
CHAPTER 79

NEUROBLASTOMA

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Neuroblastoma is a tumor of the peripheral nervous system that accounts for 8% of childhood cancers.¹ The spectrum of clinical behavior manifested by this tumor ranges from spontaneous regression with no therapy to rapidly progressive disease in spite of combination chemotherapy.²⁻⁵ According to a variety of clinical and laboratory prognostic factors, low-, intermediate-, and high-risk groups of patients can be defined at diagnosis based on expected outcome after conventional therapy. Classifying neuroblastoma patients into risk groups is important to avoid overtreatment or undertreating a given patient.

The clinical diversity of neuroblastomas is associated with molecular genetic and other biologic differences. For example, patients who are cured by surgery alone have localized tumors that lack genomic amplification of the *MYCN* proto-oncogene, do not grow in vitro, and usually are histologically differentiated. By contrast, conventional treatment is rarely successful for patients whose metastatic neuroblastomas exhibit amplification of the *MYCN* proto-oncogene, and are poorly differentiated.

Forty percent of children with neuroblastoma have low- or intermediate-risk tumors, and they nearly all become long-term, disease-free survivors following conventional therapy, which includes surgery, local irradiation, and chemotherapy. However, 60% have high-risk tumors, and these patients infrequently become long-term survivors after conventional therapy. A phase III study has shown improved event-free

survival for high-risk neuroblastoma patients treated with aggressive chemoradiotherapy followed by the differentiating agent 13-cis-retinoic acid. However, as tumor recurrence remains a significant problem for high-risk neuroblastoma, more effective therapeutic approaches must be developed and tested in prospective randomized trials.

This chapter reviews the clinical features of neuroblastoma and the various clinical and laboratory methods used for diagnostic and prognostic assessment of the patient. We then discuss currently available therapeutic approaches based on the prognosis of the patient and briefly review new approaches to therapy being tested in clinical trials.

Natural History, Diagnosis, and Staging

CLINICAL FEATURES

Neuroblastoma is predominantly a disease of early childhood. About one half of neuroblastoma patients are diagnosed within the first 2 years of life.^{4,6} Approximately 50% of infants and 70% of older neuroblastoma patients have disseminated disease at diagnosis.⁷ Presenting symptoms in such patients are often manifestations of widespread tumor, such as weight loss, bone pain, pallor, and easy bruising. These vague symptoms can result in delays in the correct

agnosis. Less common is the incidental discovery of a mass. Occasionally, the presenting symptom is due to neurogenic defects resulting from extension of paraspinal tumors to the epidural space,⁸ Horner's syndrome from a mediastinal tumor, or a paraneoplastic syndrome related to the tumor, such as opsoclonus-myoclonus⁹ or vasoactive intestinal peptide-induced watery diarrhea.¹⁰

The primary tumor can arise at any point where there is an issue of the sympathetic nervous system; the majority of primary tumors arise in the adrenal glands (Fig. 79-1).⁴ The most common site of metastatic disease is the bone marrow, followed by the bone, liver, and lymph nodes. Although the older literature contains reports of neuroblastomas arising in parasympathetic peripheral nerves, such tumors are now considered to be distinct from neuroblastoma.^{11, 12}

INITIAL EVALUATION

The extent of disease should be determined by evaluating the primary site, potential sites of metastatic disease, and the degree of elevation of tumor markers. Tests should include a chest radiograph; computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis; skeletal survey or ^{99m}Tc-diphosphonate bone scan; or both, and a ¹³¹I-metaiodobenzylguanidine (MIBG) scan.¹³⁻¹⁶ Bilateral iliac crest bone marrow aspirates and biopsies should be performed, as this increases the probability of detecting tumor in the marrow.¹⁷ Analysis of urine for catecholamine metabolites^{5, 18} (vanillylmandelic acid [VMA] and homovanillic acid [HVA]) can aid in the diagnosis and in monitoring tumor response; measurement of serum ferritin¹⁹ aids in assessing the patient's risk group (see the section Serum Markers).

Surgery, whether for complete or partial resection of the primary tumor or for biopsy, is necessary in patients with local (stage 1 and 2) or regional (stage 3) disease. This provides tumor tissue for diagnosis and prognostication, and also allows examination and biopsy of regional lymph nodes. Patients with disseminated disease (stages 4 and 4-S) who have demonstrable tumor cells in bone marrow and elevated urine HVA or VMA, or both, do not require surgery to establish a diagnosis. However, patients with stage 4 or 4-S disease who are diagnosed in the first year of life must be tested for *MYCN* gene amplification, which can be carried out on tumor tissue or bone marrow having >10% tumor cells. Biopsy or excision of primary or metastatic tumor is also strongly recommended for stage 4 patients older than 1

year at diagnosis because prognostic and biologic information obtained from tumor tissue may guide future therapies. If urine HVA and VMA are normal in a patient with disseminated disease, tumor tissue must be obtained to establish the diagnosis. In addition to tissue submitted for histopathology, tumor tissue should be used to prepare nonfixed touch preparations for *MYCN* analysis by fluorescence in situ hybridization (FISH); fresh tissue in culture medium should be submitted for ploidy and cell culture; and as much tissue as possible should be frozen immediately, without fixation, for future diagnostic and prognostic studies. Such frozen material is not only invaluable for research but can also be used as needed for diagnostic immunohistochemistry or confirmatory analysis of various prognostic markers. Because laboratory investigations of biologic, diagnostic, prognostic, and therapeutic questions are dependent on both frozen and cultured viable tumor tissue, every effort should be made to plan for full utilization of tissue before surgery is undertaken.

DIAGNOSIS

Establishing a diagnosis of neuroblastoma is often routine but can occasionally be difficult.²⁰ Histopathologic examination of primary or metastatic tumor is usually diagnostic. However, undifferentiated neuroblastomas can be confused with primitive neuroectodermal tumor (PNET), peripheral neuroepithelioma, Ewing's sarcoma, rhabdomyosarcoma, lymphoma, and even leukemia.^{20, 21} A number of diagnostic markers exist that are valuable in resolving diagnostic dilemmas. Before the current battery of diagnostic tests was available, it was common to consider any extracranial small, round cell tumor of neural origin to be a neuroblastoma. However, clinical and biologic studies now assist in distinguishing neuroblastoma from related neural tumors, including peripheral PNET and esthesioneuroblastoma.^{11, 12, 22-26} For most of these tumors, the clinical presentation of the patient aids in distinguishing them from neuroblastoma; we have summarized the clinical features of these tumors in Table 79-1.

Catecholamines. Catecholamine metabolites are abnormally elevated in the urine of nearly all patients with neuroblastoma.^{5, 18} A diagnosis of neuroblastoma can be established by demonstrating that the tumor is catecholamine positive and that it is a small, round cell tumor (the latter can be determined with primary or metastatic tumor, or with a marrow aspirate and biopsy). However, every effort to obtain tumor tissue should be made to ensure the potential

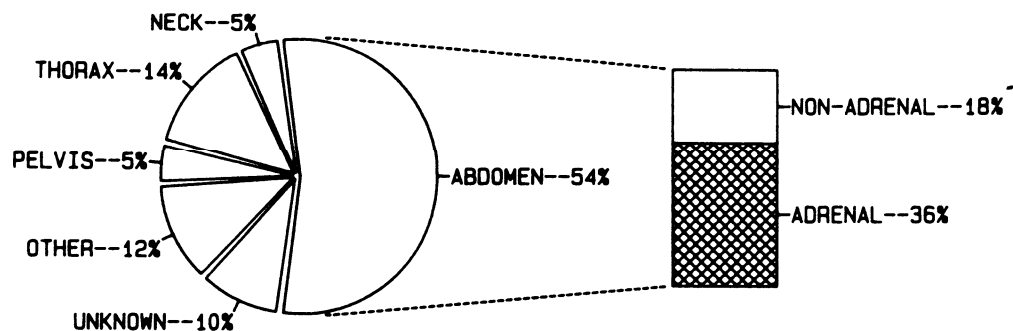


Figure 79-1. Sites of origin for primary neuroblastoma. (Data from Coffey N. Neuroblastoma: review of the literature and an examination of factors contributing to its enigmatic character. *Cancer Treat Rev* 1976;3:61 and Hayes FA. In: Pizzo PA, eds. *Principles and practice of pediatric oncology*. Philadelphia: JB Lippincott, 1989:607.)

Table 79-1. Comparison of Neuroblastoma and Related Neural Tumors

Tumor	Site or Origin	Histopathology	Ultrastructure	Catecholamines	Cytogenetics	MYCN Amplification	Other Markers
Neuroblastoma	Sites of sympathetic nervous system	Small, round tumor with neurofibrillary stroma, occasionally with pseudorosettes and/or ganglion cells	Neural, including neurosecretory granules	Most are positive	1pdel, double minutes, and homogeneously staining regions	Present in 30%	Most HLA class I negative; NSE + TH positive
PNET	Thorax, chest wall, pelvis, extremities	Primitive small, round cell tumor	Neural, including neurosecretory granules	All negative	Many have t(11;22)	All negative	HLA class I positive NSE positive TH negative
Esthesioneuroblastoma	Olfactory nerve	Primitive small, round cell tumor	Neural, including neurosecretory granules	Most are negative	Some have t(11;22)	Negative in all studied	HLA class I positive

PNET, primitive neuroectodermal tumor; NSE, neuron-specific enolase; TH, tyrosine hydroxylase.