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Practical Application of the International Neuroblastoma Risk Group Staging System: A Pictorial Review

Fernanda Del Campo Braojos, MD[a,b], Lane F. Donnelly, MD[a,c,d,*]

[a] Department of Radiology, Texas Children's Hospital, Houston, TX
[b] Department of Radiology, Hospital da Crianca e Maternidade de Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil
[c] Department of Radiology, Stanford University School of Medicine, Stanford, CA
[d] Center for Pediatric and Maternal Value, Lucile Packard Children's Hospital at Stanford, Stanford, CA

Because of issues with the previous staging system, the International Neuroblastoma Risk Group Staging System (INRG-SS) was created in 2009. The INRG-SS is based on preoperative imaging, rather than surgical, staging and emphasizes Imaging-Defined Risk Factors as the determining factors between L1 and L2 stages. Like with the introduction of any new tool, based on the authors' experience, there has been a time-lag related to adoption of the **INRG-SS** staging system by radiologists. This pictorial essay offers a practical approach to learning and utilizing the INRG system, emphasizing use of the descriptive terms which determine the presence or absence of imaging-defined risk factors.

Introduction

Neuroblastoma is the most common extracranial solid tumor in children. It can occur in multiple sites along the sympathetic nervous system and represents the most common extracranial solid malignancy in pediatric population.[1] At the moment of diagnosis approximately 60% of patients can have disseminated metastatic disease, especially involving bones, lymph nodes, and liver.[1] The prognosis is highly variable with some widespread tumors demonstrating spontaneous regression without therapy while others have progressive aggressive disease leading to death despite maximum modern therapy.[2] Predictors of this widely variable biological behavior include age of diagnosis, serum lactate dehydrogenase level, histologic tumor grade, N-MYC gene amplification, DNA ploidy, aberrations of 1q and 11q chromosomes, and clinical anatomic staging.[3]

Because anatomic and surgical staging is essential to prognosis and treatment planning, there has been emphasis on staging systems. The *International Neuroblastoma Risk Group* Staging System **(INRG-SS)** was created in 2009. This system is based on preoperative imaging, rather than surgical staging, and emphasizes the use of Imaging-Defined Risk Factors (**IDRFs**) as the determining factors between L1 and L2 stages. There are several issues that may be contributing to a slow adoption of the INRG-SS by radiologists. First, many radiologists are most familiar with the *International Neuroblastoma Staging System (*INSS*)* which was created in 1988. Second, the number and historic presentation approach of **IDRFs** can be overwhelming to radiologists attempting to learn the new system. This pictorial essay offers a practical approach to learning and utilizing the INRG system, emphasizing use of the descriptive terms which determine the presence or absence of IDRFs. The retrospective selection of case material for this pictorial essay was approved by our Institutional Review Board.

The INSS staging system for neuroblastoma was created in 1988 and updated in 1993.[4] It has been previously described in detail.[4,5] Stage 1 is localized tumor with complete gross excision. Stage 2 is localized tumor with incomplete gross excision. Stage 3 is unresectable unilateral tumor infiltrating across the midline (beyond the opposite side of the vertebral column) or unresectable midline tumor with bilateral extension. Stage 4 is presence of distant metastatic disease (lymph nodes, bone, bone marrow, liver, skin, and other organs). And, Stage 4S is localized primary tumor (Stage 1 or 2) with metastatic tumor limited to involvement of the skin, liver, and/or bone marrow in a child less than 1-year of age.[4] The remarkable thing is that while the prognosis for Stage 4 neuroblastoma is poor, the prognosis for Stage 4S is excellent, often resolving without treatment.[6]

If most care providers are familiar with the INSS and it has been in use for 30 years, what are the driving factors to switch to a new staging system, the INRG-SS? The problems are related to the inability to respectively review the INSS results because it is based on findings at surgery.[5,7] Also, reproducibility can be an issue as stage can vary from stage 1 to stage 3 based on variation in the surgeon's experience and expertise.[5,7] In addition, tumors that are expected to spontaneously regress often are managed nonsurgically and therefore cannot truly be staged using the INSS. In addition, unlike imaging studies, surgical evaluation is not retrospectively reviewable and this has important implications for data collection for clinical trials. These issues lead to the creation of an imaging based neuroblastoma staging system, the INRG-SS.[5-9]

*Reprint requests: Fernanda Del Campo Braojos, MD, Lucile Packard Children's Hospital at Stanford Professor, Stanford University School of Medicine, Stanford Children's Health, 180 El Camino Real Ste M384, Mail Code: 5885, Palo Alto, CA 94304.
E-mail addresses: lanefd@stanford.edu, lane.donnelly@stanford.edu (L.F. Donnelly).

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TABLE 1
INRG tumor stages

Stage	Description
L1	• Local tumor: absence of IDRFs
L2	• Local tumor: presence of one or more IDRFs
M	• Distant metastatic disease (except below)
MS	• Metastatic disease – confined to skin, liver, and/or bone marrow • Child <18 months of age

International Neuroblastoma Risk Group Staging System

The **INRG-SS** was created by an international effort between multiple pediatric oncology groups.[8,9] It is based on preoperative imaging, rather than surgical, staging. Because of this, the results are retrospectively reviewable and are considered more reliable than the narrative of what was found at surgery.[5,7] L1 versus L2 staging determination is dependent upon the presence or absence of an IDRF. The INRG-SS has four tumor stages: L1, L2, M, and MS. The **INRG-SS** tumor stages are summarized in Table 1. L1 represents localized tumor not involving vital structures as defined by the absence of any IDRFs. Stage L2 is localized tumor which does involve vital structures as determined by the presence of one or more IDRFs. M represents distant metastatic disease. MS is metastatic disease in children less than 18 months with involvement confined to the skin, liver, and/or bone marrow. Note that the INRG-SS Stage MS, which is similar to the previous INSS Stage 4S, extends the age of eligibility from the previous 1 year to 18 months.[5,7,9]

Use of the INRG-SS allows for the staging of neuroblastoma to be done using preoperative imaging rather than findings at surgery. This has allowed cases that are being managed nonsurgically to be staged as well as has made retrospective review of staging more reliable than the narrative of what was found at surgery. It has also positioned the radiologist front and center in the staging process.

Vocabulary (Descriptive Term Definition) That Determines the Presence or Absence of *Imaging-Based Risk Factors*

The most potentially challenging part of adapting to and using the INRG-SS is determining whether there is the presence or absence of IDRFs, which differentiates between L1 and L2. Some approaches to describing what is considered IDRFs have listed the potential IDRFs by anatomic locations: neck, cervicothoracic junction, thorax, thoracoabdominal junction, abdomen and pelvis, intraspinal tumor extension, and infiltration of adjacent organs and structures.[5,9] This creates a long list of possibilities. In our opinion, the potential of having to memorize or even operationalize use of that list can be intimidating and impractical to radiologists. We believe that a better approach is to focus on the descriptive terms that determine whether an IDRF is present or absent organized by the vital structure that might be involved. These include arteries, veins, airway, spinal canal, and parenchymal organs.[5,7]

A summary of such descriptive terms and which indicate a positive IDRF, organized by type of vital structure involved, is shown in Table 2. One of the issues that can cause some confusion is that some descriptive terms commonly used in radiology to describe effects on multiple organs, such as “compression”, only are used to describe the airway in the **INRG-SS**. For arteries, an IDRF is not considered present unless there is *encasement*, which is defined as greater than 50% of the circumference of the artery, is surrounded with tumor (Fig 1). When there is separation (Fig 2) or contact (Fig 3), an IDRF is **not** considered to be present. For veins, there has to be flattening of the vein with complete absence of a visible lumen for an IDRF to be considered present (Fig 4). Narrowing of the vein with a venous lumen still visible is not considered an IDRF (Fig 5). One exception to the above is the renal arteries and veins. If a tumor has contact with the renal artery or vein, it is considered “invasion” which is an IDRF.

For the airway, *compression* to any degree is considered an IDRF (Fig 6). Compression has been defined as “short axis of the airways to be reduced”.[5] Beyond this, what constitutes compression in terms of how do you know that the short axis of the airway is reduced as compared to what it would normally look like is not well defined. If the airway is abutted by tumor and does not have the oval or round configuration expected at that level, consider it compressed and an IDRF present.

For the spinal canal, if there is intraspinal extension of the tumor into the spinal canal that involves more than one-third of the area of the canal at that axial level, *invasion* and an IDRF is considered present (Fig 7). If there is tumor extension into the canal but it involves less than one-third of the area of the canal at that axial level, an IDRF is not necessarily considered present (Fig 8). However, for the spinal canal, there are other circumstances that are considered an IDRF. These include: 1) mass

TABLE 2
Definitions of descriptive terms that determine imaging defined risk factors

Vital structure	Term	Definition	IDRF
Arteries	Separation	Fat plane between artery and NBT	**No**
	Contact*	NBT abuts artery with no visible plane present. <**50%** of circumference of artery in contact with tumor	**No**
	Encasement	NBT abuts artery with no visible plane present. >**50%** of circumference of artery in contact with tumor	**Yes**
Veins	Flattening with visible lumen	NBT resulting in narrowing of vein with visible lumen, without complete flattening	**No**
	Flattening without visible lumen	NBT resulting in complete flattening of vein without visible lumen	**Yes**
Airway	Compression	NBT about airway and results in any deformity of airway resulting in decreased caliber of any degree	**Yes**
Spinal canal (intraspinal extension)		Either no extension into spinal canal or NBT extension that involves less than one-third of the volume of the canal at that level	**No**
	Invasion	NBT extension into the canal that involves more than one-third of the volume of the canal at that level, is associated with cord compression or abnormal signal in the cord, or at the T9-T12 level (potential involvement of Artery of Adamkiewicz)	**Yes**
Nonvascular vital structures	Infiltration	NBT extending into a parenchymal organ, pancreaticoduodenal block	**Yes**

NBT, neuroblastoma.
*Note that contact of the tumor with the renal arteries or veins is automatically considered an IDRF even when encasement is not present.

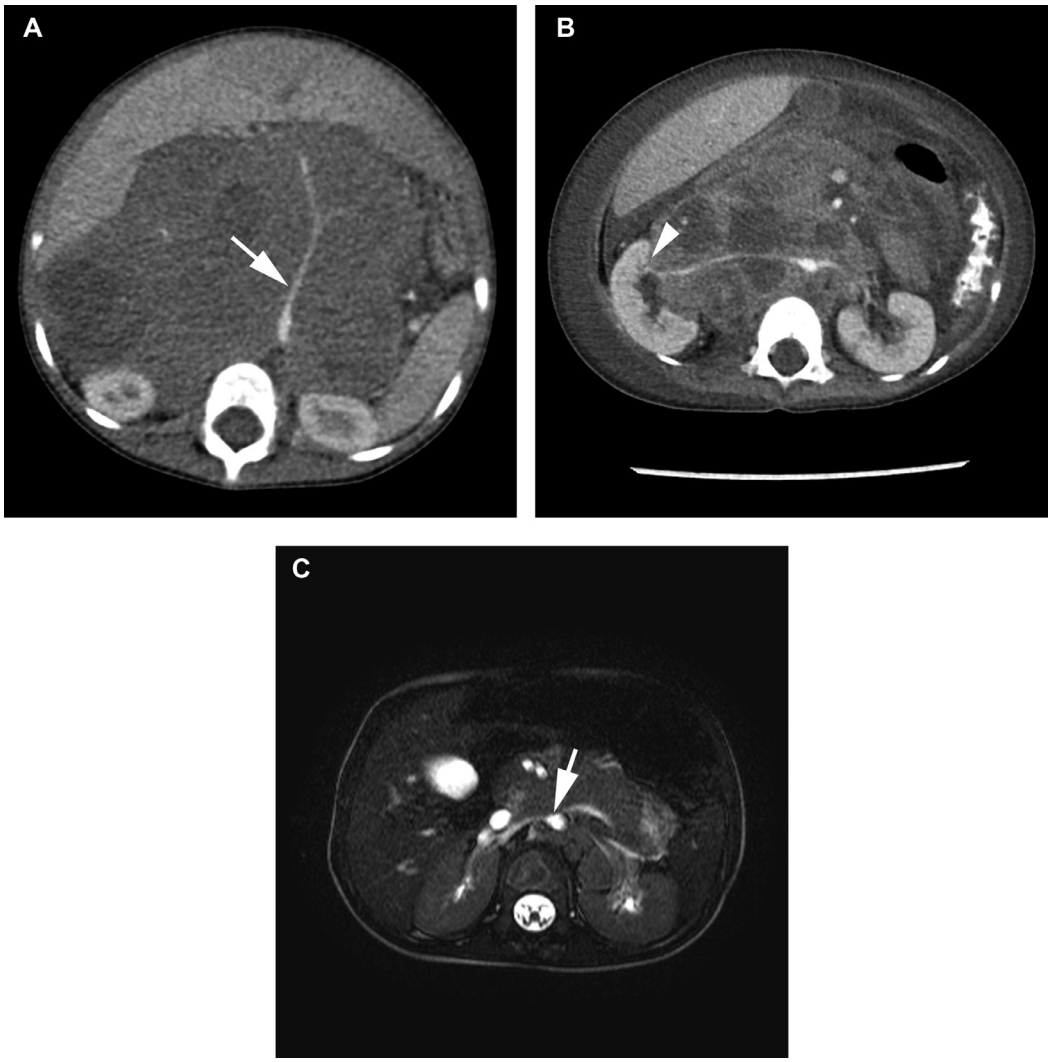

FIG 1. Arterial encasement, consistent with the presence of an IDRF (L2). (A) Contrast-enhanced CT of 1-year-old male with a retroperitoneal solid mass with complete *encasement* of the aorta and celiac axis (arrow). Note there is also *flattening* of the inferior vena cava without a visible lumen (an additional IDRF). (B) Contrast-enhanced CT of 3-year-old boy with a heterogeneous, mainly right retroperitoneal mass, *encasing* both renal arteries and aorta (positive IDRF). Note there is also renal parenchyma *infiltration* on the right side (arrow head) (an additional example of an IDRF) and *flattening* of the inferior vena cava to the extent that it is not visualized (a 3rd example of an IDRF). (C) T2-weighted MR image of 2-year-old boy with a retroperitoneal tumor that *encases* right renal artery and aorta (arrow).

inside the spinal canal, with signs of cord compression; lack of fluid detectable in leptomeningeal spaces; or abnormal signal within the cord 2) mediastinal masses that have any degree of canal involvement between T9-T12 (because of high risk of cord injury related to the Artery of Adamkavich). In addition, involvement of the greater sciatic foramen by a pelvic mass when a pelvic tumor extends beyond a line drawn from the spine of the ischium and the lateral margin of the sacrum is also considered and IDRF.

Finally, for the involvement of nonvascular vital structures like parenchymal organs, including the pancreatoduodenal block, infiltration of the tumor into any of those structures is considered an IDRF (Figs 1B, 4, 9).

The presence of an IDRF determines that a lesion is an L2, rather than an L1. However, if there is distal metastatic disease, the lesion is either staged as M (Fig 10) or MS (if meets criteria) (Fig 11), regardless as to whether IDRFs are present.

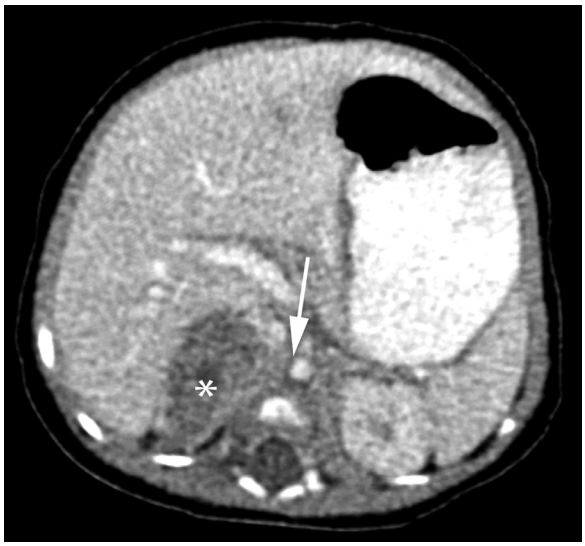

FIG 2. Arterial separation, consistent with absence of IDRF (L1). Contrast-enhanced CT in a 1-month-old girl with a right adrenal mass (*) showing *separation* (arrow) with the aorta. There is also compression without flattening of the inferior vena cava with visible lumen (also not an IDRF).

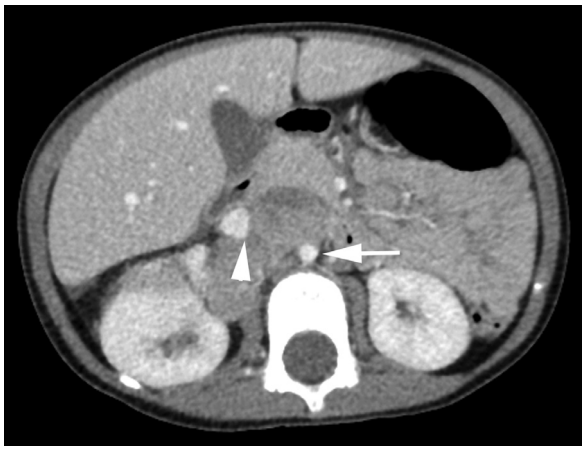

FIG 3. Arterial contact, consistent with the absence of an IDRF (L1). Contrast-enhanced CT in a 3-year-old boy with a right adrenal gland tumor demonstrating *contact* with aorta circumference lesser than 50% (arrow). The inferior vena cava lumen is visible (arrow head) (also no IDRF).

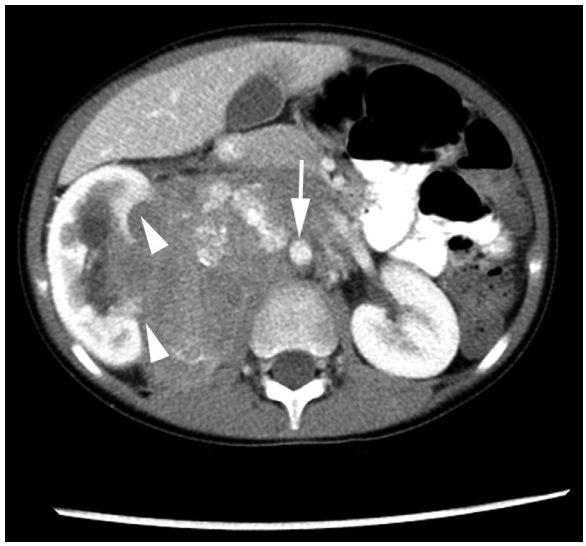

FIG 4. Venous flattening, consistent with the presence of an IDRF. Contrast-enhanced CT in a 4-year-old girl with a predominantly right retroperitoneal partially calcified mass with complete *flattening* of the inferior vena cava, without any identifiable lumen (IDRF). There is also *encasement* of the aorta (arrow) (2nd IDRF) and right renal parenchyma *infiltration* (arrow heads) (3rd IDRF).

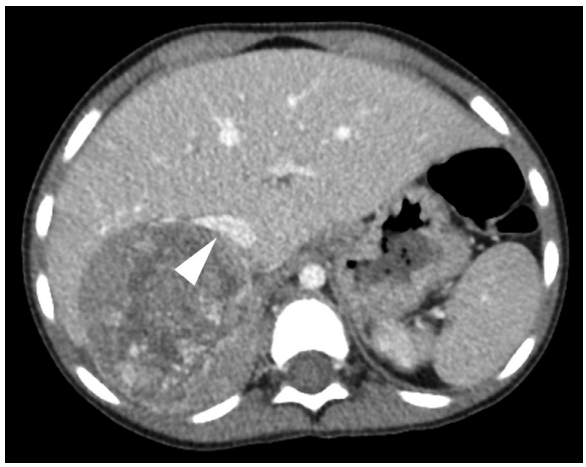

FIG 5. Venous compression without flattening, consistent with the absence of an IDRF. Contrast-enhanced CT of a 3-year-old boy with a right adrenal gland tumor *narrowing* the inferior vena cava (arrow head) with visible lumen.

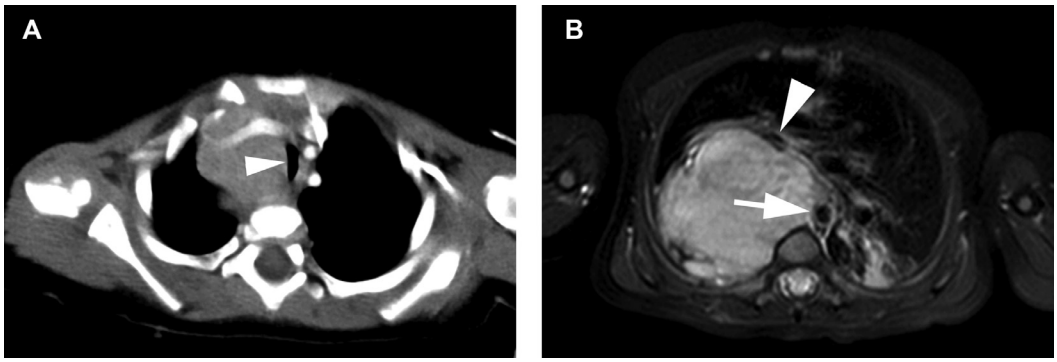

FIG 6. Airway compression, consistent with the presence of an IDRF (L2). (A) Contrast-enhanced CT in a 1-year-old girl with a **s**uperior mediastinal mass showing *compression* and displacement of the trachea (arrow head). (B) Axial T2-weighted MR image in a 1-year-old boy demonstrates a right mediastinal mass *compressing* the right main bronchus (arrow head) and making *contact* with the descending aorta (arrow) (not a second IDRF).

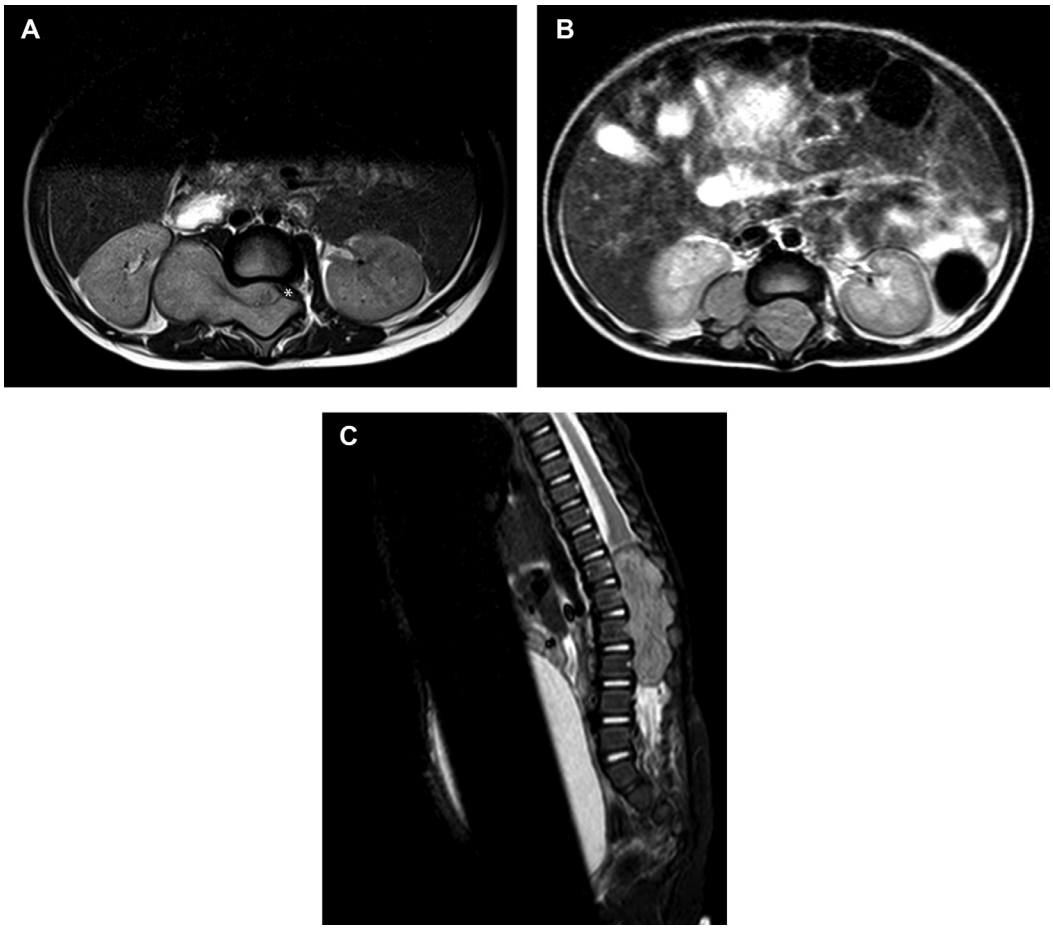

FIG 7. Invasion of the spinal canal, consistent with the presence of an IDRF (L2). (A) Axial T2-weighted MR image in a 1-year-old girl with retroperitoneal neuroblastoma shows intraspinal extension involving more than one-third of lumbar spinal canal, with no leptomeningeal spaces visible and with displacement and compression of the spinal cord (*). (B) Axial T2-weighted MR image in a 1-month-old girl with a retroperitoneal mass with intraspinal extension filling the entire canal and obliterating visualization of the cord at that level. (C) Sagittal T2-weighted MR image in same patient as in (B) shows complete filling of the spinal canal with tumor. Note distended bladder.

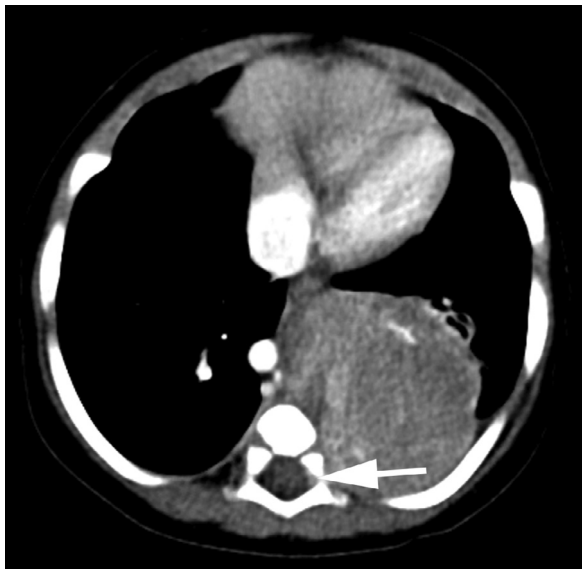

FIG 8. Noninvasion of the spinal canal but involvement of T9-T12 consistent with the presence of an IDRF (L2). Contrast-enhanced CT of a 6-month-old boy with a left side mediastinal tumor. There is enhancing tissue inside the left portion of the spinal canal (arrow), involving less than one-third of the area of the canal in that axial level. However, because the tumor involves the costovertebral junction between T9 and T12, it is consistent with an IDRF.

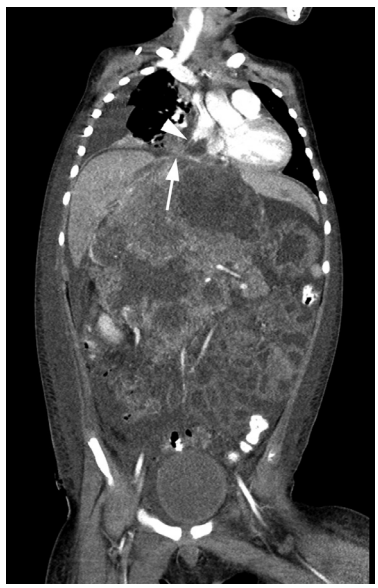

FIG 9. Infiltration of structures, consistent with the presence of an IDRF (L2). Contrast-enhanced CT with 3-year-old boy with extensive retroperitoneal solid mass with contiguous extension into mediastinum. The mass infiltrates the pericardium (arrowhead) and involves both sides of the diaphragm (arrow) (IDRF), insinuating infiltration of that as well.

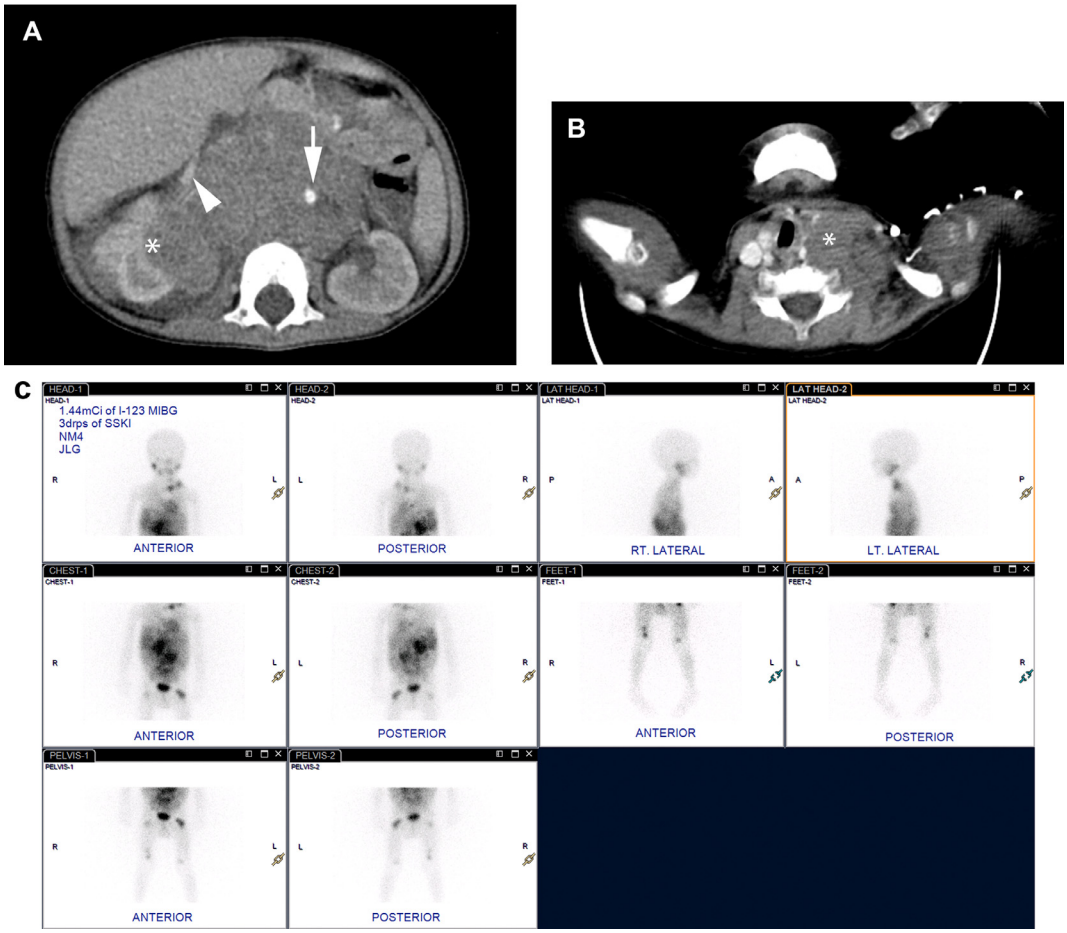

FIG 10. Metastatic disease consistent with stage M in a 1-year-old male with primary retroperitoneal neuroblastoma with extensive metastatic disease. (A) Contrast-enhanced CT of the abdomen shows solid mass *encasing* the aorta (arrow) (presence of an IDRF), *flattening* the inferior vena cava but with a visible lumen (arrow head) (not an IDRF), and *infiltrating* the right kidney parenchyma (*) (presence of an IDRF). (B) Contrast-enhanced CT of the neck showing abnormally enlarged supraclavicular lymph node (*) with associated displacement and compression of the trachea (presence of an IDRF). (C) MIBG study demonstrates increased tracer uptake in multiple bones, within left neck and superior mediastinum adenopathy, and throughout the mid abdomen. Positive MIBG in the bones makes this a stage M, rather than MS.

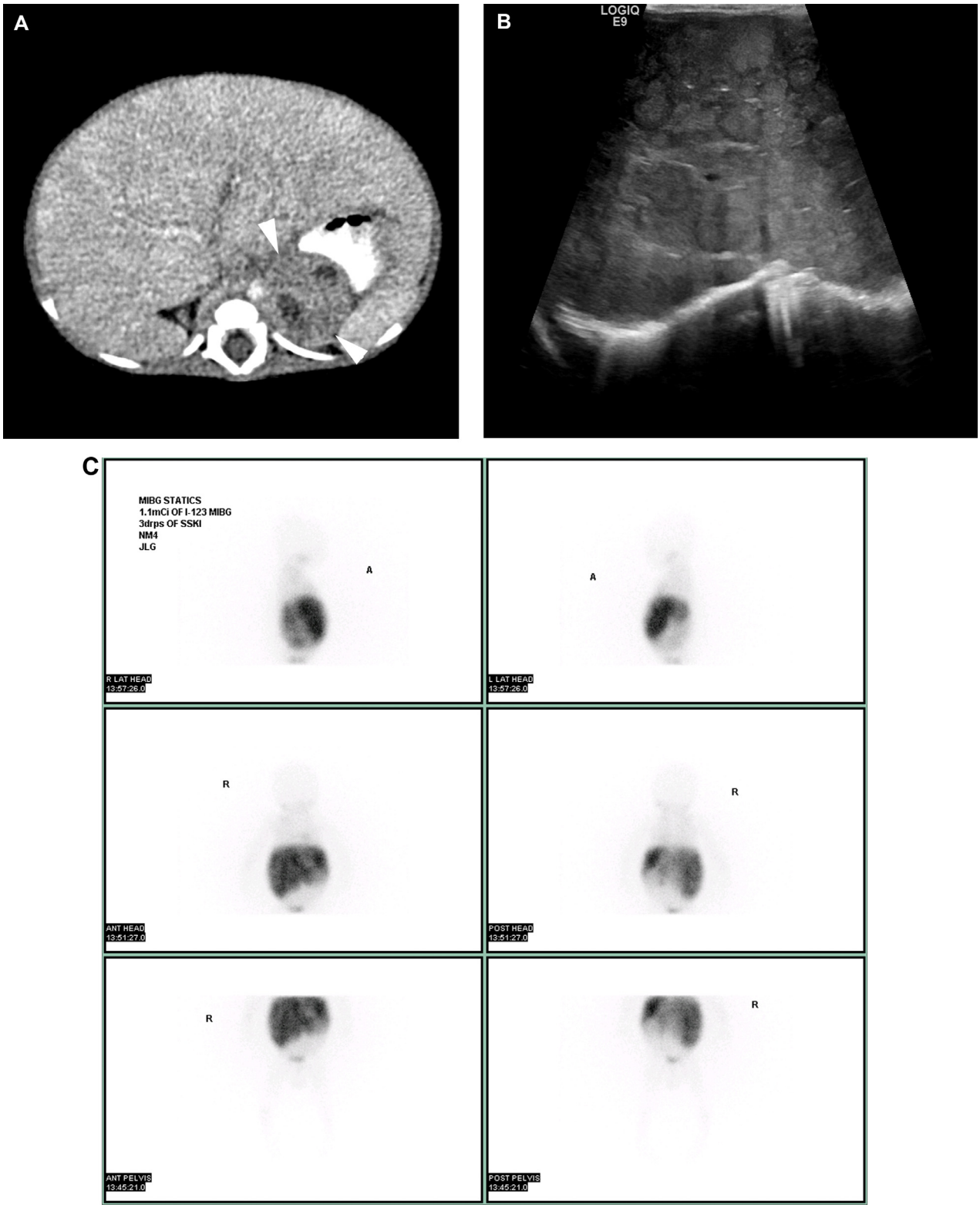

FIG 11. Metastatic disease confined to the liver consistent with MS stage in a 2-month-old boy. (A) Contrast-enhanced CT of the abdomen shows a left adrenal mass (arrow heads). The liver is diffusely heterogeneous. (B) Ultrasound through the liver shows multiple metastatic masses. (C) MIBG shows avid radiotracer uptake by the left adrenal mass and increased radiotracer uptake throughout the liver. No abnormal uptake is seen within the skeletal system.

Conclusion

Neuroblastoma imaging at time of diagnosis plays a critical role in patient's treatment planning strategies. This pictorial essay is intended to present a practical approach to using the **INRG-SS** classification system. This approach emphasizes the definitions of descriptive terms that determine whether an IDRF is present or absent.

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