



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroblastoma

Version 1.2024 — February 7, 2024

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NCCN Guidelines Version 1.2024 Neuroblastoma

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Rochelle Bagatell, MD/Chair €
Abramson Cancer Center
at the University of Pennsylvania |
Children's Hospital of Philadelphia

Julie R. Park, MD/Vice-Chair €
St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center

Sahaja Acharya, MD §
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins |
Johns Hopkins Children's Center

Jennifer Aldrink, MD ¶
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute | Nationwide
Children's Hospital

Jenna Allison, MD €
Fred & Pamela Buffett Cancer Center | Children's
Hospital & Medical Center

Elizabeth Alva, MD, MSPH €
O'Neal Comprehensive Cancer Center at UAB |
Children's of Alabama

Carola Arndt, MD €
Mayo Clinic Comprehensive Cancer Center

Melissa Bear, MD ‡
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center | Riley Children's
Health

Daniel Benedetti, MD, MA €
Vanderbilt-Ingram Cancer Center | Monroe Carell Jr.
Children's Hospital at Vanderbilt

Erin Brown, MD ¶
UC Davis Comprehensive Cancer Center

Steve Cho, MD †
University of Wisconsin Carbone Cancer Center |
American Family Children's Hospital

Alanna Church, MD ≠
Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center | Dana-Farber/Boston
Children's Cancer and Blood Disorders Center

NCCN

Lisa Hang, PhD
Ryan Schonfeld, BA

Andrew Davidoff, MD ¶
St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center

Ami Desai, MD, MSCE ‡ €
The UChicago Medicine
Comprehensive Cancer Center

Steven DuBois, MD, MS €
Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center | Dana-Farber/Boston
Children's Cancer and Blood Disorders Center

Douglas Fair, MD, MS €
Huntsman Cancer Institute at the University of Utah |
Primary Children's Hospital

Joaquim Farinhas, MD, MBA †
Moffitt Cancer Center

Douglas Harrison, MD ‡ €
The University of Texas
MD Anderson Cancer Center

Frederick Huang, MD ‡ €
Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine |
St. Louis Children's Hospital

Susan Kreissman, MD €
Duke Cancer Institute |
Duke Children's Hospital & Health Center

Margaret Macy, MD €
University of Colorado Cancer Center |
Children's Hospital Colorado

Brian Na, MD ‡ € Ψ
UCLA Jonsson Comprehensive Cancer Center |
UCLA Mattel Children's Hospital

Praveen Pendyala, MD §
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute |
Cleveland Clinic Children's

Navin Pinto, MD €
Fred Hutchinson Cancer Center |
Seattle Children's Hospital

Stephanie Polites, MD, MPH ¶
Mayo Clinic Comprehensive Cancer Center

Raja Rabah, MD ≠
University of Michigan Rogel Cancer Center |
C.S. Mott Children's Hospital

Hiroyuki Shimada, MD ≠
Stanford Cancer Institute |
Lucile Packard Children's Hospital

Leonora Slatnick, MD ‡
Huntsman Cancer Institute at the University of Utah
| Primary Children's Hospital

Elizabeth Sokol, MD ‡ €
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University |
Ann & Robert H. Lurie Children's Hospital of Chicago

Clare Twist, MD €
Roswell Park Comprehensive Cancer Center |
Roswell Park Oishei Children's Cancer and Blood
Disorders Program

Kieuhoa Vo, MD €
UCSF Helen Diller Family Comprehensive Cancer
Center | UCSF Benioff Children's Hospital

Tanya Watt, MD €
UT Southwestern Simmons Comprehensive Cancer
Center | Children's Medical Center Dallas

Suzanne Wolden, MD §
Memorial Sloan Kettering Cancer Center

Peter Zage, MD, PhD ‡ €
UC San Diego Moores Cancer Center |
Rady Children's Hospital-San Diego

φ Diagnostic radiology
‡ Hematology
‡ Internal medicine
† Medical oncology
Ψ Neurology/Neuro-oncology
φ Nuclear medicine
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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DIAGNOSTIC WORKUP

- **Tissue Sampling^a**
 - ▶ **Surgical resection should be considered in the setting of localized disease, particularly in the absence of image-defined risk factors (IDRFs). When biopsy rather than upfront resection is indicated, open biopsy may be preferred in some clinical scenarios if adequate tissue is not obtained/obtainable by less invasive means.**
 - ◊ See [Principles of Pathology \(NEUROB-A\)](#) for molecular testing considerations and additional information.
 - ▶ **Multiple core biopsies may provide adequate tissue; the need for full histologic and molecular evaluation of specimens must be considered. When sufficient tissue is obtained, the use of additional tissue for research purposes is encouraged.**
 - ▶ **Fine needle aspiration is not recommended**
 - ▶ **Review of frozen sections by an experienced pathologist is important to determine specimen adequacy, as some samples may be necrotic at the time of initial biopsy.**
- **Bilateral bone marrow aspirates and trephine biopsies**
 - ▶ **In rare cases, marrow may be the only source of diagnostic material. In those cases, every attempt should be made to obtain material for the full complement of molecular testing.**
 - ◊ See [Principles of Pathology \(NEUROB-A\)](#) for molecular testing considerations and additional information.

ADDITIONAL WORKUP

- **History and Physical (H&P): attention to abdominal exam for mass and organomegaly; thorough neurologic exam.**
- **Family history: attention to relatives with neuroblastoma or other childhood cancers¹**
- **Additional considerations**
 - ▶ **Essential:**
 - ◊ Complete blood count (CBC) with differential
 - ◊ Comprehensive metabolic panel
 - ◊ Homovanillic acid (HVA)/Vanillylmandelic acid (VMA): required for diagnosis if only diagnostic tissue is bone marrow or if no biopsy is to be obtained initially
 - ▶ **Useful in selected cases:**
 - ◊ Prothrombin Time (PT)/international normalized ratio (INR) if liver is involved or if there is concern for bleeding
 - ◊ Lactate dehydrogenase (LDH), ferritin may be considered
 - ◊ Pregnancy test (for patients of childbearing potential)
 - ◊ Audiogram if platinum containing chemotherapy is indicated
 - ◊ Echocardiogram if chemotherapy is indicated, especially if anthracycline-containing chemotherapy is indicated
 - ◊ Electrocardiogram (ECG) should be considered if chemotherapy is indicated
 - ◊ Fertility/fertility preservation: Refer to fertility specialists for discussion of possible options and appropriate timing (for patients with high-risk disease)

- **Imaging**
 - ▶ **Cross-sectional imaging (MRI with/without contrast or CT with contrast) to evaluate soft tissue disease**
 - ▶ **MRI of spine with/without contrast in the setting of paraspinal disease or concerns regarding involvement of nerve roots or spinal cord**
 - ▶ **MRI of brain with/without contrast or CT skull/orbits with contrast if neurological symptoms are present or if otherwise clinically indicated**
 - ▶ ¹²³Iodine-meta-iodobenzylguanidine (I-MIBG) imaging (with SPECT or SPECT/CT, where available) to assess for metastatic disease
 - ▶ **Fluorodeoxyglucose (FDG)-PET should be obtained in patients with MIBG non-avid disease or suspected mixed-avidity disease^b**
 - ▶ See [Principles of Imaging \(NEUROB-B\)](#) for Radiology Initial Workup and additional information

Risk
Classification
[\(NEUROB-2\)](#)

^a The following patients should have biopsy delayed until after therapy is started and the patient is medically stable:

- ▶ Patients <2 months of age with existing or evolving hepatomegaly (Twist CJ, et al. J Clin Oncol 2019;37:115-124.)
 - ▶ Infants in whom safety considerations (coagulopathy, impending organ failure) preclude biopsy
 - ▶ In these cases, biopsy should be performed when it is safe to do so to obtain tissue for molecular testing
- (Patients <6 months of age with L1 adrenal tumor with maximum diameter ≤3.1 cm diameter if solid or 5 cm if at least 25% cystic component do not require a biopsy (Nuchtern JG, et al. Ann Surg 2012;256:573-580).)

^b Not required in patients <6 months of age with L1 adrenal tumor with maximum diameter ≤3.1 cm diameter if solid or 5 cm if at least 25% cystic component. (Nuchtern JG, et al. Ann Surg 2012;256:573-580).

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[References on
NEUROB-12](#)



NEUROBLASTOMA RISK CLASSIFICATION^c

Clinical Stage ^d	MYCN amp	Age	Other Features (Ploidy/International Neuroblastoma Pathology Classification [INPC]/Histology/Extent of Resection/Clinical Symptoms)	Risk Group	
L1 ^e	No	Any	Any	Low risk	
	Yes	Any	Completely resected	Low risk	
	Yes	Any	Incompletely resected	High risk	
L2	No	<18 months	Any	Intermediate risk	
		18 months to <5 years	FH ^f	Intermediate risk	
			UH ^f	High risk ^h	
	≥5 years	Differentiating per INPC ^f	Intermediate risk		
		Undifferentiated, poorly differentiated ^f	High risk ^h		
Yes	Any	Any	High risk		
M	No	<12 months	Any	Intermediate risk	
	Yes			High risk	
	No	≥12 to <18 months	UH, ^f DNA index (DI)=1, or segmental chromosomal aberrations (SCA+) See Principles of Pathology (NEUROB-A)	High risk	
				FH, ^f DI>1, and SCA- (category 2B) ²	Intermediate risk ⁱ
	Yes		Any	High risk	
Any	≥18 months	Any	High risk		
MS	Unknown	<12 months	Symptomatic ^g	Intermediate risk	
	No		UH, ^f DI=1, or SCA+	Intermediate risk	
	Yes		Asymptomatic, FH, ^f DI>1, and SCA-	Low risk	
	No	12 to <18 months	Any	Any	High risk
				UH, ^f DI=1, or SCA+	High risk
FH, ^f DI>1, and SCA-				Intermediate risk	
Yes		Any	High risk		

FH: Favorable histology; UH: Unfavorable histology

Adapted from Irwin MS, Naranjo A, Zhang FF, et al. Revised Neuroblastoma Risk Classification System: A report from the Children’s Oncology Group. J Clin Oncol 2021;39:3229-3241.

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[Footnotes on NEUROB-2A](#)
[References on NEUROB-12](#)

NEUROB-2



NEUROBLASTOMA RISK CLASSIFICATION FOOTNOTES

^c See [Principles of Pathology \(NEUROB-A\)](#) and [Principles of Risk Classification \(NEUROB-C\)](#) for additional considerations.

^d See [ST-1 for International Neuroblastoma Risk Group \(INRG\) Staging Criteria](#).

^e Perinatally diagnosed children with L1 tumors will be discussed in the treatment section. See [Low-Risk Disease \(NEUROB-3\)](#) and [Principles of Systemic Therapy \(NEUROB-D\)](#).

^f Pathology should be reviewed by a pathologist with expertise in classification of neuroblastoma.

^g Infants in whom safety considerations (coagulopathy, impending organ failure) preclude biopsy, especially those with hepatomegaly leading to respiratory compromise. Symptomatic patients should start intermediate risk treatment emergently prior to biopsy. Once symptoms have resolved following initial therapy, patients should undergo biopsy and risk assignment should be revised based on available data. See Hsu LL, et al. *Med Pediatr Oncol* 1996;27:521-528 for symptoms; a total score ≥ 2 should lead to emergent therapy.

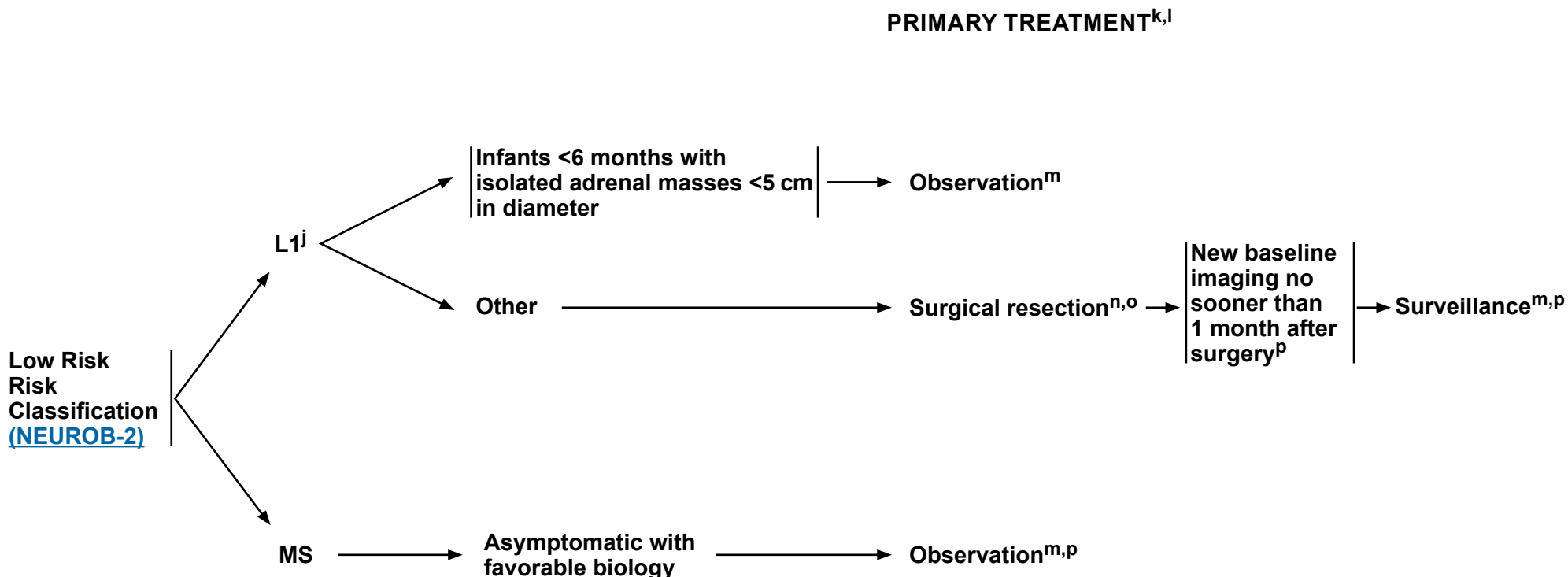
^h Cooperative groups outside North America may treat these patients as intermediate risk.

ⁱ Cooperative groups outside North America may treat all patients with INRG Stage M disease ≥ 12 months as high risk.

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LOW-RISK DISEASE



^j Obtain MIBG scan once to confirm localized disease. If the patient is <6 months of age with adrenal tumor, no MIBG scan is required, unless signs and symptoms implicate distant sites of disease.

^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^l [Principles of Surgery \(NEUROB-E\)](#).

^m Use ultrasound for surveillance when clinically indicated and appropriate.

ⁿ Obtain cross-sectional imaging once to delineate new baseline disease status at least 1 month postoperatively, then transition to ultrasound for surveillance if possible.

^o If resection is incomplete and patient has *MYCN* amplification, see [Risk Classification \(NEUROB-2\)](#).

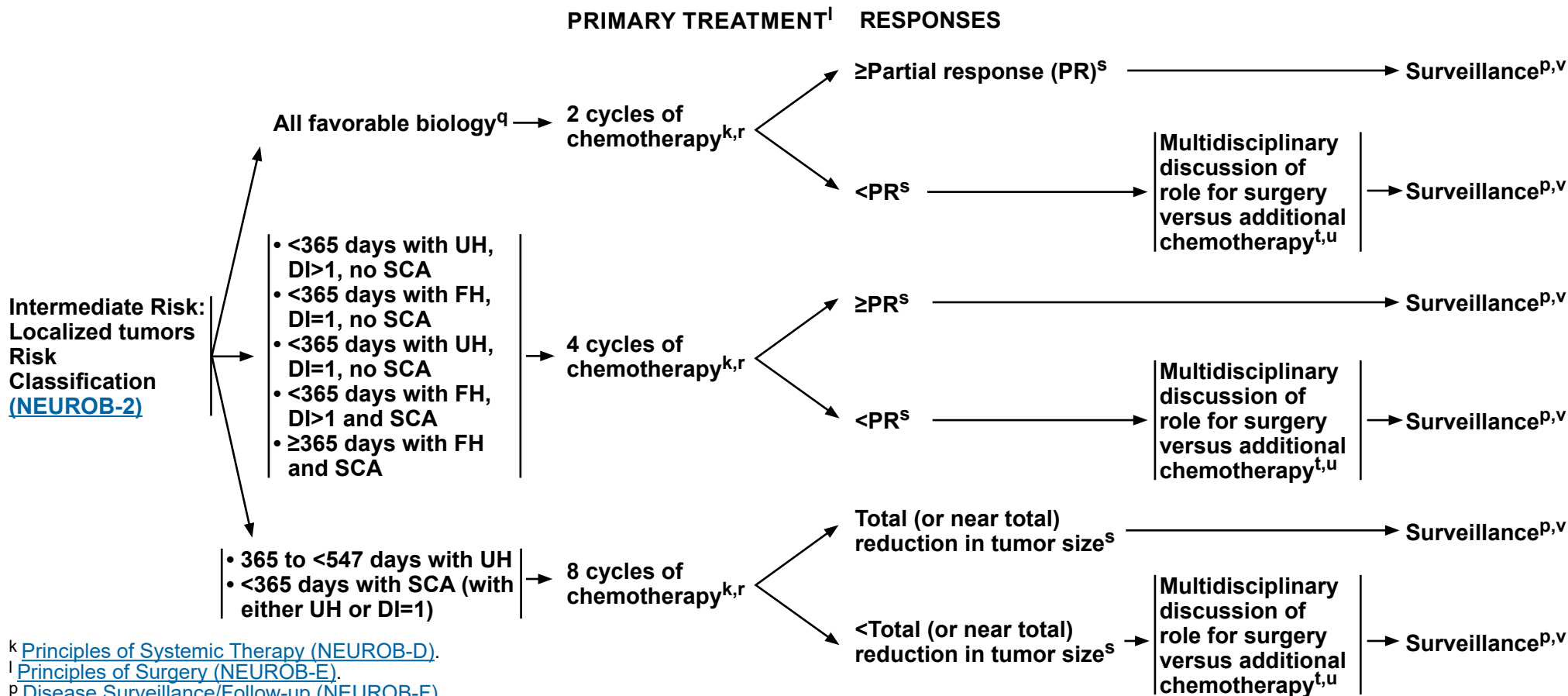
^p [Disease Surveillance/Follow-up \(NEUROB-F\)](#).

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INTERMEDIATE-RISK DISEASE



^k Principles of Systemic Therapy (NEUROB-D).

^l Principles of Surgery (NEUROB-E).

^p Disease Surveillance/Follow-up (NEUROB-F).

^q Favorable biologic features include favorable histology, DI >1, no SCA. If SCA or histology status are not available, consider as unfavorable.

^r Audiologic assessment and echocardiogram should be obtained at diagnosis and again at end of therapy.

^s Historically measured by volume. See [NEUROB-D 1 of 11](#) and [Response Assessment \(NEUROB-G\)](#).

^t Multidisciplinary discussions should be undertaken on an iterative basis. Surveillance should begin once the response or reduction in primary tumor size noted above is achieved, with chemotherapy and/or surgery.

^u If additional chemotherapy is given, consider 2–4 additional cycles with repeat primary tumor imaging after every 2 cycles. Consider surgery if chemotherapy has led to stable disease or minimal improvement in tumor size. Multidisciplinary discussion is important in decisions surrounding surgery and additional chemotherapy. Consider biopsy as the tumor may have differentiated and additional treatment may not be required. If 8 cycles of chemotherapy have been given and the tumor remains unresectable, consider treatment with second line chemotherapy as per Twist CJ, et al. J Clin Oncol 2019;37:3243-3255.

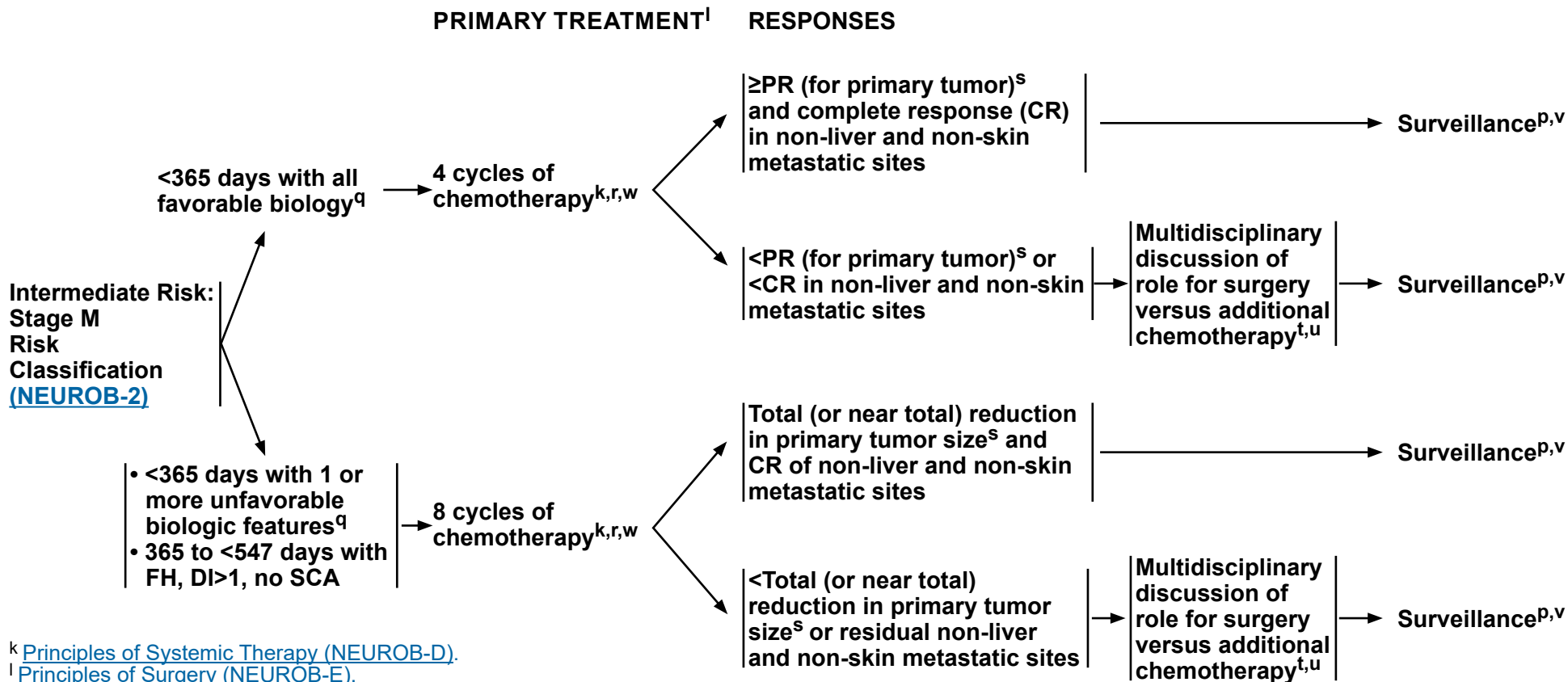
^v If the treatment endpoint has been achieved, obtain MIBG scan as part of the end of therapy evaluation.

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INTERMEDIATE-RISK DISEASE



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^l [Principles of Surgery \(NEUROB-E\)](#).

^p [Disease Surveillance/Follow-up \(NEUROB-F\)](#).

^q Favorable biologic features include favorable histology, DI >1, no SCA. If SCA or histology status are not available, consider as unfavorable.

^r Audiologic assessment and echocardiogram should be obtained at diagnosis and again at end of therapy.

^s Historically measured by volume. See [NEUROB-D 1 of 11](#) and [Response Assessment \(NEUROB-G\)](#).

^t Multidisciplinary discussion should be undertaken on an iterative basis. Surveillance should begin once the response or reduction in primary tumor size noted above is achieved, with chemotherapy and/or surgery.

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^v If the treatment endpoint has been achieved, obtain MIBG scan as part of the end of therapy evaluation.

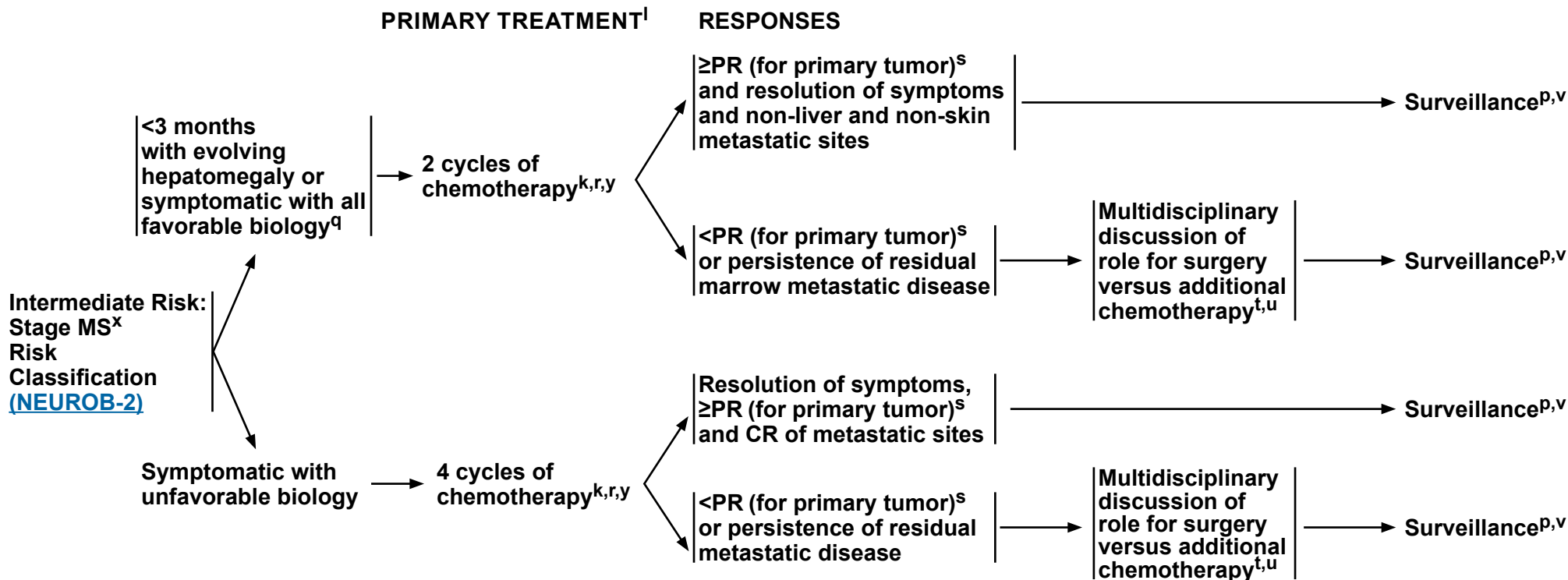
^w Evaluate all prior sites of disease after 4 cycles if only 4 cycles of chemotherapy are planned. If 8 cycles are planned, evaluate after cycles 4 and 8.

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INTERMEDIATE-RISK DISEASE



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^l [Principles of Surgery \(NEUROB-E\)](#).

^p [Disease Surveillance/Follow-up \(NEUROB-F\)](#).

^q Favorable biologic features include favorable histology, DI >1, no SCA. If SCA or histology status are not available, consider as unfavorable.

^r Audiologic assessment and echocardiogram should be obtained at diagnosis and again at end of therapy.

^s Historically measured by volume. See [NEUROB-D 1 of 11](#) and [Response Assessment \(NEUROB-G\)](#).

^t Multidisciplinary discussion should be undertaken on an iterative basis. Surveillance should begin once the response or reduction in primary tumor size noted above is achieved, with chemotherapy and/or surgery.

^u If additional chemotherapy is given, consider 2–4 additional cycles with repeat primary tumor imaging after every 2 cycles. Consider surgery if chemotherapy has led to stable disease or minimal improvement in tumor size. Multidisciplinary discussion is important in decisions surrounding surgery and additional chemotherapy. Consider biopsy as the tumor may have differentiated and additional treatment may not be required. If 8 cycles of chemotherapy have been given and the tumor remains unresectable, consider treatment with second line chemotherapy as per Twist CJ, et al. *J Clin Oncol* 2019;37:3243-3255.

^v If the treatment endpoint has been achieved, obtain MIBG scan as part of the end of therapy evaluation.

^x For infants who are too unstable to undergo biopsy before starting treatment, chemotherapy may be initiated and a biopsy obtained when it is safe to do so.

^y Evaluate all prior sites of disease after 2 cycles if only 2 cycles of chemotherapy are planned. If 4 cycles are planned, perform the complete evaluation of all sites of prior disease after 4 cycles.

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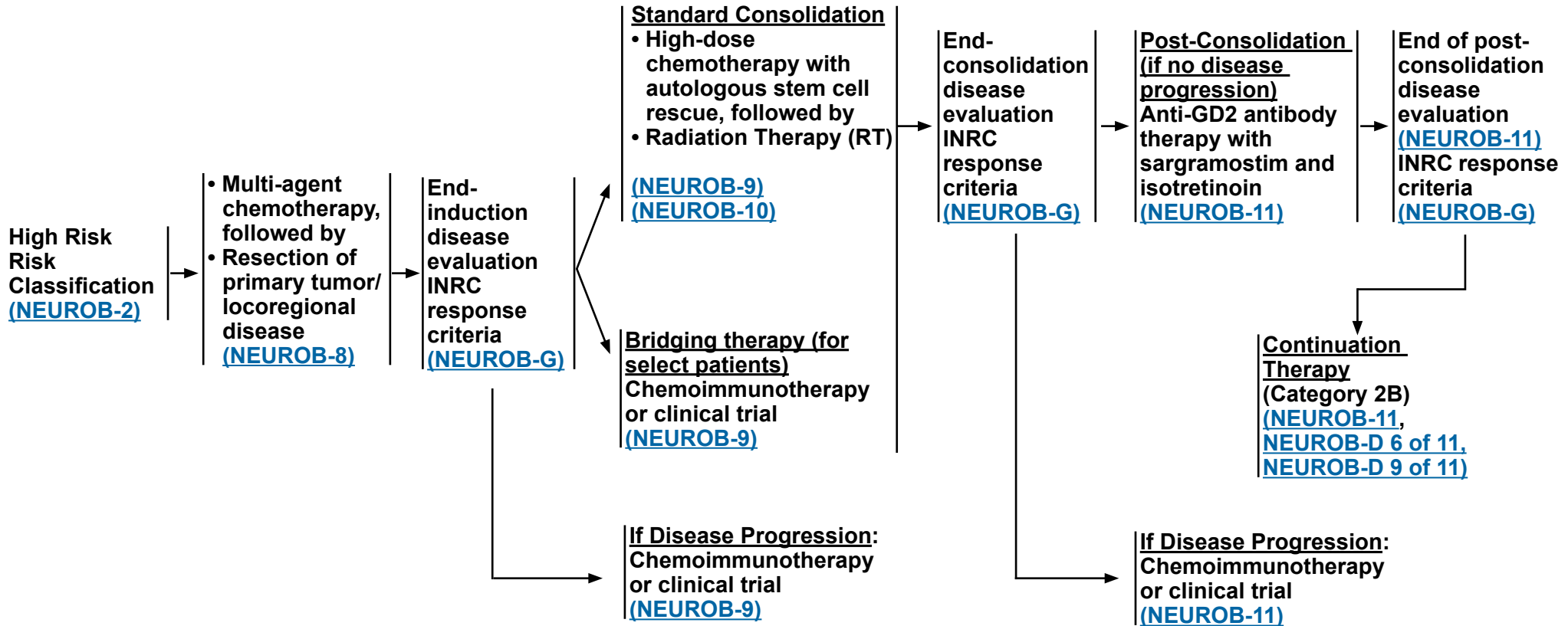


OVERVIEW OF TREATMENT FOR HIGH-RISK NEUROBLASTOMA

INDUCTION THERAPY

CONSOLIDATION THERAPY

POST-CONSOLIDATION THERAPY



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HIGH-RISK DISEASE

INDUCTION THERAPY



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^l [Principles of Surgery \(NEUROB-E\)](#).

^z Anatomic imaging of primary site prior to surgery.

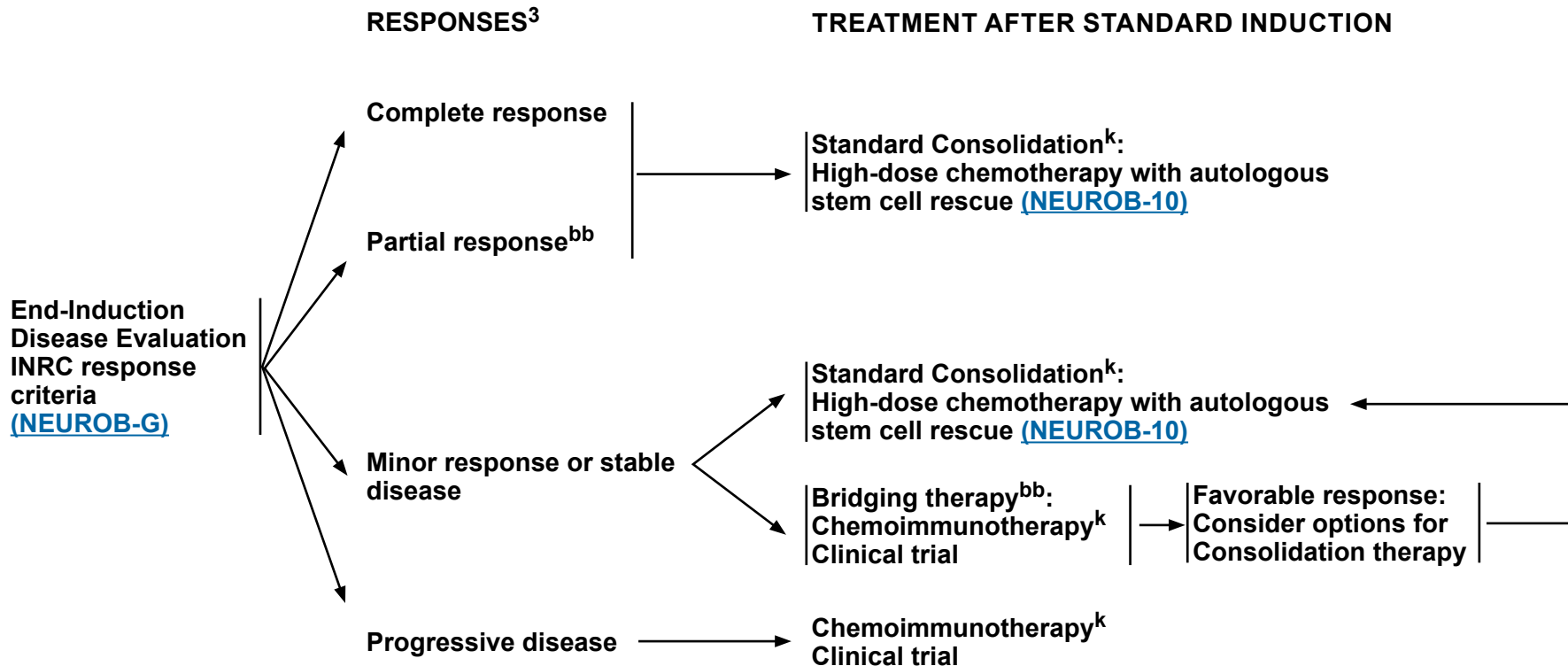
^{aa} Subtotal resection if gross total will jeopardize vital organs, major nerves, and/or major vessels.

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HIGH-RISK DISEASE



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^{bb} Bridging therapy may be appropriate in select patients depending upon degree of response. See [Principles of Systemic Therapy \(NEUROB-D 4 of 11\)](#).

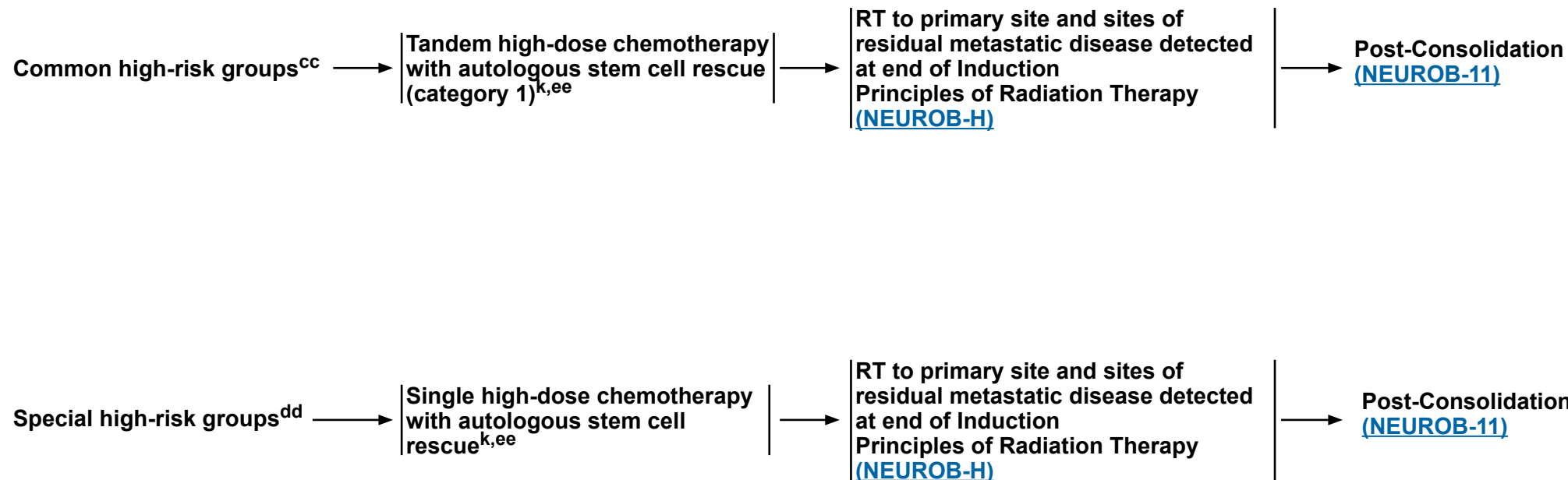
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[References on NEUROB-12](#)



HIGH-RISK DISEASE

CONSOLIDATION THERAPY



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^{cc} Common high-risk groups include all other categories not included as part of special high-risk groups.

^{dd} Special high-risk groups include:

Stage L2, ≥18 months, *MYCN* non-amplified, and unfavorable histology

Stage M, 12 to <18 months, *MYCN* non-amplified, and any of the following unfavorable features: unfavorable histology; diploid DNA content; and/or presence of segmental chromosomal aberrations.

^{ee} Non-myeloablative approaches have been evaluated in single institution studies and may be appropriate in select patients. (Kushner BH, et al. *Oncotarget* 2016;7:4155-4166; Kushner BH, et al. *Oncotarget* 2017;8:95293-95302). Single transplant is currently standard in Europe. (Ladenstein R, et al. *Lancet Oncol* 2017;18:500-514.)

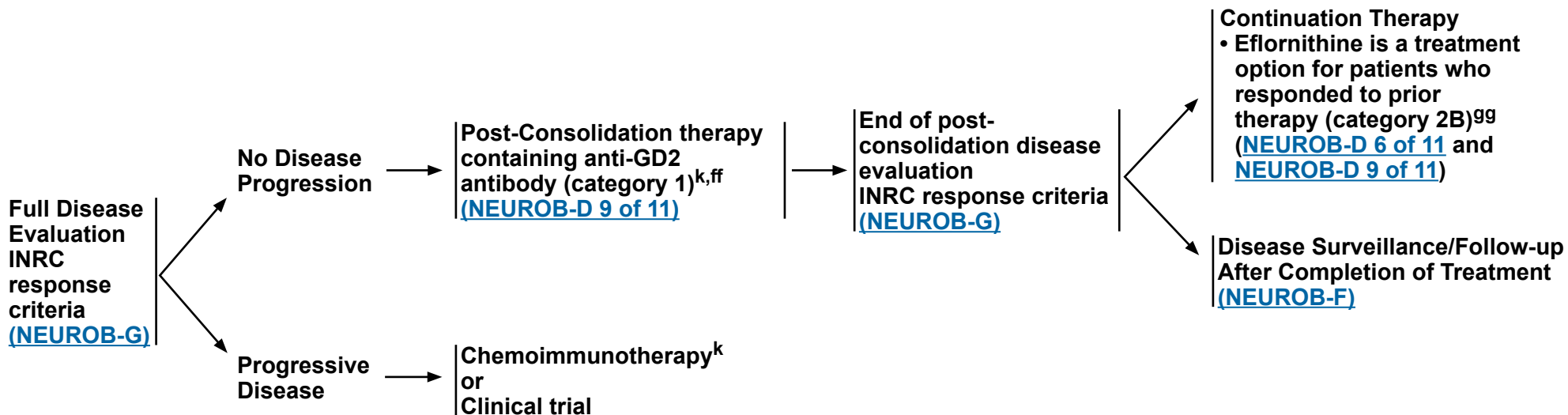
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HIGH-RISK DISEASE

POST-CONSOLIDATION THERAPY^k



^k [Principles of Systemic Therapy \(NEUROB-D\)](#).

^{ff} ¹²³I-MIBG scan (FDG-PET, if MIBG non-avid) recommended after first 3 cycles of post-consolidation therapy. Additional disease evaluations (anatomic imaging of primary site and/or bone marrow evaluation) if residual disease present at start of post-consolidation.

^{gg} Serial monitoring of hearing with audiograms or brainstem auditory evoked response is essential as most patients with high-risk neuroblastoma are at a critical age for language development.

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- ¹ Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and neuroblastoma predisposition and surveillance. *Clin Cancer Res* 2017;23:e98-e106.
- ² Sokol E, Desai AV, Applebaum MA, et al. Age, Diagnostic Category, Tumor Grade, and Mitosis-Karyorrhexis Index Are Independently Prognostic in Neuroblastoma: An INRG Project. *J Clin Oncol* 2020;38:1906-1918.
- ³ Park JR, Bagatell R, Cohn SL, et al. Revisions to the International Neuroblastoma Response Criteria: A consensus statement from the National Cancer Institute Clinical Trials Planning Meeting. *J Clin Oncol* 2017;35:2580-2587.

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PRINCIPLES OF PATHOLOGY

Sampling

- It is imperative that pathology workflows are designed to accommodate histologic diagnosis with prognostic classification and molecular profiling as required for treatment.
- Tissue requirements:
 - ▶ Guidance on which evaluations are indicated for each patient based on clinical criteria are outlined below, based on requirements for risk stratification for treatment selection. Enrollment in clinical trials may require additional testing.
 - ▶ Typical tissue considerations:
 - ◇ For primary diagnosis (tumor or metastasis):
 - Surgical resection if clinically indicated
 - Incisional biopsy: >1 cm³
 - Tissue cores: at least 10 cores, ideally 20–30 mm in length obtained using a 16-gauge needle
 - ◇ Bilateral bone marrow biopsies and clot sections alone may not be sufficient to assess characteristics relevant to INPC¹
- These tissue quantity requirements can be challenging to accommodate. In some cases, open rather than minimally invasive procedures may be required to obtain adequate specimens for all required testing.²
- Advanced knowledge of how much tissue is required and the condition of the tissue (formalin-fixed paraffin-embedded [FFPE], fresh, frozen, touch preparations, etc) will increase the likelihood that required testing can be completed.
- A coordinated diagnostic sampling effort including pathologists, oncologists, surgeons, and radiologists is recommended.^{3,4}

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**NEUROB-A
1 OF 4**

**PRINCIPLES OF PATHOLOGY****Histologic Classification**

- **Diagnosis should be determined according to the International Collaboration on Cancer Reporting (ICCR) and INPC.^{5,6}**
- **Determination of INPC should be done using the diagnostic sample obtained prior to the initiation of therapy.**
- **The histologic diagnosis of neuroblastoma is typically made based on hematoxylin and eosin (H&E) staining. In the setting of small samples, unusual locations, or undifferentiated subtype, immunohistochemical stains are helpful.**
 - ▶ **Neuronal markers: Chromogranin, Synaptophysin**
 - ▶ **Neural crest markers: PHOX2B (strongly recommended), tyrosine hydroxylase**
- **The INPC classifies peripheral neuroblastic tumors into two prognostic groups (Favorable Histology and Unfavorable Histology),⁵⁻⁷ based on:**
 - ◇ **Tumor category based on Schwannian stroma development and subtyping based on degree of neuroblastic differentiation:**
 - **Neuroblastoma (Schwannian stroma-poor)**
 - **Undifferentiated subtype: This diagnosis relies heavily on ancillary tests, such as immunohistochemistry and/or molecular analysis**
 - **Poorly differentiated subtype**
 - **Differentiating subtype**
 - **Ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor)**
 - **Grade of neuroblastic differentiation (undifferentiated subtype, poorly differentiated subtype, or differentiating subtype) is determined for the neuroblastoma component in this category.**
 - **Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)**
 - **Ganglioneuroma (Schwannian stroma-dominant)**
 - **Note that the diagnosis of ganglioneuroblastoma, intermixed (Schwannian stroma-rich) or ganglioneuroma (Schwannian stroma-dominant) from a biopsy sample (rather than resection sample) should include a comment: “Favorable histology based on review of limited material”, indicating the possibility of sampling issue resulting in missing a neuroblastoma nodule.**
 - ◇ **Mitosis and karyorrhexis index (MKI):**
 - **Assessed by estimating mitotic and karyorrhectic nuclei per 5000 neuroblastic cells.**
 - **Based on the MKI, all tumors in the neuroblastoma (Schwannian stroma-poor) category and neuroblastic components of ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant) category are further classified into 1 of 3 classes:**
 - **Low MKI: <100/5000 cells**
 - **Intermediate MKI: 100–200/5000 cells**
 - **High MKI: ≥200/5000 cells**
 - ◇ **Age at diagnosis**

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**PRINCIPLES OF PATHOLOGY****Molecular Genetic Testing Considerations:**• **Prognosis:**

- ▶ Risk stratification for primary treatment depends heavily on molecular tumor profiling ([Principles of Risk Classification \[NEUROB-C\]](#))
- ▶ Amplification of *MYCN* is associated with aggressive disease
 - ◊ Due to the strong prognostic association, it should be assessed on all neuroblastomas and neuroblastomatous nodules of ganglioneuroblastoma nodular tumors.
 - ◊ Can be assessed by fluorescence in situ hybridization (FISH) (using a reference probe), by microarray, or by next-generation sequencing (NGS) (see “assay selection” below)
 - ◊ Status by FISH is defined as follows: not amplified (2 copies per cell), gain (>2–8 copies per cell or <4-fold increase), amplified (>8 copies per cell or ≥4-fold increase, can be >30-fold increase⁸)
- ▶ Segmental chromosomal aberrations (SCAs) may be associated with aggressive disease, depending on other factors^{9,10}:
 - ◊ The most extensively studied segmental chromosome aberrations include 1p, 11q, 17q, 3p, 4p, 1q, and 2p.
 - ◊ Can be assessed by microarray or by NGS (see “assay selection” bullet)
- ▶ Ploidy evaluates the amount of DNA within tumor cells
 - ◊ A DNA index of 1 may be associated with aggressive disease, depending on other factors including age
 - ◊ Can be assessed by flow cytometry or estimated by NGS
- Identification of potential molecular targets for therapy:
 - ▶ Molecularly-targeted therapies are emerging in pediatric solid tumors, including neuroblastoma.^{11,12}
 - ▶ Amplification and sequence variants in *ALK* predict response to targeted agents.¹³⁻¹⁶
 - ▶ As research and drug discovery continue to evolve, additional testing for therapeutic biomarkers may be indicated.

• **Assay selection:**

- ▶ Next generation sequencing:
 - ◊ Has become widely available and is increasingly feasible with FFPE tissue
 - ◊ Is recommended to simultaneously evaluate *MYCN* amplification, SCAs, and *ALK* alterations if the panel or approach:
 - Provides robust assessment of copy number status.
 - Provides coverage of the relevant regions of *ALK* and other neuroblastoma-associated genes
- ▶ Assessment of the status of standard prognostic biomarkers can also be done using FISH and microarray, but these will not identify sequence variants in *ALK* and other neuroblastoma-associated genes
- Incidental identification of germline alterations:
 - ▶ Whether using single-gene or broad testing approaches, genetic alterations that may be associated with cancer predisposition or other germline inherited conditions will be identified.^{17,18}
 - ▶ Dedicated germline testing may be indicated based on the family history, clinical presentation, or the presence of alterations identified by molecular tumor profiling.
 - ▶ Involvement of genetic counselors and molecular laboratory professionals with experience in germline genetics is helpful in resolving questions of etiology of variants (germline vs. somatic) and in supporting the patient and family in navigating this complex issue.

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**PRINCIPLES OF IMAGING****General Principles**

- Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors of the sympathetic nervous system that arise from the embryonic neural crest and are referred to collectively as neuroblastic tumors, all with similar imaging appearance.^{1,2}
- A diagnosis of neuroblastic tumor is usually suspected based on the patient's age and the appearance of the tumor on imaging.¹
- The combination of imaging studies to be used during the initial evaluation of a child with a suspected neuroblastic tumor is dependent upon the symptoms that are present and the suspected sites of disease.^{a,3}
- Local extension of neuroblastoma mainly consists of vascular encasement, infiltration of adjacent soft tissues and organs (mainly the kidneys and liver), and infiltration of the foramina and epidural space of the spinal canal when the primary tumor arises from a paraspinal sympathetic chain.
- Approximately 50% of patients present with localized or regional disease, and approximately 35% of patients have regional lymph node spread at time of diagnosis.⁴
- The International Neuroblastoma Risk Group (INRG) Task Force developed the INRG Staging System (INRGSS) and the INRG Risk Classification System for neuroblastoma, which have profound implications for imaging and an increased role for radiology.¹
- While soft-tissue tumor volume was previously used as measurement of response in the prior INRC, the revised INRC uses RECIST criteria for measurement of soft tissue disease, using the single longest dimension.^{5,6}

Goals of Imaging

- Identify features consistent with a neuroblastic tumor.⁷
- Assess for presence of IDRFs to classify tumors as L1 or L2 disease by the INRG Staging System.^{b,c,2}
- Help estimate potential surgical risk associated with local tumor excision.
- Assess for presence and degree of regional and distant metastatic disease.
- Facilitate post-treatment response assessment and disease surveillance.

Ultrasound

- When an abdominal or pelvic tumor is suspected in a child, ultrasonography (US) is often the first imaging examination performed because it is widely available and noninvasive.
- Although US is not associated with exposure to radiation, interobserver reproducibility is low and there is limited assessment of highly calcified tumors because of acoustic shadowing.
- While US can be helpful as an initial screening imaging study, magnetic resonance or computed tomographic (CT) images should be obtained at the time of diagnosis for accurate staging and treatment planning.

CT/MRI:

- Both MRI and CT are routinely used for imaging of soft-tissue disease, depending on availability and institutional expertise.
- CT is rapidly performed and widely available, with superior detection of calcifications. It allows rapid acquisition without motion artifacts, and reduces the need for sedation.
- MRI is superior for evaluating spinal involvement and does not involve use of ionizing radiation.
- Both CT and MRI may be performed at the initial evaluation, especially if the tumor is paraspinal.
- Both modalities demonstrate typical features of primary tumors and metastasis to the liver, lymph nodes, bone, and skin.^{7,8}

^a See COG: <https://www.childrensoncologygroup.org/newly-diagnosed-with-neuroblastoma>.

^b [INRG Staging \(ST-1\)](#).

^c [Descriptions of IDRFs \(NEUROB-B 3 of 4\)](#).

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PRINCIPLES OF IMAGING

Nuclear Imaging:

- Iodine 123 (¹²³I-MIBG) is used for imaging of neuroblastic tumors, especially metastatic sites of disease.⁹
 - ▶ Obtain prior to resection of the primary tumor, if possible
 - ▶ Not required in patients <6 months of age with a localized adrenal tumor in longest diameter ≤3.1 cm if solid or 5 cm if >25% cystic component.
 - ▶ Baseline ¹²³I-MIBG imaging may be delayed in patients <2 months of age or those weighing less than 2.5 kg with suspected primary tumors within the adrenal glands.
 - ▶ Novel radiotracers are in development but there are insufficient data currently available to incorporate routinely for diagnostic imaging and response assessment.
- As an analog of norepinephrine, MIBG is taken up by norepinephrine transporters. Uptake is demonstrated in up to 90% of neuroblastoma tumors.
- The high specificity and high sensitivity with improved accuracy for localization make MIBG imaging the test of choice for identification of metastatic disease.¹⁰ ¹²³I-MIBG is the agent of choice for diagnostic imaging. ¹³¹I-MIBG may be useful in resource-limited settings.⁹
- In addition to MIBG whole-body planar scintigraphy (vertex of head through feet), SPECT or SPECT/CT should be performed at sites of known or suspected disease, where available, due to improved sensitivity and anatomic localization of disease sites.¹⁰
- Interpretation of MIBG tumor uptake is performed by means of semiquantitative scoring of body segments. The modified Curie score¹¹ and the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) score¹² are the two most commonly used systems. In North America, the modified Curie score is used.
- When neuroblastoma tumors are not MIBG avid, or when MIBG imaging and anatomic imaging do not correlate, FDG-PET/CT or PET/MRI are useful alternative or supplemental diagnostic tools.

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**PRINCIPLES OF IMAGING**
DESCRIPTIONS OF IDRFs²

Anatomic Region	Description
Multiple body compartments	Ipsilateral tumor extension within two body compartments (ie, neck and chest, chest and abdomen, or abdomen and pelvis)
Neck	<ul style="list-style-type: none"> • Tumor encasing carotid artery, vertebral artery, and/or internal jugular vein • Tumor extending to skull base • Tumor compressing trachea
Cervicothoracic junction	<ul style="list-style-type: none"> • Tumor encasing brachial plexus roots • Tumor encasing subclavian vessels, vertebral artery, and/or carotid artery • Tumor compressing trachea
Thorax	<ul style="list-style-type: none"> • Tumor encasing aorta and/or major branches • Tumor compressing trachea and/or principal bronchi • Lower mediastinal tumor infiltrating costovertebral junction between T9 and T12 vertebral levels
Thoracoabdominal junction	Tumor encasing aorta and/or vena cava
Abdomen and pelvis	<ul style="list-style-type: none"> • Tumor infiltrating porta hepatis and/or hepatoduodenal ligament • Tumor encasing branches of superior mesenteric artery at mesenteric root • Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery • Tumor invading one or both renal pedicles • Tumor encasing aorta and/or vena cava • Tumor encasing iliac vessels • Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (whatever the location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomenigeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

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**PRINCIPLES OF RISK CLASSIFICATION**

Risk classification is assigned¹⁻⁵ based on outcome data generated over recent decades. Event-free survival (EFS) and overall survival (OS) outcomes are influenced by key prognostic risk factors including:

- Age at diagnosis
- International Neuroblastoma Risk Group (INRG) Stage ([ST-1](#))
- Tumor *MYCN* status (presence or absence of *MYCN* amplification)
- Histopathology (Favorable or Unfavorable based on International Neuroblastoma Pathology Classification [INPC])
- Presence or absence of SCAs
- DNA index (diploid or hyperdiploid)

It should be noted that treatment substantially impacts outcome, and outcomes achieved often reflect the impact of different types of therapy within a given risk group. However, risk classification must occur in practice prior to the start of therapy. The risk assignments that follow therefore reflect pre-treatment decision-making, taking into account treatment administered to prior patients with neuroblastoma over time.

Risk	5-year EFS ¹	5-year OS ¹
Low	90.7% ± 1.0%	97.9% ± 0.5%
Intermediate	85.1% ± 1.4%	95.8% ± 0.8%
High	51.2% ± 1.4%	62.5% ± 1.3%

¹ Irwin MS, Naranjo A, Zhang FF, et al. Revised Neuroblastoma Risk Classification System: A report from the Children's Oncology Group. J Clin Oncol 2021;39:3229-3241.

² Sokol E, Desai AV, Applebaum MA, et al. Age, diagnostic category, tumor grade, and mitosis-karyorrhexis index are independently prognostic in neuroblastoma: An INRG Project. J Clin Oncol 2020;38:1906-1918.

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**LOW- AND INTERMEDIATE-RISK DISEASE****PRINCIPLES OF SYSTEMIC THERAPY**

Patients with low- and intermediate-risk (ie, non-high risk) neuroblastoma have excellent survival. Recent clinical trials have focused on reduction of therapy for patients with favorable biology and have been successful in maintaining excellent outcomes with these strategies.¹⁻³

Over the past 2 decades, the staging system, risk classification system, and response criteria definitions for neuroblastoma have evolved. It is important to note that published results from clinical trials for patients with non-high-risk disease utilized a legacy staging system (International Neuroblastoma Staging System [INSS]) and older response criteria⁴ or protocol-specific response criteria.³ These NCCN guidelines are based on published data from clinical trials of patients with non-high-risk disease, but also bridge the transition to currently used staging, classification, and response criteria systems where applicable.⁵⁻⁷

In all patients with neuroblastoma except those with completely resected INRG Stage L1 disease, detection of *MYCN* amplification in tumor cells leads to assignment to the high-risk group rather than low- or intermediate-risk groups⁷ ([NEUROB-2](#)). For symptomatic infants with INRG stage MS disease who are too ill to undergo biopsy at the time of initial presentation, therapy is started with a presumptive assignment to the intermediate-risk group. However, if a biopsy undertaken when the patient is clinically stable identifies tumor cells with *MYCN* amplification, the patient would then be reassigned to the high-risk group.

Treatment approaches for low risk INRG L1 tumors involve surgical resection, except in patients under 6 months of age with adrenal tumor with maximal diameter ≤ 3.1 cm diameter if solid or 5 cm if at least 25% cystic component. In these infants, observation is recommended. In patients with INRG MS disease who are asymptomatic and have tumors with favorable biology, observation is also the preferred approach.

Intermediate-risk treatment involves a combination of moderate intensity multi-agent chemotherapy and surgical resection. The COG study ANBL0531 aimed to decrease number of chemotherapy cycles given to patients with more favorable tumor biology, by allowing for a larger residual primary tumor following chemotherapy \pm surgery, compared to treatment endpoints utilized on legacy clinical trials. Patients were assigned to receive a minimum number of cycles based on age, stage, and tumor biologic features. Using this strategy, after completion of the assigned number of cycles, disease response was assessed and decisions regarding additional systemic therapy, surgery, or surveillance were made. In the ANBL0531 clinical trial, protocol-specific criteria for disease response were used, and primary tumor response was assessed by tumor volume reduction. The goal for groups of patients with localized, favorable biology tumors was to achieve at least 50% reduction in the primary tumor volume, while patients with localized disease with less favorable tumor biologic features were to continue therapy until a goal of 90% reduction in primary tumor volume (very good partial response [VGPR]) was achieved. The goal treatment endpoint for metastatic disease response for patients with the equivalent of INRG MS disease and those with intermediate risk INRG Stage M disease were also protocol-specific, and not identical to the legacy international neuroblastoma response criteria.⁴

Since the completion of ANBL0531, the neuroblastoma response criteria have been updated and no longer include VGPR as a response category. Additionally, in the current system of response assessment, tumors are measured with a single dimension as per Response Evaluation Criteria in Solid Tumors (RECIST), rather than by tumor volume ([NEUROB-G 1 of 4](#)). Until additional data become available regarding the use of the revised response criteria in assessment of disease in patient with non-high-risk neuroblastoma, the committee supports utilizing either volume or 1-dimensional assessments of primary tumor response in this group of patients.

For patients who have not achieved the targeted tumor reduction goal with the initial course of chemotherapy prescribed, multidisciplinary discussion should take place. For some patients, surgical resection may be appropriate to reach the targeted treatment end point. If surgery cannot be performed safely to achieve the proposed degree of tumor reduction, additional chemotherapy may be given with re-evaluation after every 2 cycles. At these timepoints, the potential risks and benefits of additional chemotherapy or surgery can be discussed by the multi-disciplinary treatment team. In some circumstances it may be reasonable to consider biopsy of the residual mass to assess for histologic differentiation, which may support observation of a tumor that fails to shrink sufficiently with chemotherapy and for which a surgical debulking is considered unsafe. In COG ANBL0531, cyclophosphamide and topotecan were used as the additional treatment for patients who did not achieve the target response with 8 cycles of the intermediate risk therapy regimen outlined on page [NEUROB-4](#).

SIOPEN treatment regimens can also be considered, as similar outcomes are achieved with the SIOPEN and COG strategies.

Note: All recommendations are category 2A unless otherwise indicated.

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**PRINCIPLES OF SYSTEMIC THERAPY****Intermediate Risk Chemotherapy^a**

COG regimen ^{3,8}		Dosing ^b
Cycle 1	• Carboplatin/etoposide	Chemotherapy dosing for young children is evolving toward dose banding. ⁹ • Carboplatin 560 mg/m ² >12 kg or 18.6 mg/kg ≤12 kg ^c D1 • Etoposide 120 mg/m ² >12 kg or 4 mg/kg ≤12 kg ^c on D1–3 • Cyclophosphamide 1000 mg/m ² >12 kg or 33.3 mg/kg ≤12 kg D1, Doxorubicin 30 mg/m ² >12 kg or 1 mg/kg ≤12 kg ^c D1
Cycle 2	• Carboplatin/cyclophosphamide/doxorubicin	
Cycle 3	• Cyclophosphamide/etoposide	
Cycle 4	• Carboplatin/etoposide/doxorubicin	
Cycle 5	• Cyclophosphamide/etoposide	
Cycle 6	• Carboplatin/cyclophosphamide/doxorubicin	
Cycle 7	• Carboplatin/etoposide	
Cycle 8	• Cyclophosphamide/doxorubicin	

SIOPEN regimen ¹⁰	Dosing ^b
• Carboplatin/etoposide	• Carboplatin 200 mg/m ² or 6.6 mg/kg and etoposide 150 mg/m ² or 5.0 mg/kg on D1–3 • Cyclophosphamide 300 mg/m ² or 10 mg/kg D1–5, doxorubicin 30 mg/m ² or 1 mg/kg D4–5, Vincristine D1 and D5 age, weight, and body surface area (BSA)-based dosing
• CADO: Cyclophosphamide, doxorubicin, vincristine	
• Number of cycles vary for different subgroups	

- Subsequent-line chemotherapy may be considered if adequate response on imaging has not been achieved, and undifferentiated viable tumor remains.³

^a Similar outcomes have been seen in COG and SIOPEN studies.

^b Mesna and dexrazoxane may be used as clinically indicated.

^c Or per infant dosing strategies.⁹

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**PRINCIPLES OF SYSTEMIC THERAPY****HIGH-RISK DISEASE**

- Patients with newly diagnosed high-risk neuroblastoma have an estimated 5-year EFS rate of 51% from a large analysis reflecting 10 years of data from the Children's Oncology Group (COG).⁷ These outcomes have improved over time as a result of increasingly intensive multimodal therapies divided into Induction, Consolidation, and Post-Consolidation phases. Much of the data summarized below is derived from national phase 3 trials and the panel encourages participation in open clinical trials when available.

Induction Therapy

- The goal of initial Induction therapy is to decrease disease burden and to achieve the best possible response prior to subsequent phases of therapy. This goal is achieved through a combination of multiagent chemotherapy and surgical resection of the primary tumor. In addition, autologous peripheral blood stem cells are collected during Induction to facilitate subsequent therapy.
- There are no contemporary data comparing North American Induction regimens that have been evaluated in prospective randomized trials. Instead, a number of Induction combinations have evolved over the last several decades, mainly based upon cisplatin- and alkylator-intensive regimens developed at Memorial Sloan-Kettering Cancer Center (MSKCC). Several different regimens have been used in national cooperative group trials enrolling >100 patients over the last 2 decades.
- These regimens yield broadly similar end-Induction response rates, with approximately 80% of patients having a partial response or better and approximately 9% of patients progressing despite these intensive regimens.¹¹ Given the lack of prospective comparative efficacy data and similar response rates, toxicity considerations have driven the evolution of Induction regimens to reduce exposure to nephrotoxic and cardiotoxic agents. The combination of topotecan and cyclophosphamide given as cycles 1 and 2 of Induction was studied initially as part of a pilot study that demonstrated the feasibility and acceptable end-Induction response rate (84%) of this approach.¹² This regimen was adopted for use in ANBL0532, demonstrating that 39.1% of patients had a partial response or better after the first 2 cycles with topotecan and cyclophosphamide.¹³ A subsequent trial, ANBL12P1, empirically reduced Induction to 5 cycles, with an 80% end-Induction response rate.¹⁴ Likewise, data from MSKCC demonstrated comparable end-Induction response rates with 5 versus 7 Induction cycles.¹⁵ Therefore, a 5-cycle Induction was included as part of the standard arm of the COG phase 3 trial, ANBL1531. The ANBL1531 Induction regimen is similar to the published ANBL12P1 regimen, with minor adjustments to dosing in order to align with updated COG chemotherapy standards. Given extensive contemporary experience with a 5-cycle Induction regimen, the panel recommends either ANBL12P1 or ANBL1531 Induction as preferred regimens, with a 6-cycle regimen from ANBL0532 an additional acceptable regimen. However, the panel acknowledges the lack of comparative data, and notes that other published chemotherapy regimens that achieve a similar end-Induction response rate could be considered as reasonable alternatives for individual patients.

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**PRINCIPLES OF SYSTEMIC THERAPY****HIGH-RISK DISEASE**

- A number of strategies to improve Induction are under investigation at this time, including early addition of an *ALK* inhibitor for the subset of patients whose tumors have been found to harbor *ALK* aberrations. In addition, interventions such as the early administration of ¹³¹I-MIBG or anti-GD2 monoclonal antibody therapy are being evaluated. As robust safety and efficacy data are not yet available to support these approaches, the panel does not recommend adoption of these approaches outside the context of clinical trials at this time.
- Surgical resection of the primary tumor and associated locoregional adenopathy is another important goal of Induction therapy (Principles of Surgery [\[NEUROB-E\]](#)). Given the aggressive nature of these tumors, upfront resection is rarely feasible and the panel recommends surgical resection after several cycles of initial cytoreductive chemotherapy. Even after initial chemotherapy, resection with negative margins remains rarely feasible and is not the recommended surgical goal. Instead, two large analyses have demonstrated improved EFS and lower local failure rates in patients who had >90% resection (North American experience) or a complete macroscopic resection (European experience).^{16,17} The panel therefore recommends this degree of resection, broadly considered a gross total resection, as the goal of primary site surgery. When vital organs, major nerves, and/or major blood vessels would be threatened or would require resection to achieve this goal, the panel recommends subtotal resection.
- The panel recommends full disease reassessment at the end of Induction. This end-Induction evaluation is a critical decision point in the treatment of patients with high-risk neuroblastoma. Prior analyses have demonstrated that patients with poor end-Induction response (less than partial response) have inferior outcomes compared to patients with more favorable end-Induction response (partial response or better).¹¹ However, analyses of randomized trials evaluating different consolidation strategies support a potential role for modern Consolidation therapies even in patients with less than a partial response to Induction. For example, the CCG-3891 trial reported higher EFS for patients with less favorable end-Induction response who were randomized to transplant (vs. continued chemotherapy).¹⁸ Likewise, the ANBL0532 trial (see below) reported a benefit of tandem transplant (vs. single transplant) independent of end-Induction response.¹³
- The panel recommends proceeding to consolidation therapy for patients with partial response or better to Induction, though the panel acknowledges that bridging therapy to improve response may be appropriate in select patients depending upon the nature of the partial response.¹⁹ Patients with progressive disease during or at the end of Induction have not typically been candidates to proceed with consolidation therapy, and the panel endorses this approach. Instead, the panel recommends non-myeloablative therapies for these patients, including a chemoimmunotherapy regimen combining anti-GD2 monoclonal antibody with chemotherapy²⁰ or participation in clinical trials for patients with first relapse. Patients with end-Induction minor response or stable disease require individualized decision-making. For patients with end-Induction minor response or stable disease not proceeding to consolidation therapy, the panel recommends a chemoimmunotherapy regimen combining anti-GD2 monoclonal antibody with chemotherapy or participation in clinical trials for patients with refractory disease. Recent retrospective data suggest that proceeding to consolidation therapy may be appropriate for patients with an inadequate response to standard Induction therapy who respond to alternative “bridging” therapies.¹⁹ Specifically, patients with incomplete response to Induction who received bridging therapy and then proceeded to Consolidation therapy had superior outcomes compared to patients who received bridging therapy and did not move on to Consolidation. Moreover, patients with a complete response to bridging therapy who proceeded to Consolidation had favorable outcomes.

Note: All recommendations are category 2A unless otherwise indicated.

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**PRINCIPLES OF SYSTEMIC THERAPY****HIGH-RISK DISEASE****Consolidation Therapy**

- A standard Consolidation phase includes both high-dose chemotherapy with autologous stem cell rescue and consolidative radiotherapy to the primary site. In North America, it is also considered standard to administer radiotherapy to sites of residual metastatic disease remaining at the end-Induction disease evaluation.
- High-dose chemotherapy with autologous stem cell rescue has been a hallmark of high-risk neuroblastoma therapy since a series of randomized trials demonstrated improved outcomes with this approach compared with continued conventional chemotherapy.²¹ The panel acknowledges that these randomized trials were conducted in a treatment era that preceded routine use of anti-GD2 directed immunotherapy and that additional work is needed to understand if subgroups of patients might benefit from consolidative approaches that do not rely on high-dose chemotherapy with autologous stem cell rescue. For example, a single institution retrospective experience suggests that similar overall survival rates may be achieved with or without high-dose chemotherapy among patients with greater than a partial response in the era of anti-GD2 immunotherapy.²²
- For patients who are candidates for consolidation therapy, the panel recommends tandem transplantation with two consecutive rounds of high-dose chemotherapy with autologous stem cell rescue for the majority of patients with high-risk disease (category 1 recommendation). This recommendation is based upon the COG ANBL0532 randomized phase 3 trial.¹³ Patients without progressive disease after a 6-cycle Induction were eligible for randomization to a single transplant with full dose carboplatin/etoposide/melphalan (CEM) or to tandem transplant with thiotepa/cyclophosphamide followed 6–10 weeks later with dose-reduced CEM ([NEUROB-10](#)). Patients randomized to the tandem transplant arm had significantly improved EFS (3-year EFS 61.6% vs. 48.4% for single transplant).
- There are two less common subgroups of patients with high-risk disease for whom a single round of high-dose chemotherapy with autologous stem cell rescue may be appropriate: 1) patients with stage L2, ≥18 months at diagnosis, unfavorable histology, AND *MYCN* non-amplified disease; and 2) patients with stage M, 12 to <18 months at diagnosis, *MYCN* non-amplified, with any of the following other unfavorable features: unfavorable histology; diploid DNA content; and/or presence of segmental chromosomal aberrations. Patients in these two groups have historically had more favorable outcomes compared to patients with high-risk disease due to *MYCN* amplification or patients with high-risk disease due to age ≥18 months at diagnosis with stage M disease. For example, in a large series from the COG, patients in these two groups had 5-year EFS rates of approximately 75%–80%.⁷ Patients in these two more favorable subgroups were non-randomly assigned to single transplant with full dose CEM in ANBL0532 and the panel endorses this approach.
- Conditioning with busulfan and melphalan (BuMel) is a preferred conditioning regimen in Europe based upon results of a randomized phase 3 trial that showed superior EFS with BuMel compared to CEM following the European rapid COJEC induction regimen.²³ In addition, the BuMel regimen was associated with lower rates of most adverse events, though the risk of sinusoidal obstruction syndrome was higher. The COG conducted a pilot trial, ANBL12P1, that demonstrated the feasibility of this approach,¹⁴ but the role of BuMel in the context of North American therapy is not currently defined. Single transplant with BuMel may be an appropriate regimen for patients with a contraindication to tandem transplant or for patients in subgroups for which single transplant is recommended.
- Radiation therapy to the primary tumor is typically administered upon recovery from high-dose chemotherapy with stem cell rescue (Principles of Radiation Therapy [\[NEUROB-H\]](#)). Neuroblastoma is a radiosensitive tumor and a commonly used dose of 21.6 Gy is recommended. Recent national trials have attempted to improve local control by augmenting radiotherapy. In COG trial A3973, a subset of patients had primary site radiotherapy fields extended to include uninvolved draining nodal stations. These patients had similar local failure rates compared to patients treated without extending the radiotherapy field and this approach is not recommended.²⁴ In COG trial ANBL0532, patients with gross residual tumor following primary site resection received a boost of 14.4 Gy to gross residual tumor.²⁵ This augmented dose did not improve local failure or EFS rates compared to the historic controls. Based upon these data, the panel does not recommend either strategy.
- The panel recommends radiation to sites of residual metastatic disease present at the end-Induction disease evaluation, recognizing that not all sites may be feasibly targeted by external beam radiotherapy. This recommendation is based upon single institution data supporting a benefit from this approach,^{26,27} though this approach has not been adopted internationally.

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**PRINCIPLES OF SYSTEMIC THERAPY****HIGH-RISK DISEASE****Post-Consolidation Therapy**

- Historically, post-consolidation therapy consisted of 6 cycles of isotretinoin administered as a differentiating agent. This approach was adopted based upon the landmark CCG-3891 trial that demonstrated improved outcomes in patients randomized to isotretinoin compared to no further therapy.¹⁸ Subsequently, the ANBL0032 trial demonstrated a significant improvement in EFS for patients randomized to receive the anti-GD2 monoclonal antibody dinutuximab + cytokines (sargramostim in cycles 1, 3, and 5; interleukin-2 in cycles 2 and 4) + isotretinoin (2-year EFS from randomization at start of post-consolidation of 66%) compared to patients randomized to isotretinoin alone (2-year EFS of 46%).²⁸ Based upon these findings, the ANBL0032 immunotherapy regimen became a standard post-consolidation regimen (category 1 recommendation for use of post-consolidation therapy with anti-GD2 antibody) ([NEUROB-D 9 of 11](#)).²⁹
- More recently, data from the SIOPEN HR-NBL1 trial have called into question the role of interleukin-2 together with anti-GD2 immunotherapy. In this trial, patients were randomized to receive anti-GD2 immunotherapy (dinutuximab beta) with or without subcutaneous interleukin-2.³⁰ Interleukin-2 did not improve outcomes, but was associated with increased toxicity. Based upon these findings, COG high-risk protocols no longer include interleukin-2 and the panel endorses this approach.
- Other anti-GD2 antibodies may be appropriate as post-consolidation therapy. For example, dinutuximab beta given with isotretinoin but without sargramostim is a commonly used post-consolidation regimen in Europe. A non-randomized comparison showed higher EFS among patients treated with this approach compared to the historic experience with isotretinoin alone.³¹

Continuation Therapy

- Eflornithine (2,5-diamino-2-(difluoromethyl) pentanoic acid hydrochloride hydrate; DFMO) is an inhibitor of ornithine decarboxylase, a key enzyme required for the synthesis of polyamines that regulate homeostasis and promote survival in cancer cells. This agent was studied as continuation therapy in a multi-center, single arm Phase 2 trial (Study 3b; NCT02395666) in children with high-risk neuroblastoma that had responded to frontline therapy that included induction, consolidation, and anti-GD2 directed immunotherapy. Patients who had a partial response or better following standard frontline therapy were eligible to enroll on study 3b following completion of immunotherapy, and received eflornithine 750 mg/m² ± 250 mg/m² twice daily for up to 2 years. Reported adverse events included transaminitis and hearing loss.³² Data from 92 patients on Study 3b were compared with an external control arm consisting of 852 patients treated with anti-GD2 immunotherapy, cytokines and isotretinoin on COG ANBL0032 who did not go on to receive eflornithine continuation therapy.³³ Patients on Study 3b had superior outcomes compared to the external control group [EFS hazard ratio 0.48 (95% CI: 0.27, 0.85); OS hazard ratio 0.32 (95% CI: 0.15, 0.70)]. Further analyses using propensity score matching and sensitivity analyses also demonstrated higher EFS and OS for patients on Study 3b, though the potential for residual confounding remains in the context of a non-randomized comparison. In December 2023, the FDA approved eflornithine for use in the continuation setting for patients with high risk neuroblastoma who have achieved a partial response or better following completion of anti-GD2 immunotherapy. The panel recommends that clinicians discuss eflornithine as a continuation therapy option with patients and families.

Disease Evaluations During Frontline Therapy for High-Risk Disease

- Following initial staging evaluations prior to the start of therapy ([ST-1](#)), patients with high-risk disease undergo anatomic imaging (CT or MRI) of the primary site prior to planned surgical resection. Full disease evaluation (anatomic imaging of the primary site, ¹²³I-MIBG scan [or FDG-PET, if MIBG non-avid disease], and bilateral bone marrow aspirates and biopsies) at the end of induction, start of post-consolidation, and at end of therapy. Patients with >5 residual MIBG-avid sites of disease at the end of induction are encouraged to have a repeat ¹²³I-MIBG scan after recovery from high-dose chemotherapy with stem cell rescue in order to prioritize metastatic sites that might be treated during consolidative radiotherapy. An ¹²³I-MIBG scan (or FDG-PET, if MIBG non-avid disease) is recommended halfway through post-consolidation therapy, with anatomic imaging and bone marrow evaluations reserved for patients with residual disease identified on the disease evaluation at the start of post-consolidation.

Organ Function Evaluations During Frontline Therapy for High-Risk Disease

- Therapy for high-risk neuroblastoma is intensive and associated with both acute and long-term toxicities (Monitoring for Late Effects [NEUROB-I](#)). During treatment, these patients require frequent laboratory monitoring, including blood counts, chemistry panels, and urinalyses. Detailed evaluation of renal function (often with nuclear medicine measurements of glomerular filtration rate) is essential before consolidation high-dose therapy. Serial monitoring of cardiac function with electrocardiograms and echocardiograms is routine. Serial monitoring of hearing with audiograms or brainstem auditory evoked response is essential as most patients with high-risk neuroblastoma are at a critical age for language development.

Therapy for Adolescents and Adults with High-Risk Neuroblastoma

- Neuroblastoma is largely a disease of young children, though adolescents and adults may occasionally present with high-risk disease. The clinical studies that inform these guidelines, including toxicity data, therefore predominantly included patients <5 years of age at initial diagnosis. The general principles of high-risk therapy should be applied to older patients with high-risk disease, though it is acknowledged that these patients may require a more individualized approach to treatment based upon comorbid conditions and tolerance of planned therapy.

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**PRINCIPLES OF SYSTEMIC THERAPY****HIGH-RISK DISEASE: CHEMOTHERAPY INDUCTION REGIMENS^{d,e,f,9,13,14}**

- Chemotherapy dosing for young children is evolving toward dose banding⁹

Cycle 1	• Topotecan 1.2 mg/m ² /dose Day 1–5
Cycle 2	• Cyclophosphamide 400 mg/m ² /dose Day 1–5
Cycle 3^e	• Cisplatin 50 mg/m ² /dose Day 1–4 • Etoposide 200 mg/m ² /dose Day 1–3
Cycle 4^e	• Vincristine (age, weight, and BSA-based dosing) Day 1–3 ⁹ • Doxorubicin 25 mg/m ² /dose Day 1–3 • Cyclophosphamide 2100 mg/m ² /dose Day 1–2
Cycle 5^e	• Cisplatin 50 mg/m ² /dose Day 1–4 • Etoposide 200 mg/m ² /dose Day 1–3
Cycle 6^g (Not currently used)	• Vincristine (age, weight, and BSA-based dosing) Day 1–3 • Doxorubicin 25 mg/m ² /dose Day 1–3 • Cyclophosphamide 2100 mg/m ² /dose Day 1–2

^d All cycles are 21-day cycles. Refer to individual literature for dosing strategies for infants/patients with lower weights/body surface areas.

^e COG trial ANBL1531 used this same regimen with a slightly different dosing strategy based upon updated COG chemotherapy standards. This Induction regimen is another preferred regimen.

^f Dexrazoxane may be used as clinically indicated. Mesna may be used with cycles 1 and 2 as clinically indicated, but must be used with cycles 4 and 6.

^g Cycle 6 was used in prior historical trial ANBL0532, but is not used in ongoing COG clinical trials. Park JR, Kreissman SG, London WB, et al. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: A randomized clinical trial. JAMA 2019;322:746-755.

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PRINCIPLES OF SYSTEMIC THERAPY

HIGH-RISK DISEASE: CHEMOIMMUNOTHERAPY (may be used as bridging therapy)^{h,20,34}

- Temozolomide 100 mg/m²/dose PO Day 1–5
- Irinotecan 50 mg/m²/dose IV over 90 min Day 1–5
- Dinutuximab 17.5 mg/m²/day IV Day 2–5
- Sargramostim 250 µg/m²/dose SQ Day 6–12
- Regimen repeated every 21 days

HIGH-RISK DISEASE: HIGH-DOSE CHEMOTHERAPY REGIMENS FOR CONSOLIDATION THERAPYⁱ

Tandem Transplant ¹³	Single Transplant Option 1 ¹³	Single Transplant Option 2 ¹⁴
Thiotepa ¹³ 300 mg/m ² /dose Day -7 to -5	Carboplatin ^{i,13} (weight, BSA, and GFR-based dosing) Day -7 to -4	Busulfan ¹⁴ (age and weight-based dosing) Day -6 to -3 (dose adjusted based upon real-time pharmacokinetics)
Cyclophosphamide 1500 mg/m ² /dose Day -5 to -2	Etoposide 338 mg/m ² /dose Day -7 to -4	Melphalan 140 mg/m ² /dose Day -1
6–10 Weeks Later and Recovery of Organ Function	Melphalan 70 mg/m ² /dose Day -7 to -5	
Carboplatin ⁱ (age, BSA, and glomerular filtration rate [GFR]-based dosing) Day -7 to -4		
Etoposide 300 mg/m ² /dose (if GFR ≥100 mL/min/1.73 m ²) Day -7 to -4		
Melphalan 60 mg/m ² /dose Day -7 to -5		

^h Refer to individual protocols for dosing strategies for infants/patients with lower body surface areas. COG trial ANBL1531 uses this same regimen with a slightly different dosing strategy based upon updated COG chemotherapy standards.

ⁱ Refer to literature for dosing strategies for infants/patients with lower weights/body surface areas and with impaired organ function.

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PRINCIPLES OF SYSTEMIC THERAPY

HIGH-RISK DISEASE: Post-Consolidation Regimen^{j,28,30,31}

Cycle 1	<ul style="list-style-type: none"> • Sargramostim 250 µg/m²/dose SQ Day 1–14 • Dinutuximab 17.5 mg/m²/dose IV Day 4–7 • Isotretinoin 80 mg/m²/dose PO twice daily Day 11–24
Cycle 2	
Cycle 3	
Cycle 4	
Cycle 5	
Cycle 6	<ul style="list-style-type: none"> • Isotretinoin 80 mg/m²/dose PO twice daily Day 11–24

HIGH-RISK DISEASE: Continuation Therapy³³

<p>For patients who have had at least a PR to prior systemic agents and have completed post-consolidation immunotherapy with an anti-GD2 antibody</p>	<ul style="list-style-type: none"> • Consider eflornithine (category 2B)^k <ul style="list-style-type: none"> ▶ BSA (m²) based dosage (Recalculate the BSA dosage every 3 months during treatment with eflornithine) <ul style="list-style-type: none"> ◇ >1.5: 768 mg (four tablets) PO twice daily ◇ 0.75–1.5: 576 mg (three tablets) PO twice daily ◇ 0.5 to <0.75: 384 mg (two tablets) PO twice daily ◇ 0.25 to <0.5: 192 mg (one tablet) PO twice daily
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^j All cycles are 28-day cycles. Refer to individual protocols for dosing strategies for infants/patients with lower body surface areas.

^k Serial monitoring of hearing with audiograms or brainstem auditory evoked response is essential as most patients with high-risk neuroblastoma are at a critical age for language development.

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PRINCIPLES OF SURGERY

- Evaluate primary tumor resectability using cross-sectional imaging; CT or MRI should be performed.
 - ▶ Evaluate for the presence of IDRFs¹
- Multidisciplinary discussion of risks/benefits and optimal timing of surgery (at diagnosis or following neoadjuvant chemotherapy) should include surgeons, radiologists, medical oncologists, radiation oncologists, and pathologists as needed.
- If upfront resection is not appropriate, a biopsy that provides adequate tissue for diagnosis and risk stratification should be performed.

General Principles of Surgery

- Understanding the heterogeneous nature of neuroblastoma is critical when determining the optimal timing and extent of surgical resection.
 - ▶ Patients with intermediate-risk disease most often require treatment with a combination of surgery and chemotherapy. If more than minimal risks of surgical morbidity exist, neoadjuvant chemotherapy should be administered initially, as systemic therapy may reduce subsequent surgical risk.²
 - ▶ In the setting of high-risk disease, neoadjuvant chemotherapy is nearly always indicated prior to resection.
- For all risk groups, the surgical approach should limit morbidity and mortality, avoid resection of vital structures, and preserve organ function.

Principles of Tumor Biopsy

- Indicated when resection at diagnosis is not possible or is not recommended due to the clinical context.
 - ▶ Generally indicated for patients with metastatic disease.
 - ▶ Generally indicated for patients with L2 tumors.
- Incisional biopsy via an open or laparoscopic/thoracoscopic approach should result in collection of >1 cm³ of fresh viable tissue.^a
- Core biopsy can be performed by a surgeon or interventional radiologist, and should result in collection of at least 10 cores to ensure that the specimen is adequate for comprehensive analysis.^{a,3}
- Pathologist assessment at the time of biopsy is recommended to ensure that the tissue biopsied is viable rather than necrotic, and likely diagnostic.^a

^a See [Principles of Pathology \(NEUROB-A\)](#) for specimen requirements.

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PRINCIPLES OF SURGERY

Surgical Approach by Risk Group

- **Low Risk**
 - ▶ Patients with INRG Stage L1 tumors are often cured with surgical resection. If upfront surgery will potentially obviate the need for chemotherapy and can be safely performed with minimal morbidity, a resection should be performed. See Low-Risk Disease ([NEUROB-3](#)) regarding infants in whom observation without biopsy or resection is appropriate.
- **Intermediate Risk**
 - ▶ The decision to proceed with upfront resection without preoperative chemotherapy is based on whether IDRFs are absent or present (L1 vs. L2) and on risk factor analysis (including evaluation of the nature of IDRFs present). When risk of surgical morbidity is deemed significant by the surgeon, neoadjuvant chemotherapy should be considered.
 - ▶ Gross total resection may be attempted following initial systemic therapy. However, preservation of vital structures and of end-organ function is of utmost importance in the intermediate risk context, as less than complete response has been shown to be an acceptable endpoint of therapy for patients with localized intermediate risk tumors.
 - ▶ Timing of resection will depend upon response to initial therapy and subsequent assessment of surgical risk.
- **High Risk**
 - ▶ Surgery is generally undertaken prior to completion of induction therapy, as extended preoperative therapy is unlikely to further reduce surgical risk after multiple cycles of chemotherapy have been given.⁴⁻⁷
 - ▶ Maximal safe resection of the primary tumor should be attempted; however, residual disease adherent to critical/vital structures should not be removed if attempts to resect it can be expected to result in surgical morbidity, organ dysfunction, and delays in the initiation of postoperative systemic therapy.
 - ▶ Resection of adjacent organs (kidney, pancreas, intestine, and neurovascular structures) is not recommended. If direct extension/infiltration of the tumor into adjacent organs is identified, tumor may be left behind. Resection of adjacent organs increases the morbidity of the surgical procedure and could impact the dosing/tolerance of adjuvant therapy. Margin-negative resection is rarely achieved in this context and is not the surgical goal.⁸
 - ▶ Nephrectomy should be avoided as neuroblastoma treatment can result in significant renal toxicity, and because postoperative renal dysfunction can limit therapeutic options.⁹
 - ▶ Tumors with vascular encasement require identification, isolation, and clearance of associated major vessels. Exposure should be adequate to safely obtain proximal and distal vascular control. Commonly, the tumor is divided over the involved vascular structure and dissected down to the adventitia to allow for vessel preservation and tumor resection, but dissection should not proceed deeper than the adventitial layer to avoid vascular injury.
 - ◊ Tumors may be resected in multiple segments; en bloc resection is not required.
 - ▶ Resection of nodal disease adherent or adjacent to the primary tumor is recommended as long as resection of this tissue is not expected to increase surgical morbidity. Resection of distant lymph nodes at the time of primary tumor resection is not required.¹⁰
- **Special considerations for infants with INRG MS disease**
 - ▶ The primary surgical role for children with MS disease is biopsy of the primary or metastatic tumor for histologic and biologic studies when it is safe to do so.
 - ▶ Infants with MS disease who are <3 months of age are at increased risk for surgical complications in the presence of massive hepatomegaly with or without coagulopathy. In some cases, systemic therapy may be required prior to biopsy. In this setting, biopsy (surgical or via percutaneous core needle) can be delayed until it can be undertaken safely.
 - ▶ In extreme situations, for infants with respiratory compromise or life-threatening symptoms secondary to hepatomegaly, laparotomy and silo placement may be considered to alleviate intra-abdominal pressure.

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PRINCIPLES OF SURGERY

Surgical Management: Cervical and Cervicothoracic

- Assess for encasement of the vertebral or carotid arteries, jugular vein, subclavian vessels, brachial plexus roots, or extension across the midline or to the base of the skull.
- Assess for tracheal compression evidenced by patient symptoms or cross-sectional imaging prior to any general anesthesia.
- Assess for extension into the thoracic cavity. If present, consider a cervicothoracic “trap door” or a median sternotomy with cervical extension incision for resection.
- Identification and preservation of vagus nerve, brachial plexus, phrenic and other major nerves should be ensured. Intraoperative nerve monitoring should be considered. Communication with the anesthesia team regarding the use or withholding of neuromuscular blockade should occur preoperatively.
- Postoperative Horner’s syndrome should be discussed with the patient/family, as this is not uncommon following resection of neck and apical chest tumors.
- There is no role for complete compartment-oriented cervical lymphadenectomy.

Surgical Management: Thoracic Cavity

- Assess for tumor encasing the thoracic aorta, vena cava, or other great vessels.
- Assess for tracheal compression evidenced by patient symptoms or cross-sectional imaging prior to any general anesthesia.
- A thoracotomy incision is generally indicated for large tumors or those with involvement of critical structures.
- A thoracoscopic approach may be indicated for selective lesions, and should be the preferred approach for biopsy.¹¹
- Avoid aggressive resection, retraction, or use of monopolar cautery near the recurrent laryngeal, phrenic, and vagus nerves.
- Extension into spinal foraminae should be assessed preoperatively with a spine MRI if indicated based on primary tumor location or clinical symptoms. Dissection close to the spinal nerve roots should be avoided. Neural foraminal extension may be resected via a thoracic approach, but deep/blind tissue extraction from this region should be avoided. Leaving residual tumor in this location is favored over risking neurologic injury.
- If known intraspinal extension is present, the case should be discussed with the multidisciplinary team, often including neurosurgery.
- Thoracic/spinal imaging of the aortic branches to the spinal cord should be evaluated preoperatively. Arterial branches to the spinal cord, including the artery of Adamkiewicz, should be preserved whenever possible for multiple level thoracic paraspinal tumors, even if some tumor is left in situ.
- Careful dissection posterior to the carina and near the right hemidiaphragm can minimize injury to the thoracic duct; any visible lymphatics should be sealed or ligated. A thorough visual inspection for lymphatic leak should be performed prior to completion of the procedure.

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PRINCIPLES OF SURGERY

Surgical Management: Abdominal/Adrenal/Retroperitoneal/Pelvic Cavity

- Assess for tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament or encasing the mesenteric arteries, celiac axis, aorta and/or vena cava, or iliac vessels.
 - ▶ Surgical resection should not compromise major vessels or increase the risk of bowel ischemia.
 - ▶ Proximal and distal vascular control should be obtained when indicated.
- Assess for tumor infiltrating one or both renal pedicles. Nephrectomy should be avoided.⁹
- Ureters may be adherent to the tumor and care should be taken to avoid injury.
- Preoperative MRI to assess nerve root and sacral involvement should be obtained when relevant in light of primary tumor location.
 - ▶ Nerve monitoring should be considered for pelvic tumors due to proximity to the lumbosacral plexus and obturator nerve.
- A laparoscopic approach can be considered depending on the location of the tumor and its relationship to surrounding structures, ie, IDRFs.^{12,13}

Surgical Management: Paraspinal

- A detailed preoperative neurologic examination should be performed and any deficits documented.
- A preoperative spine MRI should be obtained.
- Urgent multidisciplinary evaluation is indicated with consideration of rapid initiation of chemotherapy. Laminectomy is rarely indicated at the time of diagnosis.¹⁴⁻¹⁷
- Progressive neurologic symptoms or acute deterioration following rapid initiation of systemic therapy should prompt urgent multidisciplinary re-evaluation.

Surgical Complications

- Intraoperative complications are site dependent.
- Hemorrhage is a major risk with infiltrative tumors. Appropriate preoperative planning or intraoperative vascular surgical consultation should be sought when necessary. Critical vessels including the aorta, carotid, subclavian, hepatic, mesenteric, or renal arteries should be preserved or repaired if injured, either primarily or with a graft, to restore flow.
- Nerve injuries may also occur, and primary repair should be considered utilizing intraoperative consultation with vascular, neurosurgical, or plastic surgical specialists.
- It is acceptable and recommended to leave a small amount of residual tumor adherent to vital structures if there is significant risk of injury with more aggressive or complete resection. An estimate of the extent of resection should be documented in the operative report.

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**PRINCIPLES OF SURGERY**
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Note: All recommendations are category 2A unless otherwise indicated.**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



DISEASE SURVEILLANCE/FOLLOW-UP AFTER COMPLETION OF TREATMENT

Risk Category ¹	Workup/Imaging
Low Risk (observation only)	<ul style="list-style-type: none"> • N/A
Low Risk (patients who underwent surgical resection)	<ul style="list-style-type: none"> • Interim H&P: <ul style="list-style-type: none"> ▶ Approximately every 3 months for Year 1, ▶ Then every 6 months for Year 2–3, ▶ Then as clinically indicated
	<ul style="list-style-type: none"> • Laboratory studies: <ul style="list-style-type: none"> ▶ Urine catecholamine levels are no longer included in the revised International Neuroblastoma Response Criteria (INRC) due to the lack of standardization in specimen collection and analysis, and due to the influence of diet on results.² However, results of catecholamine testing may be helpful during surveillance. ▶ If elevated at diagnosis, consider obtaining spot catecholamine levels during surveillance.
	<ul style="list-style-type: none"> • Imaging: <ul style="list-style-type: none"> ▶ US of primary site^a <ul style="list-style-type: none"> ◇ Approximately every 3 months for Year 1, ◇ Then every 6–12 months for Year 2–3, ◇ Then as clinically indicated

^a Cross-sectional imaging may be required depending on the location of the primary tumor.

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DISEASE SURVEILLANCE/FOLLOW-UP AFTER COMPLETION OF TREATMENT

Risk Category ¹	Workup/Imaging
<p>Intermediate Risk (adapted from ANBL0531³ and ANBL1232)</p>	<ul style="list-style-type: none"> • Interim H&P: <ul style="list-style-type: none"> ▶ Approximately every 3 months for Year 1, ▶ Then every 6 months for Year 2, ▶ Then annually for Year 3–5 • Consider audiologic assessment depending on degree of exposure to ototoxic agents
	<ul style="list-style-type: none"> • Laboratory studies: <ul style="list-style-type: none"> ▶ Urine catecholamine levels are no longer included in the revised INRC due to the lack of standardization in specimen collection and analysis, and due to the influence of diet on results.² However, results of catecholamine testing may be helpful during surveillance. ▶ If elevated at diagnosis, consider obtaining spot catecholamine levels during surveillance.
	<ul style="list-style-type: none"> • Imaging: <ul style="list-style-type: none"> ▶ CT or MRI cross-sectional imaging of primary site <ul style="list-style-type: none"> ◇ Approximately every 3 months for Year 1, ◇ Then every 6 months for Year 2, ◇ Then annually for Year 3, ◇ Then as clinically indicated ▶ ¹²³I-MIBG scan with SPECT, if available (for MIBG avid tumors for patients with INRG Stage M disease at diagnosis) <ul style="list-style-type: none"> ◇ If positive at diagnosis and at completion of therapy, obtain MIBG imaging until a negative scan is achieved or patient is 36 months from completion of therapy <ul style="list-style-type: none"> – Every 3–6 months in Year 1, – Then annually in Year 2–3, – Then as clinically indicated

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DISEASE SURVEILLANCE/FOLLOW-UP AFTER COMPLETION OF TREATMENT

Risk Category ¹	Workup/Imaging
<p>High Risk (adapted from ANBL0532⁴ and ANBL1531)</p>	<ul style="list-style-type: none"> • Interim H&P: <ul style="list-style-type: none"> ▶ Every 3 months for Year 1, ▶ Then every 6 months for Year 2–5
	<ul style="list-style-type: none"> • Laboratory studies: <ul style="list-style-type: none"> ▶ Urine catecholamine levels are no longer included in the revised INRC due to the lack of standardization in specimen collection and analysis, and due to the influence of diet on results.² However, results of catecholamine testing may be helpful during surveillance. ▶ CBC with differential. Obtain with imaging. ▶ Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺; and creatinine, alanine aminotransferase (ALT), bilirubin <ul style="list-style-type: none"> – Every 3 months for Year 1, – Then every 6 months for Year 2–3, – Then annually for Year 4–5 ▶ Thyroid studies including TSH (and Free T4 if TSH is abnormal) <ul style="list-style-type: none"> – Every 6 months for Year 1–2, – Then annually for Year 3–5 ▶ Hemoglobin A1c (HgbA1c), ferritin, and reproductive health labs (follicle-stimulating hormone [FSH], luteinizing hormone [LH], anti-Mullerian hormone) <ul style="list-style-type: none"> – As clinically indicated ▶ Audiologic assessment <ul style="list-style-type: none"> – Annually for 1–5 y, – Then as clinically indicated – Studies of survivors of high-risk neuroblastoma suggest high rates of severe ototoxicity (requiring hearing aids)⁵ ▶ Echocardiogram <ul style="list-style-type: none"> – If normal at the end of therapy, obtain every 2–5 years based on total anthracycline dose and radiation dose with potential impact to heart (Monitoring for Late Effects [NEUROB-I]) ▶ Pulmonary function tests <ul style="list-style-type: none"> – As clinically indicated
	<ul style="list-style-type: none"> • Imaging: <ul style="list-style-type: none"> ▶ CT or MRI cross-sectional imaging of primary site <ul style="list-style-type: none"> – Every 3–6 months for Year 1, – Then every 6 months for Year 2, – Then annually for Year 3, – Then as clinically indicated ▶ ¹²³I-MIBG scan with SPECT, if available (for MIBG avid tumors) <ul style="list-style-type: none"> – Every 3–6 months for Year 1, – Then every 6 months for Year 2, – Then annually for Year 3, – Then as clinically indicated ▶ FDG-PET scan (for MIBG non-avid tumors) <ul style="list-style-type: none"> – Every 3–6 months for Year 1, – Then every 6 months for Year 2, – Then annually for Year 3, – Then as clinically indicated
	<ul style="list-style-type: none"> • Bilateral bone marrow aspirates and biopsies: <ul style="list-style-type: none"> ▶ If negative at the end of therapy, obtain only as clinically indicated.

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DISEASE SURVEILLANCE/FOLLOW-UP AFTER COMPLETION OF TREATMENT REFERENCES

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**RESPONSE ASSESSMENT**

Component	Method	International Neuroblastoma Response Criteria (INRC) Component Response ¹
Primary Site	RECIST/Functional Imaging ^{1,2}	Complete response (CR): <10 mm residual soft tissue at primary site, AND complete resolution of MIBG or FDG-PET^a uptake (for MIBG non-avid tumors) at primary site
		Partial response (PR): ≥30% decrease in longest diameter of primary site, AND MIBG or FDG-PET^a uptake at primary site stable, improved or resolved
		Stable disease (SD): Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site
		Progressive disease (PD): >20% increase in longest diameter taking as reference the smallest diameter on study (this includes the baseline diameter if that is the smallest on study), AND a minimum absolute increase of 5 mm in longest dimension^b

Footnotes^a Used for tumors that do not demonstrate MIBG uptake.^b Fluctuating MIBG or PET avidity is insufficient for PD in the absence of an increase in measurement that meets criteria for PD.**References**¹ Park JR, Bagatell R, Cohn SL, et al. Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. *J Clin Oncol* 2017;35:2580-2587.² Bagatell R, McHugh K, Naranjo A, et al. Assessment of Primary Site Response in Children With High-Risk Neuroblastoma: An International Multicenter Study. *J Clin Oncol* 2016;34:740-746.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**RESPONSE ASSESSMENT**

Component	Method	INRC Component Response ¹
Metastatic bone/ soft tissue	RECIST/Modified Curie or SIOOPEN score ^{1,3,4}	CR: Non-primary target and non-target lesions measure <10 mm, AND Lymph nodes identified as target lesions decrease to a short axis <10 mm, AND MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely
		PR: ≥30% decrease in sum of diameters of non-primary target lesions compared to baseline, AND all of the following: <ul style="list-style-type: none"> • Non-target lesions may be stable or smaller in size AND • No new lesions AND • ≥50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥0.1 to ≤0.5) or ≥50% reduction in number of FDG-PET avid bone lesions^{c,d}
		SD: Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions
		PD: Any of the following: <ul style="list-style-type: none"> • Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma • Any new bone site that is MIBG avid • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma • >20% increase in the sum of the longest diameters taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions • Relative MIBG bone score ≥1.2

Footnotes^c Complete resolution of MIBG or PET avidity is not required.^d Relative score is the absolute score for bone lesions at time of response assessment divided by the absolute score of bone lesions at baseline, prior to therapeutic interventions.**References**

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**RESPONSE ASSESSMENT**

Component	Method	INRC Component Response ¹
Bone marrow	INRC/Burchill ^{e,5}	CR: Bone marrow with no tumor infiltration noted on reassessment, independent of baseline tumor infiltration
		SD: Bone marrow with tumor infiltration that remains positive with >5% tumor infiltration on reassessment but does not meet criteria for complete response, minimal disease, or progressive disease
		Minimal disease (MD): Bone marrow with ≤5% tumor infiltration that remains >0 to ≤5% tumor infiltration at subsequent reassessment, OR bone marrow with no tumor infiltration that has ≤5% tumor infiltration on reassessment, OR bone marrow with >20% tumor infiltration that has >0% to ≤5% tumor infiltration on reassessment
		PD: Bone marrow without tumor infiltration that becomes >5% tumor infiltration on reassessment, OR bone marrow with tumor infiltration that increases by >2-fold and is >20% tumor infiltration on reassessment

Footnote

^e Recommend >5% viable tumor as reliable level for detecting response.

References

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**RESPONSE ASSESSMENT**

Overall Response¹	
Complete response (CR)	All components CR
Partial response (PR)	PR in at least one component and all other components CR, minimal disease (bone marrow), PR or not involved at baseline
Minor response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD
Stable disease (SD)	SD in one component with no better than SD or not involved at baseline in any other component, no component with PD
Progressive disease (PD)	Any component with PD

Notable features of the INRC

- Changes in urinary catecholamine levels (HVA and VMA) do not impact response assessment
- ⁹⁹Tc scintigraphy should not be used for response assessment
- Specific requirements for timing of response are indicated within treatment algorithms and differ across risk groups
- While novel radiotracers are in development to assess response, insufficient data are currently available to permit incorporation into the INRC^{6,7}

¹ Park JR, Bagatell, R, Cohn SL, et al. Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 2017;35:2580-2587.

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**PRINCIPLES OF RADIATION THERAPY****General Principles for RT in Patients with High-Risk Neuroblastoma**

- RT is indicated for nearly all cases of high-risk neuroblastoma, but is generally not used for patients with non–high-risk disease.
 - ▶ RT will be delivered after recovery from high-dose chemotherapy with stem cell rescue unless there is an indication for emergent RT.
 - ▶ Intensity modulated RT (IMRT) or proton therapy can be used to reduce the risk and/or magnitude of side effects.
 - ▶ The primary site is always irradiated. Metastatic sites are only irradiated if there is concern for active disease after completion of induction chemotherapy, demonstrated by MIBG/FDG uptake and/or persistent soft-tissue mass >1 cm³.
 - ▶ If radiation to metastatic sites is indicated, they should be irradiated concurrently with the primary site.
- The panel recognizes that not all metastatic sites may be feasibly targeted by external beam radiotherapy. The recommendation to irradiate metastatic sites is based upon single institution data supporting a benefit from this approach^{1,2} though this approach has not been adopted internationally.
- Simulation
 - ▶ Patients should be supine with appropriate immobilization for CT simulation.
 - ▶ 4D-CT is recommended for targets that are subject to respiratory motion.
 - ▶ Consider addition of MRI simulation for paraspinal sites.
- Target Volume Definitions
 - ▶ Primary Site:
 - ◊ The gross tumor volume (GTV) will include the postoperative tumor bed, any residual disease identified after surgery and initially involved regional lymph nodes. The tumor bed will be defined by the post-induction chemotherapy, pre-surgery volume, respecting pushing borders, and operative findings, not readily identified on imaging. Relevant CT and/or MRI studies completed after induction chemotherapy and prior to surgery should be fused to the CT simulation for target delineation.
 - Special consideration: if the primary tumor was resected prior to induction chemotherapy, GTV will be based on the tumor volume at diagnosis.
 - ◊ The clinical target volume (CTV) = GTV + 1 cm, confined to anatomical borders. For instance, CTV need not extend into uninvolved kidneys, abdominal organs, or bones.
 - ◊ If the tumor is subject to respiratory motion, an internal target volume (ITV) should be utilized based on the 4D-CT.
 - ◊ The planning target volume (PTV) = CTV + 0.3–0.5 cm, depending on the institution’s standard, immobilization method, and modality of in-room verification imaging.
 - ▶ Metastatic Sites
 - ◊ The metastatic GTV (mGTV) is defined by the post-induction chemotherapy volume.
 - ◊ Metastatic CTV (mCTV) = mGTV + 1 cm, confined to anatomic borders.
 - ◊ Metastatic PTV (mPTV) = mCTV + 0.3–0.5 cm, depending on the institution’s standard, immobilization method, and modality of in-room verification imaging
 - ◊ Special consideration: In the case of parenchymal brain metastases, treatment of the entire craniospinal axis may be considered as the risk for distant central nervous system (CNS) relapse is high with focal RT.
- Neuroblastoma is a radiosensitive tumor and a commonly used dose of 21.6 Gy is recommended ([NEUROB-H 2 of 2](#)). Augmented RT approaches have not resulted in improved local control based on data from recent trials.^{3,4}

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[References on
NEUROB-H 2 of 2](#)

NEUROB-H
1 OF 2

**PRINCIPLES OF RADIATION THERAPY**

Dose definitions	
Site	Dose
Primary site and involved regional lymph nodes ^a	21.6 Gy in 1.8 Gy per fraction
Metastatic sites that are concerning for active disease after induction chemotherapy ¹	21.6 Gy in 1.8 Gy per fraction

Organs at Risk (OAR) ^b	Dose Constraints
Contralateral Kidney	V18 Gy<25% Mean dose ≤ 14.4 Gy
Ipsilateral Kidney	Mean dose ≤ 18 Gy V14.4 Gy <100% V18 Gy<75%
Liver	Mean dose <18 Gy
Vertebrae (applies if PTV extends into vertebral body)	Minimum 18 Gy to cover vertebrae to prevent asymmetrical growth
Bilateral lungs	V20 Gy<30%
Ipsilateral lung	V20 Gy<30%
Contralateral lung	V20 Gy<10%

- **Emergent RT (4.5 Gy in 1.5 Gy/fraction) should be considered in clinical scenarios including the following:**
 - ▶ **Hepatomegaly leading to respiratory distress**
 - ▶ **Orbit or optic pathway disease leading to vision loss**

Footnotes

^a Boosting residual disease after surgery to 36 Gy did not improve cumulative incidence of local progression.³ An ongoing European trial includes a randomization in which patients with residual disease either receive a boost or received standard dose therapy.

^b Adapted from COG ANBL 1531 (NCT03126916) study protocol.

References

¹ Casey DL, Pitter KL, Kushner BH, et al. Radiation Therapy to Sites of Metastatic Disease as Part of Consolidation in High-Risk Neuroblastoma: Can Long-term Control Be Achieved? *Int J Radiat Oncol Biol Phys* 2018;100:1204-1209.

² Polishchuk AL, Li R, Hill-Kayser C, et al. Likelihood of bone recurrence in prior sites of metastasis in patients with high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2014;89:839-845.

³ Liu KX, Naranjo A, Zhang FF, et al. Prospective Evaluation of Radiation Dose Escalation in Patients With High-Risk Neuroblastoma and Gross Residual Disease After Surgery: A Report From the Children's Oncology Group ANBL0532 Study. *J Clin Oncol* 2020;38:2741-2752.

⁴ Braunstein SE, London WB, Kreissman SG, et al. Role of the extent of prophylactic regional lymph node radiotherapy on survival in high-risk neuroblastoma: A report from the COG A3973 study. *Pediatr Blood Cancer* 2019;66:e27736.

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**MONITORING FOR LATE EFFECTS****Monitoring for Late Effects ≥2 Years After Completion of Systemic Therapy**

- Late effects and survivorship care are specific to the individual, the age at which neuroblastoma is diagnosed, and the wide range of therapies used to treat it. Generalized recommendations for screening for late effects would not be appropriate or accurate for many patients. It is strongly recommended to create a survivorship care plan specific to each individual patient.

High-Risk Disease

- Patients with high-risk neuroblastoma (especially those treated with myeloablative therapy) are at particularly high risk of hearing impairment,^a endocrine deficiencies, and growth retardation. Additional late effects common to patients with high-risk disease include:
 - ▶ Chronic kidney disease
 - ▶ Impaired fertility
 - ▶ Cardiotoxicity
 - ▶ Neurocognitive impairment
 - ▶ Second malignant neoplasms
- Screening for sensorineural hearing loss due to platinum chemotherapy and eflornithine is of particular importance. While the [COG Survivorship Guidelines](#) outline the minimum recommended frequency for audiologic assessment, children with impaired hearing should be referred to institutional audiology and/or otolaryngology teams to determine the appropriate schedule for subsequent evaluations.
- Patients treated for high-risk neuroblastoma are at risk for neurocognitive impairment. Risk appears to be impacted by chronic health conditions and specific treatments received.¹
- Fertility preservation is an option for some patients with high-risk disease. When possible, referral to fertility specialists for further discussion prior to initiation of chemotherapy is recommended.

Non-High-Risk Disease

- Patients who receive chemotherapy for non-high-risk disease typically receive lower cumulative doses of chemotherapeutic agents and limited to no external beam radiotherapy, and are therefore at lower risk of long-term toxicities compared to patients with high-risk disease. However, patients with non-high-risk disease constitute a heterogeneous group, and there is a wide range of cumulative chemotherapeutic exposures.
- Refer to the [COG Survivorship Guidelines](#) for appropriate screening and counseling related to: thyroid, cardiac, pulmonary, renal, bone, reproductive health, subsequent cancers (with special attention to thyroid and kidney), and other treatment-associated late effects.

Footnote

^a Consider audiologic assessment during key periods for speech development, depending on exposure to ototoxic agents.

Reference

¹ Hesko C, Liu W, Srivastava DK, et al. Neurocognitive outcomes in adult survivors of neuroblastoma: A report from the Childhood Cancer Survivor Study. *Cancer* 2023;129:2904-2914.

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**INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG) STAGING****Descriptions of INRG Tumor Stages¹**

Tumor Stage	Description
L1	Localized tumor not involving vital structures, as defined by the list of IDRFs, and confined to one body compartment
L2	Local-regional tumor with presence of one or more IDRFs
M	Distant metastatic disease (except stage MS tumor)
MS	Metastatic disease in children younger than 18 months, with metastases confined to skin, liver, and/or bone marrow

¹ Brisse HJ, McCarville MB, Granata C, et al. Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project. *Radiology* 2011;261:243-257.

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**ABBREVIATIONS**

ALT	alanine aminotransferase	H&P	history and physical	NGS	next-generation sequencing
		HgbA1C	hemoglobin A1c		
BSA	body surface area	HVA	homovanillic acid	OAR	organ(s) at risk
				OS	overall survival
CBC	complete blood count	ICCR	International Collaboration on Cancer Reporting	PD	progressive disease
CNS	central nervous system	IDRF	image-defined risk factor	PR	partial response
COG	Children's Oncology Group	I-MIBG	iodine-meta-iodobenzylguanidine	PT	prothrombin time
CR	complete response	IMRT	intensity-modulated radiation therapy	PTV	planning target volume
CTV	clinical target volume	INPC	International Neuroblastoma Pathology Classification		
DI	DNA-Index	INR	international normalized ratio	RECIST	Response Evaluation Criteria in Solid Tumors
		INRC	International Neuroblastoma Response Criteria		
ECG	electrocardiogram	INRG	International Neuroblastoma Risk Group	SCA	segmental chromosomal aberration
EFS	event-free survival			SD	stable disease
FDG	fluorodeoxyglucose	INRGSS	INRG Staging System	SIOPEN	Society of Pediatric Oncology Europe Neuroblastoma
FFPE	formalin-fixed paraffin-embedded	INSS	International Neuroblastoma Staging System	SPECT	single-photon emission computerized tomography
FH	favorable histology	ITV	internal target volume		
FISH	fluorescence in situ hybridization	LDH	lactate dehydrogenase	TSH	thyroid-stimulating hormone
FSH	follicle-stimulating hormone	LH	luteinizing hormone		
		mCTV	metastatic clinical target volume	UH	unfavorable histology
		MD	minimal disease		
GFR	glomerular filtration rate	mGTV	metastatic gross tumor volume	VGPR	very good partial response
GTV	gross tumor volume	MKI	mitosis and karyorrhexis index	VMA	vanillylmandelic acid
		mPTV	metastatic planning target volume		
H&E	hematoxylin and eosin	MR	minor response		

**NCCN Categories of Evidence and Consensus**

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



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DISCUSSION UNDER DEVELOPMENT