M.A. Hayat *Editor*

Tumors of the Central Nervous System

Volume 1
Gliomas: Glioblastoma (Part 1)

Springer

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Gliomas: Glioblastoma (Part 1)

Edited by

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ISBN 978-94-007-0343-8 e-ISBN 978-94-007-0344-5
DOI 10.1007/978-94-007-0344-5
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2011923069

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 not only provide current information but also facilitate exchange of information, resulting in rapid progress. In this endeavor, the main role of scientific books is to present current information in more detail after careful additional evaluation of the investigational results, especially those of new or relatively new 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 six-volume series of handbooks.

In the era of cost-effectiveness, my opinion may be a 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. Interobservor or intraobservor variability in the interpretation of results in pathology is not uncommon. Interpretive 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 an 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.

An attempt has been made to achieve the above-mentioned goals in the present, first volume of this series of handbooks, *Tumors of the Central Nervous System.* The volume presents almost all aspects of Gliomas: Glioblastoma tumors. The volume discusses specifically details of relevant molecular genetics, diagnosis (using, for example, biomarkers, immunohistochemistry, and imaging techniques), therapies (including targeted therapy, resection, chemotherapy and cannabinoids, immunotherapy, hormonal therapy, anti-VEGF therapy, combination of bevacizumab and irinotecan as well as bortezomib and celecoxib, cyclosporine, interleukin-6, interferone, heparin, oncolytic adenovirus, chemovirotherapy, and radiotherapy). A constructive evaluation of commonly used methods for primary and secondary cancer initiation,

progression, relapse, and metastasis is presented. The toxic side-effects of treatments are pointed out. Also are included prognostic factors and crucial role played by cancer stem cells in malignancy. Risk of cancer survivors developing other cancers is pointed out.

There exists a tremendous, urgent demand by the public and the scientific community to address to cancer prevention, diagnosis, treatment, and hopefully cures. This volume was written by 150 oncologists representing 17 countries. Their practical experience highlights their writings which should build and further the endeavors of the readers in this important area of disease. The volume provides unique, individual, practical knowledge based on the vast practical experience of the authors. The text is divided into subheadings for the convenience of the readers. It is my hope that the most up-to-date information contained in this volume will assist the readers in reaching to a more complete understanding of globally relevant cancer syndromes. I am also hoping that this information will help the practicing readers in their clinical work. I am grateful to the contributors for their promptness in accepting my suggestions. I respect their dedication and diligent work in sharing their invaluable knowledge with the public through this volume.

I am thankful to Dr. Dawood Farahi and Dr. Kristie Reilly for recognizing the importance of scholarship (research, writing, and publishing) in an institution of higher education and providing resources for completing this project.

Union, New Jersey M.A. Hayat
July 19, 2010

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Part I
Introduction

Chapter 1

Introduction

M.A. Hayat

Keywords Gliomas · CNS · Astrocytomas · Genetics · Mutation · Temozolomide

Gliomas

Gliomas are the most common tumors accounting for 49% of all primary brain tumors and ~2% of all new cases of cancer in the United States. Approximately, 18,000 new gliomas are diagnosed each year in the United States and >60% belong to the most malignant grade IV glioblastomas. Most of these tumors are untreatable, and patients survive as an average of <12 months, and 16,000 will die of this disease during this time despite 30 years of intensive efforts to find an effective chemotherapy. Even lower grade astrocytomas frequently progress toward a higher grade and hence carry a similarly dismal prognosis. Gliomas are not common neoplasms, for their incidence ranges from 5 to 10 per 100,000 people, although their frequency is slightly increasing. As mentioned earlier, the majority of the CNS tumors are malignant gliomas and their high mortality rate leads this relatively infrequent malignancy into the third and fourth leading cause of cancer-related death among 15- and 54-year old men and women, respectively. In fact, malignant gliomas arise in individuals of any age, but are more common in older persons, with a peak in incidence during the sixth and seventh decades of life.

A glioma is a type of neoplasm that starts in the brain or spine. The name glioma is appropriate because it arises from glial cells. Gliomas are the most frequent tumors of the CNS, especially in the brain. Numerous classification systems are in use. Gliomas are classified based on the cell origin, grade, and location. Based on the cell type, they are classified below (http://en.wikipedia.org/wiki/Glioma):

Ependymomas:	ependymal cells
Astrocytomas:	astrocytes
Oligodendrogliomas:	oligodendrocytes
Mixed gliomas:	cells from different types of glia

Classification based on the grading system (increased cellular density, nuclear atypias, mitosis, vascular proliferation, and necrosis) is given below.

Low-grade:	gliomas are well-differentiated (non-anaplastic)
High-grade:	gliomas are undifferentiated (anaplastic)

Classification based on the location is given below. Gliomas can be classified according to whether they are above or below a membrane in the brain called the tentorium that separates the cerebrum (above) from the cerebellum (below).

Supratentorial:	above the tentorium (in the cerebrum), mostly in adults (70%).
Infratentorial:	below the tentorium (in the cerebellum), mostly in children (70%).

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 1*,
DOI 10.1007/978-94-007-0344-5_1, © Springer Science+Business Media B.V. 2011

Glioblastoma Multiforme

Glioblastoma multiforme is the most frequent primary brain tumor in adults, and accounts for most of the 18,500 primary brain tumor cases diagnosed each year in the United States. Based on standard histopathologic grading, >40% of the CNS tumors are WHO grade IV glioblastoma that accounts for >50% of all malignant gliomas. The incidence of this tumor in the United States is ~2.36 cases/100,000 persons. Glioblastoma is one of the most devastating human cancers because of its rapid growing nature, infiltrating growth, resistance to radiotherapy and chemotherapy, and rapid progression from diagnosis to death. It is a rapidly fatal tumor, and most patients succumb to this disease within 12–18 months from the time of diagnosis. Without therapy, patients die within 4 months, while median survival of those receiving optimal, aggressive treatments, such as surgery, radiation, and chemotherapy, is ~15 months. Despite aggressive management, glioblastoma invariably recurs and prognosis remains dismal, with a median survival of only 3–5 months at recurrence. In fact, this primary brain tumor is virtually incurable despite advances in neurosurgical instrumentation and adjuvant therapies. These statistics clearly show that glioblastoma is among the most aggressive neoplasms. Novel, targeted therapeutic approaches are needed, which are discussed in other chapters.

Glioblastoma tumors display extensive morphological and molecular heterogeneity, and thus may reflect their origin from different population of astrocytes, and possibly from oligodendrocytic and ependymal cell lineages. Glioblastomas, however, consist mainly of undifferentiated anaplastic cells of astrocytic origin, which exhibit marked nuclear pleomorphism, necrosis, and vascular endothelial proliferation. These tumor cells are arranged radially with respect to the necrotic region, and occur most frequently in the cerebrum of adults. Giant cell glioblastoma is a histologic form with large often multinucleated, unusual tumor cells.

The highly invasive nature of glioblastoma makes surgical resection rarely curative. In addition, these invading cell types are more resistant to radiation and chemotherapy. Glioblastoma cells invade initially as single cells, and travel along white matter tracts and blood vessel walls, and through the subpial glial space. Some of these cells travel long distances and do not generally invade through blood vessel walls and/or bone. Glioblastomas rarely metastasize outside the brain. This invasive behavior differs from that shown by other cancer cells that metastasize to the brain. Moreover, the latter invading cells are more delineated from the surrounding brain tissue, subsequently invade short distances as groups of cells, and invade through blood vessel walls and/or bone.

Glioblastoma can be classified into primary type and secondary type. Although these two types develop through mutations of different genetic pathways (see below), both behave in a clinically indistinguishable manner and the survival rates are also similar. Primary glioblastoma shows amplification of the epidermal growth factor receptor (EGFR), accompanied by deletions in the *INK4a* gene with loss of p14 and p16. These tumors also show marked amplification of the loss of heterozygosity (LOH) on chromosome 10 (10q), PTEN mutation, deletion of *CDKN2A* and *MDM2* genes. Primary glioblastomas, in addition, are thought to show overexpression of the G protein coupled receptor 26 (GPR26) (Carter et al., 2009). This biomarker could be a suppressor of primary glioblastoma development. Additional studies are required using larger number of samples to confirm these results.

On the other hand, secondary glioblastoma frequently acquires mutations within the tumor suppressor protein p53 (*p53*) (Dai and Holland, 2001). Such mutations allow the accumulation of additional aberrations, resulting in the progression of malignancy from low-grade astrocytoma to high-grade glioblastoma, but rarely in the development of primary glioblastoma. Secondary glioblastomas also show overexpression of PDGF and PDGF receptors.

Molecular Genetics

Complex biology and molecular heterogeneity of these tumors have made it difficult to develop effective therapy. Recent studies have focused on deciphering the molecular biology of gliomas. These studies indicate that multiple chromosomal abnormalities, receptor anomalies, and oncogene and tumor suppressor dysregulation are characteristics of high-grade gliomas (Maher et al., 2001).

Genetic studies demonstrate that primary or de novo giloblastomas typically are found in older patients

with alterations in the EGFR but without *TP53* mutations, while secondary glioblastomas tend to arise from gradual progression of lower-grade lesions with primarily *TP53* mutations but without changes in the EGFR. More recent microarray studies indicate that the glioblastoma tumor genotype corresponds with survival phenotype, and that expression data can be used to classify these tumors in genomic subgroups with phenotypic significance (Marko et al., 2008). In this study, 43 genes code for proteins that may be functionally significant in the molecular genetics of glioblastomas. This information can be used to assign unknown tumors into genotypic subgroups that associate directly with the survival phenotypes. Although these and other related findings are beginning to contribute to decisions regarding patient management, their translation into clinically relevant context has been difficult. Thus, a persistent gulf exists between glioblastoma research and treatment of this disease.

In the past, cytogenetic studies of human gliomas have implicated a gain of chromosome 7p and loss of chromosome 10q as important markers of glioblastoma. Other genetic studies have identified EGFR (HER-1) as the gene most frequently increased in gene dosage as a result of the 7p gain, whereas 10q deletions target phosphatase and tensin homolog (*PTEN*) gene. Both EGFR and PTEN control the activation state of the Ras-Raf-mitogen activated protein kinase (MAPK) and phosphoinositol–3–Akt pathways that control cell proliferation, growth, and apoptosis in glioblastoma (McLendon et al., 2007). *PTEN* is a tumor suppressor gene located on the long arm of chromosome 10 at 10q23, and in its mutated form is most common in solid cancers, while EGFR protein is overexpressed not only in brain tumors but also in many other cancer types.

Both *EGFR* and *PTEN* mutations also cause aberrant activation of the phosphoinositide – 3 – kinase pathway. This pathway activates multiple down-stream kinases, including protein kinase C type 1 (PKC1) (Ohgaki and Kleihues, 2007). A recent study demonstrates that PKC_1 is activated in glioblastoma because of aberrant upstream P13K signaling. Repression of RhoB is a key downstream event in PKC_1 signaling, leading to enhanced cell motility (Baldwin et al., 2008). This repression by PKC_1 also provides a mechanism for down regulation of RhoB in glioblastoma and the PKC_1– mediated loss of actin stress fibers. In the light of this information, PKC_1 should be evaluated further as a potential drug target for glioblastoma therapy.

Glioblastoma Stem Cells

Glioblastoma tumors were among the first solid tumor in which stem cell-like features (cancer stem cells) were identified. Such cells constitute a subpopulation of tumor cells that later differentiate into progenitor – like tumor cells or differentiated tumor cells. Biological properties of cancer stem cells are one of the reasons for the failure of chemotherapy in long-term survival of glioblastoma patients. It is known that a number of tumor types overexpress multidrug resistance proteins that protect them against cytotoxic drugs that are able to kill proginator and differentiated cells. As a result, cancer stem cells give rise to recurrent tumors. A recent study has shown that temozolomide preferentially eliminates glioblastoma cancer stem cells and prolongs the survival of patients (Beier et al., 2008). This drug spares more differentiated tumor cells.

However, the relevant question is whether chemoresistance of glioblastoma stem cells is due to reduced drug uptake or due to drug efflux. An in vitro study indicates that neither of these two alternatives are fully applicable to answer this question (Eramo et al., 2006). According to this study, drug resistance by glioblastoma stem cells depends on abnormalities of apoptotic pathways such as over-expression of anti-apoptotic factors or silencing of key death effectors. In other words, altered expression of apoptosis – related proteins may render normal neural stem cells or glioblastoma stem cells strongly resistant to death receptor ligands and inflammatory cytokines. More extensive studies are required to fully understand the mechanisms of chemoresistance by glioblastoma stem cells.

Kang and Kang (2007) and Kang et al. (in this volume) have developed a dissociated cell system for fascilitating identification and characterization of cancer stem-like cell subpopulations in glioblastoma, which showed resistance to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, Carmustine) chemotherapy. (This drug is the most commonly used pharmacological agent in chemotherapy of glioblastoma following surgery and radiation therapy). This and other similar

studies clearly indicate that glioblastoma contains subpopulations of cells with intrinsic resistance to therapy, which can repopulate the tumor after treatment. The identification of the cell types involved in drug resistance phenomenon is critical in improving the therapeutic outcome of glioblastoma and better anticancer strategies.

Treatment

The choice of treatment for malignant gliomas, including glioblastoma, should depend on various factors such as age of the patient, the volume and localizations of the mass (tumor), and the quality of life considerations. Therapeutic alternatives include chemotherapy, total resection, subtotal resection with postoperative radiotherapy, cyst aspiration and/or biopsy followed by radiotherapy. A number of therapeutic agents, including temozolomide, nitrosoureas, procarbazine, etoposide, irinotecan, and platinum analogs, are being used for treating recurrent gliomas, but responses are usually transient (Padros et al., 2006). Treatment of drug resistant glioma with imatinib mesylate and chlorimipramine is described by Bilir and Erguven in this volume.

There has been increasing hope that temozolomide (an alkylating agent) is efficacious against malignant gliomas, as this agent has shown activity in the treatment of newly diagnosed and recurrent gliomas (Stupp et al., 2005). Temozolomide, in addition, is relatively well-tolerated. However, the treatment with this drug, like other chemotherapeutic agents, is resisted by gliomas. A known factor responsible for the resistance is methylguanine – 0^6 – methyltransferase (MGMT) expression. Clinical trials have demonstrated that promoter hypermethylation of the MGMT gene and low level expression of this protein are associated with an enhanced response to alkylating agents (Sasai et al., 2008). Thus, MGMT is a molecular marker for patients with glioblastoma (Hegi et al., 2004). For additional information, see page... and the chapter by Beir and Beir in this volume.

Recently, encouraging results were obtained by using liposomal peglyated doxorubicin (PEG-DOX) in patients with glioblastoma (Glas et al., 2007). This drug shows moderate efficacy against this malignancy within and outside clinical studies. Telozolomide is an alkylating drug, while PRG-DOX is non–alkylating. PEG-DOX can be used in combination with telozolomide to achieve a synergistic efficacy. However, additional studies are needed to recommend using PEG-DOX.

Another point of view is that comparatively, ionizing radiation is the most effective therapy for glioblastoma (WHO grade IV glioma); however, this therapy, as pointed out earlier, remains only palliative because of radioresistance. Although the mechanisms responsible for this resistance have not been fully elucidated, some evidence is available indicating that cancer stem cells contribute to glioblastoma radioresistance through preferential activation of the DNA damage checkpoint response and an increase in DNA repair capacity. Recent studies show that CD133 (Prominin-1) – expressing glioma cells survive ionizing radiation in increased proportions compared with most tumor cells that lack CD133 (Bao et al., 2006). Thus, targeting DNA damage checkpoint response in cancer stem cells may overcome the radioresistance, and offer a therapeutic model for malignant brain cancers.

Glioblastomas present as diffuse tumors with invasion in normal brain frequently recur or progress after radiation as focal masses, suggesting that only a fraction of tumor cells is responsible for regrowth. It has been accepted that glioblastomas contain a small number of cancer stem cells that have the capacity to self-renew and are essential for the continuous outgrowth of the tumor. These cancer stem cells are highly tumorigenic, while the more differentiated glia-like cells, which form the majority of cells in glioblastoma tumors, are only poorly tumorigenic.

In the light of limited effectiveness of temozolomide or radiotherapy alone against glioblastoma, the temozolomide-radiotherapy paradigm is considered by some workers to be the best therapy for this disease. Optimal treatment of patients with newly diagnosed glioblastoma consists of the use of this drug concurrently with radiotherapy and adjuvantly thereafter. Radiotherapy is applied at the dosage of 75 mg/m^2/day for 42 consecutive days, followed by 6 adjuvant cycles of this drug at a dosage of 150–200 mg/m^2/day for 5 consecutive days.

Antivascular EGF therapy is another approach being used against malignant gliomas. This approach is based on the realization that rapidly dividing glioma cells require adequate oxygen and nutrient delivery through coopting existing blood vessels and the

formation of new vessels (angiogenesis). The delivery of these substances can be reduced or stopped by treating the patients with antivascular growth factor human monoclonal antibody bevacizumab (de Goot and Yung, 2008). According to these authors, the use of this antibody, in combination with irinotecan, can significantly improve the 6-month prognostic progression-free survival of patients with malignant gliomas. However, the impact of cytotoxic chemotherapy on the efficacy of the antibody remains to be answered.

Reactive oxygen species (ROS) are mediators of various cell signaling pathways. Nox family NADH oxidases are a major source of ROS production in various cell types, which play a crucial role in many physiological and pathological processes. NOX4 is prominently expressed in various neuroepithelial tumors, and its expression is critical for neoplastic proliferation. Shono et al. (2008) have demonstrated that the expression levels of NOX4 mRNA were significantly higher in glioblastoma (WHO IV) than those in other astrocytomas (WHO II and III). They also indicated that specific knockdown of NOX4 expression with RNA interference resulted in cell growth inhibition and enhanced induction of apoptosis by chemotherapeutic agents, such as cisplatin, in glioma cell lines. In the light of this information, development of treatments targeting NOX4 in human malignant gliomas should be explored. The delivery of oncolytic adenovirus into intracranial glioma is discussed by Kanzler et al. in this volume

In conclusion, the therapeutic failure in glioblastoma patients is, in part, attributable to the highly diffuse invasiveness of these tumors. The difficulties in detecting and destroying (excising) such tumors are related to the migration of single glioma cells within healthy brain tissue at large distances from the main primary tumor. Such disseminated cancer cells escape cytoreductice surgery and radiotherapy.

Temozolomide

Temozolomide (TMZ) is the most commonly used chemotherapeutic drug for newly diagnosed glioblastoma and recurrent gliomas. It is a DNA – alkylating agent, and is usually well-tolerated depending on the dosage. Sensitivity to this drug is correlated with the hypermethylation of the 0^6 – methylguanine – DNA – alkyltransferase promoter glioma cells. This reaction leads to the absence of AGAT DNA repair protein that repairs the 0^6 – methylguanine adduct created by TMZ (Hegi et al., 2006). In other words, TMZ achieves its cytotoxic effect mainly by methylating the 0^6 position of guanine. This adduct is removed with the DNA repair protein 0^6 – methylguanine – DNA – methyltransferase (MGMT) that is expressed in a subgroup of glioblastoma. MGMT is a repair enzyme that removes promutagenic 0^6 – methylguanine adducts in DNA to protect cells from acquisition of G:C —▶A:T mutations.As expected, TMZ is most effective against tumors lacking MGMT expression due to a methylated MGMT promoter.

TMZ also exerts antitumor effects by impairing angiogenic processes. In vitro and in vivo studies have shown antiangiogenic activity by TMZ even when it is used alone (Mathieu et al., 2008). The efficacy of TMZ can be further enhanced by combining this treatment with bevacizumab. This antibody also has an antiangiogenic effect although with a different mechanism of action. Antiangiogenic compounds also increase the therapeutic benefits of radiotherapy (Nieder et al., 2006). A phase 2 pilot study of bevacizumab in combination with TMZ and regional radiotherapy for the treatment of patients with newly diagnosed glioblastoma recently reported that toxicities were acceptable to continue enrollment, and a preliminary analysis of efficacy showed encouraging mean progression-free survival (Lia et al., 2008).

Temozolomide is often prescribed five times for a 28 day regimen, at a dose of 150–200 mg/m^2 (Neyns et al., 2008). This treatment depletes AGAT activity in peripheral blood mononuclear cells and may improve the antitumor activity. Daily dosing for 6 weeks during radiation therapy has become the standard care for newly diagnosed glioblastoma. This regimen is thought to have low acute toxicity, in terms of causing thrombocytopenia and neuropenia, no cumulative toxicity, and not associated with an increased incidence of secondary malignancies, such as treatment – related myelodysplastic syndrome, acute leukemia, or aplastic anemia.

Although TMZ significantly increases the proportion of patients surviving for ~2 years, longer survival is still rare. Caution is warranted in the use of dose-dense regimens of TMZ for extended periods of time because of its immunosuppression effect. TMZ is a

potentially carcinogenic alkylating drug and thus poses the risk for secondary malignancies. Temozolomide-based chemotherapy for glioblastoma is discussed by Beier and Beier in this volume.

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Chapter 2

Molecular Classification of Gliomas

Kikuya Kato

Abstract Molecular markers have been intensively explored to overcome the limitations in the histopathological diagnosis of gliomas. Gene expression profiling, i.e., genome wide analysis of gene expression, has given rise to new molecular classification schemes. In particular, diagnostic systems for differential diagnosis of anaplastic oligodendroglioma and glioblastoma, or for prediction of prognosis for displastic astrocytoma, anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma have been constructed through studies employing machine learning. Classification by gene expression profiling has also revealed molecular classes with distinct biological characteristics not detected by histopathology. The promoter methylation of the O^6-methylguanine methyltransferase gene has been reported as prognostic as well as predictive for alkylating agents such as temozolomide in glioblastoma. Partly due to technical difficulties in detection of methylation with PCR, the results of studies are not necessarily consistent. However, a recent study with bisulfite sequencing revealed good prognostic ability, which promises future clinical application. Among other molecular markers, 1p-/19q- has been established as a prognostic factor in oligodendroglial tumors, and is being used as a diagnostic test in several institutes. *IDH1* and *EGFR* are being explored for differentiation of primary and secondary glioblastoma, and as a possible predictive factor for molecular targeted drugs, respectively. Adequate prospective studies will help evaluate the ability of the above classification schemes as diagnostics tests to support histopathological diagnoses.

Keywords Gene expression profiling · MGMT promoter methylation · 1p-/19q- · IDH1

Introduction

Risk assessment is an important clinical aspect for malignant tumors, including gliomas. Invasion and metastasis are significant features of malignant tumors, and a stage classification system has been invented to simplify the interpretation of complicated pathological information from certain tumors, such as gastrointestinal cancers. However, gliomas are macroscopically less complicated, are restricted to the brain, and do not require any simplification of the pathologic information. Because the histology of a glioma is informative for assessing the malignant potential of gliomas, histological classification, especially grade classification, is critical for predicting prognosis. Currently, the standard for classifying tumors of the central nervous system is the 2007 version of the WHO classification standard (Louis et al., 2007).

However, the standard grade classification system is limited in diagnostic accuracy, and there is a wide range in the prognosis even within the same grade. Diagnosis depends on individual pathologists, and the results are often not concordant among multiple pathologists (Coons et al., 1997). Therefore, it is desirable to have more objective diagnostic systems.

Recent developments in anti-cancer drug research have resulted in a new type of diagnostic approach that is often called “personalized medicine.” The goal of personalized medicine is the selection of patients

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M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 1*,
DOI 10.1007/978-94-007-0344-5_2,

with particular molecular diagnoses for treatment with a specific anti-cancer drug. Temozolomide (Temodar) is an imidazotetrazine-based second-generation alkylating agent, the leading compound in a new class of chemotherapeutic agents, and is now a standard for post-operative adjuvant chemotherapy for glioblastoma (Stupp et al., 2005). It has been shown that the methylation status of the O^6-methylguanine methyltransferase (*MGMT*) gene promoter is strongly correlated with the efficacy of temozolomide (Hegi et al., 2005). If a methylation assay could be established as a diagnostic test, then oncologists may quickly and effectively identify patients who may benefit from treatment with temozolomide. Some molecular-targeted drugs, such as trastuzumab or gefitinib, are already used for patients who undergo routine diagnostic tests that involve selection based on aberrations of target genes; the selection process allows for the treatment of patients who will successfully respond to the therapy. Because most anti-cancer drugs in the pharmaceutical pipeline are molecular targeted, personalized medicine will definitely be important for the treatment of gliomas as well.

Several molecular changes in gliomas have been extensively studied for possible clinical applications. In this review, I will focus on two topics: gene expression profiling and *MGMT* promoter methylation. Several studies have indicated a strong correlation between gene expression patterns and the malignant potential of gliomas. In addition, *MGMT* promoter methylation has also been extensively studied. Additional molecular markers, such as 1p-/19q-, *EGFR*, and *IDH1*, will also be discussed in the last part of this review.

Gene Expression Profiling: General Introduction

Gene expression profiling is the genome-wide analysis of gene expression, i.e., the simultaneous measurement of the gene expression level of thousands of genes or ideally, all the genes in the genome. Technological advancements such as DNA microarrays have been essential for gene expression profiling. After the introduction of DNA microarrays, researchers have applied this technology to cancer diagnostics. One example of the success in using this approach is the ability to predict prognosis for breast cancer patients: van't Veer and colleagues found a strong correlation between gene expression patterns and the malignant potential of breast cancer (van't Veer et al., 2002). This work led to the development of MammaPrint, a microarray-based diagnostic system that assists in the decision-making process of whether to treat the patient with adjuvant therapy.

Gene expression profiling studies are characterized by the need for specific statistical techniques to handle the high volume of data. Aside from developing diagnostic systems, many studies have focused on the biological aspects of gene expression profiles. For this purpose, statistical approaches that are categorized as "class discovery" or "unsupervised feature extraction" have been used. The most popular technique is cluster analysis (Eisen et al., 1998), which creates groups of genes or samples based on similarities found in the gene expression profiles. In this type of analysis, the biological characteristics of each group are deduced from gene function and clinical information. However, because the classification obtained by class discovery is not necessarily correlated with outcomes or clinical parameters, many studies have performed class discovery mainly with genes known to be correlated with clinical outcomes. This approach enables easy accessibility to biological discussions and often maintains a correlation with clinical parameters. However, such classification has not been optimized to function as a diagnostic test. As discussed previously (Dupuy and Simon, 2007), class discovery is not the method of choice to construct a diagnostic system.

To construct a diagnostic system, different statistical approaches categorized as "supervised prediction" are used. Supervised prediction was originally developed in the field of machine learning. First, diagnostic genes that are correlated with a specific outcome, such as survival, are selected. Then, a classification algorithm is constructed to calculate a single diagnostic score from the expression values of the diagnostic genes (Dupuy and Simon, 2007). The main feature of this type of diagnostic system is the requirement of such an algorithm. Conventional molecular diagnostic tests usually use the level of a molecular marker as a diagnostic score, without requiring a complicated algorithm. Considering this feature, the Food and Drug Administration (FDA) created a new category of diagnostic tests known as "in vitro diagnostic multivariate index assays" (IVDMIA). MammaPrint is the first IVDMIA cleared by the FDA.