

M.A. Hayat  
*Editor*

# Tumors of the Central Nervous System

Volume 8

Astrocytoma, Medulloblastoma,  
Retinoblastoma, Chordoma,  
Craniopharyngioma,  
Oligodendroglioma, and Ependymoma

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# Tumors of the Central Nervous System

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## Volume 8

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Edited by

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 Springer

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*Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena.*

Richard J. Reed, M.D.



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## One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test, may revert to normal cells. Tumor shrinkage, regression, reversal, or stabilization is not impossible.

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guin et al. 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al. 2008). These and other studies justify the “wait and see” strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless *MYCN* gene is amplified. Infants with nonamplified *MYCN* and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without *MYCN* have excellent survival with minimal or no treatment. Another example of spontaneous shrinkage and loss of tumors without any treatment is an intradural lipoma (Endoh et al. 1998).

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### Overtreatment

An example of unnecessary surgery is the removal of all the armpit lymph nodes after a biopsy when a sentinel node shows early stage breast cancer; removal of only the sentinel node may be needed. Limiting the surgery to the sentinel node avoids painful surgery of the armpit lymph nodes, which can have complications such as swelling and infection (such limited surgery is already being practiced at the Memorial Sloan-Kettering Cancer Research



Center). Radiation-induced second cerebral tumors constitute a significant risk for persons undergoing radiotherapy for the management of cerebral neoplasms. High-grade gliomas are the most common radiation-induced tumors in children (Pettorini et al. 2008). The actual incidence of this complication is not known, although it is thought to be generally low.

There were an estimated 217,730 new cases of prostate cancer in the United States in 2010 with 32,050 deaths, making it the second leading cause of cancer deaths in men. The risk of death for men in the United States between the ages of 55 and 74 years due to cardiovascular disease surpasses that of prostate cancer. Cardiovascular disease is the most common of the chronic non-communicable diseases that impact global mortality. Approximately, 30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by cardiovascular disease alone. Currently, there are more than 2,000,000 men in the United States who have had radical or partial prostate surgery performed. Considering this huge number of prostate surgeries and the absence of a cumulative outcome data, it seems appropriate to carefully examine the benefits of radical surgery.

Prostate cancer treatment is an example of overtreatment. Serum prostate specific antigen (PSA) testing for the early detection of prostate cancer is in wide use. However, the benefit of this testing has become controversial. The normal cut-off for serum levels of PSA is 4 ng/ml, so any man presenting a PSA above this level is likely to require rectal biopsy, but only in 25% of men with serum levels of PSA between 4 ng and 10 ng/ml have cancer (Masters 2007). The PSA threshold being used for biopsy ranges between 2.5 and 3.4 ng/ml. Up to 50% of men presenting with prostate cancer have PSA levels within the normal range. It is apparent that screening of prostate cancer using PSA has a low specificity, resulting in many unnecessary biopsies, particularly for gray zone values (4 ng – 10 ng/ml). According to one point of view, the risks of prostate cancer overdetection are substantial. In this context, overdetection means treating a cancer that otherwise would not progress to clinically significant disease during the lifetime of the individual. Overdetection results in overtreatment. The advantages and limitations of PSA test in diagnosing prostate cancer were reviewed by Hayat (2005, 2008).

Recently, the FDA cleared the use of NADiA (nucleic acid detection immunoassay) ProVue prognostic cancer test. This proprietary nucleic acid detection immunoassay technology identifies extremely low concentrations of proteins that have not been routinely used as a diagnostic or prognostic aid. It is an *in vitro* diagnostic assay for determining the rate of change of serum total prostate specific antigen (PSA) over a period of time. The assay can quantitate PSA at levels <1 g/ml. This technique can be used as a prognostic marker in conjunction with clinical evaluation as an aid in identifying the patients at reduced risk for recurrence of prostate cancer for years following prostatectomy. It targets the early detection of proteins associated with cancer and infectious diseases. This technique combines immunoassay and real-time PCR methodologies with the potential to detect proteins with femtogram/ml sensitivity (10–15 g/ml). Additional clinical information is needed regarding its usefulness in predicting the recurrence.

A significant decrease in the risk of prostate cancer-specific mortality is observed in men with few or no comorbidities. Indeed, active surveillance in lieu of immediate treatment (surgery or radiation, or both) is gaining acceptance. Most men with prostate cancer, even those with high-risk disease, ultimately die as a result of other causes (Lu-Yao et al. 2009). Debate on this controversy is welcome, but narrow opinions and facile guidelines should lead to fact and new information; men worldwide deserve it (Carroll et al. 2011). Automatic linking positive diagnosis with treatment, unfortunately, is a common clinical practice. Unfortunately, even men who are excellent candidates for active surveillance in the United States often undergo some treatment. Deferment of treatment is advised in men with low-risk disease.

First whole genome sequences of prostate tumors were recently published online in Nature journal (vol. 470: 214–220, 2011). This study revealed that rather than single spelling errors, the tumor has long “paragraphs” of DNA that seem to have broken off and moved to another part of the genome (rearrangement of genes), where they are most active. These portions of DNA contain genes that help drive cancer progression. The mutated genes involved include *PTEN*, *CADM2*, *MAG12*, *SPOP*, and *SPTA1*. This information may lead to the development of more efficient, less invasive ways to diagnose and treat this cancer. Such information, in addition, should lead to personalized therapeutics according to sequencing results of different gene mutations or chromosomal rearrangements. The urgent need of such studies becomes apparent considering the huge number of new cases of prostate problem is reported every year.

It is known that chemotherapy can cause very serious side-effects. One most recent example of such side-effects was reported by Rubsam et al. (2011). Advanced hepatocellular carcinoma (HCC) induced by hepatitis C virus is treated with Sorafenib. It is an oral multikinase inhibitor that interferes with the serine/threonine kinases RAF-1 and B-Raf and the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the platelet-derived growth factor receptor-beta. Although sorafenib is effective in regressing HCC, it shows serious side-effects including increasingly pruritic and painful skin changes (cutaneous eruption).

It is well established that radiation doses are related to risk for subsequent malignant neoplasms in children with Hodgkin’s disease. It has been reported that increasing radiation dose was associated with increasing standardized incidence ratio ( $p=0.0085$ ) in survivors of childhood Hodgkin’s disease (Constine et al. 2008). Approximately, 75% of subsequent malignancies occurred within the radiation field. Although subsequent malignancies occur, for example, in breast cancer survivors in the absence of radiotherapy, the rise increases with radiation dose.

In addition to unwanted side effects of some drug excipients (e.g., propylene glycol, menthol) may pose safety concerns in some patients. Excipients are defined as the constituents of the pharmaceutical formulation used to guarantee stability, and physicochemical, organoleptic and biopharmaceutical properties. Excipients frequently make up the majority of the volume of oral and parenteral drugs. Not all excipients are inert from the biological point of view. Although adverse drug reactions caused by the excipients are a

minority of all adverse effects of medicinal products, the lack of awareness of the possible risk from excipients should be a concern for regulatory agencies, physicians, and patients (Ursino et al. 2011). Knowledge of the potential side effects of excipients is important in clinical practice.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, or chemotherapy? Although the conventional belief is that cancer represents an “arrow that advances unidirectionally”, it is becoming clear that for cancer to progress, it requires cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression, and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Eric Hayat

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## Preface and Introduction, Volume 8: Tumors of the Central Nervous System

It is recognized that scientific journals and books not only provide current information but also facilitate exchange of information, resulting in rapid progress in the medical field. In this endeavor, the main role of scientific books is to present current information in more details after careful additional evaluation of the investigational results, especially those of new or relatively new therapeutic methods and their potential toxic side-effects.

Although subjects of diagnosis, drug development, therapy and its assessment, and prognosis of tumors of the central nervous system, cancer recurrence, and resistance to chemotherapy are scattered in a vast number of journals and books, there is need of combining these subjects in single volumes. An attempt will be made to accomplish this goal in the projected ten-volume series of handbooks.

In the era of cost-effectiveness, my opinion may be minority perspective, but it needs to be recognized that the potential for false-positive or false-negative interpretation on the basis of a single laboratory test in clinical pathology does exist. Interobserver or intraobserver variability in the interpretation of results in pathology is not uncommon. Interpretative differences often are related to the relative importance of the criteria being used.

Generally, no test always performs perfectly. Although there is no perfect remedy to this problem, standardized classifications with written definitions and guidelines will help. Standardization of methods to achieve objectivity is imperative in this effort. The validity of a test should be based on the careful, objective interpretation of the tomographic images, photo-micrographs, and other tests. The interpretation of the results should be explicit rather than implicit. To achieve accurate diagnosis and correct prognosis, the use of molecular criteria and targeted medicine is important. Equally important are the translation of molecular genetics into clinical practice and evidence-based therapy. Translation of medicine from the laboratory to clinical application needs to be carefully expedited. Indeed, molecular medicine has arrived.

This is the eighth volume in the series, Tumors of the Central Nervous System. As in the case of the seven previously published volumes, this volume mainly contains information on the diagnosis, therapy, and prognosis of brain tumors. Various aspects of seven types of brain tumors (Astrocytoma, Medulloblastoma, Retinoblastoma, Chordoma, Craniopharyngioma, Oligodendroglioma, and Ependymoma) are discussed. An update of medulloblastoma classification is presented, and an overview of ependymoma is also included. Prognosis based on genetic aberrations for ependymoma patients is elaborated. The WHO grade II

ependymoma shows more aberration than those found in the WHO grade I ependymoma. Insights into the understanding of molecular pathways involved in tumor biology are explained. For example, the role of E-cadherin gene instability, carbonic anhydrase II, urokinase plasminogen activator, and Wnt signaling in meningiomas is discussed in detail. Genetic and clinical features associated with recurrence in meningioma patients are explained, and the role of erythropoietin receptor in the recurrence is included. It is discussed that OTX2 transcription factor functions as an oncogene in medulloblastoma. Molecular mechanisms underlying chemoresistance in medulloblastoma are discussed. Clinically important microRNA genes in medulloblastoma are included. The role of molecular genetics and epigenetic mechanisms in schwannomas is explained, including the role of cyclin D1 in vestibular schwannoma. The genetic hybridization method indicates that genomic instability increases during retinoma/retinoblastoma transition. Also, the role of epigenetics in the development of retinoblastoma is explained. The role of survivin in diagnosis and prognosis of patients with retinoblastoma is presented. The risk of increased second malignancy (e. g., soft tissue sarcoma, osteosarcoma, and melanoma) in the long-term survivors of retinoblastoma after treatment with radiotherapy is pointed out. Such information leads to the development of effective drugs, and knowledge of involved pathways and signaling facilitates targeted therapies in cancer.

The subtypes of meningiomas are determined using perfusion magnetic resonance imaging. The diagnosis of sporadic meningoangiomas using imaging technologies is explained. Diagnosis of incidentally discovered meningioma and cystic papillary meningioma is also included. Diagnosis of facial nerve schwannoma, vestibular schwannoma, and intermediate nerve schwannoma is presented. Treatments for atypical meningioma, benign meningioma, oncocytic meningioma, intracranial meningioma, and cavernous sinus meningioma are presented. A number of treatments of patients with specific brain cancer types are detailed. Therapeutic methods such as neurosurgery, Gamma knife radiosurgery, and adjuvant radiation for this cancer are included. The effect of the extent of resection on the survival of patients with malignant brain astrocytoma is explained. Large number of treatments, including radiosurgery, retrosigmoidal craniotomy, and immunotherapy, for vestibular schwannoma patients are detailed.

Therapy of medulloblastoma patients with bortezomib is also included, so is hyperfractionated radiotherapy for these patients. It is explained that immunohistochemistry of CAM5.2 cytokeratin is useful in discriminating chordoma from chondrosarcoma. The treatment of patients with chordomas and chondrosarcomas using particle radiotherapy is described. Endonasal endoscopic transclival approach is recommended for skull base chordomas. Similar approach is used for primary and recurrent craniopharyngioma patients. Radiotherapy is also effective for craniopharyngioma patients. Treatment with bevacizumab for recurrent oligodendroglioma is recommended. Chemotherapy is also recommended for intracranial ependymoma patients. Magnetic resonance imaging is useful for diagnosing extradural ependymoma. Diagnosis of primary malignant ependymoma of the abdominal cavity is explained. Correct diagnosis, effective treatment, and manage-

ment of medulloblastoma patients are emphasized. The quality of life, after treatments of both meningioma and schwannoma patients, is discussed.

Introduction to new technologies and their applications to tumor diagnosis, treatment, and therapy assessment are explained. For example, nanotechnology-based therapy for malignant tumors of the CNS is detailed. Molecular profiling of brain tumors to select therapy in clinical trials of brain tumors is included. Several surgical treatments, including resection and radiosurgery, are discussed. The remaining two volumes in this series will provide additional recent information on this and other aspects of CNS malignancies.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against this terrible disease. It would be difficult for a single author to discuss effectively the complexity of diagnosis, therapy, and prognosis of any type of tumor in one volume. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of the CNS cancer. I hope these goals will be fulfilled in this and other volumes of this series. This volume was written by 98 contributors representing 14 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the reader in this important area of disease. I respect and appreciate the hard work and exceptional insight into the nature of cancer provided by these contributors. The contents of the volume are divided into seven subheadings: Introduction, Diagnosis and Biomarkers, Therapy, Tumor to Tumor Cancer, Imaging Methods, Prognosis, and Quality of Life for the convenience of the reader.

It is my hope that the current volume will join the preceding volumes of the series for assisting in the more complete understanding of globally relevant cancer syndromes. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure, and hopefully prevention. In the light of existing cancer calamity, financial funding by governments must give priority to eradicating this deadly malignancy over military superiority.

I am thankful to Dr. Dawood Farahi and Dr. Kristie Reilly for recognizing the importance of medical research and publishing through an institution of higher education. I am also thankful to my students for their contributions to the preparation of this volume.

M. A. Hayat



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