Management of Neuroblastoma in Pediatric Patients

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KEYWORDS

• Neuroblastoma • Pediatric surgery • Risk status • Resection • Treatment • Staging • Survival • Local control

KEY POINTS

- Assessment of neuroblastoma risk is paramount.
- Thorough resection of high-risk tumors improves local control.
- Incomplete resection or even observation alone may be the optimal treatment of specific risk types of neuroblastoma.
- Image-defined risk factors, the International Neuroblastoma Pathology Classification, and biological factors have replaced anatomic staging based on resection status.
- Antibody therapy has made a major impact on outcomes for patients with high-risk neuroblastoma.

INTRODUCTION

Neuroblastoma is characterized by great heterogeneity and is the third most common solid tumor and the most common abdominal tumor in childhood. High-risk neuroblastoma still is associated with a poor prognosis, with 5-year event-free survival in the 50% to 60% range. Additionally, overall survival follows the event-free survival curves, indicating relapse often cannot be treated successfully. Major advances have been made, however, based on a more thorough understanding of underlying biology, which may translate into more accurate risk stratification. This is true for both treatment intensification and deintensification. For instance, prospective (but not randomized) cooperative group data now are available from both the North American and European organizations supporting extensive tumor debulking in high-risk

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disease. In contrast, external beam radiotherapy has all but been eliminated for patients with intermediate-risk neuroblastoma, and neonatal tumors now can be observed safely thanks to a pioneering surgeon-led study.

Furthermore, systemic therapies have improved and include the routine incorporation of antineuroblastoma monoclonal antibodies, which have a particular activity against bone marrow metastases. This makes surgical efforts and other locoregional control more effective.

This article describes a brief history of neuroblastoma therapy, current staging and risk status, and the role of the surgeon in the various risk groups.

HISTORICAL ASPECTS

The first description of neuroblastoma is ascribed to Rudolf Virchow who called it an abdominal glioma.[1] Felix Marchand first connected these tumors with the autonomic nervous system, including the adrenal medulla, whereas William Pepper was the first to describe the clinical pattern now designated MS disease in infants (low amount of bone marrow, liver, and skin metastases but no cortical bone involvement).[2] James Homer Wright[3] was the first to describe the pseudorosettes still used diagnostically by pathologists. Karl Herxheimer used silver staining to visualize the tumors in 1914, and Harvey Cushing and S. Burt Wolbach showed that spontaneous regression was possible in some neuroblastomas, a first hint that risk assessment would be of great importance in this disease.[3,4] Robert Gross and C. Everett Koop were pioneers in neuroblastoma surgery in the United States.[5,6] Finally, neuroblastoma is the first cancer for which *MYCN* amplification has been used to assess risk.

CLINICAL PRESENTATION

Clinical presentation of neuroblastoma depends on the anatomic location of the primary tumor, stage or extent of disease and risk status. Patients with cervical primaries that are thought to arise from the stellate ganglion may present with Horner syndrome, which may be subtle at times. Parents may note that the affected side is dry and more flushed during exercise. The pupillary constriction may be difficult to appreciate in dark-eyed children, and the lid droop can be minimal. Tumors in the chest may be asymptomatic and grow to great size until dyspnea initiates a work-up. Abdominal and pelvic tumors also may reach great size and may be asymptomatic and incidentally discovered by palpation of a mass. The presence of metastases actually may be the first clinical indication of neuroblastoma. The most frequent site of metastases is the cortical bone and bone marrow. Both sites can give rise to bone pain, which causes limping or refusal to walk if it involves the lower extremity or pelvis. When the spine is involved, compression fractures can occur. Neuroblastoma may invade through the spinal foramina into the epidural space, and paraparesis, or Frank's paraplegia, may be the result. Bone metastases to the orbits can cause hemorrhage within the orbit and subsequent periorbital ecchymoses, colloquially referred to as raccoon eyes. Tumors arising in the pelvis from the sympathetic chains, or organ of Zuckerkandl, may affect the sacrum and pelvic nerves, causing a neurogenic bladder. Physical impingement may cause a partial rectal obstruction with severe constipation.

DIAGNOSTIC AND STAGING STUDIES

Laboratory Findings

Lactate dehydrogenase (LDH), ferritin, and catecholamine metabolites and urinary catecholamines often are checked when neuroblastoma is suspected. LDH is

nonspecific; however, high serum levels can be caused by large tumor burden or high proliferative activity; levels higher than 1500 IU/L seem to be associated with a poor prognosis.[7–9] Ferritin levels greater than 150 ng/mL also can result from a large tumor burden or rapid progression; it often is seen in advanced neuroblastoma and, like elevated LDH, indicates a poor prognosis.[7,9] Serum ferritin often decreases to normal when patients are in clinical remission. Elevated urinary catecholamines are present in greater than 90% of patients with neuroblastoma.[10] These laboratory tests also can be used to monitor a patients' disease progression.

DIAGNOSTIC IMAGING

Radiographs

A posterior mediastinal mass, observed most commonly in the thoracic region, can be seen on a chest radiograph.[11] Abdominal radiography is not the standard for initial assessment of abdominal neuroblastomas. As many as half of these tumors, however, can be seen as a mass with fine calcifications.[7]

Ultrasonography

Ultrasonography (US) is the most common initial imaging modality used to assess a suspected abdominal mass. When a mass has been confirmed, computed tomography (CT) or magnetic resonance imaging (MRI) is used for further assessment, because these modalities are more sensitive and accurate than US.[12]

Computed Tomography and Magnetic Resonance Imaging

The accuracy of contrast-enhanced CT in defining the extent of neuroblastoma is 82% and increases to 97% when performed with technetium 99m bone scintigraphy.[13] Although some believe MRI has replaced CT, others consider CT the gold standard imaging modality when combined with bone scintigraphy.[14] Intraspinal tumor extension and metastases to the bone and bone marrow, however, are seen better on MRI.[15] The definition of encasement of major vessels also is observed better with MRI, especially with angiography.[15] A CT scan of a left adrenal neuroblastoma is depicted in **Fig. 1**.

Metaiodobenzylguanidine Imaging

Metaiodobenzylguanidine (MIBG) imaging is used to assess the bone and bone marrow for involvement by neuroblastoma. MIBG is transported to and stored in the chromaffin cells in the same way as norepinephrine.[7] The sensitivity and specificity

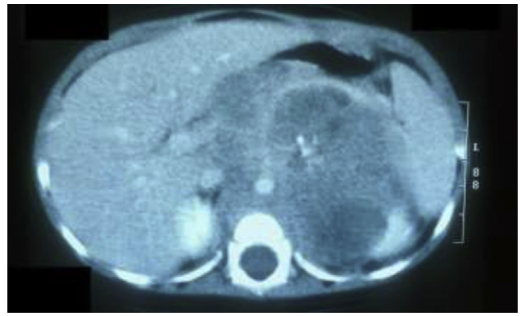

Fig. 1. A large neuroblastoma originating from the left adrenal gland.

of MIBG in detecting neuroblastoma with metastases to the bone and bone marrow are 82% and 91%, respectively. MIBG imaging largely has replaced technitium 99m bone scintigraphy for those patients whose tumors take up MIBG.

Image Defined Risk Factors

In the past 10 years, there has been a realization that staging and risk assessment based on radiographic imaging before therapy have many advantages, not the least of which is a uniform, preoperative approach agreed to by multiple pediatric cooperative groups. The list of image-defined risk factors (IDRFs) is lengthy but easily understood as a factor that complicates surgical resection in an anatomic site. For instance, a solitary, small adrenal mass does not have IDRFs. When that has metastasized to regional lymph nodes. However, the celiac axis can have many IDRFs. For blood vessels and peripheral nerves, the encasement must be greater than 50% of the vessel or nerve circumference to count. Neural foraminal involvement extending through the foramen or into the epidural space also an is IDRF. Using this logic, a staging system was devised. L1 tumors are localized and lack IDRFs. L2 tumors are localized but have IDRFs. M tumors have distant metastases. The stage assigned to metastatic neuroblastoma in children under 1 year of age with favorable biological factors (MS) is a special category (discussed later). Tumors with heavy regional lymph node involvement are considered localized unless distant nodes (>2 nodal echelons removed from the primary tumor) are positive for neuroblastoma.

PATHOLOGY

As discussed previously, neuroblastoma is a tumor of cells derived from the neural crest and can originate anywhere neural crest cells migrate, such as the adrenal medulla, paraspinal sympathetic ganglia, and the organ of Zuckerkandl.[7] Neuroblastoma is a small, round, blue cell tumor, which (especially when undifferentiated) must be distinguished from other tumors that fall into the small, round, blue cell group, such as Ewing sarcoma, non-Hodgkin lymphoma, and rhabdomyosarcoma. Histologically, neuroblastoma is distinguished by the presence of neuritic processes (neuropil) and Homer Wright rosettes (neuroblasts surrounding eosinophilic neuropil). Tumor cells can vary from undifferentiated cells to fully mature ganglion cells, and the tumors can have variable degrees of schwannian cell stroma intermixed as wavy bundles and sheets of spindle cells that produce factors important for neuronal differentiation.[16,17] Immunohistochemical analysis reveals positive staining when using antibodies to neuroblastoma-specific antigens, such as synaptophysin, neuron-specific enolase, and chromogranin; staining is negative when using antibodies to actin, desmin, cytokeratin, leukocyte common antigen, vimentin, and CD99.

TUMOR BIOLOGY

Histopathologic Classification

The first classification system was developed by Shimada and colleagues in 1984[18]; it was an age-linked classification system based on tumor morphology. Neuroblastomas were separated into 2 prognostic groups, favorable histology and unfavorable histology.[18] The International Neuroblastoma Pathology Classification was developed in 1999 and modified in 2003. It is adapted from the original Shimada system, and it remains an age-linked system, depending on the differentiation grade of the neuroblasts, the mitosis-karyorrhexis index (MKI), and the presence or absence of schwannian stroma.[19,20]

DNA Content

Although normal human cells have 2 copies of each of 23 chromosomes (46 chromosomes = diploid cells), a majority (55%) of primary neuroblastomas are triploid or near-triploid/hyperdiploid, containing between 58 and 80 chromosomes. The rest (45%) are near-diploid (35–57 chromosomes) or near-tetraploid (81–103 chromosomes).[7,21] The DNA index is the ratio of the number of chromosomes present to a diploid number of chromosomes (46). Therefore, diploid cells have a DNA index of 1.0, and near-triploid cells have a DNA index ranging from 1.26 to 1.76. Patients with near-diploid or near-tetraploid tumors usually have unfavorable clinical and biologic prognostic factors and poor survival rates compared with those patients who have near-triploid tumors.[22]

Amplification of MYCN

In the developing nervous system and other tissues, *MYCN* encodes a nuclear phosphoprotein that forms a transcriptional complex by associating with other nuclear proteins.[23] The expression of *MYCN* increases the rate of DNA synthesis and cell proliferation and can function as a classic dominant oncogene, cooperating with activated *ras* to transform normal cells.[24,25] *MYCN* amplification is present in 25% of primary neuroblastomas; the presence in advanced disease is 40%, whereas the presence in low-stage disease is only 5% to 10%.[26] Amplification of *MYCN* is an important prognostic indicator, because it is associated with advanced stages of disease, rapid tumor progression, and poor outcomes.[26,27]

RISK STATUS

Risk status in neuroblastoma depends on patient age and clinical factors, including stage, *MYCN* amplification, histopathology, segmental chromosomal aberrations, and ploidy. Age at diagnosis is the primary patient-related characteristic, and analyses have shown that children diagnosed before 18 months have a lower risk.[28] Diagnosis after 18 months of age is associated with a worsened event-free survival.

MYCN amplification is present in 25% to 35% of high-stage tumors but only 5% of low-stage tumors. It is an indicator of high biological risk except in the rare instance of a small, isolated, completely excised neuroblastoma. Diploid tumors are associated with worse outcomes than aneuploid or polyploid tumors in children under 18 months of age. Finally, there is a type of neuroblastoma grading system that stratifies tumors into favorable or unfavorable categories based on their MKI. In addition to these factors, many molecular findings have been associated with increased risk. These include 17q gain and loss of chromosome 1p or 11q.

The algorithms that use these factors to determine risk are complex and change slightly based on new knowledge. It is recommended that the most recent schema be consulted when determining the risk status for patients. It also is recommended that all neuroblastoma cases be discussed at a multidisciplinary tumor board to assess risk.

In 1993, The Children's Oncology Group (COG) and cooperative groups in Europe and Japan adopted the International Neuroblastoma Staging System (INSS).[29,30] This system emphasizes the extent of the primary tumor, presence and location of positive lymph nodes, and metastasis as means of categorizing patients into stages 1, 2 A/2B, 3, and 4/4S.[30] This staging system, along with tumor biology, was the basis of COG risk stratification prior to 2010. This system divides patients into low-risk, intermediate-risk, and high-risk groups to guide treatment.[30] In the early 2000s, the International Neuroblastoma Risk Group Staging System (INRGSS) began to replace

the INSS.[31] It currently is the staging system used in ongoing COG studies. The advantage of the INRGSS is that it is not dependent on a resection variable but rather on pretreatment imaging combined with age and biological variables like *MYCN* amplification. According to the INRGSS system, tumors are assessed for surgical risk factors that predict unresectability using IDRFs and are separated into L1 (no IDRFs), L2 (at least 1 IDRF), M (metastatic), or MS (the equivalent of 4S in the INSS).[30] Based on this stage, along with age, histology, and tumor biology, patients are grouped into very-low-risk, low-risk, intermediate-risk, and high-risk groups. Regardless of which system is chosen, the stage and risk status of the patient have a great impact on treatment.

TREATMENT

Generally, small, localized, and easily removed lesions are considered low risk. The primary surgery for many of these tumors is resection. It is becoming more evident, however, that some of these patients can undergo observation alone.[32] Larger tumors with locoregional spread also are treated by resection, but some of these lesions can be quite extensive. Therefore, a course of neoadjuvant, multiagent chemotherapy may shrink the tumor and reduce vascularity, making resection easier. Also, the presence of IDRFs may dictate a course of chemotherapy. There is little evidence, however, that encased vessels are completely freed by this approach. Chemotherapy for intermediate-risk patients usually is given in a series of 2 cycles followed by radiologic assessment. If resection cannot be completed after 8 cycles (discussion about reducing the number of cycles is ongoing), observation often is performed, depending on the overall tumor response to chemotherapy and details of the biologic risk assignment. External beam radiotherapy is avoided with intermediate-risk tumors.

In summary, the current standard of treatment of children with neuroblastoma is based on stage as well as risk stratification; this takes into account clinical and biologic variables predictive of relapse.[7] The age at diagnosis (<18 months or $\geq$18 months) and stage at diagnosis are the most important clinical variables,[28,33,34] whereas *MYCN* amplification status and histopathologic classification are the most important biologic factors.[26,27,35]

VERY-LOW-RISK AND LOW-RISK GROUPS

The very-low-risk group exists only in the INRG risk group classification system and includes stage L1 without *MYCN* amplification and stage MS without *MYCN* amplification or 11q aberration. The low-risk group includes INSS stage 1, stage 2 A/2B without *MYCN* amplification and greater than 50% tumor resection, and stage 4S without *MYCN* amplification.[30] This group also includes INRG stage L1, stage L2 without *MYCN* amplification or 11q aberration, and stage M or MS without *MYCN* amplification or 11q aberration if the patient is less than 18 months old.[30]

The goal for this risk group is complete primary tumor resection, accurate staging by biopsy of nonadherent nodes, and adequate tissue sampling for molecular biologic studies.[30] As discussed previously, a significant portion of younger patients in this group can be treated with expectant observation.[30] Patients with low-risk disease over the age of 18 months have an overall survival of greater than 90%, with almost all patients receiving surgery alone.[36–38] Therefore, the standard treatment of patients with low-risk disease is surgery without chemotherapy or radiotherapy except for those in the observation arm.

INTERMEDIATE-RISK GROUP

The intermediate-risk group includes INRG stage L2 without *MYCN* amplification, but with 11q aberration or poorly differentiated histology, and stage M without *MYCN* amplification, but with diploid tumor and age less than 18 months.[30] This group also includes INSS stage 2 A/2B without *MYCN* amplification and less than 50% tumor resection, stage 3 without *MYCN* amplification, age less than 547 days with any histology or age greater than 547 days with favorable histology, and stage 4 or stage 4S without *MYCN* amplification and age less than 547 days.

The surgical goals for patients with intermediate-risk disease are to establish the diagnosis, resect as much of the primary tumor as safely as possible, accurately stage the disease through the sampling of nonadherent lymph nodes, and obtain an adequate amount of tissue for diagnostic studies.[30] Patients with unresectable tumors are treated with chemotherapy per COG guidelines. The most active agents against neuroblastoma are cyclophosphamide, doxorubicin, carboplatin, and etoposide.[7] Patients are monitored with CT or MRI after chemotherapy to assess response and resectability of the tumor.

HIGH-RISK GROUP

The high-risk group includes INRG stages L1 and L2 with *MYCN* amplification, stage M with *MYCN* amplification or age greater than 18 months, and stage MS with *MYCN* amplification or 11q aberration. This group also includes INSS stage 2 A/2B with *MYCN* amplification, stage 3 with *MYCN* amplification or without *MYCN* amplification but age greater than 547 days with unfavorable histology, stage 4 with *MYCN* amplification, or without *MYCN* amplification from ages 365 to 547 days with unfavorable histology, or age greater than 547 days regardless of tumor biology, and stage 4S with *MYCN* amplification.

The goal of surgery in patients with high-risk disease is an initial diagnostic biopsy to obtain an adequate amount of tissue for biologic studies. Treatment after diagnosis begins with neoadjuvant chemotherapy, followed by complete resection of the primary tumor.[30] High-risk patients also may receive myeloablative consolidation therapy with stem cell rescue and targeted therapy for any residual disease.[7] Immunotherapy with anti-GD2 antibodies has become standard treatment after consolidation therapy. Radiotherapy may be used for symptomatic residual disease and/or palliation.

The surgical approach to high-risk neuroblastoma has been influenced recently by the publication of cooperative group prospective (but not randomized) studies with a principal aim of assessing the impact of extent of resection on outcomes. Two studies, one from the COG and the other from SIOPEN, are consistent and show a distinct and independent effect of more extensive resection of primary loco-regional disease on the cumulative incidence of local progression.[39,40] The impact of more extensive resection on the cumulative incidence of local progression is shown in **Fig. 2**.

The SIOPEN study, which is larger with greater than 1500 patients, also showed that improved event-free and overall survival correlated with more extensive resection.[40] This is the first time such data have been available.

SURGICAL TECHNIQUES

Initial Biopsy

The goal of biopsy is to obtain an adequate amount of tissue for both diagnosis and clinically relevant molecular studies like *MYCN* amplification. Biopsy should take

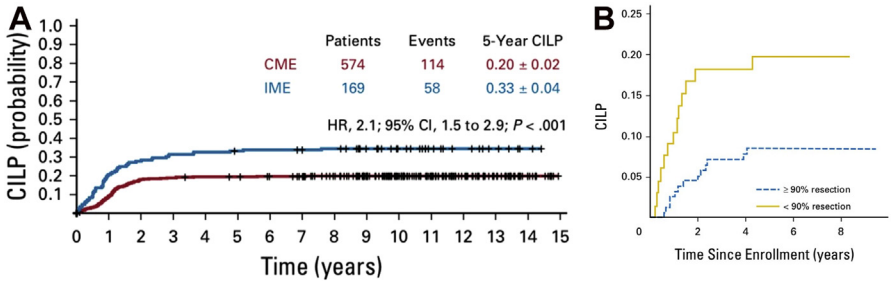

Fig. 2. (*A*) Shows the results of the High-Risk Neuroblastoma Study 1.8 (HR-NBL1)/SIOPEN study for cumulative incidence of local progression. (*B*) Shows the results from the COG A3973 trial. CILP, cartilage intermediate layer protein; HR, hazard ratio; IME, intermediate medical education.

into account each patient's overall status at the time of biopsy, because some patients may have breathing problems secondary to large abdominal or thoracic masses, bleeding and anemia from low platelets secondary to marrow infiltration, or severe bone pain because of osseous metastases. Laparoscopy, laparotomy, or percutaneous needle biopsy all are acceptable, as long as the diagnosis is obtained along with salient molecular studies. If a needle technique is used, the placement of a trocar to allow multiple needle passes as well as packing of the needle tract with hemostatic agents is preferred. For desperately ill patients, the finding of neuroblastoma cells in the bone marrow combined with a positive MIBG scan is considered adequate. The surgeon should ensure that an adequate biopsy has been obtained before leaving the operating room.

Cervical Lesion

Most primary cervical lesions occur in infants less than 1 year of age and have favorable biologic features. The approach to remove these lesions typically is a transverse neck incision followed by dissection of the carotid sheath contents.[30] Large lesions may require division of the sternocleidomastoid muscle for adequate exposure. In cases of grossly positive lymph nodes, a formal lymphadenectomy with a modified neck dissection technique should be performed.[30] The approach is depicted in **Fig. 3**.

Cervicothoracic Lesions

Primary cervical lesions may extend into the chest through the thoracic inlet. Adequate exposure is integral to achieving gross total resection of these tumors.[30] This usually can be achieved using a trap-door thoracotomy, which can be modified for lesions with a larger cervical component by extending the neck incision superior along the anterior border of the sternocleidomastoid.[30] Lesions that extend into both hemithoraces can be exposed reliably using a clamshell thoracotomy at the fifth interspace. Nerve stimulation often is 'used to monitor the vagus nerve and the brachial plexus.[30]

Mediastinal Lesions

The posterior mediastinum is the second most common primary site for neuroblastomas. Mediastinal lesions generally can be approached through a muscle-sparing posterolateral thoracotomy. Infiltration through spinal foramina may require foraminotomy.[30] This is depicted in **Fig. 4**. For L1 tumors, thoracoscopy is a reasonable alternative to thoracotomy.

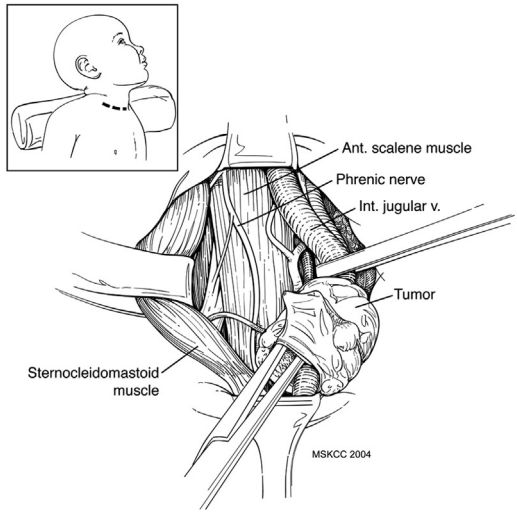

Fig. 3. Resection of a cervical neuroblastoma. ANT, anterior; INT, interior; v, vein.

Upper Abdominal and Retroperitoneal Lesions

A majority of neuroblastomas originate from the adrenal gland or sympathetic ganglia and are found in the upper abdomen. There is frequent involvement of regional lymph nodes in the ipsilateral paraaortic or the pericaval chains as well as interaortocaval

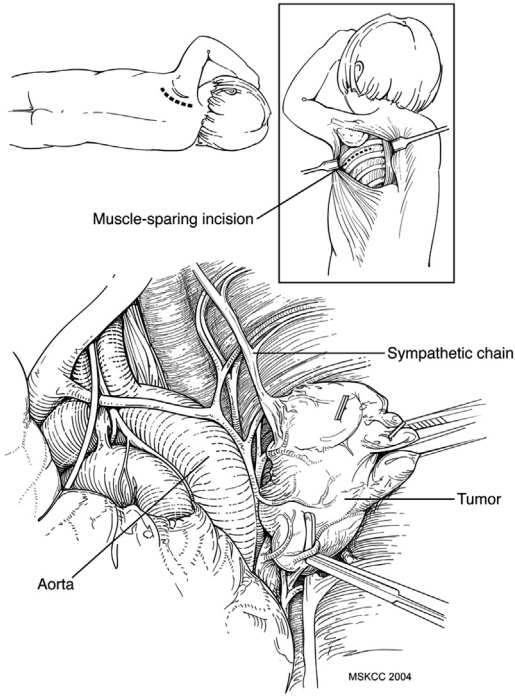

Fig. 4. Left thoracotomy for mediastinal neuroblastoma.

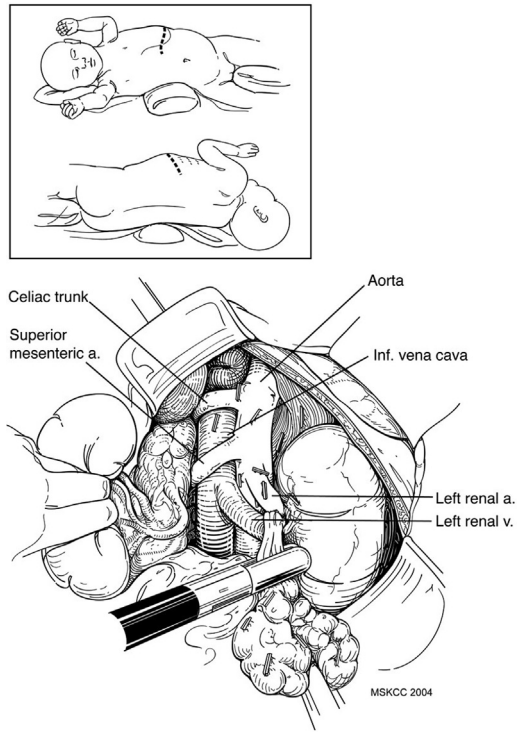

Fig. 5. Technique of left thoracoabdominal resection. Bivalving of the tumor is acceptable and necessary for neuroblastoma resection. A, artery; inf, inferior; v, valve.

lymph nodes. The primary tumor and involved lymph nodes often create a confluent mass that encases but does not invade the great vessels of the abdomen. For these tumors, a thoracoabdominal approach is ideal.[30] The surgical approach is depicted in Fig. 5, and the outcome of surgery in Fig. 6.

Pelvic Lesions

Pelvic tumors can be challenging to resect due to the encasement of iliac vessels and infiltration of the lumbosacral plexus. A midline incision extending from the umbilicus to the pubic symphysis provides good exposure of the pelvis and allows adequate

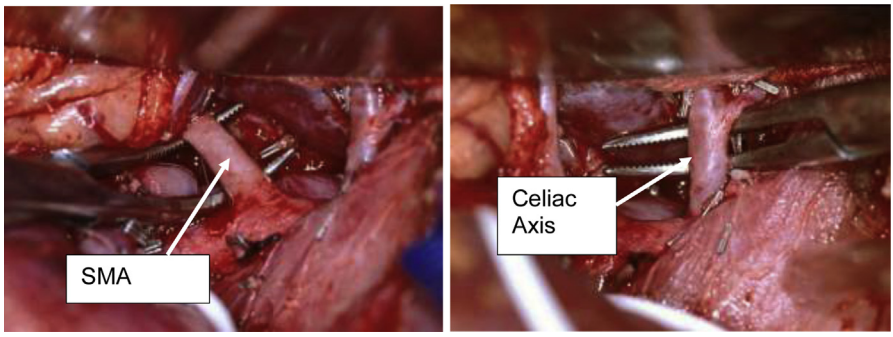

Fig. 6. Results of gross total resection of the tumor depicted in Fig. 1.

control of the distal aorta and vena cava.[30] Internal iliac vessels, if involved, may be ligated and resected without significant morbidity.

Surgical Complications and Mortality

Neuroblastomas that involve and/or encase major vascular and neural structures in their site of origin or surrounding nodes have a higher risk of surgical complications.[30] The most serious surgical complications include massive hemorrhage, major vascular injury, and respiratory failure requiring ventilatory support. The site of the tumor determines the possible surgical complications. Cervical and upper mediastinal resections can be associated with a permanent postoperative Horner syndrome. Paralysis can result from the excision of epidural tumors or tumors heavily involving spinal foramina.[41] Excision of retroperitoneal neuroblastomas can result in nephrectomy or renal infarction.[42] After the removal of pelvic tumors, there is increased frequency of complications, such as foot drop.[43] Despite the extent of these massive resections, operative mortality is rare. Complications after primary tumor resection in patients with high-risk tumors are reduced after initial treatment with neoadjuvant chemotherapy[44] that reduces tumor volume.[45,46]

SUMMARY

The key to effective neuroblastoma therapy is accurate risk stratification. This determines treatment, including surgical intervention. Resection alone is the standard of care for very-low-risk and low-risk neuroblastoma. Intermediate-risk tumors also may be treated with neoadjuvant chemotherapy and resection. A complete gross resection usually is not necessary for intermediate-risk neuroblastoma. Recent data indicate that a complete gross resection is a desired goal, if feasible, for high-risk neuroblastomas.

CLINICS CARE POINTS

- Realize that in neuroblastoma an R0 resection rarely is feasible.
- Resect or observe very-low-risk and low-risk tumors
- Resect intermediate-risk tumors either primarily, if feasible, or after neoadjuvant therapy. Complete gross (R1) resection is not necessary, although should be done if relatively straightforward.
- R1 resection of the primary tumor and regional involved lymph nodes is the goal of surgery for high-risk tumors if safe and feasible. This should be done after neoadjuvant therapy.
- In general, removal of normal organs (kidneys) should be avoided during neuroblastoma resection, if possible.

DISCLOSURE

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