

M.A. Hayat
Editor

Tumors of the Central Nervous System

Volume 4
Brain Tumors (Part 2)

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Volume 4

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System
Volume 4

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Nervous System

Brain Tumors (Part 2)

Edited by

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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 MD

Preface

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 fourth volume in the series, Tumors of the Central Nervous System. As in the case of the three previously published volumes, this volume mainly contains information on the diagnosis, therapy, and prognosis of brain tumors. Insights on the understanding of molecular pathways involved in tumor biology are explained, which lead to the development of effective drugs. Information on pathways (e.g., hedgehog) facilitates targeted therapies in cancer. Tumor models are also presented, which utilize expression data, pathway sensitivity, and genetic abnormalities, representing targets in cancer. For example, rat model of malignant brain tumors using implantation of

doxorubicin with drug eluting beads for delivery is explained. The future of pathway-driven therapies for tumors is summarized.

The importance of personalizing cancer care is emphasized. The need for supportive measures for survivors of brain cancer is pointed out, so is the quality of life monitoring. The need of rehabilitation therapy for patients with primary and metastatic brain tumors is also emphasized.

Role of MicroRNA in distinguishing primary tumors from metastatic tumors is discussed. Advantages and limitations of chemotherapy (e.g., temozolomide and doxorubicin) are discussed. The complexity of tumor to tumor transfer is explained; examples discussed are: brain metastases from breast cancer and brain metastases from melanoma. Identification and characterization of biomarkers, including those for metastatic brain tumors, are presented. Genomic analysis for identifying clinically relevant subtypes of glioblastoma is included.

A large number of imaging modalities, including Fourier transform infrared imaging, elastic light single-scattering spectroscopy, diffusion tensor imaging, quantitative FDG-PET, intraoperative magnetic resonance imaging, functional magnetic resonance imaging, and ultrasound, are detailed to study progression and invasion of gliomas, intraoperative brain tumor detection, quantitative analysis of pyramidal tracts in brain tumor patients, diagnoses of peripheral nerve sheath tumors, targeted cancer chemotherapy, skull base tumors, growth of malignant gliomas, trigeminal neuralgia, and disappearing brain lesions.

Introduction to new technologies and their applications to tumor diagnosis, treatment, and therapy assessment are explained. Molecular profiling of brain tumors to select therapy in clinical trials of glioblastoma is included. Several surgical treatments, including resection, Gamma knife surgery, and radiosurgery, are discussed. The remaining six volumes in this series will provide additional recent information on this and other aspects of other types 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 103 contributors representing 15 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, government funding 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.

Union, New Jersey
April 2011

M.A. Hayat

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Part I
Introduction

Chapter 1

Epidemiology of Primary Brain Tumors

Isabelle Baldi and Hugues Loiseau

Abstract Epidemiology of primary brain tumors includes a descriptive approach (determination of prevalence and incidence) and an analytical approach (identification of risk factors). Among risk factors, some are intrinsic to the person and others are external causes that are more easily preventable. Descriptive epidemiological data have concluded an increase of annual incidence of primary brain tumor in most industrialized countries. Main explanations for this increase are the ageing of the population and a better access to the diagnostic imaging, albeit it is not possible to exclude changes in risks factors. Comparing incidences between registries is difficult. Spatial and temporal variations constitute one explanation for the discrepancies and evolutions of coding methods another one. Intrinsic factors likely to modify the risk are age, genetic predisposition and susceptibility, gender, race, birth weight, and allergy. Extrinsic factors likely to modify the risk are mainly radiation exposures. Many studies concerning, among others, electro magnetic fields, and especially cellular phones, pesticides, substitutive hormonal therapy, and diet have been published. Until now, results remain globally inconclusive. Weak incidence of primary brain tumors constitutes a huge limiting factor in the progress of knowledge, both on incidence and risk factors. Important mobilization of the neuro-oncological community is mandatory to obtain consistent and valuable data that will lead to a significant improvement in our knowledge of brain tumor epidemiology.

Keywords Brain tumor · Medulloblastoma · Hematopoietic neoplasms · Li-Fraumeni syndrome · Turcot's syndrome · Ependymoma

Introduction

Considering that principles of epidemiology began to form in the second half of the 20th century, it is a relatively new scientific approach to health problems. Nevertheless, the oldest population-based tumor registry in the world started in Connecticut as early as 1941 with a retrospective registration from 1935, followed by the Danish Cancer Registry in 1942. This demonstrates the foremost concern of improving knowledge in the field of cancer and the early and dynamic role of cancer physicians in this research area. Subsequently, several hundreds of cancer registries were established worldwide, and the International Agency for Research on Cancer was established in 1965 as a specialized research center of the World Health Organization (<http://www.iarc.fr/>). Epidemiology makes it possible to describe the incidence and mortality due to cancer (descriptive epidemiology), and to identify risk factors for cancer, the strength of their association with the disease, and the potential causal relation (analytical epidemiology), with the underlying purpose of improving cancer prevention.

Some common difficulties are encountered with registries for different tumor sites. One of them is the need for a multidisciplinary approach for registering cases, because views and coding systems change with time. Considering brain tumors, two classifications are used: the International Classification of Disease for

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Oncology (ICD-O) with the morphology codes and the site codes (Fritz et al. 2000), and the World Health Organization's histological classification of primary brain tumors (Louis et al. 2007). According to these classifications, worldwide registries do not necessarily include exactly the same subtypes of brain tumors, which may explain some differences in the incidence rates. The evolution of coding systems with time and the poor reproducibility for histological assessment of some tumors, such as gliomas, also make comparisons difficult. Many published data have included different tumor types which could have a similar origin. That could explain some discrepancies in the results.

Descriptive Epidemiology of Primary Brain Tumors

Methodological Endpoints

Various parameters can be used to describe the burden of brain tumors in human populations and to help in medical care planning. The most common ones are the prevalence and the incidence of these diseases. Data concerning prevalence rates of brain tumors (proportion of people alive on a certain date in a population who previously had a diagnosis of brain tumor) are scarce and controversial. Some estimations have been given by the International Agency for Research on Cancer, based on incidence and survival data (Pisani et al. 2002), but they appear lower than those calculated in the United States from the Central Brain Tumor Registry of the United States, which are about 130/100,000 for benign and malignant tumors (Davis et al. 2001).

The main indicator allowing spatial and time-related comparison is annual incidence (i.e., number of new brain tumors in 1 year and in a given population, usually per 100,000 inhabitants).

Annual incidence rates reported by some of the main registries worldwide are summarized in Table 1.1 according to histological subtypes. Incidence rates vary in the published studies, mainly due to differences in study methodology. The global rate ranges from 8.5 to 19.25/100,000. Primary brain tumor incidence in children is 4.9/100,000 in Sweden (Dreifaldt

et al. 2004) and 2.5/100,000 in Germany (Kaatsch et al. 2001), but studies do not consider the same age limit for childhood.

Neuroepithelial tissue tumors, tumors of the meninges and those of the cranial and spinal nerves represent the main histological subtypes, and account for ~85% of the primary brain tumors in adults. In adults, the main histological types are the neuroepithelial tumors (mainly represented by gliomas), tumors of the meninges, tumors of the cranial and spinal nerves, lymphomas and hematopoietic neoplasms, and germ cell tumors. In adults, the incidence of neuroepithelial tumors ranges from 2.2 (Kuratsu et al. 2001) to 7.8/100,000. The incidence of glioblastomas, the most malignant type of gliomas, ranges from 1.6 (Liigant et al. 2000) to 4.5/100,000. The incidence of meningioma presents the widest variations, ranging from 1.3 (Arora et al. 2009) to 7.8/100,000 (www.cbtrus.org). The annual incidence of schwannoma is 1.1/100,000 and the incidence of vestibular schwannoma is 0.55/100,000 (Schellinger et al. 2008). In children, neuroepithelial tissue tumors alone account for ~75% of primary brain tumors. Histological subtypes differ in children, astrocytoma predominating (pilocytic astrocytoma) together with embryonal medulloblastoma and followed by ependymoma.

Even when caution is used when comparing incidence due to variations in the period of recording and in diagnostic tools (radiology, histology, autopsy), it may be assumed that the burden of primary brain tumor in health care systems is likely to be underestimated for several reasons. First, some cancer registries do not record benign tumors, a situation although more frequent in the past decades, slowly changing since the recent recommendations (McCarthy et al. 2002). Secondly, some registries only collect histologically confirmed cases, while the proportion of cases without histological confirmation has been shown to reach up to 31%. Third, some specific cases, such as malignant transformation, secondary localization, and occurrence of tumors at different sites observed in inherited genetic syndromes, are not systematically recorded in registries. Yet, these tumors have an impact in terms of public health and health-care planning.

Primary brain tumors are topographically distributed according to a volumetric gradient (i.e. supratentorial tumors are more frequent than infratentorial tumors, which are more frequently observed than spinal tumors).

Table 1.1 Incidence data from the main registries of central nervous system tumors around the world

Country	Rochester	Greece	Kumamoto	Cyprus	Austria	California	Estonie	Finland	Israel	England	France
Authors	Radhakrishnan et al. (1995)	Gousias et al. (2009)	Kuratsu et al. (2001)	www.cbtrms.org (2009)	Wöhner et al. (2009)	Brown et al. (2009)	Ligant et al. (2000)	Larjawaara et al. (2008)	Saderzki et al. (2008)	Arora et al. (2009)	RSTNC
Age-adjusted population	local	Greek population	Japanese population	US	US	US	World	World population	World population	World	World
Period of recruitment	1950–1989	2005–2007	1989–1998	2002–2006	2005	2001–2005	1986–1996	2000–2002	2001–2003	1995–2003	2000–2007
Number of cases	339	56	2129	85,670	1688	24,293	1665	331	548	54,336	1983
Population	70,000	488,435	1,850,000		8,200,000	36,500,000	1,500,000				1,300,000
Histological confirmation (%)	63.1	91	70.9		80.9		80.8	99	95		77.9
Histological classification	WHO (1993)		WHO (1993)	WHO	ICDO-3	WHO (1993)	WHO (1993)	ICDO-3	WHO (2002)	WHO (2000)	WHO (2000)
Ages	All	>20	All	All	All	All	All	20–69	>18	<85	All
Age-adjusted incidence	19.1		10.97	18.28	18.1	14.3	8.46		9.21	9.21	19.25
Tumours of neuroepithelial tissue	6.14	5.73		6.49	7.26		3.72	4.7	5.24		7.83
Pilocytic astrocytoma				0.34	0.57	0.3		0.3		0.31	0.26
Diffuse astrocytoma	1.30			0.10	0.75		1.27	0.7		0.08	0.32
Anaplastic astrocytoma				0.41	0.44	0.4	0.46	0.5		0.18	0.39
Unique astrocytoma variants				0.10						0.02	0.06
Astrocytoma, NOS			0.57	0.44		0.3		0.03		0.75	0.12
Glioblastoma	3.60	3.69		3.11	3.40	2.6	1.58	2.0	3.26	1.89	5.22
Oligodendroglioma	0.60			0.31	0.70	0.3	0.22	0.5		0.07	0.14
Anaplastic oligodendroglioma				0.14		0.1				0.21	0.09
Ependymoma/anaplastic ependymoma	0.20			0.28	0.57	0.2	0.22	0.2		0.25	0.30
Ependymoma variants				0.09							0.08
Mixed glioma	0.10			0.19		0.2	0.11	0.5		0.08	0.51
Glioma malignant, NOS			1.56	0.42		0.3		0.02			0.25
Choroid plexus				0.04				0.01		0.03	0.04
Neuroepithelial				0.02	0.05					0.09	0.05

Table 1.1 (continued)

Country	Rochester	Greece	Kumamoto	Cbrus	Austria	California	Estonie	Finland	Israel	England	France
Benign and malignant neuronal/glioma neuronal and mixed				0.27	0.29				0.01		0.29
Pineal parenchyma	0.04			0.03	0.07				0.05		0.01
Embryonal/primitive/medulloblastoma	0.30	0.07	1.08	0.20	0.25	0.2	0.32		0.28		0.23
Tumors of cranial and spinal nerves				1.66	1.36		0.40				2.27
Nerve sheath, benign and malignant	0.90			1.66	1.24	1.5			0.66		
Tumors of meninges				6.40	5.31	4.5	1.63		1.38		6.07
Meningioma	7.80		3.40	6.17	5.23				1.28		5.92
Other mesenchymal, benign and malignant				0.07	0.08						0.15
Hemangioma	0.20			0.14							0.00
Lymphoma and hematopoietic neoplasms				0.47	0.57						
Lymphoma	0.20		0.29	0.47	0.48	0.4					0.61
Germ cell tumors and cysts				0.08	0.09						
Germ cell tumors, cysts and heterotopias			0.20	0.08					0.06		0.10
Tumors of sellar region				2.08	1.81						
Pituitary	2.80		2.06	1.95	1.63	2	0.36		0.82		
Craniopharyngioma	0.30		0.17	0.13					0.12		0.21
Local extension from regional tumors				0.02							
Chordoma/chondrosarcoma				0.02					0.01		0.05
Unclassified tumors				1.10							
Hemangioblastoma	0.20			0.15					0.10		0.26
Neoplasm, unspecified	0.80			0.95			1.63				0.59
All other				0.01	1.78		0.96		0.91		0.73

Whatever the registry, variations in incidence rates according to age appear triphasic. A first moderate peak is observed between 0 and 15 years of age, corresponding to the childhood brain tumors. The incidence is low between 15 and 35 years of age, but an increase is observed thereafter until 70 or 75 years of age. Beyond this age, decreasing incidence is usually observed. Some variations have been reported both in the incidence rates and in the peak age of incidence (i.e., 65, 70 or 75 years of age). Countries differ in public health resources and the age pyramid, which may explain such differences. However, variations in age adjustment within studies may also partly explain the differences: some incidence rates are crude while others are standardized in the US or world population.

Increasing incidence rates were reported from the 1970s worldwide, a trend that appeared more pronounced in subgroups such as the elderly and children. The annual increase was ~1% per year in adults and from 1 to 2% in children with some variations according to the histological subtypes. Since the 1990s, some data tend to report a plateau. Some authors have considered the increase in the rates to be artefactual with three main explanations for this: (1) ageing of the populations, (2) improvement in health access and in diagnostic procedures, corresponding to the introduction of CT-scan during the 1970s and then MRI during the 1980s; (3) adjustment of neurosurgical procedures despite aging, leading to an increase in the rate of histological confirmation of gliomas, even in the elderly (up to 98% in some cancer registries).

However, these arguments are not consistent with some other findings such as the continuous increase in some histological types such as meningiomas or in some population groups such as children.

Most of the histological subtypes have increased except the primary brain lymphomas, that have a stable or decreasing incidence. This situation is explained by important changes in the therapeutic armamentarium with the introduction of highly active anti-retroviral therapy (HAART), which has led to the end of lymphoma in AIDS patients. The incidence of grade 2 and 3 astrocytomas also appears to be decreasing, but this is explained by changes in histological classification in favor of oligodendroglioma and mixed tumors.

Analytical Epidemiology of Primary Brain Tumors

The descriptive epidemiology of brain tumors highlights geographical and temporal variations, which suggest the possible role of both intrinsic and extrinsic factors. We present here the main hypotheses studied to date.

Endogenous Risk Factors

The most important factor associated with an increase in the risk of brain tumour is age, albeit some specific types (medulloblastoma and pilocytic astrocytoma) occur rather specifically in children. Incidence rates are below 10/100,000 before the age of 35, and exceeds 40/100,000 after the age of 65.

Even if between-country or between-continent comparisons are biased by methodological registration differences, data from within-country comparisons suggest consistent differences in brain tumor incidence between ethnic groups (Darefsky and Dubrow, 2009; Sadetzki et al. 2008). White populations (Northern America, Australia, and Europe) present the highest rates, approximately two-fold the rates of black people or Asians. These differences concern most of the histological subtypes and tumor types. They might result from genetic, nutritional or environmental factors, but also possibly from greater access to diagnostic facilities and medical care in some ethnic groups.

Incidence of brain tumors is clearly related to sex, with opposite patterns for meningiomas and gliomas. Higher rates of meningiomas in women, specifically during reproductive period, were identified as early as 1930 by Harvey Cushing (McKinley et al. 2000) and are constantly observed in all countries. The opposite pattern is observed for gliomas with higher rates in men. The differences in incidence between sexes suggest that sex hormones and/or genetic differences between males and females may play a role in the occurrence of these tumors.

Birth weight and height are objective measures that have been suggested to be crude markers in children of prenatal conditions and exposures (as indicators of maternal nutritional status, diseases and exposures). It has also been hypothesized that the insulin-like