

Pediatric Facial Plastic and Reconstructive Surgery

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Chapter 17: Malignant and Benign Tumors of the Head and Neck in Children

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Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in infants and children. The peak incidence of rhabdomyosarcoma occurs in children between 2 and 5 years of age, and a second peak is seen in teenagers between 15 and 19 years of age. In the final report of 686 patients from the First Intergroup Rhabdomyosarcoma Study (IRS), the median age at diagnosis for a child presenting with rhabdomyosarcoma of any primary site was 7 years; 4% of patients were less than 1 year of age at presentation; 38% were younger than 5 years of age, and 63% were 10 years of age or younger.

Rhabdomyosarcoma occurs somewhat more frequently in boys than in girls, at a ratio of approximately 1.4:10. The annual incidence of rhabdomyosarcoma in the USA has been estimated to be 4.4 per million in white children and 1.3 per million in black children.

The most common site of origin for rhabdomyosarcoma is in the head and neck - the orbit, eyelid, and cranial parameningeal region (35%), followed by the genitourinary tract (21%), extremities (19%), trunk (9%), retroperitoneum (5%), and others.

The conventional histopathologic classification system proposed by Horn and Enterline in 1958 is still utilized widely today, though there have been many recent challenges to this system as a result of advances in the sensitivity of cytologic and histologic techniques.

Embryonal rhabdomyosarcoma is the most common form of childhood rhabdomyosarcoma, accounting for 56% of all cases, and the majority of pediatric head and neck rhabdomyosarcoma, including orbital primaries. Embryonal rhabdomyosarcoma is a tumor of early childhood, most commonly presenting between 3 and 12 years of age. The histomorphology of embryonal rhabdomyosarcoma usually consists of a mixture of small, spindle-shaped cells, with tapering bipolar cytoplasmic extensions, and small round to oval lymphocyte-sized cells with little cytoplasm.

Botryoid rhabdomyosarcoma is a subtype of embryonal rhabdomyosarcoma. The botryoid refers to the gross appearance of these tumors, which are found beneath the mucosal lining of hollow organs or of body cavities, or the nasopharynx, and which manifest clinically as grape-like exophytic masses protruding into the adjacent lumen. Histologically, these lesions have a hypocellular to acellular myxoid central region with a densely cellular peripheral region just below the overlying mucosa known as the "cambium layer". Although interesting, these tumors are quite rare in the head and neck, and account for only 5% to 6% of pediatric rhabdomyosarcoma at all sites.

Alveolar rhabdomyosarcoma, sometimes called the rhabdomyosarcoma of adolescence, typically occurs in individuals 10 to 25 years of age and most commonly is found in the trunk or extremities. Most series show approximately 20% or less of head and neck rhabdomyosarcomas to be of the alveolar subtype.

The histomorphology of alveolar rhabdomyosarcoma classically shows a framework of interlacing fibrous trabeculae that separates small nests of quite undifferentiated round or oval cells in which the central cells are loosely cohesive, forming a pattern that microscopically mimics pulmonary alveolar spaces.

Pleomorphic rhabdomyosarcoma, often referred to as the adult type of rhabdomyosarcoma, is very rare in the pediatric population, being found in less than 1% of all pediatric patients included in the IRS-I and IRS-II studies. Its histomorphology is variable, classically showing large anaplastic cells, multinucleated tumor cells, spindle and strap cells, and tumor giant cells. They often occur in extremities. The diagnosis of pleomorphic rhabdomyosarcoma is becoming rare, even in adults, as more of these tumors are now classified as pleomorphic malignant fibrous histiocytomas.

Juvenile-type embryonal and alveolar rhabdomyosarcoma, nonetheless, do occur in adults, and must be considered in the differential diagnosis of small cell tumors in the adult population. The biologic behavior of these tumors in younger adult patients has been shown to be similar to their behavior in the pediatric population.

As with any histopathologic categorization system that is applied to a spectrum of neoplasia, the conventional system as outlined by Horn and Enterline for rhabdomyosarcoma cannot be applied to all related tumors. Nearly 20% of the 1,626 specimens that were included in the IRS-I and -II studies could not be classified in these four conventional categories. Extrasosseous Ewing's sarcoma (5%), small round cell sarcoma, type indeterminate (STI) (8%), and another group described as unclassifiable sarcomas (NOS) (5%), are other recognized categories of small cell mesenchymal sarcomas that are included in the treatment protocols and analyses of the intergroup rhabdomyosarcoma studies I and II.

The staging system for rhabdomyosarcoma utilized in the multicenter, cooperative group trials of the IRS is the most popular staging system in use today in the USA (Table 1). It is a classification system that depends largely on the results of the initial surgical procedure, and is therefore of limited initial value prior to surgery. Additionally, there is no way to incorporate variables such as tumor histologic subtype, tumor size, and tumor location. The IRS is attempting to compare this surgico-pathologic staging system to a new pretreatment, modified TNM staging system (the IRS TGNM system), which accounts for the other important variables previously mentioned in regard to tumor behavior. Other staging systems for pediatric rhabdomyosarcoma, some based on pretreatment criteria alone, also exist.

The histologic subtype of rhabdomyosarcoma has been shown to correlate with patient survival. Patients with alveolar rhabdomyosarcoma and the lesser known small round cell sarcoma, type indeterminate (STI), show decreased survival compared to the other histologic subtypes of rhabdomyosarcoma. Patients with embryonal rhabdomyosarcoma and extrasosseous Ewing's sarcoma have intermediate prognosis, and patients with the botryoid variant of embryonal rhabdomyosarcoma have the best prognosis for survival.

Table 1. *Surgical-pathological grouping system used in intergroup rhabdomyosarcoma studies I and II*

Group	Description
I	Localized disease, completely resected (regional nodes not involved)
A.	Confined to muscle or organ of origin
B.	Contiguous involvement with infiltration outside the muscle or organ of origin (as through fascial planes)
II	
A.	Grossly resected tumor with microscopic residual disease; no evidence of regional node involvement
B.	Regional disease, completely resected (regional nodes involved and/or extension of tumor into an adjacent organ); all tumor completely resected with no microscopic residual tumor
C.	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual tumor
III	Incomplete resection or biopsy with gross residual disease
IV	Distant metastatic disease present at diagnosis (lung, liver, bones, bone marrow, brain, and distant muscle and nodes).

Additionally, alveolar rhabdomyosarcoma has shown the highest proportion of distant metastasis and the lowest occurrence of local progression. Alveolar rhabdomyosarcoma also may manifest a higher rate of regional lymph node metastasis, but this trait is debatable.

The behavior and prognosis of rhabdomyosarcoma depends in large part on the site of the primary tumor. In the head and neck region, rhabdomyosarcoma most commonly presents in the orbit, followed in descending order of frequency by the pharynx (nasopharynx, oropharynx, and hypopharynx), the soft tissues of the head and neck, the temporal bone, and the paranasal sinuses. Other areas of presentation include the oral cavity, parotid gland, infratemporal fossa, nasal cavity, and larynx.

More than one-fourth of head and neck sarcomas arise in the orbit. When the primary tumor is in the orbit or eyelid, the presentation is usually a progressive unilateral proptosis in a child less than 13 years of age. The requirement for surgery is limited to biopsy, and the survival rate with multiagent chemotherapy and radiotherapy is excellent (93% 3-year survival). Regional lymph node metastases are unusual because these tumors usually present early, and because the orbit is scantily supplied by lymphatics.

Parameningeal sites include the nasopharynx, middle ear and mastoid region, nasal cavity, paranasal sinuses, infratemporal fossa, and pterygoid fossa. Parameningeal rhabdomyosarcoma is of special interest because of the potential for direct spread to the meninges and into the central nervous system. Clearly, meningeal involvement at diagnosis is an unfavorable prognostic sign. Of 57 patients with nonorbital parameningeal sarcoma from the IRS-I study, 20 patients (35%) developed meningeal sarcoma and 90% (18/20) died of this

complication. This has led to the development of "intensive" IRS treatment protocols involving aggressive meningeal radiotherapy with whole cranial or craniospinal radiation, multiagent systemic chemotherapy, and intrathecal chemotherapy administered via lumbar puncture. Even with such aggressive treatment, the 3-year survival among IRS patients with nonorbital parameningeal tumors with meningeal extension has been 57% compared with 90% among those patients with meningeal involvement. Extensive erosion of the craniofacial bones or skull base, or both, independent of meningeal involvement, appears to be an important predictor for local treatment failure in controlling nonorbital rhabdomyosarcoma of the head and neck. Identified risk factors for meningeal involvement are intracranial extension of tumor, bony erosion of the cranial base, and cranial nerve palsy.

Nonorbital nonparameningeal pediatric rhabdomyosarcoma occurs in the neck, parotid region, cheek, masseter muscle, oral cavity, oropharynx (usually the tonsil or soft palate), larynx, hypopharynx, scalp, face, and pinna. As a group, these tumors have been shown to have an intermediate prognosis. However, patients with a primary tumor in the neck were found to have a significantly worse prognosis, with only a 54% relapse-free survival rate, being more likely to relapse locally or distantly. Nonorbital rhabdomyosarcoma of the head and neck has a low incidence of cervical lymphatic metastases (approximately 3%); as a result, prophylactic radical neck dissection is not recommended.

Management of a suspected head and neck rhabdomyosarcoma in a pediatric patient should begin with a diagnostic evaluation, including a complete history and a thorough physical examination. Laboratory studies should include a complete blood count, urinalysis, chest x-ray, and blood chemistry profile including creatinine, bilirubin, uric acid, alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT) or AST, and lactic dehydrogenase (LDH).

Metastatic spread of rhabdomyosarcoma occurs both by lymphatic and hematogenous routes, the most common sites of hematogenous metastatic disease being the lung, bones, and bone marrow. Metastases to the lungs are frequent, and are evaluated best by computed tomography (CT) of the chest. Evaluation for osseous metastases is accomplished with conventional bone scans and bone marrow aspirate.

Regional tumor extent can be evaluated radiographically with CT, looking for evidence of skull base erosion or other extensive bone erosion. Magnetic resonance imaging (MRI) also is helpful in delineating the precise extent of these tumors. Rhabdomyosarcoma enhances after administration of MRI contrast media and shows a high-intensity signal on T2-weighted images. Unfortunately, other relatively common tumors of the head and neck such as lymphoma and nasopharyngeal carcinoma often also have the same signal intensity characteristics as rhabdomyosarcoma. Surgical management should include an attempt at complete tumor extirpation if possible without inflicting major functional disability. At times it is ill-advised to attempt complete removal of the tumor at initial surgery. In these situations, the initial surgical procedure simply will be a biopsy of the mass. Biopsy alone is advocated for orbital rhabdomyosarcoma because of the excellent long-term results with combined radiation and chemotherapy without surgical extirpation. In certain circumstances, particularly with parameningeal head and neck rhabdomyosarcomas, definitive resection of the tumor may need to be withheld until at least a partial course of chemotherapy and radiation therapy has been given.

The importance of obtaining clear surgical margins without microscopic residual disease remains at issue. Survival curves from IRS-I data indicate that patients with microscopic residual disease postoperatively (group II cases) fare no worse than patients without any residual disease (group I). The presence of macroscopic disease postresection, however, has been a poor prognostic sign in all IRS studies.

Prior to IRS studies, radiation dosages in the range of 6.00 cGy were given routinely to patients with rhabdomyosarcoma. Though local control rates with such radiotherapy were promising, long-term complications were excessive. In IRS-I, -II, and -III, radiation dosages in the range of 4.000 to 5.500 cGy were found to result in effective local tumor control. Dosages less than 4.000 cGy led to increased local recurrence rates. Radiation therapy is currently recommended to all patients with residual disease following surgical resection. Data from IRS-I indicates that radiation treatment is not necessary in patients with group I disease. IRS studies currently are piloting the use of hyperfractionated radiation therapy (5.940 cGy) for patients with advanced stage disease. With such therapy, long-term consequences of high-dose radiotherapy may be minimized.

Chemotherapeutic agents with usefulness in rhabdomyosarcoma include vincristine, actinomycin D, cyclophosphamide, cis-platinum, doxorubicin, etoposide, ifosfamide, and melphalan. Each has shown efficacy in single agent trials. The combination of vincristine, actinomycin D, and cyclophosphamide (VAC) has become the foundation from which IRS chemotherapy studies are evaluated.

In IRS-I, patients with group I disease exhibited an 82% to 84% relapse-free survival when treated with VAC (irrespective of radiotherapy). Patients with group II disease did as well when treatment with triple agent VAC was compared to treatment only with vincristine plus actinomycin D (without cyclophosphamide). Furthermore, patients with group III and group IV disease found no additional benefits when anthracyclines (Adriamycin) were added to their VAC regimen. Three-year relapse-free survivals of 60% to 70% were seen in these advanced-stage patients.

In IRS-II, the VAC regimen was intensified by repeating the three drugs over 4-week intervals during 2 years of therapy. The benefits of using anthracyclines again were examined in IRS-II. To date, overall survival rates for all patients treated with IRS-II appear to be significantly better than for those patients treated with IRS-I. In IRS-III, the addition of cis-platinum and etoposide to VAC regimens is being examined. In pilot studies for upcoming IRS-IV protocols, trials of melphalan plus VAC, ifosfamide plus etoposide plus VAC, and ifosfamide plus doxorubicin plus VAC are being studied in advanced stage disease. Finally, most regimens recommend the use of central nervous system prophylaxis in patients with meningeal involvement with rhabdomyosarcoma. Prophylaxis generally consists of some combination of radiotherapy and triple agent intrathecal chemotherapy (hydrocortisone, cytosine arabinoside, methotrexate). Per IRS guidelines, patients whose tumors extend intracranially from the primary site should receive both cranial radiotherapy plus intrathecal therapy. In patients with cerebrospinal fluid involvement, the radiation should include the entire craniospinal axis. Patients whose tumors do not extend intracranially, but do cause cranial nerve palsies or erosion of the skull base, should receive extended field radiotherapy to the site of disease plus intrathecal therapy. Patients with parameningeal tumors that do not extend intracranially, do not erode the skull base, do not cause cranial nerve palsies, and do

not involve the cerebrospinal fluid, do not require intrathecal chemotherapy or cranial irradiation. They should receive extended field radiotherapy to the primary site, however.

Additional Comments Regarding Management

In cases of suspected rhabdomyosarcoma, preoperative consultation with the hematology-oncology service and the pathology department should be obtained. Anderson et al recommend that the initial surgical procedure in a case of suspected rhabdomyosarcoma be performed at a tertiary care center so that adequate facilities for thorough histopathologic evaluation are available. At times, fresh tissue is needed for advanced tumor marker studies. Frequently, electron microscopy, which requires special fixation of the tissue in solutions such as glutaraldehyde, is necessary to achieve a diagnosis in these cases. In addition, if frozen section suggests the tumor to be rhabdomyosarcoma, a bone marrow aspiration and biopsy can be performed at the time of surgery to evaluate the status of the bone marrow and, if a parameningeal site is involved, the child can undergo a diagnostic lumbar puncture during the same anesthetic administration.

The IRS-III program is collecting data that will determine whether there is a difference in the prognosis of group III patients whose tumors have been debulked at the time of initial biopsy in cases where total tumor extirpation is not a feasible option. The incomplete surgical removal (debulking surgery) will be categorized as less than 50% tumor excision versus greater than 50% tumor excision.

Additionally, it is hoped the IRS-III study will provide information regarding the efficacy of secondary operations, wherein a delayed resection of the primary tumor is performed after the first 20 weeks of treatment.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

Soft tissue sarcomas of childhood may be divided into two general groups: rhabdomyosarcoma and nonrhabdomyosarcoma (non-RMS) sarcomas. Each group accounts for about 50% of soft tissue sarcomas in children. Non-RMS soft tissue sarcomas of the head and neck region include fibrosarcomas, alveolar soft part sarcomas, synovial sarcomas, hemangiopericytomas, and neurofibrosarcomas. These lesions typically present as firm, slowly enlarging masses. Associated symptomatology is determined by the location and degree of mass effect exerted by the tumor itself. Both local extension and hematogenous metastases commonly occur.

Two age peaks, one in infancy/early childhood and the other in adolescence, are common with these tumors. Prognosis, in general, appears to be related to the age at presentation. Non-RMS soft tissue sarcomas of infants and young children often exhibit a benign behavior, requiring surgical excision alone. Non-RMS soft tissue sarcomas in adolescent patients are typically aggressive in nature, and require multimodal treatment.

Wide local excision remains the mainstay of treatment for all non-RMS soft tissue sarcomas. The ability to achieve a gross tumor resection is probably the most important determinant of disease-free survival. Obviously, total resections are not always possible in managing these tumors. For cases in which surgical resection is incomplete (with either

microscopic or macroscopic residual disease), adjuvant therapy is required.

For congenital fibrosarcomas in young children, there is no evidence that either chemotherapy or radiotherapy is needed in the primary treatment of grossly resected tumors. Radiation therapy in dosages of 4,000-6,000 cGy may be used for local control of unresectable disease. Chemotherapy regimens such as VAC (vincristine, dactinomycin, and cyclophosphamide), or ifosfamide plus etoposide may be used in treating unresectable or metastatic congenital fibrosarcoma. Fibrosarcomas of young adults commonly employ VAC-type regimens for primary disease control.

Grossly resected neurofibrosarcomas, like congenital fibrosarcomas, are treated best with surgery alone. No benefits have been found in using adjuvant chemotherapy after gross resections have been performed. Chemotherapy for unresectable primary or metastatic disease remains ill-defined. Trials combining doxorubicin, vincristine, dactinomycin, and cyclophosphamide have shown only marginal results in treating neurofibrosarcomas. Ifosfamide and etoposide are currently being studied in neurofibrosarcomas. Radiation therapy remains useful in achieving local control for both microscopic and macroscopic residual disease.

In contrast to other soft tissue non-RMS sarcomas, hemangiopericytomas are best treated by wide local excision in combination with chemotherapy. The high incidence of metastatic disease and the excellent response to chemotherapy have led many investigators to utilize chemotherapy in controlling primary disease. Cyclophosphamide, vincristine, methotrexate, doxorubicin, and mitoxantrone all have been tried with some success. Radiotherapy is reserved for local control of microscopic and macroscopic residual disease.

Alveolar soft part sarcomas remain extremely difficult to treat. Though 80% of patients will be alive 2 years following surgical resection, the majority of patients will eventually relapse and die of progressive disease. The most frequent sites of occurrence of alveolar sarcomas are the orbit and tongue. Females are affected more commonly than males. As many as one-third of all patients may present with metastatic disease prior to even identifying the primary lesion. Bone, brain, and lungs are the most common sites of metastases. Current initial management relies upon gross surgical resection. Chemotherapy is rarely used in the treatment of grossly resected primary disease. Responses to radiation therapy have been reported to be poor.

Synovial sarcomas occur most commonly in young adults, and rarely in children. Due to its rarity, treatment guidelines for pediatric patients with synovial sarcomas remain unclear. Combinations of wide local excision with high-dose radiotherapy (> 6,000 cGy) are being compared to excision alone. The role for adjuvant chemotherapy is not yet documented for young adults with resected disease. VAC chemotherapy regimens have shown some promise in unresected or recurrent disease.

A full discussion of osteogenic sarcomas and Ewing's sarcomas is beyond the scope of this text. Osteogenic sarcomas and Ewing's sarcoma comprise over 80% of all malignant bone tumors in children. Though extremity and trunk lesions are much more common, skull, mandibular, and maxillary lesions may occur in both tumors. As extensive debulking procedures are not often possible upon presentation, a limited resection for diagnostic

purposes is usually the initial surgical procedure performed. Adjuvant chemotherapy is then given for several courses before a more definitive resection is attempted. Multiple courses of chemotherapy subsequently follow. High-dose methotrexate, cis-platinum, and doxorubicin have shown high response rates in osteogenic sarcomas. VAC regimens with doxorubicin, and ifosfamide/etoposide regimens, have commonly been used on Ewing's sarcomas. Whereas osteogenic sarcomas are highly radioresistant, Ewing's sarcomas are radiosensitive.

Neuroblastoma

Neuroblastoma is the most common malignancy in infants under 1 year of age. About 500 new patients present with neuroblastoma annually in the USA.

Neuroblastoma arises from fetal neural crest cells of the sympathetic nervous system. The biologic behavior of neuroblastoma is one of the most fascinating of all pediatric malignancies. Spontaneous regression, as well as spontaneous and induced maturation to benign ganglioneuroma, is seen. Neuroblastoma most frequently arises in the adrenal medulla and presents as a hard abdominal mass. Other presentations include respiratory symptoms secondary to posterior mediastinal disease, urinary obstruction secondary to spinal cord compression from "dumbbell"-shaped paraspinal neuroblastoma extending through the vertebral foramen.

Only 2% to 4% of all neuroblastomas are cervical primaries. Primary cervical neuroblastoma most often occurs during the first 6 months of life and may be present at birth. Neuroblastoma may present as a firm indolent lateral neck mass. There may be associated feeding and respiratory disorders (hoarseness, stridor, dysphagia) secondary to mass effect on the pharynx, esophagus, larynx, or trachea. Ipsilateral Horner's syndrome from involvement of the cervical sympathetic ganglia and heterochromia of the iris representing a related neural crest cell abnormality may be presenting signs. Metastatic disease to the neck from more inferior primary sites is a more common etiology of cervical neuroblastoma and this possibility always must be considered.

Approximately two-thirds of all children with neuroblastoma have metastatic disease at presentation. Neuroblastoma spreads via local lymphatics as well as hematogenously to bone, bone marrow, and liver. Metastatic neuroblastoma to the head and neck may present as proptosis and periorbital ecchymosis if orbital infiltration has occurred. Bone metastases may present as masses over the skull and mandible. Subcutaneous metastatic nodules are bluish, nontender, mobile, and may be widespread.

Recommended metastatic evaluation includes CT, radionuclide bone scan, and metaiodobenzylguanidine (MIBG) scanning. MIBG is a norepinephrine analogue that is taken up by neuroblastoma tissue and can be labeled with a radionuclide to detect primary or metastatic disease. The urine should be checked for elevated catecholamines and bone marrow aspiration may be appropriate. The classic staging system for neuroblastoma proposed by Evans in 1971 is based on the extent of disease (Table 2).

Table 2. *Evans staging system for neuroblastoma*

I	Tumor confined to the organ or structure of origin.
II	Tumor extending in continuity beyond the organ or structured of origin but not crossing the midline; regional lymph nodes on the homolateral side may be involved.
III	Tumors extending in continuity beyond the midline; regional lymph nodes bilaterally may be involved.
IV	Remote disease involving bone, parenchymatous organs, soft tissues or distant lymph node groups, or bone marrow.
IV-S	Patients who would otherwise be stage I or II but who have remote disease confined to one or more of the following sites: liver, skin, or bone marrow (without evidence of bone metastases).

Treatment

Surgery, radiation therapy, and chemotherapy all play a role in the treatment of neuroblastoma. Stage of the disease, as well as the age of the patient, influence the therapeutic regimen and prognosis. Children under 1 year of age have the best prognosis. Localized neuroblastoma that can be resected without gross residual tumor and with which there is no regional lymph node involvement usually is treated surgical resection alone. It is important to sample regional lymph nodes, if identifiable, at the time of surgery for staging purposes. Microscopic residual disease does not appear to worsen the prognosis significantly.

Stage II neuroblastoma also is treated initially by careful surgical excision, with a 90% disease-free survival rate unrelated to size of the primary tumor, intraspinal involvement, extent of resection, and subsequent treatment with radiotherapy or chemotherapy, or both. In general, chemotherapy is not recommended as primary therapy in these patients, but may be used to salvage patients who relapse. Neuroblastoma is relatively radiosensitive and radiation has been included as part of the treatment for many patients with group II and III disease. The optimum radiation dose is not known as there is not a well-defined dose-response curve for the tumor. Tumors have been treated with doses ranging from 900 to more than 4.000 cGy, together with systemic chemotherapy. Patients with metastatic disease or poor prognostic features have been treated with total body irradiation, high-dose chemotherapy, and autologous bone marrow rescue, giving long-term survival rates of 40% to 50% in selected patients.

Patients with stage III or IV neuroblastoma require multiagent chemotherapy with or without radiation therapy. Delayed surgery often is employed. Chemotherapeutic agents used for neuroblastoma include cyclophosphamide, doxorubicin, cis-platinum, etoposide, and vincristine. Purged autologous, or allogenic, bone marrow transplantation, following high-dose chemotherapeutic preparative regimens, is reserved for patients who fail standard chemotherapy.

The management of stage IV-S neuroblastoma remains controversial. Treatment approaches range from supportive care only to surgical removal of the primary tumor. Chemotherapy is debatable, but probably is required in patients with massive liver or bone marrow metastases.

Esthesioneuroblastoma (olfactory neuroblastoma) is a related tumor of the olfactory area, thought to be of either neuroectodermal or neural crest origin. Twenty percent of cases occur in childhood or adolescence. Management is primarily with surgery and radiotherapy, usually with radiotherapy following surgery. Preoperative chemotherapy and radiation therapy followed by surgical resection have been promoted in advanced cases. Recently, good results have been reported with craniofacial resection alone, without radiotherapy, in patients diagnosed with esthesioneuroblastoma limited to the nasal cavity without evidence of cribriform plate erosion.

Thyroid Cancer

Thyroid cancer is an uncommon disease in childhood. The annual incidence in the USA is 5 cases/million/year for children less than 20 years of age. Girls are affected more than boys and the majority of children affected are over 10 years of age.

The association of well-differentiated thyroid carcinomas with prior radiation therapy became apparent in the 1950s. In the 1940s, radiotherapy was frequently used to treat tonsillar and adenoidal hypertrophy, cystic hygromas, and hemangiomas. This led to an epidemic of thyroid cancer in children. Thyroid cancer also has been shown to follow radiation for other malignancies, in particular Hodgkin's disease.

Other factors implicated in the development of thyroid cancer include prolonged thyroid-stimulating hormone (TSH) stimulation and thyroiditis. Medullary carcinoma of the thyroid (MCT) most often occurs in patients with multiple endocrine neoplasia (MEN) type II. These are autosomal dominant disorders. Patients also develop pheochromocytoma, hyperparathyroidism and, in type IIb, mucosal neuromas.

Four histologic types of thyroid cancer are described: papillary, follicular, medullary, and anaplastic or undifferentiated. Papillary carcinoma of the thyroid is the most common type and represents 80% of cases in children. Follicular adenocarcinoma is the second most common type representing 5% to 10% of thyroid cancers in children. Many tumors have mixed papillary and follicular elements and are classified under papillary carcinoma. Treatment and prognosis for papillary, follicular, and mixed type are similar, so they are often grouped together as well-differentiated carcinoma of the thyroid. Medullary carcinoma of the thyroid develops from the parafollicular or C cells of the thyroid, and represents about 5% of childhood cases. Anaplastic or undifferentiated carcinomas are rare in children but are highly aggressive and metastasize widely.

Children with thyroid cancer usually present with a solitary thyroid nodule or cervical adenopathy, or both. Most patients (70%) will have cervical metastases at diagnosis. Pulmonary metastases are present in about 15% of patients at diagnosis. Bone metastasis can also occur. Patients with MEN IIb also may demonstrate dysmorphic facial features and mucosal neuromas.

The majority of patients are euthyroid at presentation with normal T_3 , T_4 , and TSH levels. Antithyroid and antimicrosomal antibodies are absent unless the patient has an associated autoimmune thyroiditis. Thyroglobulin levels may be elevated and can serve as markers for response to therapy or relapse. Screening tests for baseline calcitonin as well as

calcitonin levels following calcium and pentagastrin stimulation are recommended for all children with a family history of MEN IIa or IIb. Routine screening can lead to early diagnosis and treatment of MCT in these patients.

Soft tissue x-rays of the neck may show calcifications in patients with well-differentiated carcinomas. Chest x-ray should be obtained due to the high incidence of pulmonary metastases. Ultrasound studies can differentiate cystic from solid masses and can separate discrete nodules from diffuse enlargement of the gland. Radioisotope scans using I-131 and technetium pertechnetate are more helpful diagnostically. Cold nodules are highly suspicious for malignancy and must be excised. Management of hot nodules is more controversial because they are less likely to be malignant. However, because of the small risk of malignancy, some surgeons recommend biopsy of all solitary nodules in children. Fine needle aspiration is frequently used for diagnosis in adults, but there is much less experience with this technique in children. Evaluation for metastatic disease should include CT scan of chest and bone scan. Currently, there is no universally accepted staging system for thyroid cancer.

Surgery is the mainstay of treatment for thyroid carcinoma. The extent of surgery needed in well-differentiated thyroid carcinoma remains controversial. Current recommendations range from simple lobectomy with isthmusectomy to total thyroidectomy with radical node dissection. Major complications from total or near-total thyroidectomy include lifelong replacement therapy with thyroxine, damage to the recurrent laryngeal nerve, and hypoparathyroidism. However, partial thyroidectomy limits the usefulness of radioactive iodine in detecting occult metastatic disease; thus, some surgeons prefer to perform total thyroidectomy in all patients.

In patients with evidence of nodal involvement, extensive lymph node dissection, as well as total thyroidectomy, is indicated. Total thyroidectomy is also indicated in patients with gross bilateral disease and metastatic disease so that radioactive iodine therapy can be used.

Patients with a family history of MEN II should be screened routinely for medullary carcinoma of the thyroid. The screening tests consist of stimulation with calcium and pentagastrin followed by measurement of immunoreactive calcitonin. When calcitonin is elevated, total thyroidectomy with lymph node dissection is indicated. When lymph nodes are positive, a modified radical neck dissection with preservation of the sternocleidomastoid muscle should be performed.

For anaplastic carcinoma, total thyroidectomy with lymph node dissection should be performed due to the local invasiveness of this neoplasm.

The ability of many differentiated thyroid carcinomas to take up iodine introduces the possibility of selectively targeting these tumors using radioactive isotopes of iodine. Iodine 131, given systemically, may be used following surgery for papillary and follicular thyroid cancers. Radiation from this type of treatment is well confined to the tumor with relatively small amounts of radiation delivered to other areas of the body. In instances where there is gross residual tumor, particularly when it does not take up iodine, external radiotherapy with doses in the range of 4,500 to 6,000 cGy may be necessary to help control local disease. Anaplastic thyroid carcinomas are usually aggressive tumors requiring multimodality treatment

with surgery, chemotherapy, and high-dose radiotherapy in the range of 5.000 to 6.000 cGy.

Prolonged TSH stimulation of thyroid tissue may contribute to the growth of metastatic tissue. Thus, it is generally accepted that patients with differentiated thyroid carcinoma be placed on thyroid suppressive therapy with levothyroxine for life.

Results of chemotherapy in treating carcinoma of the thyroid are disappointing. Adriamycin alone demonstrates some effectiveness and, in combination with cisplatin, may have additional benefits.

Overall prognosis for patients with well-differentiated carcinoma of the thyroid is excellent. Even though children are more likely to have metastatic disease at diagnosis than adults, their disease-free survival rates approach 90%. Importantly, recurrences can occur as long as 20 years after initial presentation so lifelong surveillance is crucial.

Lymphomas of the Head and Neck

Lymphoma is the second most common solid malignancy in children under 15 years of age, second only to solid tumors of the central nervous system. Therefore, the otolaryngologist can expect to encounter lymphomas as the most common extracranial solid tumor of the head and neck in children. Together, Hodgkin's lymphoma and non-Hodgkin's lymphoma account for approximately 12% of all childhood cancer, but Hodgkin's and non-Hodgkin's lymphoma differ so greatly that they are best discussed separately.

Hodgkin's Disease

The age at onset of Hodgkin's disease demonstrates bimodal incidence peaks. In industrialized countries, the earliest peak occurs in the mid-to-late 20s, and the second peak occurs in late adulthood. It appears that less than 10% of all cases of Hodgkin's disease occurs in children 15 years of age or younger. Hodgkin's disease is quite rare before age 5 years. From 5 to 11 years of age, boys with Hodgkin's disease outnumber girls 3:1, but by age 17 the male to female ratio becomes 1.5:1, due to an increased incidence in girls at the time of puberty.

Presentation

The usual clinical presentation is persistent painless cervical adenopathy, "rubbery" in consistency, and located in the supraclavicular fossa or, commonly, in the lower half of the neck. Upper neck node involvement is less frequent. The nodes may be tender if they are rapidly enlarging. Nearly 80% of children have unilateral or bilateral neck involvement at diagnosis. Approximately two-thirds of patients will have some mediastinal involvement at presentation and a chest radiograph is an important part of the initial evaluation if lymphoma is suspected in order to evaluate for mediastinal tumor and to assess the patency of the thoracic airway. Hodgkin's lymphoma, less commonly, also can present as axillary adenopathy and, in 4% of cases, the primary disease will present in a subdiaphragmatic state such as peripheral inguinal, femoral, or superficial iliac lymphadenopathy.

Splenomegaly or hepatomegaly, or both, indicate advanced disease. The most common extranodal sites of involvement are intrathoracic structures such as pulmonary parenchyma, pleura, and pericardium. Extranodal involvement of these structures usually occurs when the tumor breaks through the nodal capsule to invade these adjacent structures. Extranodal involvement of Waldeyer's ring is very uncommon, but has been reported in Hodgkin's disease.

Approximately one-third of children present with systemic symptoms such as unexplained fevers, night sweats, and unexplained weight loss of 10% in the previous 6 months. These symptoms are felt to be secondary to the elaboration of cytokines by the tumor cells.

Histologic Subtypes

According to the currently utilized Rye classification system, Hodgkin's disease is divided into four histologic subtypes (Table 3).

Table 3. *The Rye classification of histologic subtypes of Hodgkin's disease*

Lymphocyte predominance (LP)
Mixed cellularity (MC)
Lymphocyte depletion (LD)
Nodular sclerosis (NS).

Each histologic subtype has its own characteristic histologic architecture and ratio of apparently normal or reactive cells, such as lymphocytes, plasma cells, and eosinophils, to the cytologically abnormal Reed-Sternberg cell.

In lymphocyte predominant Hodgkin's disease, the cellular proliferation involves benign-appearing lymphocytes. The lymph node architecture may be partly or completely destroyed. The histologic picture may be misinterpreted as benign hyperplasia. Often, several sections must be examined before the diagnostic Reed-Sternberg cells are found.

In mixed cellularity Hodgkin's disease, Reed-Sternberg cells are plentiful; the lymph node architecture is usually diffusely effaced. Focal necrosis may be present. Mixed cellularity subtype is seen most commonly in children 10 years of age or less.

In lymphocyte depletion Hodgkin's disease, there is a scarcity of lymphocytes and a predominance of abnormal cells. Fibrosis and necrosis are common. Lymphocyte depletion Hodgkin's disease is quite rare in children.

The nodular sclerosis variant of Hodgkin's disease is distinguished histologically by a thickened capsule with bands of birefringent collagen, which divide the tumor into discrete nodules and by the lacunar variant of the Reed-Sternberg cell. The nodular sclerosis variant occurs more frequently in adolescents and young adults. It has a propensity to involve the lower cervical, supraclavicular, and mediastinal lymph nodes.

Nodular sclerosis appears to be the most common form of childhood lymphoma, accounting for 39% to 63% of cases in larger series, followed, in descending order of frequency, by the mixed cellularity subtype (19% to 34%), the lymphocyte predominant subtype (13% to 23%), and, finally, the relatively rare lymphocyte-depleted subtype of Hodgkin's disease (1% to 5%).

Staging

The Ann Arbor staging classification system, adopted in 1971, remains the most popular system today (Table 4). This system is based on the assumption that Hodgkin's disease usually spreads from one adjacent nodal area to another, at least early in the disease.

If extralymphatic spread of disease remains local, so that it is amenable to treatment by radiotherapy, the substage designation "E" is applied.

Table 4. *Ann Arbor staging system for Hodgkin's disease*

Stage	Definition
I	Involvement of a single lymph node (I) or of a single extralymphatic organ or site (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of an extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement.

The absence or presence of unexplained fever $> 38^{\circ}\text{C}$, night sweats, or unexplained loss of 10% or more of body weight in the 6 months preceding admission are denoted in all cases by the suffix letters A or B, respectively.

Initial clinical staging is based upon physical examination, laboratory studies, chest radiographs, thoracic CT scans, bone marrow biopsy, and lymphography. Final pathologic staging can be based only on the results of surgical staging, which usually involves a laparotomy, splenectomy, and multiple liver biopsies. Any liver involvement represents stage IV disease. Laparotomy results in a change of stage in 20% to 30% of patients. Staging laparotomy is a major surgical procedure with significant potential postoperative complications, including intestinal obstruction secondary to adhesions and postsplenectomy bacterial sepsis by encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Nonetheless, surgical staging has been shown to result in improved relapse-free survival compared to clinically staged children. In almost all cases, patients who will be treated with radiotherapy alone should undergo pathologic staging including a staging laparotomy prior to beginning treatment.

Treatment

Treatment strategies for Hodgkin's disease include radiotherapy, multiagent chemotherapy, or a combination of the two modalities. The effective control of disease by these nonsurgical means has limited the initial role of surgery to a diagnostic biopsy. Accurate pathological staging that involves laparotomy is important in treatment planning and is another important role for surgery in the management of this disease.

Hodgkin's disease is a very radiosensitive tumor, and radiotherapy has been used in the treatment of this disease since the 1920s. Current radiotherapy techniques include involved field irradiation (IFI), when radiation is directed to areas of known disease, extended field irradiation (EFI), which involves radiation to additional sites adjacent to the involved area, and total lymphoid irradiation (TLI).

Involved field irradiation alone is felt by some investigators to be appropriate treatment for selected children with favorable presentations of clinically stage I disease and favorable histologic prognosis confined to the upper third of the neck or the inguinal-femoral area. In these patients, laparotomy may not be needed, but due to the scarcity of such patients, this approach has not been analyzed completely. In general, involved field radiotherapy will lead to a high relapse rate in all but the most favorable situations and, although salvage with chemotherapy and further radiation is useful, cure rates after relapse do not approach those achieved when aggressive treatment is administered initially. Most patients with clinical stage I or stage II disease should undergo a staging laparotomy.

Total nodal irradiation has been used alone in the past for treatment of stage III disease, with a 10-year survival rate of approximately 70%, and a relapse-free survival rate of 40% to 57%. Similarly, patients with advanced-stage disease have achieved only 40% to 60% long-term survival rates when treated with chemotherapy alone. Failures in treating advanced-stage disease with either chemotherapy or radiotherapy alone have led to the development of combined modality therapies. These combined programs, such as the use of low-dose radiotherapy and combination chemotherapy, yield the highest cure rates and are applicable particularly to young children with advanced-stage bulky disease (mediastinal masses greater than one-third the size of the thorax) and to those young children who are yet to undergo their major growth and development.

The MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone), and the subsequently introduced ABVD regimen (Adriamycin, bleomycin, vinblastine, imidazole carboxamide) are the most commonly used compounds in the multiagent chemotherapy regimens utilized in pediatric Hodgkin's disease. Although the MOPP regimen, introduced in the 1960s, is the most studied and accepted regimen, new trials with ABVD, and MOPP with ABVD plus low-dose involved field irradiation, have shown excellent survival and freedom from relapse in pediatric patients with Hodgkin's disease.

Even though dramatic strides have been made in the treatment of Hodgkin's disease, complications of therapy continue to be a major problem. Arrest of soft tissue and bony growth often occur in irradiation fields in children who have undergone prior irradiation therapy for Hodgkin's disease. Avascular necrosis and slipped femoral capital epiphyses have been reported in children receiving radiotherapy and chemotherapy that has included

prednisone.

Endocrine dysfunction has been associated with both irradiation and chemotherapy. Hypothyroidism is common following neck irradiation. Gonadal toxicity remains a significant problem for patients treated with MOPP therapy or with pelvic irradiation. Ovarian transposition before pelvic irradiation is recommended for affected females. ABVD appears to carry a much lower risk of sterility than MOPP in both males and females. Another major complication affecting treated patients is the increased risk of second malignancies seen in Hodgkin's disease. Patients treated with irradiation alone are at increased risk of developing secondary solid tumors, whereas patients treated with chemotherapy (or combined treatment) are at increased risk for developing acute nonlymphocytic leukemia or non-Hodgkin's lymphomas. Most secondary leukemias and non-Hodgkin's lymphomas occur within the first 5 years from the initial Hodgkin's disease diagnosis, whereas solid tumors are usually seen 10 years or more following initial diagnosis.

In summary, therapy for Hodgkin's disease in the pediatric patient should be curative in intent, and tailored to the age of the child and to the stage and extent of the disease, with concern for possible long-term complications of the therapy.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is not a single disease but a heterogeneous group of neoplasms that arise from the constituent cells of the immune system, together comprising approximately 10% of all pediatric cancers. Childhood non-Hodgkin's lymphomas differ significantly from the majority of non-Hodgkin's lymphoma seen in adults, and instead appear to be immunologically closely related to the childhood lymphoid leukemias.

In contrast to Hodgkin's disease, which has a bimodal incidence curve, the incidence of non-Hodgkin's lymphoma increases throughout life with increasing age. Approximately 97% of cases of non-Hodgkin's lymphoma occur in patients older than 20 years of age. The annual incidence of non-Hodgkin's lymphoma in children younger than 15 years of age is estimated at 9.1 per million in white children and 4.6 per million in black children. Non-Hodgkin's lymphoma occurs 1.5 times more frequently than Hodgkin's disease in childhood.

Children with acquired or inherited immune deficiency syndromes have a greatly increased risk of developing a malignant lymphoma. This group includes those patients receiving immunosuppressive agents associated with organ transplantation, patients with severe combined immunodeficiency, and patients with Wiskott-Aldrich syndrome, and ataxia-telangiectasia.

The etiology of non-Hodgkin's lymphoma, as with most neoplasms, remains unclear. An oncogenic role has been proposed for the Epstein-Barr virus (EBV), since EBV DNA and EBV nuclear antigen have been found in the tumor cells of patients with endemic Burkitt's lymphoma. This, however, has not been a consistent finding in patients with nonendemic Burkitt's lymphoma.

There are many classification schemes for non-Hodgkin's lymphoma. For childhood disease, the working formulation for non-Hodgkin's lymphoma is now widely used. Utilizing

this classification scheme, over 90% of non-Hodgkin's lymphoma can be categorized into three major subtypes, all of which histologically show high-grade malignancy. *Small, noncleaved lymphoma* (both Burkitt's and non-Burkitt's type), which represents 38.8% of all childhood non-Hodgkin's lymphoma, is usually a B cell-derived tumor. *Lymphoblastic lymphoma* represents 28.1% of childhood non-Hodgkin's lymphoma and is usually T cell-derived. *Large cell lymphoma* represents 26.3% of all childhood non-Hodgkin's lymphoma. Follicular pattern non-Hodgkin's lymphoma is almost universally absent in children.

The histopathology of non-Hodgkin's lymphoma is characterized by progressive effacement of normal lymph node architecture by malignant cells and, in non-lymphoid tissue, by infiltration of neoplastic cells between the normal organ-specific cells, collagen, or muscle fibers of involved tissues. The constellation of clinical findings at presentation often correlates well with the pathologic subtype.

The majority of children with lymphoma present with intrathoracic tumors, most often in the mediastinum, which can cause symptoms of dyspnea and dysphagia. Superior vena cava syndrome may develop, with swelling of the head, face, and upper extremities. Low-dose radiotherapy often is required in the initial management of such cases to control the tumor mass.

Patients with small, noncleaved lymphoma usually present with abdominal pain or swelling, a change in bowel habits, and iliac or inguinal adenopathy. Signs may mimic appendicitis. In cases of endemic Burkitt's lymphoma in Africa, jaw involvement is found in approximately 70% of children less than 5 years of age and in approximately 25% of children greater than 14 years of age.

In sporadic cases of Burkitt's lymphoma (nonendemic), jaw involvement occurs in 15% to 20% of patients, and is not age related.

Large cell non-Hodgkin's lymphoma often presents in atypical locations, such as facial, lung, and intracerebral locations as well as in the nasopharynx and bone. Large cell non-Hodgkin's lymphoma are frequently seen in children with inherited or acquired immunodeficiency syndromes and in patients receiving immunosuppressive therapy.

Staging

There are several staging systems for childhood non-Hodgkin's lymphoma based predominantly on tumor volume, but no staging system is uniformly acceptable. Tumor burden at presentation is the major determinant of treatment outcome in childhood non-Hodgkin's lymphoma.

Progression of a childhood non-Hodgkin's lymphoma does not follow an orderly pattern of local spread as is often seen in Hodgkin's lymphoma. Instead, rapid dissemination from apparently localized site of disease is often seen. Approximately 30% of patients with childhood non-Hodgkin's lymphoma will have head and neck lymphadenopathy at diagnosis.

In most staging systems, children with non-Hodgkin's lymphoma fall into two broad categories. Those with localized lymphoma or bulky abdominal lymphoma that has been

resected are classified as stage I or stage II. The patients with central nervous system metastases, extensive intrathoracic disease, unresected abdominal tumor, or bone marrow involvement are classified as stage III or stage IV. By convention, children with greater than 25% lymphoblasts in the bone marrow are classified as having acute lymphoblastic leukemia (ALL).

Bone marrow aspiration and lumbar puncture with cerebrospinal fluid cytologic examination are included in the staging workup, but staging laparotomy is not recommended in non-Hodgkin's lymphoma because chemotherapy is utilized universally.

Presentation

Approximately 24% of all non-Hodgkin's lymphomas originate in extranodal sites, with 34% of these involving head and neck structures. This compares with 15% of childhood non-Hodgkin's lymphomas, which arise in the head and neck area. Primary tumors arising from Waldeyer's ring may present with middle ear effusion or nasal obstruction. Among adults, the palatine tonsil is the most common extranodal primary site for non-Hodgkin's lymphoma, but less than 5% of pediatric non-Hodgkin's lymphoma are believed to arise in the palatine tonsils or adenoids.

Asymmetric or painless, progressive, persistent enlargement of the tonsils or adenoids without evidence of local infection, and with or without associated atypical adenopathy should alert the surgeon to the possibility of non-Hodgkin's lymphoma.

The presentation of pediatric non-Hodgkin's lymphoma can be quite varied and unusual. Burkitt's lymphoma may present with any or all of the following characteristics: a facial mass, floating teeth, odontalgia, cervical adenopathy, sore throat, or neurological changes such as diplopia, cranial nerve VI and VII palsies, and mental nerve paresthesia.

Non-Hodgkin's lymphoma of the head and neck can be difficult to diagnose even with biopsy, and MRI has proven most helpful in localizing areas of tumor involvement, often facilitating adequate biopsy. Indolent, slow-healing wounds are sometimes seen.

Head and neck non-Hodgkin's lymphoma may present as a mass involving Waldeyer's ring, including the base of tongue, lingual surface of epiglottis, paranasal sinuses, or nose. The nasopharynx is the most common site of origin, with tumor most frequently arising from the fossa of Rosenmüller or from the lymphatic tissue about the torus tubarius.

Treatment

The mainstay treatment for all non-Hodgkin's lymphomas, no matter the histologic type or clinical stage, is chemotherapy. Children with non-Hodgkin's lymphoma have a significantly better prognosis when treated with chemotherapy than with radiation alone. Radiation, when given in conjunction with chemotherapy, does not appear to offer any therapeutic benefits. Radiotherapy does have definite application in the treatment of some emergency situations, however, due to tumor mass effects (such as superior vena cava syndrome).

The primary role for surgery in the treatment of childhood non-Hodgkin's lymphoma is to obtain tissue for diagnosis. Tissue should be given unfixed to the pathologist for frozen section, immunologic and molecular studies, and for karyotyping. Surgical debulking of the tumor is beneficial but often not possible. Patients with large abdominal masses in which complete resection is performed have a better prognosis than patients with unresected tumors. Due to the anesthesia and surgical risks in patients with tracheal compression secondary to large mediastinal masses, surgical debulking is rarely attempted in such cases.

All children with disseminated non-Hodgkin's lymphoma should be watched closely for the development of tumor lysis syndrome. Hyperuricemia, electrolyte abnormalities, and renal failure are hallmark features of this complication. Allopurinol administration, vigorous intravenous hydration, and alkalinization of the urine (to increase urinary excretion of uric acid) should be instituted at the onset of therapy. Chemotherapy should begin promptly within 24 to 48 hr from the time of diagnosis. Children with Burkitt's lymphoma who present with large abdominal masses are especially prone to such masses. Deaths in the first 2 weeks of therapy as a consequence of tumor lysis syndrome are not uncommon.

At present, children with non-Hodgkin's lymphomas are categorized into two therapeutic groups: (a) lymphoblastic lymphomas, and (b) nonlymphoblastic lymphomas. Burkitt's lymphomas, large cell lymphomas, and undifferentiated lymphomas are grouped in the latter category. A variety of agents, including cyclophosphamide, methotrexate and vincristine, have shown efficacy in single-drug studies. Recent evidence suggests that intrathecal chemotherapy for central nervous system prophylaxis may be necessary only in patients with head and neck primary tumors.

"Localized" lymphoblastic lymphomas respond well to multiagent chemotherapy. Treatment regimens such as COMP (cyclophosphamide, vincristine, methotrexate and prednisone) or a ten-drug regimen termed LSA₂-L₂ have produced 3-year survival rates over 90%. No differences between 6 months and 18 months of chemotherapy have been noted in treating localized lymphoblastic lymphomas. Treatment of disseminated lymphoblastic lymphomas also has shown excellent promise with multiagent chemotherapy. Unlike localized lymphoblastic lymphomas, there does appear to be a significant advantage to using LSA₂-L₂ chemotherapy instead of COMP in treating children with disseminated disease. One recent trial reported a 76% disease-free survival rate for LSA₂-L₂ treated patients versus a 26% survival rate for those treated with COMP.

Treatment for childhood nonlymphoblastic lymphomas also has been studied extensively using COMP or LSA₂-L₂. Children with disseminated Burkitt's lymphoma (stage III to IV) have showed superiority with the COMP regimen over LSA₂-L₂. Anderson et al reported a 2-year disease-free survival rate of 57% for patients with Burkitt's lymphoma treated with COMP compared with a 28% survival rate for patients treated with LSA₂-L₂. Patients with localized Burkitt's lymphoma (stage I to II) appear to do equally well with COMP or LSA₂-L₂. Since COMP therapy is usually well tolerated, it generally has been favored as the treatment of choice for localized disease. Treatment of localized disease for 6 months of chemotherapy has been shown to be adequate. Much longer regimens have been used in treating disseminated disease.

Salvage therapy for recurrent disease has proven extremely difficult. Autologous or allogeneic bone marrow transplantation following reinduction chemotherapy has shown only marginal results in this group of patients.

Posttransplant Lymphoproliferative Disease

Posttransplant lymphoproliferative disease (PTLD) is a relatively new disorder once felt to be related to non-Hodgkin's lymphoma. PLTD is not a single disorder but a spectrum of proliferation of B lymphocytes seen in up to 40% of the immunosuppressed pediatric posttransplant recipients. PTLD can present as a solid tumor, a parenchymal infiltrate, or as an enlargement of lymphoid tissues. Histopathologically and clinically, the process ranges from benign to malignant. There is an association with EBV infection.

In the head and neck, airway obstruction is the most common symptom either from hypertrophy of components of Waldeyer's ring, or from frank intratracheal and paratracheal masses. PTLD may mimic infectious mononucleosis.

The underlying pathophysiology is felt to be a loss of T-cell control of B-cell proliferation in these immunocompromised patients (ie, a failure of immune surveillance). Treatment involves removal of the hypertrophic lymphoid tissue as well as reduction of the immunosuppressant therapy. Mortality approaches 25%.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC), a primary malignancy of the nasopharyngeal epithelium, is a rare tumor in childhood, accounting for less than 1% of all childhood malignancies. The age-incidence curve for nasopharyngeal carcinoma in North America is bimodal, with the first incidence peak occurring between ages 15 and 25. Racial differences in the incidence of nasopharyngeal carcinoma in children are not clearly established. Much work is underway investigating the relationship between Epstein-Barr virus (EBV) and nasopharyngeal carcinoma. Antibody titers against EBV may be useful in the diagnosis and in following the clinical response of nasopharyngeal carcinoma to treatment.

The World Health Organization (WHO) promotes the classification of nasopharyngeal carcinoma into three morphologic groups: keratinizing squamous cell carcinoma (WHO type 1), nonkeratinizing squamous cell carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3), a histologically diverse group. WHO types 2 and 3 tumors are common in childhood. Keratinizing squamous carcinoma (WHO type 1), which is less radiosensitive and has a poorer prognosis than the less differentiated tumors, fortunately is rare in children.

Delay of diagnosis is common in pediatric nasopharyngeal carcinoma, often ranging from 4 to 6 months. Cervical adenopathy from regional lymph node metastasis is the most common presenting sign. The node may be tender, mimicking infection. Pain is reportedly the main symptom in children, presenting as otalgia, headache, or pain in the metastatic lymph nodes. Presentation also may include blood-stained mucoid nasal discharge, nasal obstruction, or epistaxis. Serous otitis media secondary to eustachian tube obstruction may occur.

Treatment

External beam radiotherapy is the mainstay of treatment for nasopharyngeal carcinoma, with or without chemotherapy. Dosages ranging from 5.000 cGy to 7.500 cGy have led to 5-year survival rates of 20% to 60%. The treatment of the cervical lymph nodes, including supraclavicular nodes, is mandatory, even in the absence of clinical adenopathy. Techniques for radiotherapy include hyperfractionation to minimize long-term side effects, and the use of intracavitary or interstitial boost radiotherapy to the site of the primary tumor to increase local tumor control. Survival rates for those patients with T₃ and T₄ tumors, or for those with cervical node metastases are significantly worse than those with T₁ or T₂ disease and no nodal involvement.

Distant metastases are the major cause of treatment failure in children with advanced primary tumors. Common sites of metastasis include the lungs, mediastinum, bones, and liver. Adjuvant chemotherapy therefore has been proposed to help control occult metastatic disease. Most studies indicate that adjuvant chemotherapy is useful in advanced cases of nasopharyngeal carcinoma of childhood, but not all studies have shown statistically significant increase in survival with chemotherapy.

The decision to use adjuvant chemotherapy may not only be based on the extent of the disease at presentation, but also on the dose of radiotherapy to be used. For example, radiotherapy dosages over 6.500 cGy may give excellent local control of nasopharyngeal carcinoma. Yet dosages in this range also may lead to significant long-term consequences in children. In such cases, adjuvant chemotherapy with lower radiotherapy dosages (approximately 6.000 cGy) should be considered. Finally, the timing of chemotherapy and radiation therapy must be considered. Whether chemotherapy should be withheld until after radiation therapy, or given both prior to and after radiation therapy, remains to be determined.

Langerhans' Cell Histiocytosis (Histiocytosis X)

In 1953, Lichtenstein proposed the term *histiocytosis X* to describe a group of related, overlapping disorders that have in common the idiopathic proliferation or migration of histiocytes with resultant local and systemic effects. Modern pathologic techniques have identified the involved mononuclear phagocytic cell in eosinophilic granuloma (unifocal histiocytosis), Hand-Schüller-Christian syndrome (chronic systemic histiocytosis), and Letterer-Siwe disease (acute systemic histiocytosis) as a Langerhans' cell, a dendritic cell of bone marrow origin. These three disorders are now collectively referred to as Langerhans' cell histiocytosis (LCH). There are other disorders of histiocytes in the pediatric population, involving mononuclear phagocytes, other than Langerhans' cells. These disorders are more rare and are not discussed here.

The etiology of Langerhans' cell histiocytosis remains unclear, but the disease is believed to be a reactive process rather than a malignant disorder. When generalized, the condition is felt to be multifocal rather than metastatic.

The incidence of LCH is approximately 0.5 per 100.000 children. LCH occurs predominantly in childhood. About 75% of cases occur before 10 years of age and 91% before age 30. LCH can be present at birth, and appears to be more common in Caucasians.

When the diagnosis of LCH is suspected, consultation with the pathologist should precede surgery. Formalin-fixed hematoxylin and eosin-stained tissue can be highly suggestive of LCH, but definitive diagnosis requires either the demonstration of intracellular Bierbeck granules by electron microscopy or of specific membrane immunologic markers. These studies require fresh or frozen tissue in special fixatives for ultrastructural studies.

Presentation

Bony lesions of the skull and associated soft tissue lesions of the scalp are the most common clinical manifestations of LCH in the head and neck. Otorrhea, unresponsive to medical management, is the most common aural finding. Otitis externa and otitis media, with or without mastoiditis and aural polyps, may be seen. Postauricular swelling from a subgaleal mass is reported in 10% to 30% of all patients with LCH. Often, nontender cutaneous erythema is seen. Conductive hearing loss is frequent with temporal bone involvement but sensorineural hearing loss, vertigo, and nystagmus are rare, suggesting that the otic capsule is not prone to histiocytic infiltration. When the temporal bone is involved, 30% of affected patients will demonstrate bilateral disease.

Oral manifestations of LCH include loosening and premature loss of teeth. Alveolar bone loss often is associated with gingival infiltration with histiocytes. Radiographic examination reveals radiolucent lesions with well-defined margins. The mandible is more commonly involved than the maxilla.

Diabetes insipidus often is seen in patients with LCH if a condition other than unifocal eosinophilic granuloma is present. In fact, the triad of diabetes insipidus, proptosis, and membranous bone disease may be seen in Hand-Schüller-Christian syndrome. Infiltrates of abnormal histiocytes and fibrosis have been found in the hypothalamus and posterior pituitary gland of patients with diabetes insipidus, possibly explaining this endocrine dysfunction. Exophthalmos can result from lesions involving the orbital walls and the associated soft tissue reaction.

A characteristic skin rash of the scalp, intertriginous areas, and the perineum and perianal areas often is found. This has been described as a form of seborrheic dermatitis. The evaluation for metastatic disease is coordinated best by a pediatric oncologist and should include a plain film skeletal survey, which is believed to be more sensitive than nuclear scanning in detecting bony lesions. A panorex of the mandible and maxilla should be obtained in patients with oral involvement. Furthermore, an audiologic evaluation should be obtained for those patients with temporal bone involvement.

Clinical Course

The outcome of LCH is variable. The younger the child and the more extensive the disease at time of diagnosis, the poorer the prognosis. A staging system for histiocytosis that considers these factors has been proposed.

The disease tends to be benign and self-limiting when the involvement is limited to only one site. It is likely that solitary eosinophilic granuloma of bone often goes undetected.

Unifocal bony disease in the head and neck can be treated successfully with either surgery or radiation therapy. LCH is a very radiosensitive disease. When surgical removal (curettage) is not feasible, localized radiotherapy can be used. Doses of fractionated radiotherapy in the range of 800 cGy provide excellent local control with little or no side effects. Low-dose radiotherapy also has been used to treat the sella turcica in patients with diabetes insipidus. Results of treatment for this condition are not as clear, but there are reports of reversal of the disease process following irradiation.

An alternative to curettage or low-dose radiotherapy is injection of isolated bony lesions with corticosteroids. In some patients, this has proven to be highly effective, nontoxic, and convenient, with relief of pain within a week or two of initiation of treatment.

Chemotherapy is indicated in almost all patients with disseminated LCH. Solitary bone lesions are rarely an indication in adults, but chemotherapy may be considered in younger children in whom such lesions may herald disseminated disease. Initial chemotherapy is given usually with the combination of daily prednisone and vinblastine given weekly. Response to treatment is evaluated in 2 to 3 months. Failure of response to one or more agents does not preclude response to others. Etoposide, vincristine, cyclophosphamide, 6-mercaptopurine, chlorambucil, and daunorubicin also have shown efficacy in LCH.

Salivary Gland Neoplasms in Children

Primary salivary gland neoplasms occurring in children during the first decade of life, particularly during the first 2 years of life, are predominantly benign. During the second decade, the incidence of carcinoma rises. These are most often mucoepidermoid and acinic cell carcinomas; less often adenoid cystic and other malignancies are seen. The pleomorphic adenoma is the most common primary epithelial salivary tumor throughout childhood.

Neoplasms of the salivary glands are so uncommon in infants and children that the actual incidence of malignant salivary gland neoplasia has been difficult to determine. Any child that presents with a firm salivary gland mass must be suspected of harboring a malignancy. Schuller and McCabe found that 35% of all pediatric salivary gland tumors were malignant. In their review, when vasoformative lesions were excluded, the percentage increased to 57.5%. A more recent study reports a much lower rate of malignancy in solid masses of the parotid gland. Camacho et al reviewed 22 pediatric patients presenting with an unknown solid parotid mass. Only one patient had a malignancy (mucoepidermoid carcinoma). The rate of malignancy of solid parotid masses in their study was only 4%. Benign pleomorphic adenoma, cat-scratch disease, atypical mycobacteria, benign follicular hyperplasia of a lymph node, and toxoplasmosis were other causes of parotid masses in children reported in their series.

Rapid growth, local pain, and facial paralysis are signs that suggest that a salivary gland mass may be malignant. Any child with a persistent or progressively enlarging lump or nodule behind, below, or in front of the ear lobe should be evaluated for a possible parotid malignancy. Furthermore, neoplasms arising in the submandibular glands and minor salivary glands are much more likely to be malignant than are parotid neoplasms.

Mucoepidermoid carcinoma is the most common salivary gland malignancy in children, accounting for 49% of malignant salivary gland tumors. Acinar cell carcinoma accounts for 12% of malignant salivary tumors in children. Undifferentiated carcinoma, adenocarcinoma, sarcoma, malignant mixed tumor, adenoid cystic carcinoma, and squamous cell carcinoma contribute to the balance of malignant salivary gland tumors in children. The peak incidence of mucoepidermoid carcinoma is in the 10- to 16-year-old age group. The first 2 years of life are relatively spared, but mucoepidermoid carcinoma has been reported to occur at 1 year of age. The parotid, by far, is the most common site of occurrence for mucoepidermoid carcinoma; however, the submandibular gland and minor salivary glands of the palate are well-described sites also.

Salivary gland malignancies in children appear to have similar biological activity as those occurring in adults and should therefore be managed according to the same basic principles. Incisional biopsy of salivary gland neoplasms is almost always contraindicated. Fine needle aspirate for cytologic evaluation, commonly used in adults, is also useful in children in some circumstances. Fine needle aspiration cannot be used to rule out malignancy, but can be helpful in preoperative planning if malignancy is suspected. The initial surgical procedure for submandibular masses should be complete excision of the submandibular gland. The initial procedure for parotid lesions should be superficial parotidectomy, if the lesion is limited to the lateral lobe.

Lateral parotidectomy is adequate resection for benign tumors, and, according to some investigators, for low-grade malignant tumors limited to the superficial lobe. Total parotidectomy is indicated if the mass extends to the deep lobe, or if histology reveals a high-grade malignancy. Other investigators feel that total parotidectomy is indicated for all parotid malignancies.

The facial nerve is preserved whenever possible, but must be sacrificed in cases of perineural invasion. If the nerve is resected due to involvement by the malignancy, an immediate facial reanimation procedure should be performed.

The efficacy of cervical lymphadenectomy in the management of pediatric salivary gland malignancy remains uncertain. Formulation of validated guidelines has not been possible due to the relative rarity of these tumors, the variability of histologic types, and the various possible modifications of neck dissection techniques. When metastatic cervical adenopathy is present, neck dissection clearly is indicated. Elective neck dissection, even in patients with high-grade malignancy, is not felt to be indicated by some investigators. Others feel that the initial surgical procedure should involve a parotidectomy with removal of the upper posterior cervical and jugulodigastric nodes, even in clinically negative necks. If frozen section examination of the lymph nodes is positive, a modified neck dissection is performed.

Salivary malignancies of the palate are managed with wide local excision involving en bloc resection. The resultant palatal defects are noted to decrease in size by 50% to 75% over subsequent years, and can eventually be closed if no recurrence is noted after 3 or 4 years.

Postoperative radiotherapy at times is indicated for suspected residual tumor, aggressive histologic subtypes, cervical metastases, and perineural invasion. Severe long-term

radiation complications are common. Palliative radiotherapy may be offered as the sole treatment modality for undifferentiated salivary neoplasms that do not allow surgical resection at the time of presentation. Chemotherapy has been used in combined modality regimens for treating biologically aggressive high-grade salivary gland malignancies.

Late Effects of Therapy for Pediatric Head and Neck Malignancy

Over the last 20 years, strategies to combat childhood malignancies have become more successful. It has been stated that 1 in every 1,000 adults over the age of 20 today is likely to be a survivor of childhood cancer. Some of the most severe long-term effects of chemotherapy and radiation therapy occur in those who have had a malignancy of the head and neck. Long-term survivors of pediatric head and neck malignancies represent a new patient population, often afflicted with difficult and subtle treatment-related adversities that may manifest themselves years after the actual treatment.

One of the most serious delayed consequences of therapy for childhood cancer is the development of a second neoplasm, the incidence rate being approximately 8%. An increased risk of developing bone sarcoma has been found in patients whose primary malignancy was treated with alkylating agents with and without radiotherapy. Radiation to the thyroid gland in doses as small as 120 cGy in a young child increases the risk of thyroid cancer 100-fold.

Endocrine deficiencies after radiotherapy for head and neck tumors are common. Primary hypothyroidism after therapeutic neck irradiation is a well-known sequela. Growth hormone deficiency in adolescence after radiotherapy has been reported widely. Late deterioration of pituitary and hypothalamic function, after 6 and 10 years, respectively, in patients receiving incidental radiation to those structures, has been reported. Central nervous system irradiation also may lead to memory deficits and learning disabilities.

The deleterious long-term side effects of radiotherapy may include clinically apparent stunting of facial bone growth, which has been found to occur in the majority of pediatric patients who have been exposed to 3,000 cGy or more of radiotherapy. As little as 400 cGy of radiotherapy has been shown to arrest soft tissue growth.

The effect of radiotherapy on dental structures is related to both the total dose of radiation and to the stage of dental development at the time of radiotherapy. Radiation doses as low as 400 cGy have been shown to cause abnormalities in developing teeth. Radiation-induced dental deformities include hypoplastic root formation, incomplete calcification, premature closure of apices, and caries. Maxillofacial abnormalities include trismus, midface hypoplasia, other types of facial asymmetry, and malocclusion. Xerostomia and an increased disposition to dental caries may result from salivary gland irradiation. Severely reduced parotid secretory activity has been reported following radiation doses of greater than or equal to 45 Gy to greater than 50% of the parotid gland volume.

Pediatric patients requiring radiotherapy fields that include the eyes, for orbital or paranasal sinus tumors, are known to develop cataracts at doses greater than or equal to 28 Gy; at doses greater or equal to 40 Gy, xerophthalmia is common.

Radiation otitis media is a well-recognized otologic consequence of local radiotherapy to the temporal bone. Although progressive sensorineural hearing loss has been reported after radiotherapy doses of greater than or equal to 60 Gy, more recent work suggests that doses less than or equal to 60 Gy are relatively safe.

Certain chemotherapeutic agents, particularly alkylating agents and procarbazine, are extremely toxic to the germinal epithelium of the tests. Ovarian dysfunction is also a well-recognized complication of therapy with alkylating agents. The surgical management of the deformities resulting from surgical extirpation and radiation therapy of pediatric head and neck malignancies is an evolving field. The problems of poor local tissue vascularity and osteoradionecrosis limit the use of many reconstructive techniques. The increased use of free tissue transfer has proven helpful in managing many of these difficult cases.

Benign Tumors of the Head and Neck

Fibro-Osseous Lesions

There are three general types of fibro-osseous lesions affecting the head and neck in pediatric patients: (a) osseous dysplasia (cementoma), (b) fibrous dysplasia, and (c) ossifying fibroma (cementifying fibroma).

Osseous Dysplasia

Osseous dysplasia is a reactive fibro-osseous lesion that most commonly occurs in the periapical alveolar bone of the anterior mandibular teeth. Radiographically, the lesions may appear as a periapical lucency or as multiple lucencies. Late lesions are radiopaque with a thin, lucent rim. The lesions, also known as cementomas, occur predominantly in black women over 20 years of age, but can be seen in younger patients. Therapy is simple excision.

Fibrous Dysplasia

Fibrous dysplasia is a congenital, metabolic, nonfamilial disorder that accounts for 7% of all nonmalignant tumors of bone. In fibrous dysplasia, normal bone is replaced by irregular trabeculae of immature, poorly mineralized fibrous tissue. The fibrous tissue may lead to bony expansion with distortion of contour and structural weakness. Fibrous dysplasia usually involves the cancellous bone, and therefore usually is found to be covered by a thinned shell of intact cortical bone. Lesion margins at the interface with cancellous bone are usually diffuse and indefinite, as opposed to the well-demarcated lesion interface in ossifying fibroma.

Grossly, the lesions of fibrous dysplasia range from white to gray to pale yellow in color, and from soft and edematous to tough, firm, rubbery, or gritty in consistency. Microscopically, the fibro-osseous tissue is composed of haphazardly arranged strands of collagen stroma and misshapen irregular bony trabeculae that are randomly oriented. Multinucleated giant cells may be found. There is an absence of osteoblastic rimming of the bony trabeculae and, under polarized light, appears woven rather than lamellar. The proportion of fibrous to osseous elements may vary considerably, even within the same lesion. Fibrous dysplasia involves a single bone (monostotic) in 70% of patients, and multiple bones (polyostotic) in 30%. The prevalence of craniofacial involvement in monostotic disease is

10% and, in polyostotic cases, nearly 50%. In McCune-Albright syndrome, polyostotic fibrous dysplasia is found in combination with areas of skin hyperpigmentation and endocrine disturbances (precocious puberty or hyperthyroidism, or both).

The average age of onset of symptoms from fibrous dysplasia is 10 years, but symptoms may occur at any age. Approximately 83% of patients with monostotic fibrous dysplasia in the head and neck region will have symptoms within the first two decades of life.

Cosmetic swelling of the facial bones is the usual initial presentation of craniofacial fibrous dysplasia. When the bones of the orbits, paranasal sinuses, or skull base are involved, symptoms may include proptosis, visual loss, diplopia, headaches, nasal obstruction, mucocele formation, epistaxis, sinusitis, epiphora, anosmia, facial paralysis, and hearing loss. Temporal bone involvement with external auditory canal obstruction or erosion of the middle ear ossicles and otic capsule have been reported. Loss of vision is the most common neurologic deficit in craniofacial fibrous dysplasia.

Radiologic appearance of fibrous dysplasia may vary from largely lucent, should the lesion be primarily fibrous, to a "ground glass" appearance, should there be considerable ossification. The surrounding bony cortex is usually intact, and there is no sclerotic bone formation surrounding the lesion. The CT scan remains very helpful in evaluating local extension of craniofacial fibrous dysplasia. In 60% to 80% of cases, dysplastic expansion of bone will become quiescent after patients reach puberty, but complete spontaneous involution of lesions is unreported. In fact, some investigators feel that growth does not stop at the end of adolescence.

Management

The mere presence of a lesion of fibrous dysplasia does not justify surgical intervention. Surgery is now recommended, however, as soon as the deformity becomes cosmetically substantial, or when important function is threatened. There is no evidence to suggest that surgery accelerates the growth rate of residual normal or dysplastic tissue. Other investigators promote early surgical excision of facial lesions as an interceptive technique to prevent development of subsequent problems.

There are several surgical approaches for fibrous dysplasia. Simple contouring of expanded bone back to normal dimensions in the facial and skull regions has been fairly effective and is still indicated in certain circumstances, particularly in the teeth-bearing regions of the mandible and the maxilla, and in the hair-covered regions of the cranium. Approximately one-fourth of patients treated with conservative contouring will have a recurrence of bony enlargement that will require surgical revision.

More recently, complete resection of bony lesions with immediate reconstruction is being proposed as more definitive management. The technique of removal, remodeling, and replacement of the dysplastic bone as a free graft has been reported. Large methyl methacrylate implants for cranio-orbital reconstruction have been used also. The relief of optic nerve compression, orbital hypertelorism, dystopia, exophthalmos, and grotesque orbitofacial deformities requires radical excision and reconstruction, usually with autogenous free grafts, often in combination with neurosurgical and ophthalmological colleagues. Invasion of fibrous

dysplasia into the grafted bone has not been seen.

A major concern in surgical planning for fibrous dysplasia is the extreme vascularity of these lesions and the potential for significant intraoperative and postoperative blood loss. Radiotherapy is not effective and may carry an increased risk of malignant degeneration. The incidence of malignant degeneration of fibrous dysplasia is approximately 0.4%, and can be seen in patients without previous radiotherapy.

Ossifying Fibroma

Ossifying fibroma (cementifying fibroma) is a histologically benign, but potentially clinically aggressive, fibro-osseous lesion. It may present as a small asymptomatic growth or as an extensive tumor with gross facial deformity. Ossifying fibromas are well defined and smoothly contoured, which contrasts with the diffuse borders seen with fibrous dysplasia.

Histologically one sees evenly spaced spicules of mature bone rimmed with osteoblasts and osteoclasts within a fibrous stroma that has loose and dense areas, with whorling.

A variation of ossifying fibroma, referred to as active juvenile ossifying fibroma, or psammomatous ossifying fibroma, is characterized by small, round, psammomatoid ossicles embedded in a cellular fibrous stroma. This represents a more aggressive variant of ossifying fibroma and occurs primarily in children and young adults. These lesions may have a rapid growth rate with local aggressive behavior, and may mimic sarcoma.

The tissue origin may be primitive mesenchymal cells, or the periodontal ligament, which is known to be capable of producing both cementum and osteoid.

Radiographically, ossifying fibroma is characterized by expansile, sharply defined margins, often with a radiolucent peripheral component. Divergence of tooth roots is seen commonly in the jaws. Ossifying fibroma is characteristically monostotic. Ossifying fibroma is usually seen between the second and fourth decades of life and women are more often affected than men.

Although it can be found anywhere, ossifying fibroma is almost exclusively found in the craniofacial area. The mandible is clearly the most common site, involved in approximately 75% of cases in most series. The ethmoid, frontal, sphenoid, orbit, occiput, and temporal bones are less common sites.

Management

Primary treatment of mandibular lesions includes simple curettage or expectant observation after biopsy. Ossifying fibroma of the midface, according to recent reports, may require a more aggressive, en bloc, wide, local resection initially in order to prevent recurrence. These sites, outside of the mandible, include the paranasal sinuses, maxilla, and orbit.

Cherubism

Cherubism is a benign, expansile fibro-osseous lesion occurring within the jaws, that manifests as a progressive, painless, and often symmetric enlargement of the mandible and maxilla, with a predilection for the mandible. Facial swelling with characteristic fullness of the cheeks is the most typical clinical sign.

Cherubism demonstrates an autosomal dominant inheritance pattern with 100% penetrance in boys and 50% to 70% penetrance in girls, with variable expressivity.

Children with cherubism typically appear normal at birth and begin to demonstrate bilateral swelling between the ages of 2 and 4 years. Cherubism has been reported as early as 14 months of age. Boys are affected twice as often as girls. Maximum jaw enlargement occurs within 2 years of onset in most cases.

The mandibular angle is the most common location for cherubism, but the maxilla may be involved in up to 67% of the cases. Premature loss of deciduous teeth and delayed eruption of the secondary dentition are hallmark signs. Jaw size usually increases rapidly during the first 2 years after onset. By age 7, the lesions become static or progress slowly until puberty. Involution of the lesion begins at puberty and continues into the late teens; the maxilla usually regresses earlier than the mandible. Not commonly, the appearance of one side will improve, while the other remains static. Cervical adenopathy is frequently associated with cherubism and usually regresses at the same time as the jaw lesions.

The radiographic findings of cherubism include irregular multilocular lucencies with sharply defined margins and thinned overlying cortex. Areas of cortex are often perforated. Teeth may be displaced, unerupted, or appear to be floating in cystlike areas.

Treatment

Treatment of cherubism is not standardized. The unique biologic behavior of the tumor should be considered when recommending management.

The expectation of spontaneous involution has led most investigators to recommend surgery only after puberty, unless functional or psychological problems prompt earlier treatment. Recurrence of tumor growth is common and repeat surgery is needed frequently in younger patients. Surgical contouring of these expanded fibro-osseous lesions in late stages of the disease has led to good results. Radiotherapy is contraindicated.

Giant Cell Lesions

Peripheral giant cell reparative granuloma presents as a sessile or pedunculated mucosally covered mass that is reddish blue in color and contains multinucleated giant cells. It usually arises from the gingiva or alveolar mucosa, most commonly in the anterior mandible. The lesions bleed easily. Frequency of occurrence is equal in girls and boys. Treatment is excision or curettage.

Giant cell reparative granuloma is an endosteal lesion seen predominantly in patients between 10 and 20 years of age. It is found usually in the mandible, anterior to the first molar. The lesion may be asymptomatic, or may present as a localized jaw deformity. Radiographically, the lesions appear as lytic expansile unilocular cavities with well-demarcated, nonsclerotic margins. However, at times, a multicystic soap-bubble appearance may be noted. The overlying bone cortex is usually intact. The lesions may cross the midline.

Simple excision of well-defined lesions and excision and curettage of more diffuse lesions is standard surgical management.

Mycobacterial Cervical Adenitis

Tuberculous cervical adenitis is caused by *Mycobacterium tuberculosis* and usually affects older children and adults. The history is usually positive for contact with a known carrier of tuberculosis. Multiple, bilateral, matted nodes are found frequently in the lower neck and upper clavicular area. The tuberculin skin test is usually positive. Mycobacterial tuberculosis is usually acquired by inhalation in this country, and chest radiographs often will show pulmonary parenchymal or hilar disease. Primary therapy for tuberculous cervical adenitis is antituberculosis antibiotic therapy. Surgical excision is indicated for adenopathy unresponsive to medical management.

Nontuberculous mycobacteria (NTM), also referred to as the "atypical mycobacteria", are found in the water, soil, and other environmental sources. The NTM group includes *M. avium*, *M. scrofulaceum*, *M. intracellulare*, and *M. kansasii*. Nontuberculous cervical adenopathy is classically unilateral, and localized to the submandibular high cervical, and preauricular nodes. Approximately 80% of culture-positive nontuberculous cervical adenopathy is due to *M. avium* complex and the remainder to *M. scrofulaceum*. Presently, only about 10% of culture-proven mycobacterial cervical lymphadenitis in the USA in children is due to *M. tuberculosis*; the remainder are due to *M. avium* and *M. scrofulaceum*. The individual lymph nodes are generally nontender, may enlarge rapidly, and may rupture with formation of sinus tracts. There is usually no history of exposure to tuberculosis, and the chest radiograph is normal.

Skin testing is of limited usefulness in diagnosing NTM infection. Recent work has been done to develop new skin test antigens specific for several of the nontuberculous mycobacterial species, but these remain unavailable commercially. Most children with NTM lymphadenitis given intermediate strength (5 TU) purified protein derivative (PPD) tuberculin will have a weakly reactive test (5 to 9 mm), but some children may have a negative response, and others may respond with 10 mm or more induration.

Surgical excision of all involved lymph nodes is the mainstay of therapy if NTM lymphadenitis is suspected. Incision and drainage is not performed to avoid a subsequent chronic draining fistula. It is important to submit excised tissue for mycobacterial culture and sensitivity studies. The success rate after excisional surgery without chemotherapy is approximately 95%. For children with recurrent disease, a second surgical procedure is usually performed. A multidrug antituberculous regimen should be considered only in the patient with disease recurrence after two or more surgical resections.

Cat-Scratch Disease

Cat-scratch disease is a common cause of cervical adenopathy in the pediatric population. The typical history would include exposure to a cat, often a juvenile cat, 3 to 5 days after which a small papule will develop at the site of exposure. This papule progresses to a vesicular and crusty state in 2 to 3 days, and within a week or two regional adenopathy develops in those nodes, which drain the dermal or conjunctival sites of inoculation. The adenopathy may be painless, but is often tender, and nearly always is limited to a single site. Axillary lymphadenopathy is most common. The second most common is adenopathy of the head and neck.

The disease is self-limiting and adenopathy usually subsides in 1 to 4 months. Cat-scratch disease may rarely, however, progress to a severe, systemic, or recurrent infection producing encephalitis, neuroretinitis, osteomyelitis, arthritis, hepatitis, splenitis, and other problems.

The etiologic agent of cat-scratch disease recently has been isolated and cultured. It is a small, pleomorphic gram-negative bacillus. It can be demonstrated by the Warthin-Starry-Silver impregnation stain in histologic specimens. The histologic appearance of cat-scratch disease also includes reticular cell hyperplasia, granuloma formation, and microabscesses. The diagnosis can be confirmed further by a positive Hanger-Sore skin test, which is reportedly positive in greater than 99% of patients with cat-scratch disease who have had adenopathy for longer than 1 week. The antigen for this skin test, which was originally prepared from aspirated pus from patients with suppurative cat-scratch disease, is not readily available to clinicians, and the diagnosis of cat-scratch disease must therefore be made on the basis of other criteria.

The treatment of cat-scratch disease is mostly supportive. Surgical removal of involved lymph nodes is not necessary for management. Aspiration of suppurative nodes with a 16- or 18-gauge needle after spraying the site with ethyl chloride has been recommended for relief of symptoms and for obtaining material for diagnosis. Incision and drainage may be necessary for more advanced abscesses.

Most antimicrobial agents have not proven effective in the treatment of cat-scratch disease. Some investigators feel trimethoprim - sulfamethoxazole has a therapeutic effect. Successful treatment of cat-scratch disease with Ciprofloxacin has been reported in a small series of patients; however, Ciprofloxacin is not approved for use in children.

Benign Tumors of the Peripheral Nervous System

Schwannomas and neurofibromas, two common benign tumors of the peripheral nervous system, are distinct clinical entities that may arise from multiple sites within the head and neck, including cranial nerves, motor and sensory cervical nerves, small distal nerves within the tongue and oral mucosa, and elsewhere, and autonomic nerves.

The schwannoma, also known as neurilemmoma, is a benign, solitary, often encapsulated, tumor that derives from the Schwann cell of a peripheral nerve sheath. Microscopically, the nerve of origin can be seen attached to and compressed by the

schwannoma. Schwannomas are almost never associated with malignant change. Retrogressive changes, such as cystic alterations or hemorrhagic necrosis, are usually present.

Histologically, solitary schwannomas are composed of two tissue types: (a) cellular Antoni type A tissue with compact spindle cells in parallel orientation, often with rows of nuclei forming a palisading pattern; when these palisading areas are oriented around parallel bundles of nerve fibers, Verocay bodies are formed. (b) Antoni type B is characterized by abundant acellular collagen matrix and a random orientation of nerve fibers. Schwannomas are seen more often in the third and fourth decades of life, but also occur in children.

Management is by complete surgical excision. Since the tumor arises from the nerve sheath, it is often possible to remove a schwannoma from larger nerves and leave the majority of the nerve axons intact. The diagnosis is confirmed by histologic examination. Recurrence after complete excision is rare.

Neurofibromas may occur sporadically as well-circumscribed, solitary lesions or in association with one of the two genetic subtypes of systemic neurofibromatosis (NF-1 or NF-2).

Several types of solitary neurofibromas are found in children, including cutaneous and subcutaneous, plexiform, elephantiasis neuromatosa, and molluscum fibrosum. The cutaneous and subcutaneous lesions arise near the termination of small cutaneous nerves and appear clinically as soft, elevated, nodular pedunculated masses with increased pigmentation in the overlying skin. Neurofibromas also can be found within the upper aerodigestive tract of children, such as the larynx, and treatment is judicious total surgical excision, if possible. Often the lesion cannot be completely removed, and repeat subtotal removal is indicated.

Generalized neurofibromatosis has been classified recently into two genetically distinct disorders that are inherited in an autosomal dominant pattern with variable penetrance. The spontaneous mutation rate is high.

Neurofibromatosis - 1

Neurofibromatosis - 1 (NF-1) (previously referred to as von Recklinghausen's neurofibromatosis or peripheral neurofibromatosis) is considered to exist when two of the following diagnostic criteria are met:

1. six or more café au lait macules over 5 mm in greatest diameter in prepubertal individuals, and over 15 mm in greatest diameter in postpubertal individuals;
 2. two or more neurofibromas of any type or one plexiform neurofibroma;
 3. freckling in the axillary or inguinal regions;
 4. optic glioma;
 5. two or more Lisch nodules (iris hamartomas);
 6. a distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis;
 7. first-degree relative (parent, offspring, or sibling) with NF-1 by the above criteria;
- NF-2 is diagnosed usually within the first decade of life.

Neurofibromatosis - 2

Neurofibromatosis - 2 (NF-2), previously known as central neurofibromatosis or bilateral acoustic neurofibromatosis, is diagnosed when an individual has (a) bilateral eighth nerve masses seen by MRI or CT scan or (b) a first-degree relative with NF-2 and either a unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity.

A full discussion of the developmental, endocrine, and neoplastic disorders associated with the neurofibromatoses is beyond the scope of this chapter and management of these patients in a multidisciplinary team facilitates comprehensive management.

The treatment for symptomatic neurofibromatosis is surgical with preservation of function when possible. The management of patients with NF-2 and bilateral vestibular nerve tumors is an interesting and dynamic topic in itself. Those patients with NF-2 may suffer cosmetic deformities from enlarging plexiform neurofibromas and also from osseous mesodermal dysplasia causing distortion of the facial skeleton, sphenoid, and temporal bones. These dysplastic changes can involve any portion of the skeleton.

Pilomatrixoma (Calcifying Epithelioma of Malherbe)

The pilomatrixoma is a benign, usually solitary cystic tumor of the skin that is believed to arise from a primitive hair matrix cell. Over half of these tumors present in the head and neck region, most frequently on the brow, lid, and cheek. There is also an affinity for the external ear. About 40% of patients present in the first decade of life, and an additional 20% present before age 20. The tumor has been found in neonates.

Clinically, pilomatrixomas present as a well-demarcated, mobile, solid or cystic nodule. The lumen typically contains cheesy amorphous debris, keratin, and possibly calcified material. The overlying skin may appear normal, or may have a reddish or bluish discoloration. The tumors are usually asymptomatic and slow growing. They may reach up to 3 cm in diameter. Complete surgical excision is the management recommended by most authors.

Teratomas and Dermoid Cysts

Teratomas are developmental neoplasms that contain elements from all three germ cell layers - endoderm, mesoderm, and ectoderm. Congenital teratomas occur with an incidence of 1:4,000 live births and affect the head and neck in only approximately 2% to 4% of cases.

Teratomas and dermoid cysts are classified into four groups according to germ layer of origin and the degree of tissue differentiation. Many authors consider any nasopharyngeal neoplasm that consists of multiple types of tissue extrinsic to their site of origin a nasopharyngeal teratoma.

Dermoid cysts (hairy polyps) are composed of epidermal and mesodermal tissue elements. They are covered with skin and contain epidermal appendages such as hair follicles, sweat glands, and sebaceous glands. Most of the mass consists of an adipose matrix with

fragments of striated muscle, cartilage, or bone. They are usually pedunculated and often occur along lines of embryonic fusion. Teratomas in the nasopharynx traditionally arise from either the lateral or the superior walls and can cause symptoms of nasal obstruction in the neonate.

Teratoid cysts are composed of ectoderm, mesoderm, and endoderm, but differ from teratomas in their poor histologic differentiation. The cyst lining may be stratified squamous epithelium or ciliated respiratory epithelium. Components of the tumor may contain fat, muscle, cartilage, bone, acinous glands, teeth, epithelial cysts, and nervous tissue.

True *teratomas* are composed of all three germ layers and cellular differentiation is advanced so that organs can be recognized in these masses.

Epignathi represent the highest degree of differentiation into a parasitic fetus that may develop organs and limbs. These tumors are usually attached to the sphenoid bone and are generally "incompatible" with life.

A classification system based on birth status, age, diagnosis of the mass, and the presence or absence of respiratory distress has been proposed (Table 5).

Table 5. *Classification system for cervical teratomas by age and clinical presentation*

Group	Characteristic
I	Stillborn and moribund live newborn
II	Newborn with respiratory distress
III	Newborn without respiratory distress
IV	Children ages 1 month to 18 years
V	Adult.

Presentation

Head and neck tridermal tumors are usually apparent at birth or in the immediate neonatal period and more than one-half of nasopharyngeal dermoids are seen within the first year of life.

Prenatal sonographic diagnosis of cervical teratomas is based on the presence of a fetal neck mass with solid and cystic components. Calcification within the tumor on plain radiographs is virtually diagnostic, but may be seen in only 16% of cases.

A history of maternal polyhydramnios has been noted in 18% of neonates born with cervical teratomas, presumably from direct esophageal compression by the tumor, which interferes with swallowing. Prematurity, stillbirth, and birth dystocia are reported also. The incidence of polyhydramnios is greatest in pregnancies yielding neonates of groups I and II, which are typically the larger tumors. Tracheal deviation and posterior displacement, detected by both plain films and ultrasound, is also a common finding.

Clinically, cervical teratomas appear as firm, frequently mobile, multilobular cystic lesions. Rapid enlargement of the cystic components can lead to airway compromise. The tumors can be found anteriorly or laterally in the neck. They may cross the midline and extend into the submandibular and floor of mouth region, as well as into the mediastinum.

Nasopharyngeal "teratomas" are most commonly dermoid cysts. These tumors arise from the palate or nasopharynx and may extend intracranially. Nasal obstruction may be a presenting symptom.

The incidence of malignant degeneration in sacrococcygeal and other noncervical teratomas in children is approximately 20%. In contrast, cervical teratomas found in adults, although more rare, are often malignant.

Management

Management of nasopharyngeal and cervical teratomas begins as early in the prenatal period as possible, often after finding the abnormal mass on routine obstetrical ultrasound imaging. Optimal management of the airway at the time of delivery may require close coordination between the anesthesiologist, nursing staff, neonatologists, surgeon, and obstetrician. Therefore, the management strategy and necessary instrumentation should be organized well in advance. Since premature delivery is known to be associated with teratoma and an unexpected delivery might compromise the team management of the airway, a decision regarding the desirability and timing of an elective cesarean section delivery must be made.

The immediate management of patients with nasopharyngeal and cervical teratomas requires establishment of an airway. In small tumors, positioning may be adequate temporarily. Endotracheal intubation to secure the airway is the least traumatic, preferred method in more severe cases. If intubation is expected to be difficult based on previous imaging studies, intubation with a pediatric rigid bronchoscope or endotracheal tube intubation utilizing a flexible nasopharyngoscope can be employed. Tracheotomy may be difficult if the lesion overlies or depresses the trachea. Further preparations and management options have been described, including maintaining the neonate on fetal circulation by paralyzing the baby with succinylcholine to prevent spontaneous ventilation while an airway is secured. Once an airway has been secured, prompt surgical excision should be performed to prevent airway-related morbidity and mortality.

Prior to surgical excision, the tumor must be imaged. The high fat content of teratomas cause a strong signal on T1-weighted MRI images, allowing differentiation from cystic hygroma, which may appear similar on CT studies. Particularly in the evaluation of nasopharyngeal tumors, a coronal CT scan provides valuable information regarding the bony integrity of the skull base, and will determine preoperatively if there is intracranial or intraorbital involvement while excluding congenital midline CNS lesions, such as encephaloceles. If the latter is present, a combined approach with neurosurgery or ophthalmology will be needed. Teratomas, classically, do not communicate intracranially.

Complete surgical excision results in a good prognosis. Long-term follow-up is indicated.

Dermoids

Dermoids of the head and neck are a class of benign developmental neoplasms related to teratomas. They are most commonly located in and around the nose, orbit, and submental region.

Orbital and nasal dermoids are complex entities in themselves and are discussed elsewhere in this text.

Submental dermoids are smooth, rounded, mobile nontender masses located in the midline above or below the mylohyoid muscle. If the majority of a submental dermoid is located above the mylohyoid, marked elevation of the floor of mouth and tongue may occur, compromising the airway. If a submental dermoid enlarges to compromise oral intake or the child's airway, then it should be excised immediately.

Surgical removal of small, submental dermoids located primarily below the mylohyoid muscle can be delayed until 3 to 6 months of age without significant risk to the airway integrity.

Dermoid cysts of the tongue have been reported and are best treated by midline glossectomy and careful surgical excision of the cyst walls and tracts.

Sternocleidomastoid Tumor of Infancy

The sternocleidomastoid tumor of infancy (STOI) is a unique perinatal fibromatosis that manifests as a firm spindle-shaped mass within the sternocleidomastoid muscle of the neonate at 1 to 4 weeks of age. This lesion is also known as "pseudotumor of infancy" and has been equated to "fibromatosis colli".

The incidence of STOI is 0.4% of newborns (ie, approximately 1 in 4,000). The mass is usually not detectable at birth but becomes apparent at between 1 and 8 weeks of age with the majority occurring between 2 and 4 weeks of age. There is usually an equal sex ratio.

The tumor presents as a firm, painless, fusiform mass within the middle or lower portion of the sternocleidomastoid (SCM) muscle. Typical size varies from 1 to 3 cm. The right and left sides appear to be equally affected by STOI. Bilateral involvement is rare, but has been reported. Either the sternal or clavicular head of the SCM, or both, can be primarily involved by the lesion. The tumor typically increases in size for a few weeks, stabilizes for 2 to 3 months, and then slowly resolves by 4 to 8 months.

Sternocleidomastoid tumor of infancy is a transient disorder that can be associated with both temporary and permanent torticollis. The pathogenesis of this disorder remains unclear. About 10% to 20% of patients with STOI will go on to develop either a progressive or delayed torticollis, and 25% will have a minor residual degree of persistent asymmetry and tightness of the SCM muscle. Congenital muscular torticollis and STOI may represent different stages of an underlying SCM muscle fibrosis. Congenital muscular torticollis usually appears at 3 to 4 years of age, and may or may not be associated with a preceding history of STOI.

Torticollis secondary to STOI can lead to permanent deformities, such as plagiocephaly (a cranial deformity characterized by a rhomboid shape) and facial hemihypoplasia (characterized by an underdevelopment of half the face). Downward displacement of the ipsilateral eye and corner of the mouth are seen also. Surgical release is indicated when medical management is not adequate.

Microscopically, STOI is composed of dense fibrous tissue and an absence of normal striated muscle. Biopsy, however, is not needed routinely in the management of these tumors. Most authors agree that the diagnosis of STOI can be based safely on the clinical history and presentation. CT and ultrasound can help localize the tumor to the SCM muscle itself. Biopsy should be reserved for cases in which the diagnosis is uncertain. The differential diagnosis includes rhabdomyosarcoma, fibrosarcoma, dermoid, and neuroblastoma.

Management

Conservative, nonoperative treatment is the recommended initial management strategy. Neck flexion and chin rotation, head positioning, and heat and massage application are all part of the initial physiotherapy program. If craniofacial asymmetry develops or if the tumor or torticollis persist beyond 1 year to 18 months, surgery is indicated. Release of the SCM muscle distally, including both the sternal and clavicular heads, and lysis of associated fibrous tissue and platysmal banding is the recommended procedure initially. Release of the superior pole of the SCM may be necessary subsequently. Total excision of the SCM appears to offer no great advantage and it places the spinal accessory nerve at significant risk. Physiotherapy must be reinstituted postoperatively to ensure optimal results.