Cancer Imaging (2011) **11,** S44–S47
DOI: 10.1102/1470-7330.2011.9008

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PAEDIATRIC ONCOLOGICAL IMAGING

Monday 3 October 2011, 13:300–15:00

Imaging neuroblastoma: what the radiologist needs to know

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Abstract

Neuroblastoma is the most common extracranial solid malignancy in children. The tumor has variable biological behavior that can be predicted by patient age, genetic features, tumor biology and extent of disease at diagnosis. Factors chosen by various cooperative groups to define risk of treatment failure have been non-uniform. Therefore, historically, it has been difficult to compare outcomes across clinical trials performed around the world. This has hindered the advancement of treatment strategies to improve survival of these patients. The International Neuroblastoma Risk Group (INRG) was established in 2004 to develop a consensus approach to pretreatment risk stratification. The result was the development of the INRG Staging System (INRGSS) which relies on imaging-defined risk factors (IDRFs) that are determined before surgery or other therapy. With the application of the INRGSS the radiologist's role in staging children with neuroblastoma is increased. This review provides an overview of the INRGSS and the IDRFs.

Keywords: *Neuroblastoma; paediatric.*

Introduction

Neuroblastoma, the most common extracranial solid pediatric malignancy, is an embryonal tumor of the sympathetic nervous system. Along with rhabdomyosarcoma, Ewing sarcoma and lymphoma, these malignancies collectively represent the small, round blue cell tumors of childhood[1]. In the United States the incidence is estimated at 1 in 10,000 births or about 500 new cases per year[2]. Neuroblastoma has been described as an enigmatic tumor because of its highly variable biologic behavior. Tumors may spontaneously regress, differentiate into benign ganglioneuromas or follow an unrelenting progressive course with ultimate fatal outcome[1–5]. More than 50% of patients present with high-risk features including large, unresectable tumors and widely metastatic disease. The prognosis for these patients remains suboptimal with a long-term survival of about 40%[1,3,4].

The International Neuroblastoma Staging System (INSS), developed in 1988 and modified in 1993, is still used by many cooperative groups today. This system relies on tumor resectability as well as pathologic features of the tumor (Table 1). A limitation of the system is that the same tumor can be classified as INSS stage 1 or 3 depending on the local surgeon's experience and expertise. Also, tumors that are expected to spontaneously regress cannot be adequately staged using the INSS. In addition, assessment of lymph node involvement is difficult to apply uniformly across institutions. These drawbacks led to heightened international collaboration to facilitate comparison of results of clinical trials

Table 1 The original International Neuroblastoma Staging System[15]

Tumor stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual; representative ipsilateral lymph nodes negative for tumor. Nodes attached to and removed with tumor may be positive
2A	Localized tumor with incomplete gross excision; ipsilateral nonadherent lymph nodes negative for tumor
2B	Localized tumor with or without complete gross excision, ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes negative for tumor
3	Unresectable unilateral tumor infiltrating across midline (beyond opposite side of vertebral column) with or without regional lymph node involvement, or midline tumor with bilateral extension via infiltration (unresectable) or lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor with disseminated disease limited to skin, liver and/or bone marrow (only in infants <1 year, marrow involvement <10% on biopsy and MIBG negative marrow)

performed worldwide. In 2004 the International Neuroblastoma Risk Group (INRG) Task Force was formed to develop the INRG Staging System (INRGSS) and INRG Risk Classification System, both published in 2009[6,7].

The INRGSS is designed to stage patients before surgery or other therapy[7]. Tumors are classified as L1 or L2 disease based on whether one or more of 20 imaging-defined risk factors (IDRF) are present. The IDRFs are imaging features that predict the risk of tumor resection. With the INRGSS, the focus has shifted from surgicopathologic staging to imaging. Since imaging can be retrospectively and centrally reviewed by experts in the field, a system based on baseline imaging features should be more robust and reproducible than one based on surgical resection. It is hoped that this will result in an accelerated refinement of risk stratification and more appropriate therapies for individual patients. The INRGSS is not intended to replace the INSS but should be used in parallel. Because INRGSS staging is based on imaging features, the radiologist's role will be increased. The purpose of this review is to heighten the radiologist's awareness of the definitions and importance of the IDRFs in neuroblastoma[6–8].

INRGSS staging based on IDRFs

There are four INRGSS stages: (1) Stage L1 tumors are localized tumors that do not involve vital structures as defined by the IDRFs (Table 2). Tumor must be confined to one body cavity, i.e. neck, chest, abdomen or pelvis. The isolated finding of intraspinal tumor extension does not fulfill the criteria for an IRDF and such tumors are considered stage L1. (2) Stage L2 tumors are local regional tumors with one or more IDRF. The tumor may be ipsilaterally continuous across body cavities. For example, a left-sided abdominal tumor with left-sided chest involvement is considered L2. However, a left-sided abdominal tumor with clearly right-sided chest involvement is considered metastatic. (3) Stage M is defined as distant metastatic disease (not contiguous with the primary tumor) except when defined as Stage MS. Non-regional, distant, lymph node involvement is considered metastatic disease. However, an upper abdominal tumor with enlarged lower mediastinal nodes or a pelvic tumor with inguinal adenopathy is considered local regional disease. Ascites and pleural effusion, even when they contain malignant cells, do not constitute metastatic disease unless they are remote

Table 2 Description of imaging-defined risk factors for the International Neuroblastoma Risk Group Staging System[8]

Anatomic region	Description
Multiple body compartments	Ipsilateral tumor extension within two body compartments
Neck	Tumor encasing carotid artery, vertebral artery, or jugular vein Tumor extending to skull base Tumor compressing trachea
Cervicothoracic junction	Tumor encasing brachial plexus Tumor encasing subclavian vessels, vertebral artery or carotid artery Tumor compressing trachea
Thorax	Tumor encasing aorta or major branches Tumor compressing trachea or main bronchi Lower mediastinal tumor infiltrating costo-vertebral junction between T9 and T12 vertebral levels
Thoracoabdominal junction	Tumor encasing aorta or vena cava
Abdomen and pelvis	Tumor infiltrating porta hepatis or hepato-duodenal ligament Tumor encasing branches of superior mesenteric artery at mesenteric root Tumor encasing origin of celiac axis or superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing aorta or vena cava Tumor encasing iliac vessels Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (any level) 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 intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

from the body compartment of the primary tumor. (4) Stage MS is metastatic disease in patients younger than 18 months (547 days) with metastases confined to the skin, liver and/or bone marrow. Bone marrow involvement must be limited to <10% of total nucleated cells on smears or biopsy. If the primary tumor shows avidity for [^{123}I]meta-iodobenzylguanine (MIBG) there must be no evidence of bone or bone marrow disease on MIBG nuclear scintigraphy. If the primary tumor is not MIBG avid, there must be no evidence of bone or bone marrow involvement on [^{99m}Tc]methyldiphosphonate (MDP) nuclear bone scan. The primary tumor can be L1 or L2 and there is no restriction regarding crossing the midline[7,8]. In addition to the IRDFs and independent of stage, three special conditions should be recorded: (1) multifocal primary tumors, (2) pleural effusion, and (3) ascites. Multifocal primary tumors are rare and may be familial[9]. They can present as synchronous or metachronous noncontiguous tumors[8]. Patients with multifocal tumors should be staged according to the greatest extent of disease as defined above.

Terms used to define IDRFs

To promote reproducible staging it is recommended that radiologists use specific terms to describe the relationship between tumors and neighboring vital structures. Vital structures are those that cannot be sacrificed without causing impaired function. The following terms and definitions should be used to describe the primary tumor[8].

(1) Separation means that a visible layer (usually fat) is present between the tumor and the neighboring structure. When a tumor is separated from a vital structure an IRDF is not present.
(2) Contact means no visible layer is present between the tumor and adjacent structure. For an artery, contact means <50% of the vessel's circumference is in contact with tumor. The term flattened is used to describe veins with reduced diameter that still have a partially visible lumen. 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 below).
(3) Encasement means that the neighboring structure is surrounded by tumor. When tumor encases a vital structure, an IDRF is present. For a vessel, encasement means >50% of the vessel circumference is in contact with tumor. Total encasement means that a vital structure is completely surrounded by tumor. A flattened vein with no visible lumen is considered to be encased.
(4) Compression is used only when referring to airways. When tumor contacts an airway and causes the short axis to be reduced, this is considered an IDRF. For other vital structures, a contact may cause displacement (abnormal anatomic location) or distortion (abnormal anatomic shape), but these situations are not considered IDRFs unless there is infiltration or total encasement.
(5) Infiltration refers to involvement of vital structures other than vessels since infiltration of a vessel wall cannot be determined from imaging. An infiltrating tumor demonstrates extension into an adjacent organ thus causing the margins between them to be absent or poorly defined. When a tumor infiltrates an adjacent structure an IDRF is present.
(6) Because surgical dissection of the renal pedicle is risky in patients with neuroblastoma, an IDRF is present even if the strict criteria for encasement are not fulfilled, that is, even if the tumor is only in contact with the renal vessels.

Several anatomic sites require further clarification. An IDRF is present when more than one-third of the spinal canal, in the axial plane, is infiltrated, the leptomeningeal fluid spaces are no longer visible or the spinal cord magnetic resonance signal intensity is abnormal. Tumors that infiltrate the spinal canal below the level of the spinal cord are considered IDRFs if they fulfill these criteria. Pelvic tumor infiltrating the greater sciatic foramen is considered an IDRF. A lower mediastinal tumor that infiltrates the costovertebral junction between the T9 and T12 vertebral levels is associated with a theoretic risk of spinal cord ischemia caused by surgical injury to the anterior spinal artery (artery of Adamkiewicz) and is considered an IDRF. Because injury to the inferior mesenteric artery (IMA) almost never causes complications, encasement of this vessel is not considered an IDRF (i.e. the IMA is not a vital structure). Kidneys can be infiltrated through the cortex, by adrenal tumors, or through the renal hilum by retroperitoneal tumors[8].

Metastatic disease

Approximately 50% of neuroblastoma patients present with metastatic disease[10]. In the INRGSS, metastatic disease is designated Stage M and is distinct from Stage MS which refers to metastatic disease in children younger than 18 months with metastases confined to the skin, liver, and/or bone marrow (<10% involvement on bone marrow biopsy with negative MIBG). Patients with lymph node involvement outside the body cavity of the primary tumor are considered to have disseminated metastatic disease. Metastases occur hematogenously, most commonly to the bone marrow (70%) or bone (55%) and less commonly to the liver. Metastatic disease to the lung and brain parenchyma is seen in end-stage disease and is becoming more commonly recognized in children undergoing current therapy who have longer survival[11]. Distant metastasis must be assessed with MIBG nuclear scintigraphy. Because approximately 10% of neuroblastoma is non-MIBG avid, MIBG imaging

must be performed before resection of the primary tumor[7]. Patients with non-MIBG avid primary tumors should be assessed with [^{99m}Tc]MDP bone scan[12]. Bone marrow involvement is assessed by both imaging and bone marrow aspirate and biopsy. One unequivocal site of abnormal, distant MIBG avidity is sufficient to define metastatic disease. However, a solitary, equivocal focus of MIBG uptake must be confirmed with additional imaging or biopsy. The use of single-photon emission computed tomography (SPECT)-CT has proven utility in accurately localizing sites of MIBG avidity when planar MIBG imaging or diagnostic CT or MR imaging is equivocal[13]. To standardize the assessment of extent of bone/bone marrow disease and response to therapy, a semi-quantitative scoring system is recommended[12].

Conclusions

As efforts are made by the international community toward standardizing the staging of children with neuroblastoma the role of the radiologist is increasing. Therefore, it is important for radiologists to be familiar with the IDRFs set forth by the INRG. Because the INRGSS is based on the extent of disease before surgery or other therapy, the criteria should be more robust and reproducible than the prior staging system, which was based on extent of surgical resection. The IDRFs have already proven valuable in predicting surgical risk and surgical outcome[14]. The goal of the INRGSS is to facilitate the comparison of clinical trials worldwide and ultimately accelerate the advancement of treatment strategies for children with neuroblastoma.

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