The new international neuroblastoma risk group staging system – implications for surgeons

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An obstacle to progress in clinical neuroblastoma research has been the lack of uniform criteria for diagnosis, staging, risk grouping and for determining response to therapy. To overcome this problem, a series of conferences have been held, resulting in the International Neuroblastoma Staging System (INSS), International Neuroblastoma Response Criteria and International Neuroblastoma Pathology Classification. Work is currently in progress designing International Neuroblastoma Risk Groups (INRG). The main intent with international uniform risk grouping is to facilitate comparison of results obtained with different treatment regimens. Since INSS is a surgico/pathologic system, it is NOT appropriate for assigning patients to risk-groups at diagnosis, before treatment. Today it is generally agreed that a patient's INSS stage may be determined by the initial treatment given. To illustrate the latter point let us consider three fully possible situations at the time of INSS staging for a patient when admitted to three different institutions: The hypothetical patient in question has a localised neuroblastoma crossing the midline and encasing one renal artery: In Institution A complete tumour excision was achieved by primary surgery. In Institution B the patient was left with a considerable macroscopic tumour residue after primary surgery, and in Institution C the patient had the entire tumour remaining after percutaneous biopsies. Correct INSS staging of this very same patient is Stage 1 in Institution A, Stage 2 in Institution B and Stage 3 in Institution C. Obviously stage, if used as a basis for risk grouping at the time of diagnosis, must be the same in all three institutions. Another limitation with INSS in this context is that stage 1 and 2 patients by definition have had their tumours excised at the time of staging. As a consequence patients that would have been staged as 1 or 2 if operated upon, cannot be properly staged if not operated upon. This will be the case for patients for whom a treatment policy of “wait and see” or “observation only” is applied. At an INRG conference in Whistler, Canada in September 2005, with 52 investigators from Australia/New Zealand, China, Europe, Japan and North America, a new staging system, the International Neuroblastoma Risk Group Staging System (INRGSS), was therefore designed to become one of the criteria used in the INRG classification system.

The INRGSS is based on radiological features, and localised disease is determined by the Image Defined Risk Factors (IDRF). The IDRFs are similar to the Surgical Risk Factors used in the LNESG1 study (Cecchetto G et al., J Clin Oncol 2005; 23: 8483-9). With modern techniques, imaging studies are considered less liable to subjective interpretation than the individual surgeon’s assessment of resectability. Stored image studies can also be scrutinized in retrospect. They are therefore well suited for central reviews.

Surgical Risk Factors (IDRFs) have been used for risk stratification in the SIOP Europe Neuroblastoma protocols for a decade. According to these protocols primary surgery is not recommended in presence of Surgical Risk Factors. It is therefore conceivable that colleagues used to work with Surgical Risk
### Table 1: IDRF – Image Defined Risk Factors

**Neck:**
- Tumour encasing carotid and/or vertebral artery and/or internal jugular vein
- Tumour extending to base of skull

**Cervico-thoracic junction:**
- Tumour encasing brachial plexus roots
- Tumour encasing subclavian vessels and/or vertebral and/or carotid artery
- Tumour compressing the trachea

**Thorax:**
- Tumour encasing the aorta and/or major branches
- Tumour compressing the trachea and/or principal bronchi
- Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12
- Significant pleural effusion with or without presence of malignant cells

**Thoraco-abdominal:**
- Tumour encasing the aorta and/or vena cava

**Abdomen/pelvis:**
- Tumour infiltrating the porta hepatis
- Tumour infiltrating branches of the superior mesenteric artery at the mesenteric root
- Tumour encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
- Tumour invading one or both renal pedicles
- Tumour encasing the aorta and/or vena cava
- Tumour encasing the iliac vessels
- Pelvic tumour crossing the sciatic notch
- Ascites with or without presence of malignant cells

**Dumbbell tumours with symptoms of spinal cord compression:**
- Whatever the localisation

**Involvement/infiltration of adjacent organs/structures:**
- Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, mesentery and others

Factors might associate IDRFs with treatment recommendations. However, to avoid misunderstanding, it must be emphasized that recommendation on treatment is NOT a part of the INRGSS, nor of the INRG. It must also be underlined that the list of IDRFs is designed for use at the time of diagnosis. The presence of IDRFs become irrelevant after preoperative chemotherapy.

### Table 2: INRGSS – International Neuroblastoma Risk Group Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>L1</td>
<td>Locoregional tumour not involving vital structures as defined by the list of Image Defined Risk Factors</td>
</tr>
<tr>
<td>L2</td>
<td>Locoregional tumour with presence of one or more Image Defined Risk Factors</td>
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<tr>
<td>M</td>
<td>Distant metastatic disease (except Stage Ms)</td>
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<tr>
<td>Ms</td>
<td>Metastatic disease confined to skin and/or liver and/or bone marrow in children under the age of 18 months</td>
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Metastatic disease is defined as disseminated disease, i.e. not one continuous tumour. Involvement of non-regional lymph nodes, or discontinuous lymph nodes, are metastatic disease. However, an upper abdominal primary with lower mediastinal nodes and a pelvic tumour with inguinal nodes, are both locoregional diseases. A mediastinal tumour with pleural effusion and an abdominal tumour with ascites are both locoregional diseases. MIBG-scintigraphy is mandatory for INRG staging, and one definitive positive lesion at a distant site is sufficient to define metastatic disease. Bone scintigraphy is needed if negative MIBG (i.e. tumour is not MIBG-avid or the primary has been removed before MIBG-scintigraphy). Bone marrow disease is determined by morphology; not immuno-cytochemistry or molecular studies. A cut-off age of 18 months was chosen for INRGSS Stage Ms, which otherwise correspond to INSS Stage 4S. This decision is based on statistical analyses which show that the beneficial effect of young age extend beyond infancy.
The midline is NOT included in the staging criteria in the INRGSS. The “midline”-dilemma is covered by the IDRFD definitions. Nor is the lymph node status included in the staging of localised disease. Accurate lymph node assessment requires operation, and many patients have not been operated upon at diagnosis. The assessment of lymph node involvement has been a problem for surgeons even after surgery. For example: not everyone is aware of the fact that a lymph node located between the aorta and the inferior vena cava is ipsilateral to a rightsided and contralateral to a leftsided tumour.

Surgery is not required for INRGSS staging. For risk grouping according to INRG, however, the biological features of the tumour must be known. For that purpose tumour excision, or at least a biopsy, is required. The Whistler conferees decided that INRGSS together with Age, MYCN Status and Histology should be used for defining the INRG. Additional statistical analyses are being performed to determine if other factors should be included in the INRG.

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References