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2005

2004 Cancer Care Annual Report

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t r a n s i t i o n s

2004 cancer care annual report



Children's Mercy
HOSPITALS & CLINICS
www.childrensmercy.org



focus on

the Ewing's Sarcoma
Family of Tumors

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Dear Colleagues,

This year's Children's Mercy Hospital's Cancer Center Annual Report focuses upon Ewing's sarcoma, one of two bone tumors that predominate in children. Typically, these tumors account for five to six percent of all childhood malignancies. However, among our adolescent population these tumors are twice as common constituting a greater proportion (eight to 11 percent) of the cancers. These tumors are predominantly affecting a group of individuals who we in Pediatric Oncology consider a high risk and forgotten population.

First, they are in a phase of transition from childhood to adulthood. Many issues are impacting their lives at this age and the quandary of who they are and who they will be as adults is so important at this age. Equally strong an issue is their feeling of invincibility at this age. For these and a myriad of other reasons, there is often a longer period of time between symptom onset and the parent's awareness and thus their cancer's diagnosis. These delays in diagnosis, as well as delays in revealing evolving complications during therapy, increase their risk for a poor outcome. Teens, as we all know, are neither children nor adults, but a group with unique challenges and needs that must be attended to in order to maximize their chance of cure and survival.

By this time in their life, these young adults are questioning whether they wish to be seen by pediatricians or by adult specializing medical practitioners. Thus, we see among this age group an increasing proportion of newly diagnosed individuals migrating towards the adult oncology specialists. Normally, we would say there is nothing wrong with this, just so they see somebody trained in the care of people with cancer. But, interestingly, recent analyses in the medical literature have now repeatedly shown that adolescents and young adults actually have a significantly better chance of cure when treated with regimens originating in the pediatric cancer clinical trials compared to therapies utilized in adults with cancer. This is also the case in Ewing's sarcoma patients where there has been seen a full 15-20 percent better survival at pediatric institutions than adult institutions. While an array of reasons may be present for this finding, it is felt to be due primarily to the more aggressive approach to therapy, which in addition to more intensive chemotherapy and doses, utilizes an integrated multidisciplinary team not always available in other settings. A pediatric oncology team approaches patients from the standpoint that they are otherwise healthy individuals with the ability to tolerate an aggressive approach, whereas an adult oncologist primarily takes care of older individuals with cancer who normally have a limited ability to tolerate aggressive chemotherapy. This limitation is generalized to the adolescents and young adults who in reality actually can tolerate the more intense regimens of pediatric oncology.



A handwritten signature in black ink that reads "Alan S. Gamis, MD, MPH". The signature is stylized and cursive.

Alan S. Gamis, MD, MPH
Director of Oncology
Chair, CMH Cancer Care
Committee

Finally, they are a part of a forgotten age group in the realm of clinical research. The patients between the ages of 15 and 35 years have the lowest participation rates in clinical trials and have had the smallest improvement in cure rates over the past several decades. Fortunately, attention is now being brought to this group of patients and the clinical trials of the National Cancer Institute's Children's Oncology Group are now targeting and including patients up to the age of 30 years and occasionally higher. Children's Mercy Hospital, as one of the larger children's cancer centers in the COG, is an active participant in these clinical trials with approximately 100 different clinical trials available for children and adolescents up to the age of 21 years diagnosed with cancer. Not only is Children's Mercy a participant in this effort but the members of the cancer program are also leaders in the fight against childhood cancer via leadership of many of these national clinical trials and the participation in the expert panels that oversee the research of the COG. A child diagnosed and treated with Ewing's Sarcoma at Children's Mercy Hospital thus benefits from this cutting edge activity. They, as well, are overseen by a multidisciplinary team of caregivers which provides a comprehensive approach to adolescents' cancer therapy as well as their future and their family's needs. I am very happy to be able to share with you the work of our team through the focus of this year's Annual Report upon Ewing's sarcoma.

Dear Colleagues,

Again this year, we are pleased to share with you the Cancer Care Annual Report from Children's Mercy Hospitals and Clinics in Kansas City. All of us at Children's Mercy are extremely proud of our nationally-recognized Hematology/Oncology team and the work they do in providing a bright future for hundreds of children with cancer each year.

The title of this year's report, "Transitions," focuses on working with teen-age patients as they transition from childhood to adulthood, and the special needs of adolescent patients with Ewing's sarcoma. But "transitions" also could apply to everything we do here at Children's Mercy. We continue to grow in facilities, programs and research as the needs of the pediatric and adolescent population in our region continue to grow and change.

I hope you will take a few minutes to review this year's annual report, which is aimed at keeping community physicians and others informed of our progress regarding the diagnosis and treatment of childhood cancer. It's essential that this treatment involves the support of the entire family, and Children's Mercy is nationally known for the unique, family-centered environment which we provide to meet each child and family's individual needs through innovative, creative venues.



Randall L. O'Donnell

Randall L. O'Donnell, PhD
President & CEO

Our goal is to provide care in a family-centered care environment...

Division of Hematology/Oncology

The Division of Hematology/Oncology at Children's Mercy Hospitals and Clinics is dedicated to providing comprehensive care to children with cancer and blood disorders. Our goal is to provide this care in a family-centered care environment in an effort to promote health and well being. The division is divided into two sections: the Section of Oncology and the Section of Hematology. The Division Chair is Gerald Woods, MD. The Division Manager is Sue Stamm, RN, MHA, CPNP.

The Section of Oncology- Section Chief-Alan Gamis, MD

The Bone Marrow Transplant Service- Director-Charles Peters, MD: provides hematopoietic stem cell rescue to patients receiving myelo-suppressive or ablative therapy which requires stem cell rescue. Stem cell rescue is accomplished by utilizing umbilical stem cells, matched-related donor cells, and matched-unrelated donor cells. Children's Mercy Hospital participates in the National Marrow Donor Program, the International Blood and Marrow Transplant Registry. Research protocols run by the Pediatric Blood and Marrow Transplant Consortium, National Institutes of



Health, and the Children's Oncology Group are also available for qualifying patients.

The Oncology Service-Director-Alan Gamis, MD: dedicated to the treatment of malignant disorders. In 2004 this service diagnosed 145 new

cases of cancer or other reportable diseases. The Oncology Service treats patients in accordance with clinical trials under the guidance of the Children's Oncology Group.

The Section of Hematology- Section Chief-Gerald Woods, MD

The Sickle Cell Disease Service-Director-Gerald Woods, MD: offers specialized care for the unique diagnostic and treatment needs of children and adolescents diagnosed with sickle cell disease. These patients and families are confronted with episodes of acute pain, life limiting chronic pain, and other long term sequelae related to this devastating disease.

The Regional Hemophilia Center-Director-Brian Wicklund, MD: supports seven sites in a five-state region to provide comprehensive treatment for both adult and pediatric patients with bleeding disorders. In addition, this service supports the diagnosis and treatment of coagulation and/or thrombosis disorders.

Children's Mercy Cancer Care Committee

The Children's Mercy Hospital Cancer Care Committee is a standing medical staff committee that provides oversight of the oncology services. The committee is chaired by the section chief for the Section of Oncology and has both physician and non-physician representation (see member listing). It is comprised of a multidisciplinary team of physicians, staff, and other discipline from across the institution. The committee meets quarterly and reviews patient acuity, program services and quality initiatives, and determines quality improvement needs and opportunities related to pediatric cancer prevention, diagnosis, treatment, and





outreach. The committee functions in accordance with the American College of Surgeons' accreditation standards.

Pediatric Hematology/Oncology Fellowship Program

The fellowship program at Children's Mercy Hospital trains the future pediatric hematology/oncology specialists. This program requires intense clinical and research training for a minimum of three years. Each fellow at Children's Mercy Hospital enters the fellowship program as a fully trained pediatrician. The first 18 months are dedicated primarily to clinical care and becoming familiar with procedures and standards of practice. The subsequent 18 months are dedicated heavily to clinical and laboratory research. The Division of Hematology/Oncology at Children's Mercy Hospital currently supports three fellowship positions.

The Children's Mercy Cancer Center Cancer Care Conferences

The Children's Mercy Cancer Center Cancer Care Conferences provide opportunities for a multidisciplinary discussion regarding newly diagnosed patients, recurrent/relapsed patients, and unusual pediatric cancer cases. The conference consists of a review of

the patient's history, physical findings at diagnosis, laboratory values, radiology exams, surgical interventions, and pathological findings. This diagnostic review is followed by a thorough review of the potential treatment options, current therapy available, response to therapy, if applicable, and anticipated prognosis. Medical specialists from oncology, surgery, pathology, radiology, radiation oncology, neurosurgery, orthopedic surgery, endocrine, psychology, and dentistry are represented. In addition, non-physician representatives include: advanced practice nursing, physician's assistants, hospital management/administration, social workers, child life specialists, chaplain, dieticians, and staff nurses. These cancer conferences offer CME credits and are conducted in accordance with the American College of Surgeons' accreditation standards.

Case Management

Each physician within the Hematology/Oncology Division works in close collaboration with an advanced practice nurse, physician assistant or nurse in expanded role to comprise a primary team for the children and family to identify. These teams coordinate every aspect of the patient's care throughout

treatment and during post-treatment follow-up. The case manager is the primary contact person for the patient and the family.

Psychosocial Services

Parent-to-Parent Program: designed to connect parents who have been through the cancer experience with parents of a newly diagnosed child with cancer. In addition, this program offers support groups on a weekly basis facilitated by parent volunteers under the oversight of a social worker.

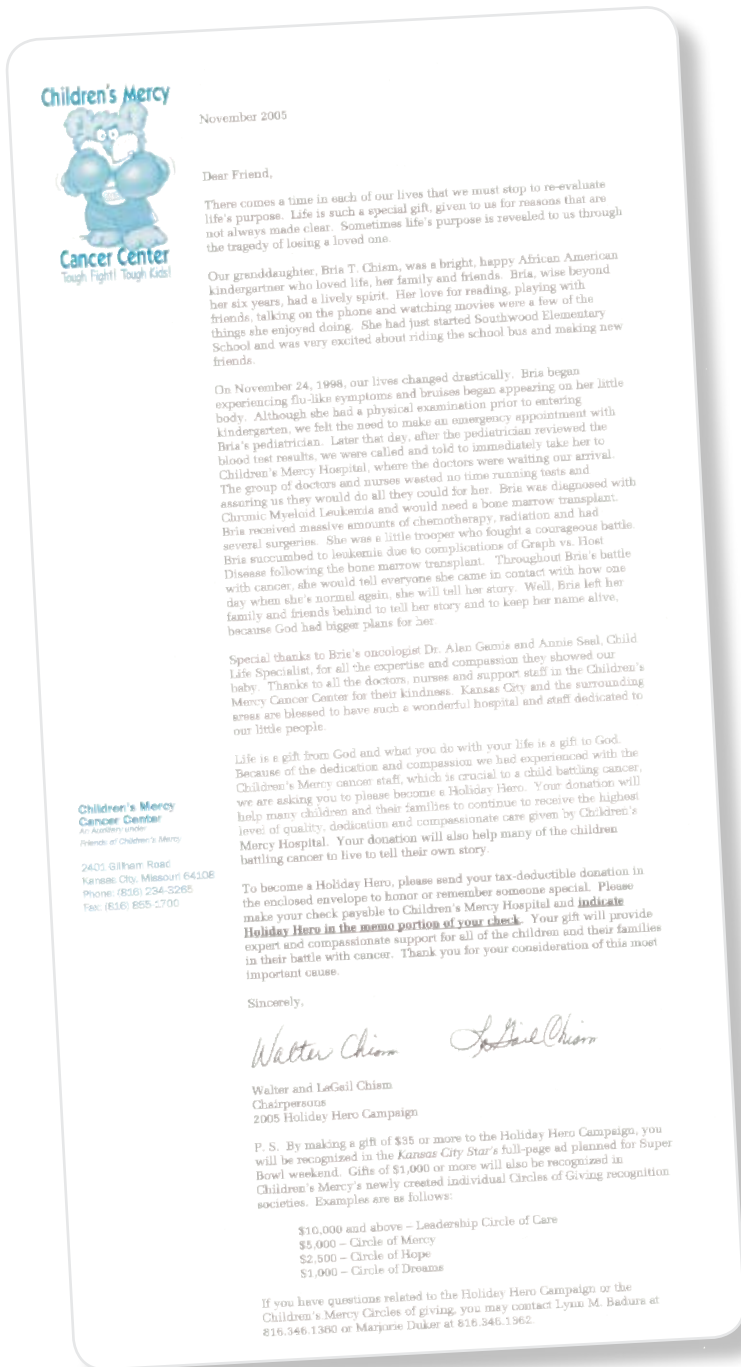
Social Work and Community Services: there are five full-time social workers dedicated to the Division of Hematology/Oncology. The primary focus of this team is to assist the patient and the family in understanding the impact the diagnosis of cancer will have on their family dynamics and life style.

Bereavement Support Group/Program: this program is offered to parents who have experienced the loss of a child. The program includes staff contacts to parents/family members during significant events such as birthdays, anniversary date for the death of the child, an annual memorial service, and the composition of a memory book.

Child Psychologist: a full-time psychologist provides support to the patient, parents, and siblings of those diagnosed with childhood cancer.

Chaplaincy: a full-time chaplain supports the spiritual needs of the patients and their families. There is a chaplain available 24 hours a day.

Child Life Therapist/Music Therapist: two full-time Child Life therapists, one full-time Child Life assistant and one part-time music



The Children's Mercy Cancer Center's Holiday Hero



A team of division members works to build strong connections among the hospital, parents/child, and each child's school.

therapist work with patients, parents, and siblings to aid in the adjustment and ongoing support associated with diagnosis and treatment of childhood cancer.

Nutrition/Pharmacy Services

Nutrition: two full-time and one part-time registered dietitians support the nutrition needs of the patient/family. In addition, there is a nutrition tech that adds support to the team.

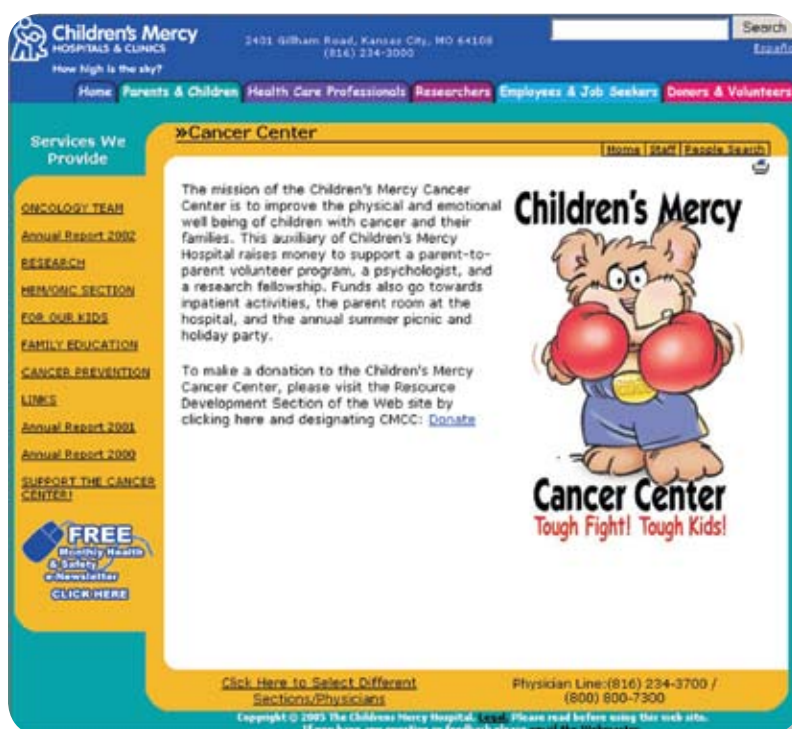
Pharmacy: two full-time pharmacists and one full-time technician support the operations of a satellite pharmacy Monday-Friday, 7:00 a.m. to 7:30 p.m. This satellite supports the inpatient and outpatient areas in preparing and dispensing chemotherapy. In addition, one full-time pharmacist provides clinical consultation to the oncology service and one full-time pharmacist provides clinical support to the Bone Marrow Transplant Service.

Cancer Outreach/School Re-entry Services

Participants: Nurse, Social Worker, Child Life Therapist/Music Therapist

A team of division members works to build strong connections among the hospital, parents/child, and each child's school. Staff is involved in identifying hospital personnel as liaisons to schools. Once identified, school staff is provided with important information and are encouraged to ask questions which ultimately provides them with a better level of comfort/understanding while interfacing with the child and family. Additionally, school mates are given accurate information and are able to ask questions to relieve anxieties regarding cancer.

In addition to providing support for current patients, members of the division also provide preventive education/outreach regarding topics such as smoking cessation and sun exposure. These programs are tailored to the appropriate age group being spoken to.



The Children's Mercy Cancer Center Web site offers patient/family education, as well as public education regarding childhood cancer.

Please visit us at www.childrensmercy.org and select "Cancer Center" from the Services/Departments menu.

Cancer Care Committee Board Members

Medical Staff Members

Andrews, Walter, MD	Surgery
Burleson, Amy, DDS	Dentistry
Cooley, Linda, MD	Cytogenetics
Covitz-Hardy, Lynne, PhD	Developmental Medicine
Dalal, Jignesh, MD	Hematology/Oncology
Emami, Abbas, MD	Hematology/Oncology
Gamis, Alan, MD, MPH Chairman	Hematology/Oncology
Gyves-Ray, Katherine, MD	Radiology
Hetherington, Maxine, MD Assistant Chairman	Hematology/Oncology
Holcomb, G. Whit, MD	Surgery
Hornig, Gregory, MD	Neurosurgery
Huseman, Carolyn, MD	Endocrinology
Lewing, Karen, MD	Hematology/Oncology
Manalang, Michelle, MD	Hematology/Oncology
Massey, Vickie, MD	Radiation/Oncology
Morello, Frank, MD	Radiology
Nicklaus, Pam, MD	Otorhinolaryngology
Peters, Charlie, MD	Hematology/Oncology
Sharma, Mukta, MD	Hematology/Oncology
Shore, Richard, MD	Hematology/Oncology
Smith, Courtney, Pharm. D.	Pharmacy / BMT
Snyder, Charles, MD	Surgery-ACOS Liaison
Woods, Gerald, MD	Hematology/Oncology
Zwick, David, MD	Pathology

Non-Physician Members

Baer, Phyllis, RN	Hematology/Oncology
Bartholomew, Joy, RN, FNP, CPON	Hematology/Oncology
Brown, Pat, MS, TLMFT	Hematology/Oncology
Burns, Susan, RN, CPON	Hematology/Oncology
Corse, Cindy, CTR	Cancer Registry
Devorin, Barb, RN, CPNP	Neurosurgery
Fournier, Julie, RN, CPON	Hematology/Oncology
Green, Nancy, Sr. CNS	Nutrition
Haynes, Cindy, Chaplain	Chaplaincy Services
Hicks, Julie, APRN, BC	Hematology/Oncology
Hutto, CJ, RN, CPON	Senior Director Allied Health
Jones, Ronald, PA-C	Hematology/Oncology
Klockau, Chris, RPh, BCOP	Pharmacy
Laurence, Kris, CCRP	Hematology/Oncology
Marcus, Bette, RN, CPON	Hematology/Oncology
Mick, Kathy, RN, CPON	Education
Ryan, Robin, CCRP	Hematology/Oncology
Seal, Annie, C.L.S.	Child Life
Stamm, Susan, RN, MSN, PNP	Hematology/Oncology
Stegenga, Kristin, RN, PCNS, CPON	Hematology/Oncology
Walter, Christy, CCRP, LPN	Hematology/Oncology



...tumors of the central nervous system and leukemia were the most frequently occurring diagnoses at Children's Mercy Hospital in 2004.

Cancer Registry

Cancer registrations begin with the identification of patients who have been diagnosed or treated for malignancies, or other certain benign / borderline conditions, at Children's Mercy Hospital (CMH) or clinics. The Cancer Registry is operated under the guidance of the Cancer Care Committee and maintains the data standard requirements of the American College of Surgeons Commission on Cancer (CoC) and the State of Missouri. During 2004, 145 new cases were added to the Cancer Registry, which is the highest yearly total of patient registration at CMH. From January 1990 until December 2004, the Cancer Registry has recorded a total of 1,384 patients.

The following specifics are included in the fundamental data collection:

- 1) Occurrence of cancer (incidence);
- 2) Types of cancer (site, morphology, and behavior);
- 3) Extent of disease at time of diagnosis (stage);
- 4) Kinds of treatment received by the patients ; and
- 5) Outcomes of treatment (survival).

These data elements are retrieved (abstracted) stored, and analyzed under strict standards of patient confidentiality. The Cancer Registry continues to monitor patients annually throughout their lifetimes. The data from the annual follow-up identifies additional treatment methods, progression or remission of disease, and the vital status of patients. Medical staff at CMH have access to survival data, as well as other valuable information concerning patient diagnosis and therapeutic efforts. This information contributes to assessing the care of the cancer patient.

As seen in recent years, tumors of the central nervous system and leukemia were the most frequently occurring diagnoses at Children's Mercy Hospital in 2004. There were 39 central nervous system tumors and 35 leukemia patients diagnosed (see Figure 1). Patients included in the registry are divided by class of case category, which indicates where the cancer was initially diagnosed (see Figure 2). The analytic patients are those eligible for inclusion in the registry's statistical reports of treatment efficacy and survival. During 2004, 96 analytic patients (class of case 1) were diagnosed at CMH, 28 patients came to CMH for treatment after diagnosis elsewhere (class of case 2). The non-analytic patients are those in class of case 3 category and also those with reportable conditions included in the registry by recommendation of the Cancer Care Committee.

Thirty-seven cancer related deaths were reported in 2004; 10 were diagnosed during that year. Leukemia and tumors of the central nervous system represented the most frequent diagnoses in this group (see Figure 3).



Cancer Registry

CHILDREN'S MERCY HOSPITAL CANCER REGISTRY 2004 FREQUENCY OF DIAGNOSIS FIGURE 1

Central Nervous System	39	(27%)
Astrocytoma	9	
Glioma	6	
Medulloblastoma	4	
Atypical Teratoid Rhabdoid Tumor	2	
Ependymoma	2	
Germinoma	2	
Primitive Neuroectodermal Tumor	2	
Benign/Borderline Tumors	12	
Leukemia	35	(25%)
ALL	22	
AML	11	
Juvenile myelomonocytic	2	
Lymphoma	12	(8%)
Non-Hodgkin's	8	
Hodgkin's	4	
Neuroblastoma	12	(8%)
Osteosarcoma	6	(4%)
Wilms Tumor	4	(3%)
Ewing's Sarcoma (EFT)	3	(2%)
Retinoblastoma	3	(2%)
Other	31	(21%)
Rhabdomyosarcoma	2	
Mixed Germ Cell	2	
Fibrosarcoma	1	
Desmoplastic Small Round Cell Tumor	1	
Angiosarcoma	1	
Undifferentiated Sarcoma	1	
Alveolar Soft Part Sarcoma	1	
Melanoma	1	
Misc. Reportable Conditions	21	

CLASS OF CASE (ACOS-COC CLASSIFICATION) AND REPORTABLE CONDITIONS FIGURE 2

Class 0 = 1

Diagnosed at CMH – received all of first course of treatment elsewhere.

Class 1 = 96

Diagnosed at CMH – received all or part of first course of treatment at CMH.

Class 2 = 28

Diagnosed elsewhere – received all or part of first course of treatment at CMH.

Class 3 = 1

Diagnosed elsewhere – received all of first course of treatment elsewhere. Now at CMH with recurrence, disease progression, or subsequent treatment.

Reportable Conditions* = 19 (Benign / Borderline)

Included in the Registry due to location of tumor or because of its propensity to recur.

*The Cancer Care Committee has approved the following conditions to be included in the Registry. These conditions are collected in addition to the histologic malignant behavior cases.

Borderline / Benign lesions of the Central Nervous System- (Beginning 1/1/04 these conditions are required to be collected and reported to the State of Missouri and are included in the analytic numbers above.)

Mesoblastic nephroma

Teratoma, regardless of locations.

Theca cell- granulosa cell tumor

Lymphoproliferative Disease

Ganglioneuroma

Myeloproliferative Disease

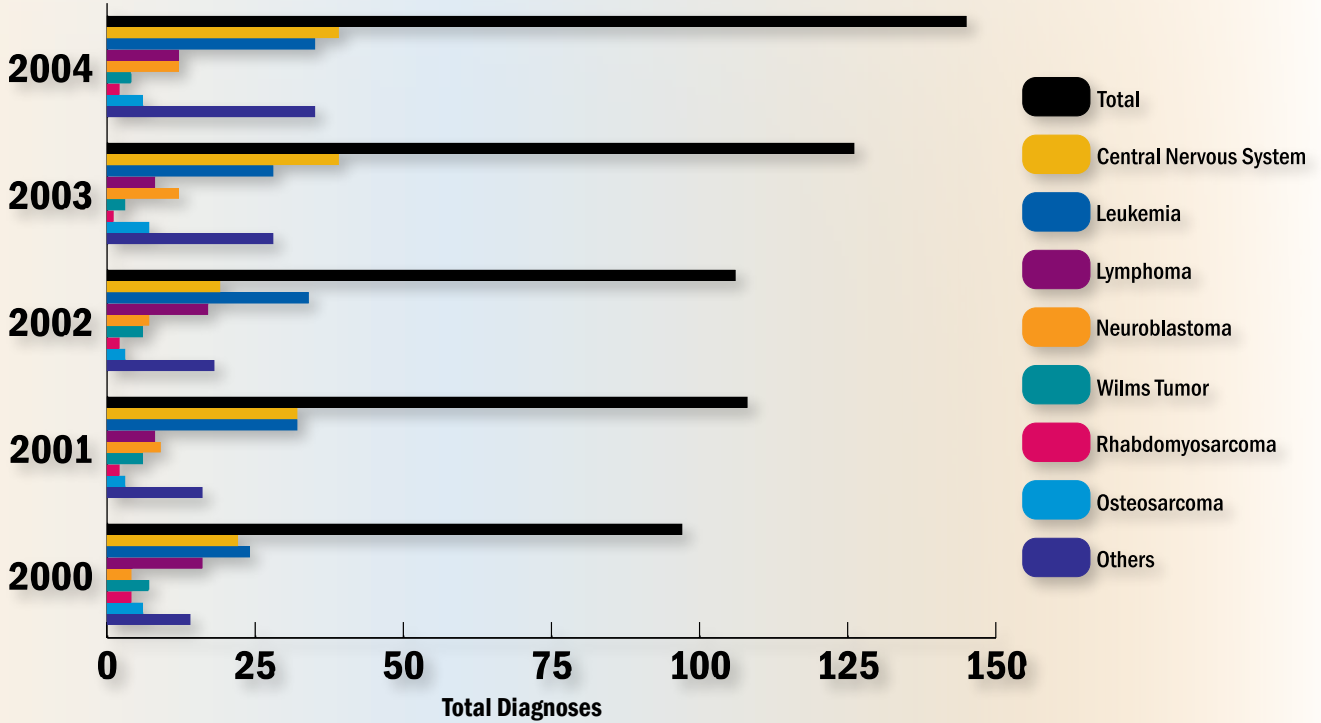
Langerhan's Cell Histiocytosis

2004 MORTALITY DATA FIGURE 3

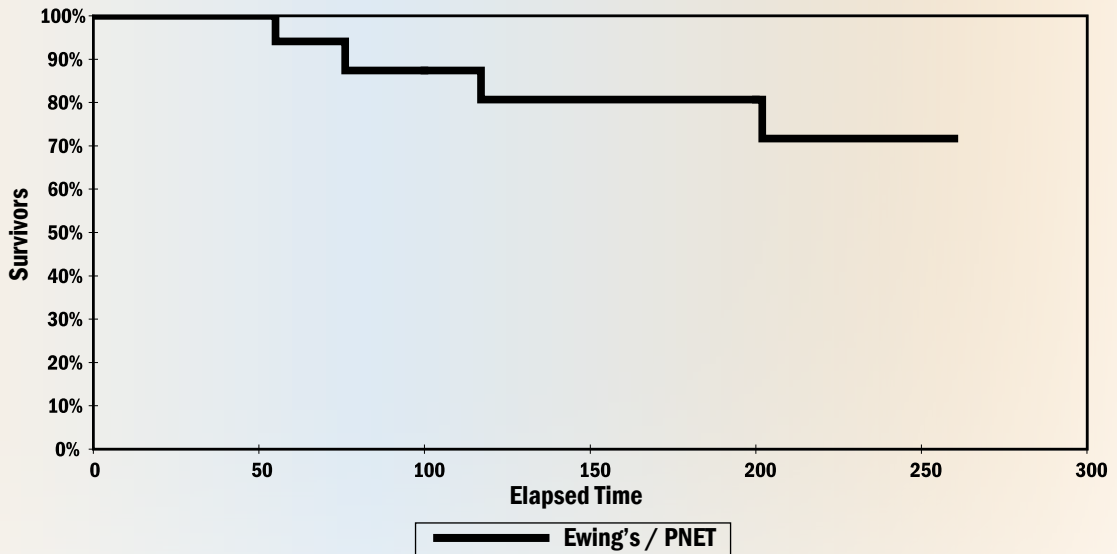
Leukemia		11
AML	8	
ALL	2	
JMML	1	
Central Nervous System		9
Astrocytoma	4	
PNET	2	
Craniopharyngioma	1	
Ependymoma	1	
Glioma	1	
Neuroblastoma		4
Osteosarcoma		3
Ewing's Sarcoma		2
Lymphoma		1
Malignant Rhabdoid of Liver		1
Fibrosarcoma		1
Hepatocellular Carcinoma		2
Malignant Langerhan's Cell Histiocytosis		1
Desmoplastic Small Round Cell Tumor		1
Angiosarcoma		1

10

A FIVE-YEAR COMPARISON OF MOST FREQUENTLY OCCURRING DIAGNOSES AT CHILDREN'S MERCY HOSPITAL
FIGURE 4



EWING'S FAMILY OF TUMORS FIVE-YEAR SURVIVAL RATE CMH 1995 - 2004



FIVE YEAR SURVIVAL DATA (10 YEAR PERIOD)

	CHILDREN'S MERCY HOSPITAL	CHILDREN'S ONCOLOGY GROUP (NATIONAL)
Number of Patients	21	62
Overall Survival (%)	72	60
EVENT FREE SURVIVAL (%)	60	58

The Ewing's Sarcoma Family of Tumors

INTRODUCTION

Ewing's sarcoma (ES), was first described as a distinct malignancy by James Ewing in 1921. Advances in immunohistochemical, cytogenetic, and molecular genetic techniques however have provided evidence that Ewing's sarcoma in fact is one of the several neoplastic diseases that are believed to originate from neuroectodermis and include Primitive Neuro-Ectoermal Tumor (PNET)/extraosseous ES (EES), malignant small-cell tumor of the thoracopulmonary region (Askin's tumor), paravertebral small-cell tumor, atypical ES, and adult neuroblastoma. Hence, the term "Ewing's Sarcoma Family of Tumors (EFT).

These neoplasms can develop in almost any bone or soft tissue, but are most common in the long and flat bones of extremities and pelvis. It is particularly less common in the spine, hands, and feet. Patients typically present with localized pain and swelling. Overt metastatic disease is found in approximately 25 percent of patients at the time of diagnosis. Microscopic

Consequently, systemic chemotherapy for treatment of occult disease has evolved as an essential component of treatment.

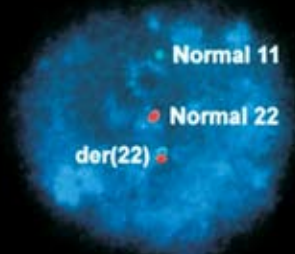
Modern diagnostic methodologies and introduction of multidisciplinary approach to treatment guided by cooperative clinical trials have resulted in a marked improvement in survival of EFT patients. According to reports by Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the five-year survival rates for these patients increased from 36 percent to 56 percent for the period of 1975 to 1994. Today, long-term survival in patients with favorable prognostic features is expected to approach 70 percent to 80 percent.

CLINICAL PRESENTATION

Primary sites – ES commonly arises in the bones of the extremities and pelvis. A small percentage of patients present with ES in bones of spine, hands, and feet. Approximately 25 percent of patients have a soft tissue primary lesion.

Signs and symptoms – Presenting complaints are usually localized pain or swelling of a few weeks or months duration. Not infrequently, trauma is the initiating event that calls attention to the lesion. The pain intensifies rapidly and may be aggravated by exercise. A firm, tender, and fixed soft tissue mass can sometimes be present as well. Clinical findings are dictated by the location of the tumor and may be loss of a joint function in juxtaarticular tumors, pleural effusion or direct lung involvement in lesions of chest wall, and back pain, weakness or loss of bowel and/or bladder control that follow the lesions of spine or sacrum. Nearly 10 percent to 20 percent of patients have signs or symptoms of fever, anorexia, weight loss, fatigue, or anemia at presentation.

11;22 Translocation Breakpoint Flanking Probes



Typical chromosomal translocation seen in Ewing's sarcoma
Fluorescence in situ hybridization (FISH) study demonstrating the (11;22)(q24;q12) translocation [der(22)] found in Ewing's sarcoma and primitive peripheral neuroectodermal tumors (PNET). Courtesy of Andrew L. Rosenberg, MD.

metastases however, is presumably present in virtually all patients. Close to 80 percent to 90 percent of patients will relapse if treated with local therapy alone (surgery and/or radiation therapy).

Approximately 80 percent of patients present with localized disease as judged by current imaging technologies. Subclinically systemic disease however, is presumed to be present in nearly all patients as evidenced by a high rate of overt metastases in the absence of systemic therapy. Patients with primary pelvic tumors are more likely to present with metastatic disease. Lung and bone are the predominant sites of metastases at the time of diagnosis or relapse. Lungs are the first site of distant spread in 70 percent to 80 percent of cases. Bone metastasis most frequently involves the spine. Metastases to lymph node, liver, and brain are uncommon.

STAGING EVALUATION

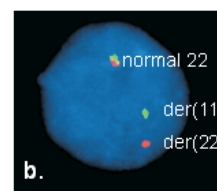
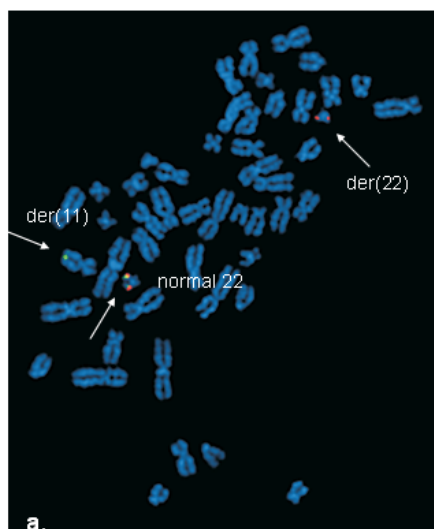
A comprehensive evaluation is required to ascertain the diagnosis and the extent “stage” of the disease before deciding on the appropriate treatment. It requires the collaboration by various specialties of oncology, radiology, surgery, pathology to name a few.

Radiographic studies – A plain radiograph often demonstrates a “permeative” or “moth-eaten” lesion that point to a series of minute destructive lesions that become confluent over time. As the tumor expands, the periosteum is elevated and produces the radiographic sign of Codman’s triangle, also described in patients with osteosarcoma. Repeated periosteal reactions deposit layers of bone in a classic “onion skin” appearance. A CT scan can provide a better view of the extent of cortical destruction and soft tissue disease. An MRI however, is the ideal tool to better delineate the tumor size, local bone and soft tissue extent, and the relationship of the tumor to the surrounding vessels, nerves, and organs. A chest CT and a radionuclide bone scan is also essential to look for pulmonary metastasis to lungs or. The role of PET scan is

currently under investigation.

Tumor biopsy is planned after a careful evaluation of the patient and the imaging studies. The biopsy material should contain a sufficient quantity of tumor to allow multitudes of diagnostic procedure required to arrive a correct diagnosis, and separate the ESFTs from a number of “small round blue cell tumors”.

The diagnosis could be established by CT guided core-needle biopsy, although an open biopsy would be more optimal. Fine needle aspiration biopsy of the primary tumor is not acceptable, but may be considered to sample suspicious sites for metastatic disease.



Karyotype: 47,XX,+10,t(11;22)(q24;q12)

FISH using the DNA probe for the EWSR1 gene, which is normally located on chromosome 22 at band q12:

- a.** A metaphase cell shows the EWSR1 probe is split by the t(11;22). The normal red/green signal is located on the normal chromosome 22; the red centromeric end of the EWSR1 probe remains on the derivative chromosome 22, while the green telomeric end of the EWSR1 probe moves to the derivative chromosome 11.
- b.** An interphase nucleus with the same probe pattern as seen in the metaphase cell.



...neoplasms can develop in almost any bone or soft tissue, but are most common in the long and flat bones of extremities and pelvis.



Osteosarcoma, primary lymphoma of bone, malignant fibrous histiocytoma of bone, acute leukemia, and metastasis, particularly neuroblastoma may be radiographically difficult to distinguish from ES.

Likewise, extraosseous ES and PNET must be differentiated from benign and malignant tumors of soft tissue.

PROGNOSTIC FACTORS

Some of the clinical and biological findings can be used to better define the prognosis and determine the intensity of treatment.

Disease extent – Presence or absence of metastasis is the key prognostic factor in ES. As stated before, patients who have metastatic disease at diagnosis have the worst prognosis. Data reported by cooperative groups in the US and the Europe indicate a five-year survival of as much as 70 percent and 10-year event-free survival of approximately 50 percent in patient who have no metastasis at diagnosis. The five-year relapse-free survival rate for patients with disseminated disease at presentation is 20-25 percent. Patients with bone and lung metastases have significantly worse than those with bone metastases alone, who in turn, fared worse than those with lung metastases only.

Tumor site and size – Patients with small primary tumors of <100 mL, and a wide resection margins frequently do well. High LDH level indicates a large tumor burden and a poorer prognosis. Incomplete surgical resection of anatomically challenging sites (e.g. pelvis or spine), is associated with a poor treatment outcome.

Response to therapy – Response to initial or induction phase of

Bilateral Bone marrow aspiration and biopsy is among the necessary components of staging to rule out bone marrow involvement and widespread disease.

Differential diagnosis – A number of benign and malignant conditions should be in the differential diagnosis of a suspected ES tumor. Clinical, radiographic, and laboratory findings in subacute osteomyelitis may closely mimic those of ES. Among nonmalignant bone lesions, eosinophilic granuloma and giant cell tumor of bone could exhibit destructive lesions somewhat similar to ES.

Some reports suggest a better outcome for children younger than 10 years of age.

chemotherapy is emerging as another important factor that accurately predicts the chance of survival rates.

Histology of the tumors in ESFT does not seem to play a significant role in the treatment results.

Age – Some reports suggest a better outcome for children younger than 10 years of age. Several small clinical trials have reported less favorable outcome in adults with ES. It is believed that a higher tumor burden, and a lack of participation in national cooperative treatment programs appear to negatively impact the final outcome.

Molecular findings – Nonrandom chromosomal translocations involving the Ewing's sarcoma (EWS) gene on chromosome 22 is a characteristic feature of EFT. These translocations result in fusion of genes on different chromosomes, that in turn encode hybrid proteins active in carcinogenesis.

At least 18 different structural possibilities for gene fusions have been reported in these tumors. There are two sources of variability: the EWS fusion partner (e.g., FLI1, ERG, ETV1, E1A, or FEV) and the breakpoint locations within the genes. This molecular heterogeneity may have some influence on the prognosis of EFT [48-51]. As an example, a better outcome is reported for patients with localized tumors expressing the most common chimeric transcript (the so-called type I transcript in which EWS exon 7 is fused to FLI1 exon 6, which is present in about 60 percent of cases) compared to other fusion types [49,50].

Variability in the EWS fusion partner (e.g., FLI1, ERG, ETV1, E1A, or FEV) and the breakpoint locations within the genes has resulted in a number of structural possibilities which may have some influence on the prognosis

of EFT. An notable finding has been the lower risk of metastasis in patients with localized tumors expressing the chimeric transcript (fusion of EWS exon 7 to FLI1 exon 6). Several genetic alterations on the other hand are associated with a worse prognosis. Deletion of the short arm of chromosome 1p, homozygous deletion of CDKN2A, and p53 mutations are notable examples of such genetic accidents.

Use of prognostic factors for treatment stratification – Lack of a uniform staging system for EFT has limited our ability to stratify treatments according to the disease stage and expected treatment outcome. Almost all currently available treatment protocols are designed on the basis of presence or absence of metastatic disease, which represents the only uniformly accepted staging system. Newer treatment protocols are beginning to design the treatment arms according to prognostic variables such as specific genetic translocations, preoperative response to chemotherapy, and site and size of tumor.

TREATMENT

The combination of surgery, chemotherapy and radiotherapy forms the backbone of treatment protocols for Ewing's sarcoma. Prior to 1960s, patients were treated by surgery and radiotherapy and long-lasting disease free survival was quite poor. As with other childhood cancers benefiting from advances in chemotherapy, we have witnessed a dramatic improvement in failure free survival of patients with ESFT. During the past two decades, Vincristine, cyclophosphamide, and doxorubicin have been the chief chemotherapeutic agents used in treatment protocols. Ifosfamide and

Magnetic resonant imaging (MRI) demonstrates increased signal intensity in the right femoral head and adjacent soft tissue in a patient with Ewing sarcoma.



etoposide are the latest drugs that have shown efficacy in preliminary trials and are being incorporated in the chemotherapy regimens. Today, we are witnessing the emergence of novel molecular-targeted treatments that are reshaping our approach to cancer treatment. Ewing's sarcoma patients no doubt will benefit from these "smart drugs."

Current treatment protocols have in common three stages of: 1) "induction" period of multiagent chemotherapy, 2) "local control" by means of surgery or radiotherapy, or both, and 3) "continuation chemotherapy". The conventional duration of this "Neo-Adjuvant" treatment has generally been about 50 weeks.

INDUCTION THERAPY

The primary goals of this 12-14 week phase are eradication of the microscopic spread of disease that are assumed to be present in almost all patients, and shrinkage of the primary tumor and any visible distant metastases, if present. An extensive evaluation is done at the conclusion of this period to determine the optimal approach to be undertaken for the control of the tumor.

LOCAL THERAPY

The choice of surgery or radiation therapy, alone or in combination, hinges on the location and size of the tumor. A careful assessment of the risks and benefits of the appropriate options is carried out and discussed with the patient and the family. Amputation, surgical debulking alone, or in combination with radiation therapy are the common means of management at this stage. Paramount in this decision making process is the best estimation of benefit obtained from a given course of action versus risks

inherent in all of the techniques being considered. A curative intent and the best possible preservation of function of the involved limb or organ are the topmost priorities in consideration. In recent years, surgery has taken a leading role over radiation therapy in situations where a total resection is feasible in patients who have no overt metastases. Equally important is the opportunity to assess the degree of tumor kill in response to the induction treatment and has profound effect in estimation of overall prognosis.

CONTINUATION THERAPY

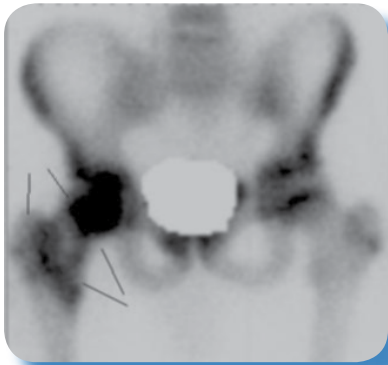
Further chemotherapy is initiated as soon as the patient has recovered from the local control measure(s). The total duration of treatment in our most recent protocol is approximately 46 to 50 weeks. Last year, The Children's Oncology Group completed a clinical trial comparing a 30-week intensified treatment to the standard, 48 weeks protocol arm. The results of this trial are not available at this time.

OFF THERAPY

Once off therapy, a close follow up at regular intervals must be established to monitor for disease recurrence or late effects of treatment. In addition to routine physical examinations and laboratory/radiographic evaluations, education of the individual and the family plays a central role in effective off therapy evaluations following cancer therapy.

While early side effects of cancer treatment such as emesis, pain, and infection are easy to recognize and control, longer term complications such as infertility, cardiac disease, or secondary malignancies may occur years or decades following the treatment. A lifelong surveillance is essential for early identification and management of these complications.

Intense technetium 99m HDP uptake in the right greater trochanter and femoral head of the same patient..



16

...early side effects of cancer treatment such as emesis, pain, and infection are easy to recognize and control...

17

Diagnostic and Treatment Support Services

Cytogenetics

Ewing's sarcoma is a member of the Ewing's sarcoma family of tumors (EWSFT). The EWSFT includes Ewing's sarcoma (EWS) of bone, extraosseous Ewing's of soft tissues (EOE), peripheral primitive neuroectodermal tumors (pPNET), and Askin's tumor of the chest wall. The tumors are thought to arise from a pluripotent neural crest (postganglionic parasympathetic) cell. The EWSFT show a spectrum of histologic differentiation, from EWS, a tumor without evidence of neural differentiation, to pPNET, a primitive neural tumor lacking ganglion cell differentiation and frank neuropil, but possessing rosettes by light microscopy and obvious neurites and dense core granules by EM.

The EWSFT is characterized genetically by rearrangement of the EWS gene, which is located on chromosome 22 at band q12, with several different genes that belong to the ETS gene family. The most common rearrangement, t(11;22)(q24;q12), is found in ~95 percent of cases. This t(11;22) creates a chimeric gene by fusion of the 5' portion of the EWS gene to the 3' sequences of the FLI1 gene at chromosome 11q24. Other variant translocations, t(21;22)(q22;q12), t(7;22)(p22;q12), t(2;22)(q13;q12), t(17;22)(q21;q12), occur in a small percentage of tumors and in each, there is fusion of the EWS gene with one of the ETS family genes. The EWS and ETS gene fusion proteins are transcriptional activators, which affect gene transcription and cell proliferation. These gene products are tumorigenic in mice.

EWS is often described as one of the "small round cell tumors" (SRCT). SRCT include neuroblastoma, rhabdomyosarcoma, lymphoma, leukemia, synovial sarcoma, and others. The SRCT often have poor

differentiation and so can be difficult to separate. Genetic analysis may be the best way to differentiate between these tumors by detection of one of the reciprocal translocations, either by cytogenetic analysis, fluorescence in situ hybridization (FISH), or reverse-transcriptase polymerase chain reaction (rt-PCR).

Pathology

Ewing's sarcomas (EWS) that originate in the bone or in the soft tissue have similar gross, microscopic and molecular genetic features. They are solid grey tumors that are not encapsulated but infiltrate and destroy the surrounding tissue with foci of hemorrhage and necrosis. Microscopically, Ewing's tumor is generally composed of small undifferentiated blast-like cells with indistinct nucleoli arranged in sheets. Tumors may, on few occasions, be composed of larger cells with more abundant cytoplasm and prominent nucleoli. The cells are frequently rich in glycogen, best demonstrated with Periodic Acid Schiff (PAS) staining, a feature which is helpful in distinguishing Ewing's sarcoma from undifferentiated neuroblastomas. Occasional Ewing's tumors have focal neural differentiation as demonstrated by the presence of neurofibrillary rosettes (i.e. so-called "Homer Wright" rosettes) that further complicates reliable diagnosis



and distinction from neuroblastoma. This limited expression of neural differentiation with the shared genetic translocation involving chromosome number 11 and 22, serve as the basis for unifying EWS with other bone and soft tissue primitive neuroectodermal tumors and led to the designation as “EWS-PNET” family or class of tumors.

Aside from occasional rosettes, EWS are so undifferentiated and lack specific architectural arrangements and cellular features that the pathologist must perform a battery of special immunohistochemical stains on the tumor to make a reliable distinction between Ewing’s sarcoma and a number of other common and rare pediatric malignant tumors that share this undifferentiated or so-called “primitive small round blue cell” morphology with EWS. Immunohistochemical staining for CD99 (MIC2 gene product) is most helpful in distinguishing EWS (+) from neuroblastoma (-). Leukocyte markers including CD45, T cell, B cell, and Tdt are helpful to distinguish EWS (-) from lymphomas and leukemias (+). Markers of skeletal muscle differentiation, myogenin and MYOD1, are helpful in excluding poorly differentiated rhabdomyosarcoma (+) from EWS (-). EWS cells also have a highly characteristic gene

number 21 and number 22 [t(21;22)(q22;q12)] that is not shared by the aforementioned look-alike tumors. These translocations can be demonstrated by conventional chromosome karyotyping, fluorescent in-situ hybridization, or by molecular genetic techniques, and provides additional diagnostic confirmation of EWS-PNET tumors.

Radiology

The mission of the Department of Radiology is to provide state-of-the-art medical imaging services in a safe and caring environment to patients, families, and referring physicians. Services are tailored to meet the patient’s medical needs while treating each child as a unique individual. The Department of Radiology provides computerized tomography (CT) including the latest development in multi-detector CT, Magnetic Resonance Imaging (MRI), ultrasound, nuclear medicine, conventional and fluoroscopic studies, as well as, leading edge interventional radiology procedures. The department is staffed by fellowship trained, board certified pediatric radiologists and a dedicated group of technologists, nurses, and clerical staff. Our mission statement is taken very seriously and guides our daily practice.

Radiation Therapy

Radiation therapy has been an important part in the management of Ewing’s sarcoma since it was first described in 1921, although the role has certainly evolved. With the use of combined modality treatment, radiation has been reserved for treating locally. In many cases, surgery has eliminated the need for radiation therapy, but in some cases, it remains an important part of the treatment plan. Better imaging now helps to tailor fields more precisely, and decrease long-term side effects. The Kansas City Cancer Centers has partnered with the Division



rearrangement involving exchange of DNA on chromosome number 11 and number 22 [t(11;22)(q24;q12)] or less frequently on chromosome

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The whole treatment team and the family needs to be supportive of the child's choices regarding mobility and function.

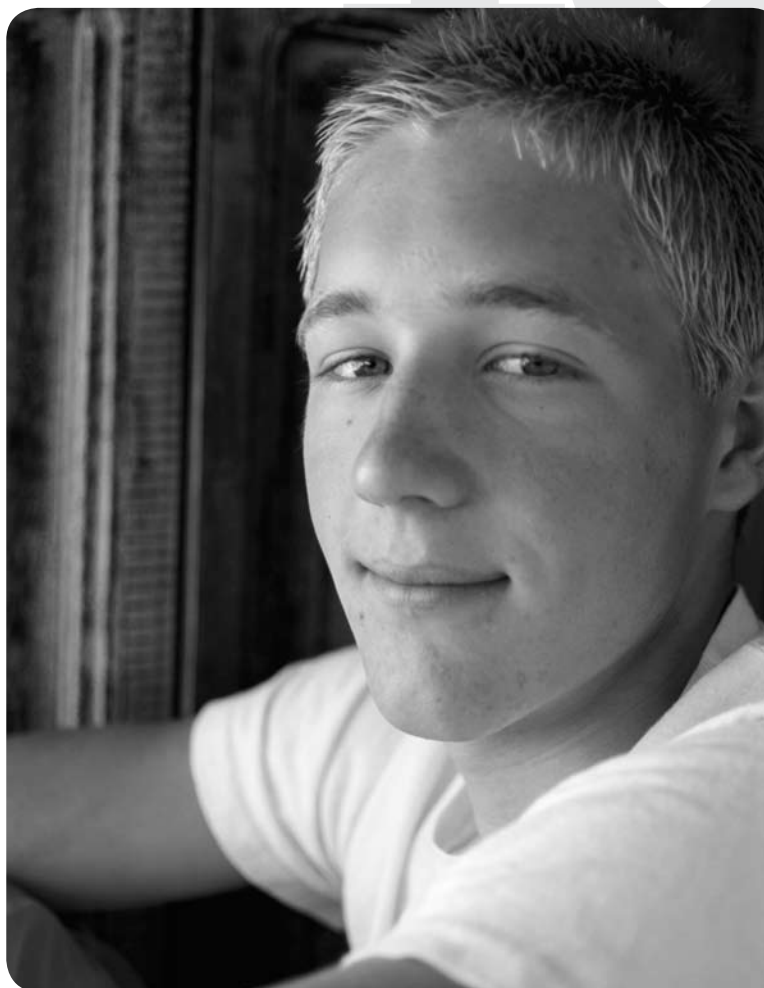
of Hematology/Oncology to ensure each pediatric patient is offered the most effective treatment options available.

Rehabilitation Services

Rehabilitation Medicine focuses on optimizing function. If a child has undergone limb salvage procedure or amputation due to Ewing's sarcoma, a major goal from a rehabilitation perspective is returning the child to activities which are normal for him. The approach may require multiple considerations, such as equipment to aid mobility (such as a walker or cane, or even a wheelchair), or a prosthetic device, coupled with a therapy program to train the child in the use of that equipment. Often children need multiple pieces of equipment, for example, a cane for walking, and a wheelchair for long distance or for speed. Endurance may be impaired, especially with a prolonged illness and the impact of his or her treatment, and therapy can additionally guide the strengthening and progressive activity needed to improve that.

Prosthetic devices for children with amputation due to Ewing's or other malignant processes need to be designed with some specialized components. Specialized knee joints and energy storing feet may enhance a child's abilities. Because body weight and the residual limb size may fluctuate during chemotherapy, adjustable temporary sockets can be used for longer times compared to other amputations, to assure optimal fit and function. Growth is also built into the prosthetic limb so that adjustments can be easily made.

If a child enjoyed sports before his illness, every effort is taken to modify the activity, or how the child approaches the sport after treatment. Even with limb salvage, some children enjoy using a sports wheelchair for speed and



meaningful inclusion and competition. The whole treatment team and the family needs to be supportive of the child's choices regarding mobility and function.

Molecular Genetics

Ewing's sarcoma displays a translocation resulting in the fusion of the EWS gene, located at 22q12, and a gene of the ETS family of transcription factors. In 90-95 percent of cases, a t(11;22)(q24;q12) leads to the gene fusion EWS-FLI1. Analysis of breakpoints indicates that the rearrangements occur through illegitimate recombination, suggesting a random process, followed by a selection for rearrangements producing a functional fusion gene.

EWS, the gene involved in all ES translocations, may fuse with several different partners in various types of sarcomas. EWS is a ubiquitously expressed RNA-binding protein. The N-terminal domain can function as a strong transactivation domain and their promoters are strongly and broadly activated, leading to unrestricted high-level expression of the resulting fusion gene. The FLI1 gene is a tightly regulated transcriptional activator normally expressed in the hematopoietic lineage. It is thought to be involved in early hematopoietic, vascular, and neuroectodermal development in model organisms. In model assays, EWS-FLI1 functions as a stronger activator of transcription than native FLI1. The transcriptional targets of this fusion gene are unknown.

The differential diagnosis of ES/PNET is broad and can include other “small round cell” tumors such as neuroblastoma, small cell carcinoma, lymphoma, ERMS, ARMS, or DSRCT. Many of these diagnoses mandate quite different treatment protocols. Molecular diagnostic RT-PCR assays for the various EWS gene fusions are helpful in sorting out the differential diagnoses. An important consideration

in the detection of these fusions is the structural heterogeneity. Up to 18 types of in-frame EWS-FLI1 chimeric transcripts have been observed (see figure below for most common types). Each fusion protein contains the transactivating amino-terminal domain of EWS (exons 1-7) and the DNA binding domain of FLI1 (encoded by exon 9). Many laboratories use an FLI1 exon 6 reverse primer along with the EWS exon 7 forward primer, which will pick up a fusion signal in 85 percent of cases of EWS-FLI1 gene rearrangements. In the minority of negative cases, other primer combinations can be used to detect the rare fusion types.

The molecular heterogeneity is clinically significant, since the different molecular variants seem to affect EWS-FLI1 activity. Patients with localized tumors at diagnosis showing the most common fusion type (see in ~2/3 of cases) have a better prognosis compared with patients with other fusion types. This may be due to the fact that the common fusion encodes a functionally weaker transactivator and is associated with a lower proliferative rate, compared to the other forms.

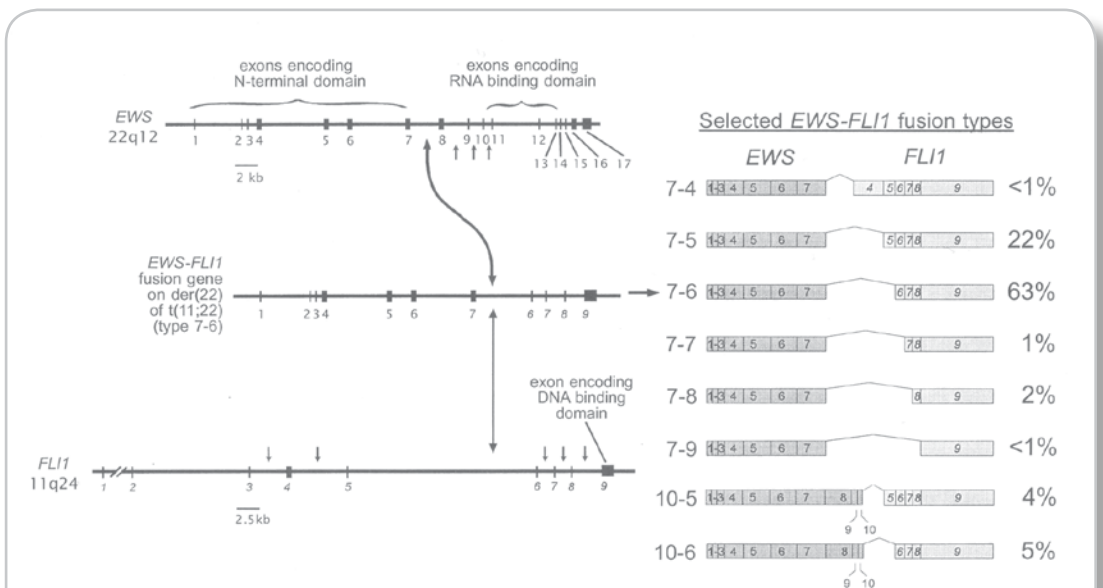


Figure 4-2. Chimeric genes and products generated by the t(11;22) translocation in Ewing’s sarcoma and peripheral neuroectodermal tumor. *Left*, The genomic structure of the EWS and FLI1 genes, as well as of the EWS-FLI1 fusion gene resulting from the most common combination of breakpoints in the t(11;22), is shown. EWS and FLI1 introns less commonly involved by the t(11;22) are indicated (small arrows). *Right*, The exon structure of the fusion transcript encoded by the EWS-FLI1 fusion gene is shown. Alternative EWS-FLI1 transcripts resulting from different combinations of genomic breakpoints in EWS and FLI1 are also shown, along with the approximate frequency of each fusion type. All forms of EWS-FLI1 contain at least exons 1 to 7 of EWS and at least exon 9 of FLI1, which encodes the DNA-binding domain. Exon dimensions are approximate.

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