Childhood Abdominal Tumors

Abdominal tumors may be painless, but they can manifest as disrupted organ function such as acute urinary obstruction, which can be painful. Abdominal masses that arise after infancy and are associated with organ dysfunction are more likely to be a malignancy. In such cases, an ultrasound examination is a useful diagnostic approach.

Two of the most common abdominal tumors in younger children are Wilms tumor and neuroblastoma.

Wilms Tumor

Wilms tumor is a solid tumor of the kidney that arises from immature kidney cells. Wilms tumor is the fourth most common type of cancer in children, representing 5% to 6% (or 500 cases) of childhood cancers diagnosed each year in the United States. The average age at diagnosis is 3 years, and girls and boys are equally affected.

Patients with Wilms tumor typically do not present with any obvious illness, but they can have a combination of the following conditions: hypertension, genitourinary anomalies, macrosomia, aniridia, hematuria, and von Willebrand disease. Pathologic findings in about 95% of cases are favorable, but in about 5%, the tumors are anaplastic and more difficult to treat.

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Patient Care

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a genetic predisposition to Wilms tumor, which can manifest as a specific congenital abnormality such as WAGR (Wilms tumor, aniridia, genitourinary malformations, and retardation), Beckwith-Wiedemann syndrome (macroglossia, omphalocele, genitourinary malformations, exophthalmos, gigantism), Sotos-cerebral gigantism (large head and brain; delayed motor, cognitive, and social development), or Denys-Drash syndrome (congenital nephropathy and gonadal dysgenesis [e.g., pseudohermaphroditism]).

Treatment for Wilms tumor includes surgical resection of the mass and subsequent chemotherapy. In cases of advanced disease, radiation therapy also may be used. Current studies at St. Jude are investigating several new strategies for improving treatment and long-term outcome for patients with Wilms tumor. These include:

• Limiting therapy and its associated side effects for patients at low risk of tumor recurrence and increasing therapy for patients at high risk of recurrence.
• Testing the activity of new drugs (e.g., topotecan) and drug combinations to treat relapsed Wilms tumor.
• Identifying tumors that are more likely to be resistant to therapy.
• Investigating potential occupational or environmental factors that contribute to the development of Wilms tumor.

Neuroblastoma

Neuroblastoma arises from neural crest cells and can occur anywhere along the sympathetic chain or in the adrenal medulla; however, 65% of tumors occur in the abdomen. Neuroblastoma is the most common malignancy in infants and the most common extracranial solid tumor of childhood. Each year, 1 in 100,000 children is diagnosed with neuroblastoma, and most are diagnosed by 2 years of age. Thus, neuroblastoma should be suspected in infants and younger children with abdominal masses; the median age of diagnosis in boys is around 36 months, and that in girls is approximately 43 months.

Neuroblastoma should be suspected if the patient appears to be ill. Patients with neuroblastoma often present with weight loss and fever and sometimes with a combination of the following symptoms: hypertension, ophthalmologic symptoms (e.g., proptosis), skin lesions, bone pain or aberrant gait, the neurologic syndrome of opsoclonus/myoclonus, and Horner syndrome. No classic genetic basis for neuroblastoma has been identified; however, this cancer is occasionally seen in children with neurofibromatosis, Beckwith-Wiedemann syndrome, or nesidioblastosis (hyperinsulinemic hypoglycemia).

Patient age, tumor stage, and certain biologic characteristics of the tumor are used to categorize the disease as low-, intermediate-, or high-risk. Surgical excision can be curative, but in cases in which the tumor has metastasized, chemotherapy (sometimes in combination with radiation therapy) is the mainstay of treatment. Current studies at St. Jude are investigating strategies for improving treatment and long-term outcome for patients with neuroblastoma. These include:

• Developing experimental chemotherapy for patients with newly diagnosed, high-risk disease.
• Testing a new anti-neuroblastoma antibody that is currently under production at St. Jude and is designed to destroy residual microscopic disease.
• Identifying new ways to detect tumor cells in the bone marrow.
• Evaluations of the effectiveness of new receptor inhibitors that impair tumor cell growth or cause cells to differentiate are in early clinical trials for patients whose disease either did not respond to standard therapy or recurred after conventional therapy.

Other Abdominal Masses

More uncommon forms of abdominal masses can also occur in children. These include renal tumors such as clear cell sarcoma of the kidney, rhabdoid tumor, congenital mesoblastic nephroma, renal medullary carcinoma, and renal cell carcinoma. They also include germ cell tumors, many types of sarcomas, and liver tumors such as hepatoblastoma and hepatocellular carcinoma. St. Jude has several studies that address these other abdominal tumors:

• Optimizing the treatment for germ cell tumors so that patients with low-risk disease receive less intense therapy, and those with high-risk disease receive intensified therapy.
• Using new chemotherapy agents for patients with rhabdomyosarcoma.
• Studying the effects of radiation therapy for sarcomas on normal tissues.
• Testing new chemotherapy agents and a combination of agents in patients whose disease has recurred.

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www.stjude.org/pediatric-rounds

St. Jude Physician
Referral Line
1-866-2ST-JUDE
(1-866-278-5833)
St. Jude Clinical Trial Protocols

Below is a subset of clinical research protocols currently conducted at St. Jude. To find out more about the objectives of the studies below and their eligibility criteria, visit www.stjude.org/protocols; send an e-mail message to protocolinfo@stjude.org; or call the toll-free Physician Referral Line, 1-888-226-4343.

Total XVI: A total therapy study using treatments based on very specific scientific details of patient disease.
- Eligibility: Patients with newly diagnosed non-B-cell acute lymphoblastic leukemia (ALL).
- Principal Investigator: Sima Jeha, MD

MEL06: A Phase II study incorporating pegylated interferon in the treatment for children with high-risk melanoma.
- Eligibility: Patients with a confirmed diagnosis of cutaneous (skin) melanoma.
- Principal Investigator: Fariba Navid, MD

HOD05: Stanford V chemotherapy with low-dose, tailored-field radiation therapy for pediatric patients with intermediate-risk Hodgkin disease.
- Eligibility: Patients with an untreated confirmed diagnosis of Hodgkin disease.
- Principal Investigator: Monika Metzger, MD

RET5: Study and treatment of patients with intraocular retinoblastoma.
- Eligibility: Pediatric patients with either newly diagnosed, untreated intraocular retinoblastoma or retinoblastoma that has been previously treated with surgery or focal therapies, with development of involvement of the other eye.
- Principal Investigator: Carlos Rodriguez-Galindo, MD

SJYC07: Risk-adapted Therapy for Children Less than 3 with Embryonal Brain Tumors, Choroid Plexus Carcinoma or Ependymoma.
- Eligibility: Patients under 3 with newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), atypical teratoid/rhabdoid tumor (ATRT), choroid plexus carcinoma (CPC) or ependymoma.
- Principal Investigator: Robert Sanders, MD

SJBG07: A Phase I trial of Vandetanib administered concurrently with local radiation therapy.
- Eligibility: Pediatric patients with newly diagnosed diffuse brainstem glioma.
- Principal Investigator: Alberto Broniscer, MD

St. Jude Researchers Discover Factors That Cause Imatinib (Gleevec™) Resistance

The targeted chemotherapy drug imatinib (Gleevec™) has revolutionized the treatment of chronic myelogenous leukemia (CML). Newer tyrosine kinase inhibitors are being developed with the aim of overcoming resistance to imatinib. St. Jude’s frontline acute lymphoblastic leukemia (ALL) protocol, Total 16, now incorporates dasatinib (SPRYCEL®) in the treatment of patients with Ph+ ALL. However, even the newer generation of tyrosine kinase inhibitors are often unable to prevent the relapse of this particularly aggressive form of ALL. This form of ALL and CML share the same critical mutation, the Philadelphia chromosome (Ph), which was the first chromosome abnormality associated with a specific kind of cancer. Ph+ ALL occurs in only 4% of childhood cases, and its presence indicates that the patient will most likely experience a poor outcome. Cells that have this mutation (Ph+ cells) produce the growth-promoting enzyme BCR-ABL.

A St. Jude team headed by Charles Sherr, MD, PhD, a Howard Hughes Medical Institute investigator and co-chair of the Department of Genetics and Tumor Cell Biology, has shown that CML and Ph+ ALL differ in one crucial aspect—many Ph+ ALL cells lack the tumor-suppressor gene Arf, which is normally present in CML cells at the time the disease is first diagnosed. Stripped of the antitumor effects of Arf and nurtured by growth factors produced in the bone marrow, Ph+ ALL cells become less responsive to imatinib and more difficult to eliminate. Sherr reasoned that the cells’ survival advantage increases their opportunity to develop mutations in BCR-ABL, and these mutations prompt imatinib resistance.

According to another team member, Richard Williams, MD, PhD (Oncology), these findings not only suggest why Ph+ ALL is often insensitive to imatinib, but they also suggest that the development of drugs that also block the ability of other factors in the bone marrow to sustain the leukemic cells should render them more susceptible to imatinib and improve the outcome of ALL patients who are resistant to current forms of therapy.

“The development of drugs that also block the ability of other factors in the bone marrow to sustain the leukemic cells should render them more susceptible to imatinib and improve the outcome of ALL patients who are resistant to current forms of therapy.” –Richard Williams, MD, PhD

Therapeutic Trends
man neurodegenerative disorders such as Alzheimer disease can occur when differentiated neurons try to multiply, but in that disease, neuronal proliferation triggers apoptosis.

The discovery that fully differentiated horizontal cells multiply to form retinoblastoma also challenges the established belief that cancer cells are most aggressive when they are undifferentiated. For example, chronic myelogenous leukemia is considered a less severe form of the disease when the leukemic cells are differentiated; the disease becomes aggressive when the tumor cells undergo genetic mutations that block differentiation. When members of the Rb gene family are inactivated in the retina, horizontal neurons that are already differentiated and fully integrated into the brain can start multiplying rapidly and produce a very aggressive cancer.

During microscopic and biochemical studies to prove that the multiplying retinoblastoma cells were horizontal interneurons, Dyer’s group showed that as the horizontal interneuron population expanded as much as 50 fold, the cells maintained their normal position in the retina and their normal synaptic connections to the other retinal cells. When horizontal cells were allowed to divide unchecked, highly differentiated tumors formed, and their comprising cells resembled normal horizontal neurons. Unexpectedly, the tumors were aggressive and spread rapidly. The investigators concluded that the function of the Rb family of genes is to prevent mature horizontal interneurons from multiplying and giving rise to retinoblastoma.

According to Dyer, the findings from this study suggest that by altering the activity of certain genes in fully developed neurons, those cells could be triggered to multiply temporarily and replace neighboring neurons that have been lost as a result of injury or neurodegenerative diseases. “Having nerves duplicate themselves might be more efficient than trying to stimulate nerve replacement by inserting stem cells into the brain, since the existing nerves would already be in the right place to restore missing brain cells,” said Dyer. “However, there is still a lot of research required to determine if it is possible to control gene activity to make this approach practical.”

This image shows two horizontal neurons that were derived from a single neuron by modulating the Rb family of tumor suppressor genes. This is the first time that researchers have shown that a mature neuron can multiply while remaining integrated in the neural network. These data suggest that in some parts of the nervous system, stem cells will not be required to regenerate neurons lost to injury or degeneration.

Gleevec™ cont. from p. 3

gest that patients who are at high risk of experiencing treatment failure may be identified by whether their leukemic cells lack the Arf gene. “The development of drugs that also block the ability of other factors in the bone marrow to sustain the leukemic cells should render them more susceptible to imatinib and improve the outcome of ALL patients who are resistant to current forms of therapy,” said Williams.

Results from this study strongly suggest that a widely held explanation for how leukemias arise is not universally applicable. “This view holds that leukemias arise from rare ‘cancer stem cells,’ which do not make up the bulk of the tumor but are the only cells required to regenerate the cancer after treatment,” Williams said. “However, the new St. Jude study reveals that the combination of BCR-ABL activity and inactivation of Arf are sufficient to generate a uniform population of leukemia-initiating cells, any one of which can expand and induce rapidly fatal disease. Rather than comprising only a rare minority of cancer stem cells, each of these ALL cells is able to trigger and propagate the disease, so an effective therapy has to prevent the multiplication of each and every one of them.”

Targeted chemotherapy is designed to block the activity of a specific molecule, a strategy that aims to make anticancer treatments more effective and less toxic. The findings from this study may shed new light on why a small percentage of children with ALL do not benefit from current treatments. The discovery could also help researchers better understand the origins of Ph+ ALL and why it becomes resistant to imatinib. Ultimately, this knowledge may lead to more effective treatments for patients whose disease does not respond to current therapies.
St. Jude scientists have found key features that distinguish influenza viruses that infect birds from those that infect humans. The team, which includes Clayton Naeve, PhD, Suraj Mukatira, PhD, Perdeep Mehta, PhD, John Obenauer, PhD, Xiaoping Su, PhD and David Finkelstein, PhD, from the Hartwell Center for Bioinformatics & Biotechnology and Robert Webster, PhD, from the Department of Infectious Diseases, computationally surveyed the sequence of amino acids in 10,671 proteins from avian influenza viruses and 13,757 proteins from human influenza viruses. Their analysis identified 32 amino acids located in the sequences of five virus proteins: PA, NP, M1, NS1, and PB2. These residues were more likely to differ in avian influenza virus proteins compared to human influenza virus proteins. Many of these markers appear in regions where host protein and viral replication occur. Once an avian influenza becomes transmissible in humans, the amino acids in the virus proteins mutate through multiple infections and eventually are indistinguishable from other human influenza viruses. Therefore, these 32 amino acids can be used to track changes in H5N1 avian influenza strains that threaten humans. “Influenza mutates rapidly, so that any marker that is not the same in bird flu but remains stable in human flu is likely to be important. If human-specific markers start accumulating in bird flu viruses that infect humans, that suggests that the bird flu may be adapting to humans and could spread.”

—David Finkelstein, PhD

“Key Differences Between Avian and Human Viruses Lead to Answers About Pandemic Possibilities

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Although the researchers have not determined what function the markers have, they did examine the influenza viruses that caused pandemics in 1918, 1957, and 1968 to determine whether the markers were present in those strains. The study focused on viruses isolated from humans during the early phase of each pandemic to determine which markers the viruses had acquired just before they sparked the outbreak. Thirteen of the 32 identified markers remained stable in these viruses, and, like the other viruses, these markers were distributed among the proteins linked to virus replication. This finding suggests that these 13 sites are required for pandemic influenza to fully function. The H1N1 virus that caused the 1918 pandemic—the most deadly pandemic known—already contained 13 of the 32 human influenza markers early in the outbreak and acquired the other 19 markers within 10 to 20 years. Clayton Naeve conveyed that, “While we can’t directly estimate how long it would take an avian virus such as H5N1 to acquire these traits, we can use these markers to roughly measure the distance between an avian influenza and a pandemic.”

Recent St. Jude Publications of Interest

St. Jude Continuing Education Series

Save the Date!

Scientific Advances in Pediatrics (combined with the Etteldorf Symposium)

Date:
April 18–19, 2008 (Fri.–Sat.)

Location:
Le Bonheur Children’s Medical Center, Memphis, TN

Program purpose:
This conference is designed for pediatricians, hematologist-oncologists, nurse practitioners, nurses and other health care professionals, interested in updating their knowledge about treatment guidelines for children with catastrophic diseases.

Topics that will be presented and much more:
- Cystic Fibrosis
- Legal Issues in Medicine
- Migraines
- Nuclear Medicine
- Updates in Solid Tumors

Presentations you don’t want to miss!
- Role of Race in Obesity and Related Complications in Adolescents
  Pedro Velasquez, MD
  University of Tennessee Health Science Center
- Sickle Cell Disease Associated with Lung Disease
  Robert C. Strunk, MD
  Donald Strominger Professor of Pediatrics
  Washington School of Medicine

Visit www.cure4kids.org/cme/27 for registration information

The Cure4Kids clinical education Web site at St. Jude is continually adding new material to its seminar archives. Go to www.cure4kids.org and log in to take advantage of the numerous educational features and the digital library, as well as live conference rooms, working groups, and other networking features.

Pediatric Renal Tumors, Pamela A. Gaillard, RN, MSN, PNP
Total XVI Protocol, Mary V. Relling, PharmD
Total XVI: Building on the successes of Total XV, Sima Jeha, MD, Dario Campana, MD, PhD, and Sue C. Kaste, DO
Pulmonary Embolism in Children, Frederico Xavier, MD, and Ulrike Reiss, MD
Familial Cancers: To Test or Not To Test, Kelly Vallance, MD, MPH, and Eniko Pivnick, MD
Pediatric Renal Tumors, Pamela A. Gaillard, RN, MSN, PNP
NOTCH1: Oncogene and Achilles’ Heel in T-ALL, Adolfo A. Ferrando, MD, PhD

Save the Date!

The Tennessee Comprehensive Cancer Control Coalition Presents the 4th Annual Summit on the Burden of Cancer in Tennessee

Date:
May 15–16, 2008 (Thur.–Fri.)

Location:
St. Jude Children’s Research Hospital

Program purpose:
The program is designed for clinical care providers, researchers, public health professionals, health educators, advocates, community-based organizations, policy makers, the business community, and members of federal, state, and local government. It will increase public awareness of the cancer burden in Tennessee and of identified strategies for addressing those burdens.

Additional information:
For additional information on these three conferences, contact Linda P. Taylor, MBA, Conference Coordinator, phone: (901) 495-2235, e-mail: lindap.taylor@stjude.org

Save the Date!

Pediatric Surgical Oncology Review Course for Fellows

Date:
March 1–2, 2008 (Sat.–Sun.)

Location:
St. Jude Children’s Research Hospital

Program purpose:
The conference is designed for general pediatric surgical fellows. The course will provide basic information to reinforce the knowledge base obtained during a general pediatric surgery fellowship.

Visit www.cure4kids.org/cme/26 for registration information
Referrals, Consultations, and Treatment Policy

Referrals
St. Jude Children’s Research Hospital welcomes referrals of children and adolescents with newly diagnosed, untreated or suspected cancer; HIV infections; or certain hematologic, immunologic, or genetic diseases. Patients are accepted based on the eligibility to enroll in an open St. Jude clinical research protocol.

Patients with certain genetic disorders, hematologic, immunologic diseases or HIV infection may be accepted anytime in their disease history based on protocol eligibility or potential to contribute to research projects. Other patients who have received treatment elsewhere may be considered on an individual basis, if they are eligible for a St. Jude clinical trial. Patients are enrolled on clinical trials designed to provide the best available care while answering important research questions.

All children accepted for treatment at St. Jude are treated without regard to the family’s ability to pay. The American Lebanese Syrian Associated Charities (ALSAC, the fund-raising organization that supports St. Jude) cover all costs of therapy, signs of recurring disease, or other questions related to the care of patients on St. Jude clinical trials and survivors.

Consultations
St. Jude provides free formal consultations to treating physicians about difficult diagnostic or medical management questions. For a formal consultation, the physician should send complete medical information, such as detailed medical history, copies of relevant diagnostic imaging evaluations, and pathology/histological material. The hospital’s multidisciplinary groups will discuss the case and offer recommendations. St. Jude does not bring patients to Memphis for consultations unless they are likely to be eligible for a St. Jude protocol.

Physician Referral Line
Phone: 1-866-2ST-JUDE (1-866-278-5833), fax: 901-495-4011, e-mail: referralinfo@stjude.org, Web: www.stjude.org/referringmds

Kids With Cancer Are a Flourishing Population
Children undergoing treatment for cancer are generally emotionally well adjusted and no more depressed or anxious than other children their age, according to a St. Jude study led by Sean Phipps, PhD, from the Division of Behavioral Medicine. In studies of depression, anxiety, posttraumatic stress, and quality of life, children with cancer do as well as—and often better than—their healthy peers. This unexpected finding that children with cancer are emotionally resilient is important, because the probability of survival of pediatric cancers has dramatically improved in recent years. According to Phipps, research has shifted toward the concerns of long-term survivors of pediatric cancers. “The ability of these children to cope with the after-effects of cancer is the major issue now. What we are learning from this population might help us learn how to improve the quality of life of children who are not doing so well.”

One explanation for these children’s successful adaptation to cancer and its treatment might be the good care, nurturing, and love the children receive. In addition, these children are not confronted with tests in school, bullies, or other common stresses their peers face. Phipps’ team examined self-reported somatic symptoms (e.g., weight loss, sleep disorders, and fatigue) of 120 children with cancer who had finished medical treatment at least 6 months previously. The team found no differences in these symptoms between children with cancer and healthy controls. In fact, pediatric patients with cancer reported slightly lower symptom levels.

Phipps and his colleagues are also studying several other areas in the growing field of positive psychology such as optimism, benefit-finding, emotional growth following a traumatic experience (e.g., cancer), and the concept that people facing adversity might benefit and become stronger in many ways because of that experience.
A previously healthy 10 y/o male was evaluated by his physician because of progressive fatigue of about 4 weeks duration. Both his academic school performance and athletic performance on the soccer field had become affected. Approximately 6 weeks previously, the patient had a URI with a low grade fever, headache and sore throat. These symptoms resolved without therapy.

On the physical exam, the boy appeared pale, had mild tachycardia and had enlarged firm non-tender lymph nodes in the anterior cervical chain. The spleen and liver was not enlarged.

The CBC showed Hgb=8, WBC=2,500 with 50% neutrophils, 10% monocytes, 40% lymphocytes, and platelet=100,000 (See figure).

Question: Is the round cell 1) the cause of the illness, 2) an innocent bystander or 3) an activated cell?

—Stephen Smith, MD