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### Patient Care

#### Safeguarding the Future: Quality of Life for Survivors

Children who remain in complete remission for 5 years are no longer cancer patients but survivors. Thanks to decades of research, the survivor population is increasing.

However, as survivors age, their longevity and quality of life are threatened by the delayed effects of cancer and its treatment. Late effects are experienced by two thirds of survivors and are severe or life threatening in 25%. Although they may appear well, survivors require lifelong, vigilant monitoring.

Monitoring begins in the St. Jude After Completion of Therapy (ACT) Clinic, which follows patients who have been in remission for 5 years and completed therapy at least 2 years previously. The clinic monitors survivors' health and well being, educates them about their special risks, refers them for specialty care, and

conducts research to identify long-term sequelae, improve frontline therapy, and enhance survivors' quality of life. "What we learn from these survivors will be considered in the design of new cancer treatment protocols," explains Dr. Melissa Hudson, director of the ACT Clinic. The clinic is staffed by Hudson (a pediatric oncologist), a full-time pediatrician, a full-time medical social worker, 6 nurse practitioners, and 12 research and administrative staff members.

cont., p. 2



Dr. Melissa M. Hudson  
Director, After Completion  
of Therapy Clinic

### Translational Research

#### Brain Tumors: Translating Laboratory Discoveries into Novel Therapies in the Clinic

Pediatric brain tumors—a diverse group of tumors defined by histologic diagnosis—are generally associated with a worse prognosis than many other common pediatric cancers, and children who survive brain tumors commonly experience serious treatment-induced adverse effects. Avoidance or reduction of these effects while maintaining or improving disease control requires the identification of new, less toxic therapies. At St. Jude, we are developing new approaches to the diagnosis and treatment of brain tumors through translational research conducted as part of our comprehensive Neurobiology & Brain Tumor Program. The program allows clinicians to apply cutting-edge therapies in current protocols while promoting a broad approach to the management of brain tumors.

The most common malignant tumor in the pediatric age group is medulloblastoma. Although survival rates for children with this tumor have increased over the past 3 decades, long-term side effects resulting from treatment for medulloblastoma remain problematic. These side effects include neuroendocrine dysfunction, intellectual deterioration, and neuropsychological

cont., p. 4

Dr. Amar J. Gajjar  
Chief, Division of  
Neuro-Oncology



### Quality of Life cont. from p. 1

Subspecialty consultations are available as well. Survivors visit the clinic annually until 10 years after diagnosis or age 18, whichever comes later. The clinic sees approximately 1500 survivors annually and provides services for another 2500 who require continued medical or psychosocial assistance.

As survivors make the transition from pediatric oncology care to pediatric and then adult community-based primary care, they remain at risk of a multitude of late adverse effects. These risks may not be clinically evident, cautions Hudson. “Some cancer-related complications do not become apparent until many years after treatment.” Community physicians, who may see only a few survivors, need specific information. The ACT Clinic emphasizes the importance of a local primary care provider to survivors and gives each survivor a clinical summary for the clinician’s reference. The summary details the survivor’s diagnosis and staging, therapy, cumulative drug and radiation exposure, transfusion history, serology results, significant clinical events, family history, special concerns about late effects, and screening recommendations. Upon discharge from follow-up in the ACT Clinic, new “alumni”

**“Some cancer-related complications do not become apparent until many years after treatment.”**

**Melissa Hudson, MD**

are given a personal health record that contains their clinical summary and key sections of their St. Jude medical record. “We hope that by providing information about the survivor’s history and health risks, the ACT clinical summary and the personal health record will help to ensure the best future care,” says Hudson.

Many survivors have no chronic health problems on completion of their cancer therapy, but health risks will follow them into adulthood and will increase with age. “Beyond the history and physical exam, asymptomatic, well-appearing survivors should be screened,” recommends Hudson, “on the basis of their specific treatment exposure and clinical characteristics.” The Children’s Oncology Group offers screening guidelines at [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).

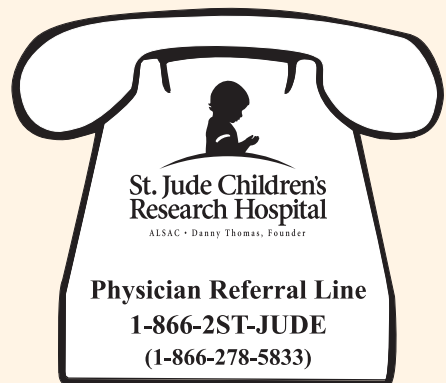
There are four broad categories of late effects: growth and development, vital organ function, fertility and reproduction, and secondary oncogenesis. Younger patients are at greater risk of growth and development problems,

whereas compromise of vital organs may cause problems only after growth or aging. Fertility is an important concern of young adult survivors. And survivors remain at increased risk of a second cancer. Hudson recommends that survivors have a personalized, systematic plan for lifelong screening, surveillance, and prevention based on their specific cancer diagnosis, therapy, genetic predisposition, health-related behaviors, and comorbid health conditions.

The ACT Clinic makes a special effort to educate survivors about their health risks and lifestyle choices. “Education is a fundamental component of our program,” says Hudson. “Survivors need accurate information about their diagnosis, treatment, cancer-related health risks, and how their behavior affects those risks.” The annual Survivors’ Conference at St. Jude is both an educational opportunity and a reunion. Physicians in survivors’ home communities can play an influential role in reinforcing sur-  
**cont., p. 3**

### Recent St. Jude Publications of Interest

- Holleman A, Cheok MH, den Boer ML, et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N Engl J Med* 2004;351:533–542.
- Merchant TE, Mulhern RK, Krasin MJ, et al. Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. *J Clin Oncol* 2004;22:3156–3162.
- Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol* 2004;5:399–408.
- Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 2004;54:208–236.
- Stewart CF, Iacono LC, Chintagumpala M, et al. Results of a phase II upfront window of pharmacokinetically guided topotecan in high-risk medulloblastoma and supratentorial primitive neuroectodermal tumor. *J Clin Oncol* 2004;22:3357–3365.



## St. Jude Clinical Trial Protocols

Below is a subset of the brain tumor protocols and clinical studies conducted at St. Jude. To find out more about the objectives of these studies and their eligibility criteria, call the Principal Investigator at the number shown or e-mail [braintumors@stjude.org](mailto:braintumors@stjude.org).

**SJMB03:** A clinical study to increase our understanding of the biology of medulloblastoma, to reduce the volume of high-dose radiation within the posterior fossa, and to test a neurocognitive intervention program to ameliorate the decline in intellectual function associated with radiation therapy

- Eligibility: Patients with **medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), or atypical teratoid rhabdoid tumor (ATRT)**; age 3 through 21 years; recent surgery; no previous radiation or chemotherapy
- Principal Investigator: Amar Gajjar, MD  
Phone: (901) 495-4599 or 495-2544

**PBTC001:** A pilot study of systemic and intrathecal chemotherapy followed by local irradiation for infants with embryonal CNS tumors

- Eligibility: Patients < 3 years old with **medulloblastoma, PNET, pineoblastoma, ATRT, intracranial germ cell**

**tumor, choroid plexus carcinoma, or metastatic ependymoma**; recent surgery; no previous radiation or chemotherapy (except corticosteroids)

- St. Jude Principal Investigator: Amar Gajjar, MD  
Phone: (901) 495-4599 or 495-2544

**PBTC014:** A phase I/II trial of the oral chemotherapy agent zarnestra (R115777) and radiation therapy in pediatric patients with newly diagnosed intrinsic diffuse brainstem glioma

- Eligibility: Patients with newly diagnosed **brainstem glioma**; age < 21 years
- St. Jude Principal Investigator: Alberto Broniscer, MD  
Phone: (901) 495-4925 or 495-4599

**PBTC016:** A phase I molecular biology study and phase II study of lapatinib (GW572016) in pediatric patients with recurrent or refractory medulloblastoma, malignant glioma, or ependymoma

- Eligibility: Patients with recurrent or refractory **medulloblastoma or PNET, high-grade glioma, or ependymoma**; age < 21 years
- St. Jude Principal Investigator: Maryam Fouladi, MD  
Phone: (901) 495-2094 or 495-2573

## Patient Care

### Quality of Life cont. from p. 2

vivors' awareness of their health needs. Information written specifically for survivors can be printed or downloaded from [survivorshipguidelines.org](http://survivorshipguidelines.org).

St. Jude's large patient base provides a unique opportunity for survivorship research. The ACT Clinic participates in protocol-driven clinical studies conducted by 13 investigators in the St. Jude Cancer Prevention & Control Program. Topics under study include assessment and treatment of attentional deficits in survivors of brain tumors; the interaction between organ senescence and treatment toxicity; factors that predispose patients to adverse health outcomes, including impaired quality of life; interventions designed to alter risk-related behaviors; factors related to skeletal complications; and patient and family adjustment.

Despite survivors' need for vigilant, lifelong medical attention, there are numerous obstacles to optimal care. "The risk factors are constantly evolving," says Hudson. The long latency of sequelae, the interaction of multiple factors, and the unknown effects of aging complicate the picture. Because cancer-related health risks can be difficult to identify and interpret, physicians who care for St. Jude survivors are welcome to call for consultation about possible disease recurrence, management of late effects, screening guidelines, or other issues related to the patient's cancer history.

### Developmental sequelae of childhood cancer

Specific late effects depend on the therapies received, and not all are age-related. However, certain sequelae are related to development.

#### • Infants/Children

Skeletal growth and development  
Cognitive function  
Vital organ development

#### • Adolescents/Young adults

Health-compromising behaviors (tanning, smoking)  
Academic/vocational issues  
Sexual/reproductive problems (intimacy, sexuality, fertility, adverse pregnancy outcomes)  
Emotional/social maturation

#### • Older adults

Premature ovarian failure      Osteoporosis  
Obesity      Hyperinsulinism  
Diabetes

Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers are available from [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).

**Brain Tumors** cont. from p. 1

difficulties. We have therefore chosen medulloblastoma and related tumors as the primary research focus of our brain tumor program.

Treatment for medulloblastoma involves a combination of surgical resection, irradiation of the craniospinal axis, and chemotherapy. In a recently concluded study (SJMB96) we used a novel treatment strategy: rather than giving chemotherapy for 1 year (the current standard in cooperative group trials), we gave our patients a short, dose-intense chemotherapeutic regimen after completion of radiation therapy. Estimated rates of event-free survival were excellent for both the average- and high-risk patients (81% and 74%, respectively, at 4 years), and, importantly, no patients had veno-occlusive disease (an adverse effect often associated with high-dose chemotherapy) or died from excessive toxicity. Additionally, we found that the chemotherapeutic regimen can be modified to eliminate etoposide (a drug associated with a high rate of secondary AML) and to reduce the total doses of cisplatin (which is particularly ototoxic) and vincristine (which is associated with

much neurotoxicity in patients who have undergone neurosurgical resection).

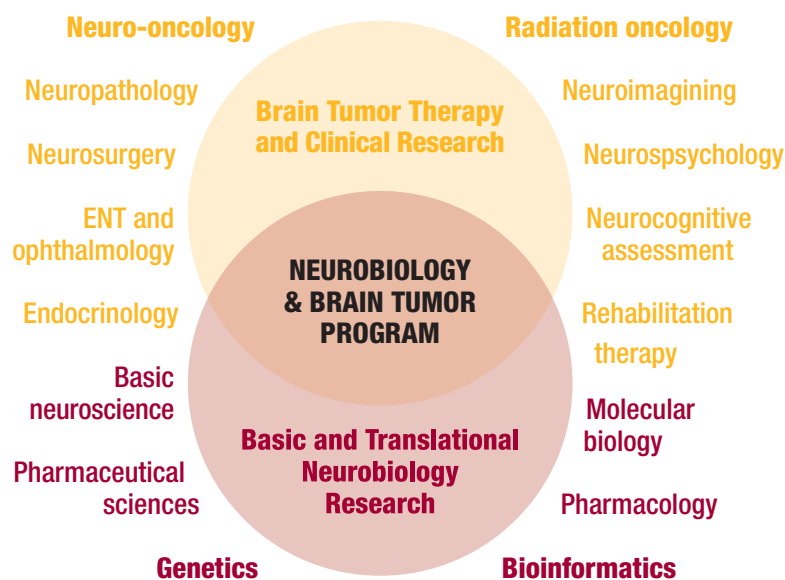
Despite these improvements in the chemotherapeutic component of the treatment, however, children who survive medulloblastoma show a decline in intellectual function (as assessed by IQ tests and tests of academic achievement) as a result of the radiation therapy they receive. This neurocognitive decline is particularly severe in young patients (< 8 years) and in patients who receive a high dose of craniospinal radiation therapy. We therefore designed a new protocol, SJMB03, with the following aims:

- (1) to increase our understanding of the biology of medulloblastoma with a view to integrating the results of biological and clinical studies;
- (2) to reduce morbidity during and after treatment, by reducing the volume of high-dose radiation to the posterior fossa and further modifying the chemotherapeutic regimen; and
- (3) to seek to reduce the impact of radiation therapy on the decline in intellectual function, by introduc-

ing a neurocognitive intervention program.

Studies of the biology of medulloblastoma have suggested that medulloblastoma forms as a result of the aberrant activation of several cell-signaling pathways, possibly the WNT (“wingless”) and SHH (“sonic hedgehog”) pathways, the ERBB pathway (by which receptor tyrosine kinases regulate cell proliferation, apoptosis, migration, and differentiation), and the PDGF pathway (by which platelet-derived growth factor promotes cell migration, survival, and proliferation). Investigation of these pathways may lead to the development of treatments based on signal-pathway inhibitors. In addition, these studies may identify new risk-stratification factors that will allow us to distinguish patients who can safely be given the highest dose of radiation from those who need to be treated more conservatively. One factor that may serve as a prognostic marker for medulloblastoma is ERBB2. Overexpression of *ERBB2*—a potent oncogene in cell culture and transgenic models of cancer—is associated with a poor clinical outcome in several human malignancies. And in a multicenter study led by St. Jude researchers, only 54% of children with average-risk disease and ERBB2-positive tumors survived 5 years, whereas all children who had average-risk, ERBB2-negative disease were alive 5 years after treatment. Various ERBB2 inhibitors (e.g., Erlotinib, also known as gefitinib) are under development as possible treatments for ERBB2-positive tumors. The availability of tumor samples from patients enrolled on the SJMB03 study will enable us to expand our studies of medulloblastoma and to identify new genetic lesions implicated in its pathogenesis.

Another area of focus of the Neurobiology & Brain Tumor Program is the development of techniques to allow the



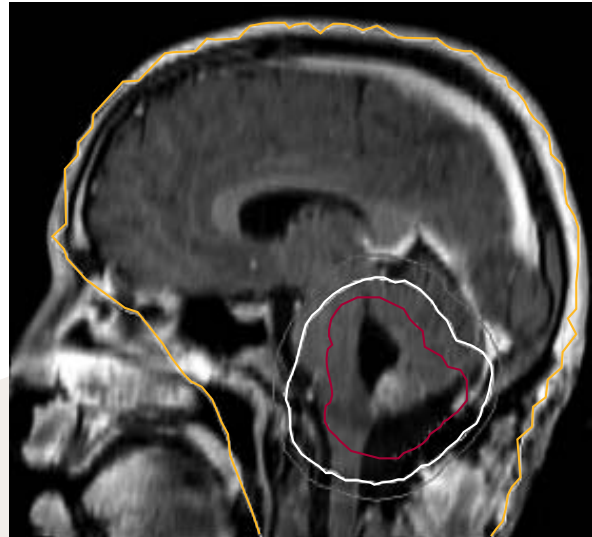
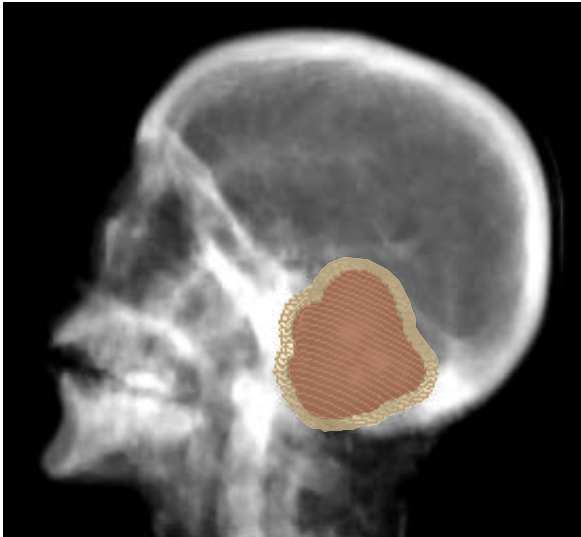
A crucial interplay between neuro-oncologists and radiation oncologists leads the coordinated efforts of a large, multidisciplinary clinical team in the management of brain tumors. Basic neurobiology research conducted as part of the Neurobiology & Brain Tumor Program at St. Jude is underpinned by an emphasis on genetics and bioinformatics and is driven by the findings of the program’s clinical research.

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### Brain Tumors cont. from p. 4

precise delivery of radiation to a tumor without damage to the surrounding normal brain. In a prospective study of the effect of highly conformal, localized irradiation of childhood ependymoma (RT1 protocol; now closed), we achieved high rates of disease control without compromising neurocognitive outcomes by using limited-volume irradiation. We will use this

finding to optimize radiation therapy for other CNS tumors, and we will design clinical trials to test the effectiveness of cognitive and behavioral—as well as pharmaceutical—interventions that may allow us to minimize radiation dose and thereby limit neurocognitive sequelae in children who survive brain tumors.



Use of highly conformal, localized irradiation allows delivery of an optimal therapeutic dose of radiation to the tumor while sparing the surrounding, normal brain tissue. Shown are images used to plan radiation therapy for patients with average-risk medulloblastoma treated on St. Jude protocol SJMB03. A lateral, digitally reconstructed radiograph (left) shows the clinical target volume (the tumor; red solid) and planning target volume (the volume to which radiation will be targeted; yellow overlay). Superimposed on a lateral, gadolinium-enhanced T1-weighted MR image (right) are isodose curves representing the outer boundaries of specified doses of radiation. The clinical target volume is bounded by the innermost, red curve. The white curve delineates the total radiation dose delivered to the primary tumor site (55.8 Gy); the outermost, yellow curve the craniospinal dose (23.4 Gy).

## St. Jude Continuing Education Series

### Bioimaging Symposium 2004

**Date:** Friday, November 5, 2004

**Location:** St. Jude Children's Research Hospital,  
St. Jude Auditorium

**Registration Fees:** \$175 (Students \$20). After October 31,  
\$250 (Students \$30)

**Program Purpose:** During this one-day conference, a panel of world experts will lead a discussion of the clinical impact of imaging technologies. A poster session open to all participants will promulgate recent research findings or work in progress. Designed for biomedical scientists, engineers, researchers, clinicians, and students.

#### Distinguished Speakers:

**Ian Cunningham, PhD, FCCPM,** Imaging Research Laboratories, Robarts Research Institute

**Gary Glover, PhD,** Director, Radiological Sciences Lab, Stanford University

**Ferenc Jolesz, MD,** Harvard University Medical School, Director, Neuroimaging Core, Center for Neurodegeneration and Repair, Professor of Radiology

**King Cheun Peter Li, MD, FRCP, MBA,** National Institutes of Health, Radiology and Imaging Sciences Program

**Benjamin Tsui, PhD,** Johns Hopkins University School of Medicine, Professor, Department of Radiology

**James Zagzebski, PhD,** University of Wisconsin School of Medicine, Chairman & Professor, Department of Medical Physics

**CME Accreditation:** A maximum of 7.25 hours of category 1 credit toward the AMA Physician's Recognition Award

**Additional Information:** Linda P. Taylor, BPS, Conference Coordinator, St. Jude Children's Research Hospital, 332 N. Lauderdale St., MS 281, Memphis, TN 38105-2794.

Phone: (901) 495-2235

E-mail: lindap.taylor@stjude.org

## Progress in Pain Management for Children

Recent decades have seen a revolution in pain management for children. St. Jude, with its large patient population, is uniquely situated to advance clinical pain management, add to current knowledge, and translate basic discoveries to clinical use.

Dr. Doralina Anghelescu, director of the St. Jude pain management service, believes that a comprehensive approach is optimal. “Because multiple factors affect pain and suffering,” she explains, “each must be addressed according to the patient’s needs.” Therefore, the pain management team is multidisciplinary, comprising 4 pediatric anesthesiologists (one board-certified in pain management), a pediatric psychologist, a clinical nurse specialist, a clinic nurse, a pharmacist, and a child life specialist.

The team operates on four principles. First, pain in children is a serious problem that requires serious evaluation and treatment. Second, children’s pain can and should be assessed. Third, drug therapy, particularly

opioids for severe pain, is the mainstay of treatment. And fourth, physical, cognitive, and behavioral therapies should be used to complement drug therapy.

“Treating pain is more than the humane thing to do,” explains Anghelescu. Pain control provides physical and mental benefits that help in the fight against cancer. Pain isn’t something that children get used to. Instead, repetitive pain can intensify a child’s response to future painful experiences. “Pain can adversely affect endocrine, metabolic, and immune function as well as increasing anxiety,” says Anghelescu. In fact, children with cancer fear needle-related procedures more than they fear their cancer.

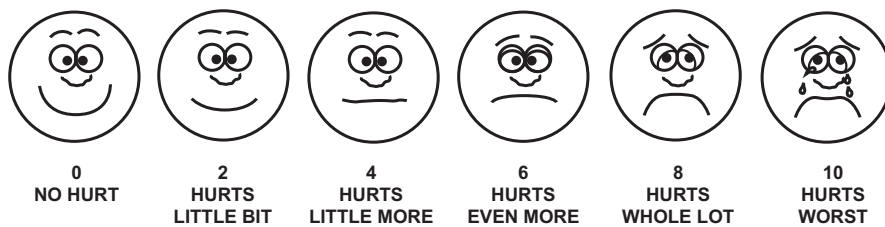
Although pain control must be individualized, St. Jude has general guide-

lines for pain management. Linda Oakes, RN, a team member, explains: “We minimize procedural pain, which is brief but can be intense and can cause anxiety in children. We avoid IM injections by using needleless systems, and we apply topical anesthetics before procedures involving needles.” St. Jude also has written guidelines for pharmacologic management of pain. However, Anghelescu notes, “It’s important to understand that pain management requires more than drugs.” Patients can be helped in many ways, including psychological intervention for unavoidable pain and related stress. Such techniques are not a substitute for drugs, but they often reduce the required dosage. Parents, child life specialists, art therapists, and social workers are important resources as well.

addiction is not a problem in treating cancer pain. “If we educate patients in the responsible care and use of their drugs and monitor them closely,” says Oakes, “there’s no problem.” Patients and their families sign a written Pain Agreement undertaking to follow the treatment plan or to share their concerns with the pain management service.

Another common concern is respiratory depression. “Physicians may be unfamiliar with the dose equivalency of different pain medications,” notes Anghelescu, “and this adds to their hesitation.” She recommends consultation with a competent pharmacist to resolve dosage questions. Opioid pharmacology is actually different in individuals who are and are not in pain, and patients with cancer pain do not appear to ex-

perience the toxic effects observed in healthy volunteers. Further, says Anghelescu, “We can’t assume that a given dosage of a given drug will address a given level of pain. If one thing doesn’t work, we try another.” At St. Jude,



The Wong-Baker FACES Pain Rating Scale is recommended for pain assessment in patients age 3 years and older. (From Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein ML, Schwartz P. *Wong's Essentials of Pediatric Nursing*, ed. 6, St. Louis, 2001, p. 1301. Copyright Mosby, Inc. Reprinted by permission.)

Accurate assessment is a major challenge of pain management in children. “Parents and caregivers can’t accurately assess a child’s pain level,” warns Oakes. “The patient is the real authority.” Fortunately, a variety of assessment tools are available. Children older than 12 years can use a numerical scale to indicate pain severity, while younger patients can choose a face on the “FACES” pain scale (see figure). For infants and toddlers, signs such as facial expression, leg position, activity, crying, and consolability can be used to estimate pain.

According to Anghelescu and Oakes, progress in pain control has required the debunking of a number of myths, such as the fear of addiction. Although physical dependence is to be expected, opioid ad-

the watchword is “titrate, titrate, titrate” to achieve effective analgesia with minimal side effects.

When a patient’s care is transferred from St. Jude to community physicians, the pain management service makes a special effort to identify medical resources for continued pain care. The patient is given a letter describing his or her pain care history. The letter is intended to convey accurate clinical information to the physician, but it also includes contact information for the St. Jude pain management service. As Anghelescu emphasizes, “Any doctor—from primary care to hospice physician—is welcome to call for consultation about a St. Jude patient’s pain management.”

## Referrals, Consultations, and Treatment Policy of the Brain Tumor Program

The Brain Tumor Program at St. Jude welcomes referral of patients with newly diagnosed brain tumors, either before or immediately after a neurosurgical procedure. Patients are treated on clinical trials designed to provide the best available care while answering important research questions. We can accept only patients who are eligible for ongoing St. Jude clinical trials. Patients who have received treatment elsewhere may still be eligible for a St. Jude clinical trial and will be considered on an individual basis.

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) covers all costs of treatment beyond those reimbursed by third-party in-



surers, and total costs when no insurance is available. ALSAC also provides assistance with transportation costs and local living expenses during treatment.

After the initial therapy has been completed, patients are typically managed in close collaboration with their private physicians. St. Jude experts in hematology, oncology, immunology, genetic diseases, and infectious diseases are available at all times for consultation regarding possible side effects of therapy, signs of recurring disease, or other questions related to patient management.

For more information about the Brain Tumor Program at St. Jude Children's Research Hospital, please call (901) 495-4599 or e-mail us any time at [braintumors@stjude.org](mailto:braintumors@stjude.org).

## Therapeutic Trends Therapy for Brain Tumors

Dr. Larry E. Kun, head of the St. Jude Department of Radiological Sciences and co-leader of the Neurobiology & Brain Tumor Program, describes the key elements in optimal therapy for brain tumors at St. Jude.

**Accurate diagnostic information** is crucial in evaluating and managing childhood brain tumors. Key to diagnosis is accurate **neuroimaging**: highly sensitive MR imaging (MRI) demonstrates tumor location and extent. Advanced MRI technology enhances diagnostic capabilities. **Functional MRI and CT/PET imaging** identify sensitive areas of brain function to guide neurosurgical approaches and identify targets in planning radiation therapy.

**Technically sophisticated neurosurgery** is the first step in tumor therapy. In collaboration with LeBonheur Children's Medical Center, we offer technically adept neurosurgical approaches to the complete resection of tumors in challenging neuroanatomic locations.

**Highly conformal, localized irradiation** delivers effective radiation doses to the tumor while minimizing damage to normal areas of the brain. High-tech irradiation requires pre- and postoperative imaging, detailed target identification, and optimized treatment planning and delivery. We have been

Dr. Larry E. Kun  
Co-Leader, Neurobiology  
& Brain Tumor Program



able to diminish the volume of brain that must be irradiated to improve tumor control, even for very young children. **Chemotherapeutic regimens** have been explored to identify dose-intensive therapy that improves outcome while reducing treatment duration and toxicity.

**Drugs targeting cell-signaling pathways** are being tested to enhance therapeutic approaches. We have identified molecular targets that offer therapeutic opportunities in the common pediatric brain tumors. We are examining several new agents that attack proteins responsible for tumor proliferation or the vascular milieu essential for tumor growth; many of these agents are oral drugs with few of the side effects of chemotherapy.

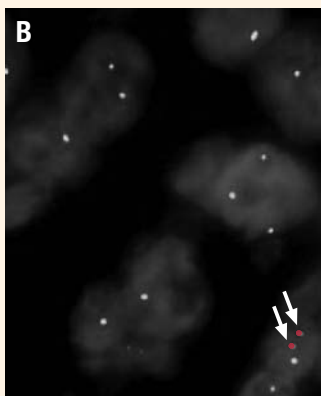
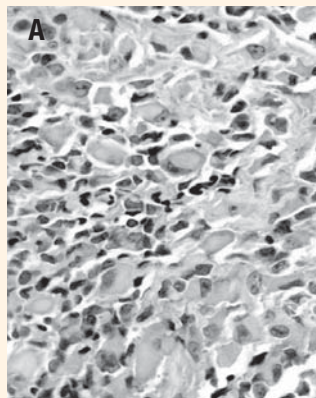
**Measurement of functional capacity** is central to developing therapeutic strategies to improve quality of life. Importantly, St. Jude has pursued one of the few trials rigorously assessing the ability of pharmacologic and behavioral interventions to improve memory and learning in our patients.

## The Rounds Quiz

### Diagnosis of Atypical Teratoid Rhabdoid Tumor

One of the most aggressive pediatric brain tumors is atypical teratoid rhabdoid tumor (ATRT), which may have significant histologic overlap with other embryonal CNS tumors. Microscopically, ATRT often contains “rhabdoid” cells with eccentric nuclei, prominent nucleoli, and large cytoplasmic filamentous inclusions (panel A).

**Question:** How is ATRT pathologically distinguished from other embryonal CNS tumors?



**Answer:** *INI1*, a cell-cycle regulatory gene, is lost or mutated in almost all ATRTs. Deletions involving *INI1* can now be rapidly detected by fluorescence in situ hybridization (FISH), a molecular diagnostic technique, as shown in panel B: most tumor cells contain the control probe signals but lack *INI1* signals (red; arrows). The absence of *INI1* signal indicates complete loss of the *INI1* gene locus and allows rapid, accurate diagnosis of ATRT.



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