Handbook for Children with Neuroblastoma

Updated Spring 2023

from the

COG Surgery Committee and American Pediatric Surgical Association

CONTRIBUTORS

Christa N. Grant, MD
Clinical Associate Professor
Maria Fareri Children's Hospital
Westchester Medical Center
New York Medical College
Valhalla, NY
Christa.Grant@wmchealth.org

Erin G. Brown, MD
Associate Professor
University of California Davis Children's Hospital
Sacramento, CA
egbrown@ucdavis.edu

Hau D. Le, MD
Assistant Professor of Surgery
American Family Children's Hospital
University of Wisconsin School of Medicine and Public Health
Madison, WI
Leh@surgery.wisc.edu

Dave R. Lal, MD MPH
Professor of Surgery
Medical College of Wisconsin/Children's Wisconsin
Milwaukee, WI
DLal@chw.org

NOTICE

The authors, editors, and APSA disclaim any liability, loss, injury, or damage incurred as a consequence, directly or indirectly, of the use or application of any of the contents of this volume. While authors and editors have made every effort to create guidelines that should be helpful, it is impossible to create a text that covers every clinical situation that may arise in regard to either diagnosis and/or treatment. Authors and editors cannot be held responsible for any typographic or other errors in the printing of this text. Any questioned dosages or instructions in this text should be cross-referenced with other sources.

Attending physicians, residents, fellows, students, and providers using this handbook in treating pediatric patients should recognize that this text is not meant to replace discourse or consultations with the attending and consulting staff. Management strategies and styles discussed within this text are neither binding nor definitive and should not be treated as a collection of protocols.

TABLE OF CONTENTS

Introduction

This handbook provides you with the current surgical management of neuroblastoma. It is based on contemporary literature and accepted best practices and is managed and updated by members of APSA's Cancer Committee and the surgery committee of the Children's Oncology Group (COG). It is designed to consolidate the most current and up-to-date material you need to know when treating your patient. Neuroblastoma management is based on stage, age, imaging, and histologic and genomic characteristics.

This handbook begins with a One-Minute Review, designed for use immediately before an operation, and includes abbreviated staging, risk stratification, surgery guidelines, and tissue handling. These follow more descriptive sections for stage, image-defined risk factors (IDRFs), surgical management for biopsy and resection, special operative considerations, and management of surgical complications. The International Neuroblastoma Risk Group Staging System (INRGSS), based upon IDRFs, has now been updated to a second version and is the staging system upon which new protocols are created.

Current research efforts in the COG focus on the de-escalation of therapy for non-high-risk patients and the intensification of therapy for high-risk patients based upon histologic and genomic characteristics. Clinicians are strongly encouraged to consult with COG representatives or the APSA COG surgeons listed below for information on open COG studies for their patients with neuroblastoma.

Suggestions for improvement are welcome.

APSA Pediatric Surgical Neuroblastoma Contacts:

Jed Nuchtern	(832) 822-3135	nuchtern@bcm.tmc.edu
Erika Newman	(734) 834-7970	eanewman@med.umich.edu
Andrew Davidoff	(901) 595-4060	andrew.davidoff@stjude.org

ONE-MINUTE REVIEW

International Neuroblastoma Risk Group Staging System (INRGSS)

L1 Localized tumor, not involving vital structures as defined by the list of image-defined risk factors (IDRF); confined to one body compartment.

L2 Loco regional tumor with presence of one or more IDRFs

M Distant metastatic disease

MS Metastatic disease in children <18 months with metastases confined to skin, liver, and/or bone marrow (marrow involvement should be limited to <10% of total nucleated cells on smear/biopsy).

SURGICAL PRINCIPLES.

Goals:

Establish diagnosis, facilitate accurate staging, and perform the most complete and safe resection upfront or after induction chemotherapy.

Principles:

Limit morbidity and mortality, avoid resection of vital surrounding structures, control bleeding and avoid major hemorrhage, preserve normal organ function, and prevent long delays in initiating postoperative chemotherapy. Gross resection acceptable.

Specific Surgical Issues:

Primary Tumor: As near complete resection as possible, gross resection accepted. Avoid nephrectomy or other major organ removal and injury to surrounding vital structures.

Lymph Nodes: Formal lymphadenectomy is not mandatory and does not affect staging. Grossly involved or adjacent lymph nodes should be removed during definitive tumor resection.

Other: Liver biopsy if clinically suspicious.

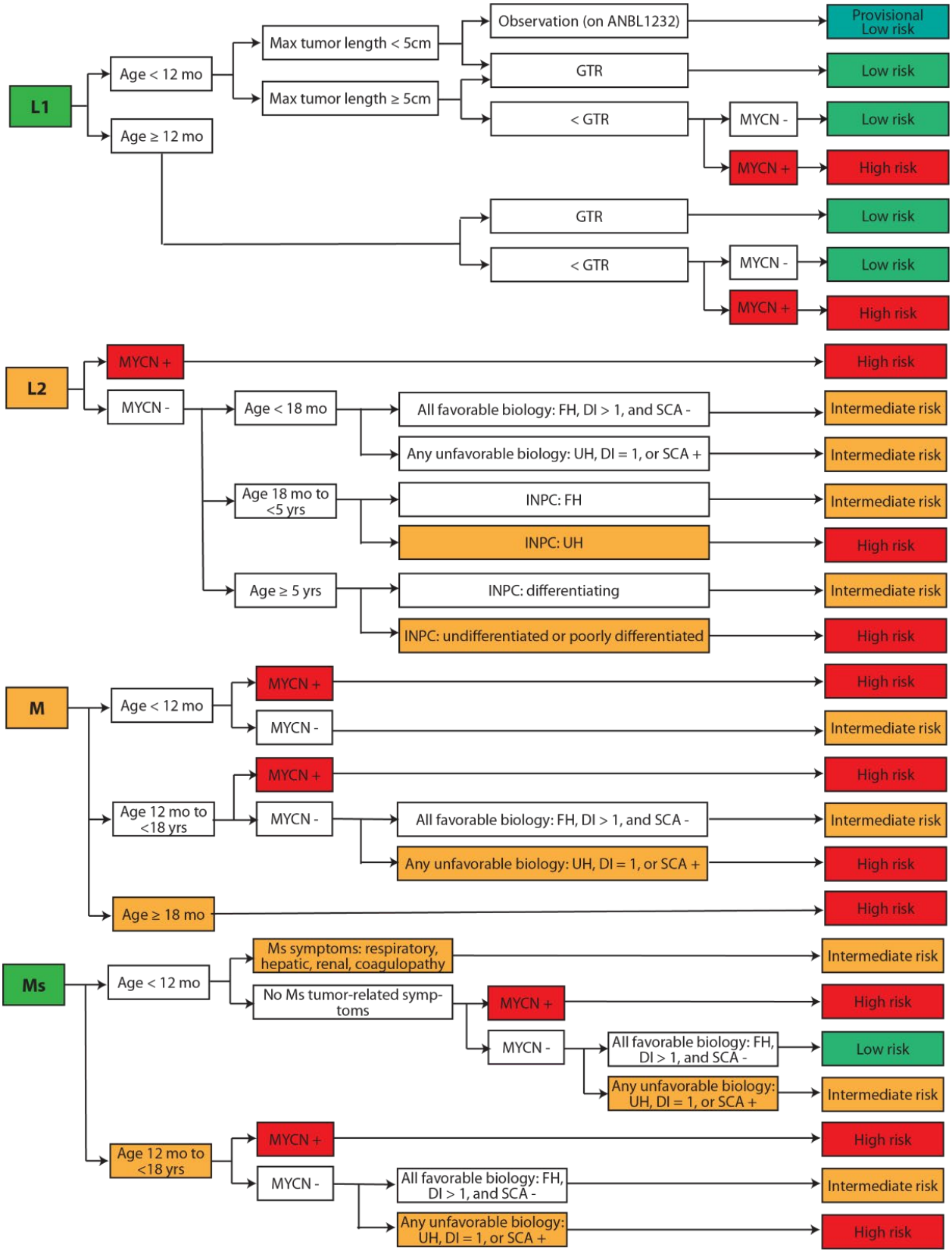
Tissue Handling for Biopsy:

Open incisional biopsy: fresh, > 1cm^3 or 1 gram in a sterile container with saline-soaked gauze. Tissue yield should approximate the open biopsy yield of 1gram or 1cm^3

Percutaneous core needle biopsy: 20 complete 16g cores is suggested as a minimum. Pathologist presence at the time of biopsy is highly recommended to ensure the tissue biopsied is not necrotic.

Observation Group:

Patients with INRG stage L1 tumors who are less than 12 months at diagnosis and have tumors < 5 cm in greatest diameter are observed without biopsy, surgical resection, or other treatment. These patients should be enrolled in the current COG non-high-risk study, ANBL1232.



Revised COG Neuroblastoma Risk Classification System. Adapted from Irwin et al. J Clin Oncol 2021. GTR: gross total resection, FH: favorable histology, UH: unfavorable histology, DI: DNA index or ploidy, SCA: segmental chromosomal aberrations, INPC: International Neuroblastoma Pathology Classification.

DETAILS OF NEUROBLASTOMA MANAGEMENT:

STAGING

INTERNATIONAL NEUROBLASTOMA RISK GROUP STAGING SYSTEM (INRGSS) AND IMAGE-DEFINED RISK FACTORS (IDRFs)

INRGSS
L1 Localized tumor, not involving vital structures as defined by the list IDRF; confined to one body compartment.
L2 Loco regional tumor with the presence of one or more IDRFs
M Distant metastatic disease
MS Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow (bone marrow involvement should be limited to <10% of total nucleated cells on smears or biopsy).

IDRFs - Current COG Definitions

Neck:
1. Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
2. Tumor extending to base of skull
3. Tumor encasing or compressing the trachea

Cervicothoracic junction:
1. Tumor encasing brachial plexus roots
2. Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
3. Tumor encasing or compressing the trachea

Thorax:
1. Tumor encasing the aorta and/or major branches
2. Tumor encasing or compressing the trachea and/or principal bronchi

Thoraco-abdominal:
1. Tumor encasing the aorta and/or vena cava

Abdomen/pelvis:
1. Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
2. Tumor encasing the branches of the superior mesenteric artery at the mesenteric root
3. Tumor encasing the origin of the celiac axis, and/or of the superior mesenteric artery
4. Tumor infiltrating or encasing one or both renal pedicles
5. Tumor encasing the aorta and/or vena cava
6. Tumor encasing the iliac vessels
7. Pelvic tumor crossing the sciatic notch

Risk factors related to symptoms and/or in situ tumor behavior at any site

1. Tumors with extension through the neural foramina at any level* **with either** symptom of spinal cord or nerve root compression OR abnormal spinal cord signal on imaging
2. Tumors with extension through the neural foramina at any level* **with** tumor invading >1/3rd of the spinal canal in the axial plane
3. Infiltration of adjacent organs/structures: pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, mesentery, and others
4. Contiguous ipsilateral tumor extension across multiple body compartments (e.g., neck and chest, chest and abdomen, abdomen and pelvis)

NOTE: Ascites or pleural effusions, whether malignant cells are present or not, are **not** considered IDRFs. Therefore, effusions in the body cavity of a local-regional tumor do not impact the INRG stage. However, a malignant effusion in a distant body cavity, while not an IDRF, is considered a metastatic disease so the INRG stage would be M.

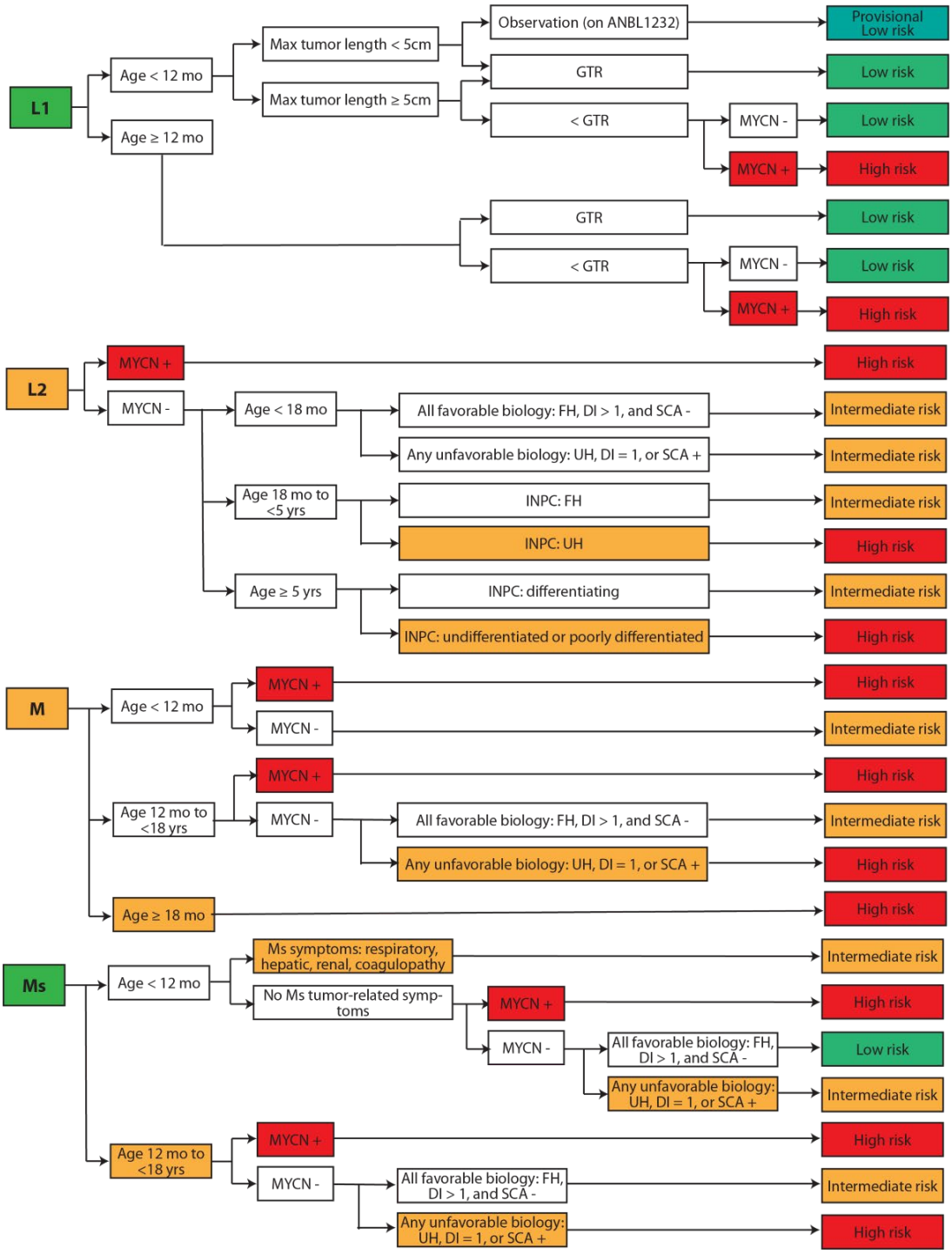
Multifocal primary tumors are not considered IDRFs.

Definitions used in designating IDRFs:

Encasement: when a tumor surrounds a structure with >50% circumferential contact or when a vein is completely flattened by the tumor with no visible lumen.
Infiltration: when a tumor extends into or deviates a vital structure, and the margin between tumor and structure on imaging is absent or ill-defined.
Compression: refers only to airways and requires a narrowing of the airway due to tumor effects (airway deviation without compression is not an IDRF).

RISK GROUP CLASSIFICATION

The INRG risk stratification system assigns patients to three overall risk groups: low, intermediate, and high. Risk group assignment is based on age, INRG stage (L1, L2, M, MS), degree of resection (L1 stage only), MS tumor-related symptoms (MS stage only), and the presence or absence of biological tumor characteristics, including *MYCN* amplification, certain segmental chromosomal aberrations (SCA), DNA ploidy, and favorable/unfavorable history (FH/UH) according to the International Neuroblastoma Pathology Classification (INPC) criteria. Based on the revised INPC, all ganglioneuromas (GN) and ganglioneuroblastomas (GNB) with the intermixed subtype are deemed to have FH, while GNB nodular subtype is considered to have UF. The diagram below illustrates how these characteristics are used for risk assignment in INRG.



Revised COG Neuroblastoma Risk Classification System. Adapted from Irwin et al. J Clin Oncol 2021. GTR: gross total resection, FH: favorable histology, UH: unfavorable histology, DI: DNA index or ploidy, SCA: segmental chromosomal aberrations, INPC: International Neuroblastoma Pathology Classification.

SURGICAL PRINCIPLES

Primary Tumor

L1 tumors may be safely resected upfront. L2 tumors may be considered for upfront resection if it is likely to be successful with minimal morbidity. For L2 tumors, resectability should be assessed by considering the degree of tumor extension into adjacent structures, fixation to, or encasement of major blood vessels, risk of hemorrhage, and the patient's overall tumor burden. The goals of surgery vary depending on the risk group. Low-risk L1 tumors may be managed with observation alone for patients under 12 months of age and tumors <5 cm in diameter or with complete excision. L2, intermediate-risk tumors may be resected up front if minimal morbidity is anticipated or treated first with neoadjuvant chemotherapy. If >50% reduction in tumor volume is achieved with chemotherapy, these tumors may be safely observed. If <50% response, surgical excision should be attempted, but a final reduction in volume of 50% is acceptable. For L2, high-risk disease, surgical resection follows neoadjuvant chemotherapy. Total resection of the primary tumor, including the involved adrenal gland, sympathetic ganglia, or lymph nodes, but without removal of or permanent damage to other structures (spleen, kidney, bowel, major nerves, and blood vessels) is the goal of this procedure. It is acceptable to leave residual disease adherent to these anatomical structures. Adhering to these principles can avoid surgical morbidity and delays in the initiation of chemotherapy. Liver biopsies are indicated if there is clinical or imaging suspicion of disease within the liver.

A variety of incisions can be used for the resection of the primary tumor. The choice of incision is based on the surgeon's preference to obtain the best exposure of the lesion and important surrounding structures. Titanium clips can be placed around sites of residual disease. See below for more on operative tips and tricks.

Under the INRGSS, lymph node dissection is not required. However, abnormal-appearing lymph nodes should be resected.

Children with initially unresectable tumors should have an initial biopsy and tunneled central venous access placement. The goal of biopsy is to obtain enough tissue for a histopathological diagnosis, *MYCN* determination, cytogenetics, and other biological studies. If feasible, the surgeon should try to obtain at least 1 cm3 or 1 gram of viable tumor tissue. Core needle biopsies may be performed, but a sufficient number of cores is critical to obtain adequate tissue. This may require an average of 20-30 cores for sufficient tissue if using a 16-gauge needle. Immediate pathologic assessment is recommended to ensure the samples include minimal necrosis and enough viable tissue for examination and studies.

Delayed surgery should be performed following neoadjuvant chemotherapy for high-risk neuroblastoma and initially unresectable tumors with the goal of preserving all organs and neurologic function while achieving the most complete tumor resection possible. Resection with microscopically negative margins is typically not feasible due to the proximity to major vascular structures and the spine. Instead, the surgeon should aim to remove all gross diseases as completely as possible. Gross total resection (GTR) is the primary goal, defined as 90% or greater tumor resection. The timing of delayed surgery is driven by the overall treatment plan, generally considered after four cycles of chemotherapy.

Children with MS diseases require an adequate biopsy of the primary or metastatic tumor for histology and biologic studies. Infants with MS disease who are less than three months of age are at particular risk for surgical complications if they have massive hepatomegaly with or without coagulopathy. In these patients, all attempts should be made to biopsy extra-abdominal sites of disease if they exist. These patients are often

started on chemotherapy without biopsy, and tumor biopsy is obtained within one month of therapy when the patients are more stable. Depending on the surgeon's institution's interventional radiology expertise, percutaneous needle biopsies may not be sufficient for thorough histologic and genomic analysis.

Cervical Primary Tumors

Pre-operative imaging studies directed to the primary tumor should include contrast-enhanced Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) extending from the lower skull to the thoracic inlet. Tumor extending into the mediastinum changes the surgical approach and should be assessed preoperatively. Encasement of the vertebral arteries, carotid arteries, jugular vein, or extension across the midline or to the base of the skull are IDRFs, and neoadjuvant chemotherapy is indicated.

Patients undergoing resection of a cervical or upper mediastinal primary are at high risk of postoperative Horner's syndrome, and this should be discussed with the family preoperatively. The exploration should be done through a transverse incision. Although Horner's syndrome is expected, every attempt is made to preserve the vagus nerve, brachial plexus, and other major nerves. Intraoperative nerve stimulation is a useful technique to avoid this morbidity and should be coordinated with the anesthesiologist so that muscle relaxants are avoided. Similarly, major blood vessels, including the jugular veins and carotid arteries, should be preserved. If total resection is not feasible, given the involvement of these structures, a small amount of gross residual tumor is accepted.

Thoracic Inlet Primaries

Imaging with either a contrast-enhanced CT scan or MRI is crucial because of the complicated anatomy in this region. The treatment teams should carefully discuss the need for and timing of resection. Usually, this area can be adequately exposed with a cervico-thoracic ("trap door") or a median sternotomy with a cervical extension incision. The vagus and phrenic nerves must be preserved, as well as the great vessels. The surgeon should leave residual tumor if firmly adherent to any of these vital structures.

Mediastinal Primaries

Resection of large thoracic paraspinal tumors is usually performed through an open thoracotomy, but there is growing literature to support safe thoracoscopic exploration and resection. Thoracoscopy is an excellent approach for tumor biopsy as well. The recurrent, phrenic, and vagus nerves are at risk and must be preserved by avoiding aggressive dissection near these structures. Tumor adherence to these nerves or blood vessels should prompt the surgeon to leave the adherent tumor rather than risk a neurovascular injury. The thoracic duct is easily injured, often in the region just posterior to the carina or near the right hemidiaphragm. The surgeon should pay special attention to this area and attempt to seal any visible lymphatic leaks.

Abdominal Primaries

The goal is a complete resection possible without putting vital organs at risk or causing disability. Tumor dissection around major vessels is often unavoidable. The surgeon must balance the goal of complete resection against the injury of major vessels that would lead to significant morbidity or hemorrhage. The major vessels include the celiac axis, superior mesenteric artery and vein, renal arteries and veins, inferior mesenteric artery and vein, and aorta and inferior vena cava. The surgeon should avoid risking kidney loss or bowel infarction in resectioning abdominal neuroblastoma. Careful tumor bi-valving over critical vessels can help the surgeon achieve a gross total resection. During this maneuver, care is taken not to

dissect into the tunica media. During complex vascular dissection, having readily available access to the proximal and distal vessel for control are vital to minimizing morbidity.

Pelvic Primaries

Tumors arising in the organ of Zuckerkandl or elsewhere in the pelvis are generally associated with excellent long-term survival, even when macroscopic diseases are left in place. In addition, the morbidity of resection in this anatomic area is very high due largely to injuries of the lumbosacral plexus or innervation to the bowel or bladder. Preoperative MRI is crucial to delineate neural and sacral involvement. Preoperative anorectal manometry and urodynamic studies may be warranted to assess for occult sphincter dysfunction. A mechanical and antibiotic bowel preparation can be helpful. In most patients, the best exposure is through a lower midline incision, depending on the judgment of the operating surgeon. Particular care should be taken when dissecting near the aortic bifurcation and at the base of the inferior mesenteric artery. The iliac arteries and veins should be identified and controlled early to avoid vascular injury. Ureters could also adhere to the tumor, and care should be taken to avoid injury. The surgeon should use nerve stimulation and consider neuro-monitoring when operating near the pelvic sidewall. Often the obturator nerve can be visualized distally near the obturator foramen, just posterolateral to the external iliac vein, and traced proximally to the area of the lumbosacral plexus. To preserve major nerves or vascular structures, leaving gross residual tumors in place should be considered.

MS Tumors

The primary tumor in patients with MS neuroblastoma should not be routinely resected.
An adequate amount of tissue may often be obtained from a biopsy of metastatic sites such as the liver or skin nodules; however, adequate biologic information cannot be obtained from bone marrow alone in patients with MS disease. If an open incisional biopsy is done, the surgeon should obtain an adequate amount of tissue (at least 1cm^3 or 1 gram) and send them to the appropriate laboratories. For patients with stage MS disease who are very ill and in whom an open biopsy to obtain tissue for diagnosis and biologic studies is considered medically contraindicated, every effort should be made to obtain some tumor tissue by core needle biopsy or needle aspiration of a metastatic site at minimum for determination of *MYCN* status. However, in these patients, biopsy may be deferred for up to one month while patients are treated with chemotherapy and stabilized.

Epidural Tumors with Intraspinal Extension

When the tumor approaches the spinal canal on imaging, a detailed neurologic examination must be performed to assess function. The format for the examination, a modification of the ASCIA scale, should be used to document the degree of neurologic dysfunction at diagnosis and at subsequent time points during and post-therapy.
Laminectomy should not be performed in neurologically asymptomatic patients. Neurosurgical evaluation should be sought if neurologic deterioration occurs during chemotherapy, and operative decompression should be strongly considered. Appropriate to the degree of neurological impairment, the treating physicians may decide that operative neurosurgical decompression is indicated under these circumstances. If feasible, the neurosurgeon should perform an osteoplastic laminotomy, with secure replacement of the laminae after decompression has been accomplished.

Management of Surgical Complications

Intraoperative complications are site-dependent. Major hemorrhage from either venous or arterial structures is of concern in tumors with more IDRFs. The principles of vascular surgery, including proximal and distal control, pertain. Crucial vessels like the carotid,

subclavian, hepatic, superior mesenteric artery, and renal arteries should be repaired primarily or with a graft to restore flow. Nerve injuries may also be incurred and should be primarily repaired using magnification. Intraoperative consultation with vascular, neurosurgical, or plastic surgical specialists could be considered if these complications occur.

Special Operative Techniques

Nerve stimulation: can be helpful in detecting motor nerves in the brachial or lumbo-sacral plexus. Nerve stimulation and neuro monitoring should always be used when dissection along the pelvic sidewall or in the neck or thoracic inlet. This requires cooperation from the anesthesiologist, as muscle relaxation must be avoided or allowed to wear off.

Ultrasonic dissector-aspirators: Some authors have described using ultrasonic dissectors (CUSA) to debulk the interior of large tumors allowing an easier capsular dissection. The technique is useful for friable tumors but not those that are stroma-rich. The surgeon should perform a generous incisional biopsy before ultrasonic dissection, as capturing the tumor specimen after it has been aspirated into the device is challenging.

The choice of incision is based on the surgeon's preference to obtain the best exposure of the lesion and important surrounding structures. This may include a trap-door incision or sternotomy with cervical extension for thoracic inlet tumors or a thoracoabdominal approach for large, extensive thoracoabdominal or upper abdominal tumors.

Thoracoscopy: Video-assisted thoracoscopy can be performed to remove small posterior mediastinal or thoracic inlet tumors, provided there is no vascular encasement. Thoracoscopy can be considered for surgical biopsy of initially unresectable thoracic tumors. One-lung ventilation, as is low-pressure carbon dioxide into the chest cavity, may be helpful.

Laparoscopy: Laparoscopic resection of small adrenal or pelvic primaries can be done for selected tumors or considered for surgical biopsy. Extensive tumors or those with significant vascular encasement or local, regional nodal spread can be more safely and completely resected using standard open approaches.

Radiofrequency Ablation, Cryosurgery: These techniques have significant drawbacks when applied to lesions in proximity to major vascular structures and should be avoided when treating neuroblastoma.

Tunneled Central Line Placement: Patients will require tunneled central venous access for chemotherapy treatment, potential stem cell transplantation, and possible apheresis. It is usually feasible and efficient to place a vascular access device and obtain a bone marrow aspirate/biopsy during the initial anesthetic. The appropriate catheter should be placed for the initiation of therapy. If stem cell transplantation is a possibility, a double-lumen tunneled catheter should be considered.

Degree of Resection

Oncology Approach and Outcomes

Treatment approaches and outcomes depend on risk groups. Patients in the very low and low-risk groups (based on INRG V1) require less intensive treatment. Most patients with low-risk diseases are treated with surgical resection and do not require chemotherapy or radiotherapy. A subset of patients with low-risk disease may simply be observed. Five-year EFS for patients with low-risk disease is between 75% and 85%.

For patients in the intermediate-risk group, most are INRG stage L2 and are treated with

neoadjuvant chemotherapy. Patients with a >50% reduction in tumor burden with chemotherapy may be safely observed, while those that do not have adequate response undergo surgical resection. The 5-year EFS for intermediate-risk patients is between 50 and 75%.

High-risk NBs are treated with multimodality therapy, including chemotherapy and cis-retinoic acid treatment. MIBG therapy, immunotherapy, and targeted therapies are also utilized based on tumor biology and risk stratification. The purpose of induction chemotherapy is to reduce tumor burden both at the primary site and at the sites of systemic disease. Standard North American induction regimens for high-risk diseases include combinations of anthracyclines, alkylators, platinum compounds, and topoisomerase II inhibitors delivered every 21 days for six cycles. Current COG treatment protocols recommend that patients with high-risk NB undergo complete GTR (> 90% resection) as a critical component of the multimodal treatment plan to achieve the best curative outcomes. Five-year EFS for patients with high-risk disease is approximately 50%.