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Introduction

Although cancer among children is relatively uncommon, it remains a significant cause of mortality in this population and is second only to accidents as a cause of death in the age group of 5-14 years. In the United States approximately 1 in 333 individuals between the ages of 0 and 20 years will be newly diagnosed with cancer each year, affecting a total of nearly 7,500 children under the age of 15 years and another 3,500 adolescents between 15 and 20 years of age. Pediatric head and neck malignancies constitute only about 5% of all childhood cancers, thereby affecting approximately 550 children/year (1).

New studies indicate that the incidence of childhood cancer continues to rise. According to a review by Albright, the overall annual incidence of cancer in children under 15 years of age rose from 11.22 cases/100,000 person-years in the time period of 1973-1975, to 14.03 cases/100,000 person-years in 1994-1996—an increase of 25%. In addition, this study found an even larger increase in the incidence of pediatric head and neck malignancies. In this subset, the incidence rate increased from 1.10 to 1.49 cases/100,000 person-years in the same timeframe—an increase of 35% (2).

The more common pediatric head and neck tumors include lymphoma (prevalence of 59%), rhabdomyosarcoma (13%), thyroid malignancies (10%), nasopharyngeal carcinoma (5%), neuroblastoma (5%), nonrhabdomyosarcoma soft-tissue sarcoma (4.5%), salivary gland malignancies (2.5%), and malignant teratomas (1%) (1). The majority of these will be covered in this grand rounds, excluding thyroid and salivary gland neoplasms, which have been covered in previous discussions.

Non-Hodgkin's Lymphoma

Lymphomas comprise approximately 11.5% of all pediatric malignancies, making them the third most common cancer. Approximately 60% of pediatric lymphomas are non-Hodgkin's lymphoma (NHL). Boys are affected more often than girls with a 3:1 ratio and the peak

incidence of NHL is between the ages of 7 and 11 years. There is an increased risk for the development of NHL in children with some form of T-cell deficiency, such as those with congenital immunodeficiency syndromes, acquired immunodeficiency syndrome (AIDS), or prescribed immunosuppressive therapy.

Histologic varieties of NHL are divided into low-, intermediate-, or high-grade categories based upon their clinical behavior and over 90% of children have high-grade disease at presentation. High-grade lesions include large cell, lymphoblastic and small cell noncleaved lymphomas. Large cell lymphomas constitute about 27% of pediatric NHL and have been demonstrated to have a t(2;5) chromosomal rearrangement in 50% of cases that results in the production of a novel chimeric protein. This type of NHL rarely presents in the head and neck region. Lymphoblastic lymphoma occurs in 29% of pediatric cases and often involves a translocation on chromosome 7 or 14 that effects the production of transcription factor TAL-1. This type of NHL most often presents with a mediastinal mass, possibly with respiratory compromise. The small cell noncleaved lymphomas are found in 34% of pediatric NHL and Burkitt's lymphoma (BL) is the most common of this subtype. The relationship between BL and Epstein-Barr virus (EBV) infection has been definitively demonstrated, up to 90% of endemic BL and 20% of sporadic BL cases have been found to have elevated EBV titers. EBV likely serves as a B-cell mitogen thereby increasing the population of lymphocytes susceptible to chromosomal abnormalities. The typical chromosomal transformations seen in BL are a translocation of the *myc* gene from chromosome 8 to immunoglobulin receptor subunit genes on chromosomes 2, 14, or 22. This translocation then leads to a malfunction in the normal regulation of the cell cycle. Presentation of endemic BL typically involves the abdomen or mandible while sporadic BL may present with disease in the abdomen or the head and neck region (1,3).

Clinical presentation of NHL in the head and neck is seen in 5-10% of children and most often involves asymptomatic cervical lymphadenopathy. Other areas that may be involved include the salivary glands, larynx, sinuses, orbit and scalp. NHL may also present in the extranodal lymphoid tissue of Waldeyer's ring and cause a diagnostic dilemma by mimicking routine adenotonsillar hypertrophy. Although the physical finding of asymmetric tonsils may stimulate one to consider an underlying serious pathology, a recent study by Harley found that 47/258 (18.2%) children undergoing tonsillectomy for airway symptoms, recurrent infection or both demonstrated some degree of tonsil asymmetry but none had evidence of malignancy on pathologic evaluation. The study conclusion was that in the absence of associated symptoms or other indications for tonsillectomy, children with asymmetric tonsils could safely be observed. Associated symptoms or findings that would, however, increase the suspicion of an underlying lymphoma include constitutional symptoms such as fever, night sweats or weight loss, significant asymmetry with a history of rapid enlargement or tonsil asymmetry in association with cervical adenopathy or hepatosplenomegaly (4).

The evaluation of the child suspected to have a lymphoma begins, of course, with a complete history and physical. Definitive diagnosis requires tissue for pathologic evaluation, which may be obtained by a tonsillectomy or open biopsy of an involved lymph node. The tissue should be sent fresh to the pathologist to allow for flow cytometry; additional studies may also include immunohistochemical staining or electron microscopy. Because most pediatric patients with NHL present with disseminated disease, a complete staging work-up must be undertaken.

This would include laboratory studies (to include LDH, LFT's, and HIV), LP with CSF analysis, bilateral iliac crest bone marrow biopsy, CT of the chest, abdomen and pelvis, and bone scan. The reasoning for such an extensive work up is that accurate clinical staging is of utmost importance in assigning patients to an appropriate treatment protocol.

Several different staging systems exist for NHL, probably the most widely used is the Ann Arbor system. In this system, Stage I indicates involvement of a single lymph node region or extralymphatic organ. Stage II implies involvement of two or more lymph node regions on the same side of the diaphragm or one lymph node region and one extralymphatic organ on the same side of the diaphragm. Stage III includes cases that involve lymph node regions on both sides of the diaphragm with or without extralymphatic organ or splenic involvement. Finally, Stage IV indicates diffuse involvement of one or more extralymphatic organs with or without lymph node involvement.

Multiagent chemotherapy is the mainstay of treatment for NHL. The most commonly used agents include cyclophosphamide, doxorubicin, vincristine, and prednisone. Some protocols for Stage III and IV disease add methotrexate and additional agents may be utilized for recurrent disease. Patients with a second relapse may be candidates for ablative therapy followed by bone marrow transplant. Radiotherapy is not routinely used for treatment of NHL but may be employed in cases where mass lesions are causing life-threatening problems (1,3).

With new and continuously evolving chemotherapeutic regimens, the overall event-free survival (EFS) for NHL in a Swedish pediatric population improved from 19% in the time period from 1975-1979 to 74% from 1980-1994. In this study population another significant prognostic factor was stage of initial disease. In the later time period, patients with Stage I or II disease demonstrated EFS of 86%, while patients with Stage III or IV disease were found to have EFS of 64% and those patients with bone marrow or CNS involvement at presentation had EFS of only 38% and 20% respectively (5). Other sources report similar survival rates of 85-95% for Stage I and II NHL, better survival rates for Stage III and IV BL—75-85%, and similar rates for Stage III and IV lymphoblastic NHL—65-75% (3).

Hodgkin's Lymphoma

Hodgkin's disease (HD) is less common in the pediatric population than NHL. The majority of children diagnosed with HD are in the 15-20 year age range, with only about 4% of cases occurring in children under the age of 10 years. Boys are affected more frequently than girls (3:1) although this ratio narrows after puberty (1.4:1). Like NHL, there is an association between HD and EBV infection with 19-59% of patients having evidence of prior EBV exposure.

There are four histologic subtypes of HD—nodular sclerosing, mixed cellularity, lymphocyte predominance and lymphocyte depletion. Overall, nodular sclerosing and mixed cellularity are the most common subtypes of HD, but in the pediatric population the lymphocyte predominance and nodular sclerosing are seen most frequently.

HD will present with asymmetric lymph node enlargement in about 90% of cases. The lymphadenopathy is described as firm, rubbery and nontender and in the neck most often

involves the supraclavicular fossa. The most common extralymphatic site of HD is the spleen, followed by the liver. Nearly one-third of patients will have associated constitutional symptoms at presentation including fever, night sweats, anorexia, weakness or loss of 10% or more of body weight (1,3).

Like NHL, lymph node biopsy with histologic evaluation is required for the diagnosis of HD. The classic histologic finding is the binucleated Reed-Sternberg cell among a mixed population of lymphocytes, histiocytes and plasma cells. Immunohistochemical staining is typically positive for the surface antigen CD40 (1,3). Once the diagnosis is made, a staging work-up similar to that for NHL, but with the addition of a staging laparotomy with splenectomy, liver biopsy and intraabdominal lymph node biopsy, is performed to define the extent of disease. Several studies have questioned the benefit of subjecting these children to staging laparotomy, one by Breuer, et al. demonstrated that 25% of patients with clinical stage I or II disease were upstaged by laparotomy findings. The same study found that in patients with clinical stage III or IV disease, 27% were downstaged after laparotomy. Mendenhall et al. categorized patients as low or high risk based on the presence of favorable or unfavorable factors. Low risk patients had a <10% chance of splenic or abdominal involvement while high-risk patients had a >80% chance of splenic or abdominal involvement. Because the extent of disease was essentially predictable for these two categories, staging laparotomy could potentially be avoided in these patients. However, only 14% of the patients evaluated in the study fell into the low risk category and only 3% qualified as high risk, leaving 83% of the total study group in an intermediate risk group that still required laparotomy (6). So, although controversy remains, since accurate staging is essential for appropriate treatment, the benefit of the procedure seems to outweigh its morbidity.

The staging system for HD is the Ann Arbor classification system as outlined above. Stages are further subclassified as A or B based upon the absence or presence of constitutional symptoms such as fever, night sweats or weight loss.

Treatment for HD is determined by the stage of disease. Localized disease, Stage IA or IIA, is most often treated with extended field radiation therapy (XRT) to a total dose of 20-40 Gy. The exception to this is patients with Stage IIA mediastinal disease, which has been found to have a high relapse rate if treated with XRT alone and may be treated with combined chemotherapy and XRT. Stage III and IV disease are typically treated with both XRT and chemotherapy, the most common regimens include MOPP—nitrogen mustard, vinblastine, procarbazine and prednisone, or ABVD—adriamycin, bleomycin, vincristine and dacarbazine.

The five-year survival rates for pediatric patients with HD are excellent. Patients with Stage I, II or III disease enjoy a 90% survival rate, while patients with Stage IV disseminated disease still have a 75-80% overall survival rate (1,3).

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a malignancy of striated muscle, is the most common soft-tissue sarcoma in children. It occurs with an incidence of 4.5 cases/1,000,000 children under 14 years old and approximately 250 children are newly diagnosed each year. Nearly 70% of cases

of RMS are diagnosed by the age of 10 years. The ratio of male:female cases is 1.5:1 and there does not appear to be a racial predilection for the disease.

There are four histologic categories of RMS—embryonal, alveolar, botryoid and pleomorphic. The embryonal subtype is most frequently encountered in children, making up 60-70% of cases. The cells in embryonal RMS can be highly variable and display several stages of differentiation. Molecular features of this subtype include chromosome 11p15 deletion, lack of gene amplification and hyperdiploid DNA. Twenty percent of affected children are diagnosed with the alveolar subtype of RMS. It is characterized by clumps of club-shaped tumor cells separated by fibrous septae. Approximately 90% of cases will demonstrate a chromosomal translocation, either t(2;13) or t(1;13), which results in the production of a new transcription factor. Another molecular difference in alveolar RMS compared to embryonal RMS is the demonstration of gene amplification and tetraploid DNA. Botryoid RMS is found in 5-10% of cases, tends to present in mucosal lined organs, and is characterized by grapelike masses of tumor cells. The pleomorphic subtype of RMS, which is quite rare in children, is characterized combination of embryonal and alveolar features.

The head and neck is the most common site of origin for pediatric RMS and is involved in 40% of cases. Within the head and neck region, the orbit is most frequently involved—1/3 of cases, followed by the oral cavity and oropharynx, face and neck, middle ear and mastoid, and nose and paranasal sinuses. Presenting signs and symptoms will be dictated by the site of the tumor but most often include a localized swelling that may be accompanied by proptosis, nasal obstruction, epistaxis, otorrhea, hearing loss, fetor or cranial nerve deficits.

The evaluation of a child with RMS must both assess the extent of the primary disease and establish whether disseminated disease is present or not. In addition to a thorough head and neck exam, CT and MRI are essential to define the extent of the tumor and delineate its relationship to surrounding vital structures. Metastatic work-up should include a chest CT, bone scan and bone marrow biopsy.

There are two commonly used staging systems for RMS—Intergroup Rhabdomyosarcoma Study clinical grouping classification (IRSCGC) and the TNM system. In the IRSCGC system, Group I is defined as localized disease that is completely excised by surgery. Group II consists of compromised or regional resection with microscopic residual disease. Group III refers to incomplete resection or biopsy with gross residual disease and Group IV consists of cases with distant metastasis. The weaknesses of this staging system are that it fails to consider local extent of tumor and whether regional lymph nodes are involved. To address these problems, the TNM system was introduced. Tumor is categorized as either T1--confined to the anatomic site of origin or T2--extension into surrounding tissue and size a--<5cm in diameter or b-->5cm in diameter. Node status is reported as N0--no evidence of regional nodal involvement, NX--regional nodal status cannot be assessed or N1--evidence of regional node involvement. Metastatic spread is reported as either M0--no metastasis or M1--metastasis present (1,7).

RMS is treated by surgery, XRT, and chemotherapy as directed by the extent of disease. Surgical excision plays an important role in local disease control of head and neck RMS and complete tumor resection with a margin of normal tissue is the goal. The exception to this is

orbital RMS, in which case, surgery has not been shown to have a survival advantage over combined chemotherapy and XRT. With improving surgical techniques, particularly in the area of skull base surgery, complete excision can, in many cases, be performed with minimal morbidity. However, when tumor extirpation necessitates sacrifice of cranial nerves or would result in significant cosmetic deformity, chemotherapy and XRT are the preferred method of treatment. Debulking procedures should be reserved for the occasional case in which necrotic tumor is causing a foul odor or tumor is growing through the overlying skin (8). The chemotherapy regimen of choice is dependent upon the origin and extent of disease and patients can be divided into low, intermediate and high-risk categories. Low risk patients, those with IRSCGC Group I or II disease, receive therapy with vincristine and dactinomycin +/- cyclophosphamide. Both the intermediate risk patients Group III disease and the high-risk patients with metastatic disease receive vincristine, dactinomycin and cyclophosphamide. Alternate chemotherapeutic agents, dose-intensification and bone marrow transplantation are methods being studied to improve responses in the high-risk patients. Radiation therapy is used in cases with gross or microscopic disease after surgery or in cases in which surgery is not feasible. Doses of 4000-4500cGy have been shown to control microscopic residual disease while 4500-5000cGy is required for gross disease and this is typically administered over a period of 5-6 weeks. The use of hyperfractionated XRT and brachytherapy are being investigated as alternatives to standard XRT protocols.

The overall survival of children with RMS has improved from a dismal 33% before 1970 to 70% today. This is largely due to the efforts of the Intergroup Rhabdomyosarcoma Study Group, which was formed in 1972 and consists of several large pediatric centers that pool their data from RMS patients. This was begun in order to accumulate information on the disease process and observe the outcome of different therapeutic regimens. Thus far, the IRSG has reported on four protocols and are working on the fifth. The 5-year survival rate after IRS-I was 55%, this improved to 63% for IRS-II, and again improved to 71% after IRS III, but remained stable at that level after IRS IV (9). There are several tumor factors known to affect prognosis including primary site and size, nodal involvement and histology. Orbital and non-parameningeal head and neck RMS have a better prognosis than parameningeal lesions. Tumors <5cm in diameter and those with no regional node involvement also have better prognosis. The extent of surgical resection also affects outcome, patients with IRSCGC Group I disease have a 90% 5-year survival which drops to 80% in Group II and 70% for Group III. Finally, genetic factors, such as DNA content, have been shown to influence prognosis with patients with hyperdiploid DNA having better outcomes than those with diploid or tetraploid DNA (7).

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood and accounts for 8-10% of childhood cancers. The annual incidence of these tumors is around 9 cases/1,000,000 in children under 15 years of age. It is the most common malignancy in children under 1 year of age and 90-95% of patients will present before the age of 10 years. Neuroblastoma is slightly more common in boys than girls and in Caucasians than in non-caucasian races. Some studies have indicated a genetic predisposition for neuroblastoma, while others have implicated possible environmental factors in the development of the disease.

The cell of origin for neuroblastoma is the neural crest cell that eventually gives rise to the sympathetic nervous system. These tumors may develop from the paraspinal sympathetic ganglia, the adrenal chromaffin cells within the adrenal medulla or other various intraabdominal paraganglia. Histologically, neuroblastoma is one of several “small blue round cell” tumors that occur in children and must be differentiated from other similar tumors such as Ewing’s sarcoma, NHL, primitive neuroectodermal tumors and undifferentiated soft-tissue sarcomas. This differentiation is aided by the use of immunohistochemical staining in which neuroblastoma will be positive for neurofilament proteins, synaptophysin and neuron-specific enolase. Electron microscopy can also aid in making the diagnosis of neuroblastoma by demonstrating dense, membrane-bound neurosecretory granules, microfilaments and parallel microtubules. Molecular studies may demonstrate genetic abnormalities associated with neuroblastoma such as deletions in the short arm of chromosome 1 or amplification of the *N-myc* oncogene.

The majority of primary neuroblastomas present as an intraabdominal mass involving the adrenal gland or retroperitoneal paraganglia. Only 2-5% of neuroblastomas will present in the head and neck region—most often as a firm mass in the lateral neck. Other possible head and neck manifestations include airway obstruction, aspiration or dysphagia, either from direct laryngotracheal or pharyngoesophageal compression or cranial nerve involvement, Horner’s syndrome, proptosis, periorbital ecchymosis, ophthalmoplegia, conjunctival or eyelid edema or papilledema. An associated finding of heterochromia irides is also possible.

The criteria necessary to make a diagnosis of neuroblastoma as established by the International Neuroblastoma Staging System includes either a definitive histologic diagnosis on light microscopy +/- immunohistochemistry, electron microscopy or the presence of elevated urine catecholamines, or a bone marrow biopsy demonstrating unequivocal tumor cells and the presence of elevated urine catecholamines. The metastatic work up for neuroblastoma is similar to that for other pediatric malignancies and includes chest x-ray, bilateral iliac crest bone marrow biopsy, bone scan, CT or MRI of the neck and abdomen.

A variety of staging systems for neuroblastoma exist that take into account tumor burden, surgical resectability and metastatic disease. The TNM criteria define Stage I disease as primary tumor <5cm with no regional or distant disease. Stage II includes tumors >5cm but <10cm with no regional or distant disease. Stage III includes tumors up to 10cm plus regional disease or tumors over 10cm +/- regional disease but without distant disease. Stage IV is defined as cases with a single primary tumor +/- regional disease and presence of distant disease. And finally, Stage V includes multicentric primary tumors +/- regional or distant disease.

Treatment of neuroblastoma involves a combination of surgery, chemotherapy and, occasionally, XRT as dictated by the stage of disease. Surgery is performed in nearly all cases with the goal of complete tumor excision if possible while avoiding damage to nearby vital structures. Adjacent lymph node chains, if involved with tumor, should also be removed. Multiagent chemotherapy is utilized for cases initially categorized as intermediate or high risk—mostly stage III and IV disease—or for cases initially categorized as low risk but that develop local recurrence. The most commonly used agents include cyclophosphamide or ifosfamide, doxorubicin, teniposide or etoposide, cisplatin or carboplatin. Although neuroblastoma is a radiosensitive tumor and XRT was used more frequently in the past, today the role of XRT is

limited to cases with widely disseminated disease or as part of ablative treatment in preparation for bone marrow transplantation.

The two most important predictors of outcome in neuroblastoma are patient age at diagnosis and disease stage. Infants less than 1 year of age generally have a better prognosis, regardless of stage, compared with children over 1 year old. The 3-year EFS in all patients with Stage I or II disease is between 75-90%. Infants with Stage III disease still have an 80-90% EFS but this drops to 60-75% in Stage IV disease. Children fare much worse with more advanced disease and have an EFS of 50% for Stage III and 15% for Stage IV disease. Genetic features associated with a poorer prognosis include deletions of chromosome 1p, *N-myc* amplification and diploid or normal DNA content (1,3,10).

Esthesioneuroblastoma or olfactory neuroblastoma is a very rare pediatric malignancy, with only about 100 cases in children reported in the literature. However, because of its location and presentation, the otolaryngologist may well be consulted to evaluate children with this disease and therefore should, at the minimum, keep this tumor in mind as a diagnostic possibility. The majority of cases of pediatric esthesioneuroblastoma have been diagnosed in teenagers and affect boys more often than girls. Presenting signs and symptoms may include facial pain or swelling, sinusitis, nasal obstruction or mass, epistaxis, proptosis, headache or neck mass. Histologically there are small round blue cells that are arranged in nests surrounded by fibrous septa and demonstrate little to no evidence of differentiation. Immunohistochemical staining may be positive for neuron-specific enolase (NSE), synaptophysin and chromogranin. The most widely used staging system for esthesioneuroblastoma is the Kadish system which categorizes tumors as Stage A—confined to the nasal cavity, B—confined to the nasal cavity and one or more paranasal sinuses, or C—extension beyond the nasal cavity or sinuses. The majority of pediatric cases described have presented with Stage C disease. There is no well-established treatment protocol for children with this disease and in the past the standard adult treatment with extensive craniofacial resection and postoperative XRT had been utilized. In the recent literature, more centers seem to be adding adjuvant or neoadjuvant chemotherapy with agents such as vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide or cisplatin. In a report by Kumar, et al on five pediatric patients with esthesioneuroblastoma, an initial favorable response was demonstrated in all of the patients. So, although extensive studies proving a distinct benefit are not available, the addition of chemotherapy seems to have the potential for improving outcomes in these patients (11).

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is rare in children but makes up approximately 5% of pediatric head and neck malignancies. This disease most frequently affects adolescents, there is no sex predilection and it occurs more often in black teenagers. In all age groups, NPC is much more common in China, where it accounts for 18% of cancers, than in North America where it is only .25% of all cancers. This increased susceptibility among the Chinese has been linked to the presence of HLA-A2 and HLA-B-Sin 2 loci. Environmental factors such as exposure to smoke or dust and a diet high in nitrosamine-rich salted fish have been linked to increased risk for NPC. Although a direct cause and effect relationship has not yet been demonstrated, there is a relationship between EBV infection and NPC. Patients with elevated EBV titers tend to have more extensive disease and poorer response to therapy.

The World Health Organization categorization of NPC includes Type I-squamous cell carcinoma, Type II-non-keratinizing carcinoma and Type III-undifferentiated carcinoma. The majority of adolescents affected by NPC have the undifferentiated type, which has also been referred to as lymphoepithelioma. This tumor is characterized by pleomorphic cells that may be described as spindle cells, transitional cells or clear cells and it can be difficult to differentiate from malignancies such as RMS and NHL.

The clinical signs and symptoms of NPC may be mild and nonspecific thereby leading to a delay in diagnosis and the presence of advanced disease. The most common presentation is a neck mass associated with hearing loss. Other symptoms may include nasal obstruction, rhinorrhea, epistaxis, headache or otalgia. Signs of cranial neuropathy indicate skull base invasion, this most often occurs through the foramen lacerum initially to effect the abducens nerve and lead to weakness of lateral gaze and diplopia. Other cranial nerves that may become involved include III, IV and V and eventually IX, X, XI and XII.

In addition to a complete history and physical, the work up of a patient with suspected nasopharyngeal mass begins with direct endoscopic examination, either with rigid or flexible scopes. CT and MRI are very useful in defining the local extent of disease. The evaluation for distant metastasis includes CT chest and abdomen and bone scan. Ultimately, the mass must be biopsied to obtain tissue for a histologic diagnosis. This can often be accomplished either with endoscopic visualization of the primary tumor or fine needle aspiration of an enlarged cervical lymph node (12).

The staging system for NPC is the TNM system. T1 tumors are confined to the nasopharynx. T2 tumors extend into the soft tissues of the nasopharynx or the nasal cavity and subcategorized into a: without parapharyngeal extension, and b: with parapharyngeal extension. Tumors that are categorized at T3 invade either bony structures or paranasal sinuses or both. And T4 tumors demonstrate intracranial spread, cranial nerve involvement or extension into the infratemporal fossa, hypopharynx or orbit. The nodal categories are N0=no regional lymph node involvement, N1=unilateral node <6cm above the supraclavicular fossa, N2=bilateral nodes <6cm above the supraclavicular fossa and N3a=nodes >6cm while N3b=nodes involving the supraclavicular fossa. The M stage is either M0 if there is no evidence of distant metastasis or M1 if such evidence is present (13).

The mainstay of treatment for NPC is XRT to the primary tumor and regional lymphatics to a total dose of 6500-7000cGy. Although in the past NPC was not considered amendable to surgical resection, improved craniofacial surgical techniques have allowed reversal of this opinion. Skull base resection for residual or recurrent disease can be beneficial to a select number of patients so long as attention is paid to minimizing morbidity (12). The majority of pediatric patients with NPC will have advanced disease upon presentation and will, therefore, require adjuvant chemotherapy. Regimens may include drugs such as vincristine, doxorubicin, cyclophosphamide, cisplatin and 5-fluorouracil (14).

The overall 5-year survival rate in pediatric NPC is approximately 40%. Patients with locally confined disease +/- ipsilateral lymph node spread fare better than patients with bilateral nodal metastasis or penetration of the central nervous system (12).

Soft-tissue Sarcomas

This diverse category of diseases accounts for about 4.5% of pediatric head and neck malignancies. Fibrosarcoma, dermatofibrosarcoma protuberans, epitheloid sarcoma, synovial sarcoma, malignant fibrous histiocytoma, hemangiopericytoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, liposarcoma and soft-tissue clear-cell sarcoma are all within this category. The majority of these tumors will present with a firm enlarging mass and additional symptoms dependent upon location. Patient evaluation for these soft tissue sarcomas is identical to that for RMS, with emphasis on adequate biopsy so that definitive tissue diagnosis can be made. Disease staging is either with the IRSCGC system as for RMS or with the same TNM system as for adult soft-tissue sarcoma. Treatment for nonrhabdomyosarcoma soft-tissue sarcoma involves combination of surgery, XRT and chemotherapy. Prognosis is greatly determined by tumor resectability as illustrated by a report that while only 1 of 26 surviving patients had a history of gross residual or metastatic disease, 29 of 36 survivors had complete tumor removal or only microscopic residual disease. Because of the proximity of these tumors to the many vital structures in the head and neck region only 30-50% of lesions will be completely resectable. In these cases, although there is no proven benefit currently, adjuvant chemoradiotherapy is typically utilized (1).

Primitive Neuroectodermal Tumor

Peripheral primitive neuroectodermal tumors (PNET) are yet another type of “small round blue cell” tumors. They are rare pediatric malignancies although 42% of PNETs present in the head and neck. PNET seems to peak in adolescents and has no sex predilection. Their true incidence is difficult to determine because these tumors can be mistakenly labeled as one of the other small round blue cell tumors such as RMS, neuroblastoma or NHL. Differentiation between these malignancies can be aided by immunohistochemistry and genetic analysis. PNET will positively stain for NSE, S100 protein and MB2 and chromosome analysis has shown an 11:22 translocation (although this has also been found in Ewing’s sarcoma). Presentation

Metastatic disease present at the time of diagnosis was demonstrated in 27% of head and neck cases. The common sites of distant spread include lung, bone and bone marrow, so diagnostic work-up should include CXR or CT chest, bone scan and bone marrow biopsy. Multimodality therapy is used for PNET and like other soft-tissue tumors emphasizes complete surgical resection if possible along with XRT and chemotherapy. Although these tumors are radiosensitive, XRT alone does not appear to be adequate. Chemotherapy protocols have included use of cyclophosphamide, doxorubicin, anthracyclines and alkylating agents. PNET is often rapidly progressive and a 2-year overall survival is only 65%, this drops to a dismal 38% in patients with disseminated disease (15).

Bibliography

1. Smith, RJ, Robinson, RA. Head and Neck Malignancies. In, Pediatric Otolaryngology Head and Neck Surgery, CW Cummings, et al Eds. Mosby, St. Louis; 1998: 229-247.
2. Albright, JT, Topham, AK, Reilly, JS. Pediatric Head and Neck Malignancies: US Incidence and Trends Over 2 Decades. Archives of Otolaryngology-Head and Neck Surgery. June 2002,128 (6); 655-659.
3. Bent JP, Hebert, RL, Smith, RJ. Pediatric Neck Neoplasms. In, Pediatric Otolaryngology, RF Wetmore, HR Muntz, TJ McGill, Eds. Thieme Medical Publishers, Inc., New York; 2000: 993-1019.
4. Harley, EH. Asymmetric Tonsil Size in Children. Archives of Otolaryngology-Head and Neck Surgery. July 2002, 128 (7); 767-769.
5. Samuelsson, BO, Ridell, B, Rockert, L, et al. Non-Hodgkin Lymphoma in Children: A 20-Year Population-Based Epidemiologic Study in Western Sweden. Journal of Pediatric Hematology/Oncology. Mar/Apr 1999, 21 (2); 103-110.
6. Beverly, RR. Hodgkin's Disease in Childhood: A Review. Journal of Pediatric Hematology/Oncology. Nov/Dec 1997, 19 (6); 502-509.
7. Ferguson, MO. Rhabdomyosarcoma. Emedicine.com/ENT/topic641.htm.
8. Daya, H, Chan, HS, Sirkin, W, Forte, V. Pediatric Rhabdomyosarcoma of the Head and Neck Is there a place for surgical management? Archives of Otolaryngology Head and Neck Surgery. Apr 2000, 126 (4); 468-472.
9. Beverly, RR, Anderson, JR, Barr, FG, et al. Rhabdomyosarcoma and Undifferentiated Sarcoma in the First Two Decades of Life: A Selective Review of Intergroup Rhabdomyosarcoma Study Group Experience and Rationale for Intergroup Rhabdomyosarcoma Study V. Journal of Pediatric Hematology/Oncology. May 2001, 23 (4);215-220.
10. Castleberry, RP. Biology and Treatment of Neuroblastoma. Pediatric Oncology. Aug 1997, 44 (4); 919-937.
11. Kumar, M, Fallon, RJ, Hill, JS, Davis, MM. Esthesioneuroblastoma in Children. Journal of Pediatric Hematology/Oncology. Aug/Sept 2002, 24 (6); 482-487.
12. McGill, TJ, Rahbar, R. Neoplasms of the Midface and Anterior Skull Base. In, Pediatric Otolaryngology, RF Wetmore, HR Muntz, TJ McGill, Eds. Thieme Medical Publishers, Inc., New York; 2000: 513-520.
13. Casanova, M, Ferrari, A, Gandola, L, et al. Undifferentiated Nasopharyngeal Carcinoma in Children and Adolescents: Comparison Between Staging Systems. Annals of Oncology. 2001, 12; 1157-1162.
14. Ghim TT, Briones, M, Mason P, et al. Effective Adjuvant Chemotherapy for Advanced Nasopharyngeal Carcinoma in Children: A Final Update of a Long-term Prospective Study in a Single Institution. Journal of Pediatric Hematology/Oncology. Mar/Apr 1998, 20 (2); 131-135.
15. Jones, JE, McGill, T. Peripheral Primitive Neuroectodermal Tumors of the Head and Neck. Archives of Otolaryngology Head and Neck Surgery. Dec 1995, 121 (12); 1392-1395.