Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors of the sympathetic nervous system that arise from primitive sympathogonia and are referred to collectively as neuroblastic tumors. They arise wherever sympathetic tissue exists and may be seen in the neck, posterior mediastinum, adrenal gland, retroperitoneum, and pelvis. The three tumors differ in their degree of cellular and extracellular maturation; immature tumors tend to be aggressive and occur in younger patients (median age, just under 2 years), whereas mature tumors occur in older children (median age, approximately 7 years) and tend to behave in a benign fashion. The most benign tumor is the ganglioneuroma, which is composed of gangliocytes and mature stroma. Ganglioneuroblastoma is composed of both mature gangliocytes and immature neuroblasts and has intermediate malignant potential. Neuroblastoma is the most immature, undifferentiated, and malignant tumor of the three. Neuroblastoma, however, may have a relatively benign course, even when metastatic. Thus, these neuroblastic tumors vary widely in their biologic behavior. Features such as DNA content, tumor proto-oncogenes, and catecholamine synthesis influence prognosis, and their presence or absence aids in categorizing patients as high, intermediate, or low risk. Treatment consists of surgery and, usually, chemotherapy. Despite recent advances in treatment, including bone marrow transplantation, neuroblastoma remains a relatively lethal tumor, accounting for 10% of pediatric cancers but 15% of cancer deaths in children.
Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors of varying maturity derived from the primordial neural crest cells that form the sympathetic nervous system. These precursor cells may remain undifferentiated (referred to as neuroblasts) or they may mature (to ganglion and Schwann cells) (1,2). A tumor composed primarily of neuroblasts is referred to as neuroblastoma (NB), a tumor composed entirely of mature ganglion cells and other mature tissue is a ganglioneuroma (GN), and a tumor with both immature and mature cell types is a ganglioneuroblastoma (GNB) (1,2). As a group, these tumors define a spectrum of sympathetic neuroectodermal tumors, ranging from the undifferentiated NB to the mature GN. The presence of immature tissue in NB and GNB indicates malignant or potentially malignant behavior; GN is considered benign. This article discusses these neuroblastic tumors, including their clinical presentation, histologic characteristics, biologic behavior, radiologic appearance, staging, and prognosis.

Neuroblastoma and Ganglioneuroblastoma
Virchow originally described NB in 1863; early reports described the tumor as a glioma of the adrenal gland. By the beginning of the 20th century, its origin in sympathetic tissue was determined by Zückerkandl and Kohn (3). The surprising discovery that NB could mature to GN was made in 1927 (4).

Approximately 500–525 new cases of NB are diagnosed each year in the United States, making it the third most common pediatric malignancy, after leukemia and central nervous system tumors. The incidence of NB is 8.0 and 8.7 per million per year in the United States for whites and blacks under the age of 15 years, respectively (5,6). NB represents 8%–10% of all childhood cancer, but, because of its aggressive nature, it accounts for close to 15% of childhood cancer fatalities. The median age at diagnosis is 22 months, and more than 95% of cases are diagnosed by 10 years of age (7). Although rare, there are documented cases of familial NB (8–10). NB may occur in newborns and may even be seen at prenatal sonography (11,12). In rare cases, NB, GNB, and GN may occur in patients with other disorders, including von Recklinghausen disease, Beckwith-Wiedemann syndrome, Hirschsprung disease, central failure of ventilation, and Di-George syndrome (13–18). Malignant peripheral nerve sheath tumors and pheochromocytoma have been described in neuroblastic tumors, making them composite tumors (19–22).

Because neuroblastic tumors derive from primordial neural crest cells destined for sympathetic differentiation, they may arise anywhere sympathetic tissue naturally occurs (Fig 1). The most common sites of origin of NB and GNB, in order, are the adrenal medulla (35% of cases), extraadrenal retroperitoneum (30%–35%), and posterior mediastinum (20%). Less common sites are the neck (1%–5% of cases) and pelvis (2%–3%) (23). Approximately 1% of patients present with metastatic disease but no discoverable primary tumor. Unusual locations such as the thymus, lung, kidney, anterior mediastinum, stomach, and cauda equina have also been described (24–29).

NB and GNB are grouped together for the purposes of cancer reporting, staging, and survival statistics because both share malignant potential, although clearly this potential is higher for NB than for GNB. They are separated at the time of original diagnosis into favorable and unfavorable types, on the basis of histologic characteristics, genetic information, and other biologic behavior factors. Accurate diagnosis, staging, and prognosis depends on histologic, electron microscopic, immunocytochemical, cytogenetic, and other molecular and biologic information (30).
Clinical Presentation

Patients with NB and GNB most often present with pain, caused by either local effects from the primary tumor or metastatic disease. Abdominal distention is the next most frequent complaint. Other presenting symptoms include malaise, irritability, weight loss, shortness of breath (from a large abdominal tumor), and peripheral neurologic deficit (from neural foraminal invasion and nerve compression by tumor) (31). Less common presentations include Horner syndrome (ptosis, pupillary constriction, and ipsilateral facial anhidrosis and flushing from a mediastinal tumor) and opsoclonus-myoclonus. Opsoclonus-myoclonus is jerking movements of the extremities and eyes, sometimes with cerebellar ataxia; the cause is unknown but it is seen in 2% of patients and is associated with a thoracic primary tumor and a better prognosis (31,32). Up to two-thirds of patients have metastatic bone disease at presentation; when this manifests as limping and irritability, it is known as Hutchinson syndrome (31).

Histologic Characteristics

Each tumor has primary and secondary histologic features. Primary features include neuroblasts and their derivatives (ganglion cells and Schwann cells) and stroma. Neuroblasts are immature, undifferentiated sympathetic cells. They are small, are rounded in contour, show little cytoplasm, and possess darker nuclei and smaller indistinct nucleoli (Fig 2). Ganglion cells are fully mature cells with abundant cytoplasm, rounded contour, and large nuclei with distinct and prominent nucleoli. Stroma is the tissue surrounding the neuroblasts or ganglion cells. It may consist of Schwann cells, fibrovascular septa, or both (Fig 3). Neuropil is the fine pattern of cellular (neuritic) processes extending from neuroblasts; it appears extracellular but is in fact a cellular extension (2,33). One characteristic feature of NB is the formation of Homer Wright rosettes (Fig 4). Rosettes are circular or ovoid columns of tumor cells arranged around a central core of neuropil. Homer Wright rosettes are typical of NB, but they are not always present (34). Secondary
Histologic features are necrosis, mitosis, hemorrhage, fibrosis, calcification, lymphocytic infiltrate, and karyorrhexis. Karyorrhexis is defined as the fragmentation of a nucleus into scattered pieces within the cytoplasm; it is an event that occurs during cell death. Karyorrhexis may be difficult to distinguish from mitosis in neuroblasts (2,35).

Two histologic classification systems are commonly used in the United States to stratify neuroblastic tumors into risk groups: the Shimada classification and the Pediatric Oncology Group (POG) classification. Both systems assess histologic features, such as cellular differentiation, to arrive at a prognostic classification (however, these are not staging systems). The POG system is based solely on the degree of differentiation of the different histologic elements. GN shows completely (100%) differentiated stromal and cellular components, NB contains less than 50% differentiated elements, and GNB is intermediate (greater than 50% differentiated cells). NB may be further subclassified as undifferentiated (the most immature NB), poorly differentiated, or differentiating (the most mature NB). Differentiation of the neuroblastic cells indicates that they demonstrate some characteristics of mature cells (differentiating cells show nuclear enlargement, nucleoli, cytoplasmic eosinophilia and enlargement, distinct cytoplasmic border, and cell processes) (36).

The Shimada classification combines histologic features and patient age at diagnosis. The histologic features consist of stroma, grade and architecture of cellular differentiation, and nuclear morphology. Tumors are classified as stroma-rich or stroma-poor. The stroma-rich (more mature) category is characterized by extensive growth of Schwannian stroma; the stroma-poor shows thin fibrovascular septa. The stroma-rich group is further subdivided into well differentiated (most mature) if composed of mature tissue, intermixed (least mature) if interrupted by randomly distributed clusters of neuroblastic cells, and nodular if showing one or a few sharply defined stroma-poor areas trapped in a mature stroma (2). Cellular characteristics are then assessed. Undifferentiated neoplasms are composed almost entirely of undifferentiated neuroblasts and less than 5% being differentiated cells (ie, neuroblasts showing differentiation into ganglion cells). Differentiating tumors show at least 5% differentiated cells. Mitosis and karyorrhexis of the tumor cells are then evaluated. Since it may be difficult to differentiate mitoses from karyorrhexis, cells with these features are counted in a sample of 5,000 cells and reported as an index (which is the total number of mitotic and karyorrhectic cells in the 5,000-cell sample). On the basis of the mitosis-karyorrhexis index (MKI), NB and GNB are subdivided into low (less than 100), intermediate (100–200), or high (over 200) MKI. High MKI correlates with unfavorable histologic characteristics and a worse prognosis (1,30). Finally, patient age is factored into the classification. The age groups of the Shimada classification system are less than 1.5 years, 1.5–5 years, and more than 5 years of age (2).

<table>
<thead>
<tr>
<th>Type</th>
<th>Favorable Histologic Characteristics</th>
<th>Unfavorable Histologic Characteristics</th>
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<tbody>
<tr>
<td>Stroma-rich</td>
<td>Well differentiated</td>
<td>Nodular</td>
</tr>
<tr>
<td>Stroma-poor</td>
<td>MKI &lt;200/5,000</td>
<td>MKI &gt;200/5,000</td>
</tr>
<tr>
<td>Age &lt;18 mo</td>
<td>MKI &lt;100/5,000 and differentiating</td>
<td>MKI &gt;100/5,000 and undifferentiated</td>
</tr>
<tr>
<td>Age 18–60 mo</td>
<td>None</td>
<td>All</td>
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Table 1. Histopathologic Age-linked Grading System of Shimada

Figure 5. Adrenal NB. Photograph of a bisected kidney reveals a heterogeneous, hemorrhagic adrenal NB arising above the kidney.
with a low or intermediate MKI and differentiating or partially differentiating tumor or 1.5–5 years old with a low MKI differentiating tumor. All other combinations are considered unfavorable histologic characteristics (1).

As an aside, it is interesting to note that microscopic neuroblastic nodules may frequently be found in infants less than 3 months of age dying of other unrelated causes. Since they are up to 40 times more common than NBs detected clinically, these nodules were initially regarded as NBs in situ that underwent spontaneous regression. Subsequent studies demonstrated that these nodules are a normal occurrence during fetal development, peaking during 17–20 weeks gestation, then regressing as part of normal fetal adrenal development. These studies suggest that such neuroblastic nodules are remnants of normal developing fetal adrenal tissue, not NB in situ (37–39).

**Gross Pathologic Features**

Neuroblastic tumors may be circumscribed or infiltrative, and most are less than 10 cm in greatest diameter. Those arising within the adrenal gland or posterior mediastinum are more likely to be circumscribed and give the appearance of having a capsule, although NB, GNB, and GN do not typically have capsules. The consistency of NB typically is soft, compared with that of the firmer GNB and GN. The cut surface of specimens may vary from tan to hemorrhagic; necrosis, hemorrhage, and calcification may be detected. The tan areas are usually composed of stroma. Hemorrhagic foci or nodules are often neuroblastic tissue (Fig 5) (33). The consistency and appearance of neuroblastic tumors vary considerably, and areas of tan stroma interposed between areas of hemorrhagic neuroblastic tissue are common. This latter feature may give the tumor a lobular appearance (40,41).

**Staging**

In 1986, an international consensus group devised the International Neuroblastoma Staging System (INSS), based on clinical, radiologic, and surgical features (Table 2). A few specific points regarding staging follow. Tumors that are grossly completely resected and have no nonadherent positive lymph nodes or metastases are stage 1, irrespective of whether they cross the midline. Tumors that invade one side of the neural canal are stage 2 (not stage 3). Tumors that extend across the midline to the contralateral aspect of the vertebral body are stage 3. Marrow involvement in stage 4S is defined as tumor cells representing less than 10% of all marrow cells in the biopsy specimen; when the marrow involvement is such that greater than 10% of all marrow cells are tumor cells, the NB is stage 4, irrespective of patient age. In the unusual case of bilateral tumors, the higher stage tumor takes precedence for patient staging (43).

**Biologic Behavior**

Neuroblastic tumors are remarkable for their varied tumoral biologic behavior. This variability is manifest in their genetic makeup and in the products they may elaborate (eg, catecholamines). Some of these features may be assessed as evidence of maturity; some are used to assist in staging and prognosis. One of the hallmarks of NB and GNB is their propensity to secrete catecholamines. Most often, the catecholamines secreted are vanillylmandelic acid (VMA) and homovanillic acid (HVA). The vast majority (90%–95%) of NB and GNB

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**Table 2**  
**International Neuroblastoma Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically</td>
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<tr>
<td>2A</td>
<td>Unilateral tumor with incomplete gross excision; identifiable ipsilateral nonadherent lymph nodes negative microscopically</td>
</tr>
<tr>
<td>2B</td>
<td>Unilateral tumor with complete or incomplete gross excision; positive ipsilateral nonadherent lymph nodes; identifiable contralateral lymph nodes negative microscopically</td>
</tr>
<tr>
<td>3</td>
<td>Tumor infiltrating across the midline (vertebral column) with or without regional lymph node involvement; or unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral regional lymph node involvement or extension by infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, or other organs (except as defined in stage 4S)</td>
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<tr>
<td>4S</td>
<td>Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin and/or bone marrow (&lt;10% tumor) in infants younger than 1 y</td>
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Source.—Modified from reference 42.
secrete catecholamines, although the tumors rarely cause symptoms of catecholamine excess. Generally, the better differentiated the tumor, the more mature the catecholamine. HVA is secreted as a metabolite of dopamine, and its level may be elevated in more mature NBs and GNBs. In comparison, VMA is a less mature metabolite of epinephrine and norepinephrine. Some centers assess a VMA-to-HVA ratio as an indicator of maturity. Ratios of less than 1 are considered favorable; ratios greater than 1 suggest an immature tumor and therefore a worse prognosis (44,45). Vasoactive intestinal peptide (VIP) may also be secreted by the tumor and may result in watery diarrhea, hypokalemia, and acidosis. It is believed that VIP is elaborated by ganglion cells within the tumor; not surprisingly, VIP-producing tumors tend to be more mature and have a better prognosis (46).

Some genetic features of NB and GNB correlate with biologic behavior. The best known is Myc-N, a proto-oncogene located on the distal end of chromosome arm 2p. When present in multiple copies (especially 10 or more), known as Myc-N amplification, it portends rapid tumor progression and a poor outcome for all patients except those less than 1 year of age and those with unfavorable histologic features according to the Shimada classification (47–49). Thirty percent of all NBs display Myc-N amplification; less than 10% of stages 1 and 2 NBs show Myc-N amplification (50). Recent studies suggest that amplification alone is not the significant feature of the Myc-N oncogene. Rather, expression of the Myc-N protein has been found to correlate with prognosis and aggressive tumor behavior in children older than 1 year. Infants with increased Myc-N expression do not have a worse prognosis, however (51).

Another important genetic feature of NB and GNB is loss of heterozygosity or deletion of the short arm (p) of chromosome 1. It is theorized that there is a tumor suppressor gene on chromosome arm 1p that is deleted in NB (52). Loss of heterozygosity correlates with aggressive tumor behavior (53,54). Gain of chromosome arm 17q is also linked with advanced stage tumors, increased age at diagnosis, Myc-N amplification, and deletions of chromosome arm 1p (55).

Deoxyribonucleic acid (DNA) content of the NB cells is another important prognostic indicator. Cells with normal or near-normal DNA content (a DNA index of 1) are diploid or near-diploid cell lines. These cell lines are associated with aggressive tumor behavior and a worse prognosis. Tumor cells with increased DNA content (DNA index greater than 1, referred to as hyperdiploid) have a better prognosis and display less aggressive tumor behavior (56,57). Some research findings suggest that hyperdiploid NB tumor with normal chromosome arm 1p stimulates Schwannian proliferation within the tumor; this Schwannian proliferation is believed to promote tumoral maturation (58). Hyperdiploid NB with normal chromosome arm 1p are thought likely to mature spontaneously (58).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Neuroblastoma Risk Groups</th>
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<tr>
<td><strong>Risk Group</strong></td>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Low</td>
<td>Stage 1, 2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Stage 4S</td>
</tr>
<tr>
<td></td>
<td>Stage 3 favorable</td>
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<tr>
<td>High</td>
<td>Stage 4</td>
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<tr>
<td></td>
<td>Stage 3 unfavorable</td>
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<td></td>
<td>Stage 4</td>
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<td>Stage 2</td>
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Source.—Modified from reference 31.
* Infants <1 y with localized or regional disease Myc-N amplification are a rare subgroup, and it is not yet well established if the unfavorable implications of Myc-N amplification override the favorable characteristic of age <1 y.
Other tumor features that influence prognosis include CD44, a glycoprotein on the surface of NB cells. Increased levels of CD44 correlate with better prognosis. Elevated serum levels of neuron-specific enolase (>100 ng/mL) and ferritin (>142 ng/mL) indicate a worse prognosis. Expression of TRK-A, a nerve growth factor, correlates with a favorable outcome (59).

By combining the Shimada classification, INSS stage, and some of the risk factors listed above, it is possible to stratify NB and GNB into low-, intermediate-, and high-risk groups. Treatment is based on risk group. Table 3 defines the risk groups and their features (42,60).

**Radiologic Appearances**

Because NB and GNB arise in a variety of locations, they have varied appearances and growth patterns. The radiologic appearance of these tumors is discussed by imaging modality, beginning with plain radiography. Radiographs may show a posterior retroperitoneal, mediastinal, or neck mass (Fig 6). Calcification is evident in at least 30% of NB at plain radiography (Fig 7) (61). Posterior mediastinal tumors may cause spreading or erosion of adjacent ribs, and both retroperitoneal and posterior mediastinal tumors may
Figures 8, 9. Bone metastases from NB. (8) Frontal radiograph of a 2-year-old boy who presented with weight loss shows an ill-defined lucent area in the submetaphyseal region (arrows). (9) Frontal radiograph of a 2 1/2-year-old boy who presented with right hip pain shows a lytic area in the femoral neck (arrowhead) and a patchy area of decreased mineralization in the intertrochanteric and subtrochanteric regions (arrows).

Figure 10. NB in a 2 1/2-year-old girl with an abdominal mass and hypertension. (a) Longitudinal US scan of the left flank reveals a large, heterogeneous mass with multiple anechoic areas, representing hemorrhage or cystic change (arrows). (b) Axial oral and IV contrast-enhanced CT scan through the midabdomen reveals a large left flank mass, with some rounded areas of low attenuation. (c) Photograph of the bisected gross specimen shows a hemorrhagic mass with fluid-filled cavities, which at further inspection proved to be a combination of hemorrhage and cystic change.
cause pedicle erosion from intraspinal extension (62). Metastatic disease may be radiographically manifested as hepatomegaly, lucent submetaphyseal zones (Fig 8), periostitis, and cranial sutural widening (from dural metastases). Skeletal metastases may also appear as focal lucent (occasionally sclerotic) areas (Fig 9) (61,63).

At ultrasonography (US), NB and GNB are heterogeneously echogenic. There may be anechoic areas within the tumor corresponding to hemorrhage or necrosis (Fig 10). Calcification is common and appears as focal echogenic areas or diffuse increased echogenicity (from very fine calcifications); distal acoustic shadowing may or may not be present (61,64). US may help delineate the tumor from adjacent organs such as the kidney, although the tumor may occasionally invade the kidney, making determination of organ of origin difficult. US may also aid in evaluation of other organs such as the liver for evidence of metastases, although this is better accomplished with CT or magnetic resonance (MR) imaging. Doppler US may be used to evaluate flow in encased vessels (63).

CT is the most commonly used imaging modality for assessment of neuroblastic tumors, because it reveals extent of tumor, organ of origin, regional invasion, vascular encasement, adenopathy, and calcification. CT of the chest, abdomen, and pelvis is standard for all newly diagnosed cases. Abdominal and pelvic tumors are usually large and heterogeneous (Fig 11), although small tumors may be homogeneous. Approximately 80%–90% of NBs demonstrate calcification on CT scans (61,63). Low-attenuation areas of necrosis or hemorrhage are frequently noted at CT and may measure up to 4 cm in diameter (61,63, 65). Vascular encasement and compression of the renal vessels, splenic vein, inferior vena cava, aorta, celiac artery, and superior mesenteric artery may occur (Fig 12), although vascular invasion is rare. Renal vessels may be sufficiently compressed to result in hypertension (66). Regional invasion of psoas and paraspinal musculature may occur, and invasion of the neural foramen into the epidural space is also frequent; these are better evaluated at MR imaging, as is regional organ invasion. Adenopathy of the renal hilum, porta hepatis, and retroperitoneum may be seen. Metastatic disease of the liver and lung are readily evaluated with CT. Liver metastases may take two forms: diffuse infiltration (seen in infants with stage 4S disease and sometimes missed at CT

Figure 11. GNB in an 8-year-old boy with a 2-year history of increasing constipation. (a) On an abdominal radiograph obtained after oral and IV contrast enhancement, the bladder is elevated because of a pelvic mass. (b) Axial unenhanced CT scan shows the heterogeneous pelvic mass (a) and the anteriorly displaced bladder (arrow).
because it may uniformly increase the parenchymal attenuation and focal hypoenhancing masses (Fig 13) (63). Lung metastases may appear as discreet nodules or confluent areas of parenchymal consolidation (67). Pleural disease is infrequent. Brain metastases are distinctly unusual but do occur; they may have a variety of appearances including hemorrhagic, solid, and rim-enhancing cystic lesions (Fig 14), all of which are demonstrated by both CT and MR imaging (68–70). A more common intracranial metastatic pattern is dural disease, which may appear as enhancing meninges and meningeal cakes and masses (Fig 15); these may cause regional mass effect on underlying brain tissue and may extend into sutures, resulting in sutural widening (Fig 16) (71). An unusual appearance exists for metastatic disease to the sphenoid bone with intraorbital extension; in these cases, a red-bluish discoloration in the

**Figure 12.** NB in a 2-year-old girl with an abdominal mass. Axial IV contrast-enhanced CT scan shows a mass arising in the retroperitoneum and encasing the aorta (straight black arrow) and left renal artery (arrowheads). The inferior vena cava is displaced anteriorly (curved arrow), and the left kidney (white arrow) is pushed laterally and rotated.

**Figure 13.** Massive liver metastases (Pepper syndrome) in a 2-month-old infant with NB. (a) Axial IV contrast-enhanced CT scan shows multiple areas of low attenuation throughout the liver. There is also a heterogeneous mass in the right flank and crossing to the left flank, which was the adrenal primary tumor (arrows). (b) Photograph of the bisected liver at autopsy shows diffuse parenchymal replacement with multiple metastatic nodules.
orbits is seen and may be mistaken for child abuse (63).

At MR imaging, NB and GNB are typically heterogeneous, variably enhancing, and of relatively low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Figs 17, 18). Calcification may be difficult to detect at MR imaging; signal voids may be apparent. Hemorrhagic areas may manifest as areas of high signal intensity on T1-weighted images, and cystic change may appear bright on T2-weighted images (72). Because of excellent tissue discrimination and multiplanar imaging, MR imaging is superior to CT for determination of the organ of

Figure 14. Brain metastases from NB in a 19-month-old child with emesis. Axial IV contrast-enhanced CT scan of the brain reveals a rim-enhancing area of low attenuation in the right frontoparietal region, resulting in subfalcial herniation. High-attenuation dural metastases are present in both frontal regions (arrow).

Figure 15. Meningeal and skull metastases in a 9-month-old girl with proptosis and an abdominal mass. Axial CT scan through the anterior skull shows a bilateral soft-tissue mass along the inner table of the skull (black arrows), with extension into the coronal sutures bilaterally (white arrows).

Figure 16. Skull metastases in a 14-month-old boy with a small primary NB. (a) Axial oral and IV contrast-enhanced CT scan of the upper abdomen shows a poorly defined, heterogeneous, low-attenuation mass anterior to the left kidney (*). (b) Axial CT scan of the skull shows destruction and expansion of the right parietal region (arrows).
Figure 17. NB arising from the organ of Zuckerkandl in a 5-month-old girl with a right lower quadrant mass. (a) Sagittal T1-weighted MR image of the abdomen shows a low-signal-intensity mass arising anterior to the lower lumbar spine (s). (b) Axial T1-weighted MR image shows a low-signal-intensity mass growing between the right psoas muscle (s) and the spine and beginning to invade the right first sacral foramen (arrow). (c) On an axial T2-weighted MR image obtained at the same level as b, the mass is high signal intensity.
Figure 18. GNB in a 15-year-old girl who presented with a cough. (a) Frontal chest radiograph demonstrates an oblong, left-sided posterior mediastinal mass (arrow). (b) Lateral chest radiograph helps confirm the posterior mediastinal mass (arrows). (c) Axial IV contrast-enhanced CT scan through the lower thorax depicts the left-sided posterior mediastinal mass (straight arrow), with a small focus of calcification. The mass encircles the aorta (curved arrow). (d) Coronal T1-weighted MR image of the posterior thorax better depicts the longitudinal extent of the paraspinal mass, which is well circumscribed.
Figure 19. NB in a 9-month-old girl who continually leaned to one side. (a) Axial unenhanced CT scan through the upper abdomen shows a posterior left-sided mass with calcification that extends into the costovertebral junction (arrow) and crosses to the right side of the patient. (b) Coronal T1-weighted MR image through the posterior thorax helps confirm the large posterior mediastinal and retroperitoneal mass extending from left to right. (c) Coronal T1-weighted IV contrast-enhanced MR image shows heterogeneous enhancement of the mass. (d) Axial T1-weighted IV contrast-enhanced MR image shows neural foraminal invasion (straight arrow), with marked thecal sac (curved arrow) displacement toward the right of the patient. The paraspinal musculature is also invaded (arrowhead).
origin and regional invasion (63). MR imaging is the preferred modality for investigating intraspinal extension of primary tumor (the so-called dumbbell NB, seen in 10% of abdominal NBs, 28% of thoracic NBs, and occasionally in cervical NBs) (Fig 19) (73). MR imaging should be performed on any patient with a paraspinal tumor (62). Epidural tumor is well demonstrated on coronal, sagittal, and axial MR images; it may be shown to displace the spinal cord or nerve roots and spread extensively up and down the epidural space (Fig 20) (74). Another advantage of MR imaging is its ability to depict marrow disease, which appears as areas of low signal intensity on T1-weighted images and high areas on T2-weighted images. This MR imaging appearance has been shown to correlate well with results of bone marrow biopsy (72,75,76). Finally, MR imaging is superior to CT in the detection of diffuse hepatic metastases in infants with stage 4S disease; these metastases manifest as areas of high signal intensity on T2-weighted images (63).

Figure 20. GN in an 8-year-old boy with long-standing right leg and hip pain. (a) Lateral radiograph of the lumbar spine shows posterior scalloping of the first through fourth lumbar vertebral bodies (arrows). (b) Sagittal T2-weighted MR image of the lumbar spine reveals an enhancing intraspinal mass invading the first through third lumbar vertebral bodies (arrows). (c) Axial T1-weighted IV contrast-enhanced MR image through the second lumbar vertebra shows the mass filling the spinal canal (straight arrows), invading the vertebral body (*), and extending laterally to the right paravertebral area (curved arrow). (d) Axial CT scan of the second lumbar vertebra shows replacement of bone with tumor. The area of replacement has sclerotic margins, suggesting it is a remodeling from invasion of a slow-growing tumor.
labeled to iodine-123, referred to as MIBG) or a somatostatin analog (pentetreotide labeled to indium-111). Scintigraphy performed with both of these radiopharmaceuticals shows uptake in primary tumor and metastases (Figs 21, 22). MIBG is taken up by catecholamine-producing tumors, so NB, GNB, GN, pheochromocytoma, carcinoid tumor, and medullary thyroid cancer may all take up this radiotracer. Although 90%–95% of NB and GNB secrete catecholamines, only about 70% of NB and GNB are MIBG positive; one of the drawbacks of MIBG imaging is that a considerable minority of tumors (30%) are not MIBG avid. MIBG scintigraphy is highly sensitive (88%) and specific (99%) for sympathetic tissue such as those found in NB, GNB, GN, carcinoid, and pheochromocytoma (but it does not enable discrimination among these tumors) (77). When MIBG-avid disease is evaluated and results are positive, MIBG scintigraphy gives an excellent map of disease (both primary and metastatic), although it does not allow marrow to be distinguished from cortical disease, which may be important for staging (78,79). Because approximately 30% of NBs and GNBs are MIBG negative, normal results do not exclude the diagnosis (80). The use of MIBG scintigraphy in routine patient assessment is controversial; a recent study showed that MIBG results did not alter staging or treatment for any of the patients studied. In the same study, recurrent NB failed to show uptake in 50% of patients with recurrence, results that suggest that MIBG scintigraphy is an unreliable indicator of recurrent disease (81). In-111 pentetreotide scintigraphy may also demonstrate neuroblastic tumors, although it does not appear to be superior to MIBG scintigraphy. Some tumors are not pentetreotide-avid, and pentetreotide uptake is not specific for neuroblastic tumors (82).

A more commonly performed scintigraphic examination is technetium-99m MDP scintigraphy, which is done for evaluation of bone disease (of both cortex and marrow; one of the limitations of the technique is its inability to discriminate between the two). Tc-99m MDP scintigraphy is initially performed on all patients with NB or GNB to assess metastatic burden. Metastases may appear as focal areas of increased uptake or as increased uptake at the metaphysis (Fig 22) (which may be incorrectly interpreted as normal childhood physeal uptake). Tc-99m MDP scans are more sensitive than plain radiographs in the detection of bone metastases from NB (83,84). The primary tumor may be Tc-99m MDP avid, and uptake has been demonstrated in as much as 74% of primary tumors and may also be seen in
metastases to the lung and liver (Fig 23) (85–87). The increased uptake does not correlate with tumor calcification but appears related to calcium metabolism in the tumor and its metastases (87).

**Treatment and Prognosis**

The most important predictors of outcome are age of the patient at diagnosis and INSS disease stage. Children with stages 1, 2, and 4S tumors have a 3-year event-free survival rate of 75%–90%. Children less than 1 year of age with stages 3 and 4 tumors have a 1-year event-free survival rate of 80%–90% and 60%–75%, respectively. Children older than 1 year with INSS stages 3 and 4 tumors have a 3-year event-free survival rate of 50% and 15%, respectively (88).

Children with low- or intermediate-risk tumors have a relatively good prognosis (Table 3). Low-risk tumors are treated with surgery only; in the unlikely event of recurrence, chemotherapy and additional surgery may be performed. Intermediate-risk tumors are surgically removed and then treated with chemotherapy. High-risk tumors are substantially more aggressive, and these patients fare considerably worse. Treatment for high-risk tumors consists of surgery and chemotherapy, with bone marrow transplantation in some cases. Even with aggressive treatment, however, the 3-year event-free survival rate for these patients is less than 15% (14). Improved 2-year survival
after bone marrow transplantation has been documented in some studies; prolonged survival is currently being assessed (89).

Complete macroscopic tumor removal at surgery (at the time of initial surgery or at subsequent exploration) influences the prognosis of some, but not all, stages. It improves survival for patients with stage 3 disease (90) (the exception to this is the child less than 1 year old who has a stage 3 tumor with favorable biologic behavior; that is, normal Myc-N expression, favorable histologic characteristics, and DNA index > 1) (91). Survival is not influenced by the timing of the surgery. Stage 3 tumors are large and may be difficult to resect completely. Because chemotherapy may cause changes in the tumor that may facilitate resection, and because timing does not affect survival, it may be advisable to perform curative surgery after chemotherapy for tumors that appear difficult to completely resect (13).

Surgery for stage 4 tumors is controversial; some studies show that gross complete resection conveys minimal increased survival (92). Chemotherapy appears to be a more potent weapon against stage 4 tumors, particularly against metastatic disease (13). Survival of patients with stage 4S tumors is unchanged by surgery; in these patients, surgery is primarily used for diagnosis and to relieve symptoms from tumor burden (13,93).

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Radiation therapy is used in patients with NB and positive intracavitary lymph nodes. Event-free survival is significantly improved by using both chemotherapy and radiation therapy in these patients. In 76% of patients with stage C disease (Pediatric Oncology Group classification: complete resection of primary tumor but with residual intracavitary lymph nodes) treated with chemotherapy and radiation therapy, a complete response was achieved, compared with 46% for patients treated with chemotherapy alone. Event-free survival and overall survival were also significantly higher in this group than in the chemotherapy only group (94).

Metastases
Bone is the most common site of metastasis, and bone metastases are present in up to two-thirds of patients at the time of diagnosis. Metastases are demonstrated at Tc-99m MDP imaging, which is a standard part of the imaging evaluation at presentation and follow-up.

Bone marrow metastases are found in 40%–60% of patients at presentation. The presence of marrow disease is best assessed with marrow aspiration or biopsy. Two patterns of marrow disease have been observed: diffuse and nodular. The nodular form corresponds to nodular marrow disease as seen in biopsy specimens and has a better prognosis, with a lower frequency of coexistent cortical metastases and excellent response to chemotherapy. The diffuse form is almost always seen with cortical metastases, is less responsive to chemotherapy, and conveys a worse prognosis (95).

Hepatic metastases are also common. Like marrow disease, liver disease may occur in nodular or diffuse form. Massive liver metastases in infants have been called Pepper syndrome (Fig 13); occasionally, the intraabdominal pressure is so severe that a mesh abdominal wall insert is needed to allow expansion and relieve pressure. Skin metastases are relatively common, especially in children younger than 1 year, and may appear as dark purple or blue masses, resembling blueberries (this appearance has been given the eponym blueberry muffin syndrome) (Fig 24). Other less common areas of metastases include the dura mater, lung, and brain, although virtually every location and organ has been documented as a site of NB metastases (68–71,96,97).

Over the past several decades, there has been an increase in the frequency of aggressive and unusual metastatic disease; it is believed that this is a result of increased survival and more aggressive treatment regimens (70).
Congenital NB

NB is the most common malignancy in the first month of life and accounts for 30%–50% of all malignant tumors at this age. NB occurring in the perinatal time frame may be divided into fetal and neonatal NB, based on the patient’s age at presentation. Both have very good prognoses but differ somewhat in their patterns of metastatic spread and organ of origin. Neonatal NB has an adrenal origin in 45% of patients. Like older children with NB, about 60% of neonates with NB have metastases at the time of diagnosis; metastases are most often found in the liver, bone cortex, marrow, and skin, although any site may be affected. Neonatal NB usually has favorable tumor biologic behavior, and the survival rate is greater than 90%. Death is most often caused by respiratory insufficiency from massive hepatic metastases (43).

Fetal NB may be discovered at obstetric US and has been discovered as early as 19 weeks, although the mean age at discovery is 36 weeks (Fig 25). Fetal NB is almost always (90% of cases) adrenal in origin and is usually stage 1, 2, or 4S. Fetal NB is associated with hepatic and, less commonly, marrow metastases (cortical metastases rarely, if ever, occur). Placental metastases are typically confined to the placental vessels, although they may rarely be discovered in the placental parenchyma. Fetal hydrops may result from placental vascular metastases, and they are theorized to cause maternal preeclampsia from catecholamine secretion (42,98,99). Fetal NB has an almost universally good outcome, and a conservative approach to tumor management in these patients is being advocated by some (11,100).

Regression and Maturation of Neuroblastic Tumors

NB and GNB may both undergo spontaneous regression and maturation to more mature neuroblastic tumors. Regression of known NB most often occurs in stage 4S tumors and takes 6–12 months on average. Regression is also well known in stage 1 and 2 tumors; overall, it probably occurs in 1%–2% of tumors (101). The cause of regression is unknown; it is theorized that apoptosis (programmed cell death) is possible in every neuroblastic tumor but that it is inactivated by...
genetic or other factors in malignant tumors (89). Maturation also occurs; how often these tumors mature is unknown (102).

Screening for Neuroblastic Tumors
Because approximately 90% of NBs and GNBs secrete VMA and HVA, interest in childhood screening via urine assay grew in hopes that earlier detection would lead to improved cure rates. Screening began in Japan in 1973 in 6-month-old infants. Unfortunately, epidemiologic analysis showed that the incidence of tumor in older children did not change, that the incidence of stage 1 tumors dramatically increased, and that the tumors discovered at screening were of low stage and favorable histologic characteristics. These results suggest that the tumors discovered at urinary screening are those likely to remain occult, to regress, or to mature (7). Similar studies and results have come from Quebec (103). Screening for NB in infancy does not appear to decrease the incidence of advanced stage disease in older children nor does it improve survival in younger children with aggressive disease (7). The impact of screening on prognosis in children 1 year of age and older is unknown (104).

Ganglioneuroma
GN is a rare tumor composed entirely of ganglion cells and Schwannian stroma; by definition, GN does not contain neuroblasts, intermediate cells, or mitotic figures (105). Because NB and GNB may mature to GN, certainly some GNs arise from NB and GNB. GNs are also documented to have arisen in NBs that were treated with chemotherapy, and they may arise de novo (56). The relative frequency of spontaneously occurring GN, GN arising from maturing NB and GNB, and GN arising from treated NB and GNB is unknown. There are rare reports of metastatic GN. It is believed that these tumors represent metastases of NB or GNB that have subsequently matured to GN; these patients have an excellent prognosis (105,106).

GN occurs in older patients; the median age at diagnosis is approximately 7 years, with different studies reporting a median age of 5.5 years, 7 years, and over 10 years (105,107–109). There is a slight female predominance, ranging from 1.13:1 to 1.5:1 (105,107). It has been estimated that the ratio of NB to GN is approximately 6:1 to 10:1 (110,111). GN occurs in the same anatomic locations as NB and GNB, although at different frequencies. The most common locations are the posterior mediastinum (41.5% of cases), retroperitoneum (37.5%), adrenal gland (21%), and neck (8%). Unusual sites include the spermatic cord, heart, bone, and intestine (108,112–114).

GN most often manifests as an asymptomatic mass discovered on a routine radiographic study, such as a chest radiograph. Sometimes GN causes local mass effect and patients present with cough, abdominal pain, or dyspnea (105). In rare cases, GN secretes sufficient quantities of VMA or HVA to manifest with flushing and other symptoms of catecholamine excess (107). Catecholamine production by GN was previously believed to be unusual, because it was theorized that more mature tumors have more mature biologic behavior. However, in the largest series of GNs to date (49 cases), 37% of the patients had elevated VMA or HVA levels (105). Other reports confirm these findings (81,110,115). Thus, although elevated catecholamine production by NB and GNB occurs in 90%–95% of patients, elevated levels may also be seen in GN and therefore do not aid in discriminating among NB, GNB, and GN (105). GN is staged with the INSS.

Pathologic Features
The histologic characteristics and gross pathologic features of neuroblastic tumors were previously described in detail. Briefly, GN is composed of ganglion cells (some of which may be immature) and mature Schwann cells (mature stroma) (Fig 3). Cellular atypia, mitotic activity, and necrosis are not features of GN. The presence of neuroblasts indicates that the tumor is a GNB or NB and excludes GN. GN averages 8 cm in diameter and may appear encapsulated, although a true capsule is infrequent. The tumors are firm, are white to yellow in color, and may appear trabeculated or whorled (Fig 26) (1,35).
Radiologic Appearances

Although GN tends to be relatively homogeneous, the imaging characteristics of GN are similar to those of GNB and NB; hence, they cannot be discriminated at imaging evaluation save for the presence of metastases, which are quite rare in GN. Plain radiographs typically show a posterior mediastinal mass, which may cause rib spreading and foraminal erosion. A mass may also be noted in the retroperitoneum, pelvis, or neck. US reveals a homogeneous, hypoechoic mass with well-defined borders. At CT, calcifications are seen in approximately 42%–60% of GNs; calcification is typically fine and speckled but may be coarse (116–119). GNs are low attenuation and homogeneous on unenhanced CT scans and demonstrate slight to moderate enhancement, which may be heterogeneous or homogeneous (116–119).

At MR imaging, GN has low signal intensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images. Several reports indicate that relatively high, heterogeneous signal intensity on T2-weighted images correlates with GN; the appearance is presumed to be caused by a combination of myxoid material and relatively low amounts of ganglion cells (119–121). MR imaging enhancement varies from mild to marked; early enhancement at dynamic MR imaging is not typically seen in GN. GN does appear to accumulate contrast material over time, however, so delayed images may show increasing enhancement (116,119,121). MR imaging is the preferred modality for detection of intraspinal extension (Fig 20) (116).

GN, like GNB and NB, may accumulate MIBG; this has been reported in up to 57% of GNs in one study (105). In this study, most of the tumors that were MIBG-avid also produced increased amounts of catecholamines. Other reports of MIBG-positive GNs confirm that MIBG uptake does not allow differentiation among NB, GNB, and GN (81,105,106,110,122).

Treatment and Prognosis

Treatment consists of complete surgical resection when possible. Complete resection ensures thorough sampling of the tumor, such that a confident diagnosis of GN can be made. Local recurrence has been reported, so periodic radiologic surveillance is performed after resection (105,123).

Conclusions

The neuroblastic tumors NB, GNB, and GN are a spectrum of sympathetic tissue tumors ranging from the very immature and malignant NB to the mature and benign GN. The great variance in biologic behavior of NB, GNB, and GN indicates that many factors influence the prognosis for a patient with a neuroblastic tumor. It is the interplay of histologic maturity, genetic composition, and patient features that make NB, GNB, and GN an enigmatic group of tumors. Although GN tends to be a more homogeneous tumor than NB or GNB, it is not possible at imaging evaluation to discriminate among these three tumors.

References


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