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Cancer Care Annual Report 2015-16

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CANCER CARE Annual Report



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Dear Reader,

This year's Children's Mercy Cancer Center annual report focuses on the most common solid tumor of childhood: neuroblastoma. It is a diverse tumor and remains a significant challenge in many ways.

Neuroblastoma varies from a tumor diagnosed in a newborn that spontaneously regresses if the child can survive the first few months, to a tumor occurring in older toddlers that remains one of our most difficult-to-cure childhood cancers. To achieve that cure requires some of the most intensive therapy we subject children to.

In addition, neuroblastoma refers to the malignant group of neuronal tumors in childhood. We still see many significant benign neuronal tumors, such as ganglioneuroma and ganglioneuroblastoma, that can also cause havoc in the child due to their space-occupying tendencies and associated metabolic derangements.

Curative therapy requires advanced pathologic and genetic techniques to guide the choice of therapeutic options, as well as advanced radiologic scanning and nuclear medicine capabilities to identify the wide metastatic spread of this tumor to guide therapy. Once therapy is initiated, the intensity of chemotherapy needed has few equals in oncology, and comprehensive supportive

care is necessary to assist the child's ability to tolerate not just a single course, but a year and a half of therapy.

Neuroblastoma is known as an infiltrative tumor presenting great challenges to the surgeon who, after chemotherapy has induced shrinkage, must then attempt to remove the remaining tumor often surrounding major organs and vessels, such as the aorta. The child must then endure not one, but two bone marrow transplants, quickly followed by radiation therapy to the prior sites of tumor. This is then followed by months of intensive antibody and associated immunotherapy, which many centers simply cannot provide outside the ICU. Only then can a parent and the child enter into the long waiting game of monitoring for possible relapse (which remains the greatest cause of failure) and for the long-term side effects.

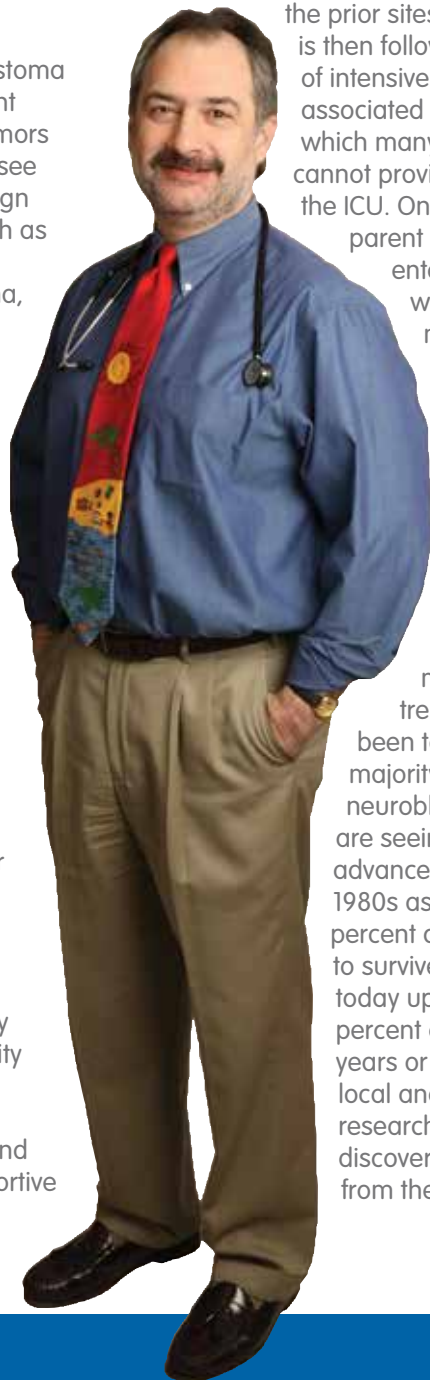
Still, there is hope. New methods of treatment have been tested in the majority of children with neuroblastoma and we are seeing tremendous advances: in the late 1980s as few as 10 percent could be expected to survive this tumor; today up to 50 to 60 percent are surviving four years or more. Through local and collaborative research endeavors, new discoveries are moving from the test tube to the

bedside and, hopefully, someday to the large national trials that have brought us so far.

I am pleased to introduce you to this year's annual report that I hope illustrates to you the breadth and depth of research, diagnostic, clinical and psychosocial resources available in the Children's Mercy Cancer Center. Today's child with neuroblastoma has a much greater chance of cure, and like those children of 20 to 30 years ago, today's child with neuroblastoma is helping make the future outcomes for children with this dreaded cancer so much more hopeful than even today.

Thank you to our donors and volunteers whose philanthropic support sustains our work. Thanks, too, to our staff and especially our children and their families for working so hard and for sacrificing so much to make the fear of this cancer someday a thing of the past.

Yours in hope,



Alan S. Gamis, MD, MPH

Professor of Pediatrics,
University of Missouri-Kansas City
School of Medicine

Adjunct Professor of Pediatrics,
University of Kansas School of Medicine

Co-Director, Drug Discovery and Delivery
Experimental Therapeutics,
NCI-designated KU Cancer Center

Section Chief, Oncology,
Children's Mercy Kansas City

Associate Division Director, Division of
Hematology / Oncology / Bone Marrow
Transplantation,
Children's Mercy Kansas City

Children's Mercy Cancer Center

The Children's Mercy Cancer Center is a multispecialty, multidisciplinary center of excellence providing state-of-the-art care for children with cancer. All children with all types of cancer are seen in the center by cancer and other pediatric specialists. The center brings together caregivers and researchers in various programs focused on specific types of cancers, specific types of therapy and specific types of patients. Through these focused programs, coordinated patient care and coordinated research can better take place. These programs synergistically work with each other further to strengthen the clinical and research efforts for our patients today and tomorrow.

The programs within the Children's Mercy Cancer Center are listed below along with their program directors. The programs include the cancer specialists (oncologists and radiation therapists), the appropriate medical and surgical specialties for that tumor or therapy, the pathology, laboratory, and radiologic specialists critical to that program's focus, specialty advanced practice providers, pharmacologists, psychosocial professionals, along with our research scientists and research administrative personnel.

Specialties represented in the Children's Mercy Cancer Center include: oncology, radiation therapy, surgery (including general, neuro-, orthopaedic, transplantation, and ENT), pathology and laboratory medicine, cytogenetics/genomics,

Tumor-focused Comprehensive Programs

Leukemia / Lymphoma - Keith August, MD, MSc
Brain Tumor - Kevin Ginn, MD
Bone & Soft Tissue Sarcoma - Kate Chastain, MD
Liver Tumor - Michelle Manalang, MD
Histiocytoses - Allyson Hays, MD

Therapy and Diagnostic-focused Programs

Experimental Therapeutics - Keith August, MD, MSc
(Interim Director)
Bone Marrow Transplantation - Rakesh Goyal, MD
Cellular Therapy - G. Doug Myers, MD
Cancer Genomics - Erin Guest, MD
Tumor Biorepository - Erin Guest, MD and
Alex Kats, MD (Pathology)

Children's Mercy Cancer Center

Tumor-focused Clinical Programs/ Clinics

Skin Cancer - Maxine Hetherington, MD
Vascular Tumors - Shannon Carpenter, MD, MS

Population-focused Programs

Survive & Thrive Program for Long-term Survivors -
Joy Fulbright, MD
Hispanic Oncology Program
- Terrie (Tristan) Flatt, DO
Adolescent and Young Adult Cancer
- Joy Fulbright, MD
Family-Centered Care Program
- Kristin Stegenga, RN, PhD

endocrinology, gastroenterology, neurology, rehabilitation medicine, genetics, infectious diseases, palliative care and ethics. These specialists not only participate intimately in the Cancer Center programs, but also work together with Oncology on the Medical Staff's Cancer Care Committee, which provides oversight for the hospital's cancer services. Children's Mercy is an American College of Surgeon's Commission on Cancer accredited children's cancer center.

The Cancer Center works in partnership with other cancer and research centers in the Kansas City region. Among these, Children's Mercy in 2015 became one of three consortium members, along with the KU Cancer Center (for adults) and the Stowers Medical Research Institute (for basic sciences), to comprise the NCI-designated KU Cancer Center, the only such center in the region. Since 2010, Children's Mercy has been the primary and only pediatric member of the KU Cancer Center's Midwest Cancer Alliance. Children's Mercy is a 25-plus year member of the National Cancer Institute's Children's Oncology Group (COG), the only such institution in the region. Children's Mercy is an American College of Surgeon's Commission on Cancer accredited children's cancer center – one of only 11 nationwide.

As noted, children of all ages, birth to 21, and with every type of cancer come to Children's Mercy. With our expanding partnerships, our researchers and clinicians are ensuring that not only are our patients transitioned to adult providers as they age, but that we still participate in their care for years to come, as well as to

provide consultation for those young and older adults with cancers for which pediatric cancer regimens offer the best chance for long-term cure. Every patient has a primary oncologist, along with a primary advanced practice nurse and a primary social worker coordinating every aspect of their care. Every discipline critical to a child's health is readily available. These include nutrition, pharmacology, Child Life, psychology, physical and occupational therapy and others. The Cancer Center provides two large units dedicated entirely to children with cancer and blood disorders: the 38-bed entirely hepa-filtered inpatient unit, which includes a 15-bed BMT unit; and the 14-room infusion bay plus 18 exam room Outpatient Clinic, all staffed with specialty trained nurses.

The inpatient teams are all staffed by board-certified hematology/ oncology physicians, specialty fellows, residents and advanced practice nurses. Hematology/ Oncology specialists are on site around the clock, 365 days a year.

Once completing their care, children and their families are monitored closely for recurrence and the late effects of therapy, eventually moving onto our Survive and Thrive program before transitioning to our Adult Survivors of Childhood Cancer program. ●

Children of
all ages,
birth to 21,
and with
every type of
cancer come
to Children's
Mercy.



Ibrahim Ahmed, DSc, MD

Division of Hematology / Oncology / Bone Marrow Transplantation

The primary specialists for most children with cancer reside within the Section of Oncology, part of the Division of Hematology/Oncology/Bone Marrow Transplantation at Children’s Mercy Kansas City. The leaders in the division include: Gerald Woods, MD, Division Director; Shannon Carpenter, MD, MSc, Associate Division Director and Section Chief of Hematology; Alan Gamis, MD, MPH, Associate Division Director and Section Chief of Oncology; and Rakesh Goyal, MD, Associate Division Director and Section Chief of Bone Marrow Transplantation.

The division has 29 board-certified or board-eligible hematology/oncology specialists; 12 within Oncology, six within Hematology, four in Bone Marrow Transplantation, and seven comprising the division’s inpatient Attending Hematology/Oncology Hospitalist group. In the 2016-2017 academic year, the division’s Fellowship Program has seven in training who have previously completed a pediatric residency; two in each of a three-year program and one research scholar in a fourth year. The division also is home to 36 advanced practice nurses and one physician’s assistant who each work individually with physicians or on inpatient teams. There are 10 social workers for the division’s children.

Research is a large focus of the division, which includes nearly 100 open trials at any given time, the division has 18 professionals dedicated to ensuring that research, clinical and laboratory, is done properly, effectively and safely for our patients and researchers.

Rounding out the division are our administrative assistants, supporting this large group of clinicians, researchers and ancillary care staff.

Most division members’ offices are located in the recently refurbished Black & Veatch building, while others are in the clinic inside the Hall Family Outpatient Clinic, both on the Children’s Mercy Adele Hall Campus.

During the weekday, five services provide coverage to the division inpatients: General Hematology/Oncology service; Attending Hematology/Oncology Hospitalist service; Chemotherapy service; Bone Marrow Transplant service, and the Inpatient Coagulation Consultative service. On weekends, there are three inpatient services.

Most patients are admitted to one of the fully heparinized, positive pressure 38 single-bed rooms on the Hematology/Oncology/Bone Marrow Transplant floor (4 Henson-Hall). There is the 24/7 in-house presence of a board-certified/

board-eligible hematology/oncology specialist; and a hematology/oncology attending, fellow and advanced practice nurse are available on call 24/7.

Outpatients are seen weekdays and on Saturdays for labs, evaluations, chemotherapy, transfusions or procedures in either the dedicated 14 infusion bay/18 exam room Hematology/Oncology clinic, or in the 4 Henson infusion room. Patients see their own primary hematology/oncology provider teams as outpatients and nursing in the clinic are, when possible, is also cohorted to ensure continuity for each patient. The Hematology/Oncology Clinic is also fully staffed by a highly selective nursing and ancillary care staff. On floor and in clinic are ever-present additional ancillary care providers who are dedicated to the hematology/oncology patient population and include pharmacists and doctorates of pharmacy, nutritionists, Child Life specialists, chaplains and psychologists. ●



Glenson Samuel, MD

Cancer Registry Review-2015

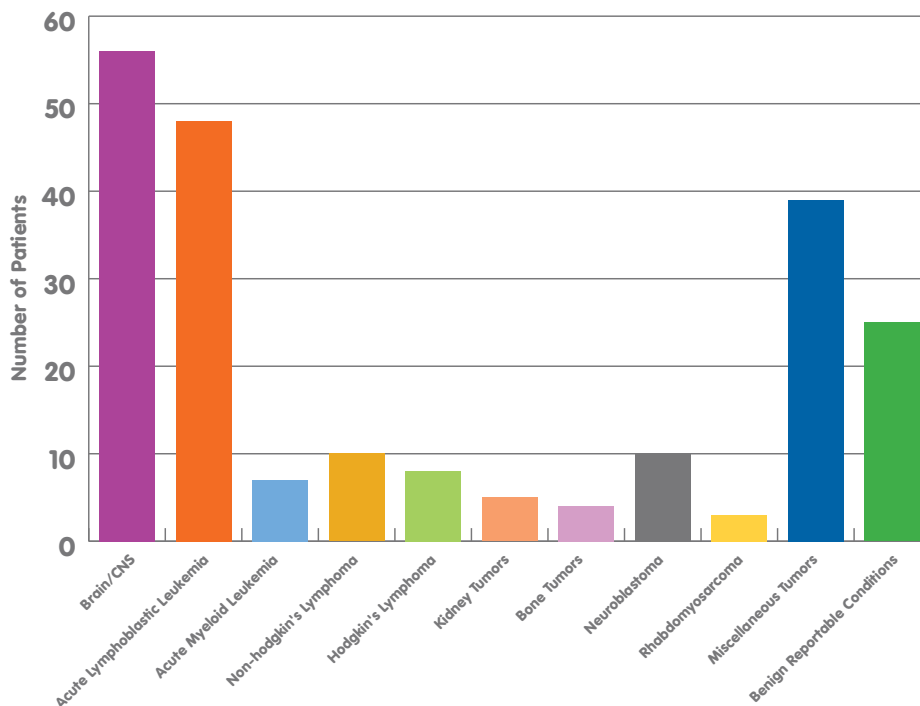
The Cancer Registry at Children’s Mercy Kansas City plays a vital part in the surveillance of cancer in our pediatric population. The Cancer Registry is a HIPPA-compliant confidential database comprised of malignant cancers, benign brain tumors and other specified benign cancers. The database is operated under the guidance of the Cancer Care Committee with accreditation approval maintained by the American College of Surgeons Commission on Cancer. Data collected, which includes diagnosis, treatment, recurrence and survival, is standardized for state and national comparisons.

Following each patient’s cancer status is a very important part of Cancer Registry data collection. Knowing outcomes of each cancer patient can assist care providers with determining best treatment methods and other long-term effects of cancer treatment. Therefore, follow-up letters inquiring about a patient’s cancer status are sent out yearly. Parents and older patients are encouraged to contact the registry by secure email at cancerregistry@cmh.edu to discuss follow-up.

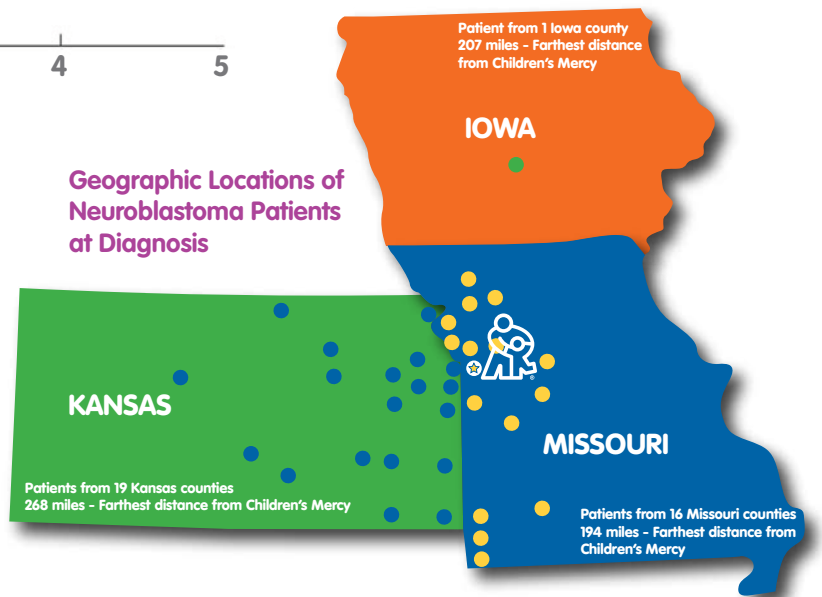
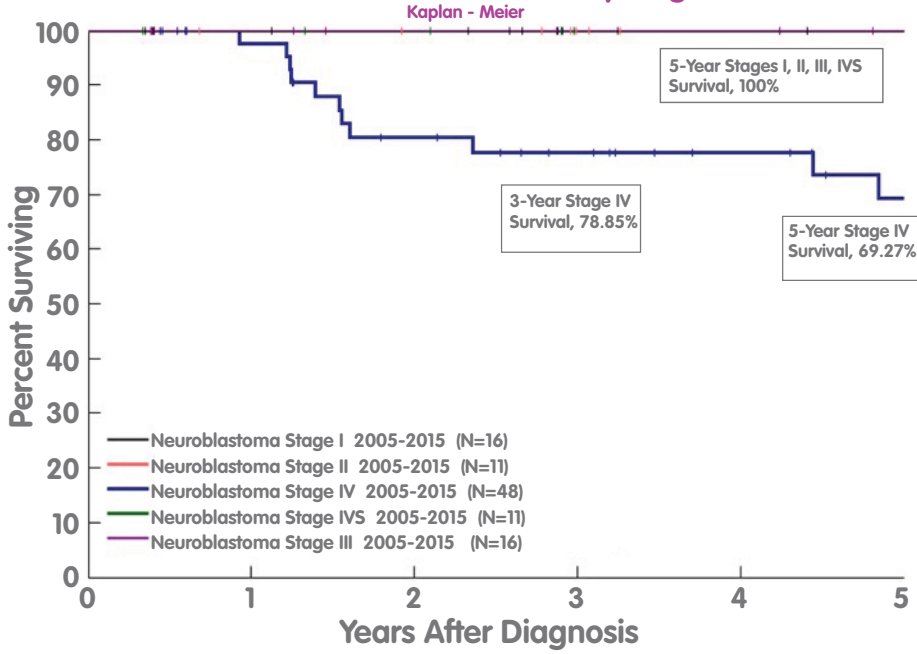
During 2015, the Cancer Registry added 215 patients to the database.

Of these patients, there were 190 patients who were diagnosed with malignancies and benign central nervous system tumors. There were 25 patients added to the registry as having benign reportable conditions. These conditions are collected at the request of the Cancer Care Committee for surveillance purposes and are not required to be reported outside our facility. Please see the Frequency by Diagnosis chart for a breakdown of cancers. ●

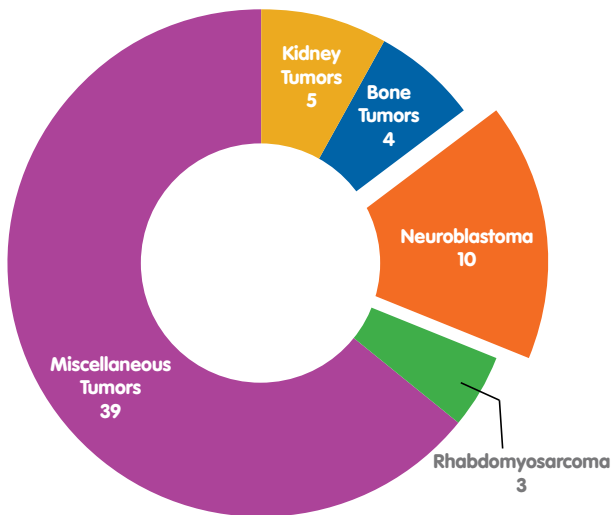
Frequency of Diagnosis by Disease Type
2015



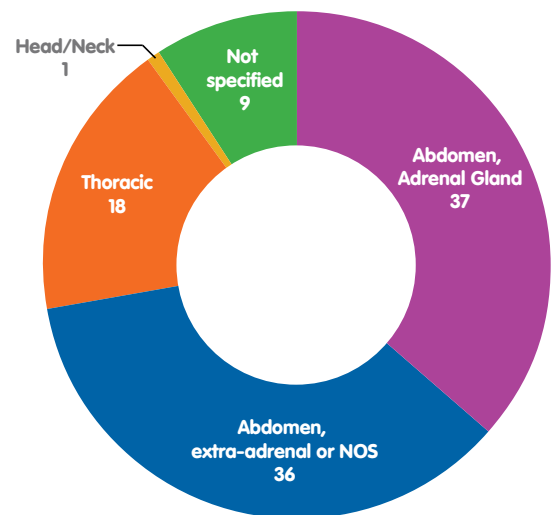
Neuroblastoma: Overall 5-Year Survival by Stage - 2005-2015



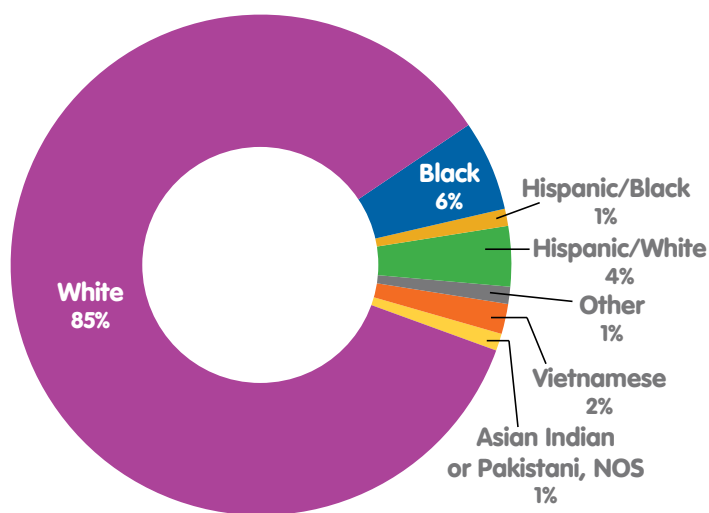
Solid Tumors 2015



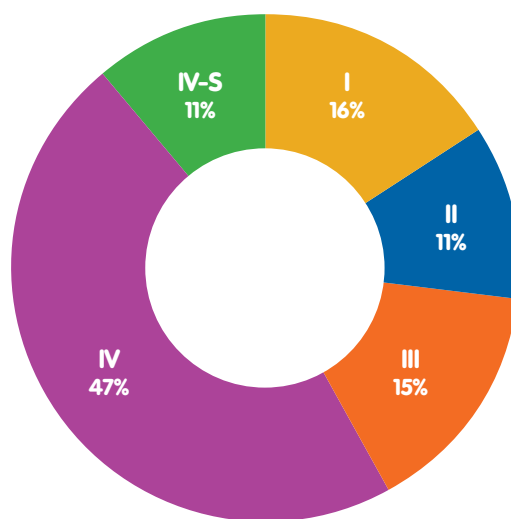
Sites of Neuroblastoma Origin 2005-2015



**Neuroblastoma Frequency by Race / Ethnicity
2005-2015**



**Neuroblastoma Stage at Diagnosis
2005-2015**



Cancer and Neuroblastoma Facts

700

children are diagnosed with neuroblastoma annually.

36 PERCENT

of neuroblastomas present with high-risk disease.

APPROXIMATELY

16,000

children are diagnosed with cancer in the U.S. each year.

60 PERCENT OF CHILDREN

enroll in a clinical trial compared with less than

5 PERCENT OF ADULTS.

90 PERCENT

of all children and teenagers fighting cancer in the U.S. are cared for at a Children's Oncology Group institution.

TEENAGERS

treated at a pediatric cancer center with pediatric cancer protocols are more likely to be cured than those treated elsewhere and on protocols designed for adults.

CHILDREN'S MERCY KANSAS CITY HAS

200+

new oncologic diagnoses each year, or

four children

are newly diagnosed with cancer each week.



THE THREE HALLMARKS OF CANCER:

- uncontrolled duplication of tumor cells growing into tumor masses
- loss of the cell's original function, leaving a nonfunctional tumor mass occupying space which our normal cells or organs require to keep us alive
- failure to remain in its original location, leading to distant tumor metastases occupying critical space throughout the body.

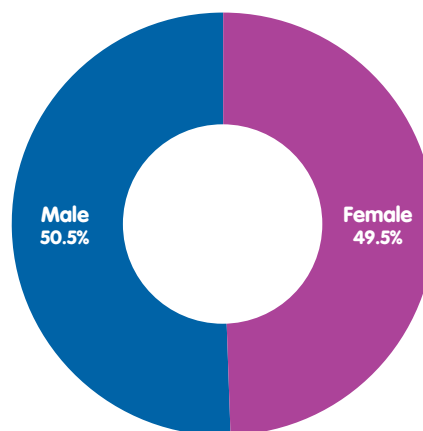
Neuroblastoma

Neuroblastoma is the most common solid tumor malignancy in children outside the central nervous system, and trails only the leukemias, brain tumors and lymphomas in frequency of diagnosis. Compared to other pediatric solid tumors, neuroblastoma is unique. This disease displays a continuum of behaviors ranging from a rather indolent tumor that spontaneously regresses to an extremely malignant tumor that relentlessly progresses. Neuroblastoma is also in a spectrum of pediatric neuronal tumors from the most benign, ganglioneuroma, to the increasingly aggressive ganglioneuroblastoma, to the malignant neuroblastoma.

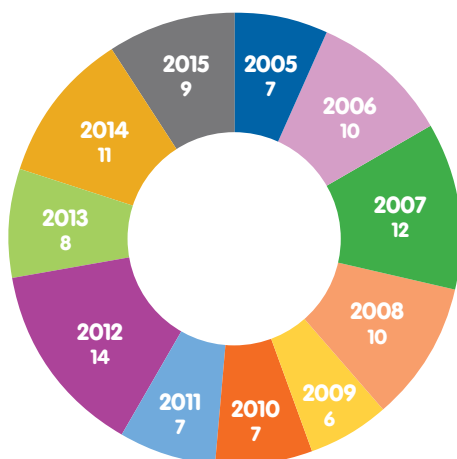
Each year in the United States more than 700 children are diagnosed with neuroblastoma (8 to 10 percent of all pediatric cancers). The median age of occurrence is 19 months. This is the most common solid tumor in those less than 1 year of age. It is very rare after the age of 10. Slightly more boys than girls (1.2 to 1) are diagnosed.

Neuroblastoma is most often sporadic, however, a small subset, less than 2 percent, has a family history of the disease. Familial neuroblastoma frequently occurs at a younger age and may present with multiple primaries, often bilaterally adrenal-based. These are typically either due to an *ALK* (anaplastic lymphoma kinase) or *PHOX2B* germline mutation, the latter associated with Hirshprung's. Both the benign and the malignant forms can occur within the same family pedigree. It is also known to occur in children with neurofibromatosis, Beckwith-Wiedeman, Li-Fraumeni, and Noonan's syndromes, though these only comprise a small percentage of all children who develop neuroblastoma.

Patients with Neuroblastoma by Gender 2005-2015

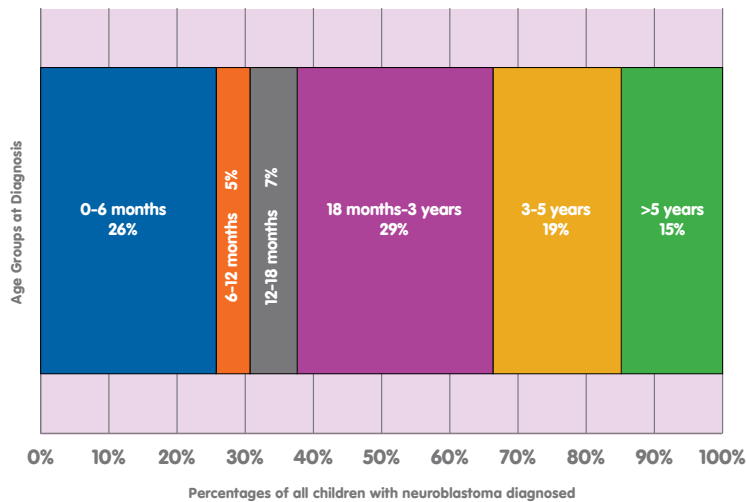


Frequency of Neuroblastoma Diagnosed by Year 2005-2015



Neuroblastoma can arise from any point along the sympathetic nervous system including the paraspinal ganglia or the adrenal medulla. The presentation often indicates the aggressiveness of the disease. The tumor may be palpated in an asymptomatic child at a well child check or the child may have vague symptoms such as achiness and constipation. It is only after these complaints persist or worsen that additional work-up is prompted. Asymptomatic children more likely have a lower stage or less aggressive neuroblastoma and may initially be thought, prior to scans, to be one of the other abdominal masses seen in pediatrics such as Wilms

Distribution of New Patients with Neuroblastoma at Children's Mercy by Age at Diagnosis 2005-2015



tumors, where patients present less ill-appearing.

Conversely, children may present constitutionally very ill. They may appear emaciated, pale, febrile and with the classic raccoon eyes finding that includes proptosis and periorbital ecchymosis due to retrobulbar metastases. These are all common in high-risk patients. Intraspinal extension through the neuroforamina (often seen as dumbbell lesions on CT or MRI) may present with decreased strength or loss of lower extremity function. The presence of neurologic symptoms is considered an oncologic emergency. Patients with extensive bone marrow disease may present with pain and symptoms associated with pancytopenia such as fatigue, pallor, bleeding or frequent infections. Two unique paraneoplastic constellations of symptoms are seen in a minority of children with neuroblastoma. The first is the opsoclonus-myoclonus ataxia syndrome seen in 4 percent of children (symptoms include jerky random eye movements and poor coordination of muscles) felt to be due to an antibody-

mediated reaction in the central nervous system. This is typically associated with low-stage favorable risk neuroblastoma, but requires specific systemic therapy to counter these symptoms. Children may have long-term neurologic and cognitive deficits from this. The other is the Vasoactive Intestinal Peptide (VIP) - Watery Diarrhea syndrome due to the aberrant secretion of VIP hormone from these tumors which often presents as failure to thrive. This too most often arises in the benign neuronal tumors or low-stage favorable neuroblastoma and resolves rapidly with surgical removal of the tumor.

Vital sign changes are seen as a result of pain or bone marrow involvement. Fevers may be secondary to an infectious process due to leucopenia, or arise from the disease process itself. Hypertension is present in about 15 percent of children with neuroblastoma and is thought to be a result of renovascular compression or elevated circulating catecholamines. Urine catecholamines, homovanillic acid and vanillylmandelic acid obtained by spot urine samples

are elevated in 90 percent of neuroblastoma patients at diagnosis, but in only about half of the children who have relapsed disease.

Metastatic extension occurs via the lymphatic and hematogenous systems. Common sites of metastases are the lymph nodes, bone, bone marrow, liver and skin. At diagnosis, a thorough metastatic evaluation is imperative to obtain important staging information that is key to treatment planning. The various imaging modalities necessary are typically available only at pediatric institutions such as Children's Mercy or large university-based hospitals. Additionally, because of the young age of children with neuroblastoma and those who have thoracic primaries, anesthesia is often required.

Neuroblastoma can be visualized by plain film radiographs, computed tomography (CT) scans (both with and without contrast), magnetic resonance imaging (MRI) and radionuclide imaging such as bone scintigram, positron emission tomography (PET) and I-123 metaiodobenzylguanidine (MIBG). The imaging modalities of choice and their combination is based on several factors, including the child's age, current state of illness, presumed staging, and may be obtained in a sequential order to build upon current radiographic findings, such that a PET may be obtained if the MIBG is negative, or an MRI of the spine if the CT is concerning for intraspinal extension. Timely access to all these imaging



modalities is imperative and are available at Children’s Mercy with radiation exposures calibrated to a child’s size.

Radiographic findings aid in determining a child’s disease stage not only by the presence or absence of metastases, but with certain “imaging defined risk factors” (IDRF). IDRFs are risk factors related to localization, involvement of vital organs and structures, and likelihood of surgical resection. They are standardized by the International Neuroblastoma Risk Group (INRG) staging system, and include encasement of the aorta or invasion of a renal pedicle for example.

Risk is also dependent on the patient’s age, tumor stage (see chart) and biologic features of the International Neuroblastoma Pathology Classification (INPC). This pre-therapy classification requires experienced pathologic determination of histology (i.e., stroma rich or poor, degree of neuroblastic maturation, and mitotic-karyorrhexis index) and genomics such as *MCYN* status, DNA ploidy, loss of 1p, loss of 11q, and gain of 17q. In general,

tumors with whole chromosomal gains or losses and/or hyperdiploid content have favorable outcomes, whereas those with structural or segmental chromosomal

abnormalities have poor outcomes [See Pathology, Cytogenetics].

The INRG (which is replacing the historic International Neuroblastoma Staging System (INSS)) divides tumors into four stages, L1, L2, M and Ms to allow data from U.S.-based cooperative group clinical trials such as the Childrens Oncology Group (COG) to be compared to other international trials.

INRG Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors* and confined to one body compartment.
L2	Locoregional tumor with presence of one or more image-defined risk factors.
M	Distant metastatic disease (except Ms).
Ms	Metastatic disease in children younger than 18 months with metastases confined to skin, liver and/or bone marrow (bone marrow involvement should be limited to < 10 percent of total nucleated cells on smears or biopsy). Primary tumor may be L1 or L2 as defined above.

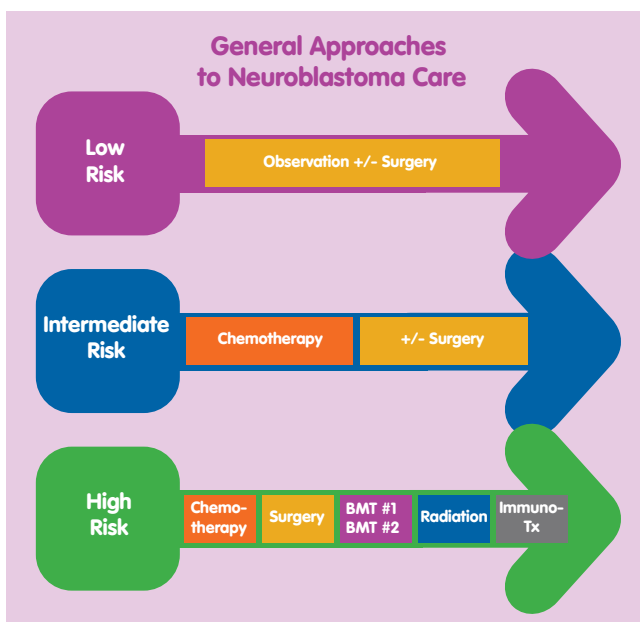
COG is a cooperative group of children’s cancer specialists sponsored by the National Cancer Institute and oversees trials for pediatrics. Children’s Mercy, a member of the NCI COG organization since the 1980s, is one of the larger participating COG cancer centers in the country. It

is the only COG center between Denver, Colo., and Columbia, Mo., and Omaha, Neb., and Oklahoma City, Okla. Our membership ensures that the most advanced therapy is available here in the Kansas City area as it is in other centers across the country. Children’s Mercy also participates in other early phase consortia, as well as bringing novel therapies such as Chimeric antigen receptor T (CAR T) cell therapy to our children who have relapsed disease. Through inclusion and participation in clinical and laboratory research trials [See Research], children here at Children’s Mercy have access to the therapies that are becoming the standard of care for the future. Now, as the pediatric consortium partner in the KU Cancer Center (with Stowers and KU), Children’s Mercy is a part of the NCI Cancer Center network, with even more access to

NIH-supported basic and translational research, in addition to our long-standing involvement in NCI-sponsored clinical research.

Based on the above evaluations at diagnosis, neuroblastoma can really be considered to be two distinct cancers with very different chances of cure. At diagnosis, patient therapy is determined by the risk of relapse, high risk and non-high risk, to both maximize the chance of

cure and minimize the risks. Clinical (age, stage) and biologic (tumor pathology, genetics) characteristics present at diagnosis identify cohorts of non-high-risk neuroblastoma patients. This non-high or good risk group may be further divided into those in whom exposure to chemotherapy or surgery may be unnecessary and simply observed, often with spontaneous regression of their tumors, or to the other good risk patient group that may need only minimal therapy, two to eight cycles based on biology and response, to also achieve an overall survival in excess of 90 percent.



Children with high-risk neuroblastoma conversely receive an aggressive year and half of therapy consisting of a complex schedule of surgery, chemotherapy, tandem bone marrow transplantation, radiation and immunotherapy. The high-dose

chemotherapy cycles require hospitalization and intensive supportive care. Surgery, most often employed after chemotherapy but before transplant, requires an experienced pediatric surgeon in order to achieve the greatest possible removal of remaining tumor [See Surgery]. Bone marrow

transplantation, involving high doses of chemotherapy and stem cell infusion, is then employed and requires weeks of hospitalization in specialized BMT units [See Bone Marrow Transplantation]. Radiation targeting and dosing is based upon location and response serially assessed throughout treatment, and which is administered by pediatric radiation therapy physicians after bone marrow transplantation [See Radiation]. After radiation, a combination of specific immunologic agents including an antibody specifically developed for neuroblastoma (anti-GD2) is administered and requires intensive supportive care while infusing each month. Finally, this unique tumor is treated with an agent, cis-retinoic acid, that functions best at the end of therapy to mop up any remaining cancer cells by causing their maturation into mature neuronal cells incapable of dividing out of control. This complex schedule of care has slowly been developed through years of research to improve the outcome for this high-risk group of children from 10 percent in the 1980s to now 50 to 60 percent in 2016. Multiple pediatric subspecialty experts that are part of an experienced team [See Advanced Practice Nursing & Cancer Center] are required to manage this complex care and are available at Children’s Mercy.

The intensity, overall length of therapy, and high-risk prognosis all require a strong multidisciplinary team that addresses pharmacologic individualized dosing and

interactions, nutrition, physical conditioning, pain control and psychosocial needs of the patient and family. This is accomplished at Children’s Mercy through embedded and specialized staff in nursing, pharmacology, nutrition, physical and occupational therapy, social work, child life, and psychology within the Cancer Center dedicated to the children with cancer.

Responses that impact therapeutic decisions are categorized based on primary and metastatic sites, as well as tumor markers. Response is also an important indicator of long-term success or cure.

Despite all this, initial resistance (refractory) and relapse remains the greatest cause of treatment failure, occurring in 30 to 40 percent of those children with high-risk neuroblastoma. For these high-risk children with resistant and/or relapsed neuroblastoma, there is no proven curative therapy, although significant translational and clinical research is ongoing here at Children’s Mercy for these children.

Children treated for neuroblastoma who go on to become long-term survivors of their cancer may have a spectrum of disease and therapy related sequelae. The majority have had abdominal or thoracic surgery,

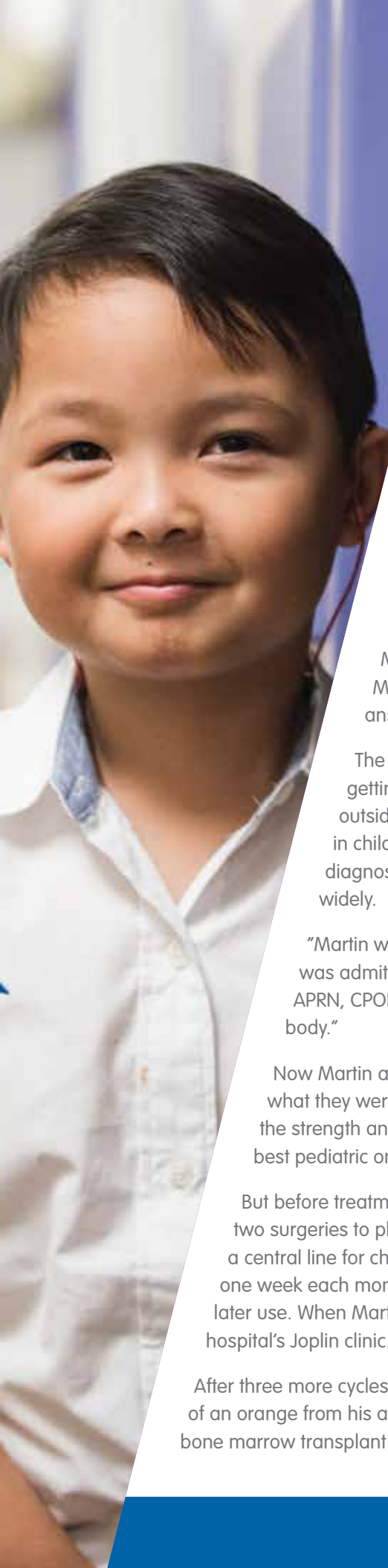
received radiation to multiple sites, have had ototoxic (platinums) and cardiotoxic (anthracyclines) chemotherapy agents and underwent an autologous stem cell transplant. It is imperative that these children be followed in a long-term multidisciplinary survivorship clinic such as Children’s Mercy’s Survive & Thrive Clinic, to screen for late effects as early detection can minimize complications and improve quality of life [See Survive & Thrive Program]. Now with more and more children surviving their cancer and living into adulthood, transitioning to adult providers knowledgeable in these sequelae is increasingly critical to prevent

or reduce later health complications. The combined program, developed by Children’s Mercy and the University of Kansas Cancer Center adult patient providers, offers a seamless transition for our patients as they become adults (as well as for those childhood cancer survivors moving into our area as adults). ●

Response Definitions in Neuroblastoma Therapy

SITE	TEST	COMPLETE RESPONSE	VERY GOOD PARTIAL RESPONSE	PARTIAL RESPONSE	MIXED RESPONSE	NO RESPONSE	PROGRESSIVE DISEASE
Primary	3 dimensional CT or MRI imaging (determine volume from product of three dimensions physical exam and/or surgical measurement)	no tumor	>90 percent reduction in 3-dimensional tumor volume	50-90 percent reduction in 3-dimensional tumor volume			
Metastases	Bone marrow ¹ (aspirate x 2 and biopsy x 2)	no tumor	no tumor	no or only one sample with tumor ²	50-90 percent reduction of any measurable lesion (primary or metastases); no new lesions; <25 percent increase in any existing lesions, exclude bone marrow evaluation	no new lesions; <25 percent increase in any lesion; exclude bone marrow evaluation	any new lesion; increase of any measurable lesion by >25 percent; previous negative bone marrow positive
	Bone X-rays and scintigraphy (Tc and/or MIBG)	no lesions	all lesions improved; no new lesions ³	all lesions improved; no new lesions ⁴			
	Liver imaging (ultrasound, CT or MRI)	no tumor	no tumor	50-90 percent reduction			
	Chest X-ray, chest CT scans if X-ray abnormal	no tumor	no tumor	50-90 percent reduction			
	Physical exam ⁵	no tumor	no tumor	50-90 percent reduction			
Tumor Marker	Urine catecholamine metabolites (HVA & VMA)	Normal	normal or both decreased >90 percent	both decreased 50-90 percent			

Brodeur G et al: JCO 1993; 11:1466-1477



Children's Mercy Helps Joplin Boy Face Neuroblastoma Head On

At just 3 years old, Martin Vu, Joplin, Mo., seemed to be a healthy, active child, jumping and playing—and then suddenly one day he wasn't.

"Martin started running a fever, so I took him to the doctor, but they could not figure out what was causing it," said Phong Vu, his father.

Over the next several days, Martin's fever continued and his symptoms became worse. "He was in a lot of pain," Vu said. "His stomach hurt and he was vomiting." When Vu took him back to the doctor, they took X-rays and did CT scans, but still were puzzled.

Meanwhile, Martin's condition continued to decline. After two months of questions, Martin was sicker than ever. His legs hurt, his back hurt, he couldn't walk. "We needed answers," his father said. So Vu requested Martin be transferred to a pediatric hospital.

The first day Martin arrived at Children's Mercy Kansas City, testing revealed why he was getting sicker—a high-risk neuroblastoma, the most common solid tumor malignancy outside the central nervous system in children and a cancer that is often diagnosed only after it has spread widely.

"Martin was a very sick boy when he was admitted," said Joy L. Bartholomew, APRN, CPON. "He had disease all over his body."

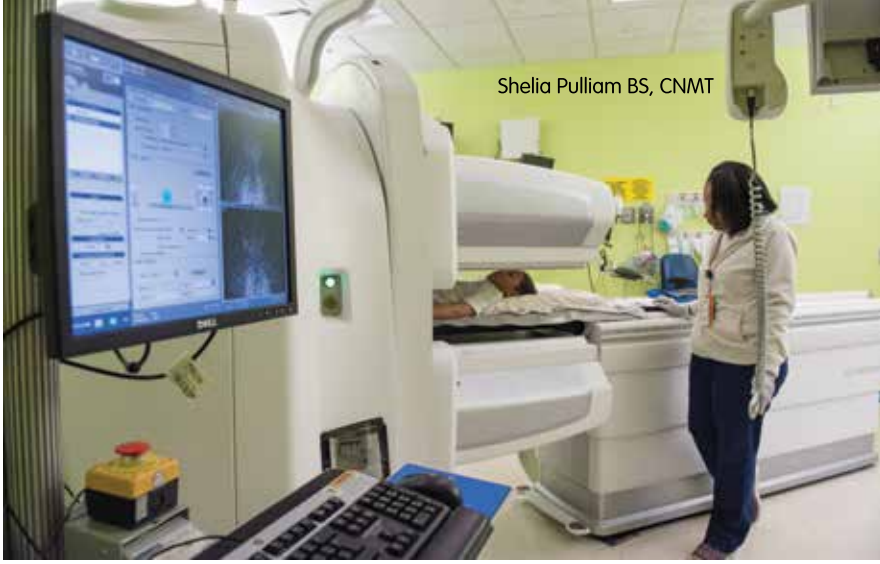
Now Martin and his family not only knew what they were fighting, they knew they had the strength and depth of one of the nation's best pediatric oncology teams in their corner.

But before treatment could begin, Martin had two surgeries to place a chest tube and implant a central line for chemotherapy and blood testing. Initially, he had two cycles of chemotherapy lasting one week each month. After the second cycle, the team harvested his peripheral blood stem cells for later use. When Martin wasn't at Children's Mercy, his blood work was monitored close to home at the hospital's Joplin clinic.

After three more cycles of chemotherapy, Martin had minimally invasive surgery to remove a mass the size of an orange from his abdomen. When he recovered, Martin received a sixth cycle of chemotherapy, then a bone marrow transplant to further target any resistant tumor remaining.



Joy Bartholomew, APRN, CPON



The next month, Martin received 20 radiation treatments, followed by six cycles of tumor-specific antibody therapy designed specifically to harness his immune system in the fight against his cancer.

“Children’s Mercy was involved in the clinical trials for immune therapy, and has more than a decade of experience with this treatment,” Bartholomew said. “This is a very intense treatment that requires a lot of supportive care from our team, but it has improved survival rates for these patients from 20 percent years ago, to 60 percent today.”

Martin is one of those survivors. Three years after his diagnosis, he’s in remission and his family’s lives are returning to normal. “Martin just celebrated his seventh birthday. He is back in school and loves it!” Vu said. “He is active again and enjoys singing. He says when he grows up, he wants to be a policeman.”

Vu, who quit his job and spent three years caring for his son, also has returned to work full time. The frequent road trips from Joplin to Children’s Mercy are now just a memory. They only go to the hospital every six months for check-ups.

Looking back, Vu said if he had not asked for Martin to be transferred to Kansas City, he’s not sure his son would be alive today.

“The staff at Children’s Mercy had the experience to take good care of him. It is the best children’s hospital. They gave Martin a chance to live and grow up. Thank you very, very much to the doctors and nurses at Children’s Mercy.” ●



Diagnosis

Radiology

Imaging plays a significant role in the diagnosis, staging and post-treatment follow-up of neuroblastoma.

Because a majority of cases of neuroblastoma present as a painless abdominal mass, ultrasound provides an excellent first-line imaging test. Ultrasound is a quick, easily accessible and pain-free examination that uses sound waves instead of radiation in the production of images. Ultrasound provides very good localization, and characterization of the mass, often demonstrating the calcification that is present in nearly all neuroblastoma cases.



Brenton Reading, MD

Once the diagnosis of neuroblastoma is highly suspected, as the result of physical exam, laboratory and initial imaging findings, the next step from an imaging standpoint is to further define the tumor and the extent of disease. This is usually accomplished with computed tomography (CT) with doses modified for the child's size or magnetic resonance imaging (MRI). Increasingly, MRI is being utilized over CT because of the lack of ionizing radiation. At Children's Mercy, child-specific protocols are in place to safely perform scans without undue stress to the child and are done with or without sedation under the direction of our sedation team and anesthesiology.

Nuclear medicine is a special division within radiology and a test called an I-123 MIBG scan remains the favored nuclear medicine study for diagnosis, staging and follow-up of neuroblastoma. The MIBG scan takes advantage of the fact that neuroblastoma is a tumor of the sympathetic nervous system. MIBG, or metaiodobenzylguanidine, is a radiolabeled molecule, that is very closely related to norepinephrine, and therefore concentrated in sympathetic nervous tissues, such as neuroblastoma. Children's Mercy is the only facility in the region with this specific I-123 capability. ●

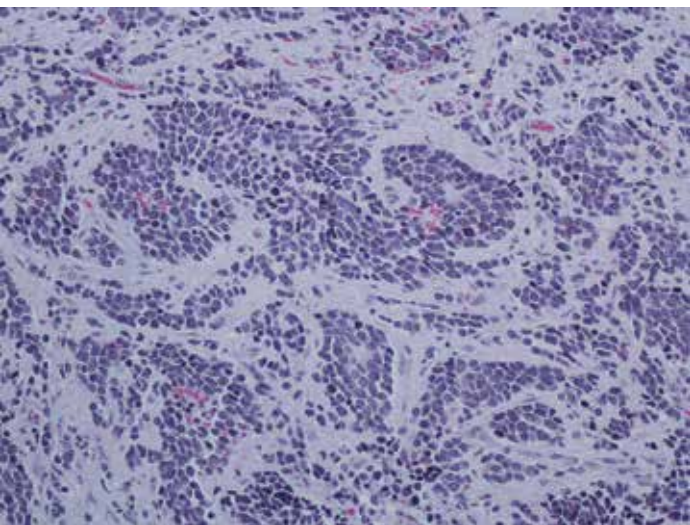
Pathology

Neuroblastoma is a solid tumor that commonly develops in the adrenal gland or along the sympathetic chain anywhere from the neck to the pelvis. It arises from the neural crest cells that are essential in normal embryologic development of the spinal cord. Morphologically, it is classified according to the degree of cell differentiation, into neuroblastoma, ganglioneuroblastoma and ganglioneuroma; the latter is a benign neoplasm. Neuroblastomas occasionally undergo spontaneous regression or maturation to ganglioneuroma.

To diagnose neuroblastoma, pathologists employ morphologic and biochemical approaches. Cutting through the tumor shows soft, tan-gray tissue, often with areas of necrosis, hemorrhage and/or cysts. Histology ranges

from sheets of primitive, undifferentiated, small, round, blue cells to mature ganglion cells in a Schwannian stroma. Rosettes of tumor cells may be present. Pathologists also use immunostains to distinguish neuroblastomas from histological mimics, such as rhabdomyosarcoma, Ewing sarcoma, Wilms tumor and lymphoma. A pathologic classification, which takes into account the degree of tumor differentiation, patient's age and the mitosis-karyorrhexis (MKI) index, helps stratify patients for different therapies. This system describes tumors as "favorable" or "unfavorable" tumors, as defined by the International Neuroblastoma Pathology Committee (INPC).

Approximately 90 percent of neuroblastomas secrete catecholamines. Catecholamines and their metabolites are useful biomarkers detectable in blood and/or urine and include dopamine, homovanillic acid and vanillylmandelic acid. When elevated prior to treatment, these biomarkers are used to monitor response to therapy and tumor recurrence. ●



Sahibu Sultan Habeebu, MD, PhD

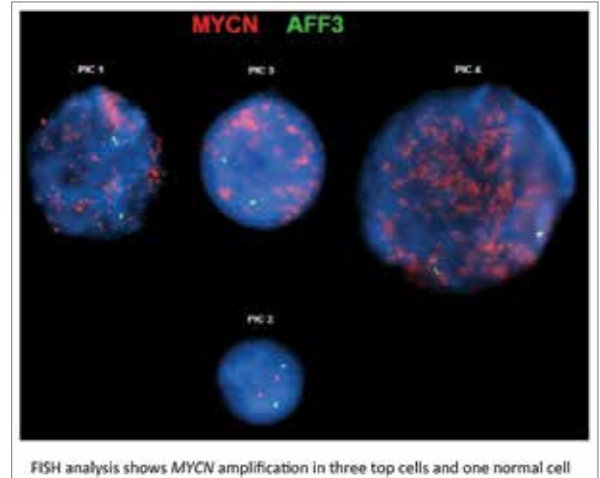
Cytogenetics

Neuroblastoma, a malignant pediatric cancer derived from immature cells of the sympathetic nervous system, is a genetically heterogeneous tumor that accounts for approximately 15 percent of all pediatric cancer deaths. Genomic alterations of neuroblastoma strongly influence tumor behavior and patient survival.

Diploid tumors with approximately 46 chromosomes have been long recognized to be associated with a less favorable outcome than near-triploid tumors with closer to 69 chromosomes. Study of tumor

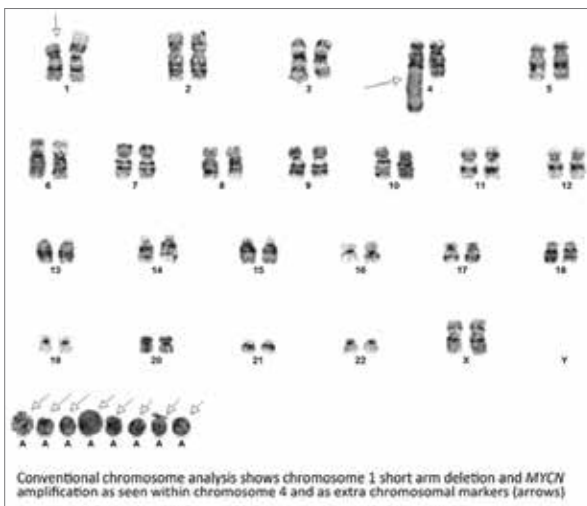
to stratify patients for therapeutic intervention.

Amplification of the MYCN gene is associated with high-risk tumors independent of tumor stage and patient age. Segmental chromosome aberrations, especially those involving chromosomes 1p, 11q and 17q impact patient outcome unfavorably. Conversely, tumors without segmental chromosome aberrations or MYCN amplification are associated with good overall survival.



FISH analysis shows MYCN amplification in three top cells and one normal cell

The recent discovery of ALK gene activating mutations in approximately 8 to 10 percent of neuroblastomas has opened an avenue for targeted therapy in this subgroup of neuroblastoma patients. ●

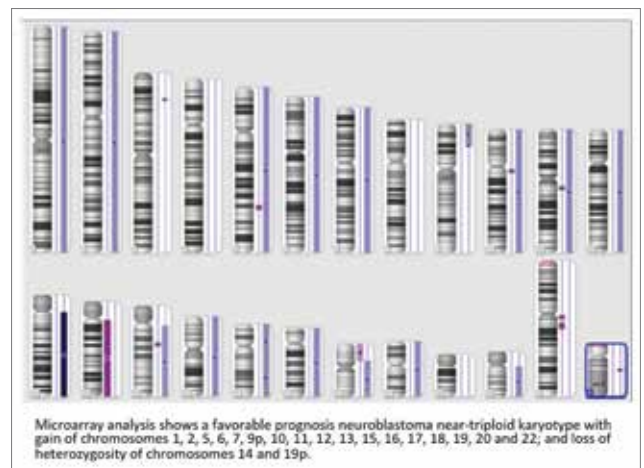


Conventional chromosome analysis shows chromosome 1 short arm deletion and MYCN amplification as seen within chromosome 4 and as extra chromosomal markers (arrows)

Fresh neuroblastoma tumor tissue processed in the cytogenetics laboratory at Children's Mercy is cultured for cell growth to assess the tumor genome for chromosome number and aberrations, while fresh or fixed tumor is used to determine MYCN amplification status. DNA isolated from tumor is used for

tissue genetics is accomplished by conventional chromosome analysis, fluorescence in-situ hybridization (FISH), and more recently microarray analysis and gene sequencing. Determination of the presence or absence of specific genomic gains and losses, gene mutations or amplification along with tumor stage and differentiation, and patient age are all factors used

microarray and sequencing. Microarray analysis provides high-resolution whole genome analysis and is the most comprehensive method for study of neuroblastoma currently available.



Microarray analysis shows a favorable prognosis neuroblastoma near-triploid karyotype with gain of chromosomes 1, 2, 5, 6, 7, 9p, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20 and 22; and loss of heterozygosity of chromosomes 14 and 19p.

Genomics and Cancer Biorepository

The Children's Mercy Cancer Genomics Program is a team effort between the Children's Mercy Cancer Center and the Center for Pediatric Genomic Medicine. The program makes next-generation sequencing research available to all oncology patients. Any patient being treated for neuroblastoma at Children's Mercy may enroll in a research protocol for genomic sequencing. Once enrolled, DNA from the patient's healthy blood cells and from the tumor cells are analyzed and compared. The team is also looking at RNA and epigenetic changes in the tumor cells. All of the genomics research work is done at Children's Mercy. The goal of the work is to better understand the cause of neuroblastoma and to develop better treatments. In some cases, genomic sequencing may help clinicians choose treatments that are targeted to a patient's tumor.

As part of the support for the Cancer Genomics Program and other research programs, the new Cancer Center Biorepository provides a core service within Children's Mercy. Patients with neuroblastoma may opt to donate blood, leftover tumor samples, DNA and clinical data to the Cancer Center Biorepository. The donated material and clinical data are stored in a protected database and are available to research scientists, with approved protocols, to study cancer and related diseases. By participating in the Biorepository, patients with neuroblastoma provide critical resources that are needed to make progress toward targeted treatments and even better cure rates for future children diagnosed with cancer.

Erin Guest, MD, is the director of the Children's Mercy Cancer Genomics Program and co-director with Alex Kats, MD (Pathology) of the Cancer Center Biorepository. For more information about either program, please contact the Hematology/Oncology office at (816) 302-6808. ●



Erin Guest, MD, and Midhat Farooqi, MD, PhD

Therapy

General Surgery

Over the last decade, there have been remarkable advances in the medical management and chemotherapy protocols for children with neuroblastoma. In parallel with these improvements, the surgical approach to children with neuroblastoma has also changed. Even though the surgical removal of the tumor still plays a major role in almost all of the treatment plans, we now know that some neuroblastomas (classified as “non-high risk”) can be managed with observation alone or with only low-dose chemotherapy. On the other hand, surgery is still necessary for children whose tumors are “high risk.”

When surgery is required, the surgery should be done by pediatric surgeons who are well-trained and experienced in the management of these tumors. Advanced stage tumors can be very complicated and difficult to remove. In order to maximize the benefits of surgery, the operation must always be done as a part of a larger, comprehensive approach to treatment.



The goal of surgery is always to completely remove the tumor and is more easily accomplished when the tumor is relatively small and has not grown into any surrounding structures (INSS Stage 1, 2 tumors). Unfortunately, as neuroblastomas expand (INSS Stage 3,4) they can infiltrate into any adjacent organs (e.g., kidney/liver) and/or can encase critical blood vessels (e.g., aorta, vena cava, renal artery and vein). These surgical obstacles can often be found on pre-operative CT scans and today are called “image defined risk factors” (IDRF). When these IDRFs are present, complete removal of the tumor is quite difficult, if not impossible, and complications from the tumor removal increase significantly. These IDRFs determined at the time of diagnosis combined with critical histologic and molecular findings from the initial biopsy has led to the most recent neuroblastoma risk classification system (INRG) now in use. As most intermediate and high-risk neuroblastomas are not resectable at diagnosis, a closely coordinated multi-modality approach is critical to future surgical resection capabilities.

The experienced pediatric surgeon on the team is critical to not only ultimately achieve the greatest resection, but to also assess the timing of this — either at diagnosis or later in therapy. Pre-operative or neoadjuvant chemotherapy is used to decrease tumor size and infiltration, allowing a greater likelihood of successful tumor resection. Through surgical research in pediatric cancer centers such as Children’s Mercy Cancer Center and in partnership with national organizations such as the Children’s Oncology Group (COG), we’ve identified that when it is not feasible to fully resect the remaining tumor, a very good partial resection of at least 95 percent of the tumor removed (without removing or injuring involved organs (e.g., kidney or liver) or vessels (e.g., renal artery/vein or aorta/vena cava) can provide equivalent opportunity for cure to a total resection. This is also important in light of the continuing therapy that will follow the surgery and which includes bone marrow transplant, radiation and immunotherapy. A very closely coordinated review with ongoing communication between the surgeon and other specialties on the neuroblastoma team allows for the vastly improved and best long-term outcomes seen today in children with neuroblastoma. ●

Bone Marrow Transplantation

Survival for children with low-risk neuroblastoma is greater than 90 percent with relatively less therapies, while survival for those with high-risk neuroblastoma was less than 20 percent when conventional chemotherapy, surgery and radiation alone were used.

Resistance of neuroblastoma cells to conventional chemotherapy remained the main reason for treatment failure in high-risk patients in the 1980s and early 1990s. In those years, the idea of chemotherapy intensification to overcome this through the use of myeloablative (bone or peripheral blood stem cell transplant) consolidation therapy was pursued. Not until the advent of peripheral stem cell collection and incorporation of it for neuroblastoma in the early 1990s did autologous peripheral blood stem cell transplant (PBSCT) become a feasible option.

A Children's Oncology Group trial of PBSCT vs. no PBSCT after conventional chemotherapy, which included Children's Mercy patients, showed that with transplant progression-free survival improved significantly to 40 percent or better.

Subsequently, children participated in a clinical trial that showed repetitive use of this approach (now called tandem transplant) resulted in nearly a 15 percent improvement in three-year progression-free survival now, in excess of 60 percent when combined with the other therapies described in this report.

As seen throughout this report, a well-coordinated multispecialty,

using PBSCs after five to six cycles of induction chemotherapy and surgical resection subsequent to the PBSCT, with radiation therapy followed by six cycles of anti-neuroblastoma immune therapy and differentiating agents. This very intensive sequence of therapies administered in a timely manner and dealing with the myriad of side effects that comes with it is

now achieving survivals only dreamed of a few years ago. With further research, we hope survivals in the future will continue to improve to not only cure all children with this cancer, but to do so without the cost of side effects they must endure. ●



multidisciplinary approach is critical to the child's chances of beating their cancer. Research such as that described above, combined with other studies that showed it was better to delay the radiation until after PBSCT rather than prior, has led to our current paradigm of sequential therapy used today.

It is now the standard of care to incorporate a tandem transplant

Radiation Therapy

Over the years, the role of radiation therapy for neuroblastoma has evolved.

For patients with low or intermediate risk disease, high survival rates with surgery and/or chemotherapy are expected, and radiation is reserved for local recurrence.

In infants with good prognosis disease (M_s disease), radiation has been used only for life-threatening conditions.

Thus radiation is reserved for those children with high-risk neuroblastoma. Most of the patients that receive radiation therapy have already had a transplant. Radiation therapy is used to treat the site

where the tumor started and sites that the tumor metastasized or spread to by the bloodstream to involve other areas of the body.

Radiation is focused treatment and with improved technology we are able to deliver the treatment precisely. Over the years, national studies have clearly shown an improvement in the overall survival with the addition of radiation therapy to treat children with high-risk neuroblastoma. Because neuroblastoma can occur in the chest, abdomen or pelvis, and can spread to many other areas of the body, the sites treated and doses are tailored for the individual. In order to deliver radiation therapy, a team consisting of the physician, nurse, physicist, therapists and support staff work closely together. This team works in close conjunction with the child's primary oncology team, radiology and surgery to ensure therapy is seamless and timely. For those who require sedation, a Children's Mercy pediatric anesthesiologist is on site.

The Children's Mercy Cancer Center works with the department of radiation oncology at the University of Kansas Cancer Center, a National Cancer Institute-designated program. ●



Antibody Therapy

Immune-mediated therapy has revolutionized cancer treatment and has significantly improved survival in high-risk neuroblastoma patients (20 percent better event-free survival and 11 percent better overall survival (Yu et al., NEJM 2010)) who have had at least a partial response to multimodal therapy.

GD2 is a molecule on the surface of nearly all neuroblastoma cancer cells, and hence is an ideal target for an antiGD2 monoclonal antibody. Initially known as ch14.18, dinutuximab (generic name) is given in combination with granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 2 and the biologic response modifier isotretinoin (ISOT) (aka cis-retinoic acid).

This treatment is delivered in a maintenance phase, which follows the consolidative therapy of tandem hematopoietic stem cell transplantation and radiation. It consists of five alternating cycles with a sixth cycle solely of ISOT.

This combination therapy has significant side effects: severe pain (GD2 is also present on nerve fibers), capillary leak syndrome, hypersensitivity reactions, fevers and hypotension, that require inpatient medical and nursing expertise for prompt detection and aggressive care management.

Safe administration requires the multidisciplinary expertise offered only in established high-volume pediatric cancer centers. Children's Mercy Kansas City has been administering this therapy for 15 years and is in the top 10 percent of experienced treatment centers nationally. Children's Mercy is currently participating in a Phase IV study assessing immunogenicity in patients receiving dinutuximab treatment, and in a Phase III study assessing efficacy in refractory or relapsed neuroblastoma. ●

Children's Mercy Kansas City has been administering this therapy for 15 years and is in the top 10 percent of experienced treatment centers nationally.

Cancer Immunotherapy Program

The Children's Mercy Cancer Center Immunotherapeutics Program is a relatively new project, focused on building infrastructure and regional collaborations of like-minded investigators.

The program began with the region's first trial of genetically modified T-cells expressing a chimeric antigen receptor (CAR) targeting GD2 in patients with neuroblastoma. At the time, this trial placed the hospital and region among a select few capable of investigator-initiated trials of this kind. It also established ongoing collaboration with the Center for Cell and Gene Therapy at Baylor College of Medicine, where the cells were produced. A similar trial of GD2 CAR expressing T-cells targeting melanoma in adults was designed at Children's Mercy and is open and ready to enroll.

Experience in this form of complex therapy was of interest to pharmaceutical companies, such as Novartis, when they intended to open the first multi-institutional study of CAR targeting CD19 in pediatric patients with acute lymphoblastic leukemia. The trial is ongoing at Children's Mercy.

In summary, the clinical trials portion of the program is robust. We are now focused on establishing the basic science and translational laboratories essential to conducting these clinical trials.

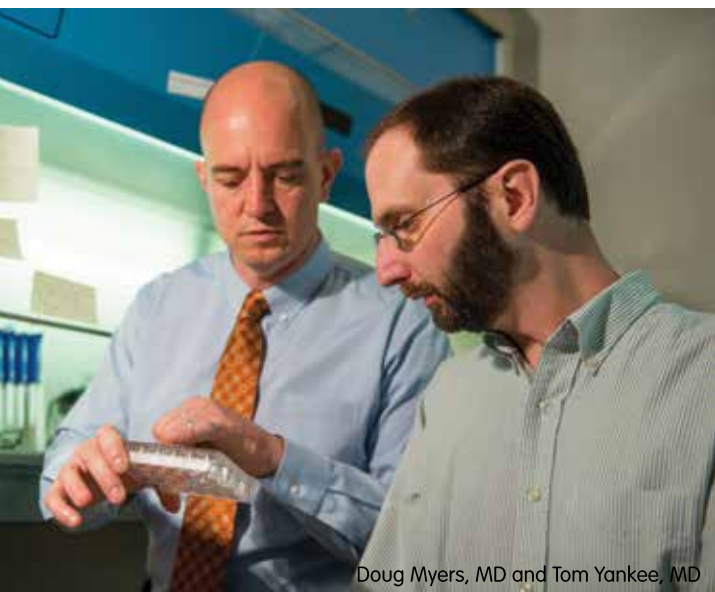
While conducting and participating in complex gene transfer studies, efforts are ongoing to expand the field of cellular immunotherapeutics and complex biologics in the region. The program is actively reaching out to investigators at the University of Kansas, Kansas State University, University of Missouri, and Kansas City Area Life Sciences Institute. A Midwest Cancer Alliance grant funds a collaboration between Children's Mercy, KU Medical Center and Kansas State University

to study new CAR constructs in well-established in-vitro models and novel immunocompetent animal models. Initial efforts at CAR constructs were presented and



well-received at the 2016 American Society of Gene and Cell Therapy meeting in Washington D.C. We will reach out further in an upcoming effort, Collaborate2Cure, sponsored by the Kansas City Area Life Sciences Institute.

It is the intention of the program to dovetail with the goals and aspirations of the developing Children's Mercy Research Institute and work synergistically with the immunotherapy interests and efforts of others in the region. We intend to develop other forms of cancer-targeting immunotherapeutics and apply lessons learned beyond the field of cancer to immune dysfunction and autoimmunity. ●



Doug Myers, MD and Tom Yankee, MD

Experimental Therapeutics

Standard therapy for high-risk neuroblastoma is the most comprehensive and aggressive treatment used to treat any cancer. Newly diagnosed children with high-risk neuroblastoma receive treatment with chemotherapy, surgery, two autologous hematopoietic stem cell transplants, radiation therapy and immunotherapy. Despite this approach, a long-term cure is expected for only 50 to 60 percent of children. For patients with relapsed disease or for those that progress while on therapy, new and innovative treatments are desperately needed.

The Experimental Therapeutics in Pediatric Cancer Program brings early phase clinical trials to patients at Children's Mercy Kansas City. For children with neuroblastoma who are not cured with initial therapy, there are a number of phase 1 and 2 trials that provide access to the newest and most promising treatments. As members of the Children's Oncology Group and the Neuroblastoma and Medulloblastoma Translational Research Consortium, we are a part of groundbreaking research, striving to transform new information about how cancer cells function into new therapies. Locally, the ET researchers are focusing on new drug discovery, drug repurposing and reformulation, pediatric-specific pharmacokinetics and modeling, and pharmacogenomics in collaboration with both the KU Cancer Center and Children's Mercy Clinical Pharmacology Program, one of the largest in the country.

The Experimental Therapeutics Team at Children's Mercy includes three physicians, an advanced nurse practitioner, a social worker and four clinical research coordinators. ●



Keith August, MD, MS



Helping Jaelee Fight Neuroblastoma with Everything She Has

The first sign that 6-year-old Jaelee Munson of Quapaw, Okla., might be sick was a persistent low-grade fever. “She started running a 100-degree fever almost every day in the spring of 2015,” said Casie Munson, Jaelee’s mom. “I carried acetaminophen with me everywhere I went.”

A few months later, Jaelee was diagnosed with mononucleosis, explaining the fevers and constant fatigue. Then her stomach began to swell. “I went to give Jaelee a bath one day and noticed her side was sticking out,” Casie said.

When a CT scan revealed a cantaloupe-sized tumor, the family’s primary care provider suspected cancer and asked whether they would like to go to Oklahoma City or Kansas City for Jaelee’s care.

“I asked him, ‘If Jaelee were your child, where would you want her to be treated?’” Casie said. “He didn’t hesitate, ‘Children’s Mercy.’” The hospital accepted her transfer immediately, and when Jaelee arrived, the cancer team went to work determining her diagnosis, then developing a treatment plan.

“When we got to Children’s Mercy, we felt like we were in the right place,” Casie said. Five more days of testing confirmed that the tumor in Jaelee’s abdomen was on her adrenal gland, and disease had spread throughout her bone marrow. She had high-risk metastatic neuroblastoma.

“We were finally getting answers,” Casie said. “We were ready to fight. All I could think is, ‘Cancer isn’t taking my child!’”

The first phase of treatment involved five rounds of chemotherapy. Jaelee was hospitalized for each with her parents staying by her side.

After completing every round, Jaelee and her family returned to Quapaw, but only briefly. “Jaelee would have fevers while her immune system was down,” said Kevin Munson, her father. “She’s been transported to Children’s by air and ground ambulance three times since April.”

The fevers and infections lengthened the time needed for her body to recover between treatments, but Jaelee stayed strong. By summer, she was posing for the Children’s Mercy calendar, and in August, doctors removed the tumor.





Shawna Mazeitis

Following surgery, Jaelee developed a hematoma that required two drains be implanted to remove the blood accumulating in her abdomen. Then she received an additional round of chemotherapy.

Now in the midst of her treatment plan, she's preparing for two bone marrow transplants, followed by radiation and finally, tumor-specific antibody therapy.

During Jaelee's treatment, the family has faced other hardships. Their home in Quapaw recently caught fire while they were in Kansas City; Casie lost her job because she missed too much work while caring for her daughter; and the family put so many miles on their vehicle making the 200-mile trip to the hospital, they had to get a new one.

Still, Children's Mercy has been at their side. "When our house caught on fire, our social worker connected us to the Red Cross," Casie said. And because she's been sick for so long, the hospital's on-site school teacher has been helping Jaelee keep up with her first-grade assignments.

Soon, Casie and Kevin hope their daughter will be back in school, playing outside and cruising around the yard in her Barbie jeep.

Until then, Jaelee is fighting cancer with every resource Children's Mercy has available.

"Everyone is very kind and considerate here. Plus, they know exactly what they are doing," Kevin added. "This place is awesome." ●

Supportive Care and the Team Approach

Advanced Practice Providers

Children with neuroblastoma require multiple physician subspecialists; pediatric oncologists, surgeons, anesthesiologists, radiation oncologists and bone marrow transplant physicians. Care extends beyond the medical team to include nurses, social workers, Child Life specialists, chaplains and nutritionists. The advanced practice provider is an instrumental part of the team and facilitates the coordination of care. Each child has a primary oncologist, an advanced practice provider and a social worker from the time of diagnosis. The child's primary advanced practice provider is the point person for all patient contact and interacts with the various members of the team to ensure all medical and supportive service needs are met. The primary advanced practice provider also provides education, reviews therapy and its affect on the child, performs physical exams and orders laboratory tests, scans and prescriptions. The child's primary advanced practice provider helps their patient and family navigate the complex world of medical care necessary for their best chance at a cure for their cancer. Inpatient advanced practice providers care for patients during each chemotherapy and immunotherapy admission and during bone marrow transplantation. The advanced practice provider care model provides personalized, efficient and coordinated care for Children's Mercy oncology patients. ●



Joy Bartholomew, APRN, CPON



Allison Rees, APRN

Oncology Nursing - Sites of Care

Outpatient Clinic – Children’s Mercy Adele Hall Campus

The Hematology/Oncology Clinic provides a multidisciplinary approach in caring for children and their families with neuroblastoma. During an appointment, the child is seen in one of our 18 exam rooms by a care assistant, a registered nurse, physician and or advanced



Goldie Benz, APRN

practice nurse, a social worker — all primary providers — along with a Child Life specialist, a nutritionist or pharmacist, depending on the care needs of the day.

The clinic also has 14 infusion rooms where highly skilled registered nurses assess the child, obtain laboratory specimens, administer chemotherapy and transfuse blood products. The registered nurses are the front line in answering parent

questions, providing education, and screening for disease and treatment-related side effects. They readily contact the providers when needed.

The clinic has 11,000 visits a year with each child cared for by a registered nurse certified in pediatric advanced life support. Due to the intensive needs of children with neuroblastoma, they will have many weekly and even daily clinic visits throughout their therapy. These children develop strong relationships with our nurses and do not hesitate in coming to their clinic appointments.

For those in the Joplin region, we offer monthly access to off-therapy exams and labs staffed by our Hematology/Oncology staff and physicians.

Inpatient Unit – 4 Henson-Hall – Children’s Mercy Adele Hall Campus

Children’s Mercy has a designated 38-bed Hematology/Oncology unit for inpatient stays, of which 15 rooms are specially designed for bone marrow transplant. The majority of high-risk neuroblastoma therapy is given in the hospital setting: chemotherapy, tandem transplant and immunotherapy. Each registered nurse on the floor has undergone specialized education and training in this disease, its treatment and side-effect management. Overseeing

this therapy is our chemotherapy service staffed by advanced practice nurses. These professionals are well-versed in all the cancer treatment plans and therapy side effects. The number of high-risk neuroblastoma patients treated each year at Children’s Mercy and the quality of registered nurse and advanced practice nurse care affords us the experience to be experts in the delivery of complex therapy such as monoclonal antibody therapy.

BMT Unit and Clinic

The initial therapy plan for all children with high-risk neuroblastoma includes a tandem transplant. Due to the complex needs of these children, the thorough assessments provided by our skilled registered nurses are even more critical. As such, there are set qualifications with additional education requirements in order to become a BMT nurse. At times, the care provided is so intricate that a BMT registered nurse may have only one patient. Transplanting 35 to 40 children at Children’s Mercy each year, these BMT nurses are experts in delivering safe, quality, complex care. Advanced practice providers specialized in transplant also oversee the child with high-risk neuroblastoma. These providers manage care, both inpatient and outpatient, assuring a high standard of care while providing a seamless transition between venues. ●

Psychosocial (FaCT) Services

Multidisciplinary care is integral to the overall outcomes and well-being of our patients. Outside of medically directed care, patients and families have many other needs that are addressed by our Family Care Team (FaCT). Regular FaCT rounds and collaboration ensures that all physical, developmental, emotional, educational and spiritual needs are met for our patients and families. The Family Care Team is available to assist from point of diagnosis through the completion of treatment and beyond.

Child Life Specialists promote a positive environment for patients and families based on their needs. This is accomplished by providing materials and guidance for developmentally appropriate play, preparing children for medical experiences, advocating for patient and family rights, and promoting a non-threatening environment. Our team tries to reduce stress and worry that may come with being in the hospital or from being ill. We help children deal with their feelings, thoughts and questions. We provide services to help children continue to learn and grow while in the hospital. Our team members encourage patients to interact with other children.

The Parent to Parent Program (PTP) continues to offer support and comfort to all of our families through the use of inpatient parent volunteers, parent rooms, Peer Match Program, and the bereavement follow-up program. There are many services offered through the PTP program including trained parent volunteers available to share, listen and support our current parents; two stocked parent rooms on the inpatient unit that offers weekly dinners, breakfasts, therapeutic and educational activities and a safe place to unwind while a child is an inpatient; and "care bags" for new families upon admission to help ease some burden of a hospital stay. The PTP program also offers an extensive bereavement follow-up program that supports families for approximately 13 months after a child's death. We have successfully introduced social media into our bereavement follow-up program and have been able to offer additional support in that way. The PTP program manager coordinates and manages a number of grants that provide support to patients and families including lunch and learns and new parent journals.

Clinical social workers are master's-level licensed professionals working as part of the primary team to provide comprehensive and compassionate family-centered care. Social workers understand that any change in the child's health can alter a family's life in many ways, and are trained to provide a thorough assessment and address the needs of the patients and families. Social workers can help with therapeutic support including adjustment to illness, crisis intervention, development of coping skills, family concerns, end-of-life and bereavement; care planning including education on advance directives, school concerns, legal issues, transition to adult care and end-of-life concerns; and community/resource referrals to assist with financial concerns, transportation and lodging needs, support and mental health referrals. Every patient has an assigned clinical social worker who follows the patient and family through diagnosis, treatment, relapse, survivorship or bereavement.



Lisa Peters, LMSW, LCSW

The Hematology/Oncology Division has two **psychologists** to assist patients and families with coping with the diagnosis and treatment of neuroblastoma and other cancers. They are available to meet with patients and their families both while hospitalized and when as outpatients. In addition to therapy services, the psychologists are also able to complete neurocognitive evaluations to assess any impact of medical treatment on brain functioning and to assist with school re-integration and planning.



An on-site **school teacher** works with patients primarily on the inpatient floor, with some availability in clinic as needed to assist with the

challenge of keeping up with school work while a patient is undergoing treatment. Our school teacher is able to communicate directly with the child's school to obtain current assignments and also to advocate for the patient's needs once they return to the school setting.

The **chaplain** working with Hematology/Oncology/BMT is available to meet and provide spiritual and emotional support for patients and families during the course of the child's illness, as end-of-life discussions are necessary, at the time of death and beyond. The chaplain can assist in contacting a family's own clergy if requested, or locating a local clergy of the patient/family's denomination or faith for families who are not from the area. The chaplain also provides education on spiritual resources and support available within the hospital, including the chapel, worship opportunities and special events. The chaplain regularly participates in hematology/oncology rounds. The chaplain also provides support to members of the staff.



Liesel Stephens, MT-BC

Music therapy services are offered to patients and families at the bedside to address the specific needs of each individual patient. Music interventions are designed after an assessment of need and generally involve the use of both live vocal and instrumental music, as well as technology. Goals may include but are not limited to the reduction of pain or anxiety; increased self-expression, movement or relaxation; and the support of developmental skills. Patients are encouraged to take an active role in making music and learning how to use music as a helpful and fun tool.



Aimee Hoflander and Hunter

Pet therapy is our newest modality to help our patients' and families' psychosocial needs while battling to beat their cancer. While visiting pets have been available for many years, last year Children's Mercy hired two new employees — Hunter and Hope — who are full-time canine employees of the hospital along with their full-time handlers. These wonderful, specially trained canines spend hours five days a week helping our children by delivering comfort, cheer and day-brightening tail wags. Hunter is stationed on the Hematology/Oncology inpatient unit when at work and can be found walking the halls or lying in bed, accepting belly rubs or just providing a kind shoulder or paw to rest upon.

Pharmacy

The Pharmacy is integral to the complete care of oncology patients.

Distinct teams within the Pharmacy include decentralized pharmacists, clinical specialist pharmacists, investigational drug service, home care and outpatient operations. We have three clinical pharmacy specialists who work with Hematology/Oncology patients and assist the primary care team in optimizing patient medications based on drug interactions, disease states and organ function.

In addition, we have four pharmacists and a technician dedicated to the review of chemotherapy orders and who are responsible for the safe production and distribution of chemotherapy to all patients within Children's Mercy. These additional pharmacists, like the pharmacy specialists, are part of the interdisciplinary rounding teams caring for inpatients. They may also spend part of their day educating both inpatient and outpatient families.

Our investigational drug service works with more than 130 open drug studies for our patients, including phase I and II oncology drug studies. We have three pharmacists and a technician dedicated to providing clinical pharmacy support and research study services for all active research studies. The clinical pharmacists also provide educational materials to our nursing staff to ensure the best care is provided to our patients involved in drug trials. Our outpatient pharmacy is available to compound many prescriptions that are not commercially available and provide care to patients as they transition to home.

Our Hematology/Oncology pharmacists are dedicated to providing education to pharmacy students through clinical rotations and lectures at our local schools of pharmacy. Children's Mercy has a nationally accredited post-graduate pharmacy residency program. ●



Nutrition

Children with newly-diagnosed neuroblastoma have a complex medical picture requiring thorough assessment of their baseline nutritional status and immediate nutrition needs, as well as formulation of a careful plan for nutrition supplementation.

Forming a trusting relationship with families from the start helps dietitians move swiftly to help families and children cope with: the needs of the child despite medical complications; the stages of grief; and new social complexities with which families must cope. Neuroblastoma complicates nutritional assessment due to the typical presence of a large abdominal mass, which often compresses stomach capacity, contributing to decreased appetite and critical organ compression even before other disease symptoms manifest.

At times, tumors must be reduced with chemotherapy for several days in order to relieve burdened organ systems, allowing a child to tolerate nutritional support, such as naso-gastric tube feedings or intravenous parenteral nutritional support. These large tumors also skew assessment of a child's weight, which further complicates nutritional assessment.

At Children's Mercy, pediatric clinical nutrition specialists utilize additional tools to properly identify malnutrition, such as the Nutrition-Focused Physical Exam. This process involves a comprehensive hands-on assessment of patients, including measuring the mid-upper arm circumference to identify signs of malnutrition and nutrient deficiencies or toxicities. Children are assessed upon diagnosis, and throughout treatment.

Nutrition care plans are tailored to each family's schedule and overall needs, with the child and family functioning as integral members of the multidisciplinary team.

Chemotherapy side effects of neuroblastoma treatment can significantly limit children's ability to support themselves with food and fluids, necessitating a feeding tube.

Childhood malnutrition can have far-reaching consequences if not corrected promptly. Thus, registered dietitians are crucial members of the team. ●

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Survive & Thrive

The Survive & Thrive Program started in 2009 to offer comprehensive medical and emotional care to childhood cancer survivors who are at least two years off treatment and five years from the date of diagnosis.

The program sees, on average, 200 survivors a year. Survivors are at risk for late effects from their cancer and treatment. Late effects of treatment can be physical or emotional and typically appear in the second decade of life. The development of late effects may be influenced by the type of cancer, the treatment, age at diagnosis and genetic predisposition. An estimated 75 percent of childhood cancer survivors will develop at least one late effect at some point during their life. Late effects may be preventable or modifiable, which is why yearly lifelong follow-up is important for all survivors.

A visit to the Survive & Thrive Clinic includes a thorough physical exam, recommendations for long-term follow-up care, education on late effects of cancer treatment and how to maintain a healthy lifestyle. Included in the visit are nutritional and psychosocial assessments. As survivors reach the teenage years, preparation for transition to adult providers is incorporated into each visit. The Survive & Thrive team works with each survivor to help them learn how to advocate for their health care needs once they leave the pediatric setting.

The Survive & Thrive team has worked closely with the Midwest Cancer Alliance, University of Kansas Hospital and University of Kansas Cancer Center to develop the Survivorship Transition Clinic. The clinic sees childhood cancer survivors who are at least 18 years old and is one option survivors have when deciding where to continue their follow-up care as adults. The Survive & Thrive team works with each survivor to develop a plan for their follow-up care after they are 21 years old. The goal is to provide each survivor and the adult providers with the information needed to ensure continued follow-up care and monitoring for late effects.

Examples of late effects that may occur in survivors with a history of neuroblastoma include hearing loss, heart dysfunction, infertility and development of a second cancer. In the Survive & Thrive Clinic, survivors will be monitored for development of late effects based on the treatment they received and according to the Children's Oncology Group Long-term Follow-up Guidelines. The team will ensure any recommended testing is performed and will monitor those results. The Survive & Thrive team works closely with health

care providers in other specialties to ensure each survivor's unique health needs are met.

In addition to clinic, the Survive & Thrive team hosts a conference for young adult survivors of childhood cancer called "I Beat Cancer... Now What?" The goal of the conference is to bring together young adult survivors to connect with each other,



Joy Fulbright, MD, and Kyla Alsman, RN, BSN

learn more about specific topics related to survivorship, and reach survivors who may not be aware of their health risks.

The Survive & Thrive Program exists to meet the needs of childhood cancer survivors through clinic visits, educational and social activities. The goal is to ensure each survivor seen in the clinic is aware of their health risks, has an individualized follow-up plan, and has help with transitioning care to adult providers. ●

Research and Data Management

Research in pediatric cancer has been the driver of improving cure rates since the 1960s. Today, the Children's Oncology Group leads the effort with more than 200 member hospitals enrolling patients in more than 70 active studies.

Children's Mercy has more than 50 of these studies available for children with newly diagnosed and recurrent cancers. The availability of a treatment study or a biology study allows a family a choice to participate in finding new and better ways to treat childhood cancer.

Beginning in the late 1990s, Children's Mercy was one of the only institutions to participate in the Phase 1 study of the monoclonal antibody, ch14.18, in patients with neuroblastoma. The positive results of this study led to the opening of a groupwide Phase 3 study in 2001, and the ultimate FDA approval of the new drug. Today, we continue to have research studies open from Children's Oncology Group, the Neuroblastoma and Medulloblastoma Translational Research Consortium, industry sponsors, and even studies designed by our own investigators.

Whether it is new drugs, new testing or investigations in quality of life or survivorship, research requires multiple steps before it can be offered to our patients and families. Within the Cancer Center, seven research professionals are dedicated to opening new studies and seeing that quality data and specimens are submitted on each of our studies. Their role includes submitting research to our institutional ethics board, answering inquiries, extracting medical information from clinical records, coordinating biological specimen collection and shipping, consenting families to research, and overseeing the adherence to research plans. By working closely with physicians, advance practice nurses, and others throughout the hospital and beyond, our research program makes us highly ranked among pediatric oncology programs.

Trials currently available at or through Children's Mercy for children with cancer can be found by at: <https://www.childrensmercy.org/cancer-clinicaltrials> ●

Hematology/ Oncology/BMT Research



PUBLICATIONS AND PRESENTATIONS OF 2015

Hematology/Oncology/Bone Marrow Transplantation

Manuscripts Published in Peer-Reviewed Journals

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Kevin Ginn, MD





Erin Guest, MD

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Maxine Hetherington, MD, and Michael Silvey, DO

Division of Hematology/Oncology/ Bone Marrow Transplantation Faculty

Division Director

Gerald Woods, MD

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Shannon L. Carpenter, MD, MS

Associate Division Director, Section of Hematology; Director, Hemophilia Treatment Center; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

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Rakesh K. Goyal, MD

Associate Division Director, Section of Bone Marrow Transplantation; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Faculty

Ibrahim A. Ahmed, MD, DSc

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Keith J. August, MD, MS

Pediatric Hematology/Oncology; Program Director, Leukemia and Lymphoma Program; Interim Director, Experimental Therapeutics in Pediatric Cancer; Children's Mercy Principal Investigator, Children's Oncology Group; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Margaret A. Boyden, MD

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Katherine M. Chastain, MD

Bone and Soft Tissue Program Director; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Terrie G. Flatt, DO

Program Director, Spanish Speaking Program; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Joy M. Fulbright, MD

Program Director, Survive & Thrive Program; Program Director, Adolescents and Young Adult Program; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Kevin F. Ginn, MD

Neuro-oncologist; Program Director, Brain Tumor Program; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Erin M. Guest, MD

Program Director, Cancer Genomics Program; Director, Cancer Center Biorepository; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

J. Allyson Hays, MD

Histiocytic Disorders Program Director; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Maxine L. Hetherington, MD

Membership Chair, Children's Oncology Group; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Gary L. Jones, DO

Assistant Professor of Pediatrics, University of Missouri-Kansas City

Ram V. Kalpatthi, MD

Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Karen B. Lewing, MD

Fellowship Program Director; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Michelle Manalang, MD

Medical Director, Liver Tumor Program; Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Carla McCrave, MD

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

G. Doug Myers, MD

Cellular Therapy Program Director; Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Mohamed A. Radhi, MD

Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Melissa S. Rayburg Jefferson, MD

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Glenon Samuel, MD

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Mukta Sharma, MD, FAAP, MPH

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Michael S. Silvey, DO

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Nazia Tabassum, MBBS

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Jaszianne Tolbert, MD

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

Melanie A. Villanueva, DO

Assistant Professor of Pediatrics, University of Missouri-Kansas City School of Medicine

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Robin Ryan, MPH, CCRP	Hematology/Oncology
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Theresa Torres, APRN, FNP, CPHON	Hematology/Oncology
Amanda Trout, LCSW	Hematology/Oncology
Amanda Woelk, CCLS	Child Life
Jennifer Wulfert, RN, MSN, CPNP	Hematology/Oncology



Pablo Angulo, DO

CONTRIBUTORS

Alan Gamis, MD, MPH – Editor

Kristy Hurst – Tumor Registrar

Joy Bartholomew, MSN, RN, FNP-BC,
CPON – Co-editor

Atif Ahmed, MD – Pathology

Sahibu Habeebu, MD, PhD, FCAP -
Pathology

Jason Tobler, MD - Radiology

Lisa Peters, LMSW, LCSW – FaCT

Richard Hendrickson, MD – Surgery

Linda Cooley, MD, MBA - Cytogenetics

Erin Guest, MD – Genomics

Keith August, MD, MS – Experimental
Therapeutics

Wendy Hein, RN, MSN, CPNP – Survive &
Thrive

Mohamed Radhi, MD – Bone Marrow
Transplant

G. Doug Myers, MD – Cellular Therapy

Robin Ryan, MPH, CCRP

Olivia Scheurman, MS, RD, LD - Nutrition



2401 Gillham Road | Kansas City, MO 64108 | (816) 234-3000