**Cancers in Childhood**

**Incidence, Leukemia, and Lymphoma**

**I. Incidence and overview**

**Although cancer is the second leading cause of death in children (12% of deaths), it is still relatively uncommon. The incidence**

**of cancer is increasing, however. Fortunately, with modern aggressive multidisciplinary therapy, 5-year survival rates for**

**children with cancer exceed 75%.**

**A. Cooperative groups**

**The treatment of children with cancer is highly specialized. Whenever possible, patients younger than 18 to 21 years of age**

**should be treated in specialized centers related to one of the major pediatric cooperative groups, such as the Children’s**

**Oncology Group. More than 90% of children younger than 10 years of age are treated in such centers, and their mortality has**

**decreased proportionally. Only about 30% of teenagers are enrolled in such centers, however, and the mortality rates in this**

**group have not shown the same improvement.**

**B. Incidence**

**Leukemia and lymphoma make up almost half of the cases of malignancy in childhood, followed by central nervous system**

**(CNS) tumors. The mortality rate for CNS cancers now exceeds that for acute lymphocytic leukemia.**

**There is no formal reporting system for malignant tumors in children in the United States. SEER (Surveillance, Epidemiology,**

**and End Results) reports from the National Cancer Institute indicate that approximately 164 cases of cancer occur per 1 million**

**population <20 years of age in the following incidences per million:**

**Leukemia—43 Neuroblastoma—8 Bone tumors—9**

**CNS tumors—29Wilms’ tumor—6 Retinoblastoma—3**

**Lymphomas—22Soft tissue sarcomas—11**

**II. Acute leukemia**

**(see Chapter 25)**

**A. Pathology**

**Acute lymphoblastic leukemia (ALL) accounts for 80% to 85% of leukemias in childhood. Acute myelogenous leukemia**

**(AML) accounts for 15% and chronic myelogenous leukemia accounts for 5% of cases.**

**In ALL, 15% to 25% of cases are T-cell, <5% are B-cell, and the remainder are precursor B-cell leukemias. Of the precursor Bcell**

**leukemias, 70% possess the common acute lymphoblastic leukemia antigen (CALLA, CD-10). They are usually also**

**terminal deoxynucleotidyl transferase–positive. Almost all are also CD-19–positive.**

**B. Treatment**

**of acute leukemias in childhood involves induction of remission, prophylaxis to the CNS, and maintenance therapy. Standard**

**treatment for ALL leads to long-term remission in >85% of cases. Induction therapy employs vincristine, prednisone, and Lasparaginase**

**with the addition of daunomycin, depending on risk stratification. Intensification therapy includes CNS**

**prophylaxis. During maintenance therapy, oral mercaptopurine is given daily and methotrexate weekly for 2 to 3 years. Many**

**patients receive monthly pulses of vincristine plus prednisone or dexamethasone. One or two cycles of a reinduction regimen**

**are often added in ALL.**

**Certain prognostic factors at diagnosis affect the outlook of children with ALL, and their treatment is modified accordingly.**

**Children with poorer prognostic features require more intensive treatment than standard therapy.**

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**Favorable prognostic factors for ALL. Average risk factors include initial white blood cell count (WBC) of**

**<50,000/μL and age 1 to 9 years. Favorable features include pre-B subtype, L1 morphology, hyperploidy, lack of**

**organomegaly, low bone marrow blasts on day 7 of induction therapy, trisomy of chromosomes 4 and 10, and t4:11 or**

**Tel/AML1 translocations.**

**Poor prognostic factors include WBC >50,000/μL, age <1 year or >10 years, massive organomegaly, lymphomalike**

**features, CNS involvement at diagnosis, mediastinal mass, failure to achieve remission by day 14 or 28, and certain**

**chromosomal translocations, especially MLL gene rearrangements (11q23) in infants, and the Philadelphia**

**chromosome.**

**AML requires intensive chemotherapy. It is often followed by allogeneic hematopoietic stem cell transplantation**

**(HSCT) in first remission, which appears to provide the best survival if a suitably matched related donor is available.**

**Otherwise, outcome with chemotherapy alone appears as good as with autologous or matched unrelated donor**

**transplant as of this writing. HSCT (allogenic, autologous, or matched unrelated) is also often recommended for**

**patients with ALL and AML who relapse.**

**C. Survival**

**The 5-year survival rate is >85% in children with “good-prognosis” ALL following standard therapy. Even children with poorer**

**risk factors who receive intensive therapy have an overall long-term survival of at least 70%. Sites of relapse include the CNS,**

**testes, and bone marrow. The risk for relapse after 2 years of therapy is very low. The 5-year survival rate with the best**

**available regimens in children with AML is 65% in first remission when consolidated with a sibling donor HSCT and about**

**50% for those without.**

**III. Lymphoma**

**A. Non-Hodgkin lymphoma**

**(see Chapter 21). In pediatrics, lymphomas can be considered to be lymphoblastic or nonlymphoblastic and localized or**

**nonlocalized. Lymphoblastic lymphomas are usually T cell and, when nonlocalized, may be the same entity as T-cell leukemia;**

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**these illnesses are usually treated in the same way. Nonlymphoblastic lymphomas are usually B cell and are frequently Burkitt**

**(or Burkitt-like) lymphoma.**

**Different combination chemotherapeutic regimens are necessary for the subtypes of lymphoma. Localized lymphomas respond**

**very well to chemotherapy even when bulky, and have a cure rate of >90%. The prognosis for disseminated T-cell lymphomas**

**is the same as for T-cell ALL. The outlook for disseminated nonlymphoblastic or B-cell lymphoma is about 50%.**

**B. Hodgkin lymphoma**

**(see Chapter 21). There is no consensus on the treatment of Hodgkin lymphoma in children, with the exception of stage IV**

**disease, which is primarily treated with chemotherapy. Chemotherapy is used for all stages of disease. Staging laparotomy is no**

**longer recommended. Splenectomy is contraindicated in young children because of fatal infectious complications and increased**

**risk for leukemia. The alternation of the COPP and ABVD regimens (defined in Appendix D-1) or a hybrid of them is**

**frequently recommended rather than either regimen alone. In children, local-field rather than extended-field radiation is**

**preferred in an effort to reduce long-term side effects, such as growth retardation and second cancers, especially breast cancer**

**in girls. Second malignancies are a major problem with the risk approaching 40% by age 35 years for girls who have been**

**irradiated. Current Children’s Oncology Group (COG) treatment regimens are evaluating modulation of therapy based on initial**

**response with a goal of minimizing toxicity while maintaining high cure rates.**

**Brain Tumors**

**Neurologic malignancies are discussed in Chapter 14.**

**I. Epidemiology**

**Brain tumors in children may be associated with certain underlying diseases, including neurofibromatosis, tuberous sclerosis,**

**and von Hippel-Lindau angiomatosis. Family clusters of CNS tumors have occasionally been reported.**

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**II. Pathology and natural history**

**A. Pathology**

**Most CNS neoplasms in children are primary tumors of the brain; the single exception is meningeal metastases, which are**

**common with leukemia and lymphoma. Astrocytomas are the most frequent type (about 50% of all cases). Medulloblastomas**

**account for 25% of cases; ependymomas, 9%; and glioblastomas, 9%.**

**B. Sites of disease**

**Brain tumors in children tend to occur along the central neural axis (i.e., near the third or fourth ventricle or along the brain**

**stem). Most brain tumors that occur during the first year of life are supratentorial. In patients between 2 and 12 years of age,**

**85% are infratentorial. In patients >12 years of age, the relative incidence of supratentorial tumors increases.**

**III. Symptoms and signs**

**A. Symptoms**

**The most common symptoms include headaches, irritability, vomiting, and gait abnormalities. Morning headaches are most**

**characteristic, but drowsiness and abnormal behavior are also common. Symptoms may be intermittent, particularly in very**

**young children who have open fontanelles.**

**B. Physical findings**

**include enlarged or bulging fontanelles in very young children and cerebellar abnormalities, papilledema, and sixth cranial**

**nerve abnormalities in older children.**

**IV. Treatment and survival**

**Survival rates for patients with low-grade astrocytomas are high if the tumor can be surgically removed (>90% at 5 years) and**

**low if the tumor is high grade (<10% at 5 years). Survival for medulloblastoma depends on both local recurrence (<25% with**

**surgery and radiotherapy) and spinal metastases (about 35% incidence without prophylactic spinal irradiation); this tumor is**

**invariably recurrent when treated with surgery alone.**

**Chemotherapy is now being used more frequently in children with brain tumors in an attempt to improve survival and to reduce**

**the use of radiation, which has devastating effects in young children. RT is deferred in children <3 years of age. Unlike**

**childhood leukemia, relatively little improvement in survival has been obtained over the years. High-dose therapy with**

**autologous HSCT support has shown some promise. In addition, experimental approaches using targeted therapies, novel**

**chemotherapy and radiation delivery systems, and dendritic cell-based vaccine trials are currently under investigation.**

**Neuroblastoma**

**I. Epidemiology and etiology**

**Neuroblastoma is the most common congenital tumor and the most common tumor to occur during the first year of life. It**

**rarely occurs in patients >14 years of age. About 40% occur in the first year of life, 35% from 1 to 2 years of age, and 25% after**

**2 years of age. Rarely, family clusters are reported.**

**II. Pathology and natural history**

**Neuroblastoma has the highest incidence of spontaneous regression of any tumor in humans.**

**A. Histology**

**Neuroblastoma closely resembles embryonic sympathetic ganglia. The tumors partially differentiate into rosettes or**

**pseudorosettes, mature ganglion cells, or immature chromaffin cells. Although histologically similar to ganglioneuromas and**

**pheochromocytomas, neuroblastomas are clearly distinctive. Electron microscopy shows typical dendritic processes that**

**contain granules with dense bodies, probably representing cytoplasmic catecholamines. The most primitive histologic type of**

**neuroblastoma is composed of small round cells with scant cytoplasm. The ganglioneuroma is composed of larger, more mature**

**ganglion cells with more abundant cytoplasm.**

**Homogeneously staining regions and double minute chromosomes seen in poor-prognosis neuroblastomas represent amplified**

**N-myc segments. Amplification of N-myc is an intrinsic property of poor-prognosis tumors and can be rapidly detected by**

**fluorescent in situ hybridization (FISH) concordant with Southern blot analysis.**

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**B. Sites**

**The most common primary site is the adrenal gland (40% of cases); a tumor of the adrenal gland produces an abdominal mass.**

**Involvement of posterior sympathetic ganglion cells results in both intrathoracic and intra-abdominal masses, the so-called**

**dumbbell tumor that causes compression of the spinal cord.**

**C. Mode of spread**

**Most cases of neuroblastoma present with widespread metastatic disease. The most common metastatic sites include bone, bone**

**marrow, liver, skin, and lymph nodes.**

**III. Diagnosis**

**A. Symptoms**

**Abdominal pain and distention, bone pain, anorexia, malaise, fever, and diarrhea**

**B. Physical findings**

**Hepatomegaly, hypertension, orbital mass and ecchymosis, subcutaneous nodules (particularly in infancy), intra-abdominal**

**mass, and Horner syndrome**

**C. Laboratory studies**

**Complete blood count (CBC), serum chemistry panel**

**Urine for total catecholamines and metabolites, including vanillylmandelic acid (VMA) and homovanillic acid (HVA)**

**Chest and abdominal radiographs**

**CT scan of the abdomen or thorax (possibly preceded by abdominal and renal ultrasound)**

**Bone scan**

**Bone marrow aspiration and biopsy to look for tumor cells**

**131I-MIBG (131I-metaiodobenzylguanidine), which is specific for neuroblastoma and pheochromocytoma.**

**Examination of tumor for amplification of the N-myc gene**

**IV. Staging system and prognostic factors**

**A. Staging system**

**StageExtent of disease**

**I Localized disease surgically removed *in toto***

**II Regional disease, unilateral**

**III Tumor crossing the midline**

**IV Metastatic disease**

**IVS Stage I or II primary tumor with metastases to liver, skin, and/or bone marrow without radiographic evidence of bony**

**involvement (usually in very young infants)**

**B. Survival and prognostic factors**

**The prognosis for neuroblastoma is closely related to the age of the patient and stage of disease.**

**Age. Patients with congenital tumors have the most favorable prognosis, even with widespread disease, and they also**

**have the highest rate of spontaneous regression without treatment. Patients who are between 1 and 5 years of age do**

**worse than patients younger than 1 year or older than 5 years of age.**

**Stage. Patients with advanced disease, except for stage IVS, have a poor survival rate. The overall 2-year survival for**

**neuroblastoma is >80% for stages I and II and <30% for stage IV. Stage IVS has a 90% survival rate. Patients with**

**stage III and IV disease who have amplification of the N-myc gene do worse.**

**The urinary VMA:HVA ratio is an indirect measure of dopamine hydroxylase. Absence of this enzyme may convey a**

**poorer prognosis (i.e., if the VMA:HVA ratio is <1.5) and may cast doubt on the diagnosis of neuroblastoma.**

**V. Management**

**A. Surgery**

**Localized disease is managed primarily by surgical resection. For metastatic disease, biopsy or excision of the primary tumor is**

**important for N-myc gene assessment. Complete resection is usually delayed until after chemotherapy is administered but may**

**be done at the time of diagnosis.**

**B. RT**

**is used for bulky tumor in combination with chemotherapy.**

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**C. Chemotherapy**

**Residual localized or advanced disease. Aggressive multimodal chemotherapy with doxorubicin, cyclophosphamide,**

**etoposide, and cisplatin, combined with surgical resection and bone marrow transplantation, has improved survival in**

**stage III and IV disease.**

**Congenital disease. In patients with congenital disease, specifically for stage IVS, chemotherapy is not used unless the**

**tumor causes significant symptoms.**

**D. HSCT**

**(usually autologous) after intensive radiation and chemotherapy appears to improve the outlook for patients with advanced**

**disease, especially when used in conjunction with post transplant 13-cis-retinoic acid.**

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**E. Future directions**

**Poor survival in the advanced stages of disease has spurred extensive research into targeted therapies. An especially promising**

**target under evaluation is GD2 (disialoganglioside). Anti-GD2 has shown some efficacy, especially in patients with infiltrating**

**marrow disease.**

**Wilms’ Tumor (Nephroblastoma)**

**I. Epidemiology and etiology**

**A. Incidence**

**Wilms’ tumor most frequently affects children between 1 and 5 years of age, and rarely those >8 years of age. The incidence is**

**about 7 per 1 million in the childhood age group. Familial clusters have been described, particularly in patients with bilateral**

**Wilms’ tumors.**

**B. Associated abnormalities**

**Wilms’ tumor has been associated with certain congenital anomalies, including genitourinary anomalies, aniridia (absence of an**

**iris), and hemihypertrophy (Beckwith-Wiedemann syndrome). Deletion of the short arm of chromosome 11 has been associated**

**with a syndrome of Wilms’ tumor, mental retardation, microcephaly, bilateral aniridia, and ambiguous genitalia.**

**II. Pathology and natural history**

**A. Histopathologic classification**

**is most accurate for determining the prognosis.**

**Wilms’ tumor. Tumors that display mature elements and few anaplastic cells have the most favorable prognosis and**

**are termed favorable histology. Unfavorable histology concerns tumors that have focal or diffuse anaplasia, rhabdoid**

**sarcoma, or clear cell sarcoma. Unfavorable histology accounts for 12% of Wilms’ tumors but almost 90% of deaths.**

**Congenital mesoblastic nephroma is a rare benign tumor that is common in infancy (the most common renal neoplasm**

**during the first month of life) and can be histologically confused with Wilms’ tumor. This tumor consists of spindleshaped,**

**immature connective tissue cells that have a distinctive fibroblastic appearance with only minimal nuclear**

**pleomorphism and mitoses.**

**B. Sites**

**About 7% of Wilms’ tumors are bilateral at the time of diagnosis.**

**C. Mode of spread**

**The lungs are the principal sites of metastases; liver and lymph nodes are the next most common sites. Bone marrow metastases**

**are extremely rare and tend to be associated with clear cell subtypes of sarcomatous Wilms’ tumor. CNS metastases are**

**extremely rare.**

**D. Paraneoplastic syndromes**

**Wilms’ tumors have been associated with increased erythropoietin (erythrocytosis) and with increased renin (hypertension).**

**III. Diagnosis**

**A. Symptoms**

**The most common symptoms include enlarged abdomen, abdominal pain, and painless hematuria.**

**B. Physical findings**

**A palpable abdominal mass is the most common finding. Hypertension is sometimes present.**

**C. Laboratory studies**

**CBC, serum chemistries, urinalysis**

**Plain radiographs of the chest and abdomen**

**CT or, preferably, MRI scan of abdomen**

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**IV. Staging and prognostic factors**

**A. Staging system**

**StageExtent of disease**

**I Well-encapsulated tumor that is surgically removed in its entirety**

**II Extension of tumor beyond renal capsule by local infiltration with extension along the renal vein, involvement of paraaortic**

**nodes, and no residual macroscopic disease**

**III Macroscopic residual disease or peritoneal metastases or contamination during nephrectomy**

**IV Distant metastases, particularly to lung**

**V Bilateral disease**

**B. Survival and prognostic factors**

**The most important prognostic factors are the histopathologic classification and the clinical and surgical staging. Age at**

**diagnosis is of minor importance, although younger patients appear to have a slightly better outcome. The overall 2-year**

**survival rate is >95% for stage I, II, and III disease, with favorable histology, and about 50% for stage IV disease.**

**V. Management**

**A. Surgery**

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**All patients must have surgery for both staging and removal of as much tumor as possible. A transabdominal incision is**

**mandatory to examine the vessels of the renal pedicle and the noninvolved kidney. The tumor bed and any residual tumor**

**should be outlined with metallic clips at the time of surgery.**

**B. RT**

**is useful for treating stage III disease and metastatic disease to bone, liver, or lung.**

**C. Chemotherapy**

**Multiple courses of combination chemotherapy are the preferred treatment. The major active chemotherapeutic agents are**

**actinomycin D, vincristine, and doxorubicin. Cyclophosphamide is an effective second-line drug. Cisplatin is active against**

**Wilms’ tumor and is being used in investigational protocols. The National Wilms Tumor Study is ongoing. The youngest**

**patients are particularly susceptible to serious toxic effects from chemotherapy, particularly hematologic, and drug dosages**

**should be reduced 50% for patients <15 months of age.**

**D. Treatment according to stage of disease**

**Surgery and chemotherapy are used for all stages of disease.**

**Stage I. RT is not necessary.**

**Stages II and III. RT is not needed for stage II with favorable histology but is used for unfavorable histology and stage**

**III.**

**Stage IV or recurrent disease. If possible, surgery can be used. Chemotherapeutic agents can be restarted if they were**

**discontinued or changed if relapse occurred during treatment. RT is useful for metastatic disease. Intensive**

**chemotherapy with autologous HSCT may be beneficial in recurrent disease.**

**Stage V. Bilateral Wilms’ tumor necessitates a special effort to preserve as much renal tissue as possible. Initially,**

**biopsy is done, and then chemotherapy followed by judicious resection of the remaining tumor. Bilateral nephrectomy**

**followed by chemotherapy, and renal transplantation is a last resort. The 3-year survival rate is 75% for these patients.**

**Rhabdomyosarcoma**

**I. Epidemiology and etiology**

**Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children; there are about 8 cases per million**

**population. Suggestive evidence of C-particle viruses in these tumors has been observed with electron microscopy, but the**

**viruses have not been isolated.**

**II. Pathology and natural history**

**A. Histology**

**Four major histologic categories of this striated muscle neoplasm have been described: embryonal (including sarcoma**

**botryoid), alveolar, pleomorphic, and mixed. Z bands can be seen with electron microscopy. Rhabdomyoblasts have acidophilic**

**cytoplasm, which is often periodic acid–Schiff stain (PAS)–positive. There**

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**are characteristic genetic alterations that can be observed. Embryonal RMS may have a characteristic loss of heterozygosity at**

**the 11p15 locus. The majority of alveolar RMS have a characteristic t(2;13) resulting in a chimeric PAX3 and FKHR fusion**

**gene product with a smaller percentage having t(1;13) involving PAX7 and FKHR.**

**B. Sites**

**The head and neck are involved in 35% of cases, the trunk and extremities in 35%, and the genitourinary tract in 30%.**

**C. Mode of spread**

**These tumors have a great tendency to recur locally and to metastasize early through the venous and lymphatic systems. Any**

**organ may be involved with metastases, but the lungs are most frequently affected.**

**III. Diagnosis**

**A. Symptoms**

**The most common presenting symptom is a painless, enlarging mass. Hematuria and urinary tract obstruction is seen with**

**primary tumors of the genitourinary tract. The painless swelling is often noticed after minor trauma that calls attention to the**

**enlarging mass.**

**B. Physical findings**

**include mass lesions, urinary tract obstruction, and a “cluster of grapes” protruding through the vaginal canal (sarcoma**

**botryoid). Exophthalmos or proptosis occurs with head and neck primaries.**

**C. Laboratory studies**

**CBC, liver function tests**

**Plain radiographs and MRI or CT scans of involved areas**

**Bone marrow aspiration and biopsy**

**Gallium (and perhaps thallium) scans**

**IV. Staging system and prognostic factors**

**A. Intergroup Rhabdomyosarcoma Study Staging System**

**StageExtent of disease**

**I Localized disease, completely resected**

**II Localized disease, microscopic residual tumor**

**IIA Grossly resected disease with microscopic residual tumor and negative lymph nodes**

**IIB Regional disease, completely resected, with no microscopic residual disease**

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**IIC Regional disease with positive lymph nodes, grossly resected**

**III Incomplete resection or biopsy with residual gross disease**

**IV Distant metastases**

**B. Survival and prognostic factors**

**Survival is closely correlated with stage. The 5-year survival rate with the standard VAC chemotherapy regimen (vincristine,**

**actinomycin D, and cyclophosphamide) is almost 100% for stage I and II disease, >60% for stage III disease, and about 40%**

**for stage IV disease. The overall survival rate is 70%.**

**V. Management**

**The treatment of RMS should be aggressive, even with localized disease. Surgery, RT, and chemotherapy should be used for all**

**cases with any residual disease.**

**A. Surgery**

**should include total excision, if possible, but radical surgery is unnecessary and unwarranted. Lymph node dissection is useful**

**for staging in extremity or genitourinary tract tumors.**

**B. RT**

**usually consists of 5,000 to 6,000 cGy given over 5 to 6 weeks to the primary tumor site with wide ports to include margins of**

**all dissected tumors.**

**C. Chemotherapy**

**The VAC regimen is most commonly given. Studies that compared doxorubicin, etoposide, and ifosfamide with VAC for**

**advanced disease showed no survival advantage, although the combination may be useful in recurrent or resistant disease.**

**Chemotherapy is necessary for patients with the following indications:**

**Adjuvantly with stage I disease**

**With RT for stage II disease**

**To shrink the primary tumor either before or after surgery for stage III and IV disease, and continued as adjunctive**

**therapy**

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**Ewing Sarcoma and Primitive Neuroectodermal Tumor (Ewing Family Tumors)**

**I. Epidemiology and etiology**

**The incidence of Ewing family tumors (EFT), Ewing sarcoma, and primitive neuroectodermal tumor (PNET) is about 1.5**

**cases per 1 million population. The disease is very rare among black children. Seventy percent of patients are <20 years of age.**

**The peak incidence is at 11 to 12 years of age for girls and 15 to 16 years of age for boys. The male-to-female incidence ratio is**

**2:1. A reciprocal translocation between chromosomes 11 and 22 in about 85% of tumors creates a chimeric ews-fli1 fusion**

**gene.**

**II. Pathology and natural history**

**A. Histology**

**EFT is a small cell tumor of bone or soft tissue characterized by islands of anaplastic, small, round blue cells (see Appendix C-**

**4, section II, for immunophenotypes of small blue cell tumors). The spectrum of EFT includes Ewing sarcoma of bone,**

**extraosseous Ewing sarcoma, and PNET. Ewing sarcoma and PNET carry the same chromosomal translocation.**

**B. Sites of disease**

**These tumors occur predominantly in the midshaft of the humerus, femur, tibia, or fibula, but they also occur in the ribs,**

**scapula, pelvis, or extraosseous sites. PNETs in the chest are called Askin tumors.**

**C. Mode of spread**

**At the time of diagnosis, 20% to 30% of these tumors have metastasized. Most metastases are to the lung. Metastases to other**

**bones or lymph nodes can also occur. CNS metastases, particularly meningeal, have been reported but are rare.**

**III. Diagnosis**

**A. Symptoms**

**Pain that is followed by localized swelling is the most frequent manifestation.**

**B. Physical findings**

**include tenderness and a palpable mass over the tumor site.**

**C. Preliminary laboratory studies**

**may show an elevated erythrocyte sedimentation rate and lytic bone lesions on radiograph (frequently, the lesions have an**

**“onion-skin appearance”). A chest radiograph and CT should be obtained in all patients.**

**D. Special diagnostic studies**

**Bone scan**

**MRI or CT scans of involved sites**

**Gallium scan**

**Positron emission tomography (PET)**

**IV. Staging and prognostic factors**

**A. Staging**

**The two major stages for Ewing sarcoma and PNET are simply:**

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**Localized disease**

**Metastatic disease**

**B. Survival and prognostic factors**

**Patients with a primary tumor in a central location have a higher incidence of local recurrence and a generally poorer prognosis**

**than do patients with tumors in other primary sites. The prognosis for patients with metastatic disease at the time of diagnosis**

**remains grave; bone metastases have the worst prognosis. High WBC and fever at diagnosis also are associated with a poor**

**prognosis. The disease-free survival depends on the response to chemotherapy.**

**V. Management**

**A. Treatment according to stage of disease**

**Localized disease. All patients with localized disease should receive intensive chemotherapy followed by complete**

**surgical resection, if possible. If resection is not feasible or complete, RT is given. RT is not needed if the tumor can**

**be removed with >1-cm margin.**

**Metastatic disease is treated with intensive chemotherapy followed by surgical resection (if possible) or RT.**

**B. Chemotherapy**

**involves multiple drugs given in multiple cycles. The most active agents include vincristine, actinomycin D, high-dose**

**cyclophosphamide, doxorubicin,**

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**ifosfamide, and etoposide; combinations of these drugs are effective. Carmustine, methotrexate, and bleomycin also have**

**activity against this disease and are useful in combination with the more active agents. The optimal combination of agents is**

**controversial. High-dose chemotherapy with autologous HSCT is often used for consolidation in advanced stage disease with**

**variable success.**

**C. Surgery**

**The initial procedure should be biopsy only. Open biopsy is preferred in children. Control of the primary tumor site is essential.**

**Surgery is used in selected patients with localized disease and in patients with bulky metastatic disease. The total removal of**

**tumor is not necessary in instances in which severe disabilities could result. Concerted efforts at limb preservation should be**

**made.**

**D. RT**

**is aimed at eradicating all disease while preserving limb function. The optimal volume of bone to be irradiated has not been**

**determined.**

**Nonbulky lesions. When combined with chemotherapy, delivering 4,000 to 5,000 cGy of RT to the entire bone with**

**an additional 1,000 to 1,500 cGy coned down to the involved site yields good results.**

**Leg-length discrepancies. In the past, when the probabilities for leg-length discrepancies were excessive (e.g., for**

**younger children with lesions near the knee), patients underwent primary amputation plus chemotherapy. Expandable**

**endoprosthetic reconstruction now makes surgical resection an option for younger children. This regimen usually**

**results in better extremity function than limbs treated with orthovoltage irradiation. Limb-salvage procedures using**

**chemotherapy are also frequently performed when appropriate.**

**Pelvic primaries. Moderate doses of RT (4,000 cGy) with limited surgery are used for pelvic primary tumors because**

**excessive morbidity is associated with large doses of radiation delivered to bowel and bladder. Chemotherapy must be**

**used as well.**

**Retinoblastoma**

**I. Epidemiology and etiology**

**A. Incidence**

**Retinoblastoma occurs in about 3 per 1 million children annually. The average age of patients is 18 months, and >90% are <5**

**years old. The incidence in Asians is four times that in whites. Patients have a high risk for other neoplasms, particularly**

**radiation-induced osteosarcomas that arise in treatment portals.**

**B. Familial retinoblastoma**

**About 40% of cases are hereditary. These have bilateral multifocal involvement, early age at diagnosis, secondary tumors, and**

**a positive family history. Siblings have a 10% to 20% chance of developing retinoblastoma if the affected child has bilateral**

**disease and about 1% if unilateral. The offspring of a patient who survived bilateral retinoblastoma have about a 50% chance of**

**developing the disease.**

**II. Pathology and natural history**

**A. Histology**

**Retinoblastoma is a malignant neuroectodermal tumor. It appears histologically as undifferentiated small cells with deeply**

**stained nuclei and scant cytoplasm. Large cells are sometimes seen forming pseudorosettes, particularly in bone marrow**

**aspirates.**

**B. Mode of spread**

**Multiple foci of tumor in the retina are typical at the outset. Most patients die from CNS extension through the optic nerve or**

**widespread hematogenous metastases.**

**III. Diagnosis**

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**A. Symptoms**

**The disease typically presents with a “cat’s eye” (white pupil or leukokoria). A squint or strabismus is occasionally noted.**

**Orbital inflammation or proptosis rarely occurs.**

**B. Physical findings**

**are usually limited to the eye, but patients must have a complete neurologic examination. Ophthalmologic examination under**

**anesthesia is essential**

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**for infants and small children, for both those with symptoms and those at high risk for developing the disease. Two**

**pathognomonic features are as follows:**

**The typical pattern of fluffy calcifications in the retinas**

**The presence of vitreous seeding by tumor cells**

**C. Preliminary laboratory studies**

**CBC, liver function tests**

**MRI or CT scans of head and orbit (both scans performed with contrast)**

**D. Special diagnostic studies**

**Lumbar puncture with cerebrospinal fluid by cytocentrifuge**

**Bone marrow aspiration and biopsy**

**Serum levels of carcinoembryonic antigen and α-fetoprotein, which are frequently elevated in this disease**

**Urinary catecholamine levels, which are infrequently elevated**

**IV. Staging system and prognostic factors**

**A. Staging system**

**The Reese-Ellsworth classification is most frequently used:**

**GroupExtent of disease**

**I Solitary lesion or multiple tumors <4 disc diameters in size at or behind the midplane of the eye**

**II Solitary lesions or multiple tumors 4 to 10 disc diameters at or behind the midplane of the eye**

**III Any lesions anterior to the midplane, or solitary lesions larger than 10 disc diameters and behind the equator**

**IV Multiple tumors, some larger than 10 disc diameters, or any lesion extending anteriorly to the ora serrata (junction of the**

**retina and ciliary body)**

**V Massive tumor that involves more than half the retina, or presence of vitreous seeding, or optic nerve involvement**

**VI Residual orbital disease, optic nerve involvement and extrascleral extension**

**B. Survival and prognostic factors**

**The prognosis is related to both stage and the interval between discovery of clinical signs and the initiation of treatment. The**

**survival rate is virtually 100% for groups I to IV and 83% to 87% for group V. After disease has invaded the orbit, the mortality**

**rate exceeds 80% despite aggressive chemotherapy.**

**V. Management**

**A. Surgery**

**is the primary modality of treatment. Prompt enucleation in unilateral disease and enucleation of the most extensively involved**

**eye in bilateral disease are most commonly employed. Another approach has been to enucleate only those eyes with optic nerve**

**involvement and to treat the remaining disease with RT. When enucleation is performed, as long a segment of the optic nerve**

**as possible should be removed. Chemotherapy, photocoagulation, cryotherapy, and plaque radiotherapy may be used in selected**

**cases.**

**B. RT**

**is given, in most cases, to either the tumor bed or the nonremoved involved eye. Usually, the dose given is about 3,500 cGy in**

**nine fractions over a 3-week period to the posterior retina. This technique, particularly when using megavoltage irradiation, is**

**used to attempt to spare the anterior chamber and avoid cataract formation; it is unsuitable for tumors at or beyond the midpoint**

**of the eye.**

**Radiocobalt applicators have been used for single lesions or discrete groups of small lesions.**

**RT without surgery is usually reserved for patients with advanced disease in both eyes, residual tumor after surgery,**

**or tumors involving the optic nerve. Most patients should not have RT without surgery.**

**Light coagulation and cryotherapy have been used for discrete lesions, particularly for small recurrences.**

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**C. Chemotherapy**

**is useful for metastatic disease. Adjuvant therapy for localized disease has not been shown to in**