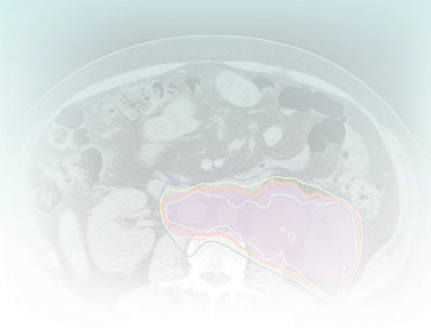
CHAPTER

72 Neuroblastoma



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EPIDEMIOLOGY

Neuroblastoma comprises 8% to 10% of childhood cancers, with 650 cases reported annually in the United States. It is the most common extracranial solid tumor in children and the most common malignancy in infants. The tumor primarily occurs in neural crest–derived tissues, and the adrenal gland is its most common location.

EARLY DETECTION

Screening has not impacted on survival or detection of high-risk neuroblastoma. Neuroblastoma-like cells are found in normal development.

BIOLOGY, CLASSIFICATION, AND STAGING

Segmental chromosomal abnormalities including deletions of 1p36 and 11q and unbalanced gain of chromosome 17q and *MYCN* amplification are associated with a worse prognosis. Neuroblastoma contains small, round, blue cells that stain for neural features. Lymphatic spread is common, as is spread to the bones of the skull, whereas lung metastases are rare. Brain metastases are seen in 5% to 10% of cases at relapse. Children younger than 18 months of age generally have localized disease, whereas older children generally have disseminated tumors.

The International Neuroblastoma Pathology Committee (INPC) classification system is the most widely used and validated. The International Neuroblastoma Response Group (INRG) staging system is replacing the previous staging systems. Staging studies include bone marrow aspirates and biopsies, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy with iodine-123–labeled metaiodobenzylguanidine (^{123}I-MIBG) (or ^{18}F-fluorodeoxyglucose–labeled positron emission tomography [FDG-PET]). Urinary catecholamines should be measured.

THERAPY

Treatment is based on risk stratification. Survival varies from 95% for patients with low-risk disease to 30% to 40% for patients with high-risk disease:

- Low-risk disease: generally treated with surgery alone with chemotherapy for progressive disease
- Intermediate-risk disease: 4 months to 8 months of chemotherapy followed by surgery and radiation therapy (21 Gy) for residual disease
- High-risk disease: surgery, induction chemotherapy with or without autologous stem-cell transplant, anti-GD2 immunotherapy, irradiation to primary site with or without metastases

Neuroblastoma comprises a range of tumors (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) that arise from primitive adrenergic neuroblasts of neural crest tissue, typically in young children. The clinical behavior, and therefore, therapy for neuroblastoma varies tremendously, depending on an array of clinical and biologic characteristics. Although some tumors regress spontaneously, others are highly malignant and often fatal.[1,2]

Significant progress in therapy has been made during the past several decades owing to an increased understanding of tumor behavior and effective risk-group stratification. Patients with low- and intermediate-risk tumors now have high survival rates with minimal intervention, and those with high-risk disease have improving survival as a result of intensive multimodality therapy.

Neuroblastoma is a fascinating and multifaceted disease. The investigation of biologic features of neuroblastoma and subsequent translation of these findings into effective therapy may serve as a model for other diseases.

ETIOLOGY AND EPIDEMIOLOGY

Neuroblastoma accounts for 8% to 10% of all childhood cancers, with approximately 650 cases diagnosed annually in the United States. It is the most-common extracranial solid tumor in children and the most common malignancy of infants. The median age at diagnosis is 17 months, and the male-to-female ratio is 1.1:1. Forty percent of patients are diagnosed when younger than 1 year of age, 89% are younger than 5 years of age, and 98% are younger than 10 years of age.[1-3]

Most primary neuroblastoma tumors occur in an anatomic distribution that is consistent with the location of neural crest tissue because the tumor arises from primitive adrenergic neuroblasts. The adrenal gland is the most common primary tumor site, accounting for 35% of cases overall. However, children younger than 1 year of age have a tumor arising from the adrenal gland in only 25% of cases. Other common sites include the low thoracic and abdominal paraspinal ganglia (30%) and posterior mediastinum (19%). Ganglia in the pelvic and cervical regions account for 2% to 3% of tumors, and in 1% the primary site is unknown.[1,4]

PREVENTION AND EARLY DETECTION

Because neuroblastomas frequently produce high levels of catecholamines, which can be detected in the urine, mass screening for the disease in infants has been performed. Extensive trials in numerous countries have shown that tumors detected by screening tend to be extremely favorable. Unfortunately, screening has not had an impact on survival or early detection of high-risk neuroblastoma.[5,6]

Microscopic neuroblastoma-like nodules frequently can be found at autopsy in infants who die of unrelated causes.[7] Furthermore, clusters of cells consistent with neuroblastoma occur uniformly in the adrenal glands of all fetuses, peaking

at between 17 weeks and 20 weeks of gestation, and then spontaneously regress by birth or in early infancy.[8] Thus, the development and subsequent regression of clusters of cells histologically identical to neuroblastoma appears to be a normal embryologic event, whereas the development of clinically detectable neuroblastoma appears to be a consequence of disruption of this normal developmental process.

The cause of neuroblastoma is not known in most cases. Prenatal or postnatal exposure to drugs, chemicals, or radiation has never been proven to be associated with an increased incidence of the disease.[1] A small fraction of neuroblastomas are familial and are usually associated with a germline mutation in the anaplastic lymphoma kinase *(ALK)* or *PHOX2b* genes. At least 20% of patients with familial neuroblastoma have bilateral or multifocal disease, which tends to present at an earlier age.[9-12]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Neuroblastoma is a model disease where improved genetic understanding of the tumor has allowed biology-based risk stratification and treatment. Numerous recurrent genetic changes have been identified in neuroblastoma and are correlated with disease outcome. Recent discoveries of germline mutations in the *ALK* and *PHOX2B* genes in a rare subset of patients with neuroblastoma (less than 1%) has been linked to hereditary neuroblastoma.[12-14] However, somatic *ALK* mutations are also found in 8% to 10% of neuroblastomas and may suggest biologically unfavorable disease. Most aggressive neuroblastomas contain genomic level instability, resulting in chromosomal rearrangement and unbalanced translocation. In contrast, less aggressive tumors tend to show whole chromosome losses and gains.[2,15,16] Those tumors that have loss or gain of whole chromosomes and few or no segmental chromosome abnormalities generally have an excellent prognosis, with many undergoing spontaneous differentiation or regression. In contrast, high-risk neuroblastoma is characterized by recurrent segmental chromosome abnormalities with nonrandom alterations of numerous chromosomes, particularly deletions of 1p36 and 11q and unbalanced gain of chromosome 17q.[17] The most critical genomic alteration is amplification of the MYCN oncogene, occurring in approximately 20 percent of neuroblastomas, and is associated with advanced disease, older age (>18 months), and a significantly poorer outcome.[18-21]

PATHOLOGY AND PATHWAYS OF SPREAD

Neuroblastoma is the most common of the small round, blue cell tumors of childhood. Other malignancies that can appear similar with standard pathology staining include non-Hodgkin lymphomas, Ewing's sarcoma, primitive neuroectodermal tumors, and soft-tissue sarcomas. Neuroblastoma can be distinguished from these other tumors by immunohistochemical staining for various markers including neuron-specific enolase, synaptophysin, and neurofilament. The characteristic histologic appearance is that of small, uniform cells containing dense, hyperchromatic nuclei and scant cytoplasm with neuropil. Homer-Wright pseudorosettes representing neuroblasts surrounding areas of eosinophilic neuropil are seen in up to 50% of cases.

Histologic subtypes represent different points along the maturation pathway and include (in order of increasing differentiation) neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Ganglioneuromas are considered benign and consist of mature ganglion cells, neuropil, and Schwann cells. Ganglioneuroblastomas have pathologic characteristics of both neuroblastoma and ganglioneuroma and can have an intermediate behavior as well.[22]

A variety of different pathology classification systems have been used for risk stratification. The International Neuroblastoma Pathology Committee (INPC) system is the most widely used and validated. Characteristics of this system are listed in Table 72-1. This represents a modification of the Shimada system that classifies tumors by patient age, the degree of

TABLE 72-1 Prognostic Evaluation of Neuroblastic Tumors According to the International Neuroblastoma Pathology Classification (Shimada System)

International Neuroblastoma Pathology Classification		Original Shimada Classification	Prognostic Group
Neuroblastoma			
Favorable	(Schwannian stroma-poor)	Stroma-poor (favorable)	Favorable
<1.5 year	Poorly differentiated or differentiating and low or intermediate MKI tumor		
1.5-5 years	Differentiating and low MKI tumor		
Unfavorable		Unfavorable	Unfavorable
<1.5 year	(a) Undifferentiated tumor*		
	(b) High MKI tumor		
1.5-5 years	(a) Undifferentiated or poorly differentiated tumor		
	(b) Intermediate or high MKI tumor		
>5 year	All tumors		
Ganglioneuroblastoma, intermixed	(Schwannian stroma-rich)	Stroma-rich intermixed (favorable)	Favorable†
Ganglioneuroma	(Schwannian stroma-dominant)		
Maturing		Well differentiated (favorable)	Favorable†
Mature		Ganglioneuroma	
Ganglioneuroblastoma, nodular	Composite schwannian stroma-rich/stroma-dominant and stroma-poor (schwannian stroma-rich)	Stroma-rich nodular (unfavorable)	Unfavorable†

Data from Shimada H, Ambros IM, Dehner LP, et al: The International Neuroblastoma Pathology Classification (the Shimada system). Cancer 86:364–372, 1999.
MKI, *Mitosis-karyorrhexis index.*
**Rare subtype, especially diagnosed in this age group; further investigation and analysis are required.*
†Prognostic grouping for these tumor categories is not related to patient age.

differentiation toward ganglion cells, amount of Schwann cell stroma present, whether the tumor is nodular, degree of calcification, and the mitosis-karyorrhexis index.[23]

Neuroblastoma commonly spreads via lymphatics to regional lymph nodes, often in the paraaortic chain, and less commonly to the next echelon of lymphatics, such as the left supraclavicular fossa (Virchow node) in patients with abdominal tumors. Hematogenous spread often occurs to bone marrow, bone, and less commonly, to liver. Neuroblastoma appears to have a proclivity for the bones of the skull and especially the posterior orbit, which can cause the clinical presentation of "raccoon eyes" from periorbital ecchymosis. Lung and brain metastases are rare at presentation. However, with improvements in systemic therapy, isolated parenchymal brain metastases are now occurring in about 5% to 10% patients with high-risk disease at relapse. These central nervous system relapses require craniospinal radiation therapy (RT) because of a high risk of leptomeningeal dissemination.[24]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The clinical presentation for neuroblastoma is highly variable because of the wide variety of disease sites. Primary tumor location and extent of disease vary with age. Most children (57%) younger than 1 year of age have locoregional disease at the time of diagnosis, whereas most children (81%) older than 1 year of age have disseminated disease. Children with abdominal tumors may present with abdominal pain, distention, or gastrointestinal disturbances but more commonly it is asymptomatic and discovered incidentally by a caregiver. Many with disseminated disease will present with fever, pain, limp, and significant irritability, especially younger children. Paraneoplastic syndromes, such as opsoclonus-myoclonus syndrome (myoclonic jerking and random eye movements) or vasoactive intestinal peptide (VIP) syndrome (intractable secretory diarrhea, with hypokalemia and dehydration caused by tumor secretion of VIP) are rare, occurring in less than 4% of patients.[25-27] The catecholamines secreted from most neuroblastomas are not likely to cause hypertension, flushing, or tachycardia.

A plain radiograph of the chest or abdomen may show a soft-tissue mass representing the primary tumor, and calcifications are present in 85% of tumors. Staging of neuroblastoma requires numerous imaging modalities. The primary tumor and regional lymph nodes should be imaged with CT or MRI. These studies should also be used to assess for metastases in the liver as well as spinal extension and resectability of the primary tumor. They also may be used to clarify the extent of bone metastases in specific locations, such as the skull.

At least 90% of neuroblastomas exhibit uptake of MIBG; thus bone metastases are primarily imaged using ^{123}I-MIBG scintigraphy. Technetium-99m (^{99m}Tc)–labeled bone scintigraphy is rarely used as a primary modality because MIBG imaging is more sensitive and specific. ^{18}F-fluorodeoxyglucose–labeled positron emission tomography (FDG-PET) can be useful in delineation of metastatic lesions in patients whose tumor is MIBG non-avid as well as in patients with low-risk disease.[28-30] Complete staging also includes two bilateral posterior iliac crest bone marrow aspirates and biopsies. A single positive result is sufficient for the documentation of bone marrow involvement.[31,32]

Because excess catecholamines are produced in most cases, urine catecholamines and their metabolites, specifically vanillylmandelic acid (VMA), and homovanillic acid (HVA) are typically measured. Urinary levels of catecholamines are often given as ratios to the urinary creatinine value.[33]

TABLE 72-2 International Neuroblastoma Staging System

Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor (nodes adherent to and removed with the primary tumor may be positive).
2A	Localized tumor with incomplete gross excision; representative nonadherent lymph nodes negative for tumor microscopically.
2B	Localized tumor with or without complete gross excision, with ipsilateral, nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline,* with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined in stage 4S).
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, or bone marrow† (limited to infants <1 year of age).

Data from Brodeur GM, Seeger RC, Barrett A, et al: International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. J Clin Oncol 6:1874–1881, 1988; Brodeur GM, Pritchard J, Berthold F, et al: Revisions in the international criteria neuroblastoma diagnosis, staging and response to treatment. J Clin Oncol 11:1466–1477, 1993.

**The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.*

†Marrow involvement in stage 4S should be minimal, that is, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if performed) should be negative in the marrow.

Neuroblastoma staging has undergone several revisions over the past years. Older staging systems, including the Evans and D'Angio classification, were replaced by the International Neuroblastoma Staging System (INSS) (Table 72-2).[31] This staging system is now being replaced by the INRG staging system (Table 72-3).[32]

In 2009, the INRG Task Force introduced a new stratification schema named the INRG classification system, which is emerging as the international standard.[21] This system includes INRG stage (Table 72-3), age, histologic category, grade of tumor differentiation, *MYCN* status, presence/absence of 11q aberrations, and tumor cell ploidy (Table 72-4). Based on this classification, patients are stratified into four different risk groups: very low, low, intermediate, and high risk. Treatment strategies are based on this classification.[32] Survival varies from greater than 90% for patients with low-risk disease to about 40% for patients with high-risk disease.

PRIMARY THERAPY

The therapeutic approach for neuroblastoma varies tremendously, depending on risk group stratification. The available treatment modalities include surgery, chemotherapy, RT, biologic therapy, or immunotherapy. The following is a discussion of therapy for low-, intermediate-, and high-risk disease,

with an emphasis on the role of RT. A basic treatment algorithm for each risk group is shown in Figure 72-1.

Very-Low-Risk Neuroblastoma

Patients with very-low-risk disease have small tumors (or asymptomatic stage 4S, now called MS disease) that will generally undergo spontaneous regression or differentiation into benign ganglioneuromas. These tumors have been successfully managed with close observation without therapeutic intervention. A recently published report by the Children's Oncology Group (COG) study of observation of perinatal neuroblastoma showed event-free and overall survival rates of 97.7 and 100%, respectively.[34]

Ms disease (formerly called stage 4s disease, where "s" represents "special") is an entity unique to neuroblastoma. This stage is defined by patients up to 18 months of age at diagnosis with metastatic disease sites limited to the liver, skin, and less than 10% involvement of bone marrow.[35] Despite it being metastatic, the overall prognosis for patients with Ms disease is good, with a recent reports showing an overall survival rate of 92%.[36] Very young infants (usually less than 3 months of age at time of diagnosis), however, may have rapid tumor progression leading to massive hepatomegaly and subsequent cardiorespiratory failure, requiring immediate intervention. Chemotherapy (per the intermediate-risk group protocols) can sometimes be successful at reversing the rapid tumor progression.[37] However, in infants with rapidly progressive disease or who have failed to respond adequately to chemotherapy, low-dose irradiation to the liver should be considered. Treatment can be given efficiently because simulation and anesthesia are not necessary; the liver generally fills the entire abdomen and can be seen on a port film, and the patients are young enough to be immobilized in a papoose. The typical fractionation schedule in this setting is 1.5 Gy for three fractions, which usually leads to rapid relief of symptoms. The risk of long-term harm to the child from radiation exposure is small because of the low dose. MYCN amplification in this cohort is rare; when present these patients should be treated with intensive therapy as per a high-risk protocol.[20]

TABLE 72-3 International Neuroblastoma Risk Group Staging System*

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

Table modified from The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol 27:298–303, 2009.
†Image-defined risk factors are surgical risks factors detected by imaging that make complete resection of the tumor unsafe at the time of diagnosis. See the primary reference for a full listing and description of these risk factors.

Low-Risk Neuroblastoma

Patients with low-risk neuroblastoma (see Table 72-3) can often be cured with surgery alone, even when only a partial resection is obtained.[38,39] Adjuvant RT was used in the past for incompletely resected tumors but has been shown to be unnecessary. Chemotherapy and RT are now reserved for progressive or recurrent disease.

Intermediate-Risk Neuroblastoma

The current treatment approach for intermediate-risk disease (see Table 72-3) consists of surgery for the primary tumor as well as standard-dose, multiple-agent chemotherapy for 4 months to 8 months. Definitive surgery may be delayed until after chemotherapy, which often makes the tumor more easily resectable.

Previously, RT was used in intermediate-risk disease; however, various studies have now shown that RT is not required as part of their initial therapy.[40]

TABLE 72-4 International Neuroblastoma Risk Group Classification System*

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					Very low
L1		Any, except GN maturing or GNB intermixed		NA			Very low
				AMP			High
L2	<18	Any, except GN maturing or GNB intermixed		NA	NO		Low
					Yes		Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		Low
					Yes		Intermediate
			Poorly differentiated or undifferentiated	NA			
				AMP			High
	<18			NA		Hyperdiploid	Low
	<12			NA		Diploid	Intermediate
M	12 to <18			NA		Diploid	Intermediate
	<18			AMP			High
	≥18						High
MS	<18			NA	No		Very low
					Yes		High
				AMP			High

Table modified from The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol 27:298–303, 2009.

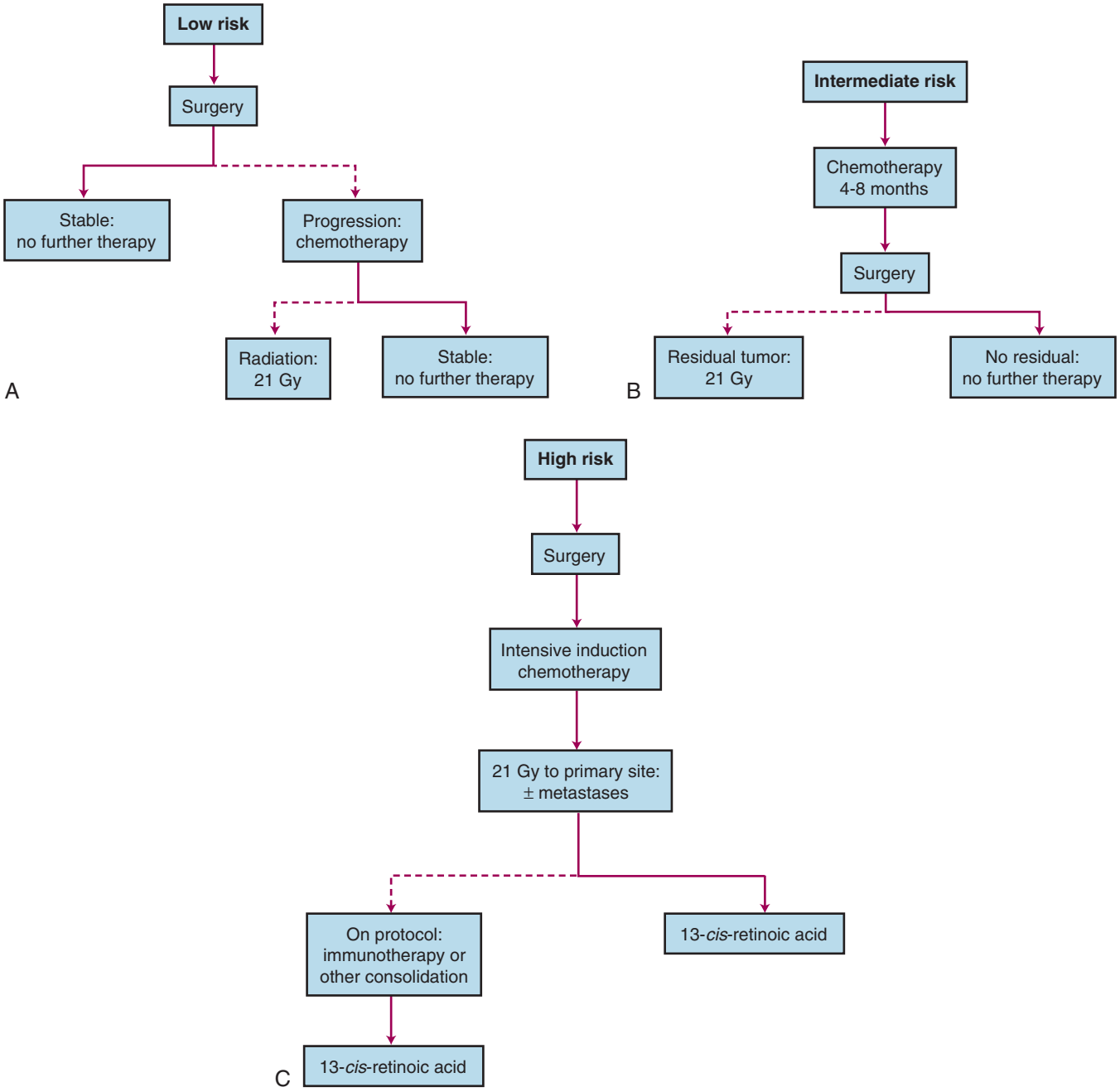

Figure 72-1 Treatment algorithm for low-risk **(A),** intermediate-risk **(B),** and high-risk **(C)** neuroblastoma.

In the COG study A3961, patients with intermediate-risk disease underwent surgery as well as chemotherapy (with cyclophosphamide, doxorubicin, carboplatin, and etoposide). The duration of chemotherapy was based on biologic risk factors for individual patients. The results of that study, published in 2010, demonstrated a 3-year overall survival of 96% among all patients, with 98% overall survival within the favorable biology group, and 93% overall survival among the patients with unfavorable biological features.[37] Importantly, these studies have shown that aggressive surgery and RT are not required to achieve excellent results. RT thus is indicated only for those with disease progression or persistent tumor after chemotherapy and second-look surgery.

High-Risk Neuroblastoma

The current therapeutic approach for high-risk disease includes intensive induction chemotherapy, surgical resection of the primary tumor, and possible myeloablative consolidation therapy with stem-cell rescue, followed by RT and biologic therapy using 13-cis retinoic acid and anti-GD2 immunotherapy to target minimal residual disease. Patients who have a complete or good partial response to induction chemotherapy have a better prognosis.[29] The induction regimens currently in use are all based on similar backbones of alkylating agents (cyclophosphamide and so on), anthracyclines (doxorubicin), and platinum compounds (cisplatin and

carboplatin). Dose and timing varies among the regimens, but published reports have shown that high-dose platinum and alkylator-based regimens have overall induction response rates (CR + VGPR + PR) of 70% to 80%.[41-46]

Consolidation therapy targets potentially resistant neuroblastoma cells using additional high-dose or myeloablative chemotherapy,[47] followed by RT. Maintenance therapy is biological and immunotherapy targeting minimal residual disease (MRD). 13-*cis*-retinoic acid is given as a monthly14-day cycles for 6 months.[47] Additionally, the COG recently reported that the addition of immunotherapy using the chimeric antibody ch14.18 directed at the neuroblastoma tumor antigen GD2, combined with the cytokines granulocyte-macrophage colony stimulating factor (GMCSF) and interleukin-2 (IL-2) significantly improved survival; 2-year event-free survival was 66% with immunotherapy compared with 46% in the control group.[48] Memorial Sloan Kettering (MSK) has also recently reported significantly improved long-term outcomes using the anti-GD2 mouse monoclonal antibody 3F8.[49,50]

The most recent COG protocol for high-risk disease, ANBL0532, included RT to the primary tumor site, regardless of the extent of surgical resection. The dose was 21.6 Gy in 1.8 Gy fractions in the case of complete resection and a boost of 14.4 Gy for a total of 36.0 Gy in the case of incomplete resection. RT was also indicated to sites of metastatic disease that demonstrated persistent MIBG avidity on the pretransplant scan. For patients with greater than five MIBG positive metastatic sites on pretransplant scan, another MIBG scan was performed 4 weeks posttransplant. RT was then limited to avid sites on that scan.

Evidence for the benefit of primary site RT comes from cooperative group trials as well as single institution series.[47] Haas-Kogan et al examined the role of RT on local control in the Children's Cancer Group study 3891. It appears that both 10 Gy to the primary site as well as 10 Gy of total-body irradiation decreased the local recurrence rate. The largest benefit was seen when patients received both local RT and total-body irradiation, for a total dose of 20 Gy. Further supporting the role of postoperative radiation therapy is a series from MSK where a total dose of 21 Gy was given in twice-daily 1.5-Gy fractions. Among 99 patients treated with irradiation to the primary site, the local failure rate was 10%.[51] Only 7 of these patients had residual disease at the primary site at the time of irradiation, and 3 of these had local recurrence, suggesting that 21 Gy is not an adequate dose for gross residual disease. Although final results are not available for the boost dose of 36 Gy in ANBL0532, this strategy may not be effective for most patients. Achieving a gross total resection of the primary tumor before RT seems to be necessary for optimal local control.

Targeted radiopharmaceuticals are also under investigation as an alternative means of delivering specific RT to metastatic tumor sites, either for refractory disease or as part of a myeloablative regimen. Targeted radioisotope therapy using MIBG for delivery of radiation in the form of iodine-131 has been tested extensively in clinical trials in patients with relapsed neuroblastoma. Efforts are currently under way by the COG to include high dose (12 mCi/kg to 18 mCi/kg) I^{131}-MIBG therapy with stem-cell rescue as primary therapy for patients with high risk disease; however, this remains somewhat controversial and the feasibility and tolerability of this approach is still under investigation.

RECURRENT DISEASE AND PALLIATION

Current approaches for treating recurrent or refractory neuroblastoma include novel cytotoxic agents and targeted delivery of radionuclides, retinoids, and other investigational agents. Cyclophosphamide and topotecan, and irinotecan and temozolomide are frequently used cytotoxic regimens.[52-55] RT plays an important role in palliation for neuroblastoma. Patients with incurable disease often live for an extended period of time. However, they often suffer severe pain and functional impairment from metastases, most commonly to bone. External beam radiation therapy (EBRT) is the most effective tool for managing painful metastases. Fractionation schemes depend on the site, field size, marrow reserves, and anticipated life span of the patient. A high-functioning child may benefit from 2-Gy fractions to 30 Gy, whereas a patient with end-stage disease may be better served by a single fraction of 7 Gy to 8 Gy.

IRRADIATION TECHNIQUES

Irradiation techniques depend on the site being treated. Most commonly, patients with high-risk disease have a primary tumor arising from the adrenal gland or abdominal paravertebral region. Radiation volume for localized neuroblastoma is determined by the surgeon's operative findings and presurgical imaging studies. Margins and normal tissue-sparing parameters vary from protocol to protocol. Based on patterns of failure data, it is important to include the paraaortic lymph nodes in the radiation field.[56] CT planning is imperative to delineate the target region as well as normal tissues, including the kidneys, liver, and in some cases, ovaries. Attention should be paid to treatment of vertebral bodies to reduce the risk of scoliosis. Simple anterior and posterior beams, as demonstrated in Figure 72-2, may be a good solution, but intensity-modulated radiation therapy (IMRT) may be better for controlling dose to adjacent organs. Proton therapy may also be considered but may lead to unacceptable kidney doses when posterior beams are used. Bone metastases are often best treated with simple opposed beams. However, more

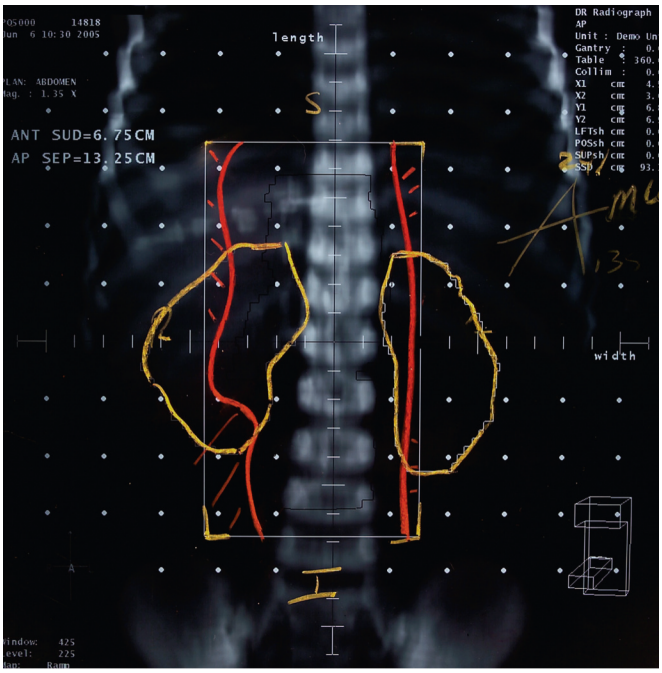

Figure 72-2 Typical anterior and posterior radiation therapy field for adrenal neuroblastoma. Generous coverage of paraaortic lymph nodes is recommended. Adequate kidney sparing is accomplished by treating postchemotherapy tumor volume.

sophisticated approaches may be needed when treating sites in the head and neck because of the complex anatomy and critical structures. Neuroblastoma is common in young children, necessitating the frequent use of anesthesia for RT. In this case, propofol is safe and well tolerated, even for twice-daily treatments.

Intraoperative radiation therapy (IORT) is not an acceptable alternative to EBRT in the context of initial therapy. A report from the University of California–San Francisco showed reasonable local control after complete resection but not after subtotal resection and a high rate of severe aortic complications in patients receiving IORT.[57] In the setting of local relapse following prior EBRT, MSK reported a relatively favorable 50% rate of local control and low rate of complications for 44 patients who underwent subsequent surgery and reirradiation with IORT for locally relapsed neuroblastoma.[58]

LATE EFFECTS

Consideration for long-term complications is critical when treating neuroblastoma. Patients treated years ago with higher doses of radiation frequently suffered from spinal deformities secondary to surgery and RT. Orthopedic problems from RT are less severe with a dose of 21 Gy but should still be considered when designing treatment fields. As a general rule, it is desirable to limit as much of each kidney as possible to doses less than 15 Gy to 18 Gy to prevent major impairment in renal function. One must also inform parents about the low risk of diabetes mellitus and second malignancies. A prospective trial is currently under way at MSK testing a stepwise reduction in radiation dose from 21 Gy to 18 Gy to 15 Gy. It is likely that even small dose reductions in this range will result in lower risks of spinal growth abnormalities and diabetes mellitus. A recent study of long-term survivors of high-risk neuroblastoma shows that the majority have late complications of therapy, including hearing loss, hypothyroidism, ovarian failure, musculoskeletal abnormalities, and pulmonary dysfunction. However, most complications were considered to be of mild-to-moderate severity.[59] All members of multimodality teams that care for patients with neuroblastoma patients must be mindful of late effects and strive to minimize complications while ensuring the best chance for cure.

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