HANDBOOK FOR CHILDREN WITH NEUROBLASTOMA
Updated Spring 2014

This handbook extracts and organizes surgically relevant information from recent COG Neuroblastoma protocols, and is designed to streamline the information you will need in treating a child with neuroblastoma. At the present time, the only protocol open is the biology protocol, ANBL00B1, with all clinical protocols recently completed.

A child with neuroblastoma should be enrolled on the biology protocol (ANBL00B1), which determines risk stratification based on histology, MYCN, and ploidy, along with additional tissue and serum analyses. The child will then be treated according to the risk stratifications based on these results. Clinical protocols were created for Intermediate Risk, (ANBL0531, closed Sept 2011) and High Risk, (ANBL0532, closed Feb 2012) tumors In addition, infants with neuroblastoma were eligible for participation on an observation protocol, (ANBL00P2, closed Aug 2012), and children with low risk neuroblastoma are provided standard operative management under P9641, closed March 2006. All these groups can still be enrolled on the biology protocol.

This handbook features a One Minute Review, which emphasizes the bare minimum refresher facts for the surgeon, and includes staging, surgical guidelines, risk stratification, and tissue handling. The remaining sections of the handbook expand on staging, risk stratification, response criteria, and important information from individual protocols.

Specific items of interest on these protocols include the inclusion of Image-Defined risk Factors as a prospective research tool, and the deletion of the old surgical checklist form. The Intermediate protocol has detailed information on specific sites of resection, and the High Risk protocol has a postoperative complications research question. (Incidence of renal atrophy, chylous ascites, diarrhea, bowel obstruction, and pulmonary complications) The Chair of the Neuroblastoma Surgery Steering Committee is Jed Nuchtern.

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This summary should make life easier for you and facilitate optimal compliance with protocol guidelines. This website will be updated as appropriate when protocols are amended. Any and all suggestions for improvement are welcome.

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ONE MINUTE REVIEW

STAGES (INSS)

I	Localized tumor, complete gross excision, LN negative.
IIA	Localized tumor, gross residual disease, with either **ipsilateral LN negative or LN sought/none found (w/specific mention in op note).**
IIB	Localized tumor, +/- gross residual disease, with **either ipsilateral LN positive or No LN sought (w/specific mention in op note).**
III	Unresectable unilateral tumor +/- LN Localized tumor with contralateral LN (+) Midline tumor (If gross resection and LN (-) or LN sought/none found, then Stage I; if gross resection and no LN sought, then Stage 3)
IV	Any primary tumor with metastases to distant LN, bone, bone marrow, liver, skin, etc.
IV-S	Localized tumor (I, IIA, IIB) mets to skin, liver, and/or bone marrow, <1 year of age.

SURGICAL PRINCIPLES

PERINATAL PROTOCOL: For babies <3 mos, sono identified adrenal mass ≤ 16 ml solid or < 65 ml cystic, no other disease, can be entered on Perinatal observation study.

GENERAL SURGICAL GOALS: Establish diagnosis, accurately stage, resect as much as possible, as safely as possible, and tissue for biology studies.

Specific Surgical Issues:

Primary Tumor	As near complete resection as possible, without damage to other structures. Avoid nephrectomy.
Lymph Nodes	Sample all grossly visible LN, normal or not. **(Vital to sample lymph node, or state 'looked for, none found')** Neck-along cervical chain, high and low neck. Thorax-upper, mid, and lower paraspinal, mediastinal, 6-9 LN total Abdomen-paraaortic, bifurcation, paracaval, aortocaval, high at diaphragm, 6-9 LN total. Pelvis-paraaortic, paracaval, bifurcation, iliac chain, 6-9 LN total.
Other	Liver biopsy if clinically suspicious.

NOTE: For babies < 60 days, with Stage IV/IVS with tense abdomen, massive hepatomegaly, at risk for severe complications, all attempts possible to biopsy extraabdominal site. If insufficient tissue obtained for Biology protocol, then treat off protocol

Subsequent OR Obtain tissue not previously obtained for biology study.
Resect recurrent/progressive/previously unresectable disease

TISSUE HANDLING

Fresh, tumor, > 1 gm (with marrow if possible) into sterile container with saline soaked gauze.

*****Surgeon's Responsibility: Prompt detailed Operative Report dictation, to be included with submission of other materials to ANBL00B1.

INTERNATIONAL NEUROBLASTOMA STAGING SYSTEM (INSS)

Stage 1

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).

Stage 2A

Localized tumor with incomplete gross resection; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

Stage 2B

Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically.

Stage 3

Unresectable unilateral tumor infiltrating across the midline[2], with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.

Stage 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).

Stage 4S

Localized primary tumor (as defined for Stage 1, 2A or 2B) with dissemination limited to skin, liver, and/or bone marrow[3] (limited to infants <1 year of age).

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1. Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript "M" (e.g. 3_M).
2. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
3. Marrow involvement in Stage 4S should be minimal, i.e., less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or marrow aspirate. More extensive marrow involvement would be considered to be Stage 4. The MIBG scan (if performed) should be negative in the marrow.
4. Proven malignant effusion within the thoracic cavity if it is bilateral or the abdominal cavity upstages the patient to INSS 3

INRG – Image Defined Risk Factors

Risk factors related to localization:

Neck:

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

Cervico-thoracic junction:

1. Tumour encasing brachial plexus roots
2. Tumour encasing subclavian vessels and/or vertebral and/or carotid artery
3. Tumour compressing the trachea

Thorax:

1. Tumour encasing the aorta and/or major branches
2. Tumour compressing the trachea and/or principal brochus
3. Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12
4. Significant pleural effusion with or without presence of malignant cells

Thoraco-abdominal:

1. Tumour encasing the aorta and/or vena cava

Abdomen/pelvis:

1. Tumour infiltrating the porta hepatis
2. Tumour infiltrating the branches of the superior mesenteric artery at the mesenteric root
3. Tumour encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
4. Tumour invading one or both renal pedicles
5. Tumour encasing the aorta and/or vena cava
6. Tumour encasing the iliac vessels
7. Pelvic tumour crossing the sciatic notch

Dumbbell tumours with symptoms of spinal cord compression:

1. Whatever the localisation

Involvement/infiltration of adjacent organs/structures:

1. Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, mesentery and others

Study	Stage	Age	MYCN	Ploidy	INPC
ANBL00B1	1	any	any	any	any
ANBL00B1	2a/2b	any	not amp	any	any
ANBL0531	2a/2b	0 – 12 yr	not amp	any	any
ANBL0531	2a/2b	0 – 12 yr	not amp	any	any
ANBL0532	2a/2b	any	amp	any	any
ANBL0531	3	<547d	not amp	any	any
ANBL0531	3	>547d – 12 yr	not amp	any	FH
ANBL0532	3	any	amp	any	any
ANBL0532	3	>547d	not amp	any	UH
ANBL0532	4	<365d	amp	any	any
ANBL0531	4	<365d	not amp	any	any
ANBL0532	4	365-<547d	amp	any	any
ANBL0532	4	365-<547d	any	DI=1	any
ANBL0532	4	365-<547d	any	any	UH
ANBL0531	4	365-<547d	not amp	DI>1	FH
ANBL0532	4	>547d	any	any	any
ANBL00B1	4s	<365d	not amp	DI>1	FH
ANBL0531	4s	<365d	not amp	any	any
ANBL0531	4s	<365d	not amp	DI=1	any
ANBL0531	4S	<365d	not amp	any	UH
ANBL0531	4s	<365d	missing	missing	missing
ANBL0532	4s	<365d	amp	any	any

ANBL00B1 NEUROBLASTOMA BIOLOGY PROTOCOL

PATIENT ELIGIBILITY

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All newly diagnosed patients with suspected neuroblastoma, suspected ganglioneuroblastoma, or suspected ganglioneuroma (maturing subtype) seen at COG institutions are eligible for this study. The date of diagnosis is defined as the date of the surgical biopsy or other definitive diagnostic procedure. A provisional (preliminary) determination of the International Neuroblastoma Staging System (INSS) stage **MUST** be reported at the time of enrollment, and definitive INSS stage must be reported within 3 weeks following diagnosis. **Every effort should be made to report definitive risk group factors (age, INSS stage, degree of resection, whether the patient is symptomatic) within 2 weeks of diagnosis, and these risk group factors MUST be reported within 3 weeks following diagnosis.** Patients may NOT enter a front-line COG therapeutic study (Low- Intermediate- or High-risk) before they are enrolled on the ANBL00B1 protocol (see protocol specific guidelines for exceptions due to the emergent need for chemotherapy).

GUIDELINES FOR PROCURING, PROCESSING AND SUBMITTING SAMPLES

ANBL00B1 is designed to allow for acquisition of centralized, high-quality data from tumor specimens (*MYCN* and ploidy and histopathology) that are essential for patient management. These data will be obtained in a CLIA-certified laboratory and results will be charted for patient management decisions. THEREFORE, PATIENT NAMES MUST BE ON ALL CLINICAL SAMPLES TO ASSURE ACCURACY IN REPORTING OF RESULTS. A checklist is provided in the informed consent document so that patients may enroll on ANBL00B1, but only obtain the clinically indicated MYCN, ploidy, histopathology, and LOH data, without participating in research studies or banking. In this case, specimens are destroyed at the Neuroblastoma Reference Laboratory. If research studies and banking are agreed to, identifiers are stripped before banking or shipment to other research labs as outlined in section 6.2.

Since institutional surgeons and pathologists must be active participants in this protocol, investigators should circulate and discuss this protocol with their pathology and surgical colleagues. Referring physicians should be encouraged to send the patient to the participating COG institution prior to any invasive procedures. Surgeons should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection. **Needle biopsies** are generally **NOT** sufficient for histological classification. The resected specimen should be placed in a sterile container, covered with saline-soaked gauze, and sent to the pathologist's attention immediately. Pathologists must maintain the sterility of tumor specimens, and allocate as generous an amount as possible for the biological studies and tumor bank, while retaining sufficient tissue to determine accurate conventional histology (diagnosis, differentiation, margins, etc.) and ultrastructural examination, as well as analysis by the International Neuroblastoma Pathology

Classification system. Sections adjacent to tissue sent for biologic studies should be taken and labeled as such for subsequent analysis.

ANBL00P2: Perinatal Neuroblastoma: Expectant Observation, A Children's Oncology Group Pilot Study

Eligibility Criteria

-Age < 3 months on the date the mass is first identified;
-Sonographically identified adrenal mass which is < 16 ml in volume, if solid, or < 65 ml if at least 25% cystic, and which does not cross the midline;
-Bone marrow aspirate and biopsy, bone scan (+/- MIBG scan) and abdominal CT or MRI scan, all of which are negative for evidence of disease outside the adrenal gland, including positive contra- or ipsi-lateral lymph nodes
-No prior abdominal surgery or chemotherapy; and,
-Consent of parent or legal guardian and institutional human studies committee approval.

The intent of the eligibility criteria is to identify a group of patients who are likely to have INSS stage 1 neuroblastoma. Appropriate screening studies will be required to assure that there is no tumor spread beyond the primary, and that no mass crosses the midline. Sonograms should be analyzed to determine the tumor volume,

$$V = (4/3)\,\pi(X/2)(Y/2)(Z/2)$$

Where X = maximum longitudinal dimension, Y = maximum transverse dimension, and Z = maximum anterior-posterior dimension, as well as any evidence of involvement of adjacent structures or distant metastases (Hirata, 1995)

On Study Evaluations

Children entered into the study will have initial radiographic identification of the adrenal mass. In most cases this will be obtained by an initial abdominal ultrasound (US) study, followed by a MRI or CT scan to rule out more widespread disease. Copies of these initial studies must be submitted for participation in the study as well as copies of subsequent US studies obtained at the prescribed intervals per section **5.2**. All US studies should include imaging of the liver with a high frequency linear transducer, to assure optimal detection of small parenchymal nodules. Whenever possible, a videotape of the real-time sonographic examination should be included with the images submitted for central review. The relevant printed images should be condensed to one or two sheets of film for each study to minimize expenses. All imaging material should be sent to Dr. Carol Barnewolt, at the address listed on page 2, for central review.

Laboratory specimens obtained at admission to the protocol include random urine for VMA and HVA, CBC and serum for electrolytes, BUN and creatinine levels. Urine specimens should be analyzed for urine catecholamine analysis (VMA and HVA in *u*g/mg creatinine) using gas chromatography/mass spectroscopy. If the participating institution would prefer to use the central laboratory for this analysis, urine specimens should be acidified upon collection (3 to 5 ml urine in 0.1 ml 0.1 N HCl) and sent, chilled or frozen, to the Study Reference Laboratory (Baylor Toxicology Laboratory, Dept. of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030).

Evaluations During the Study

Children will have follow-up US studies obtained at the prescribed intervals during the

course of the study. In addition, all patients will undergo CT or MRI imaging of the abdomen at weeks 6 and 42. The sequence of studies will be terminated if a 50% increase in the volume of the mass is noted and the child is taken to surgery. If an increase in volume of the lesion is noted, but it is not of an adequate magnitude to mandate resection, then continued sonographic evaluation at 3-week intervals should be performed until a stable tumor volume is noted on two successive studies or the patient goes off-observation. After the mass has stabilized in volume on two consecutive 3 week studies, the next sonogram/urine VMA/HVA will be at a six week interval and the following studies at the regularly scheduled time. For example, if growth were noted at the six week ultrasound and tumor volume was stable on the 9 and 12 week studies, the study times would be at 6, 9, 12, 18, 30, 42, 66, and 90 weeks; if growth were noted at 30 weeks, the schedule would be: 30, 33, 36, 42, 66, and 90 weeks; if growth were noted at 42 weeks, the times would be: 42, 45, 48, 54, 66, and 90 weeks.

Urinary catecholamine levels, VMA and HVA, will be obtained at presentation and at the time of each subsequent ultrasound study, even if the values are below the upper limit of normal. If these metabolites show an increase in value of greater than 25% (and actual value is abnormal) or if the VMA/HVA ratio decreases below 0.5 (and the actual HVA value is above normal), the time interval to the subsequent studies (sonograms and urine catecholamine sampling) will be decreased to three weeks. If the elevated value does not return to baseline (or the upper limit of normal, whichever is greater) within twelve weeks or the VMA/HVA ratio does not rise above 0.5 within six weeks, the patient will come off-study and surgery will be recommended without regard to the tumor volume. On the other hand, if the catecholamine values do return to baseline, subsequent studies will take place 6 weeks later and then at the regularly scheduled times as delineated above.

If, during the course of the study, a patient has elevated urinary catecholamine levels which persist after complete normalization of the abdominal ultrasound studies, i.e., apparent disappearance of the adrenal mass with persistent biochemical evidence of neuroendocrine tumor cell function, this should prompt evaluation by cervical, thoracic and abdominal CT/MRI imaging, bone marrow aspirate/biopsy and bone scan to rule out the presence of occult disease. Any evidence of disease should be treated as progressive disease and handled appropriately. These studies should be repeated in six weeks or at the regularly scheduled interval, whichever is sooner, until the catecholamine levels normalize, or the patient comes off observation due to progressive disease.

If a patient completes the 90 week observation period without triggering resection due to an increase in tumor volume or catecholamine values, yet the VMA and/or HVA values remain elevated, any persistent adrenal mass should be resected as per the surgical guidelines. Patients with elevated catecholamines without evidence of an adrenal mass at the completion of the observation period should undergo CT/MRI imaging of the neck, chest and abdomen as well as bone marrow aspirate/biopsy and bone scan. Any evidence of disease should be treated as progressive disease at this point and handled appropriately.

Tumor growth or increase in catecholamine values that meet criteria for surgical intervention will not be considered progression or an “event” unless the patient has progressive disease (higher than INSS stage 1) at the time of resection.

If a patient experiences any of the following, the occurrence must be reported to the C.O.G. Data Center within five working days using the Immediate Notification Report screen:

- Referral to surgery due to increase in tumor volume or catecholamine secretion;
- Progressive disease or recurrence;
- Secondary malignancy;
- Death

Surgery

Standard surgical approach should be utilized for adrenalectomy along with sampling of both adjacent lymph nodes and nodes that are located inferior and superior to the adrenal along the lateral aspect of the vena cava for right-sided lesions and the aorta for left-sided lesions. Operative Report and Checklist should be completed and forwarded to the study center. The children who receive surgery due to tumor progression should be enrolled in the neuroblastoma biology study (ANBL00B1) and considered for participation in the then current therapeutic protocols of the national cooperative oncology groups.

Patients whose masses persist after the 90-week observation period will be advised to undergo surgical resection if the residual volume of the mass is greater than 2ml. Patients with masses smaller than 2 ml will be offered surgical resection at the discretion of the treatment team consistent with the community standard of care for a small adrenal lesion in a two-year-old toddler. **Surgery must be reported via the Immediate Notification Report screen within 5 working days of referral.**

Non-Observation Arm (parents opting for surgery immediately)

Data regarding operative report, pathology report and initial diagnostic radiographic studies for those infants where the parents elect to proceed with resection of the lesion should be submitted when parents sign the alternative consent for submission of information whether or not the lesion is a neuroblastoma. An institution will receive credit for a therapeutic study entry for these patients.

6.2 STANDARDS FOR SURGERY FOR LOW RISK NEUROBLASTOMA (from P9641)

6.21 Initial Operative Procedure

The goal of this procedure is to establish the diagnosis, to resect as much of the primary tumor as is safely possible, to accurately stage disease through sampling of non-adherent regional lymph nodes, and to obtain adequate tissue for biologic studies.

6.211 Primary Tumor

Resectability should be assessed by consideration of extension into adjacent structures, fixation to, or encasement of, major blood vessels, risk of hemorrhage, and the patient's overall tumor burden. 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 is the goal of this procedure.

6.2111 Children with 4S disease require adequate biopsy of the primary or metastatic tumor for histology and biologic studies. Resection of the primary tumor is required if metastatic disease has resolved and a mass persists at the primary site after treatment of observation.

Infants with INSS 4 or 4S disease who are less than 60 days of age are at particular risk for surgical complications if they have massive hepatomegaly with or without coagulopathy. In these patients, all attempts possible should be made to biopsy extra- abdominal sites of disease if they exist. Percutaneous needle biopsies, although adequate for MYCN and ploidy, are NOT sufficient for Shimada classification. Patients are not eligible for P9641 unless all three biologic factors (MYCN, ploidy, histopathology) are known. If these cannot be determined from biopsy of extra-abdominal disease, then these patients should be registered on the biology study if possible and treated with standard care off protocol. The study chair or vice-chair should be contacted by phone or e- mail by the treating physician to discuss all infants less than 60 days of age with significant abdominal distension due to hepatomegaly and who presumably have low-risk disease, prior to registration on P9641.

6.2112 Nephrectomy should be avoided at initial exploration except for children who would be rendered entirely free of any residual disease.

6.212 Lymph Nodes

All grossly visible lymph nodes must be sampled, regardless of whether they appear normal or not. The operative report should clearly identify the site from which lymph nodes are removed and also must differentiate nodes that are contiguous and attached to the primary tumor versus those which are not. This is essential to differentiate INSS stage 1 with positive attached nodes versus INSS 2B with positive regional nodes. This should also be identified on the pathology submission form. Label all nodes as to site of origin. It is ideal to sample the following number of nodes in the various anatomical locations.

Neck: Sample nodes along the cervical chain both adjacent to the tumor and high and low in the neck.

Thorax: Sample nodes from upper, mid-, and lower paraspinal or mediastinal chains (total 6-9 nodes).

NOTE: Avoid metal clips in patients with thoracic primaries if possible. The artifact produced by these clips makes interpretation of CT scans for residual disease unreliable. Titanium clips may be used to mark residual tumor.

Abdomen: Sample nodes from as high under the diaphragm as possible, from the immediate paraaortic drainage level of the primary tumor and from the area of bifurcation of the aorta (total 6-9 nodes). Try to obtain nodes from paracaval (right) interaortocaval (mid), and paraaortic (left) chains and label. Mesenteric portal and celiac nodes may also be sampled.

Pelvis: Sample nodes from paraaortic and paracaval chains, the aortic bifurcation, and from both iliac chains, from the aortic bifurcation area and the iliac chain (total 6-9 nodes).

6.213 Liver Biopsy

Liver biopsies for children are indicated if there is clinical or imaging suspicion of disease within the liver. Efforts should be made to biopsy the involved area.

6.22 Recommended Subsequent Surgical Procedures

A second or subsequent surgical procedure should be undertaken in the following situations:

6.221 To obtain tissue for definitive biological testing and risk group assignment from patients referred to your institution after biopsy of neuroblastoma, but in whom biologic risk was not established.

6.222 To attempt resection of residual disease that was initially biopsied (< 50% resected) and treated with chemotherapy.

6.223 To attempt resection of recurrent or progressive local/regional disease during post-surgical observation, or during or after completion of chemotherapy.

6.224 To resect, if feasible, disease which persists after treatment of recurrent or progressive disease (see Appendix IV) with Courses I and II of chemotherapy, with or without radiation therapy.

6.225 To resect, as much as safely possible, progressive INSS Stages 2A, 2B, or 3 tumorif the progressive tumor is a threat to function of vital organs. Radiodense clips should be placed at the margins of the perimeter of the recurrent disease to facilitate delivery of radiation therapy field boosts (should it be required) regardless of the completeness of the resection.

6.226 For evaluation of presumptive new disease.biopsied (< 50% resected) and treated with chemotherapy.

6.223 Other Surgical Procedures

While not mandated by this study, a subsequent surgical procedure may be undertaken by investigator choice, without penalty, to attempt resection of initially unresectable disease which has spontaneously, or after chemotherapy, regressed to stable but persistent disease.

Reasons for this procedure must be clearly explained on the flow sheets.

ANBL0531: RESPONSE- AND BIOLOGY BASED THERAPY FOR INTERMEDIATE RISK NEUROBLASTOMA
SURGICAL GUIDELINES

Surgical rationale
The overall surgical goal in intermediate-risk patients with neuroblastoma is the most complete tumor resection consistent with preservation of full organ and neurologic function. The exception to this is the infant with stage 4S disease in whom only an adequate biopsy for diagnosis and assay of biological parameters is required. In addition, the surgeon is responsible for the preservation and delivery of an adequate surgical specimen to the appropriate laboratory for crucial biologic analyses; including determination of *MYCN* amplification, ploidy, and molecular genetic analyses. In general, as much of the tumor as possible is resected that is also consistent with preservation of organs (spleen, kidney, bowel etc.) and major nerves and blood vessels. **This may necessitate leaving residual disease adherent to these anatomical structures.** Titanium clips should be placed around sites of residual disease.

As many of these patients will have either localized or loco-regional disease, preoperative assessment of resectability is essential. In anticipation of the institution of a pre-operative staging system using International Neuroblastoma Risk Groups (INRG) criteria, the surgeon should refer to the imaged-defined risk factors listed in Appendix V during initial assessment. An assessment of pre-operative surgical risk, according to guidelines in Appendix V, will be performed for all patients on this study, with the data collected on ANBL00B1. This information will not be used prospectively on ANBL0531 to dictate operative plan or chemotherapy treatment group assignment. If the primary tumor is judged to be unresectable, diagnostic biopsy will be obtained and chemotherapy will be administered according to protocol guidelines. Delayed surgery will be performed with the goal once again of achieving the most complete tumor resection consistent with preservation of full organ and neurologic function. Timing of delayed surgery is dependent upon treatment group. Group 2 patients will undergo resection after 2 cycles of chemotherapy, group 3 patients after 4 cycles, and group 4 patients after 4 or 8 cycles. INRG image-defined risk criteria are used for the initial assessment only and are not repeated for tumors that have been treated with chemotherapy.

Pre-operative management
Adequate pre-operative imaging of the primary tumor and sites of regional spread is done by computerized axial tomography, magnetic resonance imaging, or a combination of the modalities. Sites of distant metastases must be ruled out by a combination of clinical and bone marrow assessment as well as bone scan and MIBG scans. When dealing with paraspinal or epidural lesions pre-operative neurosurgical consultation is recommended and a baseline neurologic assessment carried out (see section 14.4.7 and Appendix VII). The planned operation should be discussed with the attending pediatric oncologist and, if possible, at tumor board and the goals of the surgery should be clearly understood by all involved services pre-operatively.

Sampling requirements

In the event that the primary tumor is not immediately resectable, an adequate biopsy to determine the diagnosis and assess biological variables like *MYCN* amplification, ploidy, and 1p or 11q abnormalities is required. Usually more than 1 cubic centimeter of viable tissue is needed for all these assays. Needle biopsies are not sufficient for INPC histologic classification. The surgeon should remember that a significant portion of the tumor may be necrotic. Frozen section examination of a small amount of tissue will verify that viable neuroblastoma is being biopsied.

For patients with stage 4S 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 fine needle aspiration of a metastatic site for at minimum the determination of *MYCN* status.

OPERATIVE MANAGEMENT FOR INTIALLY RESECTABLE PRIMARY TUMORS

Cervical Primary Tumors

Pre-operative imaging studies directed to the primary tumor should include contrast enhanced computerized tomography extending from the lower skull to the thoracic inlet. Tumor extending into the mediastinum changes the surgical approach and should be appreciated preoperatively. Magnetic resonance imaging is also a useful study. Encasement of the vertebral or carotid arteries, jugular vein, or extension across the midline or to the base of the skull are INRG image-defined high-risk factors and neoadjuvant chemotherapy is indicated.

All patients undergoing resection of a cervical or upper mediastinal primary will have a post-operative Horner's syndrome and this should be discussed with the family preoperatively. The exploration should be done through a transverse incision. Although a Horner's syndrome is inevitable, every attempt is made to preserve the vagus nerve, brachial plexus, and other major nerves. Intraoperative nerve stimulation is very useful and should be coordinated with the anesthesiologist so that muscle relaxants are avoided. Similarly, major blood vessels, including the jugular vein and carotid artery are preserved. If tumor is seriously adherent to these structures a partial removal should be done.

Thoracic Inlet Primaries

Imaging with either a contrast enhanced CT scan or MRI is crucial because of the very complicated anatomy in this region. Also, the need for resection should be carefully discussed among the treating services. The attending surgeon should also discuss the situation with the ANBL0531 surgical representatives (Dr Stan Adkins or Dr Peter Mattei). Usually, this area cannot be adequately exposed without a cervico-thoracic ("trap door") incision. The vagus and phrenic nerves should be preserved at all costs as well as the great vessels. The surgeon should leave residual tumor if strongly adherent to any of these structures.

Mediastinal Primaries

Resection is usually performed through a posterolateral thoracotomy. The recurrent, phrenic, and vagus nerves are at risk and should be avoided. Strong 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. The surgeon should pay special attention to this area and attempt to seal any visible lymphatics.

Abdominal Primaries

The goal is the most complete resection possible without putting organs at risk. Tumor masses encasing major visceral vessels that are not easily dissectible should be left in place. The major vessels include the celiac axis, superior mesenteric artery and vein, renal arteries and veins, and the inferior mesenteric artery. At no point should the surgeon risk kidney loss, or bowel infarction in resection of intermediate-risk abdominal neuroblastomas.

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 disease is left in place. In addition, the morbidity of resection in this anatomic area is very high due in large part to injuries of the lumbosacral plexus or innervation to the bowel or bladder. Preoperative MRI is crucial to delineate the neural and sacral involvement. A mechanical and antibiotic bowel preparation should be used. In most patients the best exposure is through a lower midline incision depending on the judgment of the operating surgeon. Dissection in the area of the aortic bifurcation and at the base of the inferior mesenteric artery should be avoided, if possible. The iliac arteries and veins should also be controlled early to avoid vascular injury. The surgeon should use nerve stimulation when operating near the pelvic sidewall. Often the obturator nerve cam be visualized distally near the obturator foramen and traced proximally to the area of the lumbosacral plexus. Incomplete resection should be done to preserve major nerves or vascular structures.

4S Tumors

The primary tumor in patients with 4S neuroblastoma should not be routinely resected. Generally, an adequate amount of tissue may be obtained from biopsy of metastatic sites such as the liver or skin nodules (adequate biologic information can not be obtained from bone marrow alone in patients with 4S disease). If an operative biopsy is done the surgeon should insure that an adequate amount of tissue (1-2 cm^3) is removed and sent to the appropriate laboratories. For patients with stage 4S 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 fine needle aspiration of a metastatic site for at minimum the determination of *MYCN* and 1p/11q status.

Epidural Tumors with Intraspinal Extension

When the tumor approaches the spinal canal on imaging (see section 17.2), a detailed examination must assess neurological function. The format for the examination, a modification of the ASCIA scale, is detailed in Appendix VII and 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 patients who are neurologically asymptomatic. If neurologic deterioration occurs during chemotherapy, neurosurgical evaluation should be sought and operative decompression 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. Operative details will be recorded] in the RDE.

Assessment of neurological function will be performed prior to each cycle of chemotherapy for all patients with paraspinal tumors (see section 7.1). Neurologic and orthopedic evaluations will be a routine part of off therapy follow-up for patients with paraspinal tumors, and will be performed at 6, 12, 24, and 36 months post therapy, and then annually thereafter. Orthopedic evaluation will include assessment of scoliosis and of extremity deformity by upright spine x-ray at these time points (see section 7.3 and Appendix VII).

Operative management of primary tumors after chemotherapy
The rationale for surgery is the same as for initially resectable tumors. Generally, as much as possible of the primary tumor and involved lymphatic metastases should be resected. INRG criteria are not applicable and the surgeon should proceed with the most complete resection possible without undue risk of mortality or significant morbidity. All organs, major vascular structures, or nerves should be preserved. **If the surgeon feels that a tumor mass is unresectable despite a reasonable attempt, it should be left in place and marked with titanium clips.**

MANAGEMENT OF SURGICAL COMPLICATIONS

Intraoperative complications
Intraoperative complications are site-dependent. Major hemorrhage from either venous or arterial structures is always possible with these infiltrative tumors. The principles of vascular surgery, including proximal and distal control, pertain. Appropriate intraoperative vascular surgical consultation should be sought if necessary. Crucial vessels like the carotid, subclavian, hepatic, superior mesenteric or renal arteries should be repaired and flow restored even if bypass grafting is required. Nerve injuries may also be incurred and should be primarily repaired using magnification.

Post-operative complications
This topic is too broad for simple discussion. Generally, large neuroblastoma resections result in significant third space losses and require vigorous fluid replacement. Because of this fluid requirement patients may require significant periods of post-operative ventilation. The need for post-operative monitoring in an intensive care environment should be anticipated.

SPECIAL TECHNIQUES (Applicable for both Intermediate and High Risk)

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

Ultrasonic dissector-aspirators

Some authors have describe the use of 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 try to perform a generous incisional biopsy prior to ultrasonic dissection as it is difficult to capture the tumor specimen after it has been aspirated into the device.

Thoracoscopy

Video-assisted thoracoscopy can be used to remove small posterior mediastinal or thoracic inlet tumors provided there is no vascular encasement. One-lung ventilation is mandatory.

Laparoscopy

Laparoscopic resection of small adrenal or pelvic primaries can be done. Extensive tumors or those with significant vascular encasement, or locoregional nodal spread can be more completely resected using standard open approaches.

Radiofrequency Ablation, Cryosurgery

These techniques has significant drawbacks when applied to lesions in proximity to major vascular structures and should be avoided when treating neuroblastoma.

Specimen requirements

As noted above an initial biopsy should obtain greater than 1 cubic centimeter of viable tumor tissue. Placement of the specimen in formalin should be avoided. Rather, the pathologist should be alerted and the specimen rapidly transferred from the operating room fresh and sterile. The surgeon should verify with the pathologist that viable tissue was sent and is being processed for COG biological studies and histopathology. Since it is hoped to extract RNA from these specimens, rapid freezing of some of the tissue is required.

RANDOMIZED TRIAL OF SINGLE VS. TANDEM MYELOABLATIVE CONSOLIDATION THERAPY FOR HIGH-RISK NEUROBLASTOMA, ANBL0532

Background for Surgical Guidelines

Biopsy at initial diagnosis is necessary to obtain adequate tissue for biologic studies and enrollment on the Neuroblastoma Biology Protocol. Resection of the primary tumor and bulky metastatic disease is usually necessary to achieve CR or VGPR after induction chemotherapy. A retrospective analysis of high risk neuroblastoma patients enrolled onto CCG 3891 demonstrated improved resectability of primary tumor after initial chemotherapy and revealed a trend toward improved survival for those patients who underwent gross total resection of primary tumor, 5-year EFS 30 +/- 3% and 25 +/- 3%, respectively (p=0.1010).).[67] Acute surgical complication rates and characteristics were independent of timing of primary tumor resection. Based upon these data, patients enrolled onto the recently completed A3973 underwent delayed surgical resection of the primary tumor after 5 cycles of chemotherapy. Tumor biopsy at diagnosis was required to obtain adequate tissue for assessment of biologic characteristics. ANBL0532 will utilize this treatment strategy and prospectively evaluate if complete primary tumor resection is predictive of local control and EFS in high-risk neuroblastoma patients.

Early and late postoperative complications are known to occur following extensive tumor resection for neuroblastoma. These complications may include adhesive bowel] obstruction, chylous leak, ipsilateral renal injury, atrophy or loss, and chronic diarrhea. Group wide studies have regularly sought data on intraoperative and 30-day postoperative complications. Adkins et al. reported normal organ removal in 19% of high-risk neuroblastoma patients who underwent complete resection of primary tumor. There was no statistical difference in acute intra-operative or peri-operative complications, including risk for hemorrhage, renal injury, wound complication or acute bowel obstruction, regardless of extent of surgical resection.[67] There is potential for bias in this study, given the retrospective collection of data. Extended observations are necessary to detect late postoperative complications, as they may relate to the extent of resection and subsequent surgical and radiotherapeutic efforts to achieve local control. Specifically, extended follow up will be necessary to detect the occurrence of adhesive bowel obstruction and renal atrophy related to surgically induced ischemic events while the risk for chylous leak or diarrhea may be related to extensive retroperitoneal dissection. Rates of these complications should be correlated with the surgical and radiotherapeutic efforts in obtaining local control as they may impact on futuremanagement decisions.

Surgical rationale

The overall surgical goal in high-risk patients with neuroblastoma is the most complete tumor resection with preservation of full organ and neurologic function if possible. In addition, the surgeon is responsible for the preservation and delivery of an adequate surgical specimen to the appropriate laboratory for crucial biologic analyses; including determination of *MYCN* amplification, ploidy, and molecular genetic analyses. Titanium clips should be placed around sites of residual disease.

Pre-operative management

Adequate pre-operative imaging of the primary tumor and sites of regional spread is done by either computerized axial tomography, magnetic resonance imaging, or a combination of the modalities. Sites of distant metastases should be evaluated by a combination of clinical and bone marrow assessment as well as bone scan and MIBG scans. When dealing with paraspinal or epidural lesions pre-operative neurosurgical consultation is recommended and a baseline neurologic assessment carried out (see section 13.4.3 and Appendix III). The planned operation should be discussed with the attending pediatric oncologist and, if possible, at tumor board and the goals of the surgery should be clearly understood by all involved services pre-operatively.

Sampling requirements

In all patients, the primary purpose of the initial surgical procedure is to obtain enough tissue to establish the diagnosis, determine stage, and secure enough properly preserved tumor for biological studies. Refer to ANBL00B1 for complete details of specimen requirements. **All patients must be enrolled onto ANBL00B1 to be eligible to participate in ANBL0532.** An adequate biopsy to determine the diagnosis and assess biological variables like histopathologic classification, *MYCN* amplification and ploidy is required. Usually more than 1 cubic centimeter of viable tissue is needed for all these assays. Needle biopsies are not sufficient for histologic classification. The surgeon should remember that a significant portion of the tumor may be necrotic. Frozen section examination of a small amount of tissue will verify that viable neuroblastoma is being biopsied. The anesthesia time while awaiting frozen section analysis can also be used to obtain bone marrow aspirations and biopsies, and for placement of a vascular access device.

For patients with stage 4S 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 fine needle aspiration of a metastatic site for at minimum the determination of *MYCN* status.

OPERATIVE MANAGEMENT

Central Line Placement

Patients will require central venous access both for treatment and apheresis. It is usually feasible and efficient to place a vascular access device and obtain a bone marrow aspirate and biopsy during the same anesthetic. The appropriate catheter should be placed from initiation of therapy.

Medcomp or similar catheters are specifically designed as tunneled, permanent apheresis catheters. It may not be possible to draw at a sufficient rate from a non-apheresis catheter that is smaller than 10Fr. If a smaller double lumen must be placed, or if it is not possible to draw at a sufficient rate (2 ml/kg/min) then it may be necessary to place an additional 8-10 Fr single lumen catheter for the apheresis. If a second, single-lumen line is needed, it is best to place it electively PRIOR to starting the mobilization cycle of chemotherapy (i.e., cycle 2 induction chemotherapy).

Diagnostic Surgery

In all patients, the primary purpose of the initial surgical procedure is to obtain enough tissue to establish the diagnosis, determine stage, and secure enough properly preserved tumor for

biological studies. The great majority of high-risk patients will undergo initial diagnostic biopsy without resection. Biopsy of the primary tumor or an accessible metastatic site is acceptable. The goal of the biopsy procedure is to obtain enough tissue for a histopathological diagnosis as well as *MYCN* determination, cytogenetics, and other biological studies. The surgeon should try to obtain at least one cm^3 of viable tumor tissue, if feasible, according to the surgeon's judgment. Complete excision of the primary tumor can occasionally be performed if the tumor is easily resectable without a lengthy procedure or extensive dissection. However, a resection should not be undertaken if it might result in significant delay in the initiation of chemotherapy or great morbidity. In some institutions the diagnosis is established by finding neuroblastoma in bone marrow specimens in conjunction with elevated urinary catecholamines.

Epidural Tumors with Intraspinal Extension

When the tumor approaches the spinal canal on imaging (see section 16.2), a detailed examination must assess neurological function. The format for the examination, a modification of the ASCIA scale, is detailed in Appendix III and 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 patients who are neurologically asymptomatic. Patients with symptomatic spinal cord compression secondary to epidural extension of neuroblastoma through neural foramina may require laminectomy, or osteoplastic laminotomy at diagnosis to prevent permanent paralysis. However, treatment with chemotherapy alone or chemotherapy and radiation therapy will frequently be sufficient to rapidly reverse symptoms of cord compression. Therapeutic decisions in neuroblastoma patients with spinal cord compression should be made with the multidisciplinary involvement of the attending pediatric oncologist, general pediatric surgeon, and pediatric neurosurgeon.

If Neurologic deterioration occurs during chemotherapy, neurosurgical evaluation should be sought and operative decompression 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. Operative details will be recorded in the RDE.

Assessment of neurological function will be performed prior to start of treatment, after 2 cycles of inductions, end-induction therapy, end consolidation therapy and end of cisRa therapy for all patients with paraspinal tumors (see sections 7.0). **Neurologic and orthopedic evaluations will be a routine part of off therapy follow-up for patients with paraspinal tumors, and will be performed at 6, 12, 24, and 36 months post therapy, and then annually thereafter.** Orthopedic evaluation will include assessment of scoliosis and of extremity deformity by upright spine x-ray at these time points (see Appendix III).

Operative management of primary tumors after chemotherapy

The majority of patients will undergo resection of the primary tumor after initial induction chemotherapy. Surgical resection should be performed when the ANC > 500/μL and the patient is medically stable after Cycle 5 of Induction. This is to allow maximal tumor reduction by chemotherapy prior to resection and to reduce vascularity. Surgical resection may be performed later in Induction, if necessary, but must occur prior to Consolidation. Surgical scheduling

SHOULD AVOID DELAYS OF MORE THAN SIX WEEKS BETWEEN CHEMOTHERAPY CYCLES.

The goal of delayed surgery is gross total resection of residual tumor in the primary site as well as tumor in areas of regional dissemination (usually lymph nodes). Resection with microscopically negative margins may not be feasible because of proximity to major vascular structures and the spine. Instead, the surgeon should concentrate on removing, as completely as possible, all gross disease. It is acceptable, and often necessary, to incise the tumor and remove it in a segmental fashion. Titanium clips should be used to mark all areas of residual disease. All attempts should be made to preserve organs, especially the kidney. Rarely, nephrectomy may be necessary for complete tumor removal but this should only be planned if the involved kidney has greatly diminished function. If pre-operatively a nephrectomy is being considered, then a differential GFR should be obtained to determine what the renal function will be in the remaining kidney. This is extremely important because carboplatin is used for consolidation and toxicity may be greater for patients with a GFR < 100. The surgical committee of the Children's Oncology Group strongly recommends kidney preservation when feasible.

It is vital that the operating surgeon dictate a detailed operative note, which should include: the completeness of resection, areas of residual disease, estimated blood loss, and any operative complication such as identification of injury to adjacent structures, removal of normal organs, renal injury and vascular injury.

Surgical resection of residual disease following HSCT is not encouraged, unless it would alter therapy.

MANAGEMENT OF SURGICAL COMPLICATIONS

Intraoperative Complications

Intraoperative complications are site-dependent. Major hemorrhage from either venous or arterial structures is always possible with these infiltrative tumors. The principles of vascular surgery, including proximal and distal control, pertain. Appropriate intraoperative vascular consultation should be sought if necessary. Crucial vessels like the carotid, subclavian, hepatic, superior mesenteric or renal arteries should be repaired and flow restored even if bypass grafting is required. Nerve injuries may also be incurred and should be primarily repaired using magnification.

Post-operative Complications

This topic is too broad for simple discussion. Generally, large neuroblastoma resections result in significant third space losses and require vigorous fluid replacement. Because of this fluid requirement patients may require significant periods of post-operative ventilation. The need for post-operative monitoring in an intensive care environment should be anticipated. Acute and long-term complications and duration of complications will be prospectively monitored, including chylous leak (thoracic and abdominal); secretory non-infectious diarrhea; bowel obstruction due to post-surgical adhesions and renal dysfunction due to vascular injury.

Pulmonary Complications: Resection of large abdominal neuroblastoma may result in significant third space losses and require vigorous fluid replacement intraoperatively and postoperatively. Because of this fluid requirement patients may require significant periods of post-operative ventilation. The need for post-operative monitoring in an intensive care environment should be anticipated. Pneumonias or other pulmonary complications related to ICU and postoperative course (including intubation >7 days) should be reported

Bowel Obstruction: Small bowel obstruction may occur for many reasons, including injury, exposure, or blunt trauma during the resection, postoperative intussusception, formation of adhesions, or related to radiation injury. Obstruction may occur in the early postoperative period, or may occur months to years later. This study will collect long term data on the occurrence, etiology, and management of small bowel obstruction in this patient population, with the aims of reporting accurate occurrence rates, along with correlation of occurrence to the extent of resection and other efforts at local control.

Chylous Leak: Extensive dissection of the retroperitoneum or mediastinum may result in either frank disruption of chylous channels, or interruption causing intraluminal lymphatic hypertension and leak. This study will collect long term data on the occurrence and evaluation of abdominal distension, chylous ascites, and chylothorax as they relate to chylous leak, with the aims of reporting accurate occurrence rates, along with correlation of occurrence to extent of resection and other attempts at local control

Renal Injury/Atrophy: Renal injury may manifest in many forms, related to the nature of the injury or insult. While nephrectomy is strongly discouraged, extensive perirenal dissection and kidney sparing surgery may still result in vascular occlusion, infarction, traumatic compression, or other injury mechanisms sufficient to cause long term dysfunction or atrophy. Additionally, radiation therapy may lead to kidney damage, again with the long term finding of atrophy. This study will collect long term data on renal function, identifying the occurrence of renal injury and atrophy, with the aims of reporting accurate occurrence rates, along with correlation to extent of resection and other attempts at local control.

Diarrhea: Extensive sympathetic denervation associated with aggressive retroperitoneal dissection may result in increased frequency of stooling or diarrhea. This study will collect long term data on the occurrence and interventions necessary for the control of postoperative diarrhea, with the aims of reporting accurate occurrence rates, along with correlation to extent of resection and other attempts at local control.

Specimen requirements
As noted above an initial biopsy should obtain greater than 1 cubic centimeter of viable tumor tissue. Placement of the specimen in formalin should be avoided. Rather, the pathologist should be alerted and the specimen rapidly transferred from the operating room fresh and sterile. The surgeon should verify with the pathologist that viable tissue was sent and is being processed for COG biological studies and histopathology. Since it is hoped to extract RNA from these specimens, rapid freezing of some of the tissue is required.