0094–0143/00 $15.00 + .00

NEUROBLASTOMA

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Neuroblastoma is a malignant tumor of neural crest origin that may arise anywhere along the sympathetic ganglia or within the adrenal medulla. The median age of diagnosis is 2 years; however, occurrence is skewed toward younger children, with nearly 35% of cases occurring under 1 year of age and the remainder under 10 years of age. Seventy-five percent of neuroblastomas originate within the abdomen or pelvis, and half of these occur within the adrenal medulla, whereas 20% originate within the posterior mediastinum and 5% within the neck.

The overall incidence of neuroblastoma in the unscreened population is 1 case per 10,000 persons, with approximately 525 newly diagnosed cases in the United States each year. In Japan and Quebec Province, where the population is screened at 3 weeks and 6 months of age using a urinary assay for urinary catecholamine homovanillic acid (HVA) and vanillylmandelic acid (VMA) produced by 85% to 90% of neuroblastomas, the incidence is closer to 1 case per 7000 individuals.[41, 50]

Neuroblastoma is an enigmatic tumor capable of rapid progression in some children and spontaneous resolution in other children usually less than 1 year of age.[3] Twenty-five percent of cases present with a solitary mass that may be cured by surgical therapy, whereas nearly 60% of cases present with disseminated disease involving most commonly lymph nodes, liver, bone, and bone marrow. In this latter group of children, survival is poor, exemplified by the fact that although neuroblastoma accounts for only 10% of all childhood concerns, it is responsible for 15% of all cancer-related deaths in the pediatric age group.[31]

This wide range of clinical behavior reflects the considerable biologic diversity of this tumor. Although progress in the treatment of neuroblastoma has been painstakingly slow, recent advances in molecular genetics and staging have increased understanding of the biologic determinants of the disease and the resultant clinical subsets.[7]

CLINICAL PRESENTATION

The most common clinical presentation of neuroblastoma is a fixed lobular mass extending from the flank toward the midline of the abdomen. Abdominal distention, anorexia, and weight loss may result from mass effect, and, occasionally, patients may experience acute onset of abdominal pain owing to hemorrhage within the lesion. Hypertension may occur owing to tumor production of catecholamine metabolites or renal vascular compression. Thoracic tumors are usually detected by chest roentgenograms taken to evaluate dyspnea or upper respiratory tract symptoms. Neck masses are usually hard and fixed and may be associated with Horner's syndrome or tracheal compression. Paraspinal tumors may occur anywhere along the spinal column where they may invade the intravertebral foramina and produce cord

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compression; consequently, these "dumbbell tumors" may result in bladder and anal sphincter dysfunction, disturbance of gait, and acute onset of paraplegia.

Metastatic disease can present in a variety of ways. Neuroblastoma tends to metastasize to cortical bone, especially skull, facial bones, pelvis, and proximal long bones. Patients may present with local swelling and tenderness, pain, lump, or a refusal to walk. Periorbital metastasis may cause proptosis or orbital ecchymosis ("raccoon eyes"). In younger children, marrow replacement by neuroblastoma cells may cause anemia and weakness. In infants, metastases to the liver may rapidly expand, causing massive hepatomegaly, gastrointestinal dysfunction, and respiratory distress requiring mechanical ventilation and surgical decompression.[29]

Approximately 2% of children with neuroblastoma present with acute cerebellar atrophy characterized by truncal or appendicular ataxia and involuntary fluttering of the eyes (opsoclonus) and muscle jerking (myoclonus) of central origin,[2] otherwise known as "dancing eyes and dancing feet syndrome." This disorder is usually associated with a small, slow-growing tumor located in the chest in 50% of cases. It is estimated that 50% of infants and children with this syndrome have neuroblastomas or ganglioneuroblastomas requiring a full evaluation. Other causes of this syndrome include encephalitis, demyelinating disorders, and brain tumors. The cause of this syndrome is unknown but is theorized to be either a peptide produced by the tumor or immunologic cross reactivity between the tumor and cerebellar neurons.[32]

Rarely, neuroblastoma may be associated with other disorders of neural crest cells, such as Hirschsprung's disease (colonic aganglionosis) or central hypoventilation syndrome (Ondine's curse). It has also been reported to occur in association with neurofibromatosis type I, Beckwith-Wiedemann syndrome, and DiGeorge syndrome.[4]

DIAGNOSIS AND STAGING

A suspicion of neuroblastoma based on history and physical examination should lead to a complete evaluation that is progressively invasive. Initial laboratory studies should include a complete blood count to identify anemia or thrombocytopenia suggestive of bone marrow invasion. Assays for the spot urinary catecholamine metabolites HVA, VMA, and urine or serum dopamine should be performed for several reasons. Elevated VMA and HVA are diagnostic of neuroblastoma if elevated 2.5 standard deviations above the mean per milligram creatinine in a patient with a positive bone marrow aspirate demonstrating small round blue cells with hyperchromatic nuclei. VMA and HVA levels fall to normal when a tumor is surgically resected, and thus tumor recurrence or progression may be followed by comparing VMA and HVA with baseline levels. VMA levels tend to be relatively higher than HVA levels in children less than 1 year of age and in children with more favorable outcome; consequently, an elevated VMA/HVA ratio may be used as a favorable prognostic indicator. Other tumor markers may be used to prognosticate and to follow the progression of disease. Serum neuron-specific enolase greater than 200 ng/mL, serum ferritin greater than 143 ng/mL, and lactic dehydrogenase greater than 1500 u all signify a poorer prognosis when elevated in comparison with normal or baseline levels.

Assessment of the primary tumor should be performed by CT scan or MR imaging with three-dimensional measurements (Figs. 1, 2). CT scan and MR imaging can also be performed to evaluate nonpalpable lymphadenopathy. Anteroposterior and lateral chest radiographs are sufficient for primary tumors located below the diaphragm (Fig. 3); however, if the chest radiograph is positive or if an abdominal mass or lymph nodes extend into the chest, chest CT or MR imaging should be performed. A newer modality, meta-iodobenzyl guanidine (MIBG) scintigraphy with iodine 131 or iodine 123 is useful in distinguishing residual active tumor from masses composed of scar tissue. The radioactive iodine-guanine complex is actively absorbed by neuroblastoma cells in nearly 80% of tumors.[24]

Because metastatic neuroblastoma has a predilection for cortical bone and bone marrow, a technetium 99 bone scan is an essential part of the initial evaluation. Plain radiographs should be obtained of positive lesions. An MIBG scan using iodine 123 is also a sensitive test for bone marrow metastases. Bone scanning in children less than 1 year of age may show so much activity that it is difficult to detect smaller lesions. For this reason, it is recommended that skeletal surveys be performed in these patients instead of, or

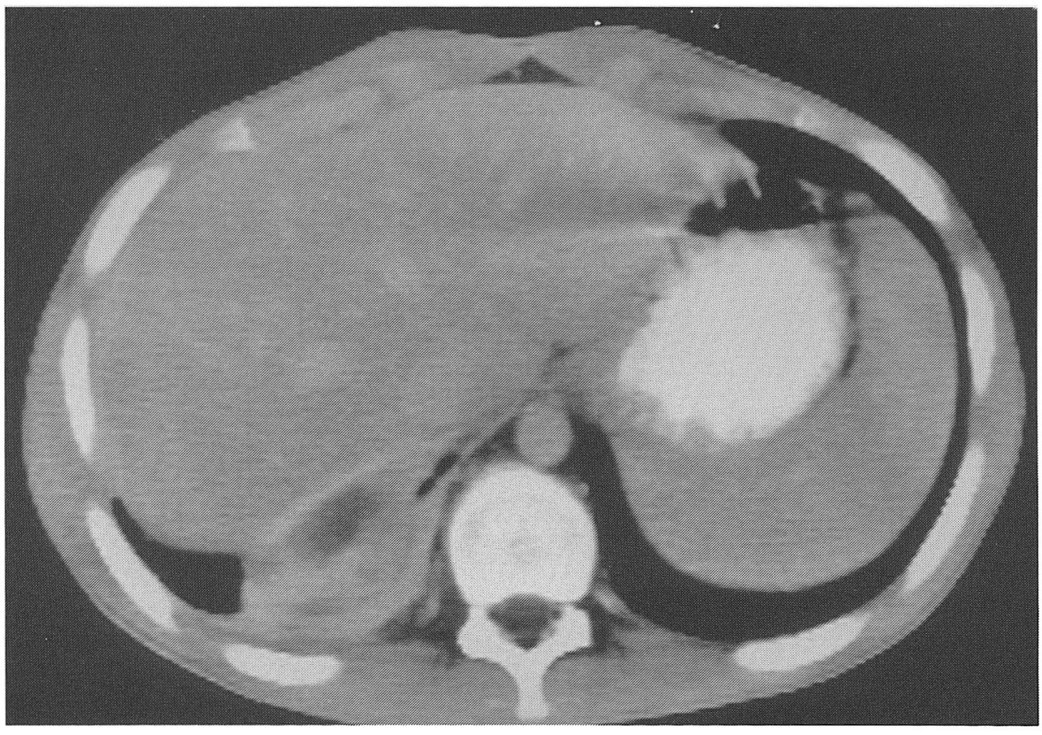

Figure 1. Computed tomography (CT) scan of a right adrenal primary neuroblastoma in an 18-month-old boy with opsoclonus myoclonus.

in addition to, a technetium 99 bone scan.[23] Bilateral posterior iliac crest marrow aspirates and core bone marrow biopsies containing at least 1 cm of marrow should also be obtained, but only a single positive site is required to document bone marrow involvement. A positive marrow by conventional hematoxylin and eosin technique confirms the diagnosis of neuroblastoma in the presence of elevated spot urine catecholamine levels, and this situation is the only circumstance in which a biopsy is not required to establish the diagnosis of neuroblastoma. Newer immunocytologic techniques are more sensitive than the conventional hematoxylin and eosin technique and are even capable of identifying

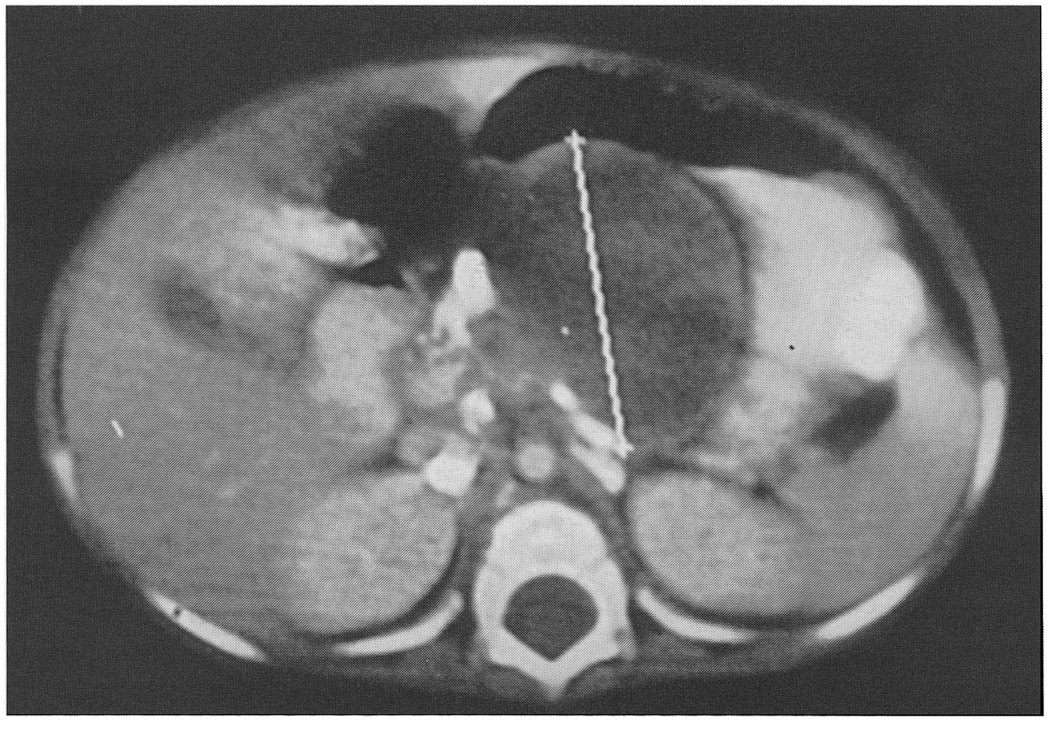

Figure 2. Stage III neuroblastoma rising from retroperitoneum with involvement from the vena cava and mesenteric vessels.

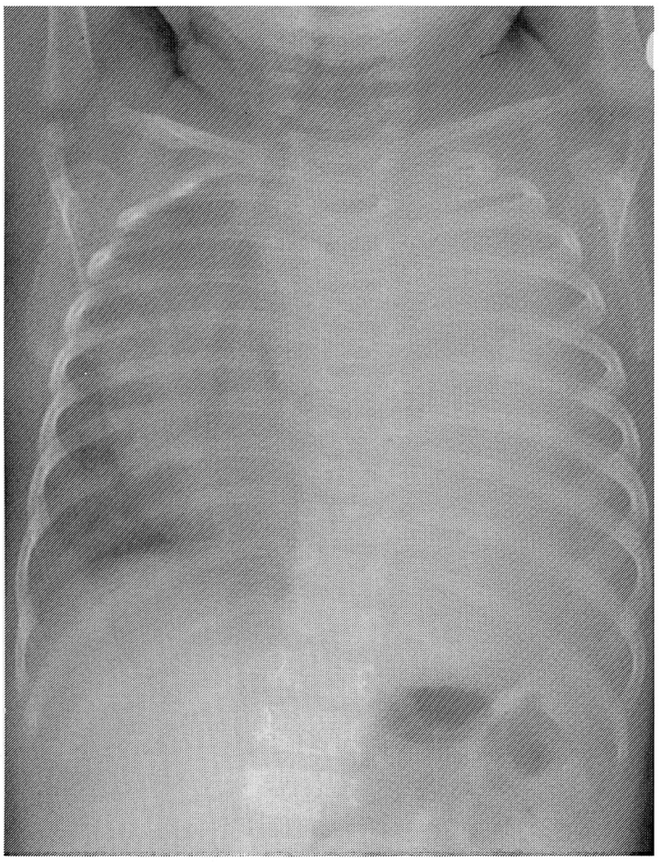

Figure 3. Chest radiograph of a large thoracic neuroblastoma in a 9-month-old girl with tracheal compression.

tumor cells in the marrow of patients with localized tumors; however, these techniques are not uniformly available and are not incorporated into current staging systems.

In a patient in whom the marrow is negative, a biopsy must be performed to establish the diagnosis of neuroblastoma. In addition, biopsy has the advantage of providing tissue for cytogenetic studies, which are of great prognostic value. Biopsy may be accomplished in several ways, including complete or partial tumor excision and open or core-needle biopsy. Surgical exploration is advisable if the primary tumor seems resectable based on imaging studies because it may facilitate diagnosis, staging, and treatment. If on surgical exploration it is perceived that less than 50% of the tumor can be safely removed, biopsy and lymph node sampling alone are warranted. If the tumor seems unresectable by imaging studies, ultrasonographic or laparoscopic-guided, core-needle biopsy should be performed. There is a discordance between imaging studies and surgical exploration approaching 38% such that tumors are downstaged at surgery nearly half the time,[33] thus surgical exploration should be employed early in the course of management if there is any suggestion of resectability based on imaging studies.

Several staging systems have been developed to classify the extent of disease and to organize the therapeutic approach to neuroblastoma. Each system (Table 1) has its strengths, but various differences have made it difficult to compare the results of clinical and biologic studies. The Evans (CCG) and St. Jude (POG) systems include similar categories for localized (Evans stage I and St. Jude stage D) and disseminated disease (Evans stage IV and St. Jude stage D). In contrast, there are significant differences between Evans stage II and III and St. Jude stage B and C. For example, the Evans system emphasizes the importance of "crossing the midline" but does not distinguish between intracavitary lymph nodes that are attached to or resected in continuity with the primary tumor and nodes that are nonadherent or distant. Furthermore, the Evans system does not require pathologic assessment of lymph nodes. In contrast, the St. Jude system clearly distinguishes between resectable and unresectable primary tumor and between adherent and distant lymph nodes but does not take into account whether the tumor crosses the midline or whether there is contralateral lymph node involvement.

These differences are completely resolved by the International Staging System,[8, 9] which has supplanted the others. This system represents a major advance in that it clearly stratifies tumors that are completely excised from tumors incompletely excised, unilateral tumors from those that cross the midline, and tumors with histologically positive lymph nodes from tumors with histologically negative lymph nodes.

PATHOLOGY

Grossly, neuroblastoma presents as a lobular fleshy tumor that infiltrates and surrounds retroperitoneal strictures. The tumor is friable, hemorrhagic, and has poorly defined margins. Microscopically, the tumor is composed of uniform small round blue cells with hyperchromatic nuclei and little cytoplasm. Microcalcification is present in 50% of tumors, and the cells typically form Homer Wright pseudorosettes with eosinophilic fibular material in the interstitial space. Some tumors may be composed of a mix of small cells and more differentiated ganglion cells classified as

Table 1. COMPARISON OF THE EVANS, ST. JUDE, AND INTERNATIONAL STAGING SYSTEM CLASSIFICATIONS

Evans System (CCG)	St. Jude System (POG)	International Staging System
Stage I. Tumor confined to the organ or structure of origin	Stage A. Complete gross resection of the primary tumor, with or without microscopic residual disease: intracavitary lymph nodes not adhered to the primary tumor histologically negative; possible positive nodes adhered to the surface of or within the primary; liver free of tumor.	Stage 1. Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable tumor histologically free of ipsilateral and contralateral lymph nodes microscopically negative
Stage II. Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline; possible involvement of regional lymph nodes on the ipsilateral side	Stage B. Grossly unresected primary tumor; nodes and liver the same as in stage A	Stage 2A. Unilateral tumor with incomplete gross excision, identifiable ipsilateral and contralateral lymph nodes microscopically negative Stage 2B. Unilateral tumor with complete or incomplete gross excision, with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes microscopically negative
Stage III. Tumor extending in continuity beyond the midline; possible bilateral involvement of regional lymph nodes	Stage C. Complete resection of primary; intracavitary nodes not adhered to primary histologically positive for tumor; liver as in stage A	Stage 3. Tumor infiltrating across the midline with or without regional lymph node involvement; or, midline tumor with bilateral lymph node involvement
Stage IV. Remote disease involving the skeleton, bone marrow, soft tissue, and distant lymph node groups	Stage D. Dissemination of disease beyond intracavitary nodes (i.e., extracavitary nodes, liver, skin, bone marrow, bone)	Stage 4. Dissemination of tumor to bone, bone marrow, liver, distant lymph nodes, and/or other organs (except as defined in stage 4S)
Stage IV-S. As defined in stage I or II, except for the presence of remote disease confined to the liver, skin, or bone marrow (without cortical bone metastases)	Stage DS. Infants <1 year of age with Evans stage IV-S disease	Stage 4S. Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin, and/or bone marrow

ganglioneuroblastoma, or ganglion cells alone classified as ganglioneuroma. These tumors demonstrate progressively controlled growth with increasingly benign clinical behavior, and maturation of neuroblastoma through various stages to benign ganglioneuroma has been well documented.[3, 21]

Neuroblastoma can be distinguished from other small round blue-cell tumors such as extraosseous Ewing's and rhabdomyosarcoma by electron microscopy and immunohistochemistry. Occasionally, it may be difficult to distinguish neuroblastoma from primitive neuroectodermal tumor (PNET), which is a neural crest tumor that arises from peripheral nerves. Similar to neuroblastoma, this small blue round-cell tumor contains rosette formations and is neuron-specific enolase positive. PNET may originate anywhere in the body, including the adrenal gland. Unlike neuroblastoma, which is B_2 microglobulin negative, 92% of PNET tumors are B_2 microglobulin positive.[25] Neuroblastoma and PNET tumors can also be differentiated by proto-oncogene expression,[30, 48] cytogenetics, and the activity of neurotransmitter biosynthetic enzymes.[48]

A histologic grading system developed by Shimada and co-workers[43] uses the presence or absence of schwannian stroma, the degree of differentiation, and the mitotic karyorrhexis index to predict a favorable versus unfavorable outcome. This system is a powerful prognostic tool as evidenced by the results of one study in which the 5-year survival of evenly matched Evans stage I, II, III patients was stratified by Shimada criteria. The survival rate was 95% for patients with favorable histology versus 35% for patients with unfavorable histology.[37] In that study, tumors with unfavorable histology were more frequently unresectable and displayed more aggressive clinical behavior than the tumors with favorable histology. The reasons for this different

behavior are unknown, but unfavorable histology is strongly associated with amplification of the N-*myc* oncogene.[44]

CYTOGENETICS

Genetic studies provide important prognostic information that may affect the treatment of neuroblastoma. Amplification of the N-*myc* oncogene located on the distal short arm of chromosome 2 is associated with rapid tumor progression and poor prognosis.[10] N-*myc* amplification seems to be an intrinsic property of some neuroblastoma cell lines that does not change with treatment. It exerts its effect by controlling the expression of cellular genes that regulate cell growth and differentiation. Nevertheless, it is not uniformly predictive because 20% of patients with N-*myc* amplification and metastatic disease are long-term survivors and 20% of patients without N-*myc* amplification have recurrence and progression of tumors.[6, 15]

Another cytogenetic abnormality that is highly predictive of a poor outcome is deletion or loss of heterozygosity of chromosome 1p.[18] Studies have shown a direct relation between 1p deletion and 17q gain, which is often the result of an unbalanced translocation between the two sites.[18, 40] Recent analysis of 313 patients with neuroblastoma revealed a 17q gain in 54%, 1p deletion in 47%, and N-*myc* amplification in 30% of the patients tested.[6] The gain of 17q strongly correlated with 1p deletion, N-*myc* amplification, and disseminated disease. The overall 5-year survival rate was 86% in patients with normal 17q versus 31% in patients with 17q gain. In patients with 1p deletion, N-*myc* amplification, and normal 17q, the rate was 67% versus 22% in patients with 1p deletion, N-*myc* amplification, and 17q gain. Interestingly, N-*myc* amplification did not occur in any tumor without concurrent 17q gain, 1p deletion, or both, suggesting that N-*myc* amplification is a later event in the sequence of genetic events leading to neuroblastoma.

Flow cytometry can also provide important prognostic information, especially in patients less than 12 months of age.[1] Diploidy or near tetraploidy predict a highly aggressive tumor and poor outcome, whereas near triploidy is associated with a favorable prognosis. In the aforementioned study,[6] triploidy was associated with an 88% 5-year survival rate versus 35% and 45% rates, respectively, for diploid and tetraploid tumors.

The *TRK* proto-oncogene is expressed in 94% of neuroblastomas in patients less than 1 year old and is inversely associated with N-*myc* amplification.[34] TRK is expressed by a high-affinity protein receptor for neurotrophin growth factor (NGF), which stimulates the growth and differentiation of neural crest derivative cells. Early in their development, these cells are dependent on NGF for survival, and deprivation of NGF leads to programmed cell death.[26] Once differentiation occurs, they are no longer dependent on NGF. Most neuroblastoma cell lines are unresponsive to NGF; however, a high level of TRK expression in patients with neuroblastoma is associated with a 5-year survival rate of 86% versus 14% in patients with a low level of TRK expression.[34]

Several genes have been identified that may confer multidrug resistance in patients with neuroblastoma. The *MDR1* gene encodes P-glycoprotein, which has been associated with the failure of chemotherapy in at least one study.[13] Another gene encodes the multidrug resistance-associated protein (MRP), which is associated with amplification of N-*myc*[5] and predictive of a poor outcome in patients with neuroblastoma.[35]

TREATMENT

Current therapy for neuroblastoma is multimodal, incorporating surgery, chemotherapy, and radiotherapy. The importance of surgery in diagnosis, staging, and the procurement of tissue for biologic studies has been discussed. Surgery has an equally important role in treatment (Fig. 4). Surgical resection of the primary tumor and adjacent lymph nodes should be the goal and may be curative for localized stage 1 and 2 disease. Whenever possible, ipsilateral nodes should be removed and contralateral lymph nodes sampled. A biopsy specimen of the liver should also be obtained.

Several studies have shown that the overall survival of patients with stage III disease is significantly improved by complete surgical resection accomplished at the first, second, or third exploration.[20, 28, 38] The only exceptions to this recommendation are patients less than 1 year of age or older children with favorable biologic characteristics (Shimada classification, N-*myc* copy number, and serum ferritin

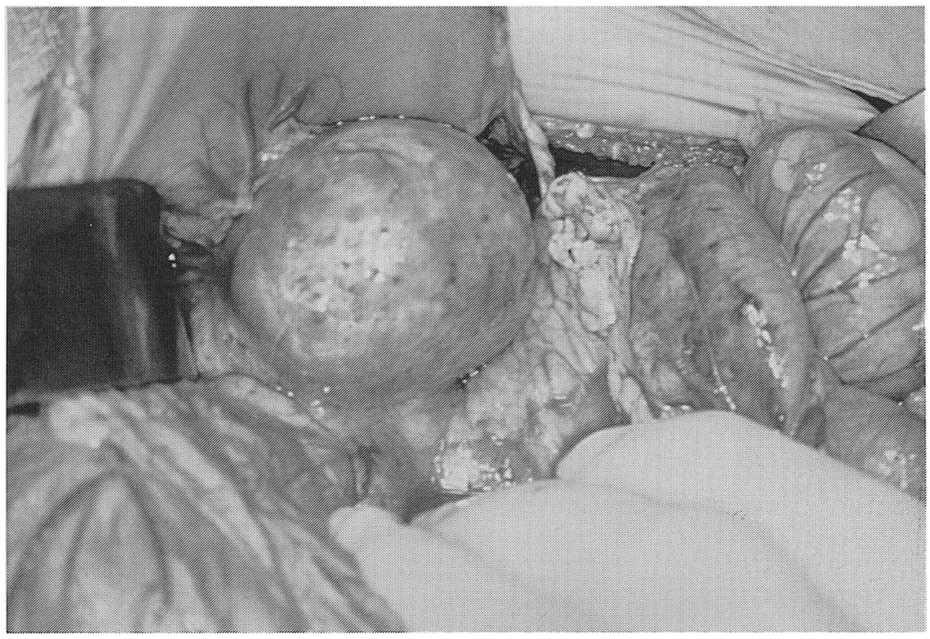

Figure 4. Typical appearance of retroperitoneal neuroblastoma at resection.

level) for whom the degree of surgical resection has no effect on survival.[28] The timing of surgery does not seem to affect overall survival or the risk of surgical complications.[20] Furthermore, tumors generally decrease in size, become less vascular and less friable, and are easier to resect following chemotherapy. For these reasons, when the resectability of a stage III tumor is in doubt, surgical exploration should be delayed 12 to 20 weeks following the initiation of chemotherapy or until tumor shrinkage is considered maximal (usually six courses). Under no circumstances should vital structures be sacrificed at the first exploration, especially in children less than 1 year of age in whom vascular injuries or spasm may lead to a vanishing or atrophied kidney. Studies have shown a significant survival advantage in children with neuroblastoma who avoid nephrectomy.[36, 46] Moreover, the risk of nephrectomy is 25% in patients undergoing initial resection compared with 9% in patients undergoing delayed resection following chemotherapy.[42]

Surgical resection of the primary tumor in patients with stage IV disease is controversial. In one study, gross complete surgical resection was feasible in 24% of patients who underwent initial exploration and in 64% of patients who underwent delayed exploration (24% overall); however, gross complete resection conferred only a slight survival advantage to these patients.[27] The resolution of metastases following chemotherapy seemed to have a far more important impact on survival than surgical resectability.

Surgical resection of the primary tumor does not affect survival in patients with stage 4S disease.[19] In these patients, surgery is used primarily for diagnosis and supportive care. Occasionally, laparotomy is required to distinguish between stage 4 and 4S disease; however, biopsy specimens should always be obtained in the safest and least invasive fashion. Rarely, surgical decompression of the abdominal cavity using synthetic material may be required to relieve respiratory distress caused by rapid expansion of the liver.

A rare but challenging tumor is the dumbbell tumor with intraspinal involvement. As mentioned previously, these patients often present with a gait disturbance or acute paraplegia and require acute decompressive laminectomy and resection of intraspinal tumor. Subsequent resection of the extraspinal tumor should follow the guidelines mentioned previously. If the tumor appears at all resectable based on imaging studies, a second operation should follow the spinal surgery as soon as possible. If the tumor appears unresectable, delayed surgical excision should follow four to six courses of chemotherapy. Radiotherapy may be indicated following the surgery depending on the age and size of the child.

Chemotherapy is the mainstay of therapy for children with locally advanced or metastatic disease. It may be administered preoperatively to patients with unresectable primary tumors and is invariably administered postoperatively to patients with residual disease. The most active agents used alone or in various combinations are cyclophosphamide,

cisplatin, doxorubicin, carboplatin, and ifosfamide. Increased dose intensity of these agents has improved response and survival of patients with stage III[28, 39] and stage IV[11, 14] disease, but overall survival in these patients remains poor. Myoablative chemoradiotherapy followed by autologous bone marrow transplant has been shown to improve short-term survival in some patients with stage IV disease when compared with continued chemotherapy.[45] Although the early results are promising, several problems include 5% to 10% therapy-related mortality and 60% relapse by 4 years.

Radiotherapy is an important adjunct to chemotherapy, particularly in patients over 1 year of age with intracavitary lymph nodes. These patients are categorized as St. Jude stage C or International stages 2B and 3. Although they account for only 10% of patients with neuroblastoma, they are a high risk group who greatly benefit from radiation in addition to chemotherapy. In a well-constructed randomized study,[12] complete response was achieved in 76% of patients with stage C disease treated with chemotherapy and radiotherapy compared with 46% of patients treated with chemotherapy alone. Event-free and overall survival were also significantly improved in the group treated with chemotherapy and radiotherapy when compared with the patients treated with chemotherapy alone. Hematopoietic toxicity was minimal, and there were no toxicity-related deaths.

OUTCOME

Outcome is dependent on the stage, biologic characteristics of the tumor, and therapy administered. Patients with stage 1 disease regardless of age achieve a 95% survival when the primary tumor is completely excised. Microscopic residual disease does not seem to affect survival, and patients older than 1 year of age with stage 2 disease can expect an 85% disease-free survival with surgery alone. Patients older than 1 year of age with locally advanced stage 3 disease achieve a 50% disease-free survival with chemotherapy and surgery, which may be increased to 70% with the addition of radiotherapy.[12] The largest group of patients older than 1 year of age with disseminated stage 4 neuroblastoma have survival rates ranging from less than 10% to 30%. Myeloablative therapy and autologous bone marrow transplant have increased event-free survival to 40% at 4 years, but the durability of this therapy is still questionable and the toxicity significant.

Children less than 1 year of age and with favorable biologic characteristics have better survival for all stages. This group has a 95% disease-free survival for stage 2 disease and nearly 90% disease-free survival for locally advanced stage 3 as well as disseminated stage 4 disease. In fact, these results have led some clinicians to suggest that complete excision is not necessary for tumors in children less than 1 year of age.[21] Stage 4S disease usually occurs in children less than 1 year of age, and the survival of this group depends on the biologic characteristics of the tumor. Survival in stage 4S approaches 90% in patients with favorable tumors and ranges from 30% to 60% in patients with unfavorable tumors.[22]

FUTURE DIRECTIONS

Although survival remains poor in most children with neuroblastoma, several recent advances have been made. Surgical techniques have been refined, and more active chemotherapeutic agents have become available. It is anticipated that chemotherapy will continue to improve, and that novel approaches to the treatment of neuroblastoma may become clinically appreciable. For example, immunity against neuroblastoma cells may be enhanced by transgenic infection of antitumor agents such as interleukin-12.[16] Newer angiostatic agents such as TNP-470 have been shown to reduce microvascular counts and the growth rate of neuroblastoma cells in animal models and may have important clinical applicability in humans.[49] Radiolabeled MIBG has been shown to have appreciable activity against neuroblastoma and is already being used in general clinical trials in Europe.[17, 47] It is hoped that these novel approaches may at least contribute to conventional therapy with minimal additional toxicity.

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