vital structures, as defined according to the list of IDRFs. The tumor must be confined within one body compartment: the neck, chest, abdomen, or pelvis. The isolated finding of intraspinal tumor extension that does not fulfill the criteria for an IDRF is consistent with stage L1 disease.

Stage L2 tumors are local-regional tumors with one or more IDRFs. The tumor may be ipsilaterally continuous

**Advance in Knowledge**

- This consensus report, written by experts representing the major international cooperative pediatric cancer study groups, will likely optimize imaging and uniform reporting for neuroblastoma staging according to the new International Neuroblastoma Risk Group Staging System.

**Implications for Patient Care**

- Use of a uniform imaging strategy will facilitate the staging of neuroblastic tumors.
- Consistent and uniform reporting and staging will greatly facilitate comparisons of risk-based clinical trials conducted in different regions of the world.
- Patients with neuroblastoma worldwide will likely benefit from the early recognition of effective treatment regimens with improved outcomes.

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**Abbreviations:**

FDG = fluorine 18 fluorodeoxyglucose
IDRF = image-defined risk factor
INRG = International Neuroblastoma Risk Group
INRGSS = INRG Staging System
INSS = International Neuroblastoma Staging System

**Author contributions:**

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Potential conflicts of interest are listed at the end of this article.
within body compartments—for example, a left-sided abdominal tumor with left-sided chest involvement should be considered stage L2 disease. However, a clearly left-sided abdominal tumor with right-sided chest (or vice versa) involvement is defined as metastatic disease.

Stage M tumor refers to distant metastatic disease (ie, not contiguous with the primary tumor), except as defined for stage MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumor with enlarged lower mediastinal nodes or a pelvic tumor with inguinal lymph node involvement is considered local-regional disease. Ascites and pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumor.

Stage MS tumor refers to metastatic disease in patients younger than 18 months (5-47 days), with the metastasis confined to the skin, liver, and/or bone marrow. Bone marrow involvement should be limited to less than 10% of all nucleated cells in the culture smears or biopsy samples. Iobenguane I 123 (MIBG) scintigraphy findings must be negative in bone and bone marrow. Provided there is MIBG uptake in the primary tumor, bone scans are not required. The primary tumor can be with or without IDRFs (stage L2 or L1), and there is no restriction regarding crossing or infiltration of the midline.

The INRGSS has profound implications for imaging, and the radiologist’s influence is clearly increased. Further discussion regarding the definitions and importance of the IDRFs was perceived to be necessary. Therefore, an international group of neuroblastoma experts was formed to prepare this special report to disseminate recommendations for imaging and staging. After the initiative from the INRG Executive Committee, six pediatric radiologists (H.J.B. [chair], M.B.M., C.G., K.K., K.B.K., S.L.W.), four nuclear physicians (F.G., V.J.L., M.S., B.L.S.), three pediatric surgeons (M.K., T.M., S.S.), four pediatric oncologists (S.L.C., B.H., K.K.M., A.D.J.P.), and a statistician (W.B.L.) were invited to participate after having been chosen by the chairs of their respective cooperative groups (INRG, SIOPEN, COG, JNBSG, GPOH). The present recommendations from this group were developed in consensus on the basis of professional experiences and review of the literature. This consensus report is provided to optimize imaging and uniform reporting for staging of neuroblastic tumors and to facilitate comparisons of risk-based clinical trials conducted in different regions of the world.

The diagnosis of neuroblastic tumor is usually suspected with a high degree of confidence on the basis of the patient’s age and imaging pattern. Before obtaining pathologic specimens or specific markers (urinary catecholamines, MIBG uptake), the most usual challenge is the differential diagnosis of renal versus extrarenal retroperitoneal tumor—that is, neuroblastoma versus Wilms tumor—since both of these neoplasms occur during childhood (18). Multiplanar imaging

### Table 1

**Descriptions of Original INSS Tumor Stages**

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically. Nodes attached to and removed with the primary tumor may be positive.</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes negative microscopically</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline (beyond the opposite side of the vertebral column) with or without regional lymph node involvement, or midline tumor with bilateral extension via infiltration (unresectable) or lymph node involvement</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S disease)</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B disease) with dissemination limited to skin, liver, and/or bone marrow (limited to infants younger than 1 year, marrow involvement of less than 10% of total nucleated cells, and MIBG scan findings negative in the marrow)</td>
</tr>
</tbody>
</table>

Source.—Reference 6.

### Table 2

**Descriptions of New INRG Tumor Stages**

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS tumor)</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>

Source.—Reference 8. Complete definitions of these stages are cited in the text. IDRFs = image-defined risk factors.
analysis usually allows demonstration of the renal or extrarenal origin of the mass. However, a large neuroblastoma invading the kidney can be mistaken for an exophytic Wilms tumor, and vice versa.

Local extension of neuroblastoma mainly consists of perivascular involvement with arterial encasement, infiltration of adjacent soft tissues and organs (mainly the kidneys and liver), and infiltration of the foramina and epidural space of the spinal canal when the primary tumor arises from a paraspinal sympathetic chain. Lymph node involvement occurs in about 30% of cases. Lymph nodes are usually located close to the primary tumor, although distant lymph nodes (previously classified as stage 4N tumors if there were no other metastatic sites) may be observed occasionally (19).

### Table 3

<table>
<thead>
<tr>
<th>Anatomic Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple body compartments</td>
<td>Ipsilateral tumor extension within two body compartments (i.e., neck and chest, chest and abdomen, or abdomen and pelvis)</td>
</tr>
<tr>
<td>Neck</td>
<td>Tumor encasing carotid artery, vertebral artery, and/or internal jugular vein</td>
</tr>
<tr>
<td>Tumor extending to skull base</td>
<td>Tumor compressing trachea</td>
</tr>
<tr>
<td>Cervicothoracic junction</td>
<td>Tumor encasing brachial plexus roots</td>
</tr>
<tr>
<td>Tumor encasing subclavian vessels, vertebral artery, and/or carotid artery</td>
<td>Tumor compressing trachea</td>
</tr>
<tr>
<td>Thorax</td>
<td>Tumor encasing aorta and/or major branches</td>
</tr>
<tr>
<td>Tumor compressing trachea and/or principal bronchi</td>
<td>Lower mediastinal tumor infiltrating left atrium between T9 and T12 levels</td>
</tr>
<tr>
<td>Thoracoabdominal junction</td>
<td>Tumor encasing aorta and/or vena cava</td>
</tr>
<tr>
<td>Abdomen and pelvis</td>
<td>Tumor infiltrating porta hepatis and/or hepatoduodenal ligament</td>
</tr>
<tr>
<td>Tumor encasing branches of superior mesenteric artery at mesenteric root</td>
<td>Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery</td>
</tr>
<tr>
<td>Tumor invading one or both renal pedicles</td>
<td>Tumor encasing aorta and/or vena cava</td>
</tr>
<tr>
<td>Tumor encasing iliac vessels</td>
<td>Pelvic tumor crossing scatic notch</td>
</tr>
<tr>
<td>Intraspinal tumor extension</td>
<td>Intraspinal tumor extension (whatever the location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal</td>
</tr>
<tr>
<td>Infiltration of adjacent organs and structures</td>
<td>Pericardium, diaphragm, kidney, liver, duodenumopancreatic block, and mesentery</td>
</tr>
</tbody>
</table>

Source: Reference 8. Conditions that should be recorded but are not considered IDRFs are multifocal primary tumors, pleural effusion with or without malignant cells, and ascites with or without malignant cells.

### Rationale for Use of Imaging Modalities

When an abdominal or pelvic tumor is suspected in a child, ultrasonography (US) is usually the first imaging examination performed because of its wide availability and noninvasiveness. Gray-scale and duplex Doppler US allows accurate localization of neuroblastoma and can help define the relationship of this tumor with adjacent organs and vessels. US is also quite effective for imaging the liver in children. In newborns, US may even depict intraspinal involvement. However, US is associated with important limitations: low interobserver reproducibility, limited assessment of highly calcified tumors because of acoustic shadowing, and marked restrictions in the retrospective data review that is mandatory for clinical trials. Surgeons and radiation oncologists also require more extensive imaging for treatment planning. Therefore, we recommend that magnetic resonance (MR) or computed tomographic (CT) images always be obtained at the time of diagnosis for accurate staging.

There currently is no consensus about the optimal imaging modality for assessing local disease. Both MR imaging and CT are routinely used, depending on local availability and the radiologist’s preference. In one multiinstitutional study (20), CT and MR imaging had statistically similar but relatively poor performance in assessing the features of local disease. However, the aim of that study was to assess the relevance of imaging for assessment of INSS stage but not IDRFs. In the absence of evidence-based criteria, we describe the advantages and limitations of both modalities in the following text.

CT is widely available in imaging departments, and current multidetector CT machines allow very fast acquisitions without motion artifacts, reducing the need for sedation. Intraspinal extension is also well depicted, and postprocessing software allows multiplanar reconstructions for accurate coronal and sagittal views. However, with CT, the use of intravenous iodine-based contrast material (with its potential risks) is required to increase the soft-tissue contrast and assess the relationships between the tumor and adjacent vessels. Moreover, CT is associated with substantial radiation exposure, and children are known to have a higher inherent sensitivity to the negative effects of ionizing radiation (21). Nevertheless, for patients requiring radiation therapy, CT is still the reference-standard technique for defining the radiation fields and dose planning (22). A preoperative CT study is therefore usually required in trials where the postoperative radiation field is determined on the basis of the preoperative (postinduction) residual tumor extension. However, although MR imaging is not yet widely available or used for patients with neuroblastoma, there is currently increasing use of this examination as a treatment-planning method (23).

MR imaging has long been recognized as an effective method for imaging neuroblastoma (10,14,16,17,20); however, to our knowledge, its superiority...
over CT for local-regional staging has not been demonstrated. Compared with CT, MR imaging offers the advantages of higher contrast resolution and the lack of ionizing radiation. There is an ongoing unresolved discussion regarding the need for gadolinium-based contrast material injection to assess neuroblastoma extension. Gadolinium-based contrast material may improve the assessment of infiltration into adjacent tissues and tumor vascularity. However, T1- and T2-weighted sequences provide excellent contrast resolution, and vessels can be displayed sufficiently without the use of contrast material (16). In one study, the accuracy of T2-weighted and gadolinium-enhanced T1-weighted sequences in defining the local-regional tumor extent were compared, and no difference was found (24).

The main limitations of MR imaging are their local availability in some countries and, as compared with CT, the need for sedation in young children because of the longer acquisition time. In patients with intraspinal extension of primary paraspinal tumors, MR imaging is the recommended imaging modality (14,25) because of the excellent visualization of the spinal cord, nerve roots, and subarachnoid spaces. Specific technical recommendations for imaging neuroblastic tumors in children, including CT scanning settings, MR sequences, three-dimensional measurement methods, and data storage, are provided in the Appendix (online).

**Recommended Terms to Describe IDRFs**

To ensure uniform tumor staging, it is recommended that radiologists use specific terms to describe the relationships between tumors and the neighboring vital structures—those entities that cannot be sacrificed without impairing function. As a part of treatment planning, these relationships should be systematically discussed by a multidisciplinary team that includes ideally radiologists, nuclear medicine physicians, surgeons, and pediatric oncologists.

Although metastatic disease (stage M or MS) is staged regardless of the local-regional tumor extent, the absence or presence of an IDRF for the primary tumor should always be assessed to aid surgical decisions.

For patients who are either observed only or treated with primary chemotherapy, imaging has to be repeated, either to document tumor regression or as a preparative assessment. Since an IDRF may disappear with tumor regression (26), reporting should include reassessment of the patient’s IDRF status. A checklist of IDRFs is provided as supplemental material (Fig E13 [online]) to facilitate and ensure uniform and correct staging at diagnosis; however, this checklist is not intended to be a substitute for the local radiologist’s report.

**Anatomic Compartments and Multifocality**

Most tumors occur in a single anatomic compartment (ie, neck, chest, abdomen, pelvic cavity). However, some tumors may extend into an adjacent compartment. This extension often increases the risk of injury to vital structures during surgery, and such lesions should be classified as stage L2 tumors, even if no other IDRF is present in each compartment. This usually occurs with cervicothoracic lesions arising from the sympathetic chain (25), lower mediastinal tumors extending into the retroperitoneum along the aorta (Fig 1), upper retroperitoneal tumors extending into the inferior mediastinum (Fig 2) or pelvis, or pelvic presacral tumors extending either upward in the abdomen around the aorta or inferior vena cava or laterally through the greater sciatic foramen.

Multifocal primary neuroblastomas are rare and may be familial (27,28). They can manifest as synchronous or metachronous noncontiguous tumors. When multifocal tumors occur, each neoplasm should be staged according to the greatest extent of disease. This special feature should be recorded but by itself is not considered an IDRF.

**Definitions of Terms to Describe Relationships between Primary Tumor and Vital Structures**

We recommend that the following terms be used to describe the primary tumor:

1. Separation means that a visible layer, usually fat, is present between the tumor and the neighboring structure (Fig E3 [online]). When a tumor is separated from a vital structure, an IDRF is not present.

2. Contact means that no visible layer is present between the tumor and the neighboring structure. For an artery, contact means that less than 50% of the vessel’s circumference is in contact with the tumor (Fig 3, Fig E4 [online]). In addition, the term flattened is used to describe veins with a reduced diameter that still have a partially visible lumen (Figs 2, 3, Fig E5 [online]). When a tumor is in contact with a vital structure or is flattening a vein without encasement, an IDRF is not present, except in the case of renal vessels (see following text).

3. Encasement means that the neighboring structure is surrounded by the tumor. When a tumor is encasing a vital structure, according to previous definitions, an IDRF is present. Encasement of a vessel means that more than 50% of the circumference is in contact with the tumor (Figs 2–5, Fig E6 [online]). Total encasement means that a vital structure (organ or vessel) is completely surrounded by the tumor. A flattened vein with no visible lumen is also considered to be encased.

4. Compression is used only when referring to the airways. When a tumor is in contact with the airways and causes the short axis of the airways to be reduced (Figs 3, 6, Fig E5 [online]), this pattern is considered an IDRF. For other vital structures (ie, neighboring organs), a contact may be associated with displacement—that is, an abnormal anatomic location—or distortion—that is, an abnormal anatomic shape—of the structure (Figs E7, E8 [online]). However, these situations are not considered IDRFs unless there is infiltration or total encasement.

5. Infiltration refers to involvement of vital structures other than vessels. Infiltration of the vessel wall cannot be demonstrated at imaging. An infiltrating tumor has extension into a neighboring organ, causing the margins between the tumor and the infiltrated structure to be lacking or ill defined (Fig E8...
When a tumor infiltrates a vital structure, an IDRF is present.

6. The term invasion was also originally included in the IDRF list to describe relationships with the renal pedicle (8); however, this is a less well-defined term. Because surgical dissection of the renal pedicle is particularly risky in patients with neuroblastoma, it was decided that an IDRF is present even if the strict criteria for encasement are not fulfilled—that is, even if the tumor is in contact with the renal vessels only. (This specific location is addressed in the following section.) The term invasion was also used to describe spinal canal involvement and is equivalent to the term infiltration for this specific location. (This specific location is addressed in the following section.)

IDRF Assessment Based on Anatomic Location

Cervical neuroblastomas arise mainly from the superior cervical sympathetic chain behind the internal carotid artery. These tumors usually extend anteriorly and laterally, displacing the carotid artery and internal jugular vein. They may also extend medially, compressing the airway (Fig E5 [online]), and upward to the skull base along the carotid artery. Intraspinal extension is usually not observed at this anatomic level. IDRFs are present when the tumor encases the carotid artery (Fig 4), vertebral artery, or internal jugular vein; extends to the
Complications is considerably increased. Associated foraminal and intraspinal extensions are also possible. IDRFs are present when the tumor encases the brachial plexus roots, subclavian vessels, or vertebral or carotid artery or when it compresses the trachea (Fig 5).

Most thoracic neuroblastomas arise from the paraspinal sympathetic chains in the posterior mediastinum. Foraminal and intraspinal extensions (ie, dumbbell tumors) are often present at this anatomic level. Surgical removal of the intraspinal component is usually not recommended at diagnosis, but it may be necessary as an emergency procedure in the presence of acute neurologic symptoms caused by spinal cord compression or ischemia. Cord compression may be diagnosed because of neurologic signs or on the basis of imaging findings. An IDRF is present when more than one-third of the spinal canal in the axial plane is invaded (ie, infiltrated) (Figs 1, 6, Fig E9 [online]), the leptomeningeal fluid spaces are no longer visible, or the spinal cord MR signal intensity is abnormal (ie, imaging features that are usually observed in patients with neurologic symptoms).

The other major surgical difficulties are related to relationships with the descending aorta and the pulmonary pedicles. Encasement of the aorta (Fig 1, Fig E9 [online]) or major branches, compression of the trachea or principal bronchi (Fig 1), and infiltration of adjacent structures such as the pericardium, pleura (Fig 1), and skull base (Fig 4); or compresses the trachea.

Cervicothoracic neuroblastomas arising from the region of the stellate ganglion are rare but associated with particular imaging patterns and surgical difficulties (26). The stellate ganglion is located above the subclavian artery at the level of the origin of the vertebral artery. When dissection of neurovascular elements in this region is needed for tumor excision, the risk of surgical

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**Figure 3**

Diagrams illustrate relationship between tumor (NB) and vessels on two views in planes orthogonal and parallel to vessel axis, respectively. (a) Contact means no visible layer is present between tumor and neighboring structure. For an artery, contact means that less than 50% of vessel’s circumference is in contact with the tumor. A vein that has a reduced diameter but still a partially visible lumen is referred to as a flattened vein, which is considered equivalent to contact. In such situations, an IDRF is not present (except for renal vessels). (b) Encasement means that vessel is surrounded by the tumor and is classified as an IDRF. Encasement of a vessel means that more than 50% of vessel’s circumference is in contact with the tumor; 100% of the circumference in contact with the tumor would indicate total encasement. In addition, a flattened vein with no visible lumen is considered equivalent to encasement and must also be considered an IDRF.

**Figure 4**

(a) Axial fat-saturated T2-weighted and (b) sagittal contrast-enhanced (gadoterate meglumine, Dotarem, Guerbet, Roissy, France) T1-weighted MR images in 4½-year-old girl with right cervical ganglioneuroblastoma. Internal carotid artery (arrow) is partially encased by tumor, with about 80% of artery circumference in contact with tumor, and tumor (•) extends to skull base (arrowhead). Both conditions are IDRFs.
Diaphragm are considered IDRFs. In our experience, the difficulties in surgically dissecting infiltrating mediastinal tumors obviously arising from the periaortic sympathetic plexuses are usually the same as those encountered with infiltrating periaortic abdominal tumors. At imaging, these tumors are ill-defined masses infiltrating adjacent structures, and they differ from well-circumscribed tumors (Fig E4 [online]) arising from paravertebral sympathetic chains.

Abdominal neuroblastomas arise from the adrenal gland, sympathetic ganglia (celiac, superior, and inferior mesenteric ganglia), or sympathetic fibers and plexuses along the aorta and its main branches. The intimate relationships between the primary tumor and abdominal vessels usually represent the main challenge for the surgeon. Therefore, accurate analyses and descriptions of all arteries and veins are critical parts of the imaging reports. The main abdominal vessels (aorta, celiac axis, superior and inferior mesenteric arteries, renal arteries and veins, inferior vena cava, iliac arteries and veins, portal vein) should be separately assessed and classified according to the terms just defined. Tumors partially or totally encasing the origin of the celiac axis (Figs 2, 7), the superior mesenteric artery, the aorta (Fig 1, Fig E6 [online]), one or both renal pedicles (Figs 2, 7, Fig E6 [online]), the inferior vena cava, or the iliac vessels (Fig E10 [online]) are IDRF positive. Since injury to the inferior mesenteric artery almost never causes complications, encasement of this vessel is not by itself an IDRF.

Renal pedicles are frequently involved in retroperitoneal neuroblastomas. In the first study of the Localized Neuroblastoma European Study Group (30) of the International Society of Pediatric Oncology, 51% of patients with localized abdominal neuroblastoma had IDRFs, and 45% of these had involvement of the renal pedicles. In the Shamberger et al series (31), 15% of children treated for abdominal neuroblastoma required nephrectomies or had a renal infarction during surgery. Furthermore, the risk for nephrectomy in children who underwent tumor excision up front...
was twice that of those who underwent resection after chemotherapy. Therefore, even isolated contact with renal vessels is considered an IDRF-positive condition (Fig 8).

The adjacent organs and structures should also be precisely assessed and classified according to the earlier defined terms. Tumors infiltrating the porta hepatis (liver hilum) (Fig 7), diaphragm (Fig 2, Fig E11 [online]), kidneys (Figs E6, E8 [online]), liver, duodeno-pancreatic block (Fig 7, Fig E6 [online]), or mesentery (Fig E12 [online]) are IDRF positive. Neuroblastomas arising from the inferior mesenteric region (organ of Zuckerkandl) more frequently infiltrate the mesentery (32) than do neuroblastomas in other locations. Regarding the kidneys, infiltration may occur directly through the cortex (usually from adrenal neuroblastomas) (Fig E8 [online]) or through the hilum along renal vessels (Fig E6 [online]) (usually from retroperitoneal neuroblastomas).

Lumbar paraspinal neuroblastomas are much less common. Frequently classified as having abdominal locations because of their anterior extension, these tumors are different from the above described retroperitoneal ones. They may be associated with foraminal and intraspinal extension (dumbbell tumors) (Fig E11 [online]), sharing the same pattern and neurologic issues as mediastinal primary tumors. As in the mediastinum, an IDRF is present when more than one-third of the spinal canal in the axial plane is invaded (Fig E11 [online]), when the leptomeningeal spaces are not visible, or when the spinal cord MR signal intensity is abnormal. Tumors involving the lumbar plexus (Fig E10 [online]) are associated with the inherent risk of surgical injury and should be classified as IDRF positive.

Pelvic neuroblastomas arise mainly from the upper hypogastric sympathetic plexus or presacral sympathetic ganglia. Pelvic organs are usually anteriorly displaced but not infiltrated. Major extension occurs along the iliac vessels and into the lumbosacral foramina. Tumors encasing the aorta, inferior vena cava, or iliac vessels (Fig E10 [online]) are considered IDRF positive. Posterior lumbar venous structures are included in the IDRF positive group only if the aorta or iliac vessels are involved. However, most pelvic neuroblastomas respect the pelvic splanchnic nerves, and these structures are not considered IDRF positive.
or sacral foraminal extensions are IDRF negative, but intraspinal extension is IDRF positive when more than one-third of the spinal canal in the axial plane is invaded.

Intraspinal tumor extension below the level of the L2 vertebra leads to radicular involvement (Fig 9) rather than spinal cord compression. This condition seldom leads to emergency neurosurgery and is usually not a contraindication to primary excision of the extraspinal tumor component. More rarely, tumors extend laterally into the gluteal region through the greater sciatic foramen (an IDRF). Dotted lines between the spine of the ischium and the lateral margin of the sacrum represent the greater sciatic foramen location.

Figure 9: (a) Axial fat-saturated T2-weighted and (b) sagittal nonenhanced T1-weighted MR images in 14-month-old boy with pelvic neuroblastoma infiltrating sacral holes and dural cul de sac (not an IDRF) (arrows). This low-situated spinal extension does not lead to spinal cord compression; rather, it leads to radicular involvement only. Tumor extends into right gluteal region (arrowhead) through greater sciatic foramen (an IDRF). Dotted lines between the spine of the ischium and the lateral margin of the sacrum represent the greater sciatic foramen location.

Figure 10: Anterior (left) and posterior (right) planar MIBG scans of 5-year-old girl with left retroperitoneal neuroblastoma. MIBG uptake in primary tumor (arrow), as well as diffuse osteomedullary metastases in cranial vault, skull base, sternum, spine, humerus, ribs, pelvis, femurs, and tibias, is visible.

Imaging of Metastatic Disease

Bone Marrow and Bone Metastases

Distant metastases of neuroblastomas are located primarily in bone marrow (70%) or bone (55%) (33). Bone marrow involvement must be assessed by using both imaging and bilateral bone marrow aspirate and biopsy. Distant metastases must be assessed by using MIBG scintigraphy, and the study must be performed before tumor excision (Fig 10) (8,34). Guidelines have been published for MIBG scanning in children (34–36).

Since there is no physiologic uptake of MIBG in bone or bone marrow, MIBG scanning is an accurate method for detecting osteomedullary metastases (Fig 10), with sensitivity and specificity estimated at 90% and 100%, respectively (37,38). MIBG single photon emission computed tomography (SPECT) enables better depiction of the small focal uptake that is difficult to visualize on planar MIBG scans, especially in areas close to intense physiologic uptake such as the...
If required in a specific study, dedicated conventional radiography or CT may be helpful in patients with MIBG-positive osteomedullary metastases for distinguishing bone marrow from cortical bone involvement. The role of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) in the setting of neuroblastoma is still under investigation. The feasibility of PET in young children, the associated radiation exposure, and the higher cost, as compared with those associated with MIBG scanning, may explain the hitherto limited use of this technique. Another limitation is the high physiologic uptake of FDG in the brain, which may hide skull locations. However, FDG PET may help define the distribution of neuroblastomas that fail to take up MIBG (42,45) (Fig 12). FDG PET is superior for liver and the bladder. Postprocessing tools also enable fusion of SPECT and CT images (Fig 11), improving anatomic localization (39–41).

One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. However, a single equivocal lesion on MIBG scans requires confirmation with another imaging modality—namely, conventional radiography, and MR imaging or CT if the radiographic findings are negative—or with biopsy. To better assess the extent of disease and the response to therapy, the use of a semiquantitative scoring system is strongly recommended (34).

Technetium Tc 99m medronate bone scintigraphy is usually not required, except in cases in which the primary tumor is not MIBG avid or MIBG positivity cannot be confirmed (ie, if the primary tumor has been removed before examination) (8). Bone scan has a reported sensitivity of 70%–78% and a specificity of 51% for the detection of bone metastases (38,42). The high physiologic uptake of the growing metaphyses in children, especially infants, may be misinterpreted as metastases or hide small metastases (43). Skeletal surveys have previously been recommended for infants with negative bone scan findings (7,43). However, in our experience, these rarely add important information and accordingly are not considered helpful. CT examinations performed to assess local disease also commonly depict bone metastases. Although CT was used in some previous protocols as a prognostic part of the staging (44), it is known to be inaccurate for detecting bone metastases because of its low sensitivity compared with that of MIBG or bone scan (20).
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Diffusion restriction because of high cellular density (55). Therefore, MR imaging could become a major imaging tool in children, allowing staging of both local-regional and distant disease. However, further studies are needed to assess the accuracy of this imaging strategy.

Other Metastatic Sites

The anatomic location of involved lymph nodes should be precisely assessed. An upper abdominal tumor with contiguous or noncontiguous enlarged lower mediastinal nodes or a pelvic tumor with contiguous or noncontiguous inguinal lymph nodes is considered metastatic (stage M). Liver and subcutaneous metastases are mainly observed in infants (Pepper syndrome, stage 4S or MS) (33). Liver metastases can be assessed with US, CT, or MR imaging. Liver metastases may manifest in one of two forms: focal masses or diffuse infiltration. The latter
Although not a staging issue, when skull base involvement is clinically suspected or depicted on MIBG or bone scans, brain MR imaging or CT should be performed to detect optic nerve compression (63), which may require emergency treatment. Figure 13 is a flowchart of the imaging strategy at diagnosis for patients with neuroblastoma—both local-regional disease and distant metastases—including mandatory and optional examinations.

Conclusion

Patients with neuroblastoma should be stratified at the time of diagnosis on the basis of reproducible imaging criteria. Increased focus on imaging enhances the role of radiologists in diagnosis and treatment planning.

Treatment strategies must be decided by the individual cooperative groups. Nevertheless, an international group has for many years used the absence of IDRFs to select patients for primary surgical treatment (30). It is therefore anticipated that the knowledge accumulated on the basis of the concept of IDRFs will become an increasingly larger integrated part of therapy planning, both for treatment protocols and for individual patients.

These guidelines can be considered a platform for further studies. As with all projects involving international collaboration, compromises had to be made to reach consensus guidelines and recommendations. However, with continuous efforts, these can be improved and updated as needed. To do so, new and accurate information has to be acquired. If incorporated into protocols and used systematically, the guidelines will facilitate the collection of consistent and standardized data that will be useful for evaluating the effect of IDRFs on patient outcomes.

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