Neurorehabilitation in Neuro-Oncology

Michelangelo Bartolo
Riccardo Soffietti
Martin Klein
Editors

Springer

Neurorehabilitation in Neuro-Oncology

Michelangelo Bartolo
Riccardo Soffietti • Martin Klein
Editors

Neurorehabilitation in Neuro-Oncology

Springer

Editors
Michelangelo Bartolo
Department of Rehabilitation
Neurorehabilitation Unit, Habilita S.p.A.
Zingonia/Ciserano, Bergamo
Italy

Riccardo Soffietti
University and City of Health and Science
Department Neuro-Oncology
Turin, Torino
Italy

Martin Klein
Department of Medical Psychology
VU University Medical Center Department
of Medical Psychology
Amsterdam
The Netherlands

ISBN 978-3-319-95683-1 ISBN 978-3-319-95684-8 (eBook)
https://doi.org/10.1007/978-3-319-95684-8

Library of Congress Control Number: 2019930720

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

A diagnosis of cancer radically alters the patient's approach to daily life. Due to advances in therapeutic strategies, the number of neuro-oncological survivors is increasing, so that consequently the impact of neuro-oncological rehabilitation of these patients gains in importance. The multidisciplinary approach not only involves physical function, fatigue, and pain but also sexual function, cognitive function, depression, employment, nutrition, and participation.

Good evidence exists for the use of physical therapy in reducing paresis and fatigue after cancer treatment, improving upper and lower extremity function and trunk control. The interventions involving pain, sexual function, cognitive function, and eventual return to employment are equally important. The effect of neurorehabilitation in these parameters is not clearly demonstrated, and more research should be undertaken.

Leopold Saltuari
Department of Neurology
Hochzirl Hospital
Zirl, Austria

Preface

The physical, cognitive, and psychosocial disorders of patients with brain tumors are numerous: in addition to neurological disorders, patients are confronted with limitations in sensory, motor, and cognitive functions as well as depression, anxiety, and fatigue as common consequences of brain tumors and their treatments. Since these disturbances may negatively affect patient's quality of life by producing long-term disability, patients may benefit from rehabilitative interventions.

The rehabilitation in the field of neuro-oncology has to be modified over time in line with the different needs in different stages of disease the patient is confronted with. In the early disease stages, rehabilitation aims at restoring functions after cancer therapies or preventing functional deterioration, while in the advanced disease stages, neurorehabilitation run in parallel to palliative care aims to favor patients' independence, prevent complications, and ultimately improve quality of life.

Chapters devoted to neuro-oncological neurorehabilitation from different disciplines are rarely included in a single volume in the field of clinical oncology, although a holistic approach to persons affected by brain tumors should in a modern vision also include the therapeutic opportunities offered by neurorehabilitation.

This book aims to provide a comprehensive, practical, and state-of-the-art guide to neurorehabilitation strategies of persons affected by tumors of the nervous system by addressing the latest developments from different subfields comprising current neuro-oncological rehabilitation.

The book is structured in two main parts: the first part is devoted to the basics of brain tumors and the main clinical features of tumors of the nervous system as well as to the essentials of therapeutic options; the second part is focused on rehabilitative issues and provides the tools for a holistic care of persons affected by a neuro-oncological disease.

With this book, we hope to provide a useful contribution to the work of all health professionals who are involved in the multidisciplinary care of persons affected by central nervous system tumors.

We would like to thank Springer Nature Switzerland AG, especially Mr. Andrea Ridolfi and Ms. Beauty Christobel Gunasekaran for their excellent contribution.

We thank in advance any reader who will report errors, omissions, or just has suggestions.

Zingonia di Ciserano, Italy — Michelangelo Bartolo
Turin, Italy — Riccardo Soffietti
Amsterdam, The Netherlands — Martin Klein

Contents

Introduction

1

Michelangelo Bartolo

Cancer has become one of the leading causes of death. If recent trends in the incidence of major cancers and population growth are seen globally in the future [1, 2], it is predicted there will be 23.6 million new cancer cases worldwide annually by 2030 [3].

Over the last 30 years, there has been an increasing incidence of brain tumours in many countries. At the same time, progress in the multimodal treatment has modestly improved survival rate. This has resulted in an increased number of brain tumours patients living longer with residual neurological deficits [4–6]. Moreover, since one third of primary brain tumours are considered malignant and aggressive, and advanced treatment strategies that show better outcomes gain ground, also late effects of treatment are increasingly been recognised as crucial. In fact postsurgical morbidity, acute, subacute, and late radiation effects on normal brain tissue, chemotherapy induced toxicity, as well as the effects of high-dose corticosteroids and anticonvulsants can all have adverse effects [7, 8].

More than 50% of brain tumour patients show three or more concurrent symptoms and/or deficits [9], evidently depending on tumour size, tumour location and lateralisation, and the invasive nature of the tumour; the most common symptoms include seizures, functional impairment, cognitive deficits, weakness, visual-perceptual deficits, sensory loss, and bowel and bladder dysfunction. Other neurologic deficits in decreasing incidence are cranial nerve palsies, dysarthria, dysphagia, and ataxia [7, 10–12]. Tumour-related fatigue remains one of the most frequent and bothersome adverse events reported by brain cancer patients during and after treatment, as it reduces the ability to complete medical treatments, and undermines the quality of life (QoL) [8].

A diagnosis of cancer is expected to cause a psychological burden by itself, but psychological factors, such as stress, anxiety, and depression can also negatively

M. Bartolo (✉)
Department of Rehabilitation, Neurorehabilitation Unit, HABILITA, Bergamo, Italy
e-mail: michelangelobartolo@habilita.it

M. Bartolo et al. (eds.), *Neurorehabilitation in Neuro-Oncology*,
https://doi.org/10.1007/978-3-319-95684-8_1

impact the disability and the person [13]. These aspects must be carefully considered in the global evaluation of the person and treatment planning because these aspects may represent confounding factors, e.g. emotional disturbances may cause impairment on neuropsychological testing that otherwise would be attributed to therapy or tumour.

Overall, these symptoms may cause significant disability similar to those seen in patients commonly admitted to rehabilitation programmes and have a relevant impact on patients' daily life, hindering their ability to function independently and to maintain usual family and social roles, influencing ultimately their QoL as well as the QoL of their family members [14]. Consequently, patient-centred care, focusing on improving QoL in patients with brain tumours, has become relevant. In recent years, many clinical trials evaluating new treatment options for brain tumour patients incorporated QoL as a relevant secondary or even primary outcome measure in addition to overall survival and progression-free survival [15]. In fact, assessment of QoL has become mandatory in all European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group clinical trials.

Actually, considering the limited survival of neuro-oncological patients, it is increasingly recognised that the choice of treatment also should entail careful consideration of its effects on the health-related quality of life (HRQoL) during the remaining survival time, being HRQoL an independent prognostic factor in both primary and metastatic brain tumours [16].

The conceptual framework proposed by the World Health Organisation: International Classification of Functioning, Disability and Health (ICF) [17] suggests that health problems may impact on many areas of a person's life and describes three different levels of impact of a health condition. The first level concerns the domain of impairment (i.e. basic level describing a problem in body function or structure as a result of disease or injury, e.g. a memory problem). The second level relates to limitations in activities or tasks that a person can perform (consequences of the impairment in daily life, e.g. the patient cannot find his car keys). The third level gauges the extent to which a person can participate in societal interactions (e.g. the patient cannot go to a birthday party of a distant friend). The ICF importantly also includes the impact of the environment on the person and describes functioning from both an individual and societal perspective [18], providing a suitable approach to explore the functional difficulties experienced by people living with cancer. According to the ICF, HRQoL as a multidimensional concept covering physical, psychological, and social domains, as well as symptoms induced by the disease and its treatment, represents a more integrated way to measure patients' functioning and well-being.

In this scenario, as cancer is viewed as a chronic disease, rehabilitation process becomes of paramount relevance in brain tumour patients when compared to other malignancies because of their extremely high rate of associated disability. Several studies focused on the issue of the functional outcome of brain tumour patients, showing that rehabilitative treatment offers significant benefit to these patients, comparable to functional gain reported for patients affected by other neurological

diseases, like stroke and traumatic brain injury [7, 11, 14]; preliminary data also demonstrate the effectiveness of cognitive rehabilitation in this population [19, 20]. A recent meta-analysis showed that physical exercise and psychological support are also useful for reducing tumour-related fatigue during and after treatment, with significantly better efficacy than drug therapy [21].

According to the "simultaneous care" model [22], rehabilitation should have a role in cancer patients both in early stage of disease, for restoring function after cancer therapy, and in the advanced stage of disease as important part of palliative care with the aim to maintain patients' independence as long as possible. Early initiation of rehabilitative and palliative care integrated with standard anticancer therapy seems to be effective for symptom management, resulting in the improvement of the QoL.

However, despite the high incidence of neurological and functional deficits in brain tumour patients and preliminary data supporting rehabilitation, in this population rehabilitation treatments are not as well established as it is for patients with other neurological conditions, probably because neuro-oncological patients are not considered good candidates to rehabilitative intervention due to their poor prognosis associated with continuing tumour growth despite intensive treatment. Literature evidence, in fact, demonstrates that rehabilitation services are difficult to access for brain tumour patients, poorly utilised and referrals were sporadic and consequential, indicative of poor awareness of rehabilitation for people with cancer among potential referrers [23].

Nevertheless, we can identify several key points that need to be addressed to develop successful care provision models that contribute to continuity of care and autonomy of the person with disability due to oncological disease, including:

(a) training for the health professionals, who should adopt an integrative approach to the person rather than providing a performance or service;
(b) implementation and dissemination of the methodology for a coordinated delivery of multidisciplinary rehabilitation, in consideration of the complexity of patient's needs (clinical, functional, cognitive, psychological, spiritual), using a holistic biopsychosocial model of care, as defined by the ICF. The management of brain tumours represents by definition a model for multidisciplinarity because of the multitude of problems which are encountered that require a multidisciplinary approach with health care providers skilled in a variety of disciplines;
(c) customisation of the rehabilitation project and programmes, defining mid- and long-term (when possible) goals, shared with the patient and caregiver, meaningful and realistic;
(d) develop ad-hoc tools to measure efficacy, efficiency, quality, and appropriateness of the interventions. The tools should take into account the person, including biological, medical, functional, and psycho-cognitive variables, as well as social interaction, participation, and QoL;
(e) continuity of care, offering dedicated care pathways that include rehabilitative care in all the stages of the disease (*simultaneous care*);

(f) focus on patient's and caregiver's QoL, adding more appropriate evaluation tools other than traditional outcome measures such as overall survival and progression-free survival.

The actual gap seems to be mostly educational and there is a great need to enhance training and knowledge for health professionals involved in the care management of neuro-oncological patients [24]. Health professionals need to meet the challenges posed by this disease and its disabilities, considering rehabilitation treatments an opportunity to obtain the best possible outcomes for these persons.

References

1. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol. 2012;13(8):790–801.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
3. De Santis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252–71.
4. Kirshblum S, O'Dell MW, Ho C, Barr K. Rehabilitation of persons with central nervous system tumors. Cancer. 2001;92:1029–38.
5. Rose JH, Kypriotakis G, Bowman KF, Einstadter D, O'Toole EE, Mechekano R, et al. Patterns of adaptation in patients living long term with advanced care. Cancer. 2009;115(18):4298–310.
6. Thorne SE, Oliffe JL, Oglov V, Gelmon K. Communication challenges for chronic metastatic cancer in an era of novel therapeutics. Qual Health Res. 2013;23(7):863–75.
7. Vargo M. Brain tumor rehabilitation. Am J Phys Med Rehabil. 2011;90(Suppl):S50–62.
8. Asher A, Fu JB, Bailey C, Hughes JK. Fatigue among patients with brain tumors. CNS Oncol. 2016;5(2):91–100.
9. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. Am J Phys Med Rehabil. 2001;80(5):346–50.
10. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, et al. Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. J Neurooncol. 1997;34(3):263–78.
11. Giordana MT, Clara E. Functional rehabilitation and brain tumour patients. A review of outcome. Neurol Sci. 2006;27:240–4.
12. Posti JP, Bori M, Kauko T, Sankinen M, Nordberg J, Rahi M, et al. Presenting symptoms of glioma in adults. Acta Neurol Scand. 2015;131(2):88–93.
13. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. Oxford: Oxford University Press; 2012.
14. Bartolo M, Zucchella C, Pace A, Lanzetta G, Vecchione C, Bartolo M, et al. Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. J Neurooncol. 2012;107(3):537–44.
15. Mauer ME, Bottomley A, Taphoorn MJ. Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. Curr Opin Neurol. 2008;21(6):745–53.
16. Meyers CA, Hess KR, Yung WK, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol. 2000;18(3):646–50.
17. World Health Organization. International classification of functioning, disability, and health (ICF). Geneva: WHO; 2001.

18. Bickenbach J, Rubinelli S, Stucki G. Being a person with disabilities or experiencing disability: two perspectives on the social response to disability. J Rehabil Med. 2017;49(7):543–9.
19. Zucchella C, Capone A, Codella V, De Nunzio AM, Vecchione C, Sandrini G, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. J Neurooncol. 2013;114(1):93–100.
20. Gehring K, Sitskoorn MM, Gundy CM, Sikkes SA, Klein M, Postma TJ, et al. Cognitive rehabilitation in patients with gliomas: a randomized controlled trial. J Clin Oncol. 2009;27(22):3712–22.
21. Mustian KM, Alfano CM, Heckler C, Kleckner IR, Leach CR, Mohr D, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3(7):961–8.
22. Meyers FJ, Linder J. Simultaneous care: disease treatment and palliative care throughout illness. J Clin Oncol. 2003;21:1412–5.
23. McCartney A, Butler C, Acreman S. Exploring access to rehabilitation services from allied health professionals for patients with primary high-grade brain tumours. Palliat Med. 2011;25(8):788–96.
24. Bartolo M, Zucchella C, Pace A, De Nunzio AM, Serrao M, Sandrini G, et al. Improving neuro-oncological patients care: basic and practical concepts for nurse specialist in neurorehabilitation. J Exp Clin Cancer Res. 2012;31:82.

Basics of Brain Tumor Biology for Clinicians

2

Hans-Georg Wirsching and Michael Weller

2.1 Brain Tumor Risk

Hereditary cancer syndromes are overall rare and account for a small minority of primary brain tumors and of cancers forming brain metastases [1, 2]. Most of these syndromes are caused by defects in DNA repair and tumor suppressor genes. Examples include Li-Fraumeni syndrome caused by mutations in the tumor suppressor genes *TP53* or *CHEK*, which can cause the formation of gliomas and breast cancer; Turcot syndrome caused by mutation of the tumor suppressor gene *APC,* or of the DNA mismatch repair genes *MLH1* and *PMS2*, causing the formation of colon cancer, medulloblastoma and, less commonly, gliomas; neurofibromatosis types I and II caused by mutations in the tumor suppressor genes *NF1* and *NF2*, which are associated with the formation of gliomas and breast cancer (*NF1*), and with the formation of multiple meningiomas (*NF2*); the hereditary breast and ovarian cancer (HBOC) syndrome most commonly caused by mutations in the DNA damage response genes *BRCA1* or *BRCA2*; Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPCC), which is caused by mutations in any of the mismatch DNA repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1,* or *PMS2,* which is associated with colorectal cancer and, less frequently, with kidney and primary brain cancers.

Other endogenous risk factors for brain tumors include risk alleles associated with the formation of gliomas in genes involved in telomere biology (*TERT, RTEL1*), in the gene encoding the epidermal growth factor receptor, *EGFR*, and in *TP53* [3]. However, the overall low penetrance of each of these risk alleles supports a polygenic pathomechanism of gliomagenesis. Risk alleles for the formation of brain metastases in breast cancer patients have been identified among genes of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway [4]. Allergy is

H.-G. Wirsching · M. Weller (✉)
Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland
e-mail: michael.weller@usz.ch

M. Bartolo et al. (eds.), *Neurorehabilitation in Neuro-Oncology*,
https://doi.org/10.1007/978-3-319-95684-8_2

associated with a decreased risk for gliomas [5] and probably also for meningiomas [6]. Meningiomas are more common in women than in men (3.5:1) [7]. A tendency to spontaneous growth arrest in post-menopausal women and the presence of progesterone receptors suggest the contribution of hormonal factors to the pathogenesis of at least a subgroup of meningiomas, albeit hormonal treatments of meningioma patients have been futile [8, 9].

Exogenous risk factors for primary brain tumors include ionizing irradiation as the only established exogenous risk factor for the development of gliomas and meningiomas, but the overall contribution of these cases to the incidence of both entities is marginal [10–15]. Exogenous risk factors for the formation of brain metastases have not been identified.

2.2 Hallmarks of Brain Tumors

2.2.1 Brain Tropism

A characteristic feature of primary brain tumors is the fact that beyond anecdotal reports, primary brain tumors do not metastasize to distant organs, i.e., they exhibit a distinct brain tropism [16]. In reverse, the formation of brain metastases from circulating cancer cells also occurs late during the disease course of most cancers, usually following the occurrence of metastases in other organs [17]. This is of note given that the brain is a highly vascularized organ receiving about 20% of the cardiac output, suggesting that the mere stochastic probability of cell-vessel contacts does not determine metastasis formation.

The blood–brain barrier (BBB) causes demarcation of the brain from circulating cancer cells. However, the lack of distant metastases of primary brain tumors is not explained by the cellular barrier function of the BBB, because disruption of the BBB is a key feature of most primary brain tumors, and a priori absent in meningiomas, which likewise rarely metastasize to distant organs. Interactions with parenchymal organ cells are thought to underlie brain tropism of primary brain tumors, but overall the underlying cause is elusive.

2.2.2 Angiogenesis

Extensive vascularization is common to many brain tumors and metastases [18]. Qualitatively, these new blood vessels are often tortuous and leaky with a disrupted BBB, allowing extravasation of larger molecules and yielding an increase in interstitial fluid pressure. The resulting vasogenic edema contributes significantly to the morbidity of patients with brain tumors by causing headache and neurological deficits. Angiogenesis is primarily driven by the vascular endothelial growth factor (VEGF) [18]. Proliferation of abnormal blood vessels is a defining criterion of glioblastoma, the most common malignant primary brain tumor constituting about half of all gliomas [19]. The anti-VEGF antibody bevacizumab effectively reverts

vasogenic edema and induces blood vessel normalization in these tumors, thereby alleviating symptom burden [18]. However, overall survival of patients with glioblastomas is not affected by anti-angiogenic therapy, as will be discussed in more detail in Chap. 6.

2.2.3 Immunosuppression

Bone-marrow derived immune cells are rare or absent in the normal brain, rendering the brain an "immune-privileged" organ that is widely protected from innate or adaptive immune reactions. The relatively low incidence of primary brain tumors compared to other cancers is striking in that context, because elimination of abnormal, cancerous cells by the immune system has traditionally been considered a key mechanism preventing cancer development in other organs. Once cancer has developed or seeded in the brain, several mechanisms mediate the evasion of anti-cancer immune responses [20]: (1) secretion of immunosuppressive molecules such as TGFβ-2, PGE, IL-10, and FGL2 by tumor cells, (2) decreased antigen processing and presentation, e.g., through down-regulation of major histocompatibility complex (MHC)-I molecules on tumor cells, (3) recruitment of tumor-associated macrophages and reprogramming towards an immunosuppressive phenotype through secretion of M-CSF, TGFβ-1, and IL-10 by tumor cells, (4) direct inhibition of adaptive immune responses through expression of immune checkpoint molecules such as PD-L1 or PD-L2 on tumor cells and macrophages, and (5) by means of metabolic reprogramming discussed further below. Therapeutic strategies to revert immunosuppression will be discussed in Chap. 6.

2.2.4 Metabolism

The brain utilizes approximately 60% of our daily glucose intake, despite constituting only about 2% of our bodyweight. In the normal brain, most glucose is metabolized by oxidative phosphorylation in the mitochondria, thereby generating up to 36 molecules of adenosine-triphosphate (ATP) per glucose molecule to meet the energetic demands of neurons and other brain cells [21]. Under hypoxic conditions in the cancer milieu cancer cells undergo a metabolic switch towards the less energetic, anaerobic glycolytic glucose metabolism generating only two molecules of ATP per molecule glucose, a process that was termed "Warburg effect" and that is common to most cancers including malignant primary brain tumors [22]. The Warburg effect is however not merely an opportunistic reaction to hypoxia, but yields the production of anabolic building blocks to generate lipids, nucleotides, and proteins to meet the high demand of cancer cells for continued growth. The generation of lactate and other by-products of glycolysis also contributes to the harshness of the tumor microenvironment and inhibition of functions of non-cancer cells, including immune cells [22]. Gliomas moreover secrete large quantities of glutamate as a by-product of glutathione synthesis, a

means to counteract oxidative stress. High concentrations of glutamate may also contribute to seizures and tissue destruction through cytotoxicity in neurons [23]. More brain-specific metabolic adaptions of cancer cells that are common to gliomas and brain metastases include preferential metabolism of acetate as a bioenergetics substrate [24].

2.2.5 Cancer Stem-Like Cells

The cellular organization of gliomas and most cancers that form brain metastases is hierarchical [25, 26]. Stem-like cells at the apex of this hierarchy give rise to more differentiated off-spring that form the bulk of the tumor. Glioma stem-like cells are adapted to and induced by hypoxia and nutrient restriction and rest in distinct stem-cell niches that are characterized by such harsh conditions [27, 28]. Moreover, interaction with the tumor vasculature can induce or maintain their phenotype, e.g., by signaling through nitric oxide or notch signaling [29, 30]. De-differentiation of non-stem-like cancer cells and assumption of a stem-like phenotype do also occur [31]. In gliomas, single cell gene expression analyses revealed that the hierarchical concept of "stemness" reflects a continuum of more or less differentiated states rather than clearly distinguishable cell types [32]. Cancer stem-like cells mediate resistance to classical chemo- and radiotherapy, in part by resting in a slow cycling or hibernating state and by preferential activation of the DNA damage response [31]. However, translation of this biological concept of stemness to molecularly targeted therapies, e.g., by inducing differentiation or utilizing drugs that selectively target stem-like cells, has failed in brain tumors [31].

2.2.6 Clonal Evolution and Therapy Resistance

Cancer growth and therapy both yield clonal selection pressure. Solid tumor entities with circumscribed growth are genetically less complex than tumors that infiltrate diffusely and may therefore be more amenable to molecular targeted therapies (discussed in Chap. 6) [33]. Most non-brain tumors and some primary brain tumors initially grow non-infiltrative and will only invade neighboring tissue or form distant metastases upon acquisition of additional genetic aberrations [17, 33]. Historically, this unidirectional model of oncogenesis was exemplified by the unraveling of a distinct sequence of mutations acquired by cells of the colon mucosa that cause the formation of adenomatous lesions and subsequently of infiltrative cancers [34]. However, genomic instability is a key feature of many cancers and causes the simultaneous generation of a vast number of clones. While only one or a few clones may dominate growth of an individual tumor, anti-cancer treatment can drive the selection of a different set of therapy resistant clones that may be present within tumors before the initiation of treatment. This multidirectional model of clonal evolution applies to most late-stage cancers and is a key characteristic of diffusely infiltrating gliomas, the most common malignant primary brain tumors [35, 36].

Recent technological advances in single-cell sequencing have improved our understanding of these biological processes and will aid in unraveling mechanisms of acquired therapy resistance.

2.3 Biological Features of Selected Brain Tumor Entities

2.3.1 Diffusely Infiltrating Astrocytomas and Oligodendrogliomas

The discovery that specific point mutations in genes encoding isocitrate dehydrogenase (IDH)-1 or -2 are present in the majority of diffusely infiltrating gliomas of WHO grades II and III was the foundation for the molecular classification of these tumors [19, 37]. Mutated IDH causes the production of 2-hydroxy-glutarate (2-HG), an oncometabolite thought to inhibit α-ketoglutarate-dependent dioxygenases and demethylases, yielding genome-wide DNA-hypermethylation, a phenomenon termed glioma CpG-island methylator phenotype (G-CIMP) [38–41]. Diffusely infiltrating astrocytomas and oligodendrogliomas comprise three major groups that are classified based on the integration of molecular information and histology [19]: (1) Astrocytomas with wild-type IDH, (2) astrocytomas with mutated IDH, and (3) oligodendrogliomas, which are defined by the co-occurrence of mutated IDH and additional co-deletion of chromosome arms 1p and 19q. The assignment of WHO grade II–IV is done mostly based on histological features of malignancy.

Details of the classification of diffusely infiltrating gliomas are summarized in Chap. 3 and implications for treatment will be discussed in Chap. 6.

Astrocytoma, IDH Wild-Type Astrocytomas with wild-type IDH comprise mostly glioblastomas (WHO grade IV), the most common malignant primary brain tumors. The incidence of these tumors increases with age and the prognosis is dismal [7]. Astrocytomas with wild-type IDH constitute a biological entity that is fundamentally different from IDH mutated astrocytomas or oligodendrogliomas. These tumors frequently harbor amplifications of chromosome 7 and loss of one copy of chromosome 10. This has clinical implications, because chromosome 10 also harbors *MGMT,* the gene encoding the DNA repair protein O6-methylguanyl DNA methyltransferase. Hypermethylation of the promoter region of *MGMT* predicts response to temozolomide in patients with diffusely infiltrating IDH wild-type astrocytomas, likely because of the lack of a second copy of *MGMT* to compensate for hypermethylation of one allele [42]. The clinical utility of *MGMT* testing will be discussed in more detail in Chap. 6.

Common gene level copy number alterations in astrocytomas with wild-type IDH include homozygous deletion of *PTEN,* homozygous deletion of *CDKN2A* and *CDKN2B*, amplification of genes encoding mitogenic receptor tyrosine kinases such as *EGFR*, *PDGFRA*, or *MET*, and cell cycle promoter genes including *CDK4* and *CDK6* that mediate transition from G1 to S phase or genes encoding p53

inhibitors such as *MDM2* or *MDM4* [33]. Activating *TERT* promoter mutations are also common in IDH wild-type astrocytomas. Less common mutations affect *TP53*, *PIK3CA*, *PIK3R1* (encoding PI3K-regulatory subunit 1), and *NF1* [33]. Attempts to further classify the genetically heterogeneous group of astrocytomas with wild-type IDH included genome-wide methylation arrays. This approach identified five glioblastoma subtypes with wild-type IDH designated receptor tyrosine kinase (RTK)-I, RTK-II, and mesenchymal as well as two profiles that were associated with distinct histone H3 mutations, $H3F3A^{G34R/V}$ and $H3F3A^{K27M}$ [43]. Gliomas with the latter mutation typically arise in midline structures and have a poor prognosis. Given these distinct clinical and molecular features, diffuse midline glioma with $H3F3A^{K27M}$ mutation (WHO grade IV) was included as a novel entity in the revised WHO classification (Chap. 3) [19].

Moreover, gene expression profiling identified three IDH wild-type glioblastoma subtypes designated proneural, classical, and mesenchymal based on similarities to known genesets [44]. Single cells that can be assigned to these whole-tumor derived subtype classifications are present simultaneously in individual tumors [32] and switching of subtypes at recurrence is common [35], thus limiting the clinical utility of such a classification approach.

Astrocytoma, IDH Mutated IDH mutated astrocytomas comprise the vast majority of WHO grade II and grade III diffusely infiltrating astrocytomas. IDH mutated glioblastomas (WHO grade IV) account for approximately 10% of all glioblastomas. Patients with IDH mutated astrocytomas are mostly young adults and the prognosis is more favorable compared to astrocytomas with wild-type IDH [33].

IDH mutation is one of the earliest events during oncogenesis of these tumors [45], but additional aberrations are required to initiate tumor formation in mice [46]. In IDH mutant astrocytomas, other common mutations affect *TP53* and the transcriptional regulator of chromatin remodelling *ATRX* [19]. There are also several genetic molecular features associated with the progression of WHO grade II to grade III and eventually to WHO grade IV. These driver events converge on dysregulation of cell division. Examples include chromosomal deletion of 9p21, which harbors *CDKN2A* and *CDKN2B*, activation of MYC and receptor tyrosine kinase (RTK) signaling, or somatic mutations in genes of inhibitors of the G1/S cell cycle checkpoint such as the retinoblastoma (Rb) pathway, or low methylation at CpG sites that regulate cell cycle progression, e.g., *TP73* [33, 47, 48].

Oligodendroglioma, IDH Mutated, 1p/19q Co-deleted Oligodendrogliomas are defined by co-deletion of chromosome arms 1p and 19q in IDH mutated tumors [19]. They almost generally harbor activating mutations in the promoter region of *TERT,* leading to aberrant telomere lengthening [49]. Other common somatic mutations in oligodendrogliomas include inactivating mutations of the transcriptional repressor gene *CIC,* the MYC suppressor gene *FUBP1,* developmental pathway genes such as *NOTCH1,* epigenetic regulator genes such as *SETD1,* and phosphorinisitol-3-kinase (PI3K) pathway genes such as *PIK3CA* [33].

2.3.2 Gliomas with Circumscribed Growth

Gliomas with circumscribed growth occur mostly in children and young adults [7]. The prognosis of these tumors is generally favorable, but multifocal growth can occur among all of these entities and pleomorphic xanthoastrocytoma and ependymomas can assume a malignant phenotype with infiltrative growth [19, 33].

Pilocytic Astrocytoma Pilocytic astrocytoma is the most common entity in this category. Pilocytic astrocytoma is considered a "single pathway disease" that rarely harbors genetic alterations other than such that result in activation of mitogen-activated protein kinase (MAPK) signaling [50]. The most common underlying genetic event is the fusion of the proto-oncogene *BRAF* and *KIAA1549,* which is associated with cerebellar tumor location and favorable prognosis [51]. Other genetic aberrations include fusion genes that involve the MAPK-pathway genes *RAF1*, *PTPN11,* or *NTRK2*, or harbor activating mutations in *NF1, FGFR1, KRAS,* or *BRAF* [50].

Subependymal Giant-Cell Astrocytoma (SEGA) SEGA is a pathognomonic feature of tuberous sclerosis and typically occurs from mutation or allelic loss of the genes encoding hamartin (*TSC1*) or tuberin (*TSC2*), both of which form the tuberous sclerosis complex, a key regulator of the mammalian target of rapamycin (mTOR)-signaling pathway in healthy cells [52].

Pleomorphic Xanthoastrocytoma (PXA) PXA almost generally harbors $BRAF^{V600E}$ mutations, often occurring together with loss of both copies of the cell cycle regulator gene *CDKN2A* [53, 54]. The genetic basis of the occasional transition of PXA to an infiltrative growth pattern is unclear [33].

Ependymomas Ependymomas constitute a molecularly more heterogeneous group that comprises a total of nine molecular subtypes [55]. Approximately two thirds of all supratentorial ependymomas harbor *RELA-C11orf95* gene fusions. The fusion protein drives aberrant NF-κB signaling and is associated with an unfavorable prognosis [55]. These tumors have been included as a novel entity in the 2016 WHO classification (Chap. 3) [19]. Fusions with the *YAP1* gene have also been identified in supratentorial ependymomas and are associated with better prognosis. Among ependymomas arising in the posterior fossa (PF), the PF-A subtype is characterized by genetic stability and probably driven by epigenetic aberrations [55]. The prognosis of PF-A ependymomas is unfavorable. Another ependymoma subtype designated PF-B is characterized by chromosomal instability and has a more favorable prognosis. Spinal ependymomas often carry *NF2* mutations and rarely recur after resection [55].

2.3.3 Medulloblastoma

The term medulloblastoma comprises at least four clinically and molecularly distinct entities designated Wnt-activated, Shh-activated, group 3, and group 4 [56, 57]. The

classification of medulloblastomas into these groups has been integrated in the revised WHO classification of central nervous system tumors of 2016 (see Chap. 3).

Wnt-Activated Medulloblastoma Wnt-activated medulloblastoma occurs in children and, less commonly, in adults. This subtype is described as having frequent oncogenic mutations of the *CTNNB1* gene encoding the Wnt down-stream signaling molecule β-catenin [58] or by germline mutations of the Wnt-signaling inhibitor gene *APC* in patients with Turcot syndrome [59]. Moreover, this subgroup has frequent loss of one copy of chromosome 6. The almost generally favorable prognosis of this group fostered an ongoing discussion on therapy de-escalation [3], which will be discussed in more detail in Chap. 6.

Sonic Hedgehog (Shh)-Activated Medulloblastoma Shh-activated medulloblastoma is common in both, infants and adults, but rarely occurs in children. It is often driven by germline mutations in the Shh-receptor gene *PTCH*, the Shh inhibitor *SUFU*, by activating mutations in the Shh-co-receptor gene *SMO*, or with amplification of the transcription factors mediating down-stream Shh signaling, *GLI1* and *GLI2* [56]. This subtype also comprises most tumors of the desmoplastic/nodular histological medulloblastoma variant. The prognosis of Shh-activated medulloblastoma is intermediate in the majority of cases with wild-type *TP53*, but co-occurrence of *TP53* mutations confers a poor prognosis [56, 60].

Group 3 and Group 4 Medulloblastoma Group 3 and group 4 medulloblastomas occur in infants and children, and only group 3 almost never occurs in adults [56]. There is a predisposition of both subtypes for males versus females. Group 3 is additionally characterized by high incidences of large cell anaplastic histology and of metastasis within the central nervous system [57]. *MYC* amplification and overexpression are characteristic of group 3 and associated with poor prognosis, but almost absent in group 4 [57, 61]. High expression levels of *MYC* and *MYCN* are also found in Wnt- and Shh-activated medulloblastoma, respectively, *MYC* expression of the Wnt-activated subtype is not driven by gene copy number gain. In contrast, group 4 commonly has *MYCN* copy number amplification, but not higher gene expression. The oncogene *OTX* is also commonly amplified and overexpressed in group 3 and group 4, and *CDK6* is commonly amplified in group 4 [57, 61]. Moreover a variety of chromosomal aberrations are characteristic of group 3 and group 4, of which gain of chromosome 1q, loss of chromosome 5q, and loss of chromosome 10q are more common in group 3, and the presence of an isochromosome 17q is more common in group 4 [60]. Gene expression profiles of group 3 and group 4 overlap with genesets involved in retinal and brain development, respectively, but the clinical significance of these traits is elusive [56].

2.3.4 Meningiomas

Meningiomas are the most common intracranial tumors in adults and their incidence is tightly associated with age [7]. They usually arise from meningothelial arachnoidal

cells that cover the brain and spinal cord, but can rarely occur in other locations such as intraventricularly, in the brain parenchyma or even in extracranial organs such as the lung [62]. Copy number alterations are overall rare in meningiomas [63]. The most common cytogenetic alteration in meningiomas is the deletion of one copy of chromosome 22 [63]. Chromosome 22 harbors the *NF2* gene, which is the most commonly mutated tumor suppressor gene in these tumors affecting close to half of all meningiomas and about 75% of WHO grade II meningiomas [64, 65]. Vice versa, chromosomal aberrations are also more frequent in *NF2* mutated meningiomas, indicating a role of the *NF2* gene product merlin for chromosomal stability [66]. Chromosomal aberrations occurring independent of *NF2* are associated with recurrence, higher WHO grade and consequently more aggressive disease course [63], and with the small subgroup of meningiomas arising years or decades after radiotherapy of the skull [67, 68]. Mutations that recurrently coincide with *NF2* mutations affect genes encoding epigenetic modifiers (*KDM5C*, *KDM6A, SMARCB1*) [63]. Recurrent mutations in *NF2* non-mutated meningiomas activate members of the PI3K/Akt/mTor pathway (*AKT1, PIK3CA, mTOR*) and of the Shh pathway (*SMO*) [63]. Mutations in *POLR2A*, which encodes the DNA-directed RNA polymerase II subunit RPB1, seem to be confined to WHO grade I meningiomas and are associated with meningothelial histology and location at the tuberculum sellae [69]. Mutations of the transcription factor gene *KLF4* are present in approximately half of all meningiomas with wild-type *NF2* and often co-occur with mutations in the gene encoding tumor necrosis factor receptor-associated factor 7 (*TRAF7*) [70, 71]. WHO grade II and grade III meningiomas have been reported to harbor mutations in *TP53, CDKN2A,* and *CDKN2B* [63, 66]. There is also an association of the rare rhabdoid histological variant of anaplastic meningioma (WHO grade III) with mutations in the *BAP1* gene [72], which encodes a deubiquitinase that functions as a histone modifier. Implications of these biological features of meningiomas for treatment strategies are discussed in Chap. 6.

2.3.5 Brain Metastases

The cancers that most commonly metastasize to the brain are lung and breast cancer, melanoma, and, to a lesser extent, renal cell carcinoma and colorectal cancer. In order to form metastases, cancers need to undergo epithelial-to-mesenchymal transition, invade, extravasate, evade the immune system, initiate angiogenesis, and adapt to organ-specific functions [17]. Molecular signatures of brain metastases have been proposed [73–75], e.g., to identify circulating tumor cells with potency to form brain metastases and enable treatment at an early stage. Examples of brain-metastasis specific genes include *ST6GALNAC5*, which encodes a brain-specific endothelial adhesion molecule that is required to transition through the BBB [75]. Other examples include upregulation of cyclic oxygenase 2, acquisition of the ability to metabolize acetate, or the expression of various *EGFR* ligands [24, 75]. Of note, many molecular traits are shared between brain metastases and malignant primary brain tumors, indicating how brain-specific factors entail certain characteristics of cancer cells that are shared between primary brain tumors and brain metastases. However, to date precise molecular programs leading to the formation of brain metastases have not been defined.

References

1. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005;23(2):276–92.
2. Ohgaki H, Kim YH, Steinbach JP. Nervous system tumors associated with familial tumor syndromes. Curr Opin Neurol. 2010;23(6):583–91.
3. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a "state of the science" review. Neuro-Oncology. 2014;16(7):896–913.
4. Le Rhun E, Bertrand N, Dumont A, Tresch E, Le Deley MC, Mailliez A, et al. Identification of single nucleotide polymorphisms of the PI3K-AKT-mTOR pathway as a risk factor of central nervous system metastasis in metastatic breast cancer. Eur J Cancer. 2017;87:189–98.
5. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst. 2007;99(20):1544–50.
6. Claus EB, Calvocoressi L, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M. Family and personal medical history and risk of meningioma. J Neurosurg. 2011;115(6):1072–7.
7. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol. 2017;19(suppl_5):v1–v88.
8. Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM. Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. J Neurosurg. 2013;118(3):649–56.
9. Ji Y, Rankin C, Grunberg S, Sherrod AE, Ahmadi J, Townsend JJ, et al. Double-blind phase III randomized trial of the Antiprogestin agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. J Clin Oncol. 2015;33(34):4093–8.
10. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006;98(21):1528–37.
11. Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med. 1988;319(16):1033–9.
12. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res. 2005;163(4):424–32.
13. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499–505.
14. Davis F, Il'yasova D, Rankin K, McCarthy B, Bigner DD. Medical diagnostic radiation exposures and risk of gliomas. Radiat Res. 2011;175(6):790–6.
15. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.
16. Schweitzer T, Vince GH, Herbold C, Roosen K, Tonn JC. Extraneural metastases of primary brain tumors. J Neuro-Oncol. 2001;53(2):107–14.
17. Chiang AC, Massague J. Molecular basis of metastasis. N Engl J Med. 2008;359(26):2814–23.
18. Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. Nat Rev Neurosci. 2007;8(8):610–22.
19. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131(6):803–20.
20. Nduom EK, Weller M, Heimberger AB. Immunosuppressive mechanisms in glioblastoma. Neuro Oncol. 2015;17(Suppl 7):vii9–vii14.
21. Brady S, et al. Basic neurochemistry: molecular, cellular, and medical aspects. 7th ed. Amsterdam: Elsevier; 2006.

22. Agnihotri S, Zadeh G. Metabolic reprogramming in glioblastoma: the influence of cancer metabolism on epigenetics and unanswered questions. Neuro-Oncology. 2016;18(2):160–72.
23. Huberfeld G, Vecht CJ. Seizures and gliomas--towards a single therapeutic approach. Nat Rev Neurol. 2016;12(4):204–16.
24. Mashimo T, Pichumani K, Vemireddy V, Hatanpaa KJ, Singh DK, Sirasanagandla S, et al. Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. Cell. 2014;159(7):1603–14.
25. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414(6859):105–11.
26. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. Nature. 2004;432(7015):396–401.
27. Flavahan WA, Wu Q, Hitomi M, Rahim N, Kim Y, Sloan AE, et al. Brain tumor initiating cells adapt to restricted nutrition through preferential glucose uptake. Nat Neurosci. 2013;16(10):1373–82.
28. Li Z, Bao S, Wu Q, Wang H, Eyler C, Sathornsumetee S, et al. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. Cancer Cell. 2009;15(6):501–13.
29. Eyler CE, Wu Q, Yan K, MacSwords JM, Chandler-Militello D, Misuraca KL, et al. Glioma stem cell proliferation and tumor growth are promoted by nitric oxide synthase-2. Cell. 2011;146(1):53–66.
30. Zhu TS, Costello MA, Talsma CE, Flack CG, Crowley JG, Hamm LL, et al. Endothelial cells create a stem cell niche in glioblastoma by providing NOTCH ligands that nurture self-renewal of cancer stem-like cells. Cancer Res. 2011;71(18):6061–72.
31. Lathia JD, Mack SC, Mulkearns-Hubert EE, Valentim CL, Rich JN. Cancer stem cells in glioblastoma. Genes Dev. 2015;29(12):1203–17.
32. Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science. 2014;344(6190):1396–401.
33. Reifenberger G, Wirsching HG, Knobbe-Thomsen CB, Weller M. Advances in the molecular genetics of gliomas – implications for classification and therapy. Nat Rev Clin Oncol. 2017;14(7):434–52.
34. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525–32.
35. Wang J, Cazzato E, Ladewig E, Frattini V, Rosenbloom DI, Zairis S, et al. Clonal evolution of glioblastoma under therapy. Nat Genet. 2016;48(7):768–76.
36. Suzuki H, Aoki K, Chiba K, Sato Y, Shiozawa Y, Shiraishi Y, et al. Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet. 2015;47(5):458–68.
37. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765–73.
38. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature. 2012;483(7390):479–83.
39. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010;17(5):510–22.
40. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807–12.
41. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell. 2011;19(1):17–30.
42. Weller M, Stupp R, Reifenberger G, Brandes AA, van den Bent MJ, Wick W, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol. 2010;6(1):39–51.
43. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann C, et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell. 2012;22(4):425–37.

44. Wang Q, Hu B, Hu X, Kim H, Squatrito M, Scarpace L, et al. Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. Cancer Cell. 2017;32(1):42–56. e6
45. Mazor T, Pankov A, Johnson BE, Hong C, Hamilton EG, Bell RJA, et al. DNA methylation and somatic mutations converge on the cell cycle and define similar evolutionary histories in brain tumors. Cancer Cell. 2015;28(3):307–17.
46. Sasaki M, Knobbe CB, Munger JC, Lind EF, Brenner D, Brustle A, et al. IDH1(R132H) mutation increases murine haematopoietic progenitors and alters epigenetics. Nature. 2012;488(7413):656–9.
47. Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell. 2016;164(3):550–63.
48. Mazor T, Pankov A, Johnson BE, Hong C, Hamilton EG, Bell RJ, et al. DNA methylation and somatic mutations converge on the cell cycle and define similar evolutionary histories in brain tumors. Cancer Cell. 2015;28(3):307–17.
49. Arita H, Narita Y, Fukushima S, Tateishi K, Matsushita Y, Yoshida A, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol. 2013;126(2):267–76.
50. Jones DT, Hutter B, Jager N, Korshunov A, Kool M, Warnatz HJ, et al. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet. 2013;45(8):927–32.
51. Hawkins C, Walker E, Mohamed N, Zhang C, Jacob K, Shirinian M, et al. BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low-grade astrocytoma. Clin Cancer Res. 2011;17(14):4790–8.
52. Chan JA, Zhang H, Roberts PS, Jozwiak S, Wieslawa G, Lewin-Kowalik J, et al. Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: biallelic inactivation of TSC1 or TSC2 leads to mTOR activation. J Neuropathol Exp Neurol. 2004;63(12):1236–42.
53. Weber RG, Hoischen A, Ehrler M, Zipper P, Kaulich K, Blaschke B, et al. Frequent loss of chromosome 9, homozygous CDKN2A/p14(ARF)/CDKN2B deletion and low TSC1 mRNA expression in pleomorphic xanthoastrocytomas. Oncogene. 2007;26(7):1088–97.
54. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011;121(3):397–405.
55. Pajtler KW, Witt H, Sill M, Jones DT, Hovestadt V, Kratochwil F, et al. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. Cancer Cell. 2015;27(5):728–43.
56. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123(4):465–72.
57. Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol. 2011;29(11):1408–14.
58. Zurawel RH, Chiappa SA, Allen C, Raffel C. Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res. 1998;58(5):896–9.
59. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, et al. The molecular basis of Turcot's syndrome. N Engl J Med. 1995;332(13):839–47.
60. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, group 3, and group 4 medulloblastomas. Acta Neuropathol. 2012;123(4):473–84.
61. Cho YJ, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, et al. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol. 2011;29(11):1424–30.
62. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: novel therapeutic opportunities. Nat Rev Neurol. 2018;14(2):106–15.