RARE cancers reduce the quality and quantity of life and present an enormous challenge to patients and their physicians. The low incidence of these tumors hinders the conduct of clinical trials and laboratory studies that might define the disease more clearly and identify effective therapies. Consequently, progress in the treatment of rare tumors often proceeds slowly and typically relies on the extrapolation of results from studies of more common cancers. Spinal cord tumors are high on the list of rare cancers for which there is an urgent need for better treatments. The pressing need to improve the outcome for patients with spinal cord tumors...
is made greater by the heterogeneity of this group of neoplasms. Spinal cord tumors arise both within (intradural) and outside (extradural) the thecal sac that surrounds the spinal cord and cauda equina, and intradural tumors can be divided further into those that develop adjacent to (extramedullary) or within (intramedullary) the spinal cord parenchyma. Each of these anatomical tumor subgroups comprises a variety of histological types. To date, there has been no coordinated effort to study the biology of spinal cord tumors.

The National Institutes of Health Office of Rare Diseases Research, the National Cancer Institute, and the National Institute of Neurological Disease and Stroke co-organized a workshop in which experts from both laboratory and clinical disciplines met to define the scope of the problem of spinal cord tumors and to provide directions for future research (Table 1). This report summarizes the key challenges to improving understanding and treatment of spinal cord tumors, and provides recommendations for a coordinated strategy for future clinical and laboratory research.

Epidemiology of Spinal Cord Tumors

Carol Kruchko (President, CBTRUS) stressed the limited nature of data available to estimate the incidence, prevalence, and long-term outcomes for spinal cord tumors. Available statistics are hindered by small sample sizes, a lack of uniform pathological criteria, and the frequent exclusion of nonmalignant spinal cord tumors. Moreover, data on nonmalignant tumors only began to be included in registration practices within the US following the enactment of The Benign Brain Tumor Cancer Registries Amendment Act (H.R. 5204) in 2004. A summary of the available sources of data on spinal cord tumors is presented in Table 2.

Using the CBTRUS, information on 3386 spinal cord tumors is available. This listing includes primary tumors of the spinal cord (International Classification of Diseases for Oncology [ICD-O] site code C72.0), spinal meninges (C70.1), and cauda equina (C72.1) with an overall incidence of 0.78 affected individuals per 100,000 person-years. The majority of these tumors are classified as primary spinal cord tumors (70%), while most of the remaining tumors are meningeal-based neoplasms (26%). The incidence of spinal cord tumors is lowest in children (0–19 years of age) and highest in older adults (75–84 years of age). Non-Hispanic whites have the highest reported incidence rates, whereas females have a higher incidence rate of spinal cord tumors than males. The most common histology is meningioma (29%) followed by nerve sheath tumors (24%), ependymomas (23%), all astrocytomas (6%), and all other tumors (18%).

Survival is poor for patients with many primary spinal cord tumors, particularly those in whom astrocytomas have been diagnosed. Moreover, these neoplasms are usually associated with high rates of morbidity, including paresis, bowel and bladder dysfunction, and sensory deficits. Survival rates are lower in children than in adults (20–64 years of age), which probably reflects the differences in the histological subtypes diagnosed in these 2 distinct age groups.

Dr. Margaret Wrensch (Department of Neurosurgery, The University of California, San Francisco) noted that there has been only one published study on risk factors for spinal cord tumors. In this report, 81 women in whom spinal meningioma was diagnosed between 1978 and 1985 were significantly or nearly significantly more likely to be postmenopausal, not currently receiving estrogen replacement therapy, nonusers of oral contraceptives, nonparticipants in high-activity sports, smokers, and exposed to high-dose radiography. Larger studies will clearly be required to confirm these risk factors.

Pathology of Spinal Cord Tumors

Dr. David Ellison (Department of Pathology, St. Jude Children’s Research Hospital) reminded workshop participants that the histopathological classification of a tumor should aim to predict its biological behavior and response to treatment and stressed that molecular analysis should serve as an adjunct to this process. However, the rarity and small sample size of spinal cord tumors have restricted the identification and description of the pathological features of these neoplasms. Dr. Peter Burger (Department of Pathology, The Johns Hopkins University) stated that spinal cord tumors are currently classified using systems developed for intracranial tumors. However, the appropriateness of these classification systems is not known, as spinal cord tumors often do not fit easily into existing subclasses of intracranial tumors.

Dr. David Ellison (Department of Pathology, St. Jude Children’s Research Hospital) presented data on the known molecular alterations associated with spinal cord tumors. A better understanding of the spectrum of molecular alterations associated with their formation and progression is critical and may assist in supporting a particular histopathological diagnosis when tissue is limited, predict the biological behavior of a given tumor, and evaluate the success of targeted therapeutics.

Although some of the current registries contain information on spinal cord tumor histology, these diagnoses are usually not centrally reviewed. The lack of a coordinated effort to procure and centrally review spinal cord tumors has prevented adequate description of the pathology of these neoplasms. Dr. George Jallo (Departments of Neurology and Neurosurgery, Johns Hopkins University) suggested that preexisting collections of spinal cord tumors currently housed at a number of institutions may provide a useful starting point for a central review of the pathology of spinal cord tumors.

Clinical Management

Experts in neuroradiology, neurosurgery, and neurooncology provided updates on their respective approaches to the management of spinal cord tumors. Dr. Zoran Rumboldt (Department of Radiology, Medical University of South Carolina) lamented that few advances have been made in diagnostic imaging of spinal cord tumors over the past 20 years. Currently, MR imaging is the best imaging modality for visualization of spinal cord anatomy and intramedullary lesions. Workshop participants noted that the imaging appearance of spinal cord tumors fre-
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In addition, Dr. Herbert Engelhard (Department of Neurosurgery, University of Illinois at Chicago) noted that many tumors are more extensive when directly visualized in the operating room than was originally appreciated on preoperative imaging. The availability of imaging that is more predictive of tumor histology and more accurately delineates the plane between normal and tumor tissues would significantly improve treatment planning and the accuracy of resection, and would reduce morbidity.

Dr. Larry Kun (Department of Radiological Sciences, St. Jude Children's Research Hospital and Chair, United States Pediatric Brain Tumor Consortium) reported that while radiation is often used as adjuvant therapy for spinal cord tumors, the low incidence of these tumors has precluded the conduct of appropriately powered prospective clinical trials that might define the precise role of this treatment. Dr. May Abdel-Wahab (Department of Radiation Oncology, University of Miami) discussed results from one of the largest retrospective studies of spinal cord tumors aimed at examining the effect of radiation and surgery on patient outcome.1 Patients were identified at 6 institutions; the study included 82 individuals who received surgery alone as initial treatment and 101 individuals who received surgery and radiation. Progression-free and overall survival for patients with ependymoma was 35 and 75% at 15 years, respectively. In these patients, overall survival was influenced significantly by the extent of resection (p = 0.04) and patient age (p = 0.03). Comparatively, patients with astrocytomas fared worse, with a 15-year progression-free and overall survival of 15 and 32%, respectively. Workshop participants noted that the role of chemotherapy is even less clear.

**Spinal Cord Tumorigenesis**

Dr. Robert Wechsler-Reya (Department of Pharmacology and Cancer Biology, Duke University Medical Center) emphasized the need to gain a deeper understanding of spinal cord tumors at the cellular and molecular levels, and to use this information to identify and test new approaches to therapy. Dr. Wechsler-Reya used the example of another CNS tumor, medulloblastoma, to illustrate how understanding the mechanisms that regulate normal development can provide insights into the processes that promote tumorigenesis. Dr. Nicholas Gaiano (Department of Neurology, The Johns Hopkins Medical School) described how the spinal cord develops from a pool of progenitor cells, which is tightly regulated by numerous cell signaling pathways previously implicated in the formation of other CNS tumors. Workshop participants agreed that identifying the various progenitor cells in the spinal cord and the critical cell signaling pathways that regulate the proliferation and differentiation of these progenitor cell populations will be fundamental to our understanding of the spinal cord tumorigenesis.

Dr. Richard Gilbertson (Department of Developmental Neurobiology, St. Jude Children's Research Hospital) reviewed the cancer stem cell hypothesis and presented evidence that spinal ependymomas arise from radial glia.
cells and contain radial glia-like cancer stem cells. Workshop participants discussed the exciting opportunities for neurobiologists, stem cell biologists, and cancer biologists to collaborate in the characterization of normal and malignant stem cells of the spinal cord, but emphasized the need to develop cell surface markers that delineate specific progenitor subtypes and/or stages of differentiation.

**Small Animal Spinal Cord Tumor Models**

Drs. George Jallo (Departments of Neurology and Neurosurgery, The Johns Hopkins University) and Bernard Maria (Department of Pediatric Oncology, Medical University of South Carolina) reviewed the current preclinical models available for the study of spinal cord tumors. These rodent models are restricted to orthotopic transplantation of rodent or human adult brain glioma cell lines into the spinal cord of immunocompromised rats. Dr. Maria demonstrated how engrafted adult brain glioma cells rapidly spread throughout the rat spinal cord and showed that they are detectable by both small animal MR and bioluminescence imaging. While workshop participants noted the value of these transplant models, they all underscored the need for improved xenograft models of human spinal cord tumors as well as spontaneous spinal tumor models in genetically modified rodents.

Drs. David Gutmann (Department of Neurology, Washington University School of Medicine) and Eric Holland (Department of Neurosurgery, Memorial Sloan–Kettering Cancer Center) reviewed some of the barriers to the generation of genetic mouse models of spinal cord tumors. Dr. Gutmann stressed the importance of identifying the cell(s) of origin of spinal cord tumors. This fundamental information will be crucial for the characterization of promoters that target clinically relevant genetic alterations to the correct cell type within the developing spinal cord. Dr. Gilbertson highlighted the importance of using high-density genetic approaches, including single nucleotide polymorphism (SNP) mapping arrays and gene expression profiling, to detect the causative genetic alterations in spinal cord tumors. Finally, Dr. Gutmann discussed the challenges of monitoring tumorigenesis in the mouse spinal cord. The rodent spinal cord is a tiny, but highly organized, anatomical structure, which poses problems for early detection of small, slow-growing neoplastic lesions. Workshop participants discussed the possibility of using other approaches, including diffusion-based imaging strategies, as has been successfully applied by Dr. Gutmann and his associates to visualize mouse optic nerve gliomas.

**The Future of Spinal Cord Tumor Research: Progress Through Collaboration**

Advances in our understanding of the biology and treatment of spinal cord tumors will not be made without a radical change in the way that we study these tumors. The rarity and heterogeneity of these tumors dictates that laboratory and clinical investigators must collaborate closely to improve the lives of all patients with spinal cord tumors. The participants in this workshop identified a number of key challenges and proposed a series of concrete recommendations (Appendix). In addition, the establishment of a single, central, population-based public registry for patients with spinal cord tumors would provide an invaluable resource to collect fixed, and when available, snap-frozen tumor material, from each patient for central histology review and future molecular studies. This resource would allow for more accurate and meaningful epidemiological studies and will facilitate the development of a new pathological classification scheme for spinal cord tumors. Central registration of patients could serve also as a useful conduit to link treatment institutions engaged in clinical trials of new diagnostic and treatment strategies. Extension of a collaborative network to include the laboratories of neurobiologists, stem cell biologists, and cancer biologists would similarly accelerate the pace of basic science research and the discovery of effective new treatments for spinal cord tumors. Lastly, the inclusion of patient advocacy groups, as represented by Linda Stophel (President, Spinal Cord Tumor Association) and Daniel Heck (Malia’s CORD Foundation) provides an important and unique perspective on the personal impact of spinal cord tumors. Together with federal and private funding agencies, they can play a galvanizing role in guiding the future of spinal cord tumor research.

**Appendix: Workshop participant recommendations**

**Epidemiology and Pathology**

- Establish a population-based public registry for patients with spinal cord tumors. This registry should also collect tumor and other biospecimens from each patient for central histology review and molecular studies as well as include follow-up data to assess patient outcome.
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- Conduct central pathology review of existing collections of spinal tumors to begin the process of developing a better classification system of these tumors.

**Clinical Management**

- Establish a cooperative network of treatment centers capable of conducting coordinated clinical trials of new diagnostic methodologies and evaluating novel treatment strategies, which is linked with a central spinal cord tumor registry.

**Tumorigenesis and Small Animal Models**

- Identify the various progenitor cells in the spinal cord and the intracellular signaling pathways that regulate their proliferation and differentiation.
- Generate antibodies to isolate spinal cord progenitor cells.
- Develop robust genetically engineered small animal models of spinal cord tumors.
- Pursue complementary use of existing human xenograft spinal cord tumor models and genetically engineered mouse spinal tumor models for preclinical studies.

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**References**