Brain Tumors

A Pocket Guide

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Editors

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Brain Tumor Primer

Malignant Glioma

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Shannon Fortin Ensign
and Alyx B. Porter

WHO CNS Classification:
Glioblastoma, IDH-wildtype
Astrocytoma, IDH-mutant Grade 3 and 4

Clinical Scenario

A 58 year old right handed man came to medical attention due to a focal motor seizure of the left lower extremity. He was found to have a 3 × 3 cm right parieto-occipital homogeneously enhancing cystic mass. He was taken to the operating room where a gross total resection was achieved by right occipital craniotomy. Post-operatively, he had a left homonymous hemianopia. Pathology demonstrated glioblastoma, IDH-wild type, MGMT methylated, ATRX retained. He received chemoradiation to a total dose of 60 Gy over 30 fractions with concomitant temozolomide 75 mg/m^2 days 1 through 42. He completed a total 6 cycles of adjuvant chemotherapy and chose not to wear tumor treating fields.

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He developed distant disease recurrence 7 months after completion of treatment. Neuroimaging revealed a new left parietal lesion and the previously treated right occipital lesion was stable. Since that area was not the primary target of previous radiation, he was presented to tumor board to discuss the safety and feasibility of re-irradiation. A multi-disciplinary team decided to proceed with radiation at a dose of 40 Gy over 15 fractions.

Six months later, an MRI demonstrated further growth of the left parietal mass with increased enhancement and surrounding edema. Additionally, he had more clinical symptoms including hemiparesis, aphasia and intractable focal seizures. He underwent resection of the left temporo-parietal mass to relieve pressure, improve symptoms, treat seizures and to determine the extent to which this was recurrent tumor or necrosis. The pathology was consistent with tumor recurrence. He was planned for therapy with bevacizumab beginning 28 days after surgery, but developed a saddle pulmonary embolism requiring hospitalization and subsequent decline in performance status. As a result of progressive clinical decline, the patient elected to enroll in hospice care. He spent 5 months in hospice and passed away 28 months from his original diagnosis of glioblastoma.

Making the Diagnosis

Gliomas arise from glial cells and neuronal precursors. They constitute 80% of all malignant primary brain and CNS tumors. Glioblastoma (GBM) is the most invasive, aggressive (grade 4) and common form. Patients can present with various symptoms including seizures, headaches, neurological deficits, and altered mental status. Magnetic Resonance Imaging (MRI) is the diagnostic modality of choice when a brain lesion is suspected. Computed Tomography (CT) scans are appropriate in emergent situations to evaluate for intracranial hemorrhage or hydrocephalus. While certain imaging characteristics are highly suggestive of GBM (heterogeneously enhancing expansile lesion), none are pathognomonic. In fact, many non-neoplastic processes can mimic gliomas, including multiple sclerosis, granulomatous dis-

eases, infections, and radiation necrosis. Tissue diagnosis is essential to confirming the suspected diagnosis. Surgical approaches can range from a minimally invasive stereotactic biopsy to a craniotomy with gross total resection. A flowchart describing the diagnostic and treatment approach for these tumors is included in Fig. 1.1.

The current tenet of glioma surgery is to achieve maximal safe resection [1]. As diffusely infiltrating lesions, the oncologic concept of negative-margin resections applicable to other tumor types cannot be applied. Multiple studies over the past decades have demonstrated a survival benefit with gross total resection. Mathematical models applied to retrospective studies revealed a progressive improvement in survival with the extent of resection increasing between 78 and 98%. A systematic review and meta-analysis of the literature revealed a significant improvement in overall and progression-free survival with gross total resection compared to subtotal resection. In glioma surgery, the definition of gross total resection remains controversial. Achieving true gross total resection is impossible due to the far-reaching invasion of tumor cells into the normal brain parenchyma. Therefore, the consensus is that this terminology refers to the enhancing compo-

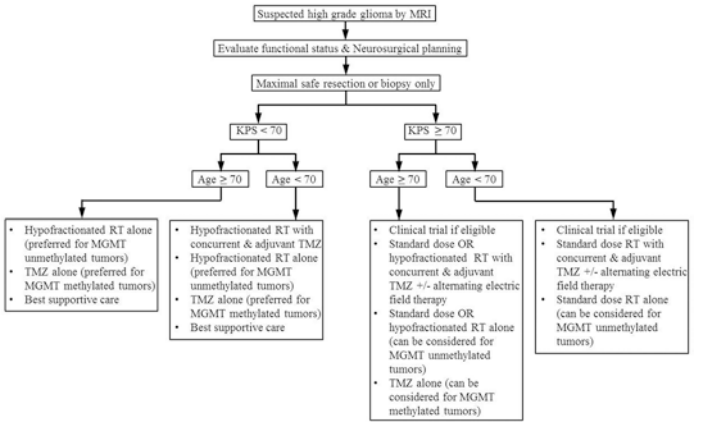

Fig. 1.1 Glioblastoma Treatment Flowchart

nent. The controversy lies in the extent of resection of the T2 hyperintense portion. Subtotal resection and biopsy (open or stereotactic) are reserved for tumors in eloquent areas of the brain, for patients with a poor performance status or multiple medical co-morbidities and cannot medically tolerate resective surgery.

Once the importance of maximal safe resection was established, multiple surgical adjuncts promising to optimize efficacy were introduced [2]. These include intraoperative imaging modalities such as intraoperative ultrasound and intraoperative MRI. The quality of available data is at best moderate. However, all imaging modalities were found to improve the rate of gross total resection. Intraoperative ultrasound is inexpensive, readily available, easy to use and can localize small areas of residual that might not be visible to the naked eye. Intraoperative MRI on the other hand, requires an expensive infrastructure but can be very helpful in determining the need for further resection.

Fluorescence in brain tumor surgery was developed in the 1990s but its use became mainstream only recently. 5-Aminolevulinic acid (5-ALA) is an imaging agent used to detect glioma cells. It is given to patients orally 3 h prior to anesthesia induction at the dose of 20 mg/kg. 5-ALA causes accumulation of fluorescent porphyrin in tumor cells exclusively. These cells then emit a red-pink fluorescent light that is visible in the oculars of the microscope while the normal brain parenchyma appears in blue. This tool is especially valuable at the normal parenchyma/tumor interface. The use of 5-ALA has been shown to improve the ability of to achieve a gross total resection in a randomized study [3].

Another surgical adjunct is direct white matter stimulation. This technique is particularly important when resecting tumors in proximity to the corticospinal tract. During resection, the white matter fibers are directly stimulated at different amplitudes to elicit a motor evoked potential. Depending on the amplitude of the stimulation, a positive response indicates the presence of the corticospinal tract within a certain distance of the stimulus. Alternatively, awake surgery can be performed with cortical stimulation to minimize injury to eloquent areas. The combination of all 3 allows us to safely expand our resection beyond the contrast enhancing portion into what is defined as supramarginal resection.

Beyond cytoreduction, the role of surgery is to provide tissue for immunohistochemical and genetic analysis. The prognosis is heavily influenced by the genetics and molecular subtypes. Isocitrate dehydrogenase (IDH) mutation is ubiquitous in low grade gliomas. Malignant astrocytoma with IDH mutations are classified as either grade 3 or grade 4 astrocytomas, depending on histologic features and molecular signature. IDH-mutant infiltrative gliomas have a better prognosis than IDH-wild-type.

Based on the 2021 WHO Classification of Tumors, the diagnosis of glioblastoma is achieved in a high grade glioma that is IDH-wild-type [4]. For the purposes of this chapter, treatment recommendations apply to IDH-wild-type glioblastoma and can be extrapolated for treatment of IDH mutant grade 3 and grade 4 astrocytomas, for which there are few randomized trials to clearly define therapy. MGMT (O6-methylguanine-DNA methyltransferase) methylation status is a predictive biomarker that determines the response to temozolomide. MGMT is a DNA repair enzyme. It is particularly effective in repairing damage caused by alkylating agents and therefore confers a resistance to temozolomide. MGMT promoter gene methylation silences it and enhances response to temozolomide. IDH and MGMT status are only 2 of multiple mutations analyzed in GBM tissue. Once the genetic and molecular signatures of the tumor have been defined, the treatment paradigm, including clinical trial eligibility, are then determined.

Post-operative Treatment

Radiation

Glioblastoma is characterized by microscopic invasive disease within the brain parenchyma outside the tumor bulk, and most high grade glioma recurrences occur within 2 cm of the initial surgical resection margin. Adjuvant fractionated radiation therapy (RT) targeting this expected relapse field confers an overall survival benefit and comprises standard of care post-operative treatment, delivered concurrently with chemotherapy [5]. While there

are several approaches to radiation therapy volume planning (EORTC vs RTOG recommendations), the accepted standard of care is the EORTC contouring approach. Radiation dosing of 60 Gy is delivered as 30 × 2 Gy fractions to the clinical target volumes (CTV), which is comprised of the gross tumor volume (GTV) + 2 cm. GTV encompasses the tumor resection cavity plus areas of residual T1 enhancement. Side effects most encountered include fatigue, cognitive decline, alopecia, and radiation dermatitis.

Elderly and frail patients may be considered for short course radiotherapy combined with chemotherapy. GBM survival decreases with advancing age and treatment is limited by toxic side effects and underlying coexisting conditions in the elderly [6], and patients over age 70 were excluded from the initial phase III study showing a benefit of combined chemoradiation versus radiotherapy alone using fractionated 60 Gy dosing [7]. Instead de-escalated treatment with hypofractionated radiation (40 Gy in 15 fractions) with concurrent and adjuvant temozolomide is a consideration in this population. Alternatively, elderly patients not fit for this strategy may be considered for hypofractionated radiotherapy or temozolomide monotherapy alone, with the latter treatment strategy more effective in patients with MGMT promoter methylation [8, 9].

Chemotherapy

Temozolomide (TMZ), a pro-drug alkylating agent which methylates DNA at the O6 position of guanine and which is able to penetrate the blood-brain barrier, is the current standard chemotherapy utilized in the adjuvant postoperative treatment of GBM [7, 10]. TMZ is delivered orally at a dose of 75 mg/m^2 daily during concurrent radiotherapy. After completion of RT, TMZ is held for 4 weeks then resumed at 150 mg/m^2 and subsequently escalated to 200 mg/m^2 days 1–5 of every 28 days for a minimum of 6 months. No study has demonstrated benefit of adjuvant chemotherapy beyond 6 months, but it should be noted that in the CATNON

study, 12 months of adjuvant therapy were given to individuals with anaplastic astrocytomas [11]. Analysis of the CATNON study also suggested that there may not be additional benefit for concurrent temozolomide in that population. Specific treatment regimens used in malignant gliomas are included in Table 1.1.

Given the emetogenicity of TMZ use of ondansetron 8 mg, granisetron 1 mg or prochlorperazine 10 mg orally 30 min before each chemotherapy dose is recommended. During concurrent chemoradiotherapy weekly blood counts may be needed to monitor for cytopenias, and liver function testing monitored midway through radiation therapy and subsequently. Lymphopenia places patients at increased risk for *Pneumocystis jirovecii* pneumonia (PJP), and prophylaxis should be considered in patients still requiring corticosteroids. TMZ should be held for platelet count under 100,000 and ANC <1500/mL until count recovery.

In younger patients (age ≤ 70) with MGMT-methylated tumors and good performance status a combined lomustine/TMZ regimen concurrent with RT and adjuvant may be considered. This is based on randomized phase III data showing an improved overall survival compared to TMZ alone (48.1 months versus 31.4 months), however increased side effects were observed in the dual treatment arm. Younger fit patients may also be considered for a clinical trial up front.

Tumor Treating Fields

Tumor treating field (TTF) therapy is offered for frontline treatment of GBM in patients who tolerate this adjunctive modality. TTF technology consists of a portable medical device where electrodes are attached to the patient's shaved scalp and transduce alternating electric fields at an optimal intensity and frequency for maximal tumor cell growth inhibition. TTF are felt to enact an antimitotic effect on the tumor hindering cell growth as their primary mechanism of action [12]. TTF are approved for use concurrent with monthly TMZ following completion of standard chemoradiation, and has proven to confer an overall survival ben-

Table 1.1 Glioblastoma treatment

Drug	Dose	Antiemetics	Supportive care	Dose delays and adjustments
Preferred first line regimens				
Concurrent with RT & Adjuvant Temozolomide (TMZ)	75 mg/m^2 PO daily during RT & 150–200 mg/m^2 PO d1–5, q28 days maintenance	Ondansetron 8 mg 30 min prior to chemotherapy and then up to every 8 h as needed	Consider PCP prophylaxis	Hold TMZ for ANC <1500/mm^3 or platelet count <50,000/mm^3
Concurrent with RT & Adjuvant Temozolomide/ Lomustine	TMZ 100 mg/m^2 PO d2–6 Lomustine 100 mg/m^2 PO d1 q28 days for up to 6 cycles	Ondansetron 16 mg IV, Dexamethasone 12 mg IV, Emend 125 mg PO	TMZ as above Lomustine: monitor PFTs at baseline and periodic	TMZ as above Lomustine: Dose adjustment for hematologic toxicity. Discontinue permanently for pulmonary fibrosis
Subsequent line regimens				
Bevacizumab	10 mg/kg IV d1, 15, q28 days	PRN	Monitor for HTN, proteinuria, bleeding	No adjustments, discontinue if indicated
TMZ	150–200 mg/m^2 PO d1–5, q28 days maintenance	Ondansetron 8 mg 30 min prior to chemotherapy and then up to every 8 h as needed	Consider PCP prophylaxis	Hold TMZ for ANC <1500/mm^3 or platelet count <50,000/mm^3

Lomustine monotherapy	Lomustine: 110 mg/m^2 q42 days	Ondansetron 8 mg po 30 min prior to chemotherapy and then up to every 8 h as needed	Monitor PFTs at baseline and periodic	Monitor for pulmonary toxicity
PCV (Procarbazine, Lomustine, Vincristine)	Procarbazine: 100 mg/m^2 PO d1–10 Lomustine: 100 mg/m^2 PO d1 Vincristine: 1.5 mg/m^2 IV d1, q42 days	Ondansetron 16 mg IV, Dexamethasone 12 mg IV, Emend 125 mg PO	Monitor PFTs as above, & monitor for constipation/ileus & peripheral neuropathy	Procarbazine & Vincristine: Hepatic dose adjustment as indicated

efit difference of nearly 5 months (20.9 months vs 16 months) compared with TMZ alone [13]. Side effects generally are mild and most prominently include a localized dermatitis under the placement of the electrodes on the scalp, which has been shown to respond well to topical steroid treatment [14].

Patients must wear these devices continuously for a goal 18 h per day, which has prompted concerns on the impact of quality of life (QoL). Questionnaires designed to assess QoL measures revealed no significant difference in global health status, emotional, social, physical, and cognitive functioning, as well as pain or leg weakness, and encouragingly patients receiving TTF had a significantly longer deterioration-free survival for several of these measures [15].

Symptom Management

Anti-epileptic therapy. Patients may present with seizures as their first symptom of GBM or experience seizures during their disease course, and approximately half of all GBM patients will be diagnosed with epilepsy during their disease [16]. Patients who develop seizures should be started on a single anti-seizure medication (ASM) for treatment using any first-line agent at the lowest effective doses. Typically levetiracetam is offered first line as this is well tolerated, though care should be used to monitor for potential neuropsychiatric side effects. While smaller studies have suggested an overall survival (OS) benefit with the use of valproate, a larger pooled analysis across four randomized trials found no difference in OS among patients on valproate as compared to other ASMs [17]. Patients who experience recurrent seizures while on therapy should have ASM levels monitored prior to dose escalation or consideration of adding a second drug. Seizure prophylaxis in a patient with no seizure history is generally not recommended, however perioperative prophylaxis may be considered with recommendations to taper and subsequently discontinue the ASM starting at 1–2 weeks post-operatively [18, 19].

Vasogenic edema management. Vasogenic edema results from local disruption of the blood-brain barrier from the tumor and is commonly encountered during disease management of patients with glioblastoma (see Chap. 10). Vasogenic edema appears on MRI as hypointense on T1-weighted images and hyperintense on T2-weighted images. Neurologic symptoms are variable however symptomatic patients require initiation of systemic steroids, with dexamethasone used as the standard agent, and clinical response should be monitored. Common starting doses of dexamethasone are 4–8 mg divided once or twice daily and subsequently a taper can be initiated once symptoms are stabilized. Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody can also be used as a steroid-sparing treatment for edema control, including in the management of edema related to radiation necrosis. Dosing is typically either 7.5 mg/kg every 3 weeks or 5 mg/kg every 2 weeks for four doses, with MRI monitoring mid-way through and at treatment completion.

Surveillance

After the initial concurrent chemoradiotherapy, it is standard practice to obtain a brain MRI with contrast 4–6 weeks following therapy completion. Thereafter, imaging is obtained every 2–4 months thereafter for monitoring assessment or earlier based on symptoms. The current criteria for imaging evaluation are based on the Response Assessment in Neuro-Oncology (RANO) Working Group, which includes guidelines for determination of progressive disease versus pseudoprogression,with progressive disease based on at least two sequential studies separated by 4 weeks and showing 25% or more increase in size or 40% or more increase in the total volume of the enhancing lesion [20, 21]. Moreover patients who are symptomatic or have tumors harboring MGMT promoter unmethylated status or IDH-wild-type are more likely to have true disease progression [22, 23]. Advanced imaging such as MRI perfusion and PET may not be widely available but can be helpful in differentiating pseudoprogression from true progression.

Treatment at Recurrence

After the determination of progressive disease and assessment of patient performance status, including a trial of steroids for treatment of symptomatic peritumoral edema if indicated, subsequent treatment can be considered for GBM. With both first and second recurrences, clinical trials should be considered. For patients with poor functional status or personal preference to not pursue additional therapy supportive care should be given. Patients with good functional status can be considered for reoperation with or without implantation of carmustine (Gliadel wafers) and/or re-irradiation if indicated. The role of laser thermal ablation in this setting is evolving. For patients in whom systemic therapy is being considered typical regimens are single-agent bevacizumab (10 mg/kg IV days 1, 15), single or combination nitrosourea-based regimens, or re-challenge with temozolomide (150–200 mg/m^2 days 1–5 every 28 days). No agent has proven superiority to another or has demonstrated improved overall survival. Nitrosourea-based regimens typically consist of lomustine (CCNU) monotherapy (100–130 mg/m^2 day 1, every 42 days), or in combinations such as procarbazine, CCNU and vincristine (PCV) (Procarbazine 100 mg/m^2 PO on days 1–10, Lomustine 100 mg/m^2 PO day 1, Vincristine 1.5 mg/m^2 IV day 1, every 42 days).

Prognosis/Survivorship

The prognosis of patients with GBM is dependent upon age and functional status at diagnosis, as well as underlying genomic profile including presence of MGMT promoter methylation and IDH status, among others. The median overall survival of all GBM patients treated with standard combined TMZ and radiation is 14.6 months [24]. Table 1.2 includes patient-facing information including guidance related to prognosis. Moreover, patients on standard chemoRT who underwent a complete, partial, or biopsy only resection had median survivals of 18.8 months vs 13.5 months vs 9.4 months, respectively. Patients under age 50 had a median OS of 17.4 months versus 10.9 months for those over age 60.

Table 1.2 Glioblastoma patient information

What type of tumor do I have?	• Glioblastoma, or Glioblastoma Multiforme (GBM) is a type of brain cancer • GBM occurs when normal brain cells become abnormal and start to grow quickly as cancer which causes damage and swelling into the normal brain
How do I treat it?	• You will undergo imaging of your brain to determine where the tumor is, and a surgeon will first perform surgery to remove as much of the tumor as possible • After recovery most patients with GBM will have both radiation treatment to the brain and chemotherapy • Some patients also opt to wear a portable device that delivers electrical fields to the brain to further slow the growth of the cancer cells • Some patients opt to consider enrollment in a clinical trial to treat GBM if available
What can I expect to experience during treatment?	• Most patients will experience some fatigue during treatment. Nausea and GI upset may also occur, but doctors are able to help treat many of these side effects with effective medicines
How will we keep an eye on this?	• Doctors will monitor your blood counts, liver and kidney function regularly during treatment • You will have periodic imaging of your brain to monitor the cancer during treatment • You may need to take steroids if there is any swelling of your brain during treatment or seizure medicine if you develop epilepsy from complications of having the brain tumor
What is my prognosis?	• In most patients with GBM the tumor comes back after treatment • While there are no treatments that can cure patients from GBM, the treatments available are often able to help prolong life and provide a quality of life which may have become diminished by having a brain tumor

Patients with MGMT promoter methylation had a median OS of 23.4 months versus 12.6 months in the unmethylated group [24]. Astrocytoma, IDH-mutations are associated with improved overall survival as compared to glioblastoma, IDH-wildtype (27.4 versus 14 months, respectively) [25].

There is limited data on survivor care for patients with GBM given that most patients succumb to their disease in a short timeline. However, studies of long term GBM survivors have identified a need for the continued monitoring of recurrences, with multiple lines of chemotherapy necessary for disease relapse. Patients also often require continuation of anti-epileptic medications, monitoring of their neurocognitive decline, and other neurological sequelae including radiation necrosis, cerebrovascular accidents, hydrocephalus and VP shunting as well as dementia. This group of patients thus requires specialized Neuro-Oncologic care for their continued monitoring [26].

Trends and Future Directions

Glioblastoma is characterized by marked heterogeneity which underlies treatment resistance, parenchymal invasion and inevitable tumor recurrence. Clinical trials utilizing targeted therapies against known signaling aberrations within GBM have yet to demonstrate significant benefit for either up-front or salvage therapy [27]. The only FDA approved targeted therapy is bevacizumab for use in recurrent glioma. Trials so far of small molecule kinase inhibitors, antibodies, or antibody drug conjugates that target aberrant receptor tyrosine kinase signaling activity have not proven to yield a PFS or OS benefit. Additionally, the use of histone deacetylase inhibitors, PARP inhibitors, or IDH1mt inhibitors are under early investigation and the effectiveness is yet to be determined [27].

Immune therapies represent another promising treatment strategy, however to date there are no FDA-approved immune-based treatments. Investigations are underway exploring immune checkpoint inhibitors (ICI), vaccines, adoptive T-cell therapies, and viral therapy [28]. Of note a subset of TMZ treated glioblastomas display hypermutation signatures at tumor recurrence [29]. This has led to the proposal that these gliomas may respond to subsequent therapy with ICI, noting that high tumor mutational burden is predictive of response regardless of disease [30]. However, early trials to date have not shown significant anti-tumor efficacy

of ICI therapy in recurrent GBM although it remains to be seen whether there is a subgroup of responders in follow-up analyses, and moreover, some evidence indicates ICI use in the neoadjuvant setting may lead to more consistent immune activation [31, 32]. Dendritic cell-based vaccines have been shown to yield durable responses in a minority of patients in clinical trials to date and studies remain ongoing [28]. Trials investigating CAR-T mostly have studied the IL-13Ra2, EGFRvIII and HER2 antigens, however with most patients not displaying significant tumor regression [28]. Likewise there has been a lack of durable response from viral directed anti-GBM therapy to date [33]. Further molecular studies to understand treatment response patterns are warranted. The current standard of care treatment for glioblastoma aims to prolong survival at best, though some patients have minimal benefit, dependent on their performance status and the tumor genetics. In the absence of any curative therapy, clinical trial participation is encouraged for all eligible patients with glioblastoma, with the hope of improving survival and quality of life over time.

References

1. Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1460–9.
2. Golub D, Hyde J, Dogra S, et al. Intraoperative MRI versus 5-ALA in high-grade glioma resection: a network meta-analysis. J Neurosurg. 2020;1–15:484–98.
3. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7(5):392–401. https://doi.org/10.1016/S1470-2045(06)70665-9. PMID: 16648043.
4. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–51. https://doi.org/10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013.

5. Corso CD, Bindra RS, Mehta MP. The role of radiation in treating glioblastoma: here to stay. J Neurooncol. 2017;134(3):479–85.
6. Laperriere N, Weller M, Stupp R, et al. Optimal management of elderly patients with glioblastoma. Cancer Treat Rev. 2013;39(4):350–7.
7. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
8. Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-course radiation plus Temozolomide in elderly patients with glioblastoma. N Engl J Med. 2017;376(11):1027–37.
9. van den Bent MJ, Tesileanu CMS, Wick W. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(6):813–23. https://doi.org/10.1016/S1470-2045(21)00090-5. Epub 2021 May 14. PMID: 34000245; PMCID: PMC8191233.
10. Margison GP, Santibanez Koref MF, Povey AC. Mechanisms of carcinogenicity/chemotherapy by O6-methylguanine. Mutagenesis. 2002;17(6):483–7.
11. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019;393(10172):678–88.
12. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res. 2004;64(9):3288–95.
13. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance Temozolomide vs maintenance Temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA. 2017;318(23):2306–16.
14. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48(14):2192–202.
15. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: a secondary analysis of a randomized clinical trial. JAMA Oncol. 2018;4(4):495–504.
16. Lote K, Stenwig AE, Skullerud K, Hirschberg H. Prevalence and prognostic significance of epilepsy in patients with gliomas. Eur J Cancer. 1998;34(1):98–102.
17. Happold C, Gorlia T, Chinot O, et al. Does valproic acid or Levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. J Clin Oncol. 2016;34(7):731–9.

18. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev. 2008;2008(2):CD004424.
19. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54(10):1886–93.
20. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963–72.
21. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics. 2017;14(2):307–20.
22. Li H, Li J, Cheng G, Zhang J, Li X. IDH mutation and MGMT promoter methylation are associated with the pseudoprogression and improved prognosis of glioblastoma multiforme patients who have undergone concurrent and adjuvant temozolomide-based chemoradiotherapy. Clin Neurol Neurosurg. 2016;151:31–6.
23. Rowe LS, Butman JA, Mackey M, et al. Differentiating pseudoprogression from true progression: analysis of radiographic, biologic, and clinical clues in GBM. J Neurooncol. 2018;139(1):145–52.
24. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459–66.
25. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol. 2009;27(25):4150–4.
26. Peters KB, Woodring S, Affronti ML, et al. Long-term survivorship in adult primary glioblastoma: clinical and neurological outcomes of a large, single-center study. J Clin Oncol. 2014;32(15_suppl):9519.
27. Gupta SK, Kizilbash SH, Daniels DJ, Sarkaria JN. Editorial: targeted therapies for glioblastoma: a critical appraisal. Front Oncol. 2019;9:1216.
28. McGranahan T, Therkelsen KE, Ahmad S, Nagpal S. Current state of immunotherapy for treatment of glioblastoma. Curr Treat Options Oncol. 2019;20(3):24.
29. Daniel P, Sabri S, Chaddad A, et al. Temozolomide induced hypermutation in glioma: evolutionary mechanisms and therapeutic opportunities. Front Oncol. 2019;9:41.
30. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med. 2017;377(25):2500–1.
31. Caccese M, Indraccolo S, Zagonel V, Lombardi G. PD-1/PD-L1 immune-checkpoint inhibitors in glioblastoma: a concise review. Crit Rev Oncol Hematol. 2019;135:128–34.

32. Ito H, Nakashima H, Chiocca EA. Molecular responses to immune checkpoint blockade in glioblastoma. Nat Med. 2019;25(3):359–61.
33. Chiocca EA, Nassiri F, Wang J, Peruzzi P, Zadeh G. Viral and other therapies for recurrent glioblastoma: is a 24-month durable response unusual? Neuro Oncol. 2019;21(1):14–25.

Diffuse Astrocytoma

2

Donna Molaie and Phioanh (Leia) Nghiemphu

WHO CNS Classification: Astrocytoma, IDH-mutant, CNS WHO Grade 2.

Clinical Vignette

A healthy ambidextrous 37 year-old male sustained a head injury after being hit by a car while riding a bicycle. He was taken to the local hospital emergency room where a CT scan demonstrated a hypodensity in the right temporal lobe, and an MRI with and without Gadolinium contrast revealed a non-enhancing, T2 hyperintense mass in the medial right temporal lobe. He was evaluated by a Neuro-Oncologist and additional history revealed 3 years of stereotyped 30-s episodes of feeling disassociation and dread, increasing in frequency over 4 months.

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He started levetiracetam 750 mg twice daily and consulted with Neurosurgery for preoperative planning. He was assessed with a functional MRI (fMRI), MRI with BrainLab, diffusion tensor imaging (DTI), and neuropsychological testing which demonstrated left hemisphere dominance for language. Subsequently, he underwent a right temporal craniotomy with a near gross total resection (GTR). The pathology demonstrated a Diffuse Astrocytoma (DA), WHO grade 2, positive immunoreactivity for isocitrate dehydrogenase 1 (IDH1) R132H mutation on immunohistochemistry (IHC), and 1p19q non-codeleted by fluoresecence in situ hybridization (FISH). Given his age, extent of resection (EOR), and personal preferences, the decision was made to monitor with serial imaging.

Clinical Features

The causes of most DAs are unknown. Genetic cancer predisposition syndromes make up less than 5% of cases and primarily involve germline mutations of *NF1*, *P53*, and mismatch repair genes [1]. The only recognized environmental risk factor is a remote history of ionizing radiation to the brain, head or neck.

Focal seizures are the most common clinical presentation. Other presentations include: incidental finding, focal motor or sensory symptoms, cognitive changes, aphasia and rarely, pressure-related headache.

Commonly affected locations are the frontotemporal and insular regions. Typical features on MRI include a cortically based, nonenhancing, homogenous T2 hyperintense signal with sulcal effacement and fullness of gyri; the presence of patchy or punctate enhancement prompts consideration of a more aggressive phenotype. MRI spectrography may be normal or demonstrate mild choline elevation, reduced NAA, absent lactate, and elevated choline: creatinine ratio. MR perfusion generally reveals no elevation of relative cerebral blood volume. On PET, FDG uptake is similar to normal white matter.

Surgical Decision-Making

Watchful Waiting or Surgery: Once a lesion suspicious for low grade glioma (LGG) has been identified on MRI, there are two primary approaches: MRI surveillance or surgical intervention (Fig. 2.1). Neurologic and epileptic symptoms, location, size of tumor, and patient preference are important factors to consider. In the past decade, general expert opinion has shifted in favor of early maximal safe resection. If a patient is symptomatic or the tumor has significant mass effect, the decision to intervene is straightforward. However, for some asymptomatic patients with small incidental lesions, watchful waiting may be acceptable but

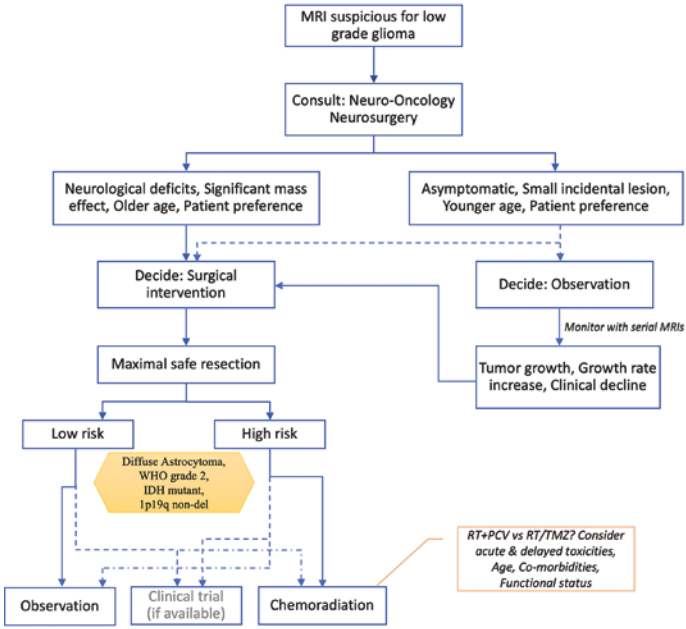

Fig. 2.1 Management flowchart for Diffuse Astrocytoma, WHO grade 2, with IDH mutation, and 1p19q intact. Dashed arrows represent management options on a case-by-case basis, influenced by patients preferences and prognostic markers

there is no clear evidence to definitively guide decision-making or to guide frequency of neuroimaging. It is important to always compare new MRI's to the baseline MRI as growth can be slow and difficult to appreciate over a short interval. MRI's every few months will appear unchanged, but when looked at over a few years, increase in size is better appreciated.

Preoperative Planning: A neurosurgeon may order a specialized MRI with DTI to guide preoperative planning. fMRI is used to map motor and sensory function relative to tumor location, helping neurosurgeons determine the resection margins to minimize deficit. If fMRI does not clearly delineate the language dominant hemisphere or if clarification of memory representation is necessary, a WADA can be performed. Additionally, neuropsychological testing is used to determine the extent of neurocognitive deficits, candidacy for awake craniotomies, and serve as a baseline.

Awake vs Open Craniotomy: If regions of critical neurologic function are not close to or do not involve tumor, awake craniotomy is generally not necessary. However, if the lesion is adjacent to critical regions, awake craniotomy with intraoperative mapping is critical to preserve neurologic function while obtaining maximal safe resection.

Resection vs Biopsy: If resection has a high risk of neurologic deficit or tumor is located in the deep structures or brainstem, biopsy may be advised. The decision between open versus needle biopsy is also based on surgical risk. Though, it is important to recognize that under-sampling with needle biopsy is common and can lead to misdiagnosis.

Pathology

According to WHO 2021 guidelines, DAs are graded as 2, 3, or 4, based on histological and molecular findings. A DA, WHO grade 2, histologically may demonstrate: nuclear atypia and increased cellularity, but without necrosis, mitoses, and endothelial proliferation [2]. Typical molecular findings include IDH mutations and no co-deletion of chromosomal arms 1p and 19q. If IDH mutation is negative by IHC, genetic sequencing should

be performed to evaluate for noncanonical mutations, especially in younger patients. IDH1 R132H is the most common. Mutations involving IDH2 have also been detected (though less frequent than IDH1) and are more common in oligodendrogliomas. Other common alterations include loss of function mutations of ATRX and TP53. Though MGMT promoter methylation is prognostic and predictive for high grade gliomas, it's role in DAs is unclear.

In regards to astrocytic tumors with normal IDH genes, also called "IDH-wildtype," additional molecular features are necessary to classify their behavior. The first and most common, is a glioblastoma [3]; an IDH-wild-type tumor that often has mutations in the TERT promoter or EGFR amplification [4, 5]. A second and more aggressive subtype is a diffuse glioma with H3 K27 mutation, typical of midline tumors. Third, genetic alterations of BRAF (V600E mutation or duplication), especially in a well circumscribed tumor, should prompt consideration of low grade variants (Pilocytic Astrocytomas or Glioneuronal tumors) [2].

Risk Stratification and Selection of Patients for Treatment

Patients can be stratified by age and EOR into risk groups, which are helpful for guiding postoperative management. From the premolecular era, age <40 with a GTR is considered low risk, while age ≥40 and any patient with incomplete resection are considered high risk. Additional factors to consider when selecting patients for immediate postoperative chemotherapy are the presence of risk factors for poor outcome: preoperative neurologic functional deficit, preoperative tumor size ≥5 cm, and tumor crossing the corpus callosum [6, 7].

Traditionally, watchful waiting or observation has been acceptable for low risk patients, while immediate postoperative chemoradiotherapy is recommended for high risk. Since the recognition of IDH mutational status's positive impact on survival, watchful waiting may also be considered in IDH-mutant DA patients <40 with incomplete resection but small residual tumor in non-eloquent locations, or ≥40 with GTR who also have other favorable markers.

Post-operative Treatment

The optimal management remains controversial with respect to: initiation time, treatment type, and chemotherapy regimen (temozolomide (TMZ) versus combination procarbazine, CCNU/lomustine, vincristine (PCV)). The key points are: (1) Traditional low risk patients, and those <40 with incomplete resection but small residual tumor in non-eloquent locations or ≥40 with GTR who also have other low risk features (pre-operative tumor size <5 cm and not involving the corpus callosum, no functional deficits), may opt for watchful waiting. (2) The decision to treat should trigger radiotherapy (RT) and chemotherapy *together*: combination therapy is superior to either treatment alone. (3) Despite RTOG 9802 demonstrating a clear survival benefit with the use of RT with PCV for DA, TMZ and RT remain a popular alternative due to its ease of use and better toxicity profile. (4) Current data is derived from the pre-molecular era. The selection of treatment should be done on a case-by-case basis, and represent a balance between the patient's goals, preferences, symptoms, risk of malignant transformation, and treatment-related toxicities (Fig. 2.1).

Timing of RT: For low risk patients, an initial watch and wait, or observe only, approach is reasonable. This is supported by the results of EORTC 22845, where low risk DA patients age < 40 with GTR were randomized to receive RT immediately after resection or at progression after watchful waiting; median overall survival (OS) was equivalent between the groups [8]. During the observation only period, patients should be followed with serial imaging, ideally with MRIs of the brain with and without contrast, every 3-6 months for the first 5 years, and gradually increase imaging intervals after that.

RT Doses: Early prospective randomized studies comparing lower doses (45–50.4 Gy) to higher doses (59.4–64 Gy) in 1.8–2 Gy daily fractions demonstrated no significant difference in OS with less toxicity [7, 9]. Subsequent studies incorporated the use of 54 Gy [10], a dose representing a compromise between EORTC and RTOG data. As of current, typical doses range from 45 to 54 Gy based on these results.

RT-Related Toxicities: Acute side effects present during and immediately after the completion of RT. These include fatigue, local alopecia, skin irritation, and symptomatic perilesional edema. Fatigue may persist for 3 months after completing RT, and hair growth typically resumes at 6 months. The timing of long-term neurocognitive deficits is less certain. Data suggest neurocognitive impairment may present >5 years after RT [11, 12]. Other long-term toxicities include risk of vascular damage and secondary malignancies.

Chemotherapy & Chemoradiotherapy: The matured results of RTOG 9802 demonstrate a clear median survival benefit of 5.5 years for high risk DA patients when PCV was administered after standard RT (RT/PCV), as compared to RT alone [13]. Despite these compelling results, RT and TMZ remains more popular amongst practitioners because of its better toxicity profile and presumption that alkylating therapies have similar efficacies [14] concurrent. This can be including concurrent and adjuvant TMZ or adjuvant TMZ alone.

Notably, TMZ monotherapy is not sufficient for treating IDH-mutant DA patients: the initial results of EORTC 22033 showed inferior PFS for patients treated with dose-dense TMZ versus RT. Similarly, preliminary results from RTOG 0424 suggested RT alone was not sufficient: high risk DA patients treated with RT/TMZ and adjuvant TMZ had improved OS as compared to historical controls treated with RT only [15]. Cumulatively, these studies suggest combination therapy is superior to chemo or RT monotherapy.

The decision to treat with RT/PCV versus RT/TMZ is different for different providers and patients; it is based on potential toxicity for a patient while considering age, co-morbidities, concurrent medications, and history of peripheral neuropathy.

As of the writing of this chapter, a phase 3 randomized trial evaluating the efficacy of vorasidenib, on oral inhibitor or IDH1 and IDH2 enzymes, in patients with residual or recurrent grade 2 IDH-mutant tumors has been published [16]. The study focused on patients who had not been previously treated with radiation or chemotherapy and demonstrated an improvement in progression-free survival and a delay to next therapeutic intervention. If approved by the FDA, Vorasidenib will be one additional drug in our arsenal and will be a particularly appealing option for patients who may want to defer radiotherapy.

Chemotherapy Dosing and Symptom Management

TMZ

1. Regimens:
   (a) Concurrent: 75 mg/m^2 oral daily concurrent with RT
   (b) Adjuvant: 150 mg/m^2–200 mg/m^2* oral on days 1–5 (D1–5) of a 28 day cycle for 12 cycles. If no or mild toxicity at 150, escalate to 200 for next cycle. (Table 2.1 describes toxicities, monitoring and dose modifications for commonly used regimens)
2. Symptom management:
   (a) Nausea: Ondansetron (or other 5-HT$_3$ serotonin receptor antagonist) on D1–42 (dose-dense) and D1–5 (adjuvant), 1 h before TMZ
   (b) Constipation: Polyethylene glycol
   (c) Drug rash: Combination of anti-H$_1$ and anti-H$_2$ histamine receptor antagonists on D1–5; if severe, add Methylprednisolone dose pack
   (d) Consider Pneumocystis Jiroveci Prophylaxis in patients with lymphopenia

PCV

This is typically initiated after RT. Cycle length is 42 days, with a goal of 6 cycles. Note: Average cycle length was 3–4 in RTOG 9802 [13] due to dose-limiting toxicities and still effective in terms of survival.

1. Regimen:
   D1: CCNU 90–110 mg/m^2 oral
   D8 &D29: Vincristine 1.4 mg/m^2 IV (round to nearest 0.1 mg, max 2 mg)
   D8–21: Procarbazine 60 mg/m^2/day oral (Available in 50 mg tabs which are given as combination of tabs over 14 days to average 60 mg/m^2/day or as a compounded medication)
2. Symptom management:

Table 2.1 Chemotherapies, toxicities, monitoring, and dose modifications

Regimen	Considerations	Side effects	Monitoring toxicity	Dose modifications[a, b]
TMZ-dose dense	• Food reduces absorption NPO 1 h before and after • Renally excreted	Fatigue, Moderately emetogenic, Constipation, Myelosuppression (nadir D14–21), Allergic-like rash (Hives), Liver toxicity, Renal toxicity, PCP Pneumonia[c], Teratogenic, Carcinogenic, Gonadotoxic, Infertility	• Weekly CBC w/ diff, CMP	• ANC < 1.5, Plt < 100 25% dose reduction
TMZ-adjuvant			• D21 CBC w/ diff • D28 CBC w/ diff, CMP	• ANC = 1.5–1.0, Plt = 100–75 & count recovery <2 weeks stay at 150 mg/m^2 daily • ANC = 1.5–1.0, Plt = 100–75 & count recovery >2 weeks 25% dose reduction • ANC = <1.0, Plt = <75 25% dose reduction

(continued)

Table 2.1 (continued)

Regimen	Considerations	Side effects	Monitoring toxicity	Dose modifications[a, b]
Procarbazine	• Activated by liver P450 • Weak MAO inhibitor • Drug/Food interactions (Alcohol, Tyramine-containing product[d], Antihistamines, Levodopa, TCAs)	Moderately emetogenic, Myelosuppression (nadir D28), Diarrhea, Flu-like symptoms, Allergic-like rash (Hives), Neurotoxic, Gonadotoxic, Infertility, Carcinogenic	• D28 CBC w/ diff • D35 CBC w/ diff • D42 CBC w/ diff, CMP • Neurological sensory exam every clinical visit	• ANC = 1.5–1.0, Plt = 100–50 & count recovery <3 weeks continue when normal • ANC = 1.5–1.0, Plt = 100–50 & count recovery >3 weeks 20% dose reduction • ANC = <1.0, Plt = <50 20% dose reduction
CCNU aka Lomustine	• Food reduces absorption NPO 1 h before and after	Fatigue, Anorexia, Moderately emetogenic, Myelosuppression (nadir D28–42), Interstitial lung disease (if >6 cycles), Impotence, Gonadotoxic, Infertility, Renal toxicity		

Vincristine	• Metabolized by liver P450 • Excreted in bile and feces	Neurotoxic (Peripheral neuropathy, Cranial nerve palsies), Jaw/parotid/bone/back pain, Constipation, Paralytic ileus, SiADH, Hypersensitivity reaction, Minimally emetogenic, Gonadotoxic, Infertility		• New neuropathic symptoms and/or exam change (areflexia, pinprick and/or vibration/proprioception) 50% dose reduction • Progressive &/or severe neuropathic symptoms discontinue

CBC w/diff Complete blood count with differential, *CMP* Comprehensive metabolic panel, *ANC* Absolute neutrophil count, *Plt* Platelet, *MAO* Monoamine oxidase, *TCA* Tricyclic anti-depressant

[a] Chemotherapies, TMZ, Procarbazine, & CCNU, should not be started until ANC > 1.5, Platelets >100

[b] Lab values are based on the lowest count, regardless of day

[c] Risk of PCP Pneumonia when TMZ concurrent with radiation, advise appropriate prophylaxis

[d] Food rich in tyramine have commonly undergone fermenting and aging, and include cheese, sourdough, smoked/pickled/fermented meats/fish, fava beans, soy sauce, etc.

(a) Nausea: Ondansetron (or other 5-HT_3 serotonin receptor antagonist) on D1 and D8–21, 1 h before CCNU and Procarbazine respectively; if severe, add Aprepitant tri-pack D1–3 (or other anti-NK_1 receptor antagonist)
(b) Drug rash: Combination of anti-H_1 and anti-H_2 histamine receptor antagonists on D8–21; if severe, add Methylprednisolone dose pack

Fertility Preservation (FP)

Alkylating agents, such as TMZ, CCNU, and procarbazine can impair fertility, and this risk is heightened with combination regimens such as PCV. For patients interested in having children, FP is recommended prior to initiation of chemotherapy. Practitioners should refer interested patients to reproductive endocrinologists. Several options exist including cryopreserving oocytes or embryos using donor sperm, and for males, sperm banking. Additionally, patients should wait 6 months after last treatment to eliminate chemotherapy toxicity prior to trying to conceive.

Of note, as the risk of infertility is less for TMZ than PCV, there are case reports of both men and women who had healthy children following treatment with TMZ and RT [17].

Surveillance

An MRI brain with and without contrast should be obtained within 2–4 weeks after completing RT and this should serve as a baseline for response assessment [18]. Thereafter, imaging should be coordinated with chemotherapy cycles, every 12 weeks. After completing treatment, patients should continue to undergo imaging surveillance at every 3 months for 1–2 years, with gradual lengthening to every 6 months after 5 years. New or worsened neurologic and/ or epileptic symptoms warrant earlier imaging.

Treatment at Recurrence

Options for treatment at recurrence include: surgery, RT, chemotherapy, clinical trials, and off-label use of experimental therapies. Repeat resection should be considered if it can be done safely. If sufficient time has elapsed from prior RT or the patient is RT-naïve, RT can also be performed. Chemotherapy options include a re-challenge of the initial regimen if significant time has elapsed since last treatment, or initiation of a new regimen if recurrence is sooner. Note, these recommendations are derived from general expert opinion as there are no prospective randomized studies evaluating the efficacy and timing of chemotherapy re-challenge. Other experimental options with no clear benefit include clinical trial participation or off-label use of IDH inhibitors and immunotherapy.

Prognosis and Survivorship

The median OS and progression free survival for DA patients with aggressive treatment is 7.8–13.3 and 4.0–10.4 years, respectively, and depends on tumor biomarkers and treatment [13]. Prognostic factors of poor survival and increased risk of malignant transformation include: age $\geq$ 40 years, preoperative tumor diameter of $\geq$5 cm, tumor involving corpus callosum and eloquent cortex, incomplete resection, and preoperative neurologic functional deficits [6, 7, 19, 20].

Epilepsy, cognitive function, and QOL, are important aspects of survivorship care. Epilepsy occurs in 75% of patients with LGGs [21], and is more common in cortically-based tumors, especially the mesotemporal and insular regions. EOR and postoperative chemoradiotherapy are associated with increased seizure control [22]. Seizures are typically well-controlled with anti-epileptic therapy (AED), and their frequency reduces with increased progression-free survival [23]. Once stable, tapering AED can be considered. Weaning after a 2-year seizure free period predicts a 15–40% risk of seizure recurrence [24, 25];

experts also recommend waiting a minimum of 1 year after last treatment to ensure tumor stability.

Neurocognitive impairment is a common long-term side effect, typically presenting >5 years after RT. [11, 12, 26] Patients may experience a measurable decline in attention, memory, executive function, language, and information processing speed. The degree of impairment can be mild to severe, and contributing factors include: tumor location/ size, surgical intervention, RT dose, chemotherapy, tumor-related epilepsy, and potentially the tumor itself. Imaging may demonstrate increased white matter changes. Attention and memory are commonly impacted; the latter is more frequently impaired when a tumor involves the temporal lobe [27], and the hippocampus, corpus callosum, and fornix are in the RT field. The use of stimulants may modestly improve cognitive function [28].

QOL is also an important factor in patient survivorship. In a prospective case-control study for LGG patients with stable tumor for 12 years, 38.5% experienced decline in health-related QOL, and had worse physical role functioning and physical QOL at 6 and 12 years respectively when compared to matched healthy controls [23]. Extrapolating from long-term QOL data of 27 survivors with stable anaplastic oligodendroglioma treated with RT or RT/PCV, 30% had severe cognitive impairment while 26% did not, 81% lived independently, and 41% were employed [29]. Note, interpretation of long-term data is inherently limited due to the attrition of patients with a longer survival. Other important aspects of survivorship care include management of anxiety, depression, sleep-wake disturbances, and neurologic deficits such as weakness, neuropathic sensory disturbance, and gait instability.

Patient Information

What type of tumor do I have? A diffuse astrocytoma is an uncommon primary brain tumor arising from the brain's supportive cells. They grow slowly and have a risk of malignant transformation. Astrocytomas are commonly located in the cortex, or outer layer of the brain. Growth or progression outside of the brain is extremely rare.

How do I treat it? The management of an astrocytoma may include a combination of regular imaging, surgical resection, RT, chemotherapy, and clinical trial participation. Timing and type of intervention needs to be assessed via a case-by-case basis, considering a patient's age, symptoms, molecular markers, and their goals and preferences.

What can I expect to experience during treatment and how will we monitor my disease? Chemoradiotherapy most commonly causes fatigue, nausea, constipation, improved seizure control, and reduced white blood cells and platelets. Side effects are typically well-managed with supportive medications and patients need to be monitored with regular blood tests and MRIs to monitor toxicity and treatment response, respectively.

What is my prognosis? With treatment, survival for patients with astrocytoma can range from 5 years to at least 15 years. This depends on: age, neurologic symptoms, tumor size and location, molecular markers, and type of treatment. To date, patients age < 40, with normal neurologic function, and pre-operative tumor <5 cm not involving the midline, who have undergone maximal safe resection followed by postoperative chemoradiotherapy have better survival. Note, these cut-offs are relative and each factor exists on its own continuum, therefore, patients should be counseled on case-by-case basis by specialized practitioners.

References

1. Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. Neuro Oncol. 2010;12:104–13.
2. Louis DN, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803–20.
3. Baumert BG, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma: a randomized phase III Intergroup study by EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033). Lancet Oncol. 2016;17:1521–32.
4. Hasselblatt M, et al. Diffuse astrocytoma, IDH-wildtype: a dissolving diagnosis. J Neuropathol Exp Neurol. 2018;77:422–5.

5. Tesileanu CMS, et al. Survival of diffuse astrocytic glioma, IDH1/2-wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria. Neuro Oncol. 2019;22:515–23.
6. Pignatti BF, et al. Cerebral low-grade glioma. 2020;20:2076–2084.
7. Karim ABMF, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) study 22844. Int J Radiat Oncol Biol Phys. 1996;36:549–56.
8. Van Den Bent MJ, Witte D, Hassel MB. Long-term efficacy of early versus delayed radiotherapy for low-grade. Lancet. 2005;366:985–90.
9. Shaw E, et al. Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study. J Clin Oncol. 2002;20:2267–76.
10. Karim ABMF, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. Int J Radiat Oncol Biol Phys. 2002;52:316–24.
11. Laack NN, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. Int J Radiat Oncol Biol Phys. 2005;63:1175–83.
12. Douw L, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol. 2009;8:810–8.
13. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and Vincristine in low- grade glioma. N Engl J Med. 2016;374:1344–55. https://doi.org/10.1016/j.physbeh.2017.03.040.
14. Darlix A, et al. Chemotherapy and diffuse low-grade gliomas: a survey within the European Low-Grade Glioma Network. Neurooncol Pract. 2019;6:264–73.
15. Fisher BJ, Hu C, Macdonald DR, et al. Phase 2 study of Temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of radiation therapy oncology group 0424. Int J Radiat Oncol Biol Phys. 2015;91:497–504. https://doi.org/10.1038/jid.2014.371.
16. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant low grade glioma. N Engl J Med. 2023;389:589–601.
17. Strowd RE, et al. Impact of temozolomide on gonadal function in patients with primary malignant brain tumors. J Oncol Pharm Pract. 2013;19:321–7.
18. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics. 2017;14:307–20.

19. Van Den Bent MJ, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005;366:985–90.
20. Chang EF, et al. Preoperative prognostic classification system for hemispheric low-grade gliomas in adults: clinical article. J Neurosurg. 2008;109:817–24.
21. Engloti DJ, Chang EG. Epilepsy and brain tumors. Handb Clin Neurol. 2016;134:267–85. https://doi.org/10.1016/j.physbeh.2017.03.040.
22. Ruda R, Bello L, Duffau H, et al. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro Oncol. 2012;14 Suppl 4(Suppl 4):iv55–64.
23. Boele FW, et al. Health-related quality of life in stable, long-term survivors of low-grade glioma. J Clin Oncol. 2015;33:1023–9.
24. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet. 1991;337:1175–80.
25. Lossius MI, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus study). Epilepsia. 2008;49:455–63.
26. Vigliani MC, Sichez N, Poisson M, Delattre JY. A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. Int J Radiat Oncol Biol Phys. 1996;35:527–33.
27. Noll KR, Ziu M, Weinberg JS, Wefel JS, Hospital S. Neurocognitive functioning in patients with glioma of the left and right temporal lobes. J Neurooncol. 2016;128:323–31.
28. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol. 1998;16:2522–7.
29. Habets EJJ, et al. Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. J Neurooncol. 2014;116:161–8.

Oligodendroglioma

3

Oluwatosin Akintola

The Clinical Scenario

A healthy 75-year-old male was brought into the hospital after a transient episode of confusion during which he was unable to shift gears in a rental car. His confusion lasted several minutes and required his spouse to take over driving. He had a fall with loss of consciousness and rhythmic right lower extremity shaking one month prior. He also noted forgetfulness and word finding difficulty over the past year. He initially underwent stroke work up with a CT/CT Angiogram head and neck. The scans showed left parieto-occipital edema concerning for an underlying mass lesion. MRI Brain confirmed presence of a large, infiltrative, multi region mass involving the parietal, temporal and occipital lobe. This tumor did not demonstrate any enhancement. Neurosurgical consultation was obtained, and a biopsy was performed. Pathology showed Oligodendroglioma, IDH-mutant, 1p19q-codeleted, CNS WHO grade 2. Functional MRI showed involvement of the mass within areas of motor activity in the precentral gyrus and diffusion tractography showed the corticospinal tract located within the

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anterior aspect of the mass. The case was reviewed by the multidisciplinary brain tumor board. Shared decision making was initiated with the patient. The patient proceeded with radiotherapy and chemotherapy, given the risk of debilitating neurological deficits if a resection of the mass was attempted.

Making the Diagnosis

The approach to patients with a brain tumor includes the history, examination and neuroimaging. Oligodendrogliomas are most often situated in the frontal and temporal lobes. Patients may present with cognitive impairment, aphasia, behavioral changes, and seizures. The symptoms at presentation are often related to the anatomic location of the tumor. Brain magnetic resonance imaging (MRI) with contrast is the preferred imaging modality. Oligodendrogliomas are diffusely infiltrating tumors with expansile changes noted in the white matter and cerebral cortex. Low grade oligodendrogliomas (grade 2) are less likely to demonstrate enhancement on MRI scans. Accurate diagnosis requires tissue sampling for histopathologic and molecular genetic testing. Stereotactic biopsy or maximally safe resection should be offered to patients depending on the location of these tumors. The localization of eloquent areas on functional MRI (fMRI) is useful for patients suffering from tumors involving brain regions important for language, motor, sensory, and visual processing. MRI diffusion tensor imaging (DTI) sequences and tractography are important tools for surgical decision making and surgical planning.

The Role of Surgery

Gross total resection is the preferred treatment if tumor location, eloquence, comorbidities, and functional status considerations favor this approach. Biopsies and partial resections are often offered based on unfavorable patient or tumor characteristics (advanced age, deep location of tumor, multi-region involvement

of tumor, significant neurological deficits, comorbidities contributing to high operative risk). A post operative MRI brain scan is required 24–48 hours following resection for baseline monitoring, treatment planning and detection of progression. Management with radiotherapy and chemotherapy is often required following surgery. After surgery, surveillance is a reasonable approach for patients with grade 2 Oligodendrogliomas who have had a gross total resection and are younger than 40 years old. MRI head scans are typically obtained every 3–6 months for 5 years, every 6 months indefinitely, or as clinically indicated.

Integrated Histopathologic-Molecular Diagnosis

Oligodendrogliomas are classified as grade 2 or grade 3 CNS tumors only [1]. Grade 2 Oligodendrogliomas are often diagnosed in younger adults aged 25–45 years old and only occasionally diagnosed in people older than age 60 [2]. Following surgical sampling via biopsy or resection, a histopathologic diagnosis of infiltrating glioma is made. The classic pathological features of oligodendrogliomas are sheet-like isomorphic round nuclei surrounded by clear cytoplasm ("fried egg" appearance) with a delicate network of branching capillaries ("chicken wire" appearance). However, IDH mutation and loss of both chromosomal arms 1p and 19q are required to make a diagnosis of oligodendroglioma [1], regardless of histological features.

The IDH mutation status may be determined using immunohistochemistry staining and/or gene sequencing. Fluorescence in situ hybridization (FISH) is often performed to assess loss of 1p and 19q [3]. However, next generation sequencing is more accurate in detecting whole-arm 1p/19q codeletion. While the designation of oligodendroglioma is molecularly defined, grade 2 or grade 3 designations are dependent on histological features. Grade 3 oligodendrogliomas (previously known as anaplastic oligodendrogliomas) are characterized by hyper cellularity, pleomorphism, elevated mitotic activity, and microvascular proliferation [1]. Oligodendrogliomas without these features are

classified as Grade 2 tumors. Homozygous deletion of *CDKN2A/B* occurs in less than 10% of oligodendrogliomas and is associated with reduced survival [4]. While *CDKN2A/B* deletion may suggest a higher-grade tumor, this finding is not required to designate grade 3 oligodendrogliomas.

Post-operative Treatment

Radiation

Involved field radiation therapy is often required following surgery. The goal of radiotherapy is to delay tumor recurrence while minimizing neurotoxicity. Radiotherapy should be offered within 3–6 weeks after surgery [5]. Nearly all patients with Grade 3 oligodendrogliomas should receive radiotherapy regardless of extent of resection [6]. Patients with grade 2 oligodendrogliomas with gross total resection of their tumors who are younger than age 40 may delay radiation in favor of radiologic and clinical observation, until evidence of recurrence [6]. High-risk profile patients (age > 40, subtotal resection or biopsy) with grade 2 tumors should proceed with radiation. Observing patients with grade 2 oligodendrogliomas and high-risk profile (age > 40, subtotal resection) may be reasonable in select cases. However, this approach should only be applied after careful consideration with the patient [7]. Clinical trials may be offered to patients with either grade 2 or 3 tumors if the patient is eligible. Radiotherapy doses of 54 Gy in fractions of 1.8 Gy are often administered to grade 2 oligodendrogliomas and other low-grade gliomas [8]. Grade 3 oligodendrogliomas receive 59.4 Gy in fractions of 1.8 Gy [9]. The target volume includes a 1–2 cm margin around the gross tumor volume as defined on fluid attenuated magnetic resonance imaging (MRI) to account for microscopic infiltration of the tumor [10].

Chemotherapy

Radiotherapy is often followed by chemotherapy. However, chemotherapy may also precede radiotherapy. Two large phase III trials showed that the receiving procarbazine, lomustine (aka CCNU), and vincristine (PCV), either prior to or after radiotherapy, nearly doubled the overall survival compared with radiation alone [9, 11]. Chemotherapy should begin 4–6 weeks after radiotherapy. The PCV regimen or temozolomide are both reasonable options for adjunctive therapy after completion of radiotherapy in patients with oligodendrogliomas. The PCV regimen is detailed in a table below. There is no consensus on the superior choice between PCV and temozolomide at this time [6]. Choice of chemotherapy in patients with oligodendrogliomas often depends on the age, functional status and physiologic reserve to tolerate chemotherapy. Temozolomide is generally better tolerated with PCV being associated with increased toxicity—myelosuppression (lomustine), pulmonary fibrosis (lomustine), drug-drug and drug-food interactions (procarbazine), and peripheral neuropathy (vinctrisine) [7]. Temozolomide is aassociated with myelosuppression to a lesser extent than lomustine. Both regimens require regular laboratory work up with complete blood count (CBC) with differential, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Temozolomide, lomustine and procarbazine are emetic. Patients receive premedication with an orally administered anti-emetic (usually ondansetron 8 mg or granisetron 1 mg) before each dose.

Surveillance

Neuroimaging with Brain MRIs is the method of choice for surveillance in patients with oligodendroglioma. Imaging intervals depend on the grade of the tumor and extent of resection.

- Grade 2 Oligodendroglioma with gross total resection—Brain MRI every 3–6 months for 3–5 years, and then every 6 months indefinitely, or more frequently as clinically indicated. It is unclear how long annual scans should continue.

- Grade 3 Oligodendroglioma—Brain MRI 4–6 weeks after completing radiation therapy for post radiation baseline evaluation. Monitoring proceeds with brain MRI every 2–3 months for 3 years, then every 3–6 months indefinitely [12].

Treatment at Recurrence (Regimens with Dosing)

Treatment after failure of first line chemotherapy is determined by the initial drug of choice. Therefore, temozolomide is a reasonable option for patients with recurrence on the PCV regimen and vice versa [6]. Bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody) is an option for patients with symptomatically recurrent disease. The role of bevacizumab is limited to serving as an alternative to glucocorticoids for management of symptomatic cerebral edema [7]. Other cytotoxic chemotherapies with penetration of the blood-brain barrier include paclitaxel, etoposide plus cisplatin, and carboplatin. However, response rates to these agents have been discouraging with most patients progressing within 12 months. As oligodendrogliomas are IDH mutant, clinical trials targeting IDH inhibitors may be offered. Other targeted therapies include PARP inhibitors, CDK4/6 inhibitors [13]. These therapies are generally experimental.

Prognosis

Although patients with oligodendrogliomas survive for several years, nearly all patients eventually succumb to their tumor. The overall median survival for low grade oligodendroglioma is reported as 15–20 years [14, 15]. Survival may exceed this range for patients with a gross total resection and with an excellent functional status without high-risk features in their tumors.

The historical survival for patients with histologically diagnosed anaplastic oligodendroglioma was approximately 5–7 years [16]. However, when isolated for truly 1p19q codeleted tumors, survival trends suggest 10–14 years [9, 11]. Survival trends are based on studies using histological grade. Recent studies show that median overall survival for molecularly defined 1p/19 co-deleted oligodendrogliomas is often not reached, suggesting more prolonged survival than initially thought. Updated survival data is needed in the context of the new classification of adult gliomas. Factors that predict worse survival include older age, poor functional status at diagnosis, subtotal resection or biopsy and large tumor size greater than 5 cm. Like most gliomas, oligodendrogliomas have profound effects on cognitive functioning. Many patients demonstrate impaired memory and report significant difficulty with executive function at the time of diagnosis and throughout their course of treatment. with biological evidence of progressive gray matter and white matter damage. Neurocognitive impairment is often a combined effect of the tumor and neurotoxicity of treatment with radiotherapy and/or chemotherapy [14]. About 80% of patients with oligodendrogliomas will develop seizures in their lifetime. They are more vulnerable to the adverse effects of anti-epileptics and are more likely to report adverse effects such as fatigue, mood changes and cognitive slowing on these medications [17].

Trends and Future Directions

According to guidelines, patients with oligodendrogliomas should be considered for clinical trials at each stage of the disease course [12]. Eligibility is determined by the patient's functional status, tumor location and pathology/molecular genetic profile of the tumor. In practice, most patients are offered clinical trials at the time of recurrence due to the efficacy of first line treatment. The CODEL clinical trial is expected to compare radiotherapy plus PCV versus radiotherapy plus temozolomide [18]. The trial aims to help address lingering questions about the first line chemotherapy regimen of choice (Fig. 3.1 and Table 3.1).

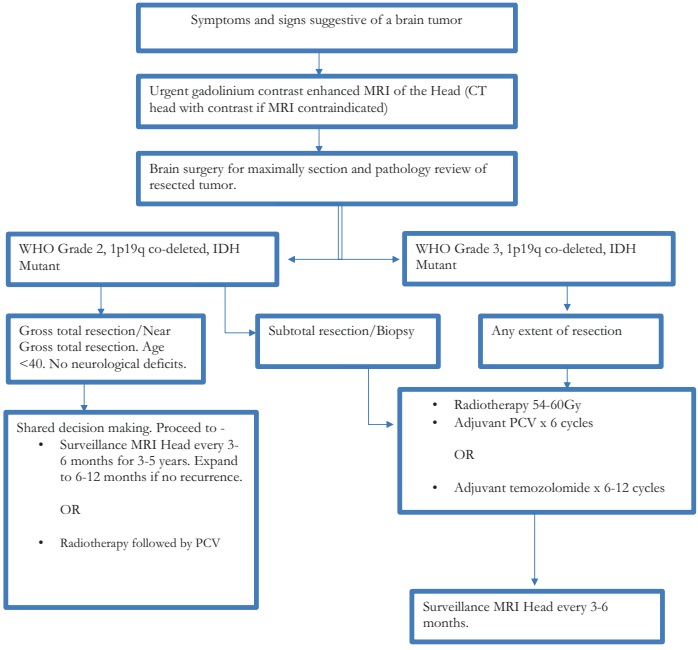

Fig. 3.1 Treatment flowchart. Treatment of newly diagnosed IDH-mutant, 1p/19q-codeleted oligodendroglioma (grade 2 and 3) in adults

Table 3.1 Chemotherapy regimens

Chemotherapy	Dose/Route of administration	Days administered (42-day cycle)
Lomustine	110 mg/m^2 orally	Day 1
Procarbazine	60 mg/m^2 orally	Days 8–21
Vincristine	1.4 mg/m^2 intravenously (maximum 2 mg per dose)	Day 8 and day 20
The PCV regimen is administered in 6- to 8-week cycles for a total of six cycles. Weekly CBC and CMP are obtained to monitor hematological and hepatic toxicity. Supportive Care: Ondansetron 8–16 mg orally (PO), given 30 min before lomustine on day 1. Dose modifications are made on subsequent cycles based on renal, hepatic and hematologic toxicities		

Table 3.1 (continued)

Chemotherapy	Dose/Route of administration	Days administered (28-day cycle)
Temozolomide (C1)	150 mg/m^2 orally	Day 1–5
Temozolomide (C2–C6)	200 mg/m^2 orally	Day 1–5
Temzolomide is administered 4 week cycles for a total of six cycles. Day 21 and day 28 CBC and CMP are obtained to monitor hematological and hepatic toxicity. Supportive Care: Ondansetron 8–16 mg orally (PO), given 30 min before lomustine on day 1. Dose modifications are made on subsequent cycles based on renal, hepatic and hematologic toxicities		

Patient Information

- Oligodendrogliomas are a rare type of brain tumor arising from oligodendrocytes within brain tissue. They commonly occur in young adults.
- Oligodendrogliomas are generally initially suspected on MRI head scans. Pathology review after surgery is required to confirm diagnosis and grade.
- Oligodendrogliomas can be low grade (Grade 2—slower growing) or high grade (Grade 3—faster growing)
- Surgery is the first level of treatment. The goal is removal of as much tumor as possible without compromising the patient's function. Oligodendrogliomas infiltrate brain tissue, therefore they are often difficult to remove completely.
- Surgery is often followed by radiation therapy. Radiation therapy is followed by chemotherapy. The order of treatment and the ability to complete treatment may vary by patient.
- MRI Head scans are obtained at least every 3 months to monitor oligodendrogliomas. If your brain tumor has not grown for many years, your physician may discuss expanding monitoring intervals with you.
- Clinical trials with experimental therapies may be on offer at the time of diagnosis and should be considered particularly at the time of recurrence.

References

1. Louis DN, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–51.
2. Morshed RA, et al. Molecular features and clinical outcomes in surgically treated low-grade diffuse gliomas in patients over the age of 60. J Neurooncol. 2019;141(2):383–91.
3. Pinkham MB, et al. FISHing tips: what every clinician should know about 1p19q analysis in gliomas using fluorescence in situ hybridisation. Clin Oncol (R Coll Radiol). 2015;27(8):445–53.
4. Appay R, et al. CDKN2A homozygous deletion is a strong adverse prognosis factor in diffuse malignant IDH-mutant gliomas. Neuro Oncol. 2019;21(12):1519–28.
5. Press RH, et al. Optimal timing of chemoradiotherapy after surgical resection of glioblastoma: stratification by validated prognostic classification. Cancer. 2020;126(14):3255–64.
6. Mohile NA, et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. J Clin Oncol. 2022;40(4):403–26.
7. Weller M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170–86.
8. Shaw EG, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol. 2012;30(25):3065–70.
9. van den Bent MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013;31(3):344–50.
10. Niyazi M, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol. 2016;118(1):35–42.
11. Cairncross G, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31(3):337–43.
12. Nabors LB, et al. NCCN guidelines insights: central nervous system cancers, version 1.2017. J Natl Compr Cancer Netw. 2017;15(11):1331–45.
13. Miller JJ. Targeting IDH-mutant glioma. Neurotherapeutics. 2022;19:1724–32.
14. Olson JD, Riedel E, DeAngelis LM. Long-term outcome of low-grade oligodendroglioma and mixed glioma. Neurology. 2000;54(7):1442–8.
15. Iwadate Y, et al. Eighty percent survival rate at 15 years for 1p/19q co-deleted oligodendroglioma treated with upfront chemotherapy irrespective of tumor grade. J Neurooncol. 2019;141(1):205–11.

16. Ostrom QT, 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.
17. Kerkhof M, et al. Seizures in oligodendroglial tumors. CNS Oncol. 2015;4(5):347–56.
18. Jaeckle KA, et al. CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design. Neuro Oncol. 2021;23(3):457–67.

BRAF-Mutated Glioma

4

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The Clinical Scenario

A 21-year-old young woman presented to the emergency room for evaluation of persistent vomiting and difficulty walking in a straight line. An MRI of the brain was obtained and showed a large right partially solid and partially cystic temporal mass (Fig. 4.1). The patient underwent a gross total resection and was diagnosed with an epithelioid glioblastoma. She received standard of care therapy with daily temozolomide and focal radiation for 6 weeks followed by six cycles of temozolomide for five out of every 28 days. Unfortunately, she rapidly relapsed and underwent a second resection with an expanded genetic analysis of her tumor. At relapse, a BRAF V600E mutation was identified and she was started on a BRAF V600E inhibitor (vemurafenib) with good disease control for approximately 2 years.

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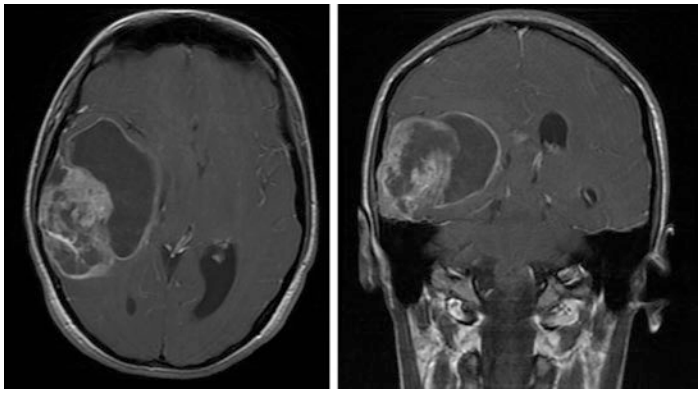

Fig. 4.1 T1-post gadolinium MRI images from a patient with a BRAF V600E-mutated epithelioid glioblastoma showing a large solid/cystic enhancing mass of the right temporal region

Making the Diagnosis

BRAF Mutations

BRAF is a serine/threonine kinase in the ERK signaling pathway that dimerizes upon activation and phosphorylates downstream MEK1 or MEK2, leading to ERK pathway activity and cellular proliferation and growth. Alterations in *BRAF* fall into two categories: single nucleotide variants (SNVs) and rearrangements. The most common SNV is the point mutation c.1799T>A, leading to an amino acid substitution of glutamate for valine (BRAF p.V600E) [1]. The V600E point mutation confers constitutive activity to BRAF and allows it to signal as a monomer, thereby dramatically upregulating intracellular ERK signaling. BRAF V600E and other point mutations are identified on CLIA-approved next generation sequencing (NGS) solid tumor panels. BRAF V600E can also be identified by a CLIA-approved immunohistochemistry stain in some laboratories, though the false negative rate for this test can be high [2]. Rearrangements occur when BRAF signaling is aberrantly activated through fusions

with another protein. These fusions generally remove the regulatory domain from BRAF and replacing it with another protein's nterminus, while leaving the kinase domain intact. The most common BRAF-fusion is with KIAA at different breakpoints including the most common fusion of *KIAA1549-BRAF* 16;9. BRAF-fusions are frequently not detected on DNA-based next generation sequencing and require specific probes or RNA-based methods (such as fluorescence in situ hybridization or NanoString sequencing) for identification [1].

BRAF-Mutation Frequency by Tumor Type

BRAF mutations have been identified in most primary brain tumor types [3–5]. The frequency of *BRAF* mutations varies widely between tumor types and between pediatric and adult cases of the same histologic diagnosis (see Table 4.1). Pediatric low grade astrocytoma, in particular, are very likely to have mutations in the MAPK signaling pathway, of which the majority are in *BRAF* [6].

Providers should consider sending NGS to evaluate for *BRAF* SNVs or fusions in tumors that have a high likelihood of containing *BRAF* alterations [7]. As NGS becomes less expensive and more widely-available, all high grade brain tumors, even those from older adults, should be evaluated for the presence of a *BRAF* mutation given its treatment implications.

Table 4.1 BRAF mutation frequency by tumor type. (Modified with permission of the authors from Ref. [3])

Tumor type	BRAF-SNV (%)	BRAF-fusion (%)
Pilocytic astrocytoma	10	60–70
Pediatric low grade astrocytoma	25–35	13
Pediatric high grade astrocytoma	10–20	<1
Adult low grade astrocytoma	5–15	5
Adult high grade astrocytoma	3	<1
Pleomorphic Xanthoastrocytoma	70–80	<1
Ganglioglioma	50	12
Papillary Craniopharyngioma	95	<1

Post-operative Treatment

Low Grade Glioma

Standard therapy in adults and children with low grade glioma (LGG) is variable and ranges from observation alone to treatment with radiation and chemotherapy, depending on tumor type and patient risk factors. In adult LGG, molecular features such as *IDH1*/2 mutations and 1p/19q codeletion are associated with a more indolent clinical course. *BRAF* mutations in LGG rarely occur alongside *IDH1/2* mutations, but retrospective data suggests the natural history of BRAF V600E-mutated LGG is better than that of other IDH wild-type diffuse astrocytoma and may be similar to IDH-mutated LGG [8]. In pediatric patients, a BRAF V600E mutation is associated with intermediate or high-risk disease and concurrent loss of *CDKN2A* conveys higher risk [6, 9]. Alternatively, the presence of *BRAF* fusions is typically associated with improved clinical outcomes [6, 10]. In adult patients, the clinical course is less predictable [3].

The integration of BRAF and MEK inhibitors (BRAFi and MEKi, respectively) into the treatment of LGG is an emerging area. As described above, BRAF V600E mutations and fusions are both common in LGG. Current successful targeted therapy is specifically directed against glioma with BRAF V600E mutations. There have been case reports documenting successful treatment in patients of all ages, as well as two arms on larger basket trials for adults [11–16]. Vemurafenib monotherapy in adults with BRAF V600E-mutated PXA resulted in a response rate of 43% (3 of 7 participants) in one arm of a basket study [12]. Dabrafenib combined with trametinib in adults with WHO grade I or II BRAF-mutated glioma (n = 13) resulted in a response rate of 69% (9 of 13 participants), with median progression free survival of 2 years places [2].

In pediatric patients, BRAF-targeted therapy has been efficacious in a range of tumor types [4, 5, 17]. Following the publication of the first response of a pediatric patient to BRAF inhibition, additional case studies and clinical trials have shown that response in pediatric CNS tumors is independent of pathologic diagnosis or

grade [14, 18–21]. In response to dabrafenib monotherapy, pediatric patients with LGG have a response rate of 71%, with a disease control rate (defined as stable disease or better for at least 6 months) of 88% [22, 23].

For adult and pediatric patients with BRAF V600E-mutated ganglioglioma, pleomorphic xanthoastrocytoma, or pilocytic astrocytoma, using BRAFi/MEKi as first-line therapy is reasonable, although additional clinical trials are needed to fully define this approach in pediatric patients [24]. In diffuse astrocytoma (WHO grade 2) the data are less clear, as only two patients were included in the dabrafenib/trametinib basket study described above. The conventional approach to patients with BRAF V600E-mutated diffuse astrocytoma has been to treat first with conventional radiation/chemotherapy and then use targeted therapy at the time of progression. Given the risk of long-term adverse events secondary to radiation in patients with diffuse astrocytoma, some providers and patients are turning to BRAFi/MEKi as first-line therapy and converting to conventional treatment modalities should the tumor fail to respond or progress on targeted therapy. The risk of toxicity associated with BRAFi/MEKi therapy is high, however, and treatment duration is at least 2 years in patients who are long-term responders. Long-term, twice-daily treatment may not be an acceptable quality-of-life to some patients. These competing factors, along with the potentially large financial burden of targeted therapy, should be considered when deciding when to initiate targeted therapy.

High-Grade Glioma

Standard first-line therapy for adults with BRAF-mutated high-grade glioma (HGG) is the same as for non-BRAF-mutated HGG. This is generally radiation with concomitant temozolomide followed by adjuvant temozolomide for glioblastoma, unless a clinical trial is available [25]. In pediatric patients, concurrent radiotherapy with temozolomide followed by temozolomide and lomustine has shown promise, although incorporation of up-front targeted therapy is currently being investigated in pediatric high

grade glioma. The overall survival of patients with BRAF-mutated glioblastoma may be better than BRAF-wild type glioblastoma due to the availability of targeted therapy for both young and older adults, but still necessitates aggressive treatment at the time of diagnosis [3, 26].

BRAF and MEK inhibitors have efficacy in a subset of HGG. While case reports have described examples of dramatic responses to BRAFi/MEKi in treatment-refractory HGG, there are also reports of non-responders [27, 28]. Sensitivity to targeted therapy in BRAF V600E-mutated HGG appears lower than in LGG: the response rate to vemurafenib monotherapy was only 9% (1 of 11 patients), but a clinical benefit (defined as stable disease for at least 6 months) was observed in 27% of high-grade glioma [9]. The response rate to dabrafenib/trametinib combination therapy was better, with a 33% response rate in adults (15 of 45 patients), with a larger subset of patients experiencing a clinical benefit [2]. Both trials primarily enrolled patients who had already received standard treatment for HGG.

The optimal time to initiate BRAF-targeted therapy is unknown given the lack of robust efficacy data and the potential toxicity, in both adult and pediatric patients. The majority of published cases are patients who have progressed following radiation, and in some cases have failed multiple lines of therapy. Notably, the toxicities of BRAFi and MEKi are generally non-overlapping with standard treatments for HGG. Some patients who respond to BRAFi/MEKi experience a dramatic clinical improvement as their tumor shrinks in response to therapy, so it is reasonable to consider a trial of BRAF-targeted therapy even in patients with a relatively poor functional status.

Targeted Therapy Regimens and Dosing

The dosing regimens of BRAF-targeted therapy used in adult glioma are currently the FDA-approved doses. For patients with BRAF V600E-mutated glioma, BRAFi/MEKi combination therapy is recommended over monotherapy for two reasons: (1)

improved tolerability, (2) increased time to resistance as indicated in melanoma clinical trials [29, 30].

The combination regimens most commonly used for primary brain tumors, along with standard dose-reductions are listed in Table 4.2. Dabrafenib/trametinib should be taken on an empty stomach. Encorafenib/binimetinib can be taken with or without food.

Surveillance While on Treatment

BRAFi/MEKi combination therapy is associated with a low risk of several potentially serious toxicities, necessitating careful anticipatory guidance and surveillance. The patterns of toxicity are predictable. Most are class effects, for which all BRAF and/or MEK inhibitors put the patient at risk, though the incidence of some toxicities varies between drugs. Surveillance for the following potential toxicities of BRAF-targeted therapy is as follows:

1. Cardiomyopathy—Left ventricular function should be assessed before starting therapy with a BRAFi, after one month of therapy, and every 2–3 months thereafter.
2. Hyperglycemia—Serum glucose levels should be monitored in patients with pre-existing diabetes or hyperglycemia who are taking dabrafenib and trametinib.
3. Liver toxicity—Liver function tests should be monitored regularly while on treatment, particularly with encorafenib and binimetinib.
4. New primary malignancies—RAF-targeted therapy can promote the growth of pre-existing or new malignancies with wild-type *BRAF*. Patients should be monitored with a full skin exam at baseline and regularly while on therapy. Patients should be counseled about the risk of new malignancies and encouraged to self-monitor as well.
5. Rhabdomyolysis—Creatine phosphokinase (CPK) and creatinine should be monitored regularly while on treatment with encorafenib and binimetinib.

Table 4.2 Treatment regimens and standard dose reductions

	Adult dosing						Pediatric dosing	
	Dabrafenib	Trametinib	Encorafenib	Binimetinib[a]	Vemurafenib	Cobimetinib[b]	Dabrafenib	Trametinib
Starting dose	150 mg twice daily	2 mg once daily	450 mg once daily	45 mg twice daily	960 mg twice daily	60 mg once daily (21 of 28 day cycle)	Age ≥ 12 years: 4.5 mg/kg/day div BID Age < 12 years: 5.25 mg/kg/day div BID (max 300 mg/day div BID)	Age ≥ 6 years: 0.025 mg/kg once daily Age < 6 years: 0.032 mg/kg once daily (max 2 mg/day)
First dose reduction	Reduce to 100 mg twice daily	Reduce to 1.5 mg once daily	Reduce to 300 mg once daily	Reduce to 30 mg twice daily	Reduce to 720 mg twice daily	Reduce to 40 mg once daily	Age ≥ 12 years: 3.75 mg/kg/day div BID Age < 12 years: 4.5 mg/kg/day div BID	Age ≥ 6 years: 0.02 mg/kg once daily Age < 6 years: 0.025 mg/kg once daily (max 2 mg/day)

Second dose reduction	Reduce to 75 mg twice daily	Reduce to 1 mg once daily	Reduce to 200 mg once daily	Stop binimetinib	Reduce to 480 mg twice daily	Reduce to 20 mg once daily	Age ≥ 12 years: 3 mg/kg/day div BID Age < 12 years: 3.75 mg/kg/day div BID	Age ≥ 6 years: 0.015 mg/kg once daily Age < 6 years: 0.015 mg/kg once daily (max 2 mg/day)
Third dose reduction	Reduce to 50 mg twice daily[d]	Stop trametinib	Stop encorafenib[c]		Stop vemurafenib	Stop cobimetinib	Stop dabrafenib	Stop trametinib

[a] Note, if binimetinib is held, reduce encorafenib to a maximum of 300 mg daily until binimetinib is resumed due to increased toxicity when encorafenib is used as monotherapy

[b] Cobimetinib is administered for 21 consecutive days, then held for 7 days during each 28-day cycle

[c] If encorafenib or binimetinib is permanently discontinued, discontinue the other targeted therapy (binimetinib or encorafenib) as well

[d] Drug is discontinued below this dose level

6. QT Prolongation—Patients starting encorafenib and binimetinib should have their QTc measured. Electrolytes should be monitored and corrected before and during treatment.
7. Vision loss—BRAFi are associated with a low risk of uveitis or retinal detachment. MEKi are associated with a risk of serous retinopathy and retinal vein occlusion. An ophthalmologic evaluation should be performed at baseline, at regular intervals (for binimetinib), and for any visual disturbance.

Specific interval monitoring recommended for dabrafenib and trametinib: dermatologic evaluation, cardiac function tests, hepatic function tests, complete blood count, serum glucose, retinal evaluation, and routine blood pressure measurement.

Specific interval monitoring recommended for encorafenib and binimetinib: dermatologic evaluation, cardiac function tests, hepatic function tests, serum chemistries, and CPK.

Specific interval monitoring recommended for vemurafenib and cobimetinib: dermatologic evaluation, cardiac function tests, hepatic function tests, complete blood count, serum chemistries, and CPK.

Management of Common Toxicities

Treatment-related toxicities are very common with BRAFi/MEKi combination therapy, but the majority are grade 1 or 2 [31]. With appropriate anticipatory guidance (see Table 4.3) and proactive toxicity management, many common toxicities can be prevented or ameliorated, improving overall treatment compliance and quality-of-life. This is critical as patients who respond may remain on treatment for years. On clinical trials, approximately 1 in 3 patients require a dose-reduction, but only 10–15% discontinued the drug entirely due to intolerance [30, 31]. This speaks to the fact that proactive toxicity management can markedly improve tolerability. Toxicities generally develop along two timeframes: within a few days of starting therapy or after a period of time on chronic therapy.

In general, for mild-moderate symptoms, patients can continue therapy—possibly on a reduced dose—while receiving supportive care to alleviate symptoms. For more severe toxicities, the

Table 4.3 Patient information handout

What type of tumor do I have?	Your brain tumor has a mutation in a certain protein called BRAF. This mutation causes more activity in your tumor cells leading to increased tumor growth
How is it treated?	In some people, chemotherapy can specifically target the mutant protein BRAF or the MEK protein that BRAF is talking to. These medicines are a combination of two different pills taken by mouth 1–2 times each day. There are several different combinations: dabrafenib/trametinib, encorafenib/binimetinib, vemurafenib/cobimetinib. Please follow your doctor's instructions for taking the medicines carefully and do not skip any doses. These medicines can make some forms of birth control less effective and can also interact with some other medicines. You may need to change some of your normal medicines or the form of birth control you are using. Please make sure all your doctors know every medicine you are taking
What can I expect to experience during treatment?	Your doctor will tell you about the symptoms this type of treatment can cause as it can be a little different for each particular set of drugs. It is relatively common to experience tiredness, nausea, diarrhea, rash, muscle pain, joint pain, and sensitive skin. You should tell your doctor right away if you develop a severe rash, any vision change, trouble breathing, swelling in one or both legs, or a new or growing bump or mole on your skin
How will we keep an eye on this?	Your doctor will tell you what regular testing you need to keep healthy on this treatment. In general, you will need to get your blood drawn regularly, your heart checked regularly (with an ultrasound test) and have regular check-ups with your oncologist, an ophthalmologist (eye doctor) and possibly with a dermatologist (skin doctor)
What is my prognosis?	The type of brain tumor you have is the most important fact your doctor will use to estimate how long you are likely to live, as the prognosis is very different depending on what type of tumor you have, where it is located, your age, and your response to therapy

offending BRAFi or MEKi should be held until the adverse event improves or resolves. With either drug combination, dose reductions are common and should occur at predetermined intervals recommended by the manufacturer (Table 4.2). In some scenarios, re-escalation of the drugs can occur after the toxicity has resolved.

Management strategies for a variety of common toxicities can be found in Table 4.4. In many situations, toxicities are temporary and dose re-escalation can be considered once the toxicity reaches ≤ grade 1.

Table 4.4 Management of common toxicities. (Modified with permission of the authors from Ref. [3])

Adverse event	Management recommendations
Rash	Implement preventative measures when initiating therapy: avoid excessive sunlight, apply sunscreen daily, topical mild-steroid (e.g. hydrocortisone 1% cream) or topical antibiotic (e.g. clindamycin cream) applied twice daily. Consider oral antibiotics (e.g. doxycycline 100 mg BID or minocycline 100 mg BID). If no improvement within 2 weeks consider holding MEKi until rash improves and then resuming at a reduced dose
Diarrhea	Institute supportive care (dietary modification, hydration, loperamide). Continue BRAFi/MEKi for uncomplicated diarrhea, but consider holding both medications for Grade > 2 diarrhea that continues >48 h, or complicated diarrhea
Nausea/ Vomiting	Promptly institute antiemetic measures. If AE is Grade 1–2 can generally continue BRAFi/MEKi, but if higher grade should hold both BRAFi and MEKi until symptoms improve
Arthralgias	Use nonsteroidal anti-inflammatory drugs for symptomatic relief. Consider temporary dose-interruption or the addition of low-dose corticosteroids (dexamethasone 2 mg daily to start) for treatment optimization. Rheumatology evaluation for severe cases
Vision change	If AE is Grade 1 continue drugs while obtaining ophthalmology consultation within a week. If Grade > 2 obtain urgent consult and hold MEKi. Dose-modification or discontinuation depends on diagnosis (uveitis, serous neuroretinal detachment, or retinal vein occlusion)
Fevers	Clinical evaluation and workup for infection. Implement anti-pyretics at first occurrence (acetaminophen, NSAID, etc.) hydration as required. Consider oral corticosteroids (e.g. dexamethasone 2 mg for 5 days). Consider dose reduction of BRAFi
Left ventricular function, decreased	Hold MEKi and re-evaluate left ventricular ejection fraction (LVEF) after 3–4 weeks. Consider resuming MEKi at a reduced dose if LVEF improves, otherwise discontinue

Table 4.4 (continued)

Adverse event	Management recommendations
Liver enzyme elevation	Continue BRAFi/MEKi for asymptomatic patients with mild elevation and observe closely for improvement. If Grade 3–4, hold both BRAFi/MEKi, consider workup for other etiologies of liver injury, and resume drugs at a reduced dose if patient improves to Grade < 1
Interstitial lung disease	For AE Grade > 2, hold MEKi while pursuing workup (consider chest CT, pulmonary function tests, infection workup, pulmonology consult). Consider symptomatic therapy with corticosteroids and resume MEKi at a reduced dose if the AE improves to Grade < 1

Treatment at Recurrence

Patients who experience disease progression after discontinuing BRAFi or BRAFi/MEKi may experience a response to re-initiation of targeted therapy [32]. Patients who progress on BRAFi alone may experience a response to BRAFi/MEKi [33]. For patients who experience progression while on combined therapy with BRAFi/MEKi, we recommend changing the treatment approach to one that involves surgery, radiation, or other chemotherapy.

Prognosis/Survivorship

Prognostic implications of BRAF mutations in glioma are still unclear and there are no prospective comparative survival data available. While the overall survival of patients with BRAF V600E-mutated glioblastoma may be better than *BRAF* wild-type glioblastoma, the exact difference and the additional time gained by targeted therapy are areas of ongoing investigation [3]. Clinical experience with these drugs has demonstrated that some patients with progressive glioma treated with BRAF-targeted therapy experience a profound improvement in their functional status.

Patients with non-V600E single nucleotide mutations are more likely to harbor passenger *BRAF* mutations. These patients likely have a similar prognosis as patients whose tumors have wild-type *BRAF* [3].

Trends and Future Directions: When Do you Consider a Clinical Trial?

The role of clinical trials in the treatment of patients with BRAF-mutated or BRAF-fusion glioma is still vitally important. Questions remain including: Should targeted inhibition be a first-line therapy for all patients? How long should targeted therapy be continued? Should targeted therapy be combined with current standards of radiation and/or chemotherapy? How well do BRAFi and MEKi penetrate the blood brain barrier and inhibit activated BRAF? Evidence suggests that movement of targeted therapy up-front is vital to the care of these patients and that all patients who are able be invited to participate in a clinical trial to further advance our understanding of best practices for these drugs.

References

1. Ryall S, Arnoldo A, Krishnatry R, Mistry M, Khor K, Sheth J, et al. Multiplex detection of pediatric low-grade glioma signature fusion transcripts and duplications using the NanoString nCounter System. J Neuropathol Exp Neurol. 2017;76(7):562–70.
2. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23:53–64.
3. Schreck KC, Langat P, Bhave VM, et al. Integrated molecular and clinical analysis of BRAF-mutant glioma in adults. NPJ Precis Oncol. 2023;7:23.
4. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, et al. Analysis of BRAF V600E mutation in 1320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011;121(3):397–405.
5. Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, et al. BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. PLoS One. 2011;6(3):e17948.
6. Ryall S, Zapotocky M, Fukuoka K, Nobre L, Guerreiro Stucklin A, Bennett J, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. Cancer Cell. 2020;37(4):569–583.e5.
7. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2020 Central Nervous Systems Cancer [Internet]. National Comprehensive Cancer Network [cited April 29, 2020].

8. Vuong HG, Altibi AMA, Duong UNP, Ngo HTT, Pham TQ, Fung KM, et al. BRAF mutation is associated with an improved survival in glioma—a systematic review and meta-analysis. Mol Neurobiol. 2017;55:3718–24.
9. Lassaletta A, Zapotocky M, Mistry M, Ramaswamy V, Honnorat M, Krishnatry R, et al. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. J Clin Oncol. 2017.:JCO2016718726;35:2934–41.
10. 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.
11. Chamberlain MC. Salvage therapy with BRAF inhibitors for recurrent pleomorphic xanthoastrocytoma: a retrospective case series. J Neurooncol. 2013;114(2):237–40.
12. Kaley T, Touat M, Subbiah V, Hollebecque A, Rodon J, Lockhart AC, et al. BRAF inhibition in BRAF(V600)-mutant gliomas: results from the VE-BASKET study. J Clin Oncol. 2018.:JCO2018789990;36:3477–84.
13. Wen P, Alexander S, van den Bent MJ, De Greve J, Dietrich S, de Vos F, et al. Updated efficacy and safety of dabrafenib + trametinib in patients with recurrent or refractory BRAF V60E-mutated high-grade glioma (HGG) and low-grade glioma (LGG). Neuro Oncol. 2019;21(Suppl 6):vi19–20.
14. Skrypek M, Foreman N, Guillaume D, Moertel C. Pilomyxoid astrocytoma treated successfully with vemurafenib. Pediatr Blood Cancer. 2014;61(11):2099–100.
15. del Bufalo F, Carai A, Figa-Talamanca L, Pettorini B, Mallucci C, Giangaspero F, et al. Response of recurrent BRAFV600E mutated ganglioglioma to Vemurafenib as single agent. J Transl Med. 2014;12:356, 014-0356-1.
16. Del Bufalo F, Ceglie G, Cacchione A, Alessi I, Colafati GS, Carai A, et al. BRAF V600E inhibitor (Vemurafenib) for BRAF V600E mutated low grade gliomas. Front Oncol. 2018;8:526.
17. Dougherty MJ, Santi M, Brose MS, Ma C, Resnick AC, Sievert AJ, et al. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. Neuro Oncol. 2010;12(7):621–30.
18. Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, et al. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer. 2014;61(6):1101–3.
19. Robinson GW, Orr BA, Gajjar A. Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. BMC Cancer. 2014;14:258, 2407-14-258.
20. Rush S, Foreman N, Liu A. Brainstem ganglioglioma successfully treated with vemurafenib. J Clin Oncol. 2013;31(10):e159–60.
21. Kieran MW, Bouffet E, Tabori U, Broniscer A, Cohen K, Hansford J, et al. The first study of dabrafenib in pediatric patients with BRAF V600-mutant relapsed or refractory low-grade gliomas. Ann Oncol. 2016;27(Supplement 6):vi552–87.

22. Hargrave DR, Bouffet E, Tabori U, Broniscer A, Cohen KJ, Hansford JR, et al. Efficacy and safety of Dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. Clin Cancer Res. 2019;25(24):7303–11.
23. Kieran MW, Geoerger B, Dunkel IJ, Broniscer A, Hargrave D, Hingorani P, et al. A phase I and pharmacokinetic study of oral Dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. Clin Cancer Res. 2019;25(24):7294–302.
24. Jones DTW, Kieran MW, Bouffet E, Alexandrescu S, Bandopadhayay P, Bornhorst M, et al. Pediatric low-grade gliomas: next biologically driven steps. Neuro Oncol. 2018;20(2):160–73. 28;11(9):10.3390/cancers11091262.
25. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
26. Zhang RQ, Shi Z, Chen H, Chung NY, Yin Z, Li KK, et al. Biomarker-based prognostic stratification of young adult glioblastoma. Oncotarget. 2016;7(4):5030–41.
27. Schreck KC, Guajardo A, Lin DDM, Eberhart CG, Grossman SA. Concurrent BRAF/MEK inhibitors in BRAF V600-mutant high-grade primary brain tumors. J Natl Compr Cancer Netw. 2018;16(4):343–7.
28. Smith-Cohn M, Davidson C, Colman H, Cohen AL. Challenges of targeting BRAF V600E mutations in adult primary brain tumor patients: a report of two cases. CNS Oncol. 2019;8(4):CNS48, 2019-0018. Epub 2019 Dec 10.
29. Marks AM, Bindra RS, DiLuna ML, Huttner A, Jairam V, Kahle KT, et al. Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib. Pediatr Blood Cancer. 2018;65(5):e26969.
30. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, openlabel, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603–15.
31. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
32. Brown NF, Carter T, Kitchen N, Mulholland P. Dabrafenib and trametinib in BRAFV600E mutated glioma. CNS Oncol. 2017;6(4):291–6.
33. Touat M, Gratieux J, Condette Auliac S, Sejean K, Aldea S, Savatovsky J, et al. Vemurafenib and cobimetinib overcome resistance to vemurafenib in BRAF-mutant ganglioglioma. Neurology. 2018;91(11):523–5.

Treatment of Meningioma

5

Rimas V. Lukas, Timothy J. Kruser, and Adam M. Sonabend

Introduction

Clinical Scenario

A 24-year-old man presented with a generalized tonic-clonic seizure. Workup revealed a left parietal dural based lesion with significant edema. He underwent a gross total resection and pathology was

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consistent with a meningioma World Health Organization (WHO) grade 2. In discussion with his clinical team, he elected to defer therapy and follow with surveillance imaging with MRI's every 3–4 months. Two years after surgery, he was found to have recurrence of the meningioma in the same location. A repeat resection was performed and revealed again meningioma WHO grade 2. He underwent fractionated radiotherapy and has been followed with surveillance imaging with no evidence of recurrence.

Meningiomas are the most common primary central nervous system (CNS) tumors. The management of these tumors spans the disciplines of neurosurgery, radiation oncology, neuro-oncology, medical oncology, and neurology, *and* receives input from neuroradiology and neuropathology. An overview of the clinical aspects of the care of these patients will be provided [1–3].

Meningiomas comprise >1/3 of all primary CNS tumors with the majority of these being WHO grade 1. Incidence increases with age and is more than twice as high in women compared to men (2.27:1) [4]. It is higher within the context of some cancer predisposition syndromes such as neurofibromatosis type 2, a neurocutaneous syndrome which follows an autosomal dominant inheritance pattern. A history of prior radiation is also associated with an increased risk of meningioma development within the radiation field, with radiation-induced tumors developing years to decades after radiation exposure. Specific gene rearrangements involving NF2 have been described in approximately half of radiation-induced meningiomas [5, 6] (Table 5.1).

Meningiomas may be incidentally noted or may be radiographically diagnosed after imaging performed due to neurologic symptomatology. Symptoms often correlate with the neuroana-

Table 5.1 Mutations and fusions in meningiomas

Mutation or fusion	Neuroanatomic location	Clinical features
NF2 mutation	NA	• Detected in ~1/2 of sporadic meningiomas • Predominantly fibroblastic and/or transitional subtypes • Germline mutation in patients with NF2. These patients have an increased incidence of meningiomas

Table 5.1 (continued)

Mutation or fusion	Neuroanatomic location	Clinical features
NF2 fusion	NA	• Present in ~1/2 of radiation induced meningiomas
SMO mutation	Olfactory groove	• Predominantly meningothelial subtype
AKT mutation	Base of skull	• Predominantly meningothelial subtype
mTOR mutation	Base of skull	• Predominantly meningothelial subtype
TERT promoter mutation	NA	• Confers a more aggressive natural history
PTCH1 mutation	NA	• Germline mutation in Gorlin syndrome (basal cell nevus syndrome) which is associated with increased incidence of meningiomas • PTCH1 is located upstream of SMO in the hedgehog pathway
SUFU mutation	NA	• Germline mutation is also seen in Gorlin syndrome (basal cell nevus syndrome) which is associated with increased incidence of meningioma • SUFU is located downstream from PTCH1 and SMO in the hedgehog pathway
SMARCB1 mutation	NA	• Germline mutation in Schwannomatosis and Coffin-Siris syndrome which is associated with increased risk of meningiomas
SMARCE1 mutation	NA	• Germline mutation is also seen in Coffin-Siris syndrome and is associated with increased incidence of meningioma

NF2 neurofibromatosis type 2, *NA* not applicable, *SMO* smoothened, *AKT* gene for protein kinase B, *mTOR* mammalian target of rapamycin, *TERT* telomerase reverse transcriptase, *PTCH1* patched-1, *SUFU* suppressor of fused homolog gene, *SMARCB1* SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 gene, *SMARCE1* SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1

tomic location of the tumor. Thus, a careful neurological history and examination often form part of the initial evaluation. Subsequent management can range from clinical and radiographic surveillance to aggressive multi-modality approaches [1–3]. A number of factors which influence these clinical decisions will be discussed below.

Diagnostic Evaluation

Neurological symptoms related to meningiomas are usually subacute in onset due to the relatively slow growth of most of these tumors when compared to other CNS neoplasms. These symptoms typically localize to the associated neuroanatomic structures which are being compressed by the tumor. Patients may also exhibit non-localizable symptoms such as positional headaches which may be associated with other symptoms of increased intracranial pressure such as nausea, vomiting, horizontal diplopia, and somnolence.

The majority of meningiomas are intracranial, arising from the dura covering the brain. A smaller number arises from the spinal dura. Occasionally, meningiomas can be found in unexpected locations such as within the ventricles. Rarely, extra-CNS metastases of meningiomas (including grade 1 meningiomas) are seen. Common locations for extra-CNS metastases include the lungs. Extra-CNS staging is *not* performed as standard of care and is only a component of symptomatic evaluation or if lesions are detected incidentally when imaging is performed for other reasons.

Imaging

The diagnostic evaluation of patients with suspected meningioma involves CNS imaging. Computed tomography (CT) may be the first modality obtained if the patient undergoes initial evaluation in an acute care setting such as the emergency department (ED). It is, however, often possible to move directly to obtaining mag-

netic resonance imaging (MRI) without accompanying CT. If CT is obtained, a hyperdense extra-axial lesion compressing the underlying brain raises suspicion for a meningioma. At times these tumors exhibit calcification, indicative of their slow growth.

MRI similarly reveals an extra-axial mass. These tumors are usually homogeneously enhancing and may exhibit a dural tail, a feature suggestive of but not pathognomonic for meningioma. A delineation between the extra-axial tumor and the underlying brain (termed a CSF cleft) is sometimes noted. This, however, can be seen with any extra-axial tumor and is not specific for meningiomas. Radiographic findings highly suggestive of meningioma, when within the appropriate clinical context, are often adequate to allow for moving forward with next steps in clinical management without a histologic diagnosis. This is one of the few exceptions to the rule in neuro-oncology of the need for confirmation of pathology prior to embarking on therapeutic intervention. There are a number of potential radiographic mimics of meningioma which should be considered when developing a differential diagnosis for these radiographic abnormalities (Table 5.2).

Finally, a number of advanced imaging studies are undergoing investigation for meningiomas. These include MR spectroscopy and advanced positron emission tomography (PET) modalities [1]. None of these are standard clinical practice at this time.

Pathology

Pathologic evaluation of tissue is necessary to establish a definitive diagnosis of meningioma. Unlike some tumors, a needle biopsy is rarely used to do so. Often, a surgical resection with an attempt at a gross total resection (GTR) or at least an extensive subtotal resection (STR) is performed as this has both diagnostic and therapeutic value. These tumors are currently classified into three grades which correlate with their natural histories and guide clinical management. Most meningiomas (~80%) are grade 1. Approximately 18% are grade 2 (also termed atypical meningioma) and only ~2% are grade 3 (also termed anaplastic *or* malignant meningioma) [4].

Table 5.2 Radiographic mimics of meningioma

Diagnostic entity	Clinical features
Dural metastases	• Most frequently seen with breast cancer and prostate cancer • In about 1/2 of patients with dural metastases skull metastases are also present
Solitary fibrous tumor	• Previously termed hemangiopericytoma • Has a high potential for local recurrence, recurrence elsewhere in the CNS, and dissemination outside of the CNS
Langerhans histiocytosis	• A histiocytic infiltrate • Extra-axial CNS involvement is not a common manifestation of CNS Langerhans histiocytosis • More common CNS involvement involves the hypothalamic-pituitary axis
Rosai-Dorfman disease	• A non-Langerhans cell histiocytosis • Often extra-CNS involvement includes lymph nodes, skin, sinuses, renal, orbit, and salivary glands • It is often self-limited • Treatment may include surgery, radiation, steroids
Erdheim-Chester disease	• A non-Langerhans cell histiocytic neoplasm • Often extra-CNS involvement includes skeletal, cutaneous, renal, and pulmonary • Approximately half of Erdheim-Chester cases have somatic V600E *BRAF* mutations • Treatment may include steroids, interferons, and BRAF targeted therapies
IgG4 related disease	• Both serum and lesional tissue can be evaluated for IgG4 • Often responds readily to steroids
Orbital pseudotumor	• Frequently limited to the orbit but in some cases can extend to the cranial dura • This is an inflammatory process treated with steroids and immunosuppressants
Sarcoidosis	• This is usually accompanied by extra-CNS involvement (particularly pulmonary) of sarcoidosis, but in some instances can be limited to the dura
Rheumatoid meningitis	• A rare manifestation of rheumatoid arthritis

Table 5.2 (continued)

Diagnostic entity	Clinical features
Dural lymphoma	• Often follows a much more indolent course than primary central nervous system lymphoma
Schwannoma	• At the base of skull schwannomas arising from cranial nerves can mimic meningiomas • CNVIII is the cranial nerve most frequently affected by schwannoma
Infectious	• A range of acute and chronic infections can involve the pachymeninges and may mimic meningioma • These infections include but are not limited to viral, bacterial, fungal, and mycobacterial infections

CNS central nervous system

Histologically meningiomas can be classified into 15 subtypes [7]. In turn, the pathologist requires familiarity with a range of histopathologic presentations of meningioma to confidently make the diagnosis. While most histologic subtypes do not influence the clinical management, there are a few which when present confer a more aggressive natural history and in turn increase the grade of the tumor (Table 5.3). Other features which increase grade include brain invasion, a higher number of mitoses, high cellularity, a high nuclear to cytoplasm ratio, prominent nucleoli, necrosis, and sheet-like growth pattern [8] (Table 5.4). It is likely that in the near future, methylation profiling may lead to a more robust prognostication for these tumors [9, 10]. At this point in time methylation profiling is not yet standard of care for meningiomas.

Next generation sequencing (NGS), will likely have a growing role in the evaluation of meningioma. Some specific findings such as *TERT* promoter mutation and *CDKN2A/B* homozygous deletion confer a WHO grade of 3. In addition, it is known that a substantial percentage of meningiomas harbor neuroanatomically exclusive mutations [11] (Table 5.1). Targeting of these mutations is undergoing investigation in various studies including a phase II cooperative group study (NCT02523014, Alliance clinical trial A071401).

Table 5.3 Histologic subtypes of meningiomas

Histologic subtype	Grade
Chordoid meningioma	2
Clear cell meningioma	2

Table 5.4 Histologic and molecular features associated with grade

	Grade 1	Grade 2	Grade 3
Histologic subtypes		Chordoid or clear cell subtypes	
Brain invasion	No brain invasion	*Or* Brain invasion	*Or* Brain invasion
Mitoses	0–3 mitoses per 10 HPF	*Or* 4–19 mitoses per 10 HPF	*Or* 20 or more mitoses per 10 HPF
Aggressive features	2 or less	*Or* 3 of the following: • Increased cellularity • Small cells with high nuclear to cytoplasmic ratio • Prominent nucleoli • Sheeting • Foci of spontaneous necrosis	Usually present

NA not applicable, *HPF* high-powered fields

Therapeutic Management

The therapeutic management of meningioma most oftentimes utilizes surgery and/or radiation. Systemic therapy at this time does not have a clearly established role and is primarily used within the context of clinical trials or for disease which has progressed after surgery and radiation. It should be emphasized that many (if not

most) meningiomas do *not* require therapeutic intervention. If upfront treatment is not recommended, clinical and radiographic surveillance is usually warranted as these tumors have the potential to grow over time and can be associated with morbidity and mortality. Of note only a third of presumed meningiomas that are discovered incidentally exhibit growth over time. Often, for small asymptomatic meningiomas the recommendation is to hold off on treatment until there is clear evidence of growth.

Surgery

Surgery serves both diagnostic and therapeutic purposes. With respect to the first, it provides diagnostic certainty to a previously clinical-radiographic diagnosis. The degree of certainty required depends on the specific clinical scenario. It also allows establishment of grade which informs the natural history and prognosis associated with the tumor. Finally, it provides tissue for advanced molecular testing including NGS and methylation profiling. With regards to therapeutic benefit, it is the one modality which decreases tumor burden and mass effect. This has the potential to alleviate at least some of the symptoms associated with the tumor.

The goal of surgery is GTR where feasible and STR when it is not. GTR may be curative in grade 1 and some grade 2 meningiomas [12]. The extent of resection is associated with risk of recurrence and progression-free survival. The most frequently utilized system for assessing extent of resection is the Simpson grading [13](Table 5.5). A number of factors, predominantly the anatomic location of tumor, limit the feasibility of a complete resection. Specific locations in which STR is planned and expected include the base of skull and the posterior portion of the patent sagittal sinus. With meningiomas involving the base of the skull there are critical vessels and cranial nerves which it is often not practical to

Table 5.5 Simpson grade of resection

Simpson grade	Extent of resection
1	GTR with removal of involved dura and bone
2	GTR with dural coagulation
3	GTR without dural coagulation
4	STR
5	Biopsy/decompression

GTR gross total resection, *STR* subtotal resection

sacrifice or to put at undue risk. In regards to the posterior portion of the sagittal sinus, if it remains patent and robust collaterals do not exist, resection which sacrifices the posterior component of the sinus leads to the substantial risk of impeding the venous outflow from the brain and the associate development of a venous infarction. If GTR is felt unlikely to be feasible (and mass effect is not problematic) definitive radiation should be entertained. In cases of STR, postoperative radiation should be considered.

If a tumor recurs, re-resection is often considered as a potential treatment option. As the number of resections increases the enthusiasm for additional resections diminishes, particularly as wound healing is impaired in the context of multiple previous surgeries and radiation. However, it is still often contemplated at every recurrence as it is one of the most effective means of addressing these tumors.

Radiation

As noted earlier, meningiomas are one of the few CNS tumors in which treatment may be initiated based upon the radiographic diagnosis within the appropriate clinical context. This is employed when the suspicion is that the tumor is a grade 1 meningioma. When the imaging or rapid onset of symptoms raises concern for grade 2 and 3 meningiomas, surgery to establish the diagnosis and grade as well as resect or debulk the tumor is the standard of care.

Radiation for meningiomas can be broadly divided into two categories, stereotactic radiosurgery (SRS) and focal fractionated radiotherapy. SRS is a means of delivering a moderate to high dose of radiation to a relatively limited area often in a single fraction. This can be delivered via a linear accelerator (LiNac) via the same device used to deliver standard fractionated radiation or one designed specifically for SRS (such as the Cyberknife device). It can also be delivered via a device utilizing a fixed cobalt source of radiation (ie Gammaknife). Each apparatus for delivery has its advantages and drawbacks. Recommendations regarding individual radiation treatment regimens (Table 5.6) are determined by tumor size, location, histology, and proximity to radiosensitive structures.

Broadly speaking, SRS is the preferred radiation method utilized for relatively small (<3 cm) grade 1 meningiomas. It differs from standard radiotherapy in that the rigidity of setup is heightened, allowing for larger doses per fraction to be delivered in a more conformal fashion than what can be delivered with standard radiotherapy. SRS may be used in place of surgery, to treat residual tumor post-operatively, or to treat progressive/recurrent disease. It has the ability to provide long-term control in the majority of patients [14]. If the meningioma is small or moderately sized it is often reasonable to treat with SRS once radiographic growth is demonstrated. This approach is felt to delay the potential SRS related toxicity while not increasing the risk to the patient. If the tumor is larger in size or located adjacent to critical cranial structures with lower radiation tolerability (Table 5.7) then fractionated SRS (defined as 2–5 fractions) is often employed as a means of limiting the toxicity, versus a fully fractionated course of standard radiotherapy. The primary short term toxicity of SRS is cerebral edema which may worsen neurologic symptoms tran-

Table 5.6 Frequently utilized radiation treatment regimens for meningiomas

RT technique	Grade I	Grade II	Grade III
Single fraction SRS	12–16 Gy	16–20 Gy for recurrent disease	Not generally appropriate
Fractionated RT	45–54 Gy	54–59.4 Gy for adjuvant or salvage indications	60 Gy postoperatively

Table 5.7 Radiation tolerability of critical structures

Structure	Single fraction limit	Fractionated RT limit
Optic nerves, chiasm	8–9 Gy max point dose	55 Gy[a]
Brainstem	<1 cc receiving 12+ Gy	55 Gy[a]

[a] Up to 60 Gy may be allowable for high-grade lesions abutting these structures

siently. In the long term, the primary concern is radiation necrosis which can develop months after the treatment and may first manifest even years after SRS. The risk of radiation necrosis is increased by prior radiation therapy in the same treatment field as well as by some medications such as targeted therapies and immunotherapies.

Fractionated radiation is when a substantial number of small fractions of radiation are administered (typically Monday through Friday) for a number of weeks to reach a high cumulative dose [15]. This modality is often used when the radiation field for the meningioma is large as well as with grade 2 and 3 meningiomas. While there is a lack of comparative studies, when evaluating results *across* studies fractionated radiation appears superior to SRS in grade 2/3 meningiomas. Another indication for fractionated radiation is meningiomas that lie in close proximity to optic structures, such as optic nerve sheath meningioma. In this setting the fractionation allows for adequate tumor dosing, while the small daily fraction allows for optic structure tolerances to not be exceeded. Outcomes in such cases show high rates of tumor control, with high rates of visual preservation [16]. However, these advantages to fractionation must be weighed against the logistical difficulties of daily transport to radiation oncology. This is of particular consideration when patients have neurological deficits or the distance to travel is far. Fractionated radiation is standard of care for the treatment of all grade 3 meningiomas regardless of extent of resection as well as for grade 2 meningiomas post-STR. Post-operative radiation in grade 2 meningiomas post-GTR is associated with high rates of local control in prospective studies, and as is currently being investigated in a randomized cooperative group trial, NRG BN003 (NCT03180268) [17].

Systemic Therapies

Systemic therapies have a limited role in the management of meningiomas at this time. It is possible, however, that this may change in the future. Much of this may be driven by our enhanced understanding of the molecular characteristics of these tumor subtypes. A number of systemic therapies have been investigating in these tumors, and unfortunately thus far none have been overly successful (Table 5.8). Studies have been predominantly single

Table 5.8 Systemic therapies investigated for the treatment of meningiomas

Hydroxyurea
Imatinib
Hydroxyurea + imatinib
Temozolomide
Irinotecan
Cyclophosphamide + adriamycin + vincristine
Interferon alpha
Mifepristone
Megestrol
Tamoxifen
Octreotide
Sandostatin LAR
Pasireotide LAR
Erlotinib
Gefitinib
Vatalanib
Sunitinib
Lapatinib
PTK787
Bevacizumab
Bevacizumab + paclitaxel
Bevacizumab + everolimus
(90)Y-DOTATOC
(90)Y-DOTATOC+(177)Lu-DOTATOC
Abemeciclib
Lutetium Lu177 dotatate

arm utilizing no control or historical controls; a single randomized clinical trial has been performed examining the anti-progestin agent mifepristone (given 70% of tumor express progesterone receptors) which revealed no impact on tumor outcomes [18]. Disappointingly, there have been no systemic regimens which have demonstrated definitive radiographic responses. In contemporary clinical practice, systemic therapies are most often utilized within the context of clinical trials or as salvage regimens for progressive disease (particularly when additional surgery or radiation are not optimal). Specific regimens which are considered include antiangiogenics, targeted therapies, traditional cytotoxic chemotherapies, and immunotherapies.

Ongoing studies which take advantage of mutually exclusive targetable mutations in subsets of meningiomas hold notable promise. In its greatest scope this is undergoing evaluation in the non-randomized multi-arm phase 2 cooperative group trial A071401 (NCT02523014). This study has separate arms for tumors with mutations in *SMO*, *AKT*, and *NF2*. Each arm is treated with a therapeutic targeting the specific aberrant pathway.

Conclusions

Meningiomas are common tumors which arise from the pachymeningeal coverings of the CNS. The natural history of most of these tumors reflects a pattern of slow growth, allowing many to be observed clinically and radiographically without therapeutic intervention. In those which require treatment, surgery can be curative and radiation, often delivered as SRS, can provide excellent long-term control. Some meningiomas, however, prove resistant to therapy and can incur both substantial morbidity and mortality. These oftentimes require repeated interventions with surgery and radiation serving as the cornerstones of their management. Systemic therapies, often within the context of clinical trials, are also added to the armamentarium when meningiomas are not amenable to further localized therapy. As these tumors are genomically less complex than other CNS tumors and are not pro-

tected by a blood brain barrier, the likelihood of therapeutic advances is high as our understanding of the molecular characterization and sub-classification improves.

References

1. Buerki RA, Horbinski CM, Kruser T, et al. An overview of meningiomas. Future Oncol. 2018;14(21):2161–77.
2. Lukas RV, Taylor JW, Kurz SC, Mohile NA. Clinical neuro-oncology for the neurologist. Neurol Clin Pract. 2020;10(5):458–65. https://doi.org/10.1212/CPJ.0000000000000765. PMID: 33299675; PMCID: PMC7717629.
3. Lukas RV, Mrugala MM. Non-malignant brain tumors. Continuum. 2020;26(6):1495–522.
4. Ostrum QT, Gittleman H, Liao P, et al. The CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol. 2018;20(suppl 4):v1–v86.
5. Sahm F, Toprak UH, Hubschmann D, et al. Meningiomas induced by low-dose radiation carry structural variants of NF2 and a distinct mutational signature. Acta Neuropathol. 2017;134(1):155–8.
6. Agnihotri S, Suppiah S, Tonge PD, et al. Therapeutic radiation for childhood cancer drives structural aberrations of NF2 in meningiomas. Nat Commun. 2017;8(1):186.
7. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231–51.
8. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131(6):803–20.
9. Olar A, Wani KM, Wilson CD, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta Neuropathol. 2017;133(3):431–44.
10. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol. 2017;18(5):682–94.
11. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet. 2013;45(3):285–9.
12. Aghi MK, Carter BS, Cosgrove GR, et al. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. Neurosurgery. 2009;64(1):56–60.
13. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry. 1957;20(1):22–39.

14. Bloch O, Kaur G, Jian BJ, et al. Stereotactic radiosurgery for benign meningiomas. J Neurooncol. 2012;107(1):13–20.
15. Gondi V, Tome WA, Mehta MP. Fractionated radiotherapy for intracranial meningiomas. J Neurooncol. 2010;99(3):349–56.
16. Paulsen F, Doerr S, Wilhelm H, et al. Fractionated stereotactic radiotherapy in patients with optic nerve sheath meningioma. Int J Radiat Oncol Biol Phys. 2012;82(2):773–8.
17. Rogers L, Zhang P, Vogelbaum MA, et al. Intermediate-risk meningioma: initial outcomes from NRG oncology RTOG 0539. J Neurosurg. 2018;129(1):35–47.
18. Ji Y, Rankin C, Grunberg S, 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;33:4093–8.

Treatment of Primary CNS Lymphoma

6

Ugur Sener and Lauren Schaff

Introduction

Clinical Scenario

A 58 year old woman with no past medical history presented to her primary care physician with forgetfulness, confusion and difficulty performing tasks at work. She was referred to a neurologist who found deficits on a mental status examination, including impaired recall, trouble with calculations, and confusion with multi-step commands. An MRI brain was ordered and demonstrated homogeneously enhancing lesions in the splenium of the corpus callosum, right temporal lobe and right parietal lobe with restricted diffusion and minimal edema. Due to concerns for lymphoma, she was not treated with corticosteroids. She underwent a staging workup including a slit lamp examination of the eye, CT chest, abdomen and pelvis and HIV

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test, all of which were normal. Two lumbar punctures revealed elevation in protein and slight elevation in cells, but negative cytology and absence of a monoclonal population with flow cytometry. She then underwent a brain biopsy that revealed diffuse large B-cell lymphoma. She began therapy with high-dose methotrexate, rituxan and temozolomide and after completing therapy she was found to have a complete imaging response. She also returned to her neurologic baseline. After induction therapy, she had an autologous stem cell transplant (ASCT) with a thiotepa-based conditioning chemotherapy regimen and has been free of disease for over 2 years.

Primary CNS lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin lymphoma (NHL) of the brain, spinal cord, cerebrospinal fluid (CSF), and/or eyes without systemic involvement. PCNSL is an aggressive malignancy that can rapidly result in significant neurologic disability, but it is highly responsive to chemo and radiation therapies and potentially curable. While immunosuppression is a risk factor for PCNSL, the disease also occurs in immunocompetent individuals. Management is not standardized across institutions and practice patterns are highly variable. Here, we will review the diagnosis, staging, and common treatment strategies for PCNSL in immunocompetent patients.

Epidemiology

PCNSL is a rare malignancy with an average age-adjusted incidence rate of 0.43 per 100,000 per year, representing 4% of newly diagnosed brain tumors [1, 2]. Median age at diagnosis is approximately 65 though PCNSL can be diagnosed at any stage of adulthood [3]. It is typically a B-cell neoplasm with diffuse large B-cell lymphoma (DLBCL) representing 90% of cases, though Burkitt, low-grade, and T-cell lymphomas can rarely present with CNS-only involvement [4].

Diagnosis and Staging

Diagnosis

Diagnosis of PCNSL requires a high level of clinical suspicion as presentation is variable depending on areas of involvement. Up to 70% of patients present with focal neurologic deficits whereas 43% present with mental status and behavioral changes [3, 4]. Seizures and symptoms of increased intracranial pressure such as headache, nausea, or vomiting can also occur. Imaging typically identifies one or more homogeneously enhancing brain lesions, often supratentorial and involving deep structures such as periventricular white matter, basal ganglia, thalamus, and corpus callosum. Magnetic resonance imaging (MRI) of the brain with and without contrast is the imaging modality of choice. In immunocompetent individuals, lesions are typically T2 hyperintense on MRI and homogeneously enhancing with contrast (Fig. 6.1). Restricted diffusion can be seen on diffusion weighted imaging (DWI) sequences. In individuals unable to undergo MRI, computed tomography (CT) of the head with and without contrast is recommended. On CT, PCNSL appears iso- to hyperdense on pre-contrast images, sometimes mimicking hemorrhage (Fig. 6.1).

Definitive diagnosis of PCNSL requires pathologic confirmation, often obtained by brain biopsy. There is no clear benefit to lesion resection. Even when a single lesion is noted on imaging, autopsy studies suggest PCNSL is a whole-brain disease responsive to chemo and radiation therapies, obviating the need for extensive debulking and associated surgical morbidity [4]. In cases of CSF or ocular involvement, diagnosis may be made by lumbar puncture or vitreous biopsy. However, it is generally not recommended to defer brain biopsy pending these results as there is urgency to initiation of treatment.

Corticosteroids can obscure pathology and lead to false negative results. When PCNSL is suspected, use of corticosteroids should always be deferred until tissue diagnosis is obtained unless life-threatening mass effect is present.

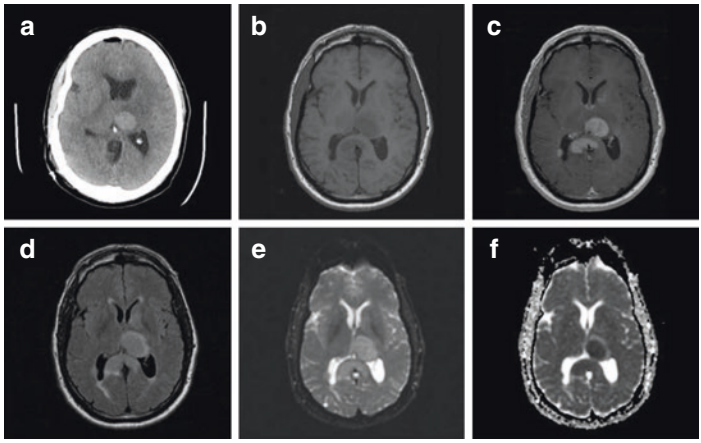

Fig. 6.1 Radiographic Appearance of Primary CNS Lymphoma. PCNSL involving the left thalamus and splenium of the corpus callosum is illustrated. On CT head, PCNSL can appear hyperintense (**a**) to isointense. On MRI brain, PCNSL typically appears T1 hypointense (**b**), uniformly enhancing with contrast (**c**), and T2 fluid attenuated inversion recovery (FLAIR) hyperintense (**d**). Diffusion restriction can be seen with lesions appearing hyperintense on diffusion weighted imaging (DWI) (**e**), and hypointense on apparent diffusion coefficient (ADC) (**f**)

Staging

Staging is required to determine the extent of disease involvement and sufficiently rule out systemic lymphoma. In addition to MRI of the brain, staging should include MRI of the whole spine with and without contrast. Ocular involvement can occur in up to 25% of cases and can be asymptomatic. Thus, slit lamp examination is recommended. Leptomeningeal involvement can occur in up to 20% of cases [3, 4]. Lumbar puncture with CSF analysis including cell count, measurement of protein and glucose, cytology, and flow cytometry should be performed if the procedure can be safely completed. Positron emission tomography (PET) imaging should also be completed to assess for systemic lymphoma involvement. If PET imaging is not available, CT of the chest, abdomen, and pelvis along with bone marrow biopsy and, in appropriate patients, testicular

ultrasound should be completed. All patients should undergo HIV testing.

First-Line Treatment

Treatment of PCNSL begins with an induction regimen with the goal of reducing disease burden, followed by consolidation to eradicate any residual microscopic disease and achieve remission. While the approach to induction treatment varies across centers, there is general consensus about the use of high-dose methotrexate (HD-MTX) in a combination regimen.

Methotrexate Therapy

Methotrexate is an inhibitor of dihydrofolic acid reductase, an enzyme required for purine nucleotide synthesis. In neoplastic cells, methotrexate interferes with DNA synthesis and cellular division, leading to cell death. Methotrexate penetrates the blood-brain barrier when administered as a rapid infusion at doses greater than 1.5 g/m^2 [5, 6]. The optimal dose for treatment of PCNSL is unknown but data suggests survival benefit with doses greater than or equal to 3 g/m^2 with many regimens calling for doses between 3.5 and 8 g/m^2.

Table 6.1 Guide to high-dose methotrexate treatment

Prior to initiation of methotrexate therapy:
Assess patient for third-space fluids: • Perform clinical examination and chest x-ray to assess for ascites and pleural effusion • If third-space fluids present, delay treatment until fluids removed or consider dose reduction • Consider transthoracic echocardiogram to assess cardiac function
Review medication risk for potential drug interactions[a]: • PPI can delay HD-MTX clearance • NSAIDs can potentiate myelosuppression and GI toxicity • TMP-SMX is a folate antagonist and should be avoided

(continued)

Table 6.1 (continued)

Laboratory evaluation to ensure[b]: • WBC ≥ 1500/μL • ANC ≥ 200/μL • Platelet count ≥75,000/μL • Serum bilirubin <1.2 mg/dL • ALT <450 U/L • Normal serum creatinine • Creatinine clearance >60 mL/min • Urine pH ≥ 7.0
Supportive measures:
Prior to infusion of HD-MTX: • 1000 mL/m^2 of intravenous fluid over 4–6 h • Sodium bicarbonate 650 mg orally night before and morning of HD-MTX administration • Additional sodium bicarbonate or acetate as needed to maintain urine pH > 7.0
After infusion of HD-MTX: • Monitor serum methotrexate level every 24 h until cleared • Monitor urine pH every 6 h, sodium bicarbonate or acetate boluses as needed to maintain pH > 7.0 • Leucovorin 10–15 mg/m^2 every 6 h, starting 24 h after start of HD-MTX infusion
If methotrexate level is toxic or AKI develops: • Promptly increase leucovorin dose, transition to IV if receiving PO • Increase IV hydration to ≥3 L/m^2 per day as tolerated, monitor for fluid overload • Review HD-MTX dosing for future cycles of treatment If AKI and toxicity • Consider glucarpidase up to 50 units/kg • Consider hemodialysis

PPI Proton pump inhibitor, *HD-MTX* high-dose methotrexate, *NSAID* non-steroidal anti-inflammatory drug, *TMP-SMX* trimethoprim- sulfamethoxazole, *WBC* white blood count, *ANC* absolute neutrophil count, *SGPT* serum glutamic pyruvic transaminase, *IV* intravenous, *PO* by mouth

[a] Selected drug interactions of interest are highlighted, not meant to be an exhaustive list

[b] Parameters as listed in the United States Food and Drug Administration package insert for methotrexate

[c] At Memorial Sloan Kettering Cancer Center, methotrexate level is considered toxic if >10,000 nmol/L at 24 h, >1000 nmol/L at 48 h, or >100 nmol/L at 72 h

HD-MTX is generally well tolerated however, can rarely be associated with serious and potentially fatal toxicities, especially if appropriate monitoring and supportive therapies are not in place (Table 6.1). Pre-treatment laboratory evaluation should be undertaken and include adequate cell count, renal function, and hepatic function. Due to the need for aggressive intravenous hydration during HD-MTX treatment, transthoracic echocardiogram should be considered for documentation of cardiac function. Methotrexate is predominantly cleared via renal excretion with contribution from the hepatic system. In patients with impaired renal function or existing liver disease, methotrexate dose reduction should be considered. Guidelines for dose reduction vary. In our practice, we consider a reduction for patients with creatinine clearance (CrCl) <60 mL/min and may reduce dose between 50 and 75% depending on the clinical situation. Dose reductions are also considered for patients with aspartate aminotransferase (AST) > 180 or bilirubin >3.1, typically to 75% of originally intended dose. In patients receiving 8 g/m^2, dose reductions are typically made for anyone with CrCl < 100 mL/min.

Methotrexate can accumulate in third-space fluids such as ascites and pleural effusions. This can result in delayed clearance and increased risk of methotrexate toxicity. Prior to initiation of HD-MTX, patients should be assessed for presence of third-space fluids by clinical examination and with a chest radiograph. If present, elimination of third-space fluids should be undertaken prior to treatment or a dose reduction should be considered.

Supportive Medication and Monitoring

Methotrexate administration can result in renal toxicity. To reduce the risk, supportive care is pre-emptively provided to all patients in the form of hydration and urinary alkalinization. As a result, methotrexate is almost always administered in the inpatient setting with continuous hydration and frequent monitoring of urine PH and serum methotrexate levels. Institutional guidelines for methotrexate administration may vary but typically involve pre-hydration with 1 L intravenous fluid over 4–6 h along with admin-

istration of sodium bicarbonate to achieve urine alkalinization to pH above 7.0. Prior to IV fluid administration, oral acetazolamide or oral bicacarbonate tablets can be used to more quickly alkalinze urine.

Intravenous hydration should be maintained after methotrexate infusion at rates between 75 and 150 mL/h as per institutional guidelines. Intravenous fluid should include sodium bicarbonate to maintain urine alkalinization and continuous monitoring of urine output and pH should be maintained until methotrexate is cleared.

Leucovorin, or folinic acid, is a rescue agent administered to reduce the risk of tissue toxicity associated with HD-MTX. Leucovorin provides a source of reduced folate, bypassing the effects of methotrexate. Leucovorin can be administered orally or by injection, typically at a dose of 10–30 mg/m^2 every 6 h, beginning 24–36 h after infusion of HD-MTX. The dose is increased in the event of toxic serum methotrexate levels and maintained until methotrexate clearance. It is important to remember that leucovorin itself does not aid in the clearance of methotrexate.

Serum methotrexate and creatinine levels should be monitored daily. At our institution, methotrexate is considered cleared and a patient safe for discharge when the serum level is 100 nmol/L or lower.

Concomitant Medications

Methotrexate also has multiple important drug interactions that must be considered before starting therapy. When HD-MTX is administered with proton pump inhibitors (PPIs), serum levels of methotrexate can be elevated and toxicity may increase. Severe myelosuppression, aplastic anemia, and gastrointestinal toxicity may occur when methotrexate is used with nonsteroidal anti-inflammatory drugs (NSAIDs). The antibiotic trimethoprim- sulfamethoxazole is a folate antagonist whose coadministration with methotrexate can potentiate toxicity and should be avoided [7].

Methotrexate Toxicity

Despite urine alkalinization and intravenous hydration, acute kidney injury (AKI) with methotrexate administration can occur through mechanisms such as precipitation in the renal tubules, vasoconstriction, and direct tubular toxicity. If AKI develops, intravenous fluids should be increased to ≥ 3 L/m^2 per day to maximize urine output [8]. AKI can result in delayed methotrexate clearance and toxic levels which can lead to systemic effects such as hepatic injury, pneumonitis, and bone marrow suppression. Gastrointestinal toxicities including oral mucositis, ulcerative stomatitis, and hemorrhagic enteritis have also been reported. Neurologic toxicities include headache, encephalopathy, leukoencephalopathy, and transient focal neurologic deficits. Rarely toxicity can be fatal.

In the event of AKI and methotrexate toxicity, glucarpidase is FDA approved to rapidly reduce serum methotrexate levels. Glucarpidase is dosed at 50 units/kg though there is evidence that lower doses may be as effective [9]. Leucovorin should not be administered within 2 h of glucarpidase injection since leucovorin is also a substrate for glucarpidase. If glucarpidase is not available, hemodialysis can be considered. In the event of delayed clearance and nephrotoxicity, reduction in methotrexate dose may be considered for future cycles. Table 6.1 provides a summary of methotrexate treatment including precautions and supportive measures that should be undertaken.

Common Induction Regimens

Data from multiple clinical trials support use of HD-MTX in combination with other chemotherapy agents as part of induction therapy for PCNSL. Due to the paucity of comparative randomized data, the optimal combination of chemotherapy agents and treatment schedule remains unknown. Induction regimens commonly used in clinical practice are summarized in Table 6.2. These include R-MVP (rituximab, methotrexate, vincristine, procarbazine), MT-R (methotrexate, temozolomide, rituximab),

Table 6.2 Common induction regimens

Induction regimen	
R-MVP (rituximab, methotrexate, vincristine, procarbazine) [10] Repeat every 28 days for 8 cycles	
• Rituximab 500 mg/m^2	Day 0 and 14
• Vincristine 1.6 mg/m^2, maximum dose 2.4 mg, stop after four total doses	Day 1 and 15
• Methotrexate 3.5 g/m^2	Day 1 and 15
• Procarbazine 100 mg/m^2/day	Day 1–7
MT-R (methotrexate, temozolomide, rituximab) [11] Repeat every 14 days for 4 cycles	
• Methotrexate 8 g/m^2	Day 1
• Rituximab 375 mg/m^2• Stop after six total doses	Day 3 and 10
• Temozolomide 150 mg/m^2 PO, odd cycles	Day 7–11, odd cycles
MATRix (methotrexate, cytarabine, thiotepa, rituximab) [12] Repeat every 21 days for 4 cycles	
• Rituximab 375 mg/m^2 • Methotrexate 3.5 g/m^2	Day −5 and 0 Day 1
• Ara-c (cytarabine) 2 g/m^2 every 12 h	Days 2 and 3 (4 doses)
• Thiotepa 30 g/m^2	Day 4
R-MBVP (rituximab, methotrexate, carmustine [BCNU], etoposide, prednisone) [13] Repeat every 28 days for 2 cycles	
• Rituximab 375 mg/m^2 on	Days 0, 7, 14, and 21
• Methotrexate 3.5 g/m^2	Days 1 and 15
• Etoposide 100 mg/m^2	Day 2
• BCNU 100 mg/m^2	Day 3
• Prednisone 60 mg/m^2/day	Day 1–5

MATRix (methotrexate, cytarabine, thiotepa, rituximab), and R-MBVP (rituximab, methotrexate, carmustine [BCNU], etoposide, prednisone) [3, 4, 10–13]. Combination of rituximab and methotrexate with no additional agents is also used. Specific considerations for each regimen are discussed here in more detail.

R-MVP

R-MVP consists of rituximab, methotrexate (3.5 g/m^2), vincristine, and procarbazine. Treatment cycles are 28 days long with methotrexate administered twice per cycle. The optimal number of cycles is not known though we favor completion of 4 (8 doses of methotrexate) with imaging for initial response obtained after two.

When to incorporate vincristine is a special consideration for the use of this regimen. Vincristine is a vinca alkaloid that inhibits microtubule formation, causing arrest of cell division during metaphase, leading to apoptosis. Toxicities from vincristine include hair loss, constipation, and most significantly, peripheral neuropathy. Vincristine is dosed at 1.6 mg/m^2, capped at 2.4 mg. The drug is only administered four times during the induction regimen to limit toxicity. CNS penetration of vincristine is questionable, and the drug may be omitted in patients with limited enhancing disease or pre-existing neuropathy. If neuropathy symptoms develop while on treatment, early discontinuation of vincristine should be considered. Vincristine is a vesicant and can cause tissue damage in the event of extravasation, mandating careful placement and confirmation of the intravenous line by an experienced individual prior to treatment.

Procarbazine is an oral chemotherapy agent with unclear mechanism of action, though likely serves as an alkylator. Procarbazine can cause hepatotoxicity and dose reduction or discontinuation should be considered if this occurs. Patients should be cautioned that ingestion of alcohol while taking procarbazine can cause a disulfiram-like reaction. Procarbazine is a weak monoamine oxidase inhibitor with potential for hypertensive crisis upon ingestion of tyramine-rich foods or coadministration of sympathomimetic agents.

R-MVP is often followed by use of filgrastim or pegfilgrastim, a human recombinant form of granulocyte colony-stimulating factor (G-CSF) which can stimulate production of neutrophils [14]. G-CSF can be started 24 h after clearance of methotrexate. Use of G-CSF is designed to prevent infectious complications of

severe neutropenia and allow for completion of chemotherapy cycles without delays or dose reductions.

MT-R

MT-R includes methotrexate, temozolomide, and rituximab. Temozolomide is an alkylating chemotherapy agent that is typically well-tolerated. Hepatotoxicity, thrombocytopenia, and lymphopenia complicated by Pneumocystis jirovecii pneumonia (PJP) can occur.

MATRix

MATRix includes methotrexate, cytarabine, thiotepa, and rituximab. Cytarabine is an antimetabolite that inhibits DNA synthesis. Cytarabine and thiotepa can both cause myelosuppression, hepatotoxicity, and pulmonary toxicity. Additional toxicities from cytarabine such as cerebellar ataxia, corneal toxicity, and gastric ulcers tend to occur with high-dose treatment.

R-MBVP

R-MBVP includes rituximab, methotrexate, BCNU, etoposide, prednisone. BCNU is an alkylator, which can cause myelosuppression and dose-dependent pulmonary toxicity, mandating monitoring with pulmonary function tests before and during treatment. In order to minimize risk of pulmonary fibrosis, BCNU has a lifetime dose limit of 1400 mg/m^2. Etoposide is a topoisomerase II inhibitor that prevents DNA replication. Etoposide can cause myelosuppression, sensitivity reaction, and skin necrosis in the event of extravasation.

Role of Rituximab

The above regimens all incorporate rituximab. Rituximab is a monoclonal antibody directed against the B-cell surface antigen CD20. It is well tolerated with infusion reactions the most commonly reported complaint. Rarely, these reactions can be fatal.

Rituximab can also be associated with hepatitis B reactivation and patients should be screened for infection with carriers closely monitored. Progressive multifocal leukoencephalopathy has also been reported.

The use of rituximab has dramatically improved outcomes in the management of systemic DLBCL however, it's role in PCNSL has recently been called into question. In the phase 2 International Extranodal Lymphoma Study Group-32 (IELSG32) clinical trial, addition of rituximab to cytarabine and HD-MTX improved overall response rate (ORR) and progression free survival (PFS) [12]. However, this phase II study was not designed for comparison of treatment groups. In contrast, the randomized open-label phase III clinical trial HOVON 105/ALLG NHL 24 demonstrated no improvement in overall survival (OS) or PFS from addition of rituximab to methotrexate, BCNU, etoposide, and prednisone therapy, though long-term data is lacking [13]. Currently, our practice is to incorporate rituximab into our treatment regimens for B-cell lymphoma, unless there is a contra-indication or a patient is felt to be high risk. There is no role for rituximab in treatment of T-cell lymphoma.

Site-Specific Therapy

The role of site-specific therapy in PCNSL is unclear.In patients with leptomeningeal disease, intrathecal (IT) therapy can be considered. Administration via an Ommaya reservoir is generally preferred over lumbar puncture due to better CSF distribution. Commonly administered agents include methotrexate (12 mg flat dose), rituximab (25 mg flat dose), cytarabine (70 mg flat dose; liposomal cytarabine 50 mg flat dose), or thiotepa (10 mg flat dose). IT chemotherapy is contra-indicated in patients with elevated intracranial pressure and caution is advised in patients with bulky leptomeningeal disease as impaired CSF flow can result in toxic drug accumulation. In general, its use can increase treatment toxicity and no clear survival benefit has been established. Methotrexate doses 3 g/m^2 or

higher is penetrate the CSF, calling utility of IT chemotherapy into question.

Similarly, the role of intraocular therapy is not clearly established in patients with ocular involvement from PCNSL [3, 4]. Intravitreal methotrexate, intravitreal rituximab, and ocular radiation can be considered as part of the induction regimen since some data suggest higher rates of ocular failure when site-specific therapy is deferred [3, 4]. However, to date, early intraocular therapy has not been associated with increased OS [3, 4].

Common Consolidation Regimens

Consolidation strategies for PCNSL include high-dose myeloablative chemotherapy followed by autologous stem cell transplantation (HDC-ASCT), high-dose non-myeloablative chemotherapy, and whole brain radiation therapy (WBRT). Though no consensus exists regarding the optimal consolidation strategy, chemotherapy regimens are increasingly favored over WBRT due to chemoresponsiveness of the tumor and potential for neurotoxicity with RT [15].

In choosing a consolidation regimen, patient age, performance status, medical comorbidities, and response to induction should be considered. In general, younger patients with good performance status, few medical comorbidities, and good response to induction should be considered for HDC-ASCT, which has been associated with >90% ORR and prolonged PFS. While there are different conditioning regimens available for HDC-ASCT, thiotepa-based regimens such as thiotepa, busulfan, and cyclophosphamide (TBC) are generally favored over BCNU-based regimens (BCNU, etoposide, cytarabine, melphalan [BEAM] or cyclophosphamide, etoposide, BCNU [CBV]) due to improved response rates [3, 4]. However, HDC-ASCT is associated with serious toxicity including treatment-related mortality, requiring thoughtful patient selection and discussion of risks and benefits.

In frail individuals, patients with multiple medical comorbidities, or in the setting of partial response to induction, consolidation with high-dose non-myeloablative chemotherapy should be

considered over HDC-ASCT. The most common nonmyeloablative consolidation regimen consists of cytarabine, with or without etoposide. Maintenance therapy with methotrexate, rituximab or temozolomide are also considerations. Alternative maintenance regimens with ibrutinib and other novel agents such as lenalidomide are currently being explored.

Finally, reduced dose WBRT (23.4–36 Gy) may provide a reasonable consolidation strategy though confers risk of neurotoxicity. Longer follow up is needed to determine the level of risk with lower doses of WBRT [10, 16]. A randomized phase 2 study of cytarabine consolidation with or without low dose WBRT demonstrated improvement in progression free survival (PFS) with the addition of low dose WBRT compared with cytarabine consolidation alone (2-year PFS 78% vs 54%, respectively), and overall survival data are maturing in both arms [17].

Relapsed Disease

Though PCNSL is responsive to induction chemotherapy, up to 15% of patients remain refractory. Relapse can occur in up to 50% of patients, most commonly within 2 years of diagnosis. No consensus exists in management of relapsed or refractory disease. Enrollment in clinical trials should be encouraged and considered the first option if available.

In individuals who had an initial durable response to HD-MTX-based induction, rechallenge with methotrexate-based therapy can be considered, especially if initial response duration was more than 12 months [18]. In patients refractory to methotrexate or with only short duration of response, the role of further methotrexate is questionable and alternate strategies such as cytarabine (with or without etoposide), temozolomide, lenalidomide, or pemetrexed could be considered.

In recent years, the availability of ibrutinib has enhanced the approach to recurrence. Ibrutinib inhibits Bruton tyrosine kinase (BTK), a key enzyme in the B-cell receptor pathway. An oral agent, it is generally well tolerated and does not require inpatient

treatment. Single-agent ibrutinib can achieve responses up to 77% in recurrent PCNSL [19]. Ibrutinib may also be used with rituximab and methotrexate and is currently being studied in other combinations. Importantly, ibrutinib is associated with pulmonary and cerebral aspergillosis as well as Pneumocystis jiroveci pneumonia (PJP), particularly in patients who have chronic corticosteroid exposure. Caution is advised and PJP prophylaxis should be considered.

Novel approaches to treating refractory or relapsed PCNSL include immunotherapy with anti-PD-1 antibodies pembrolizumab and nivolumab. Anti-PD-1 checkpoint inhibitors such as pembrolizumab may have a role in PCNSL treatment given PD-1 overexpression reported in >50% of these tumors [20, 21].

For individuals with relapse after non-myeloablative high-dose chemotherapy, HDC-ASCT can be an option with 58.6-month OS reported in patients successfully completing transplant in one study [3, 22].

In individuals unable to undergo HDC-ASCT and refractory to other treatments, WBRT can be considered.

Expectations from Treatment

1. Age and Karnofsky Performance Status (KPS) at diagnosis have been identified as predictors of outcome in PCNSL [4]. According to the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score, the expected median OS for patients with age ≤50, age >50 with KPS ≥70, age <50 with KPS <70 is 8.5 years, 3.2 years, and 1.1 years respectively [4]. However, PCNSL is highly responsive to chemotherapy and radiation therapy. Treatment should be attempted even in elderly patients with low KPS, particularly if status is a result of disease. Clinical benefit and response to methotrexate may be seen after only one or two doses.

PCNSL has a high rate of recurrence, particularly during the first 2 years after diagnosis. National Comprehensive Care Network guidelines recommend surveillance brain imaging every 3 months for the first 2 years after treatment, then every 6 months for another 3 years, and annually thereafter. Periodic spine imaging, CSF analysis, and ocular examination should be considered depending on initial areas of involvement.

Patient Information

The following information is intended to be shared with patients and family members of individuals with primary central nervous system lymphoma to provide an overview of the condition and its management.

What Type of Tumor Do I Have?

Primary central nervous system lymphoma (PCNSL) is a type of cancer caused by malignant cells originating from the immune system. Unlike systemic lymphomas, in PCNSL, the cancer cells are confined to the brain, spine, eyes, and/or the cerebrospinal fluid without involving other parts of the body. In most cases, PCNSL originates from a type of immune cell called B-cells, which are normally responsible for making antibodies to fight infection. Rarely, a different type of immune cell called T-cells can give rise to PCNSL.

How Do I Treat It?

Treatment of PCNSL involves two phases. During the first phase, called induction, we administer multiple chemotherapy drugs in combination to kill cancer cells with the goal of eliminating all visible tumor. In the second phase, called consolidation, we administer additional treatment such as high-dose chemotherapy followed by stem cell transplantation or whole brain radiation therapy to eradicate any residual microscopic disease.

What Can I Expect to Experience During Treatment?

Most induction regimens for PCNSL utilize a combination of multiple chemotherapy agents including methotrexate.

Administration of methotrexate requires admission to the hospital for fluids, safety, and monitoring. Your doctor may prescribe a medication called rituximab to be administered prior to your arrival to the hospital. Then you will receive hydration with intravenous fluids, followed by methotrexate infusion. Your hospital team will monitor your urine output and labs including the level of methotrexate in your blood. You will receive another medication called leucovorin to protect you from side effects of methotrexate. It can take 3–5 days, on average,to clear methotrexate. Once this happens, you can be discharged. You may receive additional medications to take while you are at home. You will typically repeat treatments every 2 weeks until the completion of induction. At that point, your doctor will order tests to assess the status of your disease. You will then together choose a consolidation regimen to complete the course of treatment.

How Will We Keep an Eye on This?

Your doctor will periodically order magnetic resonance imaging (MRI) scans of your brain and/or your spine to monitor the disease. Additional tests such as positron emission tomography (PET) scans and lumbar punctures to evaluate your cerebrospinal fluid may be required. Once you complete consolidation, expect to have MRI scans every few months for monitoring. You should also report any new symptoms to your doctor.

What Is My Prognosis?

Even though PCNSL is a very serious disease requiring treatment, it is responsive to chemotherapy and radiation therapy. While on average people with PCNSL live 24 months, it is possible to cure the disease with the treatments that are currently available. Up to 40% of patients are alive 5 years after the diagnosis. These statistics are likely improving as novel treatments are being developed.

References

1. Ostrom QT, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21(Supplement_5):v1–v100.
2. Villano JL, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011;105(9):1414–8.
3. Schaff LR, Grommes C. Updates on primary central nervous system lymphoma. Curr Oncol Rep. 2018;20(2):11.
4. Grommes C, DeAngelis LM. Primary CNS lymphoma. J Clin Oncol. 2017;35(21):2410–8.
5. Borsi JD, Moe PJ. A comparative study on the pharmacokinetics of methotrexate in a dose range of 0.5 g to 33.6 g/m2 in children with acute lymphoblastic leukemia. Cancer. 1987;60(1):5–13.
6. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med. 1975;293(4):161–6.
7. Al-Quteimat OM, Al-Badaineh MA. Practical issues with high dose methotrexate therapy. Saudi Pharma J. 2014;22(4):385–7.
8. Howard SC, et al. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–82.
9. Schaff LR, Lobbous M, Carlow D, Schofield R, Gavrilovic IT, Miller AM, Stone JB, Piotrowski AF, Sener U, Skakodub A, Acosta EP, Ryan KJ, Mellinghoff IK, DeAngelis LM, Nabors LB, Grommes C. Routine use of low-dose glucarpidase following high-dose methotrexate in adult patients with CNS lymphoma: an open-label, multi-center phase I study. BMC Cancer. 2022;22(1):60. https://doi.org/10.1186/s12885-021-09164-x. PMID: 35027038; PMCID: PMC8756618.
10. Morris PG, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 2013;31(31):3971–9.
11. Rubenstein JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol. 2013;31(25):3061–8.
12. Ferreri AJ, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217–27.
13. Bromberg JEC, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2019;20(2):216–28.

14. Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. BioDrugs. 2009;23(3):175–86.
15. Thiel E, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 2010;11(11):1036–47.
16. Glass J, et al. Phase I and II study of induction chemotherapy with methotrexate, rituximab, and Temozolomide, followed by whole-brain radiotherapy and postirradiation Temozolomide for primary CNS lymphoma: NRG oncology RTOG 0227. J Clin Oncol. 2016;34(14):1620–5.
17. Omuro AM, DeAngelis LM, Karrison T, Bovi JA, Rosenblum M, Corn BW, et al. Randomized phase II study of rituximab, methotrexate (MTX), procarbazine, vincristine, and cytarabine (R-MPV-A) with and without low-dose whole-brain radiotherapy (LD-WBRT) for newly diagnosed primary CNS lymphoma (PCNSL). J Clin Oncol. 2020;38(15_suppl):2501.
18. Pentsova E, Deangelis LM, Omuro A. Methotrexate re-challenge for recurrent primary central nervous system lymphoma. J Neurooncol. 2014;117(1):161–5.
19. Grommes C, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. Cancer Discov. 2017;7(9):1018–29.
20. Chapuy B, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. Blood. 2016;127(7):869–81.
21. Nayak L, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017;129(23):3071–3.
22. Soussain C, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. J Clin Oncol. 2008;26(15):2512–8.

Adult Medulloblastoma

7

Tresa McGranahan and Sonia Partap

The Clinical Scenario

Clinical Presentation

MB are rapidly growing malignant tumors and patients typically develop neurologic signs and symptoms over the course of weeks to months. For adults, the median age of MB diagnosis is 30 years and diagnosis over 40 years of age is rare. The most common presenting symptoms are headache, dizziness and imbalance. Other neurologic signs and symptoms can vary depending on the extent of disease. For example, cerebellar signs and symptoms include changes in gait, balance, vision and coordination as well as nausea, vomiting and vertigo. There may be compression of the fourth ventricle, resulting in elevated intracranial pressure (ICP) due to obstructive hydrocephalus. Typical symptoms of elevated ICP are early morning headaches and double vision (due to cranial nerve 6 palsy) although elevated ICP may result in loss of conscious-

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ness. Brainstem, spinal cord, and leptomeningeal spread can occur and result in additional symptoms. Metastasis of MB outside of the central nervous system have been reported but are rarely presenting symptoms.

Physical exam should include evaluation for papilledema and detailed cranial nerve testing as well as particular attention towards findings such as head titubation/head bobbing, truncal ataxia and wide based ataxic gait.

Genetic Testing

Multiple genetic syndromes have been reported in association with MB: Li-Fraumeni syndrome, Familial adenomatous polyposis (FAP), Cowden syndrome, Gorlin syndrome, Turcot's syndrome, Rubinstein-Taybi syndrome. For this reason, detailed family history is recommended for all patients. All patients with WNT and SHH subtypes should be referred for genetic counseling and testing. Group 3 and 4 patients should be referred for genetic counseling if family history of BRCA-associated cancers or homologous recombination repair deficiency [1].

Radiographic Finding

By definition, MB arises in the cerebellum however, location and enhancing pattern differ by molecular subtypes (Table 7.1). On CT, MB are hyperdense and with limited vasogenic edema. On MR imaging, MB typically has heterogeneous enhancement and may contain cysts, necrosis, calcifications and hemorrhage. On T1-weighted images these are isointense or hypointense and T2-weighted images may be hyperintense or heterogeneous. MB often restricts diffusion on DWI/ADC and DWI is very sensitive for detecting non-enhancing nodules.

Given high rates of metastasis all patients require MRI full spine pre- and post-contrast imaging. This imaging may demonstrate nodular enhancement or with leptomeningeal spread, linear enhancement along the pial surface. T2 imaging should also be obtained as not all metastatic lesions are contrast enhancing.

Table 7.1 Medulloblastoma molecular subtypes

Subtype	Prevalence	5-year OS	Histology	Location	MRI features	Rate of metastasis
WNT	15%	80%	C>>LCA	Foramen of Luschka	Hemorrhage	Rare
SHH	60%	70%		Cerebellar hemisphere	Strong DWI, more edema	5%
TP53wt	Majority		C, DN			
TP53 mutant	Rare		LCA			
Non-WNT/Non-SHH						
Group 3	Rare		C, LCA			High
Group 4	25%	45%	C, LCA	Midline	Minimal contrast	30–40%

OS overall survival, *wt* wildtype, *C* classic, *LCA* large-cell/anaplastic, *DN* desmoplastic/nodular

In adults, the most common etiology of a cerebellar mass is metastasis from a solid cancer (for example lung or breast cancer) and not MB. The radiographic differential also includes ependymoma, choroid plexus papilloma, hemangioblastoma and glioma. For children, the radiographic differential includes atypical teratoid rhabdoid tumor, ependymoma, and pilocytic astrocytoma.

Staging

Chang stage (Table 7.2) is used to document extent of disease and for risk stratification [2]. Given high rates of metastasis in MB, as well as implications for treatment, all MB require CNS staging. An MRI brain should be obtained both preoperative as well as within 48 h after surgery. This is essential for determining the amount of residual disease before post-surgical inflammation changes predominant. Patients also require MRI spine obtained pre-operatively or 2–3 weeks after surgery. If there is no radiographic evidence of leptomeningeal spread, CSF should be sampled from the lumbar spine 2 weeks postoperatively to reduce the risk of false positive results from surgical debris. Often due to

Table 7.2 Chang staging

Tumor classification	
T1	<3 cm
T2	>3 cm
T3a	>3 cm with spread into the aqueduct of Sylvius and/or foramen of Luschka, cerebral subarachnoid space, third or lateral ventricles
T3b	>3 cm with unequivocal spread into the brainstem; for T3b, surgical staging may be used in the absence of involvement at imaging
T4	>3 cm with spread beyond the aqueduct of Sylvius and/or the foramen magnum
Metastatic classification	
M0	GTR and no evidence of CSF or distant spread
M1	Tumor cells found in CSF
M2	Intracranial tumor beyond primary site
M3	Gross nodular seeding in subarachnoid space
M4	Metastasis outside of neuroaxis (e.g. bone, bone marrow)

hydrocephalus, pre-operative lumbar spine sampling of CSF is not considered safe. Due to concerns for dural enhancement following lumbar puncture, MRI of spine should be obtained prior to lumbar sampling of CSF. Systemic staging (PET, CT, bone scan) is only recommended if there are concerning symptoms.

Pathologic and Molecular Findings

MB is an embryonal tumor with histology of small round blue cells with mitosis. Histologically, MB is divided into three subtypes (classic, large-cell/anaplastic, and desmoplastic/nodular). Large-cell/anaplastic subtype is associated with worse prognosis compared to other groups [3]. As of WHO 2016, MB are also divided into four molecular subtypes (WNT, SHH, Group 3 and Group 4) which overlap with the histological subtypes [4] (Table 7.1). All MB subtypes are WHO grade 4 tumors.

WNT-MB subgroup represents 15% of adult MB. This subgroup is characterized by activation of the WNT/beta-catenin pathway and typically has classic histology, however rarely is large-cell/anaplastic. WNT-MB has the best prognosis for both adults and children, however the 5 year survival in adults is 80% compared to over 95% in children. On MRI, the WNT subgroup often arises from the cerebellar peduncle and has higher rates of hemorrhage. Even without suspicion based on family history, 6–8% of patients with WNT-MB had germline APC mutations so all of these patients should have genetics referral [1].

SHH-MB subgroup is the most common subtype in adults representing 60% of adult MB. This subgroup is characterized by mutations in the sonic-hedgehog (SHH) pathway and subdivided into TP53 wildtype and mutant. In adult MB, the majority of SHH-MB are TP53 wild-type. All histologic subtypes are seen in SHH-MB, however large-cell/anaplastic is more common in TP53 mutant SHH-MB. The 5-year overall survival is 70% in adults. SHH-MB are more often in the cerebellar hemispheres, although they may be midline in adults. There is often a greater degree of edema surrounding SHH-MB compared to other subtypes. Genetics referrals

should also be considered for SHH subgroups with consideration of germline testing for TP53, PALB2 and BRCA2.

Non-WNT/Non-SHH subgroup: The 2021 WHO is comprised of the "Group 3" and "Group 4" subtypes that were previously defined in the 2016 WHO, as well as other molecular subtypes that has emerged with more granular methylation and transcriptome profiling.

Group 3 subgroup is extremely rare in adults with reports ranging from 0 to 5%. This subgroup may have classic or large cell/anaplastic. Rates of metastasis are high contributing to the poor prognosis of this group for both children and adults [5].

Group 4 subgroup is the second most common subgroup in adults representing 20–25% of adult MB. Histologically this may have classic or large cell/anaplastic morphology [6]. In adults, Group 4 MB is metastatic in 35–40% of patients contributing to the poor prognosis with median overall survival of less than 3 years [3, 6]. Group 4 MB are more often midline and enhance less than other subtypes.

First Line Treatment

Clinical Risk Stratification

The majority of studies have not found the risk stratification used in children (Table 7.3) to be prognostic in adults. As a result, multiple definitions have been used to characterize high and average

Table 7.3 Childhood clinical staging of medulloblastoma

	High risk	Average risk
Age of child	Less than 3 years	Older than 3 years
Extent of resection	STR or biopsy	GTR/NTR
Presence of metastatic disease	Metastatic disease (M1–3)	M0
Histology	Large cell/Anaplastic	Classic

GTR gross total resection, *NTR* near total resection, *STR* subtotal resection

risk MB in adults. The majority of studies have found metastasis (Chang M1–4), anaplastic histology and brainstem involvement to be associated with worse prognosis. Risk stratification based on age or residual disease remains unclear in adult MB especially since the identification of molecular subgroups.

Surgery

Surgery is an essential component for diagnosis and management of MB. The goal of surgery is removal of as much visible tumor as can be done safely without resulting in new neurologic deficits. Residual tumor volume of less than 1.5 cm^2 is considered a gross total resection (GTR). In the setting of brain stem involvement, leaving residual tumor volume is considered safe. In adults with group 4 tumors there is a progression free survival benefit to GTR [7] however maximal safe resection in all patients is recommended.

In addition to diagnosis and debulking, surgery may also be needed for management of hydrocephalus. Obstructive hydrocephalus is common at presentation of MB and patients may require CSF diversion even prior to initial work up. For many patients, debulking surgery can relieve obstruction, however some may require shunt placement for treatment of the hydrocephalus. Regardless of initial hydrocephalus management, development of signs and symptoms related to elevated ICP should lead to prompt evaluation for hydrocephalus with head imaging and funduscopic examination.

Craniospinal Irradiation

Surgery and radiation remain the cornerstone of treatment for adult MB while the role of chemotherapy is questioned in adults. The standard of care is to start craniospinal irradiation (CSI) within 4 weeks of surgery and retrospective data have found that adult patients who started radiation after this window trend towards worse survival [8]. Proton CSI is favored over photon CSI due to data that found adult MB patients had less weight loss,

nausea, vomiting, hematologic toxicities and esophagitis when treated with protons [9]. The range of dose for CSI is between 23.4 and 39.6 Gy and tumor bed is boosted to between 54 and 55.8 Gy. Despite the limitations to risk stratification noted above, CSI to a dose of 36 Gy in 20 fractions is typically used for patients determined to be high risk due to the presence of metastasis, anaplastic histology or brainstem involvement. For patients without these high risk features, a CSI dose of 23.4 Gy in 13 fractions with the same tumor bed boost to 54–55.8 Gy is used.

Focal radiation to sites of metastatic disease vary based on location and tolerance of tissues. Typical doses are 50.4 Gy for intracranial metastasis or below the conus and 45 Gy for focal spinal metastasis above the conus. In the setting or radiographic leptomeningeal disease, the dose of CSI is increased to 39.6 Gy. While dose reduction is being studied in average risk WNT tumors in patients up to 21 years of age (NCT02724579, NCT01878617), this is not recommended for adults outside of clinical trials.

Systemic Therapy

MB is sensitive to chemotherapy, however at this time there is no standard chemotherapy regimen for adult MB. Most chemotherapy regimens have been adopted from pediatric studies as only three prospective, single arm, adult MB clinical trials have resulted and none included molecular subtypes. Most retrospective studies have not found benefit to chemotherapy, however a recent meta-analysis did find improved survival combining a wide variety of chemotherapy protocols (neoadjuvant, concurrent and adjuvant). As a result, treatment guidelines from EANO-EURACAN recommend treatment of all patients with chemotherapy in addition to CSI regardless of risk factors or molecular subtype [7].

The role of chemotherapy in adult MB is an area in need of prospective clinical trials. Whenever possible patients should be referred for participation in clinical trials. The treatment recommendations differ between NCCN and EANO-EURACAN; these authors' recommendations are reflected [7]. Neoadjuvant chemo-

Table 7.4 First line chemotherapy following irradiation

Packer—42 day cycle	CVP—28 day cycle
D1: Lomustine 75 mg/m^2	D1–4: Cisplatin 25 mg/m^2
D1: Cisplatin 70 mg/m^2 (consider carboplatin AUC 4 as alternative)	D1–4: Etoposide IV 40 mg/m^2
D1, D8, D15: Vincristine 1.5 g/m^2 (2 mg max)	D4: Cyclophosphamide 1000 mg/m^2
4–8 cycles pending tolerability	Goal: 4 cycles

AUC Area under the curve

therapy is not recommended. Given toxicity and unclear benefit, chemotherapy concurrent with radiation (vincristine or carboplatin) are not recommended. It is important to note that other groups do advocate for use of concurrent chemotherapy [8]. NCCN guidelines support adjuvant chemotherapy of either the "Packer Protocol", consisting of platinum agent (carboplatin or cisplatin), lomustine and vincristine [10], or "CVP" with cyclophosphamide, etoposide, cisplatin [11]. In fit adult MB patients, adjuvant chemotherapy with "Packer Protocol" should be considered (Table 7.4). There are several older multi-drug regimens that have been reported but are not favored as first line therapy.

Surveillance

Most adult MB recurrences are reported within 6 years of diagnosis, however, the high rate of late recurrences in adult MB mandates lifelong surveillance. The median time to tumor progression is 24–50 months, however there is an increased risk of recurrence in adults after 7 years and recurrences have been reported after 14 years from diagnosis [12].

During treatment, patients should have an MRI of the brain and spine completed one month following CSI. For patients who have metastatic disease to the spine or systemic metastasis, all surveillance imaging should include known sites of disease. For patients without metastatic disease, the role of spine surveillance is debatable as 50% relapses occur in posterior fossa and absence of intra-

cranial progression is predictive of absence in spine. Systemic surveillance (bone surveillance and PET imaging) have been discussed but at this time are not recommended for adults. These authors recommend MRI brain and spine every 3 months for the first year. If no spine involvement, MRI brain alone can be monitored every 3 months for the second year after diagnosis though there is no standard. In children, spine MRI is obtained serially as well until 5 years from diagnosis. During years 3–7, imaging frequency can be spaced to every 6 months. Annual MRI surveillance for the known sites of disease should be continued indefinitely.

Prognosis

True prognosis and survival data are limited given rarity of disease, wide variations in treatment and limited prospective studies. For adults, the SEER and CBTRUS databases estimate 2, 5 and 10 year survival as 85–89%, 74–78% and 67–68% [13, 14]. Molecular subtypes help with stratifying prognosis with WNT having the best prognosis of 5 year survival of 80%, followed by SHH with a 5 years survival of 70% and Group 4 of 5 year survival of less than 50% [3].

Recurrent Disease Treatment

At the time of recurrent disease, repeat staging should be completed with MRI spine, CSF sampling and survey of systemic symptoms with consideration of CT chest and abdomen or PET scan. There is very limited data to guide treatment of recurrent MB and estimated survival after recurrence is 15 months. For this reason, all patients should be evaluated at a comprehensive brain tumor center for consideration of clinical trials.

Local treatment options at recurrence include, re-resection and re-irradiation. While there are increased risks of toxicity with re-irradiation, stereotactic radiosurgery has been reported to result in an 89% disease control rate [15].

Table 7.5 Recurrent treatment options

First choice	Enroll in a clinical trial	
Other options		Dosing reference
Local therapy	Re-resection	
	Re-irradiation	Brandes et al. (2015) [15]
Chemotherapy	Bevacizumab and temozolomide	
	Temozolomide	
	MOPP (methotrexate, procarbazine, vincristine, prednisone)	Kunschner et al. (2001) [11]
	Lomustine + platinum ± vincristine	Gill et al. (2008) [16]
	CVP (cisplatin-cyclophosphamide-etoposide)	See Table 7.4
	Tandem autologous stem cell transplant	Gill et al. (2008) [16]
Targeted therapy	Vismodegib	Li et al. (2019) [17]
	Sonidegib	Li et al. (2019) [17]

Chemotherapy is favored for multifocal relapse however there have been no studies comparing efficacy of various treatments. Responses have been reported with several treatments listed in Table 7.5.

For patients with SHH- MB, SMO inhibitors vismodegib and sonidegib are well tolerated and should be considered for recurrent SHH- MB [17]. There are current prospective trials studying these agents in newly diagnosed SHH disease as well (NCT01878617, EORTC-1634-BTG).

Survivorship

The survivorship issues for adult MB parallel those for other malignant brain tumors with complications of neurologic injury from site of disease as well as long term effects of radiation and chemotherapy.

Fertility: All patients should be offered referral to fertility preservation clinics prior to start of treatment.

Cognitive: Consistent with other studies of whole brain radiation in adults, survivors of adult MB have cognitive impairment. Studies have identified the cognitive domains most impacted are learning, memory, visuospatial skills and reasoning [18]. Differences in cognitive outcomes between proton and photon radiation have never been proven for adults. In pediatric MB however, there is retrospective data that suggests superior global IQ, perceptual reasoning and working memory with protons compared to photons. Both groups had impaired processing speed [19].

Endocrine: Treatment with CSI places patients at risk for pituitary dysfunction as well as primary endocrine organs. The majority of data for endocrinopathies following treatment for MB are based on childhood survivors. The risk of thyroid dysfunction (primary or second) for children treated with CSI range from 20 to 69%.

Patients who underwent CSI should have annual surveillance for endocrine dysfunction with TSH and free T4, gonadal steroids and AM cortisol. There should be a low threshold for shorter intervals of endocrine screening if patients clinically decline with unexplained weight loss, excessive fatigue, nausea or orthostatic symptoms.

Ototoxicity: Ototoxicity develops in 48% of patients treated for MB most often as a complication from treatment. Platinum based chemotherapies, particularly cisplatin, cause ototoxicity that should be monitored during treatment as well as long term. Carboplatin can be considered in lieu of cisplatin as it has less ototoxic effects. Cochlear dose of radiation can also impact ototoxicity and studies in children have found that reducing the cochlear dose of radiation reduces grade 3 and 4 ototoxicity [8].

Neuropathy: Multiple studies in adult MB highlight the risk of peripheral neuropathy with vincristine [8, 10]. Given the high risk of neuropathy with vincristine, as noted above these authors do not support including concurrent vincristine during radiation in adults. If vincristine is used in adjuvant chemotherapy, close monitoring is necessary and discontinuation if grade 2 motor or sensory neuropathy develops.

Radiation related neurologic injury (radiation necrosis): Brain and spinal radiation injury can occur in MB similar to other brain tumors. Radiation injury in the brain stem can be particularly toxic presenting with weakness, dysarthria or dysphagia. With proton radiation, these changes occur 8–18 months following the start of radiation [8].

Genetic screening: A high prevalence of genetic predisposition were found in WNT and SHH subtypes of both childhood and adult MB. Current recommendations are that all patients with WNT and SHH MB should be referred for genetic counseling and testing as standard of care [1].

Secondary Malignancy: Patients treated with radiation and chemotherapy remain at risk for secondary malignancies. There is no standard accepted screening however the risks include (but are not limited to) skin cancer, secondary brain tumor (meningioma, glioma), sarcomas, leukemia and thyroid malignancy [20].

Vascular Complications: CSI may result in a multitude of radiation induced/accelerated vascular complications in the brain as well as cardiovascular system. Cerebral microhemorrhages have been reported to occur in 67% of patients by 4 years after treatment [21]. Other vascular complications include radiation vasculopathy and resulting ischemic strokes as well as cavernomas. Additionally, spinal radiation may place cardiac structures at increased risk, for this reason childhood cancer survivor guidelines recommend echocardiogram every 5 years following spine radiation.

Future Directions

Adult MB is a rare adult malignancy and at this time there are limited prospective clinical trials to guide treatment. All patients with MB should be referred to a comprehensive brain tumor center for consideration of clinical trials even inquiring at pediatric centers for clinical trial options. Table 7.6 includes samples of patient-facing education in lay terms to help patients understand their condition and options.

Table 7.6 Patient education

Patient question	Patient information
Type of tumor	Adult medulloblastomas are rapidly growing brain tumors. They develop from cells in the posterior fossa, or back lower area of the brain. They are extremely rare in adults and more common in children
Symptoms	Often adult patients with medulloblastoma present with headache, vision changes, dizziness or imbalance
Next steps	These tumors have a high risk of spreading in the fluid surrounding the brain and spinal cord. MRI of the patient's spinal cord and a sample of the spinal fluid is necessary to see if the tumor has spread
Treatment	Because these are rare tumors, referral to a center that specializes in brain tumors is recommended Surgery is the first step of diagnosis and treatment This is followed by radiation to the area the tumor was seen on the MRI as well as the whole brain and spinal cord. This radiation is typically delivered 5 days a week over 6 weeks Chemotherapy may be given after radiation.
Side effects	Tumor resection: Often after surgery patients will need to work with a therapist to improve speech or movement Radiation: Risks include hair loss, nausea/vomiting, decrease in blood counts and headaches however full discussion of side effects should occur with treating radiation oncologist
Monitoring	These tumors have a high risk of growing back. For that reason, patients will need to be monitored with MRIs for life. Initially these will be every 3 months but overtime the frequency of MRIs will decrease
Genetic testing	Multiple genetic syndromes have been reported in association with medulloblastoma. All patients should be considered for genetic counseling and patients with WNT and SHH subtypes will need genetic testing
Prognosis	Medulloblastomas are potentially curable, however may recur even more than a decade from the time of diagnosis. Over 70% of patients who undergo treatment live longer than 5 years

Current clinical trials are exploring the role of molecular stratification and incorporation of targeted agent. Given improved outcomes in WNT subgroup MB, reduced doses of radiation are also being explored in patients up to 21 years of age. The role of chemotherapy in treatment of adult MB remains unclear but may confer a benefit [22]. There have only been three prospective adult MB clinical trials that have results [10, 12, 23]. None of these studies used molecular stratification. There is urgent need for a prospective randomized clinical trial in adult MB of adjuvant chemotherapy.

References

1. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018;19:785–98.
2. Chang CH, Housepian EM, Herbert C Jr. An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastomas. Radiology. 1969;93:1351–9.
3. Zhao F, Ohgaki H, Xu L, et al. Molecular subgroups of adult medulloblastoma: a long-term single-institution study. Neuro Oncol. 2016;18:982–90.
4. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803–20.
5. Kool M, Korshunov A, Remke M, 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;123:473–84.
6. Remke M, Hielscher T, Northcott PA, et al. Adult medulloblastoma comprises three major molecular variants. J Clin Oncol. 2011;29:2717–23.
7. Franceschi E, Hofer S, Brandes AA, et al. EANO–EURACAN clinical practice guideline for diagnosis, treatment, and follow-up of post-pubertal and adult patients with medulloblastoma. Lancet Oncol. 2019;20:e715–28.
8. De B, Beal K, De Braganca KC, et al. Long-term outcomes of adult medulloblastoma patients treated with radiotherapy. J Neurooncol. 2018;136:95–104.
9. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. Int J Radiat Oncol Biol Phys. 2013;86:277–84.

10. Beier D, Proescholdt M, Reinert C, et al. Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro Oncol. 2018;20:400–10.
11. Kunschner LJ, Kuttesch J, Hess K, Yung WK. Survival and recurrence factors in adult medulloblastoma: the M.D. Anderson Cancer Center experience from 1978 to 1998. Neuro Oncol. 2001(3):167–73.
12. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M. Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer. 2007;110:2035–41.
13. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21:v1–v100.
14. Li Q, Dai Z, Cao Y, Wang L. Comparing children and adults with medulloblastoma: a SEER based analysis. Oncotarget. 2018;9:30189–98.
15. Brandes AA, Bartolotti M, Marucci G, et al. New perspectives in the treatment of adult medulloblastoma in the era of molecular oncology. Crit Rev Oncol Hematol. 2015;94:348–59.
16. Gill P, Litzow M, Buckner J, et al. High-dose chemotherapy with autologous stem cell transplantation in adults with recurrent embryonal tumors of the central nervous system. Cancer. 2008;112:1805–11.
17. Li Y, Song Q, Day BW. Phase I and phase II sonidegib and vismodegib clinical trials for the treatment of paediatric and adult MB patients: a systematic review and meta-analysis. Acta Neuropathol Commun. 2019;7:123.
18. Harrison RA, Kesler SR, Johnson JM, Penas-Prado M, Sullaway CM, Wefel JS. Neurocognitive dysfunction in adult cerebellar medulloblastoma. Psychooncology. 2019;28:131–8.
19. Kahalley LS, Peterson R, Ris MD, et al. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. J Clin Oncol. 2020;38:454–61.
20. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol. 2013;15:97–103.
21. Roongpiboonsopit D, Kuijf HJ, Charidimou A, et al. Evolution of cerebral microbleeds after cranial irradiation in medulloblastoma patients. Neurology. 2017;88:789–96.
22. Franceschi E, Bartolotti M, Paccapelo A, et al. Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients? J Neurooncol. 2016;128:235–40.
23. Moots PL, O'Neill A, Londer H, et al. Preradiation chemotherapy for adult high-risk medulloblastoma: a trial of the ECOG-ACRIN Cancer Research Group (E4397). Am J Clin Oncol. 2018;41:588–94.

Treatment of Ependymoma

8

Jing Wu and Surabhi Ranjan

The Clinical Scenario

A 43-year old woman presented with 4 months of progressive headaches and neck pain. A brain MRI image with gadolinium contrast revealed a large homogeneously enhancing mass within the fourth ventricle extending through the foramina of Luschka and Magendie and inferiorly to the lower aspect of C2 vertebrae. These lesions caused mass-effect on the brainstem and upper cervical cord (Fig. 8.1).

The patient underwent a resection of the intraventricular mass. A postoperative MRI of the brain showed a 1 cm × 0.8 cm residual tumor. An MRI image of the cervical, thoracic and lumbar spine was obtained for staging, which showed no signs of tumor dissemination. A lumbar puncture was performed 2 weeks after the surgery and no malignant cell was found in the cerebrospinal fluid. The patient's pathology report was reviewed and showed a well delineated tumor with monomorphic cells of variable density and round to oval nuclei with speckled chromatin. Perivascular pseudorosettes were observed. The patient was diagnosed with a grade 2 ependymoma. She received involved field radiation ther-

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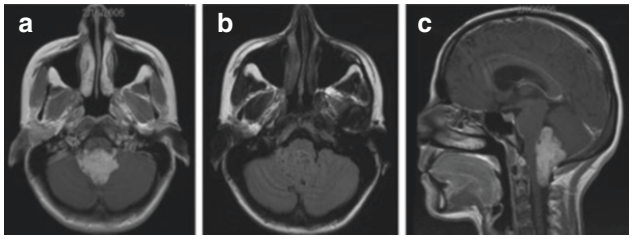

Fig. 8.1 (**a**) Axial T1 post-contrast MRI revealing an irregular hyperintense mass within the fourth ventricle and compressing the surrounding brainstem. (**b**) Appearance of the lesion on T2 FLAIR sequence. (**c**) Sagittal T1 post-contrast sequence

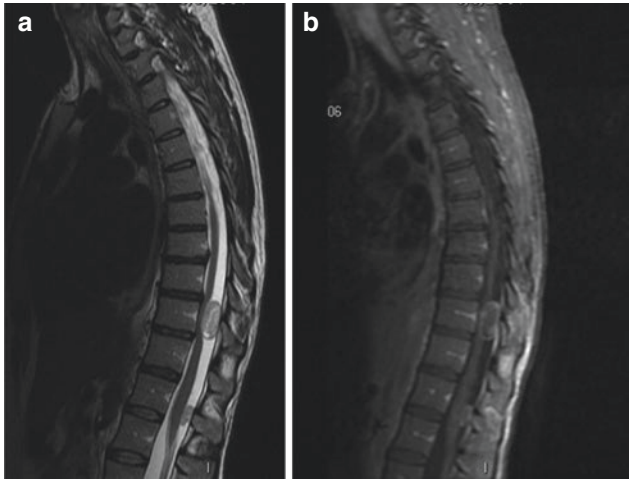

Fig. 8.2 Sagittal T2 sequence (**a**) and T1 post-contrast sequence (**b**) of the thoracic MRI showing sausage-shaped intradural and extramedullary masses at the T10 and T12 levels

apy to the residual tumor and tumor bed to a total dose of 59.4 Gy in 33 fractions. Three years later, the patient started complaining of progressive back pain radiating to the lower anterior abdomen. An MRI of the spine revealed intradural extramedullary masses at T10 and T12 level (Fig. 8.2). These tumors were resected and a pathological exam confirmed a grade 2 ependymoma. No evi-

dence of recurrence was found in the brain or cerebrospinal fluid (CSF). Postoperatively, she received focal radiation to the T10 and T12 regions. Her low back pain was resolved after the treatment and she remained symptom-free and without disease progression for 30 months following the focal radiation to the lower thoracic spine.

Making the Diagnosis

Surgical Role

Surgical resection is the mainstay of the current treatment of ependymoma. The surgical procedure is essential to establish a pathological diagnosis and collect tissue for genomic analysis to determine each case's unique molecular features. If the tumor cannot be resected safely due to its location, a biopsy of the lesion is still required to confirm the pathological diagnosis prior to the treatment. The extent of surgical resection has been consistently shown as a prognostic marker in pediatric and adult studies [1–4]. Patients with gross total resection (GTR) have improved outcomes with a lower rate of local recurrence and improved overall prognosis. Patients who underwent subtotal resection, even with the addition of radiation therapy, have an increased chance to have disease progression [5]. Myxopapillary ependymoma was previously classified as a grade 1 tumor due to long survival time and potential for cure after gross total resection, but some myxopapillary ependymomas may present with late recurrence or dissemination and have been upgraded to grade 2 in the 2021 WHO Classification of CNS Tumors. A postoperative MRI obtained within 24–48 h of surgery is recommended to determine the extent of the resection. GTR is defined as no residual contrast-enhanced or non-enhanced lesion seen on postoperative MRI and a report of no residual tumor by the operating surgeon. If there is extensive residual disease showing on the immediate postoperative MRI and the lesions can be resected readily, a second-look surgery can be beneficial [6, 7].

Ependymomas are known for a high rate of CSF dissemination as compared to other gliomas with studies reporting a rate of 7–10% [8, 9]. CSF analysis is recommended as staging in addition to imaging of the entire neuroaxis. However, a lumbar puncture should be deferred by at least 2 weeks postoperatively to avoid confusing findings in the CSF. A CSF analysis positive for malignancy should be repeated after another week to rule out false positive CSF dissemination as it will change the treatment paradigm [10].

Key Pathologic and Molecular Findings

The pathognomonic features of ependymoma are perivascular pseudorosette and true ependymal rosettes [11]. Pseudorosettes are characterized by tumor cells arranged radially around a blood vessel with a perivascular anuclear zone of fine fibrillary processes. Ependymal rosettes are formed when cuboidal or columnar tumor cells are arranged around a central lumen.

An overview of WHO classification will be in a separate chapter. Briefly, ependymomas are classified from grades 1 to 3. Grade 1 ependymomas include subependymomas. Myxopapillary ependymoma is a WHO grade 2 tumor which arises in the region of the conus medullaris, cauda equina and filum terminale. Tumor cells are radially arranged in papillary fashion around vascularized, mucoid, fibrovascular cores. When resected en bloc, these tumors have excellent prognosis. However, 34–40% of the cases will have local recurrent and dissemination along the neuraxis [12, 13]. Grade 2 and 3 ependymomas are designated based on tumor location: spinal, supratentorial, or posterior fossa; and further designated based on molecular findings. Supratentorial ependymomas include ZFTA-fusion positive and YAP1-fusion positive. The entity formerly known as ependymoma RELA fusion position, in the 2016 WHO, is now included in the ZFTA-fusion positive subgroup [14]. Posterior fossa ependymomas include group PFA and group PFB. Spinal ependymomas include a distinct subgroup of spinal ependymoma, MYCN-amplified. In the 2021 WHO, the designation of “anaplastic” ependymoma has been removed,

however ependymoma may be classified by pathologists as grade 2 or grade 3 according to histopathological features [15].

Subependymomas are WHO grade I tumors, which are slow growing, exophytic and consist of bland to mildly pleomorphic mitotically inactive cells embedded in a fibrillary matrix. These tumors are characterized by intraventricular location and are most commonly found in the fourth ventricle. Subependymomas have excellent prognosis.

The above case represents a posterior fossa ependymoma. The pathognomonic features of ependymoma are perivascular pseudorosette and true ependymal rosettes. Pseudorosettes are characterized by tumor cells arranged radially around a blood vessel with a perivascular anuclear zone of fine fibrillary process. Ependymal rosettes are formed when cuboidal or columnar tumor cells are arranged around a central lumen.

Ependymomas have three distinct histopathological variants without clinicopathological significance. These are papillary ependymoma, characterized by well-formed papillary, clear-cell ependymomas which have oligodendrocytes-like appearance and tanycytic ependymoma, which have elongated cells with spindle-shaped nuclei. It is important to know that geographic necrosis is not a diagnostic feature by itself without association with high proliferation index and vascular proliferation. Non-pallisading necrosis can be seen in grade 2 ependymoma, while pseudopallisading necrosis and microvascular proliferation are common in grade 3 ependymomas.

Transcriptome and methylome profiling have recently identified nine molecular subgroups of ependymoma, each into three central nervous system (CNS) compartments of supratentorial, posterior fossa and spinal compartments [16]. These molecular subgroups have a better clinical and prognostic association than the histological classification and form the basis of the 2021 WHO integrated molecular classification. Supratentorial ependymomas are divided into ZFTA-fusion positive, which includes the RELA fusion gene and a poor outcome, and YAP1-fusion positive, which has a relatively good prognosis. Posterior fossa ependymomas are categorized into PFA and PFB. PFA are found in infants, have balanced genomes, a higher extent of CpG island methylation and

have poor prognosis [16, 17]. PFB are found in children and adults, have genome-wide polyploidy, low CpG island methylation and good outcomes. Posterior fossa subependymoma has a balanced genome and a good outcome. Ependymomas occuring in the spine include are spinal ependymoma, myxopapillary ependymoma, and subependymoma. Spinal ependymomas have frequent NF2 gene mutation and frequently occur in neurofibromatosis type 2 patients. These have good outcomes. Spinal myxopapillary ependymomas have genome-wide polyploidy and good prognosis. Spinal subependymomas are associated with 6q deletion and have good prognosis.

Post-operative Treatment

Radiation Therapy

Due to a lack of prospective studies and rarity of ependymomas, there is a wide variation in radiation treatment recommendation among experts. The decision for adjuvant radiation in treatment of ependymoma depends on the tumor grade, extent of resection and status of tumor dissemination. In general, patients with anaplastic ependymoma, patients with subtotal resection and disseminated tumors are treated with upfront adjuvant radiation. Cranio-spinal irradiation (CSI) is not recommended unless the patient has evidence of wide-spread dissemination. The role of radiation therapy is unclear for WHO grade 2 ependymomas with gross total resection, and general consensus is that patients can be observed clinically and radiographically after complete removal of a grade 2 ependymoma [11]. Patients with spinal cord grade 2 ependymomas with subtotal resection generally undergo upfront radiation therapy. A recent retrospective study on 1058 patients found improved progression free survival, but no improvement in overall survival with the use of adjuvant radiation therapy in WHO grade 2 spinal ependymoma [18]. Similarly, another study evaluating 348 patients with spinal cord ependymoma showed an improvement in PFS with adjuvant radiation but no improvement in OS [19]. A total dose of 59.4 Gy to the involved field using

conventional fractionation of 1.8 Gy per day in 33 fractions can be used [20]. Children between 12 and 18 months with a gross total resection have been treated with a total dose of 54 Gy [20]. The dose to the optic chiasm and spinal cord should be limited to 54 Gy or less [21].

Patients with myxopapillary ependymoma which have been resected en bloc (without the breach of capsule) are associated with very low risk of recurrence (0–10%) do not require any adjuvant radiation [22, 23]. Local radiation to the spinal lesion is administered in patients with sub-totally resected myxopapillary ependymoma. In contrast to adults, pediatric myxopapillary ependymomas do not have a benign course and a majority of patients present with disseminated spinal disease [24]. In fact, a pediatric myxopapillary ependymoma study found that patients who underwent a subtotal resection followed by radiation fared better than patients who underwent GTR alone [25].

For disseminated ependymoma, debulking of the primary tumor should be attempted. Craniospinal irradiation may be considered in patients using a dose of 36 Gy in 1.8 Gy fractions with a boost of 59.4 Gy to the primary tumor and metastases. A combination of chemotherapy and focal irradiation can also be used.

Subependymomas are considered WHO grade I benign tumors and no adjuvant radiation treatment is recommended after surgical resection.

Proton therapy has been considered more in the management of ependymomas due to its feature of sparing normal tissues. It may be the most beneficial for young patients with tumors that require radiotherapy near critical structures. Prospective studies with extended follow-up are warranted to investigate the effect of proton versus photon therapies in both pediatric and adult ependymomas.

Chemotherapy

The role of chemotherapy is not established in ependymoma. Chemotherapy has been most investigated in pediatric studies. Due to the concern for severe radiation toxicity to the developing

brain among infants, chemotherapy has been used in an attempt to defer the radiation to the developing nervous system [26, 27]. Alternating procarbazine and, carboplatin, etoposide and cisplatin, cyclophosphamide and vincristine that are used postoperatively have been found to be active antineoplastic regimen but no tumor has shown more than 50% reduction. The second prospective AIEOP protocol for pediatric patients investigated four courses of vincristine, etoposide and cyclophosphamide after radiation in patients with anaplastic ependymoma [7]. The VEC regimen used vincristine at 1.5 mg/m^2 on day 1, cyclophosphamide 1 g/m^2 infused in one hour for 3 doses, 3 h apart on day 1 and etoposide 100 mg/m^2 infused in 2 h, days 1, 2 and 3. Each cycle was of 3–4 weeks duration, for a total of 4 cycles.

The children's oncology group has an ongoing Phase 3 trial COG ACNSS0831 evaluating maintenance chemotherapy versus observation, following induction chemotherapy and radiation therapy in treating children with newly diagnosed ependymoma. One of its experimental arms uses a chemotherapy regimen consisting of vincristine on day 1 and 8, of courses 1 and 2, carboplatin on day 1 of courses 1 and 2, and cyclophosphamide on day 1–2 of course 1 only. Etoposide is administered on day 1–3 of course 2. Another experimental arm uses vincristine on day 1, 8 and 15 of course 1–3 only, etoposide on days 1–3, cisplatin on day 1, cyclophosphamide on days 2 and 3.

The role of chemotherapy was not studied prospectively in adults until a clinical trial by The Collaborative Ependymoma Research Network (CERN) investigators, where they rationalized to test a dose-dense temozolomide regimen in combination with lapatinib in recurrent ependymoma. Some evidence of treatment efficacy as disease control and objective response were found. However, the survival benefit cannot be determined.

Given the positive correlation between patients with no residual tumor and prognosis, a bridge chemotherapy approach has been used in several studies [7, 28]. This approach uses chemotherapy as a conduit to reduce the bulk of residual tumor, after the first surgery so that a second-look surgery or irradiation can be undertaken (Table 8.1).

Table 8.1 Upfront pediatric chemotherapy regimens for ependymoma

Clinical trial	Patient age group and number	Treatment	Chemo regimen	PFS	OS
Second AIEOP, 2016 [7]	3–21 years with intracranial ependymoma, N = 160	Group 1: Residual tumor, any grade—VEC chemo (upto 4 cycles), possible second surgery, RT + boost Group 2: No residual tumor, WHO grade II—RT Group 3: No residual tumor, WHO grade III—RT followed by VEC × 4	VEC vincristine at 1.5 mg/m^2 D1, cyclophosphamide 1 g/m^2 D1 and etoposide 100 mg/m^2, days 1, 2 and 3 for 4 cycles of 3–4 weeks Supportive treatment: granulocyte colony stimulating factor	Grade II, 5-year: 75.3% Grade III, 5-year: 57%	Grade II, 5-year: 90.5% Grade III, 5-year: 73.3%
UKCCSG/ SIOP study, 2007 [27]	Children under 3 years, N = 89	Surgery, followed by four courses of alternating myelosuppressive and non-myelosuppressive drugs repeated every 56 days for a total of 7 cycles	Course 1, carboplatin 550 mg/m^2 + vincristine 1.5 mg/m^2 Course 2, methotrexate 8000 mg/m^2 + vincristine 1.5 mg/m^2 Course 3, cyclophosphamide 1500 mg/m^2 with mesna Course 4, cisplatin 40 mg/m^2	3-year event free survival, 42.7% 5-year event free survival, 37.5%	3-year overall survival, 76.8% 5-year overall survival, 60%

(continued)

Table 8.1 (continued)

Clinical trial	Patient age group and number	Treatment	Chemo regimen	PFS	OS
French Society of Pediatric Oncology, 2001 [26]	Children under 5 years with intracranial ependymoma, N = 73	Surgery, chemo (3 courses in of 21 days each, 7 cycles) Salvage radiation for disease progression or relapse following chemotherapy	Course A: Carboplatin 15 mg/kg, day 1 + procarbazine 4 mg/kg/day on days 1–7 Course B: Etoposide 5 mg/kg/day on days 22 and 23 + cisplatin 1 mg/kg/day on days 22 and 23 Course C: Vincristine 0.05 mg/kg on day 43 + cyclophosphamide 50 mg/kg on day 43	2-year PFS, 33% 4-year PFS, 22%	2-year OS, 79% 4-year OS, 59%
German HIT study, 2000 [29]	Pediatric anaplastic ependymoma, N = 55	HIT 88/89: Surgery, sandwich chemo, radiation HIT 91: Surgery followed by randomization to either RT + weekly vincristine and maintenance chemo OR Sandwich chemo followed by RT	Sandwich chemo: 2 cycles of ifosfamide, etoposide, methotrexate, cisplatin and cytarabine Maintenance chemo: 8 cycles of methotrexate, cisplatin and vincristine	45 months	3-year OS: 75.6%

There is no role for upfront chemotherapy in adult patients with ependymoma, other than in a clinical trial setting.

Other Modalities

With more identified unique molecular features and genomic alterations are discovered, targeted therapies regimen has been tested in the setting of clinical trials. For example, it was discovered that co-expression of ERBB2 and ERBB4 is elevated in more than 75% of ependymomas and a high expression of ERBB receptors is associated with an aggressive tumor behavior. Therefore, lapatinib, an inhibitor of ERBB2 receptor, has been tested in a clinical trial of recurrent ependymoma when combined with temozolomide, a commonly used alkylating agent (NCT00826241). Another example is that VEGF inhibition was tested as a therapeutic approach given the elevated VEGF expression in most of the ependymoma. A combination of VEGF monoclonal antibody and carboplatin has been tested in the recurrent ependymoma (NCT01295944). More recently, marizomib, a second-generation irreversible proteasome inhibitor which penetrates the blood brain barrier has been tested in recurrent ependymomas with a characteristic signature *C11orf95-RELA* fusion, which drives tumorigenesis in 70% of supratentorial ependymomas by activating the NF-KB transcription pathway (NCT03727841).

Surveillance

Surveillance guidelines for ependymoma patients are rather arbitrary and extrapolated from clinical trials. Patients with intracranial ependymoma should be followed with an MRI brain with and without contrast every 3 months for the first year after treatment, then every 3 months for the second year, and every 4–6 months afterwards [7]. It is reasonable to add a contrast-enhanced MRI of the entire spine every 6–12 month in the first year for staging, or if symptoms attributed to spinal cord involvement are suspected. For patients with disseminated ependymoma, the entire neuraxis

is imaged with contrasted MRI brain and spine every 3 months for the first 2 years after treatment, then every 4 months for the next 2 years and every 6 months thereafter.

Treatment at Recurrence

Most patients develop tumor recurrence at the primary site. At the time of recurrence, staging for dissemination and CSF should be performed. Treatment approaches for recurrent ependymoma, again rely on surgery and radiation. Patients should undergo a maximal safe surgical resection followed by involved field radiation or reirradiation. Stereotactic radiosurgery or focal fractionated reirradiation is often used. Craniospinal irradiation is sometimes utilized but best avoided. A retrospective study on 101 pediatric patients showed that brain radiation was well-tolerated by most patients [30]. After irradiation, the median progression free survival was 27.3 months and the median overall survival was 75.1-months. The 10-year cumulative incidence of severe radiation necrosis after reirradiation was 7.9%. Opportunities should be investigated for clinical trial enrollment.

Prognosis and Survivorship

Rather than the tumor grade, the prognosis of ependymoma depends on age and tumor location. A retrospective study on 123 patients with adult ependymoma found an overall survival of 221 months for all intracranial ependymomas and 67 months for anaplastic ependymoma [31]. The overall survival for spinal tumors was longer and could not be calculated due to the small number of events. In this study, the median time to first recurrence was 21 months for intracranial ependymomas, versus 25 months for spinal tumors.

Supratentorial ependymal tumors have a worse prognosis in adults. A meta-analysis of 183 adult patients with intracranial ependymomas showed that supratentorial ependymoma has had a progression-free survival of 24 months and overall survival of

61 months, as compared to a median progression free survival of 144 months in infratentorial ependymoma, whose median overall survival could not be calculated [32].

Patients with group A posterior fossa ependymomas have a significantly poor prognosis as compared to group B posterior fossa ependymomas. Patients with group A posterior fossa ependymomas are significantly younger (median age of 4 versus a median age of 39 for group B posterior fossa ependymomas), commonly male, more frequently classified as WHO grade 3 ependymoma and a higher incidence of metastasis at the time of recurrence. For group A tumors, the progression free and overall survival rates are 24% and 48% respectively, in contrast to 92% and 98% for group B tumors [33].

Subependymomas are benign tumors, most commonly arising from the floor of the fourth ventricle and lateral ventricles and often discovered at autopsy. Symptomatic patients are managed with maximal safe tumor resection and restoration of the normal CSF flow. Long-term outcomes are excellent, provided there are no postoperative complications [34].

Adult myxopapillary ependymomas have good outcomes. Encapsulated myxopapillary ependymomas, which were treated with a gross total resection with and intact capsule have a low recurrence rate of 10%, whereas those with a piecemeal resection or a subtotal resection have a higher recurrence rate of up to 19% [23]. Overall survival with a gross total resection is 19 years and with subtotal resection 14 years [23]. The 10-year overall survival of patients with myxopapillary ependymoma is 92–93% and the median time to recurrence is 26–30 months [35, 36]. While age less than 36 years was a negative prognostic marker, the use of adjuvant RT and a greater extent of surgical resection increased progression free survival [36]. Pediatric myxopapillary ependymomas have a less favorable outcome as compared to adults. A large retrospective study of 95 pediatric patients less than 20 years of age, reveals a 5-year progression free survival rate at 73.7% and a 5-year overall survival rate of 98.9% [25]. In the pediatric population, addition of radiation therapy following resection significantly improves progression free survival [25].

As survival for childhood central nervous system cancers have improved, there is an increasing focus on their long-term effects in children and adolescents. Patients may have received surgery, focal or cranio-spinal radiation therapy and chemotherapy. Neurological, cognitive, auditory and endocrine dysfunctions are common in this population, especially among children who were treated at a young age [37]. Patients who receive craniospinal radiotherapy experience significant decline in IQ over time as compared to patients who received focal radiation or surgery alone. Children younger than 3 or 4 years may experience a devastating longitudinal decline in IQ. Apart from radiation therapy, hydrocephalus and posterior fossa syndrome contributes to a neurocognitive decline.

Adult patients with intracranial or spinal ependymomas have a high symptom burden. Adult patients with intracranial ependymoma commonly have problems with vision, language, and concentration whereas patients with spinal ependymoma developed limb weakness, sexual dysfunction, radiating pain and change in bowel pattern [38].

Trends and Future Directions

Better understanding of ependymoma biology and molecular features will provide more opportunities of developing targeted and personalized therapeutic strategies. Robust preclinical studies and clinical trials are essential for the development of novel therapy. Collaborations between scientists and clinicians specializing in adult and pediatric neuro-oncology should foster rapid translation of laboratory science into clinical trials. The rarity of ependymomas makes it challenging to perform large scale or randomized clinical trials. A collaborative effort between academic centers should be the future direction to advance the care for ependymoma patients (Table 8.2).

Table 8.2 Patient information

What type of tumor do I have?

Ependymoma is a primary central nervous system tumor, which means it begins in the brain or spinal cord. Ependymoma arises from the ependymal cells that line the brain cavities (ventricles) and the fluid-filled space which runs through the spinal cord. Ependymomas occur in both children and adults. Tumors in the lower half of the brain are more common in children, but those in the spinal cord are more common in adults. The cause of ependymoma is not fully understood

Based on how cancer cells appear under the microscope, the World Health Organization (WHO) grades ependymomas into grades 1, 2 and 3. A lower grade indicates a slow-growing cancer and a higher grade means that the cancer is more aggressive.

There are different types of ependymoma depending on the tumor location, the mutations in the tumor, and the grade of the tumor.

- Subependymomas are WHO grade 1 tumors
- Spinal ependymomas are ependymomas that occur in the spinal cord. These include
  - Spinal ependymoma (WHO grade 2 or 3)
  - Spinal ependymoma MYCN-amplified (WHO grade 2 or 3)
  - Myxopapillary ependymoma (WHO grade 2)
- Posterior fossa ependymomas are ependymomas that occur in the back part of the brain. These include
  - Posterior fossa ependymoma (WHO grade 2 or 3)
  - Posterior fossa ependymoma, group PFA (WHO grade 2 or 3)
  - Posterior fossa ependymoma, group PFB (WHO grade 2 or 3)
- Supratentorial ependymomas are ependymomas that occur in the upper part of the brain. These include
  - Supratentorial ependymoma (WHO grade 2 or 3)
  - Supratentorial ependymoma, ZFTA fusion-positive (WHO grade 2 or 3)
  - Supratentorial ependymoma, YAP1 fusion-positive (WHO grade 2 or 3)

Your medical team will determine which type and grade of ependymoma you have, based on pathological and molecular study on the tumor tissues obtained from a surgery or biopsy. Ependymoma rarely grow or metastasize outside of the central nervous system (brain and spinal cord), but may spread to other areas of the central nervous system through the cerebrospinal fluid

(continued)

Table 8.2 (continued)

How do I treat it?
The first goal in treating an ependymoma is to have surgery to remove as much of the tumor as can be done safely. Sometimes, your medical team may recommend a second surgery if there is tumor that can still be seen on an MRI scan after your first surgery. In some patients, a complete surgical removal of the tumor isn't possible if the tumor is located in a critical location of the brain or spinal cord. In these cases, a biopsy is still recommended so that your medical team can make an accurate diagnosis of the type of ependymoma
It is important to know that the treatment recommendation for ependymoma may differ even among ependymoma experts. As ependymomas are rare tumors, patients should be preferably treated at a brain and spine tumor center, which have experience in treating this type of tumor. Grade 2 ependymomas with a complete surgical removal may be observed with serial MRIs and clinic visits. Grade 2 ependymomas that are not completely removed and Grade 3 ependymomas will need to be treated with radiation after you heal from surgery. Your team will also perform MRIs of the brain and entire spine to find the extent of tumor spread. A spinal tap will also be done to find out if there are microscopic tumor cells in your brain and spinal fluid. In rare circumstances, if there is an extensive spread of the tumor, the entire brain and spine may need to be treated with radiation
Some centers will offer you a clinical trial for voluntary participation. It is advised to discuss all options with your oncologist, the expectations from treatment, and possible side effects
What can I expect to experience during treatment?
Symptoms depend on the location of the ependymoma and type of planned treatment. Patients with ependymoma in the brain may experience headaches, memory difficulty, speech problems, seizures and balance issues. Patients with ependymoma of the spine may feel neck or back pain, numbness, pain in the arms or legs, and weakness in arm or leg
During treatment with radiation, patients may experience fatigue, sleep disturbance, memory impairment (if tumor is in the brain), pain from the tumor location and sometimes swelling of the tumor. You may need treatment with steroids to control the swelling
Most patients with ependymoma get treatment from a team of experts such as a neurosurgeon, a neuro-oncologist, a radiation-oncologist, nurse practitioner or a physician assistant and a nurse. Sometimes, you may be referred to see a neuropsychologist for memory testing and palliative care for pain. Your medical team will work closely with you to improve your symptoms and quality of life

Table 8.2 (continued)

How will we keep an eye on this? Patients have MRIs and evaluation in a doctor's office every 3 months for the first 2 years of treatment and then every 4–6 months thereafter. These MRIs and clinic visits are usually conducted with a neuro-oncologist. It is very important for ependymoma patients to continue follow-up with their neuro-oncologist as these tumors usually recur, sometimes after many years from initial treatment
What is my prognosis? The prognosis of ependymoma depends on many factors such as the patient's age, the location of tumor, extent of surgical removal, the tumor grade, tumor's genetic profile and the type of treatment received. Patients live longer and with lesser recurrence if the tumor is fully removed with surgery. Patients with spinal cord ependymomas have better outcomes as compared to ependymomas in the brain

References

1. Rodriguez D, Cheung MC, Housri N, Quinones-Hinojosa A, Camphausen K, Koniaris LG. Outcomes of malignant CNS ependymomas: an examination of 2408 cases through the Surveillance, Epidemiology, and End Results (SEER) database (1973-2005). J Surg Res. 2009;156(2):340–51. https://doi.org/10.1016/j.jss.2009.04.024.
2. Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, et al. Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg. 1998;88(4):695–703. https://doi.org/10.3171/jns.1998.88.4.0695.
3. Healey EA, Barnes PD, Kupsky WJ, Scott RM, Sallan SE, Black PM, et al. The prognostic significance of postoperative residual tumor in ependymoma. Neurosurgery. 1991;28(5):666–71; discussion 71–2. https://doi.org/10.1097/00006123-199105000-00005.
4. Duffner PK, Krischer JP, Sanford RA, Horowitz ME, Burger PC, Cohen ME, et al. Prognostic factors in infants and very young children with intracranial ependymomas. Pediatr Neurosurg. 1998;28(4):215–22. https://doi.org/10.1159/000028654.
5. Vera-Bolanos E, Aldape K, Yuan Y, Wu J, Wani K, Necesito-Reyes MJ, et al. Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients. Neuro Oncol. 2015;17(3):440–7. https://doi.org/10.1093/neuonc/nou162.
6. Foreman NK, Love S, Gill SS, Coakham HB. Second-look surgery for incompletely resected fourth ventricle ependymomas: technical case

report. Neurosurgery. 1997;40(4):856–60; discussion 60. https://doi.org/10.1097/00006123-199704000-00042.
7. Massimino M, Miceli R, Giangaspero F, Boschetti L, Modena P, Antonelli M, et al. Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. Neuro Oncol. 2016;18(10):1451–60. https://doi.org/10.1093/neuonc/now108.
8. Peschel RE, Kapp DS, Cardinale F, Manuelidis EE. Ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys. 1983;9(7):1093–6. https://doi.org/10.1016/0360-3016(83)90402-9.
9. Fangusaro J, Van Den Berghe C, Tomita T, Rajaram V, Aguilera D, Wang D, et al. Evaluating the incidence and utility of microscopic metastatic dissemination as diagnosed by lumbar cerebro-spinal fluid (CSF) samples in children with newly diagnosed intracranial ependymoma. J Neurooncol. 2011;103(3):693–8. https://doi.org/10.1007/s11060-010-0448-6.
10. Gerstner ER, Pajtler KW. Ependymoma. Semin Neurol. 2018;38(1):104–11. https://doi.org/10.1055/s-0038-1636503.
11. Wu J, Armstrong TS, Gilbert MR. Biology and management of ependymomas. Neuro Oncol. 2016;18(7):902–13. https://doi.org/10.1093/neuonc/now016.
12. Akyurek S, Chang EL, Yu TK, Little D, Allen PK, McCutcheon I, et al. Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center. J Neurooncol. 2006;80(2):177–83. https://doi.org/10.1007/s11060-006-9169-2.
13. Bagley CA, Wilson S, Kothbauer KF, Bookland MJ, Epstein F, Jallo GI. Long term outcomes following surgical resection of myxopapillary ependymomas. Neurosurg Rev. 2009;32(3):321–34; discussion 34. https://doi.org/10.1007/s10143-009-0190-8.
14. 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. https://doi.org/10.1007/s00401-016-1545-1.
15. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–51. https://doi.org/10.1093/neuonc/noab106. PMID: 34185076; PMCID:
16. 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. https://doi.org/10.1016/j.ccell.2015.04.002.
17. Mack SC, Witt H, Piro RM, Gu L, Zuyderduyn S, Stutz AM, et al. Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. Nature. 2014;506(7489):445–50. https://doi.org/10.1038/nature13108.

18. Brown DA, Goyal A, Takami H, Graffeo CS, Mahajan A, Krauss WE, et al. Radiotherapy in addition to surgical resection may not improve overall survival in WHO grade II spinal ependymomas. Clin Neurol Neurosurg. 2020;189:105632. https://doi.org/10.1016/j.clineuro.2019.105632.
19. Oh MC, Ivan ME, Sun MZ, Kaur G, Safaee M, Kim JM, et al. Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord ependymomas. Neuro Oncol. 2013;15(2):208–15. https://doi.org/10.1093/neuonc/nos286.
20. Merchant TE, Bendel AE, Sabin ND, Burger PC, Shaw DW, Chang E, et al. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. J Clin Oncol. 2019;37(12):974–83. https://doi.org/10.1200/jco.18.01765.
21. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol. 2009;10(3):258–66. https://doi.org/10.1016/s1470-2045(08)70342-5.
22. Abdulaziz M, Mallory GW, Bydon M, De la Garza Ramos R, Ellis JA, Laack NN, et al. Outcomes following myxopapillary ependymoma resection: the importance of capsule integrity. Neurosurg Focus. 2015;39(2):E8. https://doi.org/10.3171/2015.5.focus15164.
23. Sonneland PR, Scheithauer BW, Onofrio BM. Myxopapillary ependymoma. A clinicopathologic and immunocytochemical study of 77 cases. Cancer. 1985;56(4):883–93. https://doi.org/10.1002/1097-0142(19850815)56:4<883::aid-cncr2820560431>3.0.co;2-6.
24. Fassett DR, Pingree J, Kestle JR. The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. Report of five cases and review of the literature. J Neurosurg. 2005;102(1 Suppl):59–64. https://doi.org/10.3171/ped.2005.102.1.0059.
25. Kukreja S, Ambekar S, Sin AH, Nanda A. Cumulative survival analysis of patients with spinal myxopapillary ependymomas in the first 2 decades of life. J Neurosurg Pediatr. 2014;13(4):400–7. https://doi.org/10.3171/2014.1.peds13532.
26. Grill J, Le Deley M-C, Gambarelli D, Raquin M-A, Couanet D, Pierre-Kahn A, et al. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol. 2001;19(5):1288–96.
27. Grundy RG, Wilne SA, Weston CL, Robinson K, Lashford LS, Ironside J, et al. Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. Lancet Oncol. 2007;8(8):696–705. https://doi.org/10.1016/s1470-2045(07)70208-5.
28. Garvin JH Jr, Selch MT, Holmes E, Berger MS, Finlay JL, Flannery A, et al. Phase II study of pre-irradiation chemotherapy for childhood intra-

cranial ependymoma. Children's Cancer Group protocol 9942: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012;59(7):1183–9. https://doi.org/10.1002/pbc.24274.
29. Timmermann B, Kortmann RD, Kuhl J, Meisner C, Slavc I, Pietsch T, et al. Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. Int J Radiat Oncol Biol Phys. 2000;46(2):287–95. https://doi.org/10.1016/s0360-3016(99)00414-9.
30. Tsang DS, Burghen E, Klimo P Jr, Boop FA, Ellison DW, Merchant TE. Outcomes after reirradiation for recurrent pediatric intracranial ependymoma. Int J Radiat Oncol Biol Phys. 2018;100(2):507–15. https://doi.org/10.1016/j.ijrobp.2017.10.002.
31. Armstrong TS, Vera-Bolanos E, Bekele BN, Aldape K, Gilbert MR. Adult ependymal tumors: prognosis and the MD Anderson Cancer Center experience. Neuro Oncol. 2010;12(8):862–70. https://doi.org/10.1093/neuonc/noq009.
32. Sayegh ET, Aranda D, Kim JM, Oh T, Parsa AT, Oh MC. Prognosis by tumor location in adults with intracranial ependymomas. J Clin Neurosci. 2014;21(12):2096–101. https://doi.org/10.1016/j.jocn.2014.05.011.
33. Witt H, Mack SC, Ryzhova M, Bender S, Sill M, Isserlin R, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell. 2011;20(2):143–57. https://doi.org/10.1016/j.ccr.2011.07.007.
34. Rushing EJ, Cooper PB, Quezado M, Begnami M, Crespo A, Smirniotopoulos JG, et al. Subependymoma revisited: clinicopathological evaluation of 83 cases. J Neurooncol. 2007;85(3):297–305. https://doi.org/10.1007/s11060-007-9411-6.
35. Tsai CJ, Wang Y, Allen PK, Mahajan A, McCutcheon IE, Rao G, et al. Outcomes after surgery and radiotherapy for spinal myxopapillary ependymoma: update of the MD Anderson Cancer Center experience. Neurosurgery. 2014;75(3):205–14; discussion 13–4. https://doi.org/10.1227/neu.0000000000000408.
36. Weber DC, Wang Y, Miller R, Villa S, Zaucha R, Pica A, et al. Long-term outcome of patients with spinal myxopapillary ependymoma: treatment results from the MD Anderson Cancer Center and institutions from the Rare Cancer Network. Neuro Oncol. 2015;17(4):588–95. https://doi.org/10.1093/neuonc/nou293.
37. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol. 2004;5(7):399–408. https://doi.org/10.1016/s1470-2045(04)01507-4.
38. Armstrong TS, Vera-Bolanos E, Gilbert MR. Clinical course of adult patients with ependymoma: results of the Adult Ependymoma Outcomes Project. Cancer. 2011;117(22):5133–41. https://doi.org/10.1002/cncr.26181.

Part II

Supportive Care Primer

Brain Edema and Corticosteroid Toxicity

9

Maninder Kaur and Reena Thomas

Principles of Treatment

In Neuro-oncology, steroids are generally used to relieve symptoms secondary to edema that affects the brain, spinal cord, and possibly nerves and nerve roots. Cerebral edema can be due to the tumor itself or can be a consequence of treatments such as radiation therapy [1]. Cerebral edema can be classified as vasogenic edema, cytotoxic edema or hydrocephalic edema. Characteristics of each type of edema are described in Table 9.1.

The primary method of treatment is with corticosteroids. It is important to treat the patient for their symptoms and not based decisions on the MRI appearance alone. We rarely recommend the use of steroids for asymptomatic patients. The rare exception is the patient with extensive vasogenic edema due to tumor or related to treatment effect, leading to midline shift or near obstruction of the fourth ventricle. In these cases, a course of steroids to prevent the patient from becoming symptomatic may be deemed reasonable.

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Table 9.1 Characteristics of each type of edema

	Vasogenic edema	Cellular edema (Cytotoxic)	Hydrocephalic edema (Interstitial)
Pathogenesis	Increased capillary permeability	Cellular swelling; glial, neuronal, endothelial	Increased brain fluid from blockage of CSF absorption
Location	Chiefly white matter	Gray and white matter	Chiefly periventricular white matter; hydrocephalus
Edema fluid composition	Plasma filtrate including plasma proteins	Increased intracellular water sodium	CSF
Extracellular fluid volume	Increased	Decreased	Increased
Capillary permeability to large molecules (insulin, albumin)	Increased	Normal	Normal
Clinical causes	• Brain tumor	• Hypoxia	• Obstructive hydrocephalus
	• Abscess	• Ischemia	• Purulent meningitis
	• Infarction/ hemorrhage	• Ischemic hypo-osmolality (water intoxication)	
	• Purulent meningitis (granulocytic edema)	• Dysequilibrium syndrome	
		• Purulent meningitis	
		• Reye syndrome	
EEG	Focal slowing	Generalized slowing	Normal (often)

Table 9.1 (continued)

	Vasogenic edema	Cellular edema (Cytotoxic)	Hydrocephalic edema (Interstitial)
Treatment			
1. Steroids	1. Beneficial	1. Not effective	1. Uncertain possibly in pseudotumor or meningitis)
2. Osmotherapy	2. Reduces volume of normal brain tissue only, acutely	2. Reduces brain volume acutely	2. Rarely useful, improves compliance
3. Acetazolamide	3. May be useful	3. No direct effect	3. Minor usefulness
4. Furosemide	4. May be useful	4. No direct effect	4. Minor usefulness

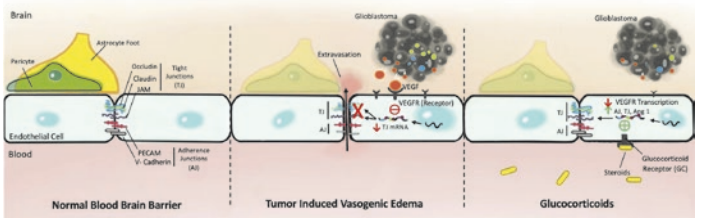

Fig. 9.1 Glucocorticoid Pathophysiology

Corticosteroids are generally divided into glucocorticoids, mineralocorticoids and adrenal sex hormones. Commonly used corticosteroids and their dosing regimens are listed in Table 9.1. Synthetic Glucocorticoids are the most widely used in cerebral edema The proposed mechanisms of glucocorticoids include the inhibition of release of several biochemical substances which have been known to increase vascular permeability or induce vasodilation (which leads to increased permeability secondary to increased hydrostatic pressure (Fig. 9.1) [2] The key factors that regulate the BBB are VEGF, Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) [3].The exact mechanism of action of steroids

is not well understood. One proposed mechanism is the upregulation of Ang-1, which is a strong BBB stabilizing factor and downregulation of VEGF a strong permeabilizing factor. It is also proposed that glucocorticoids may also aid by moving the edematous fluid into the ventricular system [4].

It is always the goal to use the lowest needed dose of steroids in order to minimize side effects, which are dose dependent. It is also important to keep in mind the anti-edema effects are also dose dependent, thus require individualization based on the patient's clinical scenario.

Management of Acute Increased Intracranial Pressure

In patients with acute onset of severe symptoms and signs of increased intracranial pressure, higher doses of steroids should be considered. Symptoms might include severe headaches, characterized by pressure-like feelings that are worse in the morning with associated nausea and vomiting. Patients may also complain of headache, dizziness or syncopal episode during activities that transiently increase ICP, such as standing, sneezing, coughing or straining during bowel movements. In these scenarios, there is a concern for symptomatic plateau waves [4] which result from elevated ICP and can lead to intermittent drop in cerebral perfusion. In such acute presentations, we recommend an initial loading dose of Dexamethasone 10–20 mg to be given intravenously. We follow this loading dose with Dexamethasone 4–6 mg two to four times a day. Decisions on dosing need to be made on a case by case basis, but in general, patient rarely get additional benefit from doses exceeding 16 mg per day.

Chronic Steroid Use and Tapering

Despite the wide use glucocorticoids, there is limited consensus regarding the dosing, duration as well as tapering protocol. This holds true as there is limited evidence from clinical trials provid-

ing any guidance [5]. Below are the recommendations from our general practice. For patients requiring chronic dosing of steroids, doses should rarely exceed 8 mg per day. Twice daily dosing is ideal, with the second dose given in the early afternoon to prevent insomnia.

Patients who are started on steroids but otherwise have minimal or no symptoms, should be tapered off rapidly. For patients who have been on steroids for a short period, the rapid taper should not cause any steroid withdrawal symptoms and they can be tapered off within a few days. The effects of a taper are typically noticeable 72 h after a dose change and tapers should involve dose adjustments every 3 days. If they have been on steroids for more than 2 weeks, then doses should by dropped by 2 mg every 3 days. For some patients who are symptomatic during their treatment course, tapering off of steroids can be very difficult. As in other cases, we recommend starting a taper by decreasing dexamethasone by 1–2 mg every 3–5 days. If patients experience neurologic symptoms due to the taper, we recommend going back to the dose they previously tolerated. The taper should then be slower, generally 0.5–1 mg every 5–7 days. In patients that can tolerate a taper and become steroid-dependent, alternative approaches should be considered [5, 6].

Steroid Toxicities

The most common neurologic side effects include behavioral changes, myopathy and insomnia. Neurologic and systemic toxicities of corticosteroids are listed in Table 9.2. Euphoria and mania are more common with exogenous steroids while depression tends to be more common with endogenous steroids as in Cushings disease. As steroids are tapered, symptoms generally resolve. However, in situations where a steroid taper is not feasible, mood stabilizers such as lithium, valproic acid, olanzapine or haloperidol can be used. It is important to note that in patients who have had steroid induced psychosis after exposure to steroids, that it does not necessarily predict that psychosis will occur on re-challenge. Psychotic features can begin acutely and typically respond to with-

Table 9.2 Neurologic and systemic toxicities of corticosteroids

Neurologic (Common)	Neurologic (Uncommon)	Non-neurologic (Common but mild)	Non-neurologic (Serious)	Steroid withdrawal syndrome
Behavioral changes (both cyclic) • Affective (Acute): Euphoria → Mania (more common with exogenous steroids) • Depression (more common with endogenous steroids like Cushing's) Affective treatment 1. Steroid taper 2. Mood stabilizers (Li, valproic acid, olanzapine or haloperidol) • Schizophrenia-like psychosis: begin acutely; may require neuroleptic treatment • Delirium: resolves with taper	**Psychosis** **Delirium** **Dementia** **Seizures** **Dependence** **Paraparesis** (epidural lipomatosis)	**Visual blurring** Treatment 1. Discontinue steroids 2. Ophthalmologist consult if concern for cataracts or glaucoma	**Osteoporosis** Treatment 1. Imaging (MRI > CT, X-ray, bone scans) 2. Discontinue steroids (reversible in younger patients) • Prophylaxis: Bisphosphonates, Calcium (1200 mg daily) and Vitamin D (400–800 IU daily)	**Myalgias, Arthralgias (steroid pseudo rheumatism)** Treatment Increase dose to prior final dose and then taper off more slowly

Myopathy Treatment Physical therapy is highly advised Proper protein intake and replacement of any Vitamin D deficiency		**Increased appetite** (weight gain) **Abdominal bloating** **Moon facies** **Urinary frequency** (nocturia) **Acne** **Edema** (legs) **Lipomatosis** (spinal cord compression) **Genital burning** (IV push) **Candidiasis** **Cataracts**	**GI bleeding** Treatment Prophylaxis for high doses or chronic use: H2 blocker or PPI Avoid sucralfate!	**Headache** **Lethargy** **Fever** **Nausea/vomiting** **Anorexia** **Postural hypotension** **Papilledema** **Pneumocystis** **Pneumonia** **Adrenal insufficiency**
Insomnia Treatment Take second dose early in the afternoon (before 2 p.m.) Good bedtime hygiene (no screen time at least 2 h prior to bed)			**Hypercalcemia** Treatment • Oral hypoglycemics • Attempt to keep glucose before 150 mg/dL	

(continued)

Table 9.2 (continued)

Neurologic (Common)	Neurologic (Uncommon)	Non-neurologic (Common but mild)	Non-neurologic (Serious)	Steroid withdrawal syndrome
Hallucinations (high dose) **Insomnia** **Tremor** **Reduced taste/smell** **Cerebral atrophy** **Hiccups**			**Osteonecrosis** (hip) **Bowel perforation** **Diabetes** **Opportunistic infection** (pneumocystis) **Glaucoma** **Kaposi sarcoma** **Pancreatitis**	

drawal of steroids, and some cases, may require treatment with a neuroleptic. Delirium can be a side effect of steroids, particularly in older patients. Steroids should be tapered off if possible along with standard delirium precautions on inpatients.

Myopathy, characterized by proximal lower extremity weakness is worse in patients who are inactive and exercise and/or physical therapy is recommended as a preventive measure. Patients note difficulty getting up from a seated position, feeling weaker while walking and older patients might feel more unsteady when walking. Proper protein intake and replacement of any Vitamin D deficiency can also be helpful in preventing further muscle weakness [1].

Insomnia can be prevented by adjusting the dosing of medication. In patients, taking twice daily regimens, taking the second dose early in the afternoon rather than at night can be very helpful. Steroid-induced nocturia may also contribute to insomnia and patients are advised to avoid drinking beverages a few hours prior to sleeping.

Hypergylcemia is one of the most common toxicities associated with corticosteroids that requires active management. In patients with persistent blood glucose above 150 mg/dL, oral hypoglycemics are indicated [7]. However, this must be done with care and glucose will need to be monitored when tapering steroids. In rare cases, oral hypoglycemics may be insufficient and insulin may be required in consultation with the patient's primary care physician.

Osteoporosis begins after a few months but may occur even within a few weeks and can lead to fractures. In brain tumor patients, osteonecrosis of hips, shoulder and clavicle may be confused with spinal cord compression or peripheral neuropathy. In patients with suspected symptoms, MRI is the most sensitive diagnostic test. In young patients, osteoporosis generally reverses itself once steroids are discontinued. Bisphosphonates, Calcium (1200 mg daily) and Vitamin D (400–800 IU daily) may be given as prophylaxis.

Blurring of vision is a common complaint and can be associated with steroids. Consultation by an ophthalmologist can be helpful to evaluate for the development of cataracts or glaucoma.

Though there is not strong evidence regarding steroids alone leading to GI bleeding secondary to ulceration, we generally

recommend prevention with use of H2 blockers or PPI while on high doses or chronic use of steroids. It is important to keep in mind that both PPI and H2 blockers can cause somnolence and confusion. H2 blockers in particular can lead to thrombocytopenia. We generally don't advice use of Sucralfate as it can prevent absorption of other medications effectively.

Preventative Measures

Gastritis is a common side effect of steroids. Gastric and duodenal ulcers can be an eventual occurrence, especially in conjunction with NSAIDS. Although there are no clear guidelines or evidence on the use of Proton Pump Inhibitors (PPIs) in patients with brain tumor, in relation to use of steroid use, gastric discomfort is a common complaint. In our practice, we recommend the use of PPI for all patients who are started on Dexamethasone >1 mg. If a patient is being tapered off steroids, then we generally advise that PPI can be stopped once the patient has come to about 1 mg of dexamethasone (or other equivalent) per day. This is in reference to the daily production of endogenous glucocorticoids. Bowel Perforation is also an increased risk in patients on steroids. Prevention by treating underlying constipation [4].

Pneumocystis pneumonia (PJP) prophylaxis with Bactrim (or equivalent) is generally recommended for patients who are on prednisone >20 mg (or dexamethasone ≥3 mg QD) for >4 weeks. In our practice, it is rare for us to keep patients on such high doses of steroids for prolonged period. We do however recommend Bactrim prophylaxis in patients who are anticipated to have a prolonged taper, as the risk of infection is increased during this time [4].

Alternative Approaches to Steroids

For refractory symptomatic edema that requires prolonged use of corticosteroids, we recommend switching treatment to steroid sparing agent. Anti-VEGF agents, such as bevacizumab or it's

biosimilar Mvasi have both shown to be beneficial in these patients who have recurrent or refractory edema, providing symptomatic relief. We use this in our patients who we anticipate will require prolonged use of steroids secondary to the edema or in those who are symptomatic from radiation necrosis. Side effects to be mindful of in these patients are hypertension, proteinuria, hemorrhage, venous thrombosis, colonic perforation.

At our institution, our practice is to dose bevacizumab at dose of 5–7.5 mg/kg. This is much lower than the recommended dose by the manufacturer at 10 mg/kg. We have found the lower rate to control the edema and radiation necrosis without the detrimental side effects which generally occur at the higher dose [8].

Patient Instructions

Timing: If giving twice a day dosing, please take the first dose early in the morning (by 8 a.m.) and second dose no later than 2 p.m. to prevent insomnia and well as nocturia which can further lead to sleep deprivation.

Stomach protection: Continue to take medications to protect your stomach from gastritis especially if you are on a higher dose (>2 mg/day) of dexamethasone. We recommend famotidine or omeprazole to be taken twice a day.

Glucose: Many patients develop elevated glucose levels, even if they had no concerns with pre- diabetes or diabetes prior to starting steroids. We recommend a close monitor on food intake as increased appetite due to steroids with potential for insulin resistance and quickly lead to elevated glucose levels that can be detrimental.

Mood: Please be mindful that steroids can cause many different mood disorders including depression, anxiety as well as frank psychosis. If you feel these are affecting your daily functioning and relationship, we advise to bring this to the attention of your prescriber.

Myopathy: To prevent weakness, especially if you are anticipated to be on steroids for a long time, we strongly advice daily

exercise regimen. This can be as little as multiple small walks around the house.

References

1. Posner JB, DeAngelis LM, Deangelis LM. Neurologic complications of cancer. Oxford: Oxford University Press; 2009.
2. Nag S, Manias JL, Stewart DJ. Pathology and new players in the pathogenesis of brain edema. Acta Neuropathol. 2009;118:197–217.
3. Kim H, Lee JM, Park JS, Jo SA, Kim Y-O, Kim C-W, Jo I. Dexamethasone coordinately regulates angiopoietin-1 and VEGF: a mechanism of glucocorticoid- induced stabilization of blood–brain barrier. Biochem Biophys Res Commun. 2008;372(1):243–8. ISSN 0006-291X. https://doi.org/10.1016/j.bbrc.2008.05.025.
4. Drappatz J. Management of vasogenic edema in patients with primary and metastatic brain tumors. In: Wen P, editor. Uptodate. 2020.
5. Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology. 1994;44(4):675–80.
6. Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: an update. Neurooncol Pract. 2015;2(1):6–12. https://doi.org/10.1093/nop/npu029. Advance Access date 9 October 2014.
7. Fardet L, Petersen I, Nazareth I. Monitoring of patients on long-term glucocorticoid therapy: a population-based cohort study. Medicine (Baltimore). 2015;94(15):e647.
8. Ajlan A, Thomas P, Albakr A, Nagpal S, Recht L. Optimizing bevacizumab dosing in glioblastoma: less is more. J Neurooncol. 2017;135(1):99–105. https://doi.org/10.1007/s11060-017-2553-2.

Tumor Related Epilepsy

10

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Epidemiology and Pathophysiology

Between 25 and 70% of patients with intracranial tumors will experience an epileptic seizure at some point during their tumor treatment course, depending on their tumor type [1, 2]. Seizures occur as the presenting symptom in 30–50% of patients with a brain tumor, while 10–30% of seizure-naïve patients will later develop seizures [3, 4]. Based on current definitions provided by the International League Against Epilepsy (ILAE), any patient experiencing a seizure during the diagnosis and treatment of a brain tumor meets criteria for a diagnosis of epilepsy [5]. Tumor-related epilepsy (TRE) is associated with significant morbidity and mortality related both to seizures and the medications used to treat and prevent seizures [6, 7]. Seizures are the leading cause for acute care utilization in patients with brain tumors [8].

The prevalence of TRE is highly dependent on tumor type and grade. Patients with neuronal tumors (e.g., ganglioglioma) are more likely to develop TRE than those with CNS lymphoma [9]. Within the population of diffuse glioma, patients with low-grade astrocytoma are more likely to develop TRE than those with anaplastic astrocytoma or GBM [4]. It is generally accepted, based on

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electrophysiologic studies, that tumoral tissue itself is not epileptogenic, rather the mechanism for neuronal hyperexcitability exists within the peri-tumoral border which can subsequently recruit broader and more remote networks of epileptogenic potential [10, 11]. Pathophysiologic excitotoxicity mediated through disruption of glutamate pathways has emerged as a predominant theory in the pathophysiology of TRE. In recent years, several genetic markers have been proposed as a mechanism for dysregulation of glutamate homeostasis. These include the expression of mutant isocitrate dehydrogenase (IDH), System x_c^- glutamate transporter, and adenosine kinase [12–15]. Validation of the association of these markers and TRE is needed.

Emergency Care and the Management of Status Epilepticus

Classically, status epilepticus (SE) is considered the most extreme form of a seizure and a life-threatening neurologic emergency that can have short and long-term consequences, including neuronal death, neuronal injury, and alterations of neuronal networks [16]. Based on the current understanding, a convulsive (tonic-clonic) seizure is considered abnormally prolonged after 5 min duration, and likely to lead to continuous seizure activity. A convulsive seizure is likely to cause long term consequences (neuronal injury/death) after 30 min. In contrast, focal SE with impaired consciousness is considered abnormally prolonged if lasting greater than 10 min and is more often associated with long-term sequelae when persisting >60 min [16].

SE is relatively common in patients with TRE, commonly occurring at tumor presentation or progression and as the precipitant cause in 4–7% of cases of SE [17]. Presentation of SE in brain tumor patients is associated with higher mortality and morbidity, but remains responsive to standard interventions [1, 2, 17–19]. Nonconvulsive status epilepticus can be the presenting sign of new brain tumors or metastatic lesions and was identified in 2% of a cohort of brain tumor patients, with roughly 50% only experiencing subclinical seizures [19].

Treatment of SE in TRE should adhere to approved institutional clinical guidelines . A standard approach to SE treatment has been promoted by the American Epilepsy Society [20], and is as follows:

1. Stabilization phase (0–5 min)
   (a) Stabilize patient (airway, breathing, circulation)
   (b) Time seizure from onset, vital signs
   (c) Assess oxygenation, supplement as needed
   (d) ECG monitoring
   (e) Check finger stick blood glucose, correct if <60 mg/dL
   (f) IV access and baseline labs, ASM levels
2. Initial therapy phase (5–20 min)—if seizure continues
   (a) Administration of a benzodiazepine (chose 1):
      - IV lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once),
      - IV diazepam (0.15–0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once)
      - IM midazolam (10 mg for >40 mg, 5 mg for 13–40 kg, single dose).
3. Second therapy phase (20–40 min), if seizure continues
   (a) A recent randomized, blinded, adaptive trial demonstrated the following interventions were equally effective and has similar rates of adverse effects [21]:
      - IV Fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose)
      - IV Levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose)
      - IV valproate (40 mg/kg, max: 3000 mg/dose, single dose)
   (b) If none of above available,
      - IV phenobarbital (15 mg/kg, single dose)

Refractory SE occurs if seizures continue despite appropriate treatment with benzodiazepines and second line anti-epileptic seizure drug therapy. Currently there is not sufficient evidence to support a standard approach to the treatment of refractory SE and patients should be treated on a case-by-case basis and guided by treatment response using continuous EEG monitoring [22].

Pharmacologic Management of TRE

Initiation and Maintenance of Pharmacologic Therapy in Patients with TRE

Patients with brain tumors who experience an epileptic seizure at any point in their tumor treatment course are considered to have epilepsy, as defined by the ILAE and require prophylaxis with an anti-seizure medication (ASM) [5]. When deciding the best first line ASM for TRE, there is currently a lack of high quality comparative effective data. The selection of an ASM for focal onset epilepsy should be based on individual patient factors (e.g., comorbid mood disorder, liver dysfunction, history of renal calculi), and with guidance from the ILAE monotherapy meta-analysis [20]. Avoidance of enzyme-inducing ASMs in patients with brain tumors is strongly recommended given established interactions between these agents and chemotherapy and accelerated metabolism of corticosteroids [9, 23]. Patients with brain tumors may also be more prone to experiencing adverse effects of older generation ASMs such as phenytoin, carbamazepine, and phenobarbital [23].

Levetiracetam (LEV) has become a popular first line ASM in patients with TRE. LEV has been shown to be safe, well-tolerated, and effective at reducing seizures in patients with TRE compared to EIASMs. However, treatment with LEV was associated with higher prevalence and magnitude of neuropsychiatric adverse effects compared with other ASMs [24–26]. Prophylaxis with valproic acid (VPA) has been promoted particularly in patients with high grade glioma after retrospective observational studies associated VPA use with prolonged survival benefit as compared to those not using VPA. However, pooled analysis of prospective randomized controlled trials in newly diagnosed glioblastoma showed no survival benefit associated with either VPA or LEV [24].

Patients not responding to first line ASM therapy may require initiation of an adjunctive agent and this approach should be no different than treatment in other focal onset epilepsies, with the caveats listed above. There are numerous non-RCT studies supporting the tolerability, safety and efficacy of newer generation ASMs (Table 10.1).

The use of ASM prophylaxis in tumor patients who have not experienced seizures is controversial as there is lack of existing evidence to support efficacy in preventing seizures. Despite the high risk of developing TRE, only a handful of well designed, class I, studies have been conducted to test the effectiveness of ASM prophylaxis in this patient population and most of these studies only evaluated the use of older generations ASMs. Using this limited body of evidence, the AAN released a practice parameter in 2000 recommending against prophylaxis in patients with brain tumors who have not yet experienced a seizure [23]. A recent practice guideline update confirmed the approach [24]. Meta-analyses of these data not only failed to demonstrate efficacy with ASM prophylaxis but identified a heightened risk of ASM-associated toxicities, including interactions with anti-cancer agents and occasional life-threatening side effects. The use of perioperative ASM prophylaxis to reduce the risk of postoperative seizure is common practice at many institutions and supported by limited data suggesting efficacy. Studies have demonstrated no significant reduction in long-term seizure risk. It is recommended practice at many institutions that seizure-naïve patients who had been started on perioperative ASM therapy be tapered off of them. With the availability of new generation ASMs, new clinical trials may be warranted to test the effectiveness and safety of ASM prophylaxis in this at-risk population.

Table 10.1 Commonly prescribed ASMs for the treatment of TRE

Drug	Preparations	Dosing	Mechanism	Pharmacokinetics	Adverse effects	Monitoring
Levetiracetam (Keppra)	Tablets: 250 mg, 500 mg, 750 mg, 1000 mg Solution: 100 mg/mL IV: 100 mg/mL	Pediatric Initial: 20 mg/kg/day, divided BID Max: 60–80 mg/kg/day Adult Initial: 250–500 mg BID, initial maintenance 1500 mg/day Max: 3000 mg/day SE 60 mg/kg, max: 4500 mg/dose	Synaptic vesicle 2A inhibition	$t_{1/2}$ = 6–8 h Time to steady state = 2 days Protein binding = 0%	Somnolence (11.7–45%), Loss of appetite (3–8%), vomiting (15%) Abnormal behavior (7–37%), irritability (6–12%) Contraindications: allergies to LEV; dose adjust for renal impairment	Routine studies not indicated. Can consider levels to assess for adherence

Drug	Preparations	Dosing	Mechanism	Pharmacokinetics	Adverse effects	Monitoring
Divalproex sodium (Depakote, Depakote ER)	Depakote: 125 mg, 250 mg, 500 mg tabs; 125 mg spinkles (BID-TID) Depakote ER: 250 mg, 500 mg extended release tabs—ONCE DAILY	Pediatric & Adult Initial: 10–15 mg/kg/day, Increase 5–10 mg/kg/day q7 days Max: 60 mg/kg/day SE 40 mg/kg, max: 3000 mg/dose ×1	Sodium channel blockade, GABA	$t_{1/2}$ = 6–15 h Time to steady state = 1–2 days Protein binding = 80–95%	Somnolence (7–16%), weight gain (6–20%), GI upset, alopecia (5–6%). Dose-related: nystagmus (7%), action tremor (9–19%), ataxia (7%), elevated plasma transaminase, and hyperammonemia. Serious: pancreatitis, thrombocytopenia (27%), and hepatic failure Contraindication: hepatic disease	Baseline: LFTs Surveillance: CBC w/diff, LFTs, VPA levels—therapeutic range 50–100, 100–120 may be necessary

(continued)

Table 10.1 (continued)

Drug	Preparations	Dosing	Mechanism	Pharmacokinetics	Adverse effects	Monitoring
Oxcarbazepine (Trileptal)	100 mg, 300 mg, 600 mg tablets; 300 mg/5 mL suspension Extended-release (Oxtellar XR): 150 mg 300 mg 600 mg tab	Pediatric: Initiation 8–10 mg/kg/day Target dosing is weight based Max: 60 mg/kg/day Adult: 600 mg/day, increase by 600 mg/day weekly Max: 2400 mg/day	Blocks voltage-sensitive sodium channels, increases potassium conductance and modulation of high-voltage activated calcium channels	$t_{1/2}$ = 5–8 h (peds), 7–11 h (adult) Time to steady state = 2–3 days Protein binding = 40%	Somnolence, headache, dizziness, ataxia, and nausea Hyponatremia (<125 mmol/L) in 3% Contraindication: Avoid with the genetic marker human leukocyte antigen (HLA) allele B*1502 as there is an increased risk for Stevens-Johnson syndrome or toxic epidermal necrolysis	Serum sodium shortly after initiation or development of symptoms suggestive of hyponatremia

Drug	Preparations	Dosing	Mechanism	Pharmacokinetics	Adverse effects	Monitoring
Zonisamide (Zonegran)	25 mg, 50 mg, 100 mg capsules	[<16 years old]: Start 1–3 mg/kg/day qhs. Gradually increase dose to 5–9 mg/kg/day [>16 years old] Start 100 mg qhs. Increase by no more than 100 mg/day q2 weeks to 400 mg daily or divided BID Max: 600 mg/day	Blocks sodium channels and reduces inward currents through T-type Ca2+ channels	$t_{1/2}$ = **60 h** Time to steady state = 14 days Protein binding = 40%	Common: somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability Increased risk of calcium or urate kidney stones Contraindication: sulfonamide allergies	None

(continued)

Table 10.1 (continued)

Drug	Preparations	Dosing	Mechanism	Pharmacokinetics	Adverse effects	Monitoring
Lacosamide (Vimpat)	Oral: 50 mg, 100 mg, 150 mg, 200 mg tabs; 10 mg/mL solution IV: 10 mg/1 mL	Adults: Initially 50 mg twice daily, increase by 100 mg/day every week to daily dose of 200–400 mg daily	Selective sodium channel slow inactivation; collapsin response mediator protein-2 (CRMP-2)	$t_{1/2}$ = 13 h Protein binding = 14%	Common: Nausea, dizziness, headache, diplopia Serious: Arrhythmias (AF, 1® AV block, prolonged PR) Psychiatric (suicidal thoughts), Drug reaction with eosinophilia and systemic symptoms	ECG prior and after to initiation of treatment in patients with known cardiac conduction problems

SE Status Epilepticus, *LFT* liver function testing, *VPA* valproic acid

References

1. Cascino GD. Epilepsy and brain tumors: implications for treatment. Epilepsia. 1990;31(Suppl 3):S37–44.
2. van Breemen MSMW, Erik B, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6(5):421–30.
3. Wychowski T, Wang H, Buniak L, Henry JC, Mohile N. Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation ASMs. Clin Neurol Neurosurg. 2013;115(11):2365–9.
4. Hildebrand J, Lecaille C, Perennes J, Delattre JY. Epileptic seizures during follow-up of patients treated for primary brain tumors. Neurology. 2005;65(2):212–5.
5. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
6. Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, Abou-Khalil B. The course of seizure disorders in patients with malignant gliomas. Arch Neurol. 1995;52(7):717–24.
7. Sutter R, Marsch S, Fuhr P, Ruegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia. 2013;54(3):502–11.
8. Wasilewski A, Serventi J, Kamalyan L, Wychowski T, Mohile N. Acute care in glioblastoma: the burden and the consequences. Neurooncol Pract. 2017;4(4):248–54.
9. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6(5):421–30.
10. Köhling R, Senner V, Paulus W, Speckmann EJ. Epileptiform activity preferentially arises outside tumor invasion zone in glioma xenotransplants. Neurobiol Dis. 2006;22(1):64–75.
11. Wychowski T, James Fessler A, Nadler J, et al. A feasibility study of electrocorticography during routine craniotomy to predict tumor-related epilepsy. Interdiscipl Neurosurg. 2020;21:100772.
12. Zhong Z, Wang Z, Wang Y, You G, Jiang T. IDH1/2 mutation is associated with seizure as an initial symptom in low-grade glioma: a report of 311 Chinese adult glioma patients. Epilepsy Res. 2015;109:100–5.
13. Stockhammer F, Misch M, Helms HJ, et al. IDH1/2 mutations in WHO grade II astrocytomas associated with localization and seizure as the initial symptom. Seizure. 2012;21(3):194–7.
14. Buckingham SC, Campbell SL, Haas BR, et al. Glutamate release by primary brain tumors induces epileptic activity. Nat Med. 2011;17(10):1269–74.

15. de Groot M, Iyer A, Zurolo E, et al. Overexpression of ADK in human astrocytic tumors and peritumoral tissue is related to tumor-associated epilepsy. Epilepsia. 2012;53(1):58–66.
16. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015;56(10):1515–23.
17. Cavaliere R, Farace E, Schiff D. Clinical implications of status epilepticus in patients with neoplasms. Arch Neurol. 2006;63(12):1746–9.
18. Knudsen-Baas KM, Power KN, Engelsen BA, Hegrestad SE, Gilhus NE, Storstein AM. Status epilepticus secondary to glioma. Seizure. 2016;40:76–80.
19. Marcuse LV, Lancman G, Demopoulos A, Fields M. Nonconvulsive status epilepticus in patients with brain tumors. Seizure. 2014;23(7):542–7.
20. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48–61.
21. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381(22):2103–13.
22. Vossler DG, Bainbridge JL, Boggs JG, et al. Treatment of refractory convulsive status epilepticus: a comprehensive review by the American Epilepsy Society Treatments Committee. Epilepsy Curr. 2020;20(5):245–64.
23. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54(10):1886–93.
24. Walbert T, Harrison RA, Schiff D, Avila EK, Chen M, Kandula P, Lee JW, Le Rhun E, Stevens GHJ, Vogelbaum MA, Wick W, Weller M, Wen PY, Gerstner ER. SNO and EANO practice guideline update: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro Oncol. 2021;23(11):1835–44. https://doi.org/10.1093/neuonc/noab152. PMID: 34174071; PMCID: PMC8563323.
25. van der Meer PB, Maschio M, Dirven L, Taphoorn MJB, Koekkoek JAF, Italian League Against Epilepsy Brain Tumor-Related Epilepsy Study Group. First-line levetiracetam versus enzyme-inducing antiseizure medication in glioma patients with epilepsy. Epilepsia. 2023;64(1):162–9. https://doi.org/10.1111/epi.17464. Epub 2022 Nov 24. PMID: 36380710.
26. Rossetti AO, Jeckelmann S, Novy J, Roth P, Weller M, Stupp R. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro Oncol. 2014;16(4):584–8. https://doi.org/10.1093/neuonc/not170. Epub 2013 Dec 4. PMID: 24311644; PMCID: PMC3956345.

11 Treatment and Prevention of Venous Thromboembolism

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Venous thromboembolism (VTE) is among the most frequent of medical complications experienced by patients with cancer and represents a significant contributor to morbidity and mortality. Risk factors for developing VTE have long been understood to include age, obesity, immobility and vascular injury among others, and cancer patients are at a higher risk due to hypercoagulability [1]. For reasons that will be discussed, patients with central nervous system malignancies are at an even higher relative risk within the general population of cancer patients. The overall risk of developing VTE in patients with high-grade gliomas is comparable, and in some descriptions surpasses, that of patients with pancreatic and gastric cancers, historically known to carry the highest risk of VTE. The reasons for this are not yet completely understood, but it is hypothesized that a combination of high tumoral expression of procoagulants, tissue factor and podoplanin—and subsequent systemic circulation of these—play a role [2]. Podoplanin in particular has been found to induce platelet aggregation, and its expression has been found to be correlated with IDH-wild-type tumors and increased risk for developing VTE [3].

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Apart from focal leg weakness or immobility, other VTE risk factors in patients with brain tumors include higher histological grade, recent craniotomy, involvement of cerebral vasculature by tumor, poor functional status (e.g. Karnofsky Performance Status score of less than 70 or Eastern Cooperative Oncology Group score of 2 or greater), active chemotherapy and exposure to anti-angiogenic treatment [4, 5]. The rate of recurrent venous thromboembolic events approaches nearly 30%, and the consequent increases in morbidity and mortality, rates of hospitalization and length of stays, to name a few, mandate an evidence-based approach to preventing, diagnosing and treating this all-too-common complication [4].

Types of Venous Thromboembolism and Clinical Diagnosis

Deep venous thrombosis (DVT) should be suspected in any patient presenting with any combination of acute or subacute swelling and pain or warmth in one or more limbs. Patients may or may not endorse calf or thigh tenderness on exam, but practitioners should be aware that general physical exam maneuvers such as Homan's test (pain in the calf or popliteal fossa with passive dorsiflexion of the ankle with the patient supine) are of low sensitivity and specificity. Similarly, our patients are at a sufficiently high risk of developing VTE that serum screening tests (e.g. D-dimer) are also of limited utility. It is advised that the routine practice should be to obtain compression ultrasonography in the suspected leg in all patients for whom clinical concern exists to definitively rule out DVT.

The presentation of acute pulmonary embolism (PE) is somewhat less straightforward, as the symptomatology can vary. The classic description of sudden onset of shortness of breath with pleuritic chest pain and cough or hemoptysis can be helpful as these represent the most common symptoms experienced by patients who develop PE. However, practitioners should remain vigilant for any symptoms that may indicate acutely compromised cardiopulmonary status. PE should be considered on the basis of isolated tachycardia or tachypnea, new unexplained intolerance of

physical exertion, and/or presyncopal symptoms. Physical exam findings may be significant for tachycardia, tachypnea, diminished breath sounds, or new oxygen requirement. Bedside EKG may be performed with relative ease, and may demonstrate sinus tachycardia (the most common EKG finding), or in cases of significant right heart strain an "S1Q3T3" pattern of a large S wave in lead I, and a Q wave with T-wave inversion in lead III. Any patient for whom an acute PE is suspected should undergo CT pulmonary angiography of the chest with contrast in the absence of contraindications without delay. In cases where imaging is equivocal, a ventilation-perfusion scan of the lungs may be considered, and in cases where patients may not be hemodynamically stable to undergo scanning, bedside echocardiography may be expediently pursued to evaluate for right heart strain.

Perhaps the most diagnostically challenging manifestation of VTE in patients with primary brain tumors is that of cerebral venous or venous sinus thrombosis. This complication occurs in up to 8% of patients with glioblastoma, and requires a high degree of suspicion to diagnose [6, 7]. To this end, understanding the pathophysiology can be helpful in recognizing its disparate manifestations. Fundamentally, thrombosis within the cerebral venous system leads to decreased flow through the cerebral vasculature and increased venous pressure, while thrombosis in the sinuses leads to obstruction of blood flow away from the brain and a consequent increase in intracranial pressure. The former mechanism leads to disruption of the blood-brain barrier with resultant leakage of plasma and localized vasogenic edema, potentially hemorrhage and decreased cerebral perfusion leading to infarction. The latter mechanism leads to signs and symptoms of intracranial hypertension, such as headaches, nausea, vomiting, transient visual obscurations, and papilledema, among others. Because of the heterogeneity of the cerebral collateral flow, ages of patients and other comorbidities, not only the symptoms but also the time course can vary widely. The most common complaint is headache, though patients may also experience focal deficits, seizures or altered mentation [8]. Elderly patients in particular are more likely to present with encephalopathy than headache, and this may be acute, subacute or chronic in evolution [9]. Historical features that may suggest cerebral venous thrombosis include recent dehydration, local infections of the head

and neck (e.g. ears, sinuses) and known involvement of cerebral veins or sinuses by tumor.

Patients with suspected cerebral venous or sinus thrombosis should undergo urgent neuroimaging, ideally with MRI of the brain and contrast-enhanced MR venography (MRV) of the head and neck. In patients with MRI contraindications or centers with limited resources, non-contrast CT of the head may obtained to evaluate for a dense triangle sign, or hyperdensity within the posterior aspect of the superior sagittal sinus representing the venous thrombus, as well as hemorrhagic or infarcted lesions lying outside the territory of known blood vessels. Contrast-enhanced CT venography (CTV) is also considered to be equivalent to MRV for the diagnosis of venous thrombosis and can just as reliably delineate the extent of thrombosis.

Prevention of VTE

Outpatient Primary Prevention

Because patients with high-grade gliomas are among those at highest risk for developing VTE among all patients with cancer, a real need exists to identify which outpatients will benefit most from pharmacologic prophylaxis. One predictive model, the Khorana score, incorporates the site of cancer, pre-chemotherapy platelet count (>350 k/uL), leukocyte count (>11 k/uL), hemoglobin level (<10 mg/dL), and BMI (>35 kg/m^2), but has yet to be validated prospectively in patients with high-grade gliomas [5]. The PRODIGE trial—which was a randomized placebo-controlled study that evaluated symptomatic DVT or pulmonary embolism occurring within 6 months after randomization to either low-molecular weight heparin dalteparin or placebo in 186 patients with newly-diagnosed high-grade glioma—did not find a statistically-significant decrease in symptomatic VTE or an increase in major bleeding, however there was a trend toward reduction in the former and a trend toward increase in the latter [10]. The AVERT trial was another randomized, placebo-

controlled double-blind clinical trial evaluating the effectiveness and safety of direct factor Xa inhibitor apixaban versus placebo in 574 patients with a solid tumor and Khorana score of ≥2 indicating intermediate to high risk of VTE. Carrier et al. found a statistically-significant reduction in VTE, with a higher rate of major bleeding episodes versus placebo [11]. It should be noted that only 4.8% of those who received the study drug had a brain tumor. Taken together, no studies have convincingly established a role for primary medical prevention of VTE for ambulatory outpatients with high-grade gliomas. We do not, therefore, routinely administer chemical thromboprophylaxis in this setting and advise vigilance for potential VTE-related symptoms in patients who are at high risk, e.g. those who are elderly (>75 years), immobile, with poor functional status and/or receiving anti-VEGF therapy.

Inpatient Primary Prevention

In alignment with ASCO and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), the approach to primary thromboprophylaxis for inpatients with medical or surgical problems requiring acute hospitalization should be pharmacologic prophylaxis with LMWH (in the absence of major bleeding or other contraindications) for all patients with active malignancy and an acute medical illness [12, 13]. All admitted patients as part of their initial evaluation should have baseline complete blood count with differential (CBC), activated partial thromboplastin time (aPTT), prothrombin time (PT), complete metabolic panel (CMP) and hepatic function (ALT/AST) panel. For our highest-risk patients (particularly those undergoing surgery), we combine mechanical (i.e. intermittent pneumatic compression devices or sequential compression devices) and chemical prophylaxis with LMWH [14]. In the post-operative patient, anticoagulation should be resumed as soon as is considered safe by the neurosurgical team, which is in general within 96–120 h post-closure. Table 11.1 provides a summary of anticoagulant agents with recommended dosages.

Table 11.1 Prophylactic and therapeutic anticoagulant dosing

Agent	Prophylactic dosing	Prophylactic dosing—obesity (≥40 mg/m^2)	Therapeutic dosing
Enoxaparin	40 mg SC daily	40 mg SC every 12 h	1 mg/kg SC every 12 h
Dalteparin	5000 U SC daily	7500 U SC daily	200 U/kg SC daily for 30 days, then 150 U/kg once daily
Fondaparinux	2.5 mg SC daily	5 mg SC daily	5 mg (<50 kg); 7.5 mg (50–100 kg); 10 mg (>100 kg) SC daily
Unfractionated heparin—SC	5000 U SC every 8 h	7500 U SC every 8 h	333 U/kg SC load, then 250 U/kg SC every 12 h
Unfractionated heparin—IV			80 U/kg IV load, then 18 U/kg/h, target aPTT of 2–2.5× control
Rivaroxaban			15 mg PO twice daily for 21 days, then 20 mg daily
Apixaban			10 mg PO twice daily for 7 days, then 5 mg twice daily

Agents	Contraindications and warnings
LMWH	• Contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min)
	• Absolutely contraindicated in patients with recent or acute (HIT)
	• Relatively contraindicated in patients with past history of HIT
Fondaparinux	• Contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min)
Unfractionated heparin	• Absolutely contraindicated in patients with recent or acute (HIT)
	• Relatively contraindicated in patients with past history of HIT

Table 11.1 (continued)

Agents	Contraindications and warnings
Apixaban and rivaroxaban	• Contraindicated in patients with stage IV/V chronic kidney disease
	• CrCl <25 mL/min (apixaban) or <30 mL/min (rivaroxaban)
	• Contraindicated in patients with active/clinically-significant liver disease
	• ALT/AST >2× ULN; total bilirubin >1.5× ULN (apixaban)
	• ALT/AST >3× ULN (rivaroxaban)
	• Concurrent use of CYP3A4 or P-glycoprotein inducers/inhibitors
	• Relatively contraindicated in patients with genitourinary or gastrointestinal tract lesions, pathology or instrumentation

Treatment of VTE and Special Circumstances

There are two phases in the treatment of confirmed VTE: initial and long-term. With regard to the initial (i.e. acute) phase, all patients with primary CNS malignancy and acute venous thromboembolism should be evaluated urgently, assessed for contraindications to anticoagulation and started on appropriate anticoagulation without delay. In this setting the preference for patients who are otherwise hemodynamically stable, not planned to undergo potential surgery and without contraindications for use of heparin is for LWMH. For patients with absolute contraindication(s) to anticoagulation (Table 11.2) and acute lower extremity DVT, a retrievable inferior vena cava filter should be considered.

Once the patient has been stabilized on their initial regimen of anticoagulation, it is appropriate to transition to long-term anticoagulation to minimize the risk of recurrent VTE, which tends to peak in the first 6 months. In this setting, the most appropriate agent is one which balances efficacy and safety with tolerability and therefore long-term adherence. We do not recommend vita-

Table 11.2 General and specific contraindications to anticoagulation

Prophylactic or therapeutic anticoagulation	Mechanical prophylaxis
Absolute	**Absolute**
• Recent CNS bleed, hemorrhagic CNS metastases	• Acute DVT
• Active major bleeding (more than 2 units in 24 h)	• Severe arterial insufficiency (graduated compression stockings)
Relative	**Relative**
• Chronic, clinically significant measurable bleeding >48 h	• Large hematoma
• Thrombocytopenia (platelets <50 k/uL)	• Skin ulcerations or wounds
• Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)	• Thrombocytopenia (platelets <20 k/uL)
• Recent major operation at high risk for bleeding	• Mild arterial insufficiency (graduated compression stockings)
• Underlying hemorrhagic coagulopathy	• Peripheral neuropathy (graduated compression stockings)
• High risk for falls (head trauma)	
• Neuraxial anesthesia/lumbar puncture	
• Interventional spine and pain procedures	
• Long-term antiplatelet therapy	

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min K antagonists (e.g. warfarin) for maintenance anticoagulation as they are inferior in efficacy to low-molecular-weight heparins [15]. For some patients, the excessive bruising, skin irritation and frequency of dosing associated with regular subcutaneous LMWH administration can detract from their quality of life, and in these cases, consideration of a direct oral anticoagulant (DOAC) should be considered. Recent trials support comparable efficacy to LMWH with similar safety profile and improved subjective quality of life measures [16, 17].

Anticoagulation in the Patient with Thrombocytopenia

Myelosuppression with thrombocytopenia is not an uncommon complication experienced by patients with high-grade gliomas on cytotoxic chemotherapy, and evidence still supports the judicious use of anticoagulants for patients with VTE. For patients whose platelets are above 50 k/uL, no dose adjustment is necessary, however platelet transfusions to maintain platelets above 50 k/uL are recommended. For patients whose platelets are between 25 and 50 k/uL with low-risk thrombi (i.e. those related to central venous catheter placement, incidental subsegmental pulmonary embolism), anticoagulation can be halved. For patients with high-risk thrombi, however (proximal DVT, symptomatic DVT), no dose reduction is recommended; rather these patients should receive platelet transfusions to maintain their platelets above 40 k/uL [16]. Anticoagulation should be held for patients whose platelets are less than 20 k/uL.

Medical Risks of Treatment

Despite the benefit of anticoagulation in preventing recurrent VTE, the risks of major bleeding—defined as a decrease in serum hemoglobin of 2 g/dL within 24 h or any bleeding into a vital organ—and non-major clinically-relevant bleeding—that which requires interfacing with healthcare provider—are 3% and 10%, respectively. Within our patient population, the foremost disease-specific

risk of anticoagulation is intracranial bleeding. Observational data describes a one-year incidence of all intracranial bleeding of 28% in patients with primary brain tumors on therapeutic LMWH versus 14% in patients not on anticoagulation, with similar reported rates for patients on DOACs [18–20]. The increased subsequent morbidity and mortality can be significant.

Vigilant monitoring for changes in renal and hepatic function as well as potential drug-drug interactions, then, is crucial in preventing these events, however not all unfortunately are preventable. In the setting of bleeding while on anticoagulation, the first steps include immediately stopping the anticoagulant, hemodynamic stabilization and prompt administration of appropriate reversal agent particularly if emergency surgery is anticipated. For specific reversal strategies please refer to the 2.2023 version of the NCCN Guidelines® for Cancer-Associated Venous Thromboembolic Disease. Obtaining neurosurgical and benign hematologic consultation is also recommended. The discussion regarding the safety of resuming anticoagulation is best individualized to each unique patient circumstance.

Patient Instructions

Patients with brain tumors are at a higher risk for developing blood clots in the veins of the legs, lungs and brain. Symptoms concerning for the development of a blood clot can include leg swelling, leg pain, leg redness, shortness of breath, chest pain that is worse with breathing, or a headache that will not go away. When a blood clot is discovered, the recommended treatment will likely be blood thinning medication to prevent these blood clots from causing more symptoms and complications from a blockage of blood flow. Starting a blood thinning medication will increase the risk for bleeding, which can range from easy bruising and prolonged bleeding of minor cuts to major bleeding which might require urgent medical care. While on blood thinning medications, it is also important to monitor for any new severe headache, sudden lightheadedness, difficulty breathing, or new neurologic symptoms which might indicate significant bleeding for which you will need to seek medical attention immediately.

References

1. Olson NC, Cushman M, Judd SE, et al. American Heart Association's Life's simple 7 and risk of venous thromboembolism: the reasons for geographic and racial differences in stroke (REGARDS) study. J Am Heart Assoc. 2015;4:e001494.
2. Sartori MT, Della Puppa A, Ballin A, Saggiorato G, Bernardi D, Padoan A, Scienza R, d'Avella D, Cella G. Prothrombotic state in glioblastoma multiforme: an evaluation of the procoagulant activity of circulating microparticles. J Neurooncol. 2011;104(1):225–31.
3. Riedl J, Preusser M, Nazari PM, Posch F, Panzer S, Marosi C, Birner P, Thaler J, Brostjan C, Lötsch D, Berger W, Hainfellner JA, Pabinger I, Ay C. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood. 2017;129(13):1831–9. https://doi.org/10.1182/blood-2016-06-720714. Epub 2017 Jan 10.
4. Nabi S, Kahlon P, Borzognia F, Arshad A, Mikkelsen T, Donthireddy V. Predictors of venous thromboembolism in patients with glioblastoma. Pathol Oncol Res. 2016;22:311–6.
5. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902–7.
6. Helmi A, Chan A, Towfighi S, Kapadia A, Perry J, Ironside S, Machnowska M, Symons SP, Fox AJ, Sahgal A, Maralani PJ. Incidence of dural venous sinus thrombosis in patients with glioblastoma and its implications. World Neurosurg. 2019;125:e189–97.
7. Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg. 2007;106(4):601–8.
8. Duman T, Uluduz D, Midi I, Bektas H, Kablan Y, Goksel BK, et al. A multicenter study of 1144 patients with cerebral venous thrombosis: the VENOST study. J Stroke Cerebrovasc Dis. 2017;26(8):1848–57.
9. Zuurbier SM, Hiltunen S, Lindgren E, Silvis SM, Jood K, Devasagayam S, et al. Cerebral venous thrombosis in older patients. Stroke. 2018;49(1):197–200.
10. Perry JR, Julian JA, LaPerriere NJ, Geerts W, Agnelli G, Roges LR, Malkin MG, Sawaya R, Baker R, Falanga A, Parpia S, Finch T, Levine MN. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010;8:1959–65.
11. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med. 2019;380(8):711–9.

12. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38(5):496–520.
13. National Comprehensive Cancer Network. Cancer-associated venous thromboembolic disease (version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed 6 Feb 2020.
14. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A, Beltrametti C, Damiani M, Andrioli GC, Pugliese R, Iorio A, Brambilla G. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998;339:80–5.
15. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M. Low-molecular-weight heparin versus a Coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146–53.
16. McBane R, Wysokinski W, Le-Rademacher J, Zemla T, Ashrani A, Tafur A, Perepu U, Anderson D, Gundabolu K, Kuzma C, Botero JP, Ferre RAL, Henkin S, Lenz CJ, Houghton DE, Vishnu P, Loprinzi CL. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost. 2020;18:411–21.
17. Einstein Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–510.
18. Bannow BTS, Lee A, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;16(6):1246–9.
19. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberg D, Zwicker JI. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. Blood. 2017;129(25):3379–85.
20. Carney BJ, Uhlmann EJ, Pligandla M, Mantia C, Weber GM, Neuberg DS, Zwicker JI. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. J Thromb Haemost. 2019;17(1):72–6.

12 Management of Neurocognitive Symptoms

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Patients with CNS involvement of their malignancy—such as gliomas, meningiomas, and primary CNS lymphoma and metastatic disease—frequently experience cognitive impairment. Additionally, cognitive sequelae from treatments such as radiotherapy and chemotherapy also lead to measurable deficits on neuropsychological assessments and negatively impact the health related quality of life (HRQOL) of these patients. Though these impairments are often localizable, network disruptions from tumor invasion, edema, and injury from treatment often lead to more broad deficits than expected.

This chapter provides an overview of cognitive symptoms commonly seen across adults with primary brain tumors of varied histologies, locations, or specific treatments. In this chapter, we discuss differential diagnoses and work-up, comorbidities and other factors in the care of this population. We also review non-

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pharmacologic and pharmacologic treatment strategies to consider and conclude with discussion of cognitive and behavioral changes near the end of life.

Causes and Differential Diagnosis

The prevalence of cognitive impairments in patients with brain tumors varies widely and changes over the illness trajectory. At diagnosis, tumor characteristics, including location, size, extent of edema, and grade, have all correlated with cognitive function. Though many patients experience improvement in cognition in the 3–6 months following resection, many remain impaired or have further decline from subsequent treatments such as radiotherapy and chemotherapy and/or tumor progression. Radiotherapy has the off-target effect of acutely injuring neuronal generation, causing inflammation, and disrupting the microenvironment that leads to degenerative changes and chronic damage to cognition. The hippocampus is particularly sensitive to radiotherapy-induced injury, resulting in common memory deficits. Chemotherapy demonstrates neurotoxic effects and, while the mechanism may be better understood for CNS penetrating drugs such as methotrexate and platinum based treatments, the mechanisms of injury for many other cytotoxic and targeted agents are less well understood. The neurotoxic effects of radiation and/or chemotherapy may be evident on MRI as diffuse leukoencephalopathy or atrophy. Additional factors such as metabolic changes, steroids, pain medication, seizures, and antiepileptic use may also exacerbate cognitive inefficiencies. Tumor progression should also be considered in patients with acute or subacute cognitive changes.

Workup for acute or subacute cognitive changes

- Metabolic abnormalities—B12, TSH, urine analysis
- Medications—offending AEDs or steroids
- Uncontrolled seizures
- Fatigue/sleep disturbance
- Under-treated psychiatric diagnosis
- Tumor progression
- Post-radiation changes—radiation necrosis or leukoencephalopathy

Clinical Presentation of Cognitive Symptoms

Brain tumor related cognitive symptoms are varied and often related to tumor site. The most commonly affected cognitive domains are those reliant on distributed functional networks and white matter tracts, rather than highly localized cognitive skills (for example thinking speed rather than facial recognition). Specifically, impairments in processing speed, executive functions, attention and concentration, learning efficiency and memory retrieval, and language are common. Fatigue and stamina, sleep, medication toxicities and co-morbid illnesses, can also contribute. Below is an overview of common areas of cognitive impairment and associated symptoms.

Slowed Processing Speed

Processing speed (i.e. thinking speed) usually refers to the speed at which cognitive operations can be performed and is an interaction between specific cognitive skills, brain network recruitment, and speed of reaction and stimulus transmission. Slowed processing is among the most common cognitive impairment found in brain tumor patients, regardless of tumor type or location. Slowed cognitive processing makes task completion more challenging. Patients experience slowed processing as difficulty keeping up with the pace of conversations, finding words, and needing more time to complete tasks. Fatigue, disruption in sleep, medication effects, comorbid illness, and impacts of active treatment may also contribute.

Slowed processing speed is prevalent in individuals with damage to white matter and subcortical systems. Radiotherapy, some antiepileptic medications, and/or certain psychiatric conditions are all associated with slowed processing speed.

Localization: subcortical white matter changes.

Executive Dysfunction and Behavioral Changes

Executive function is generalized localized to the frontal lobes and is the higher order processing responsible for engagement in self-directed, self-serving, and independent behaviors. It allows prioritization of what to pay attention to and how to respond, and whether or not one attempts a behavior at all. Executive functions are very vulnerable to injury from brain tumors and related treatments leading to difficulty formulating a desired goal; and the planning, sequencing, and execution required to achieve it. Problem solving, self-monitoring, and ability to perform tasks are often compromised. Executive dysfunction is often linked to negative impacts on gainful employment, transportation use, and reduced quality of life.

Changes to behavioral and emotional control associated with executive dysfunction particularly impacts social and interpersonal functioning. Patients may express emotional flattening or lability, irritability or excitability, impulsivity, carelessness, and inflexibility. Insight and judgment may also be impaired and contribute to poor understanding of their cognitive or behavioral changes.

Lesions in the dorsolateral prefrontal cortex may result in perseverative or inflexible behavior, lack of awareness, and easy distractibility. These individuals also have a tendency to exhibit reduced memory and learning, particularly freely recalling information despite having intact recognition of the newly learned material. Orbitofrontal disruption may result in impulsiveness, inappropriate social behavior, and mood lability. Anterior cingulate gyrus lesions can lead to abulia, reduced engagement, and poor motivation and social interaction. More diffuse frontal deficits are more likely to cause disinhibition.

Localization: frontal lobe (dorsolateral prefrontal area, orbitofrontal, anterior cingulate gyrus), intraventricular, posterior fossa.

Attention and Concentration Impairment

Majority of everyday functions rely on intact attention and concentration for successful completion. Being able to effectively divide or shift attention depends on availability of resources to manage competing task demands. Selective attention, or the ability to focus on chosen stimuli while ignoring distractions, often susceptible to effects of brain disorders including tumors. Other aspects of attention, such as sustaining a state of mental concentration over a period of time, dividing attention between competing stimuli, or alternating attention between two tasks are also impacted by brain disease or injury. Radiotherapy, changes in mood, and fatigue in brain tumor patients impact the arousal and vigilance needed for attentional focus. Patients often describe themselves as being highly distractible and have difficulty completing tasks.

Localization: frontal lobe, language dominant hemisphere.

Memory and Learning Impairment

Memory is not a single operation, but rather the integration of several systems to function, including some areas more vulnerable to injury, such as attention (as described above). Memory is frequently impacted by brain tumors and related treatments, especially tumors located in the frontal and temporal lobes and thalamus. Problems with memory may also be more salient to patients if tumors are located in the third ventricle region. Patients with brain tumors in the left hemisphere tend to have more trouble learning and remembering verbal information, though visual memory may remain intact. Memory based impairments are often reported by patients as forgetfulness and difficulty learning new tasks.

Localization: frontal and temporal lobes (dominant hemisphere), thalamus, diencephalon, corpus callosum.

Language Impairment

Patients with tumors located in the language dominant hemisphere may exhibit deficits in expressive and receptive language, and verbal learning/memory. However, slowed and incoherent speech are seen in tumors of the non-dominant hemisphere. Patients with language impairments report difficulties naming objects, understanding conversations, and/or following verbal instructions.

Localization: language dominant hemisphere.

Clinical Management and Recommendations

Cognitive screening can inform early detection of cognitive changes and be helpful in determining additional assessment needs. Management of cognitive sequelae of brain tumor and related treatment begins with assessment. By providers asking patients and caregivers early and often about cognitive changes, patients can receive timely intervention to improve quality of life. It is crucial early in the disease course to identify the neuropsychiatric changes, investigate co-morbid causes, and identify, when possible, functional impairment experienced by the patient.

Standardized cognitive screening instruments are one method used in medical settings for brief assessment of cognitive functioning—e.g. the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE) and the Neurobehavioral Cognitive State Examination (NCSE). It should be noted, however, that these tools vary regarding their sensitivity and specificity for detecting cognitive impairments in the brain tumor population. A focused interview of symptoms may be more effective to identify cognitive concerns and appropriate referrals/interventions (Tables 12.1 and 12.2). This interview should also include questions about mood, sleep, and fatigue given their cognitive impact. Ideally, patients who report cognitive symptoms or are observed to have cognitive challenges should be referred to a

Table 12.1 Examples of patient and provider discussion of cognitive symptoms and associated referral considerations

Examples of reported cognitive concerns	"I forget what I am saying during a conversation" "I'm always late! I can't multitask anymore" "I'm trying to take my medication every day, but I keep forgetting" "I have a hard time finding the right words. I know what I want to say, but I can't get it out"
Provider follow-up questions	Do you have more trouble learning and remembering new things? Do you have more trouble making decisions? Do you have more trouble finding the words you want to use? Does it take you longer to do things? Do you feel easily rushed?
Clinical and/or collateral observations	• Easily distracted by stimuli in the environment (e.g. sounds, movements) • Pauses during conversation, loses train of thought mid- sentence. Asks others to reorient them to what they were talking about • Late and missed appointments • Forgetful
Patient education	• Minimize environmental distractions, such as having conversations in quiet areas • Ask others to repeat information • Pre-plan to do one task at a time and avoid multitasking • Consider using an alarm for when to take medications • Organizational strategies such as using calendars, to-do lists, and structured daily routines • Encourage others to slow down rate of speech and use alternative words to describe what you mean
Referral considerations	Neuropsychology; speech therapy

neuropsychologist for comprehensive cognitive and emotional assessments and, if available, consideration for cognitive rehabilitation.

Table 12.2 Examples of patient and provider discussion of mood/behavior symptoms and associated referral considerations

Examples of reported mood/behavior concerns	"I have been feeling down lately and not really interested in much" "I get so irritable and impatient" "The littlest things seem to worry me. I can't turn my brain off"
Provider follow-up questions	Is this a change compared to before your diagnosis? How bothersome is this symptom to you? Do these symptoms get in the way of things that are important to you? How ready are you to do something different about these symptoms?
Clinical and/or collateral observations	• Tearful • Blunted expression • Tense, irritable, restless • Negativistic
Patient education	• Encourage scheduling daily pleasant activities (such as socialization, hobbies, and other interests) • Encourage self-care (such as meditation, self-affirmations, exercise, journaling, and relaxation strategies) • Sleep hygiene and fatigue management with self-pacing emphasis • Anxiety, depression, and anger-management education • Managing over-stimulation education
Referral considerations	Psychiatry; psychology

Common reasons to refer for neuropsychological evaluation for brain tumor patients

- Patient and/or caregiver report cognitive complaints interfering with their HRQOL
- Provider observes cognitive changes as compared to baseline
- Evaluate cognitive status and level of care needs
- Determine cognitive and emotional status to inform treatment planning and rehabilitation needs
- Document support for disability and/or accommodations
- Evaluate decisional capacity (financial, testamentary, medical decisions, etc.)

Non-pharmacological Interventions

Non-pharmacological interventions are effective methods of managing cognitive symptoms including patients with cancer. Cognitive training and rehabilitation, exercise, and meditation/mindfulness-based stress reduction have demonstrated efficacy. Other non-pharmacologic approaches to treat sleep, fatigue, and mood can also be helpful in improving cognition and are discussed below.

Cognitive Training and Rehabilitation

Cognitive rehabilitation is the standard of care to address cognitive impairments in other neurologic diseases such as traumatic brain injury, multiple sclerosis, and stroke. Mechanistically, cognitive rehabilitation gains are second to neuroplasticity through the brain's ability to relearn and establish alternative cognitive pathways. Studies in brain tumor populations, though limited, demonstrate overall positive effects, particularly in areas of attention and memory. By using cognitive retraining and teaching compensatory strategies to improve skills and decrease environmental demands, patients are better able to optimize their cognition and learn new ways to achieve their goals. Careful neuropsychological evaluation of cognitive strengths and weaknesses is a substantial prerequisite to inform treatment planning for appropriate cognitive rehabilitation strategies and other interventions to improve cognition. Cognitive rehabilitation is likely most beneficial in medically stable patients who feel their cognitive vulnerabilities are influencing their daily life.

Exercise

Exercise shows promise as a supportive care intervention to counteract the adverse cognitive impact of brain tumors and related treatment. Regular physical activity, specifically cardiorespiratory fitness, can offset hippocampal damage. Aerobic exercise is associated with improvements in cognition through increasing neuro-

genesis, enhanced angiogenesis, and upregulation of neurotrophins, such as BDNF. Exercise may also aid in reduction of endogenous corticosteroids and pro-inflammatory cytokines, decrease oxidative stress, preserve brain volume, improve vascularization and blood flow, and increase hormones beneficial to neural structure and function. Regular exercise can improve depression and overall distress in patients with brain tumors. Exercise related improvements in mood, reduced stress, cancer-related fatigue, and sleep disruption may indirectly benefit cognitive functioning particularly attention and memory consolidation.

When considering exercise for patients with brain tumors, it is important to address safety concerns, especially for those who are acutely ill or actively undergoing treatment. The American College of Sports Medicine (ACSM) states, "exercise testing and prescription are best done by exercise professionals and physical therapists in consultation with the cancer care team." The American Cancer Society (ACS) recommends cancer survivors take part in regular physical activity (with consultation of cancer team and exercise professional), avoid inactivity and return to normal daily activities as soon as possible, aiming to exercise at least 150 min per week, and include strength training at least 2 days per week (cancer.org.).

Meditation/Mindfulness Based Stress Reduction

Though mindfulness based stress reduction is not extensively studied in the brain tumor population, it shows great benefit in reducing negative psychological stress effects on neurogenic inflammation. Mindfulness practice improves attentional capacity and executive functioning through activation of the cingulate cortex. Studies demonstrated both short-term and sustained cognitive improvement.

Mood and Behavior Management

Depression and anxiety are commonly seen in the brain tumor population and negatively influence cognition. Problematic psy-

chiatric symptoms may be difficult to distinguish from cognitive impairment with normative grieving, expected physiological effects of the tumor and related treatments such as fatigue, loss of appetite, or sleep disruption. The subtly progressive (rather than dramatic) nature of these mood changes may further delay symptom detection. Psychologists and other mental health providers can help patients learn more effective coping strategies, and how their thoughts, feelings, and behaviors act together to contribute to their distress. Further evaluation of possible psychotropic medication may also be beneficial.

For patients with more severe and difficult to manage behavioral issues, such as disinhibition and agitation, it is important to consider psychotropic medications and/or psychiatry consultation. Further, referrals to rehabilitation professionals for specialized caregiver training and support regarding de-escalation and behavior modification may be useful. In milder cases, cognitive rehabilitation can re-teach problem-solving, and increase awareness and self- monitoring. In more severely impaired individuals, environmental restructuring is indicated (e.g. creating a daily routine with alarms and written cues, linking behaviors together that occur naturally such as medication and meals, reducing environmental stimulation such as lowering light and sound, etc.). For non-verbal individuals, it is important to track issues regarding untreated pain and other irritants.

De-escalation strategy: the four D's

- Delay: "I want some time to consider what you are saying, let's talk about it later"
- Distract: go for a walk or suggest another activity
- De-personalize: realize the attacks are more than likely part of the disorder, not personal
- Detach: get support to avoid taking things personally and getting upset

Sleep and Fatigue Management

Sleep disruption and fatigue often exacerbate cognitive difficulties, especially attention, concentration, learning, and memory. Optimizing sleep hygiene, managing emotional stressors, increas-

ing exercise, and considering pharmacologic sleep aids should be considered. Exercise has particularly been associated with improved sleep and reducing cancer related fatigue. Utilizing fatigue management strategies, such as pacing, avoiding sensory overstimulation, can help to improve energy and stamina. Patients who have concurrent mood and sleep issues may particularly benefit from behavioral treatment such as cognitive behavioral therapy for insomnia (CBTi). In some cases, evaluation for obstructive sleep apnea and circadian rhythm issues may additionally yield therapeutic effects.

Anticipatory guidance for managing mood and sleep

- Establish a bedtime routine with winding-down activities
- Refrain from stimulating activities before bed (e.g. screen exposure, emotionally triggering material, etc.)
- Limit caffeine later in the day
- Avoid lying in bed awake for extended periods of time
- Encourage daily pleasurable and meaningful activities
- Increase social connection (e.g. talk to friends, support group, engage in counseling)
- Maintain consistent physical activity
- Encourage relaxation and meditation

Pharmacologic Interventions

Several medications used in management of attention disorders or dementia, have been investigated for safety and efficacy in cognitive management of brain tumor patients and are discussed below (Table 12.3).

Methylphenidate

Methylphenidate is a dopaminergic and noradrenergic agonist approved for treatment of attention deficit hyperactivity disorder. It is a CNS stimulant that has demonstrated improvement in attention and processing; with particular efficacy in long-term survivors of childhood cancers treated with either radiotherapy or

Table 12.3 Pharmacologic management of cognition in brain tumor patients

Treatment	Indication	Starting dose and goal dose	Toxicities
Methylphenidate	Slowed processing speed, executive dysfunction, fatigue	5 mg to titrate up to ~40 mg daily in divided doses	Insomnia Palpitations Appetite suppression
Modafenil	Slowed processing speed, executive dysfunction, fatigue	100 mg daily to titrate up to 200 mg daily	Appetite suppression
Donepezil	Preservation of verbal memory and concentration with radiation	5 mg daily to increase to 10 mg daily	GI toxicity
Memantine	Preservation of verbal memory, executive function and processing speed with radiation	20 mg daily	GI toxicity

chemotherapy. In an adult clinical trial, patients with primary brain tumors who were treated with radiotherapy ± chemotherapy and received methylphenidate at 10 mg or 18 mg twice daily for 4 weeks demonstrated improvement in processing speed and executive function. It should be noted that findings were in patients who were actively on therapy; therefore, improvements may be secondary to treatment response rather than methylphenidate.

Methylphenidate starts at a lower dose and is titrated slowly—starting at 5 mg daily with titration up to 40 mg daily in divided doses for efficacy. Common toxicity includes insomnia, palpitations, decreased appetite, and dependency. Recommend close monitoring for patients with active seizures as it may lower seizure threshold.

Modafenil

Modafenil decreases GABA in hypothalamus responsible for sleep-wake cycle regulation (approved for treatment of narcolepsy). In a study randomizing patients on active treatment to modafinil 200 mg daily versus methylphenidate, there was significant improvement in processing speed, executive function, and fatigue. However, as discussed above with methylphenidate, this study did not include a placebo to account for possible improvements secondary to treatment response.

Modafenil is often well-tolerated and is started at 100 mg daily with titration up to 200 mg daily and can be considered in patients with contraindications for methylphenidate. The most common toxicity is decreased appetite and weight loss.

Donepezil

Donepezil is an acetylcholinesterase inhibitor approved in Alzheimer's disease and used in primary brain tumor patients undergoing radiotherapy to preserve concentration and memory. Patients treated with donepezil 10 mg improved in verbal memory and concentration after 24 weeks. The long-term use of donepezil is unknown as most trials stopped treatment after 24 months. The timing of use is unknown with either concurrent radiation or following radiation.

The recommended starting dose of donepezilt 5 mg daily, which can be increase to 10 mg daily. Donepezil is generally well tolerated with GI toxicity as the most common side effect.

Memantine

Memanatine is a NMDA antagonist neuroprotectant and approved for Alzheimer's disease, Lewy body dementia, and other types of dementia. Memantine was studied in a placebo-controlled trial in brain metastases patients receiving radiation. At 20 mg daily for 24 weeks, there was less decline in verbal memory, executive function, and processing speed compared to placebo, though the

dropout rate was high in this clinical trial. Additional studies support preserving cognition by combining memantine with whole brain radiation with hippocampal avoidance.

Individuals with brain tumors who meet criteria for clinical depression and/or anxiety may consider antidepressants such as selective serotonin reuptake inhibitors (SSRIs). Though SSRIs may not directly improve cognition, effective mood management can lead to improvement in cognitive symptoms, as discussed above. Similarly, antipsychotics may improve HROL in patients with significant behavioral problems.

Consideration for Cognitive and Behavioral Changes at End of Life

As patients near the end of their life, issues such as acute confusion, reduced communication, and diminished memory can be quite distressing for both patients and caregivers. In general, reducing environmental stimulation (e.g. low light and noise, limited visitation), planning activities when the patient is most alert, and providing calm reassurance (as needed) are helpful strategies. Rapid changes can magnify confusion, and consistency in care providers, talking through tasks with simple instructions (such as helping with ADLs), and maintaining a consistent daily routine help to minimize confusion. Other strategies include ensuring sensory adaptation for hearing and vision, keeping instructions simple with frequent repeating, and using diversional activities (e.g. folding items, looking at pictures, etc.). Antipsychotics such as olanzapine, haloperidol, or quetiapine may be helpful toward the end of life for effective behavior management for treatment of agitation and disorientation.

In conclusion, patients with CNS involvement of their malignancy commonly experience cognitive impairment from direct injury from tumor or radiotherapy/chemotherapy, and may be exacerbated by seizures, medications, mood and sleep disturbances. These symptoms can significantly impair their quality of life and are important to identify and treat with a combination of both non-pharmacologic and pharmacologic interventions.

Suggested Reading

Coomans MB, van der Linden SD, Gehring K, Taphoorn MJB. Treatment of cognitive deficits in brain tumour patients: current status and future directions. Curr Opin Oncol. 2019;31(6):540–7.

Cormie P, Nowak AK, Chambers SK, Galvão DA, Newton RU. The potential role of exercise in neuro-oncology. Front Oncol. 2015;5:85.

Correa DD, DeAngelis LM, Shi W, Thaler HT, Lin M, Abrey LE. Cognitive functions in low-grade gliomas: disease and treatment effects. J Neurooncol. 2007;81(2):175–84.

Johnstone B, Stonnington HH, editors. Rehabilitation of neuropsychological disorders: a practical guide for rehabilitation professionals. 2nd ed. New York: Psychology Press; 2009.

Karschnia P, Parsons MW, Dietrich J. Pharmacologic management of cognitive impairment induced by cancer therapy. Lancet Oncol. 2019;20(2):e92–e102.

van Lonkhuizen PJC, Klaver KM, Wefel JS, Sitskoorn MM, Schagen SB, Gehring K. Interventions for cognitive problems in adults with brain cancer: a narrative review. Eur J Cancer Care. 2019;28(3):e13088.

Madhusoodanan S, Ting MB, Farah T, Ugur U. Psychiatric aspects of brain tumors: a review. World J Psychiatry. 2015;5(3):273.

Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol. 2017;13(1):52–64.

National Institute for Clinical Excellence, Great Britain, and National Health Service. Improving supportive and palliative care for adults with cancer: the manual. London: National Institute for Clinical Excellence; 2004.

Ng JCH, See AAQ, Ang TY, Tan LYR, Ang BT, King NKK. Effects of surgery on neurocognitive function in patients with glioma: a meta-analysis of immediate post-operative and long-term follow-up neurocognitive outcomes. J Neurooncol. 2019;141(1):167–82.

Parsons MW, Hammeke TA, editors. Clinical neuropsychology: a pocket handbook for assessment. 3rd ed. American Psychological Association; 2014.

Robinson GA, Biggs V, Walker DG. Cognitive screening in brain tumors: short but sensitive enough? Front Oncol. 2015;5:60.

Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3(3):159–68.

van den Bent MJ, Wefel JS, Schiff D, Taphoorn MJB, Jaeckle K, Junck L, Armstrong T, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011;12(6):583–93.

Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. Br J Cancer. 2004;90(9):1691–6.

Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin. 2015;65(2):123–38.

Zeng Y, Dong J, Huang M, Zhang J-E, Zhang X, Xie M, Wefel JS. Nonpharmacological interventions for cancer-related cognitive impairment in adult cancer patients: a network meta-analysis. Int J Nurs Stud. 2020;104:103514.

Zimmer P, Baumann FT, Oberste M, Wright P, Garthe A, Schenk A, Elter T, et al. Effects of exercise interventions and physical activity behavior on cancer related cognitive impairments: a systematic review. Biomed Res Int. 2016;2016:1820954.

Weyer-Jamora C, Brie MS, Luks TL, Smith EM, Hervey-Jumper SL, Taylor JW. Postacute cognitive rehabilitation for adult brain tumor patients. Neurosurgery. 2021;89(6):945–53. https://doi.org/10.1093/neuros/nyaa552. PMID: 33586764; PMCID: PMC8600173.

Weyer-Jamora C, Brie MS, Luks TL, Smith EM, Braunstein SE, Villanueva-Meyer JE, Bracci PM, Chang S, Hervey-Jumper SL, Taylor JW. Cognitive impact of lower-grade gliomas and strategies for rehabilitation. Neurooncol Pract. 2020;8(2):117–28. https://doi.org/10.1093/nop/npaa072. PMID: 33898046; PMCID: PMC8049427.

Chemotherapy-Related Toxicities and Management

13

Haroon Ahmad and David Schiff

Chemotherapies used in the treatment of brain tumors vary widely, ranging from oral outpatient regimens for gliomas to intensive inpatient courses for less common brain tumors. To cover all chemotherapy-induced toxicities in neuro-oncology would be an arduous task. Here, we concentrate on toxicities of the most common chemotherapies for brain tumors.

Generally, these more common chemotherapies are well-tolerated and have reasonable logistics of administration. The traditionally challenging regimen of procarbazine, lomustine (CCNU), and vincristine (PCV) is being less preferentially used, in favor of temozolomide (TMZ). Another set of tumor drugs with complex toxicity profiles, the checkpoint inhibitors (CPIs), have yet to become a major component in brain tumor management.

We will review the most common regimens with their frequent and infrequent adverse effects. Unique traits and clinical pearls are included for each therapy. Common side effect management is

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discussed afterwards. The management of TMZ is discussed most extensively as a neuro-oncologist should be adept in navigating a patient through this bread-and-butter regimen. This chapter is not a comprehensive reference on toxicities, rather a clinically oriented tip sheet.

Temozolomide

TMZ is the most commonly used chemotherapy in the management of brain tumors. Overall, it is a well-tolerated oral agent that is conveniently taken at home. For both low- and high-grade gliomas, it is standard of care. TMZ is less commonly used in other refractory brain tumors.

Dosing can vary from 75 mg/m^2/day during the induction phase of glioma treatment to 200 mg/m^2 for 5 days every 28 days in adjuvant cycles. Dose reductions are usually made by 25–50 mg/m^2 in the setting of leukopenia or thrombocytopenia, or with significant clinical side effects.

The most commonly experienced side effects are nausea (53%), vomiting (42%), headache (41%), fatigue (34%), and constipation (33%) [1]. Nausea can be tempered by administering ondansetron 30–60 min prior to taking the TMZ, which is standard of care. Symptoms can be further mitigated by taking the TMZ 30–60 min before bedtime. Other anti-nausea medications such as promethazine and dexamethasone can be used and will be discussed further. Patients should be advised that mild intermittent nausea is expected, but any vomiting or persistent nausea should be discussed with the neuro-oncology team. Patients benefit from proactive bowel regimens. This should be emphasized in those with prior history of motility issues. Over-the-counter regimens using typical stool softeners and motility agents (docusate and senna) are effective. As-needed (PRN) polyethylene glycol can be added for refractory constipation, and occasionally a suppository may be needed. Hydration should be encouraged throughout.

Anorexia is common, occurring in 9% of patients [1]. Tapered weight should be recorded at each visit and tracked over time.

Corticosteroids can stimulate appetite, but are not specifically used for this indication. Management of weight loss is discussed further in the next section.

Fatigue varies widely. Some patients are able to continue working throughout adjuvant cycles, while others require dose reductions due to impact on quality of life. Approximately 4% of patients experience grade 3–4 fatigue [1]. Other factors causing fatigue must also be taken into consideration such as patients' recent radiation therapy, mood disorders, or adjustment disorders. Concurrent medications such as anti-epileptic drugs (AEDs) may also contribute. A few interventions can be used to alleviate fatigue including supplementation with dexamethasone, structured physical activity, regulated sleep patterns. Stimulant medications are uncommonly used.

During the concurrent phase of radiation and chemotherapy: these constitutional symptoms tend to peak around week 4–5 of therapy. Similarly, during the adjuvant cycles, patients often remark that their most difficult days are on days 4–5 of the cycle. However, each patient reacts differently, and some report their worst week after they have completed the TMZ dose.

Completed blood count (CBC) with cell differential and comprehensive metabolic panel (CMP) work should be checked weekly during the induction phase. During the adjuvant phase, labs should be checked monthly around the nadir, recommended as "within 48 h of day 22" [1]. Lymphopenia, Neutropenia, and thrombocytopenia can occur with TMZ with incidences of 55%, 14%, and 19% for grade 3–4, respectively [1]. The nadir for these values typically occur about 3–4 weeks after administration, and this is the ideal time to check labs. Absolute neutrophil count (ANC) should be monitored and therapy paused for values less than 1000. Granulocyte colony-stimulating factors (GCSF) are typically not used, unless neutropenia is severe or neutropenic fever develops. Lymphocytes should also be closely monitored, with pneumocystis pneumonia (PJP) prophylaxis initiation with absolute lymphocyte count (ALC) consistently below 600. It should be noted that the FDA package insert recommends PJP prophylaxis for the entire induction phase of TMZ, but not all neuro-oncologists find this necessary as the prophylactics them-

selves have potential side effects. PJP prophylaxis choices are discussed in the following section. Thrombocytopenia with platelet values less than 100,000 should delay the next cycle of therapy. Exceptions can be made based on which way a platelet value is trending. TMZ dose should be titrated down by 25–50 mg/m^2 for grade 3–4 neutropenia or thrombocytopenia. Specific management of neutropenia, thrombocytopenia, and lymphopenia is also discussed in the next section.

TMZ has no specific drug-drug interactions, though adverse effects can be additive with other medications, such as thrombocytopenia induced by certain AEDs.

TMZ is a teratogen; both men and women of child-bearing age should be strongly advised to use birth control during the therapy. TMZ can cause long term azoospermia and infertility. Patients should consider spermatocyte banking or oocyte retrieval prior to the initiation of treatment. It is critical that these topics be discussed with appropriate patients at the time of consent.

PCV: Procarbazine, Lomustine (CCNU), Vincristine

These medications will be discussed together as the traditional glioma regimen uses them in tandem. The PCV regimen is still considered standard of care for patients with oligodendroglioma and is used in recurrent gliomas. PCV therapy is recommended for about 6–7 cycles, but patients sometimes do not complete therapy due to toxicity. It should also be noted that the three-drug regimen is also logistically complicated.

Procarbazine is administered for 14 consecutive days during days 8–21 of each cycle. It is generally well-tolerated but can cause mild nausea, fatigue, and anorexia in some. Procarbazine has the potential for interacting with several medications and foods, as a monoamine oxidase (MAO) inhibitor. Tyramine-containing foods should be avoided, such as red wines, yogurt, and cheese. It can also cause a disulfiram-like reaction with alcohol. There is also a rare systemic allergic

syndrome which can lead to dangerous angioedema. An early, and more common, sign of this is urticaria and the drug should be discontinued. Finally, the MAO inhibition could cause dangerous surges in serum catecholamine levels if taken with sympathomimetic drugs. Notably, selective serotonin reuptake inhibitors should be avoided to reduce the risk of serotonin syndrome [2].

Lomustine (CCNU) is given on day one of the PCV cycle. In addition to nausea and vomiting, lomustine causes more severe leukopenia and thrombocytopenia with nadir of 5–6 weeks. In the PCV regimen, this occurs around the same time as the procarbazine nadir and the effect can be additive. Lomustine is a nitrosourea, with potential for pulmonary fibrosis. This will be discussed in the carmustine section.

Vincristine is an intravenous medication infused on days 8 and 29 of the PCV cycle. Vincristine is well-known for the risk of producing peripheral neuropathy. This adverse effect is dose dependent and can range from mild peripheral dysesthesias, to severe sensorimotor neuropathy causing gait ataxia and disability. It is critical to assess neuropathic symptoms at each visit, and to conduct a focused neurological exam. Areflexia can be an early sign and cessation of vincristine should be considered. Vincristine is a vesicant and must be administered by vesicant certified providers; irreversible skin necrosis can occur if administered incorrectly [3].

Each of PCV's three components are teratogens and can cause decreased fertility. As with TMZ, birth control and sperm/oocyte banking discussions are prudent with all appropriate patients at the time of consent.

PCV is a relatively toxic and complicated regimen. The combined risk of grade 3–4 anemia, neutropenia, and thrombocytopenia are 7%, 10%, and 28%, respectively [4]. The hematologic effects, diet restrictions, dosing logistics, and risk of neuropathy have caused it to be slowly supplanted by TMZ. Finally, it should be mentioned that many centers now just use "PC" regimen for gliomas, meaning that vincristine is left out due to side effect profile and lesser perceived efficacy in gliomas.

Carmustine (BCNU)

BCNU is another nitrosourea chemotherapy used for the treatment of gliomas. It is typically administered intravenously but is also FDA approved as a biodegradable implant placed during tumor surgery. When used intravenously, it has a side effect profile similar to lomustine.

Nitrosourea-induced interstitial pulmonary fibrosis (PF) is a rare but serious complication. Most cases onset within 3 years but it can manifest years later. In a study of 17 pediatric brain tumor patients treated with carmustine: 6 (35%) died within 3 years due to PF and another four (23.5%) died within the next 13 years [5]. Another 6 (35%) of the surviving patients had clinically evident PF at 25 year follow up [5]. The risk of PF is dose-dependent and most cases reported cumulative doses of 1110 mg/m^2 and 1400 mg/m^2 for lomustine and carmustine, respectively [6, 7]. Patients should have baseline pulmonary function tests (PFTs) including diffusing capacity of carbon monoxide (DLCO). The PFTs should be repeated as the cumulative dose approaches 1000 mg/m^2 or if any pulmonary symptoms develop. Some guidelines recommend checking more regularly, especially in patients with pre-existing pulmonary disease. Worsening of >10% in PFTs or DLCO should necessitate further workup and cessation of the drug.

Nitrosoureas uncommonly cause renal or hepatic injury. A comprehensive metabolic panel is usually done with lab tests prior to each dose and liver function tests (LFTs) should be tracked.

Bevacizumab

Bevacizumab is a monoclonal antibody and is used to treat recurrent gliomas and radiation necrosis. Standard dosing for glioblastoma is 10 mg/kg every 2 weeks, though alternative doses ranging from 7.5 to 15 mg/kg every 2–3 weeks have been used. For the most part it is well tolerated, with patients noting mild fatigue.

Hypertension (HTN) is a common side effect of bevacizumab, occurring most frequently in patients with preexisting HTN. Generally, this can be managed with titrations in patients' anti-HTN medication dosage. It is helpful to have a primary care provider involved in these decisions. Blood pressure readings must be below 150/90 for each administration.

Proteinuria and eventual nephrotic syndrome are complications of bevacizumab. It is important to assess a baseline creatinine clearance prior to starting treatment and a screening urine dipstick test prior to each administration. Dipstick readings of 2+ or greater should lead to a 24-h urine collection. If >2 g of protein is collected over 24 h, bevacizumab should be suspended, and it may be helpful to involve nephrology [8].

Hemorrhage and coagulopathy are both risks of bevacizumab. History of ischemic stroke, DVTs, MI/angina, or petechial intratumoral hemorrhage are not contraindications for use, but patients with recent ischemic events should be approached with caution. In a study of patients treated with bevacizumab: grade 3–4 arterial thrombotic events occurred in 2.6% of patients, compared to 0.8% in control arms [8]. Posterior reversible leukoencephalopathy (PRES) is another reported risk, but clinical studies reported an incidence of <0.1% [8].

For patients undergoing surgical procedures, bevacizumab should be held for 3–4 weeks. For dental procedures above the gumline, it is generally okay to proceed. Finally, bevacizumab is teratogenic. However, there is no human data on the long-term effects of male or female fertility.

Irinotecan

Though irinotecan is not yet well-proven in its efficacy in recurrent gliomas, it is occasionally used. It is administered as an infusion every 2 weeks, often combined with bevacizumab. The most common unique side effect is diarrhea. It has been shown to occur in up to 88% of patients, with 31% reporting grade 3–4 severity [9]. Diarrhea can occur within 24 h of administration, often as a cholinergic-like toxidrome: with rhinorrhea, increased salivation,

sweating, and flushing. More commonly, diarrhea occurs days to weeks after the infusion, without the cholinergic symptoms. It should be treated with scheduled antimotility agents (if infectious etiology is not considered,) such as loperamide or atropine. Hydration and electrolytes should be monitored if diarrhea is persistent. Cytopenia, fatigue, and nausea are also possible side effects, but generally less commonly. Labs should be checked prior to each infusion.

Irinotecan is metabolized by cytochrome P450 and inducers and inhibitors should be avoided. It is teratogenic but has not been shown to affect long term fertility.

Checkpoint Inhibitors

CPIs, including PD-1, PD-L1, and CTLA-4 inhibitors are a newer class of immunotherapeutics which are now widely used in oncology. Neuro-oncologists will most commonly encounter them when treating patients with brain metastases. Their benefit is not yet established in gliomas.

By definition, CPIs release the immune system to cause an inflammatory response within the body. This mechanism leads to end-organ toxicity: meningitis, dermatitis, hepatitis, hypophysitis etc. The toxicity is often reversible if identified early enough. Drug cessation and treatment with corticosteroids usually is sufficient. In refractory cases intravenous immunoglobulin and plasmapheresis can be used.

Management of Specific Chemo-Induced Side Effects

Nausea/Vomiting

Pre-administering ondansetron 30–60 min prior to most chemotherapies is helpful in dampening most nausea. Other PRN abortives can be used including prochlorperazine or metoclo-

pramide to good effect. If nausea is affecting quality of life, or vomiting is frequent, chemotherapy dose adjustments should be considered. Other useful medications included in guidelines are often overlooked, including dexamethasone, olanzapine, benzodiazepines, aprepitant, and cannabinoids. Many of these agents can treat more than one of the patient's symptoms.

Weight Loss

Weight loss can be due to true anorexia from chemotherapy or from sensation of nausea. Patient weight should be tracked at each visit and early intervention from nutrition/dietary consultants should be considered if a patient has lost 5–10% of their baseline weight. Dexamethasone can be used to stimulate appetite by improving gut motility. Patients occasionally complain of a metallic taste, though this is often due to the radiation therapy and hopefully will dissipate with time. Dieticians can often recommend interventions to deal with this metallic sensation such as using plastic utensils or coffee-flavored foods. Constipation should also be assessed and managed.

Fatigue

Fatigue and malaise may be the biggest contributor to a patient's inability to return to work. As with the other side effects discussed, fatigue can be multifactorial. A combination of chemotherapy, radiation therapy, mood disorders, and sleep patterns can contribute. Adrenal insufficiency should be assessed in patients with recent corticosteroid use. Hydrocortisone supplementation is needed for morning cortisol levels less than 10, with possible endocrinology involvement. Pituitary insufficiency should also be assessed in patients who have received radiation therapy that involves that region of the brain.

Peripheral Neuropathies

Neuropathies from vinca alkaloids (vincristine) and platinum-based chemotherapies are common and are dose dependent. They can manifest as loss of sensation, dysesthesias, sensory ataxias, or less commonly autonomic neuropathies. Burning, painful neuropathies are more treatable than loss of sensation. Gabapentin and pregabalin are widely used, though can cause lethargy. Duloxetine has been shown to improve pain and quality of life in chemotherapy-induced painful neuropathy [10].

Cytopenia and Bone Marrow Suppression

CBC with differential should be monitored frequently during any chemotherapy regimen and an attempt should be made to draw labs around the nadir for each drug. An ANC of <1500 cells/mm^3 is considered mild and a dose/cycle modification should be considered. Moderate neutropenia with ANC of <1000 may necessitate pausing therapy and a dose adjustment. For ANC values <500, neutropenic precautions should immediately be instituted. GCSF like filgrastim and pegfilgrastim are not typically used as glioma therapy is considered palliative but can be considered for severe neutropenia.

Lymphocytes are often depleted early in glioma therapy. Patients with ALCs consistently below 700 cells/mm^3 should be started on PJP prophylaxis. Trimethoprim/sulfamethoxazole is commonly used on a Monday-Wednesday-Friday schedule. Daily atovaquone or monthly pentamidine inhalations can be considered for patients with sulfa drug allergies.

Platelet counts are also checked routinely and are depleted by the more toxic regimens. Thrombocytopenia of <100,000 can be a warning to consider delaying the next cycle and/or modify the dose. Levels <50,000 should halt treatment, and <10,000 necessitates platelet transfusions.

Bone marrow suppression is a long-term risk for procarbazine, nitrosoureas, and even TMZ. Delayed or unrecovered CBC counts should prompt consideration for hematologic evaluation and possible bone marrow biopsy.

There is a risk of developing secondary malignancies with these chemotherapies. Unfortunately, the typical glioma patient does not have a life expectancy lending towards a significant absolute risk. One study cited 2.9–13 cases of secondary hematologic malignancies per 1000 patient years, in patients treated for glioma with various combinations of alkylating agents [11]. The secondary malignancy risk of chemotherapy should not be a major factor in most neuro-oncology patient management.

Teratogenic Effects and Decreased Fertility

All the chemotherapies discussed are teratogenic and both male and female patients must be on a consistent form of birth control. The potential risk of post-treatment infertility must also be discussed at the time of consent. This is a difficult decision for many patients as sperm and egg banking programs are not usually covered by insurance.

Conclusion

Glioma chemotherapy toxicity is tolerable for most patients, which is a critical consideration given the palliative nature of these treatments. A neuro-oncologist must be adept in navigating the dosage and timing of these drugs in order to preserve quality of life, especially in patients with glioblastoma (Table 13.1).

Table 13.1 Common neuro-oncology chemotherapies and toxicities

	Common toxicity (>10%)	Less common toxicity	Lab nadir	Dosing and reduction	Pregnancy and fertility	Interactions	References
Temozolomide	Fatigue, nausea, vomiting, headaches, constipation	Neutropenia, lymphopenia, thrombocytopenia	3–4 weeks	75 mg/m^2 in induction phase. 150–200 mg/m^2 in adjuvant cycles. Decrease by 25–50 mg/m^2 for toxicity	Pregnancy category D. Can decrease male fertility	None significant	[1]
Procarbazine	Nausea, vomiting, leukopenia, anemia	Myelosuppression, serotonin reaction, hypertensive crisis, secondary malignancies (rare)	3–6 weeks	100 mg/m^2/day. Dose reductions in 50 mg increments due to standard tablet dose	Pregnancy category D. Azoospermia and infertility reported with procarbazine in human trials (though combined with other therapies)	Avoid MAO inhibitors (e.g., SSRIs) Avoid tyramine-containing foods and alcohol	[2]

Vincristine	Peripheral neuropathy	Constipation, ileus, skin necrosis (vesicant)	None significant	1.4 mg/m^2 IV, dose cap of 2 mg	Pregnancy category D	Metabolized by and weakly induces CYP3A4 enzyme	[3]
Lomustine	Neutropenia, lymphopenia, nausea, vomiting	Pulmonary toxicity, renal toxicity	WBC 5–6 weeks, Platelets 4 weeks	80–110 mg/m^2 each cycle. Reduce to 70% for hematologic toxicity	Pregnancy category D. Affected male fertility in preclinical studies	None significant	[7]
Carmustine (intravenous)	Nausea, vomiting, facial flushing, neutropenia, lymphopenia, thrombocytopenia	Pulmonary toxicity, hepatic toxicity	WBC 5–6 weeks, Platelets 4 weeks	200 mg/m^2 IV each cycle	Pregnancy category D. Affected male fertility in preclinical studies	None significant	[6]

(continued)

Table 13.1 (continued)

	Common toxicity (>10%)	Less common toxicity	Lab nadir	Dosing and reduction	Pregnancy and fertility	Interactions	References
Bevacizumab	Fatigue, hypertension, proteinuria, impaired wound healing	Nephrotic syndrome, venous or arterial clots, PRES, bowel perforation	None significant	10 mg/kg every 2 weeks for gliomas 7.5 mg/kg every 3 weeks for 4 doses, for radiation necrosis	Pregnancy category C. May impair fertility but may be reversible per preclinical data	None significant	[8]
Irinotecan	Diarrhea, nausea, vomiting, weakness	Leukopenia, nausea, vomiting, anemia	WBC, about 2 weeks	125 mg/m^2 every 2 weeks	Pregnancy category D	Metabolized by CYP3A4	[9]

This table is not meant to be comprehensive

MAO Monoamine oxidase, *SSRI* Selective Serotonin Reuptake Inhibitor, *CYP3A4* Cytochrome P450 3A4 enzyme, *CP450* Cytochrome P450 enzyme

References

1. Merck IWS, NJ, USA. Temodar (Temozolomide) [Package Insert]. US Food and Drug Administration. Revised 2015.
2. Sigma-Tau Pharmaceuticals IG, MD. Matulane (Procarbazine) [Package Insert]. US Food and Drug Administration. Revised 2008.
3. Hospira ILF, IL. Vincristine sulfate [Package Insert]. US Food and Drug Administration. Revised 2013.
4. Jutras G, Belanger K, Letarte N, et al. Procarbazine, lomustine and vincristine toxicity in low-grade gliomas. Curr Oncol. 2018;25(1):e33–9.
5. O'Driscoll BR, Hasleton PS, Taylor PM, Poulter LW, Gattameneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med. 1990;323(6):378–82.
6. Bristol-Myers Squibb Company P, NJ. BiCNU (Carmustine) [Package Insert]. US Food and Drug Administration. Revised 2007.
7. NextSource Biotechnology M, FL. Gleostine (Lomustine) [Package Insert]. US Food and Drug Administration. Revised 2014.
8. Genentech ISSF, CA. Avastin (Bevacizumab) [Package Insert]. US Food and Drug Administration. Revised 2009.
9. Pfizer Injectables. NY N. Camptosar (Irinotecan) [Package Insert]. US Food and Drug Administration. Revised 2014.
10. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309(13):1359–67.
11. Momota H, Narita Y, Miyakita Y, Shibui S. Secondary hematological malignancies associated with temozolomide in patients with glioma. Neuro Oncol. 2013;15(10):1445–50.

Radiation Related Toxicities and Management

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Sara J. Hardy and Michael T. Milano

Introduction to Cranial Radiotherapy

Radiotherapy plays an important role in management of many types of brain tumors. Cranial radiotherapy is typically administered form a source outside the patient (external beam radiotherapy or EBRT), delivered via ionizing radiation produced through either radioactive decay (for example, using cobalt-60 in Gamma Knife-based radiosurgery) or acceleration of electrons into a target to produce photons or x-rays (linear accelerators). Proton therapy is a form of particle therapy that can also be used for EBRT [1, 2]. Conventionally fractionated radiation is given in 1.8–2 Gy per fraction. Standard treatment with whole brain radiation therapy (WBRT) (with or without hippocampal sparing) is typically 30 Gy in 10 fractions. Stereotactic radiosurgery delivers high doses of radiation in 1–5 fractions using highly precise delivery systems [2].

In radiotherapy planning, the radiation fields and treatment schedule are optimized to allow appropriate radiation dose to the target while sparing normal tissues. While simple beam arrange-

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ment are often still used in palliative radiation (including WBRT without hippocampal sparing), 3D-conformal radiotherapy and intensity modulated radiotherapy (IMRT) are often used to match the high dose radiation region to the target volume as defined on imaging. Normal tissue structures are also delineated on imaging in order to minimize radiotherapy dose and radiotherapy toxicities [2]. Different normal tissues have different sensitivities to radiation, and radiotherapy tolerance guidelines for some normal tissues are summarized in the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) reviews [3].

Radiotherapy-Related Toxicity in the Central Nervous System (CNS)

Acute Cranial Radiation Side Effects

Acute side effects occur days to weeks after irradiation [4]. Aside from fatigue, the majority of acute side effects from cranial radiotherapy can be predicted from the dose distribution. Worsening intracranial edema can occur in the high dose region; this can cause headaches, nausea/vomiting, altered mental status, or worsening of focal neurologic symptoms. Less frequent symptoms include vertigo or seizures. Symptoms are typically transient and managed with corticosteroids [5]. If the acoustic structures are in the radiation field, patients can experience serous otitis media due to eustachian tube dysfunction, occasionally requiring over-the-counter decongestants. This will usually resolve several weeks after completion of radiotherapy, but if persistent, can be treated using myringotomy [6]. Alopecia can occur over the whole scalp with WBRT or in patches with partial brain radiotherapy. Permanent hair loss is more common with higher radiation doses [7]. If the parotid gland is irradiated, patients can experience parotid swelling, dry mouth, and tenderness consistent with parotitis [8].

Skin may be exposed to radiation incidentally during radiotherapy of intracranial lesions, particularly superficial tumors,

potentially causing radiotherapy-related dermatitis [4]. Risk of dermatitis is significantly impacted by systemic therapy. For example, concurrent phenytoin and cranial radiation can cause Erythema Multiforme associated with Phenytoin and Radiation Therapy (EMPACT) [9]. Concurrent BRAF inhibitors can also lead to grade 3 skin toxicity with cranial radiation [10].

Treatment of cerebellopontine angle tumors such as vestibular schwannomas can rarely cause facial numbness and weakness (92–98% trigeminal nerve preservation and 93–97% facial nerve preservation in a modern series) [11]. Even more rarely, hemifacial spasm, spontaneous, intermittent, and repetitive contraction of the unilateral facial muscle, can occur. Steroids are given to reduce swelling and compression on the facial nerve. Of note, in the general population, hemifacial spasm is most commonly caused by vascular compression of the facial nerve rather than tumor [12]. Hydrocephalus is an uncommon side effect that is seen mainly with SRS for larger cerebellopontine angle tumors. In one series of larger volume vestibular schwannomas between 3 and 4 cm, 5% of patients developed symptomatic hydrocephalus after single-fraction radiosurgery requiring ventricular-peritoneal shunt placement [13].

In adults, the major functional bone marrow sites are the pelvis and the vertebrae [14]. For that reason, craniospinal radiation which treats the meninges, whole brain, spinal cord, and thecal sac, can cause decreased blood counts. Decrease in lymphocytes and neutrophils will be seen initially, then decrease in platelets and erythrocytes [15].

Unrelated to the radiotherapy dose distribution, fatigue and anorexia often occur by the second week of radiotherapy and typically improve by 2 weeks after completion. This is thought to be due to acute inflammation and cytokine production during radiotherapy [4].

Shorter radiotherapy courses like radiosurgery typically cause less fatigue. In a study of acute side effects experienced by patients during radiosurgery or 2 weeks after, one-third of patients had mild to moderate side effects including nausea, dizziness/vertigo, seizures, and new persistent headaches, which were generally self-limited [16].

Late Cranial Radiation Side Effects

Late side effects from radiation occur ≥6 months after radiotherapy. There are multiple etiologies including vascular injury, damage from inflammation, impaired neurogenesis, and production of reactive oxygen species. Multiple factors impact the risk of long-term complications including treated brain volume, radiation dose and fractionation, systemic therapy, surgery, and host factors such as age or history of autoimmune disease [4].

Radiation-Induced Necrosis (Also Called Radionecrosis)

Description: Radionecrosis typically occurs 1–2 years after radiation is completed. Per the QUANTEC review, the risk of radionecrosis with conventionally fractionated radiotherapy is 5% at 5 years for a dose of 72 Gy [4]. This complication is more common with SRS due to the higher dose per fraction and dose heterogeneity within the target. The major factors that predict the risk of radionecrosis from SRS are total dose, fractionation, tumor size, volume of brain receiving 10–12 Gy, and concurrent systemic therapy including HER2 antibodies, EGFR and VEGF tyrosine kinase inhibitors, and immune checkpoint inhibitors [17–19]. Symptoms from radionecrosis are dependent on location in the brain and include seizures, focal neurologic symptoms, headache, nausea, and vomiting, and result from reactive brain edema at the site of necrosis.

Work-up and diagnosis: It can be difficult to differentiate between radionecrosis and tumor progression on structural MRI scans. Perfusion MRI generally shows increased cerebral blood volume in the setting of recurrent tumor compared to radionecrosis; there may be decreased accuracy in the setting of hemorrhage. On diffusion-weighted imaging, recurrent tumor often has lower ADC values than necrosis. With MR spectroscopy, the choline-creatine ratio and choline-N-acetyl aspartate ratio are significantly higher in recurrent tumor than in radionecrosis. FDG-PET has a

sensitivity and specificity for the diagnosis of recurrent tumor of 86% and 22%, but may have false positives in the setting of subclinical seizures [20].

Treatment: The clinical course of radionecrosis is variable. It may be asymptomatic or resolve after a short course of corticosteroids. In patients with radionecrosis who are refractory to corticosteroids or for whom corticosteroids are not a good option, bevacizumab may be considered for treatment (Fig. 14.1). A small randomized clinical trial showed that patients with radionecrosis treated with bevacizumab 7.5 mg/kg every 3 weeks for a total of four doses had improvement either in neurologic symptoms or on imaging [21]. There was also a larger trial that compared bevacizumab 5 mg/kg every 2 weeks for four doses with glucocorticoids in 112 patients with temporal lobe necrosis. Patients with history

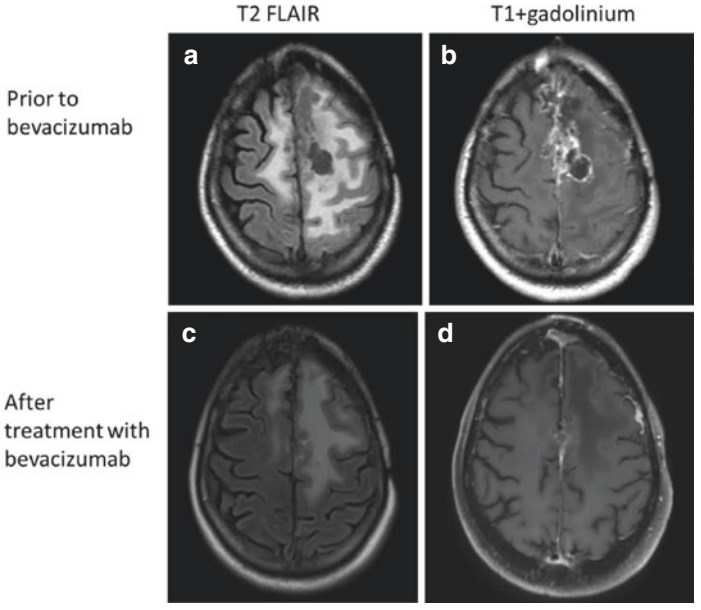

Fig. 14.1 MRI brain for patient with radiation necrosis after radiotherapy (**a**, **b**) before and (**c**, **d**) after treatment with bevacizumab

of bleeding related to radiation or tumor, active CNS hemorrhage, inadequately controlled hypertension, and recent intra-abdominal fistula, perforation or abscess were excluded. The trial showed that patients on bevacizumab had higher radiographic response (66% vs 32%) and more clinical improvement (62% vs 43%) at 60 days with similar recurrence rates at 6 months (29% vs 27%) when compared to corticosteroids. 20% of both groups experienced hypertension. In the bevacizumab arm, one patient had an ischemic stroke and four patients had hemorrhage, while one patient on the glucocorticoid arm had an infection [22]. There is also data for laser interstitial thermal therapy in the treatment of radionecrosis [23]. For severe radionecrosis, surgical resection may be required.

Pseudoprogression

Description: Pseudoprogression refers to a phenomenon seen in 20–30% of patients treated with radiotherapy for high-grade glioma, for whom their first post-radiation MRI (within the first 3 months) shows increased contrast enhancement that eventually subsides without any change in therapy. The mechanism is thought to be transiently increased permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide. This occurs more frequently in patients with a methylated *MGMT* gene promoter [24] Of note, high grade glioma patients on combination lomustine and temozolomide were noted to have prolonged and increased late pseudoprogression in a randomized phase 3 clinical trial [25].

Work-up and diagnosis: Typically, the contrast enhancement that characterizes this finding will resolve on subsequent MRIs.

Treatment: No treatment is typically required, though corticosteroids may be used for management of neurological symptoms. In cases, where patients become corticosteroid-dependent or have significant toxicities from corticosteroids, bevacizumab can be considered.

Eyes and Optic Pathways

Radiation can impact multiple structures within the eyes and optic pathways including the optic nerves.

Optic Neuropathy

Description: Optic neuropathy from radiation can be due to two clinical syndromes that present with different symptoms. Anterior ischemic optic neuropathy results from vascular injury to the distal portion of the optic nerve. Patients experience gradual painless visual loss 2–4 years after completing radiotherapy. Retrobulbar optic neuropathy is caused by damage to the proximal segments of the optic nerve. Visual field deficits and rapidly progressive vision loss, which are sometimes associated with ocular, periorbital, or retrobulbar pain. These are frequently due to disk abnormalities. Both types of injury are correlated with increasing patient age, total radiotherapy dose >59 Gy, and daily fraction size >2 Gy [4]. Systemic therapy may impact the risk of optic neuropathy from radiation, and there have been reports of late onset optic neuropathy in patients on bevacizumab [26].

Work-up and diagnosis: Work-up should include a clinical eye exam including fundoscopic exam to confirm optic neuropathy. MRI brain is also helpful. Lumbar puncture can be considered if inflammatory or neoplastic cause is suspected [27].

Treatment: Hyperbaric oxygen, corticosteroids, and anticoagulation have been tried with limited efficacy.

Ocular Neuromyotonia

Description: Ocular neuromyotonia is characterized by tonic spasms of extraocular muscles innervated by a specific extraocular nerve that occurs during sustained eccentric gaze (hyperaction of the muscle). It can occur after radiation to the pituitary or skull base (involving the ocular motor nerves), nerve compres-

sion due to tumor/vasculature, or in the setting of myasthenia gravis and thyroid eye disease. The etiology may be nerve demyelination and ephaptic transmission vs calcium channel dysfunction [28].

Work-up and diagnosis: Ocular neuromyotonia should be considered in differential for transient recurrent diplopia. Ask the patient to look in a specific direction for several seconds and see if this elicits a transient abnormality in eye movements. Patients with suspected ocular neuromyotonia should get an MRI brain if there is not a clear cause. The differential for diplopia also includes stroke, intracerebral aneurysms, brain tumors, and giant cell arteritis [27].

Treatment: Episodes can be treated with carbamazepine or lacosamide.

Other Eye Disorders

Description: Radiation can damage different parts of the eye and orbit. Cataracts are the most common effect to the lens. Radiation typically causes posterior subcapsular cataracts. Radiation retinopathy occurs at ≥40 Gy and develops 6 months to 3 years post-treatment. Corneal ulceration can occur with doses ≥40 Gy. The ocular surface is covered by a tear film, made up of aqueous, mucinous, and lipid layers produced by the lacrimal and meibomian glands. Radiation that disrupts the structures that produce these elements will cause dry eyes or xerophthalmia. Atrophy of the meibomian glands occurs at doses <30 Gray while damage to the lacrimal gland occurs at 50–60 Gy.

Work-up and diagnosis: All of these are identified with a comprehensive eye exam.

Treatment: Xerophthalmia is typically managed artificial tears or anti-inflammatory drops that treat the inflammatory component of dry eyes. Radiation-induced cataracts are treated using lens replacement.

Sensorineural hearing loss: Radiation can cause hearing loss months to years after completion of treatment. Risk factors include age, radiation dose to the cochlea, and ototoxic systemic

therapy such as cisplatin. Higher frequencies are more sensitive to radiation dose. SRS for vestibular schwannoma typically results in gradual sensorineural hearing loss over years, possibly related to cranial nerve injury (from tumor and/or radiotherapy) or radiotherapy-mediated cochlear injury.

Work-up and diagnosis: Sensorineural hearing loss can be evaluated using standard audiometry.

Treatment: Symptoms can be managed with hearing aids as needed for quality of life.

Central Hypopituitarism

Description: Radiation-induced hypopituitarism can occur when the hypothalamic-pituitary axis receives significant radiation dose. Factors that affect risk in fractionated radiotherapy include total dose, fraction size, age at time of radiation, and length of time after radiotherapy. Specific hormone deficiencies are summarized in Table 14.1. The growth hormone (GH) axis is particularly sensitive and is frequently the only site affected with lower dose fractionated radiotherapy (≥18 Gy). GH deficiency may be asymptomatic in adults but can cause decreased muscle mass and increased adipose tissue. At higher doses, gonadotropins, TSH, ACTH, and prolactin can be affected. LH/FSH and TSH deficiency can occur with doses >40 Gy. LH/FSH deficiency can cause amenorrhea or oligomenorrhea in women and low testosterone in men. Infertility, sexual dysfunction, and decreased libido can occur. TSH deficiency may be subclinical, but can manifest with fatigue, constipation, cold-intolerance, and weight gain. Clinically relevant ACTH deficiency increases with hypothalamic-pituitary axis dose >50 Gy with symptoms of fatigue, weakness, nausea, vomiting, anorexia, and abdominal cramping. Additionally, ACTH deficiency can lead to life threatening complications in the setting of severe illness including hypoglycemia and hypotensive shock. Hyperprolactinemia can occur with doses >50 Gy due to damage to the hypothalamus and loss of hypothalamic inhibition of prolactin release, leading to amenorrhea, infertility and/or decreased libido. Some studies suggest that GH

Table 14.1 Syndromes seen in radiation-induced hypopituitarism, radiotherapy doses, symptoms, screening, and management [29]

Syndrome	RT dose	Common symptoms	Screening	Hormone replacement
Central adrenal insufficiency	>50 Gy	Fatigue, weakness, nausea, vomiting, anorexia, abdominal cramping, complications in the setting of illness such as hypotension	Serum cortisol levels at 8–9 a.m., corticotropin stimulation test	Hydrocortisone
Central hypothyroidism	>40 Gy	Fatigue, cold intolerance, constipation, weight gain	Serum free T4 and TSH	Levothyroxine
GH deficiency	≥18 Gy	Decrease in muscle mass and increased adipose tissue, fasting hypoglycemia	GH stimulation testing (singe GH measurements are not helpful)	GH
Central hypogonadism in males	>40 Gy	Infertility, sexual dysfunction, decreased libido, decreased bone density, decreased energy, decreased muscle mass	Serum testosterone, FSH, and LH (perform in the absence of illness and before 10 a.m. after overnight fast)	Testosterone
Central hypogonadism in females	>40 Gy	Oligomenorrhea or amenorrhea, infertility, sexual dysfunction, decreased libido	Serum estradiol, FSH, and LH	Estrogen

deficiency is the first to emerge after injury to HPA, followed by deficiencies of gonadotropin, ACTH, and TSH [29].

Work-up and diagnosis: The diagnosis is established through bloodwork (Table 14.1). Radiation dosimetry should also be reviewed to establish dose to the hypothalamic pituitary axis [29].

Treatment: Hypopituitarism can be managed through endocrine replacement therapy and is quite treatable (Table 14.1) [29].

Vascular Malformations and Microbleeds

Description: Vascular malformations such as cavernomas (clusters of abnormal dilated blood vessels with blood-filled cavities, see Fig. 14.2) and telangiectasias (dilated capillaries with a thin endothelial lining can form as late radiation sequelae years after radiotherapy. Cerebral microbleeds occur in both adults and children who have received radiotherapy, typically years after. They form primarily in regions that received at least 30 Gy, but also in lower dose regions [30]. Children are more susceptible to developing these late sequelae compared to adults who receive cranial radiation [31].

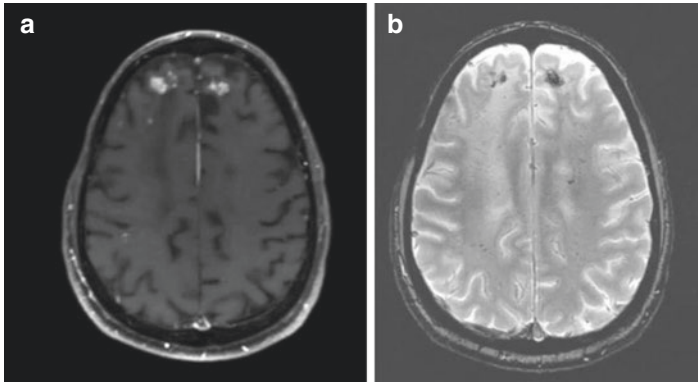

Fig. 14.2 Patient with frontal cavernomas on imaging 11 years after treatment with radiotherapy for a glioma shown on the (**a**) T1 + gadolinium sequence (**b**) susceptibility weighted imaging sequence

Work-up and diagnosis: Cavernomas and telangiectasias can be visualized on MRI scans, particularly on susceptibility-weighted sequences, CT angiography, or cerebral angiography. Cerebral microbleeds are best seen on susceptibility-weighted sequences such as gradient echo sequences.

Treatment: Asymptomatic cavernomas can be managed conservatively. Resection is indicated for symptomatic lesions (progressive neurologic deficit, intractable epilepsy, and recurrent hemorrhage). For surgically inaccessible lesions, SRS may be considered. Telangiectasias are managed conservatively.

Atherosclerosis and Ischemic Stroke

Description: Similar to other vascular radiation side effects, children are more susceptible to accelerated atherosclerosis and ischemic stroke. Risk factors include receipt of chemotherapy, young age, radiation dose, and diagnosis of neurofibromatosis type 1. After cranial radiation, individuals can develop either focal stenosis or Moya Moya, a syndrome with progressive occlusion of the arteries of the circle of Willis leading to development of collateral vessels [31]. While it may be an overestimate now, given the advances in radiation techniques that lead to more sparing of normal tissue, one study reported a 16% rate of large vessel arteriopathy at 10 years for patients who received radiation for childhood brain tumors [32]. Ischemic stroke also occurs after cranial radiation and is well-studied in the pediatric population. A Childhood Cancer Survivor Study analyzed leukemia and brain tumor survivors, finding 0.8% rate of stroke in leukemia survivors, 3.4% rate of stroke in brain tumor survivors, and higher rates (6.5%) in survivors who received both cranial radiotherapy and alkylating agents [33]. Significant radiation dose to the circle of Willis increases risk of stroke events [34].

Treatment: Management of stroke in cancer survivors who have received cranial radiation is extrapolated from management of other stroke patients. However, there is some evidence that in the setting of stenting for high grade carotid stenosis, there is higher rate of in-stent restenosis [31]. One population-based study

showed a significant reduction in stroke in patients post radiotherapy to the thorax, head, and neck who were on statins, so there is some data for statin use in this population [35]. Other strategies to decrease risk of vasculopathy include delaying radiotherapy if the patient is very young, using lower radiotherapy doses, and using more conformal radiotherapy. For long-term follow-up, Children's Oncology Group guidelines recommend annual neurologic exam for survivors who received ≥18 Gy cranial radiotherapy and MRI if clinically indicated [31].

SMART Syndrome

Description: SMART (stroke-like migraine attacks after radiation therapy) syndrome is an extremely rare syndrome seen 1–5 years after radiotherapy characterized by recurrent episodes of complicated migraine symptoms along with focal neurologic deficits. The majority of patients will have received a dose of >50 Gy and received radiation to the posterior fossa. It is potentially a reversible radiation vasculopathy, but the pathology is not well understood [36].

Work-up and Diagnosis: Differential diagnosis should include transient ischemic attack, stroke, and seizures. MRI and vascular imaging can be performed to rule out acute stroke or recurrent tumor. It may also show characteristic MRI features for SMART syndrome including focal gyral thickening and gyriform contrast enhancement most commonly in the parieto-occipital region [37]. Electroencephalography (EEG) can be done to rule out seizure. Other considerations for differential diagnosis include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, posterior reversible encephalopathy syndrome, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [37].

Treatment: There is some evidence that corticosteroids can decrease neurologic deficits, though this is controversial. Per a recent review, the majority of patients received antiepileptic medications including valproate, levetiracetam, phenobarbital, phenytoin, lamotrigine, carbamazepine, topiramate, and

oxcarbazepine. Aspirin, propranolol, verapamil, and various anticonvulsants were used most frequently over long-term, but only aspirin and verapamil reduced frequency and severity of episodes [36].

Radiation-Related Cognitive Decline

Description: In recent decades, there has been significant interest in the effect of radiotherapy on cognition. Contributing factors include the brain tumor(s) themselves, medications such as corticosteroids and antiepileptics, age and other host factors, systemic therapy, surgery, and factors specific to the radiotherapy including total radiation dose, fraction size (larger doses causing greater normal tissue damage), and radiation field [38]. In 1989, Deangelis et al. published an 11% risk of radiation-related dementia in 47 patients undergoing WBRT for brain metastases . Notably, three patients received large daily fractions (5–6 Gy), one received concurrent adriamycin, and one received concurrent lonidamine (a radiosensitizer) [39]. However, modern studies with standard WBRT treatment regimens have shown more subtle declines in verbal learning and memory and executive function in brain metastases patients receiving WBRT at 4 months [40]. Recently, hippocampal sparing WBRT has shown improvement in neurocognitive decline compared to standard WBRT [41]. However, it remains unclear whether SRS for multiple metastases has better cognitive outcomes than hippocampal sparing WBRT. There are randomized clinical trials studying this [23], as well as others evaluating SRS for up to 20 brain metastases.

Work-up and diagnosis: Neurocognitive change in patients who have received radiotherapy is often multi-factorial. Initial

assessment should include history to identify other factors such as medications, mood disorders, sleep disturbances, as well as screen for endocrine abnormalities which are both common and could result from cranial. Screening for other causes of neurocognitive decline, such as vitamin deficiencies (B12), metabolic abnormalities, hydrocephalus, tumor recurrence, or stroke may be warranted.

Treatment: Based on recent trials, many treatments begin at time of initial radiotherapy using new radiation techniques to reduce complications. A trial in young patients showed improved IQ and decreased neuroendocrine complications with conformal radiotherapy in conventional fractionation using stereotactic technique compared to conventional radiotherapy [42]. Additionally, there are retrospective studies that proton therapy may cause less cognitive decline compared to non-proton-based radiotherapy, and a randomized trial (NRG BN005; NCT03180502 is underway [43]. As noted above, hippocampal sparing WBRT has now become standard of care and work is being done to compare this to SRS for multiple metastases. There is evidence for some medications as well. There is evidence that memantine started at the time of WBRT increases time to neurocognitive decline [44]. A phase 3 trial of donepezil showed no significant difference in the primary outcome (a composite score of cognitive performance, subjective confusion, and fatigue) between patients who received donepezil compared with those who received placebo, but did show improvement in some domains such as memory and may be an option in some patients [45]. There are mixed data for methylphenidate and modafinil, but they can be considered for patients with significant fatigue or attentional deficits [38] (Table 14.2).

Table 14.2 Late side effects from radiotherapy, work-up, and management

Complication	Patient population	Work-up	Imaging findings	Timing	Management
Treatment effects					
Radiation necrosis	Patients treated with radiosurgery or receiving >60 Gy in conventional fractionation	Imaging, typically MRI with perfusion or MRS, PET/CT	Favor tumor: increased cerebral blood volume, lower ADC values than necrosis, on MR spectroscopy choline-creatine ratio and choline-N-acetyl aspartate ratio higher, FDG-PET avidity	Most commonly 1–2 years	Steroids, bevacizumab, laser interstitial thermal therapy, resection if needed
Pseudoprogression	Patients with glioma; more common in MGMT methylated tumors on temodar ± lomustine	Serial imaging	Increased contrast-enhancement on T1 post-gad	Within 3 months of radiation	Typically no change in treatment; if symptomatic, steroids and/or bevacizumab can be administered
Vision changes					

Complication	Patient population	Work-up	Imaging findings	Timing	Management
Optic neuropathy	Increased risk with increasing patient age, total radiotherapy dose >59 Gy, and daily fraction size >2 Gy	A clinical exam including fundoscopy to confirm optic neuropathy. MRI brain is also helpful. Lumbar puncture can be considered if inflammatory or neoplastic cause is suspected	Optic nerve atrophy on imaging	2–4 years after radiotherapy	Hyperbaric oxygen, corticosteroids, and anticoagulation have been tried with limited efficacy
Ocular neuromyotonia	Radiation to the pituitary or skull base (involving the ocular motor nerves)	Eye movement exam after sustained eccentric gaze, MRI brain	n/a	Years after radiotherapy	Carbamazepine or lacosamide
Cataracts	Radiation dose >7 Gy to lens	Eye exam	n/a	2–3 years post radiotherapy	Lens replacement
Dry eyes	30 Gy to meibomian gland, 50–60 Gy to lacrimal gland	Eye exam	n/a	Years after radiotherapy	Artificial tears, anti-inflammatory eye drops

(continued)

Table 14.2 (continued)

Complication	Patient population	Work-up	Imaging findings	Timing	Management
Serorineural hearing loss	Cranial radiotherapy with mean dose to cochlea >45 Gy, exposure to ototoxic chemotherapy	Audiogram	n/a	Months to years after radiotherapy	Hearing aids as needed
Vascular complications					
Cavernomas	Children and adults after radiotherapy	MRI with T1, T2, susceptibility weighted imaging	T1- and T2-weighted images include a "popcorn" pattern of variable image intensities consistent with evolving blood products	Years after radiotherapy	Observe asymptomatic lesions, Resection Indications for symptomatic lesions (progressive neurologic deficit, intractable epilepsy, and recurrent hemorrhage), consider SRS if surgically inaccessible

Telangiectasias	Children and adults after radiotherapy	MRI with T1, T2, susceptibility weighted imaging	Hypo- to isointense on T1, iso- to slightly hyperintense on T2, faint enhancement on T1 postcontrast, dark on SWI	Years after radiotherapy	Conservative management
Stroke-like migraine attacks after radiation therapy (SMART) syndrome	Received a dose of >50 Gy and received radiation to the posterior fossa	MRI brain with contrast	Focal gyral thickening and gyriform contrast enhancement most commonly in the parieto-occipital region	1–5 years after radiotherapy	Aspirin, propranolol, verapamil, anticonvulsants
Accelerated atherosclerosis	Child and adults, particularly if radiation dose to circle of Willis	MRA, CTA, cerebral angiography	Focal stenosis, vessel collateralization	>5 years	Statins, aspirin, antiplatelets
Cognitive change	Children and adults who receive partial or whole brain radiation therapy	Metabolic work-up, vitamin B12, MRI brain, neuropsychological testing, depression/ anxiety screen	n/a	4 months to years after radiotherapy	Memantine, investigational strategies

Patient Advice

Whole brain radiation: This is typically given over 10 days (2 weeks). During the initial planning session, the patient will be fitted for a mask to give the radiation treatment safely. Patients will typically feel fine for the first week, but will start to have some tiredness starting the second week. This should resolve about 2 weeks after completing treatment. Less common symptoms include headache, poor appetite, nausea, vomiting, and worsening of neurologic symptoms. Most patients will have hair loss, but it will typically grow back. Some patients will have hearing changes due to an issue with the middle ear, which should improve on its own. Studies show that many patients have changes in memory months to years after completing radiation treatment. Patients may receive a medication called memantine and/or treated using a technique called hippocampal sparing to decrease these side effects.

Radiosurgery: Patients will receive radiation treatment over 1–5 days. During the initial planning session, the patient will be fitted for a tight mask to give radiotherapy safely. Some patients will have mild tiredness the week after completing this treatment. About one-third of patients have immediate mild to moderate side effects after radiosurgery. They typically resolve on their own, but may be treated with a short course of corticosteroids.

Partial brain radiotherapy for glioma: Most patients are treated with 27–30 radiation treatments given over 5–6 weeks. It is possible that the radiation oncologist will recommend a shorter treatment based on the specific case. During the initial planning treatment, the patient will be fitted for a mask to give the radiotherapy safely. The radiation oncologist will coordinate with a neuro-oncologist (or medical oncologist) so that chemotherapy will be started appropriately. Most patients will experience tiredness starting in the second week of radiotherapy. This will gradually worsen during treatment. There is usually patchy hair loss. Hair

may not grow back even after treatment ends. Patients may experience headaches, nausea, vomiting, seizures, or changes in neurologic symptoms. Patients will start to feel more normal about 2 weeks after radiotherapy ends and should be mostly recovered by 4–6 weeks after the end of treatment.

References

1. Baskar R, et al. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9(3):193–9.
2. Mitin TM. Radiation therapy techniques in cancer treatment. UptoDate.
3. Marks LB, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10–9.
4. Marks PRLSCL. ALERT—adverse late effects of cancer treatment. Springer. 2014.
5. Lawrence YR, et al. Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S20–7.
6. Jereczek-Fossa BA, et al. Radiotherapy-induced ear toxicity. Cancer Treat Rev. 2003;29(5):417–30.
7. Lawenda BD, et al. Permanent alopecia after cranial irradiation: dose-response relationship. Int J Radiat Oncol Biol Phys. 2004;60(3):879–87.
8. Cairncross JG, et al. Acute parotitis and hyperamylasemia following whole-brain radiation therapy. Ann Neurol. 1980;7(4):385–7.
9. Kandil AO, et al. Multifocal Stevens-Johnson syndrome after concurrent phenytoin and cranial and thoracic radiation treatment, a case report. Radiat Oncol. 2010;5:49.
10. Anker CJ, et al. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). Int J Radiat Oncol Biol Phys. 2016;95(2):632–46.
11. Meijer OW, et al. Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: a single-institution study. Int J Radiat Oncol Biol Phys. 2003;56(5):1390–6.
12. Han MS, et al. Hemifacial spasm caused by small epidermoid tumor, misinterpreted as delayed secondary hemifacial spasm caused by vestibular schwannoma treated with gamma knife surgery. World Neurosurg. 2019;130:410–4.
13. Yang HC, et al. Gamma knife radiosurgery for larger-volume vestibular schwannomas. Clinical article. J Neurosurg. 2011;114(3):801–7.

14. Hayman JA, et al. Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. Int J Radiat Oncol Biol Phys. 2011;79(3):847–52.
15. Petersson K, et al. Haematological toxicity in adult patients receiving craniospinal irradiation—indication of a dose-bath effect. Radiother Oncol. 2014;111(1):47–51.
16. Werner-Wasik M, et al. Immediate side effects of stereotactic radiotherapy and radiosurgery. Int J Radiat Oncol Biol Phys. 1999;43(2):299–304.
17. Kim JM, et al. The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. J Neurooncol. 2017;133(2):357–68.
18. Minniti G, et al. Single-fraction versus multifraction (3 × 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis. Int J Radiat Oncol Biol Phys. 2016;95(4):1142–8.
19. Lehrer EJ, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. Radiother Oncol. 2019;130:104–12.
20. Shah R, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. Radiographics. 2012;32(5):1343–59.
21. Levin VA, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys. 2011;79(5):1487–95.
22. Xu Y, et al. Bevacizumab monotherapy reduces radiation-induced brain necrosis in nasopharyngeal carcinoma patients: a randomized controlled trial. Int J Radiat Oncol Biol Phys. 2018;101(5):1087–95.
23. Suh JH, et al. Current approaches to the management of brain metastases. Nat Rev Clin Oncol. 2020;17:279–99.
24. Wen PY, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963–72.
25. Herrlinger U, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019;393(10172):678–88.
26. Kelly PJ, et al. Unexpected late radiation neurotoxicity following bevacizumab use: a case series. J Neurooncol. 2011;102(3):485–90.
27. Biousse VN. Nancy, neuro-ophthalmology illustrated. New York: Thieme; 2009.
28. Roper-Hall G, Chung SM, Cruz OA. Ocular neuromyotonia: differential diagnosis and treatment. Strabismus. 2013;21(2):131–6.
29. Sara Hardy IS, Milano M, Vates E, Constine L. Hypopituitarism. In: PDB, Chang EL, Lo SS, Sahgal A, Suh JH, editor. Adult CNS radiation oncology. Springer. 2018.

30. Wahl M, et al. Relationship between radiation dose and microbleed formation in patients with malignant glioma. Radiat Oncol. 2017;12(1):126.
31. Murphy ES, et al. Review of cranial radiotherapy-induced vasculopathy. J Neurooncol. 2015;122(3):421–9.
32. Nordstrom M, et al. Large vessel arteriopathy after cranial radiation therapy in pediatric brain tumor survivors. J Child Neurol. 2018;33(5):359–66.
33. Bowers DC, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006;24(33):5277–82.
34. El-Fayech C, et al. Cerebrovascular diseases in childhood cancer survivors: role of the radiation dose to Willis circle arteries. Int J Radiat Oncol Biol Phys. 2017;97(2):278–86.
35. Boulet J, et al. Statin use and risk of vascular events among cancer patients after radiotherapy to the thorax, head, and neck. J Am Heart Assoc. 2019;8(13):e005996.
36. Zheng Q, et al. Stroke-like migraine attacks after radiation therapy syndrome. Chin Med J (Engl). 2015;128(15):2097–101.
37. Makar GS, Siegal T, Syrow L. Stroke-like migraine attacks after radiation therapy (SMART) syndrome: a rare, reversible complication of radiation therapy. Headache. 2020;60:998–9.
38. Hardy SJ, et al. Cognitive changes in cancer survivors. Am Soc Clin Oncol Educ Book. 2018;38:795–806.
39. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. Neurology. 1989;39(6):789–96.
40. Chang EL, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037–44.
41. Brown PD, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. J Clin Oncol. 2020:Jco1902767.
42. Jalali R, et al. Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain tumors: a randomized clinical trial. JAMA Oncol. 2017;3(10):1368–76.
43. https://clinicaltrials.gov/ct2/show/NCT03180502
44. Brown PD, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15(10):1429–37.
45. Rapp SR, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. J Clin Oncol. 2015;33(15):1653–9.

15 Neurosurgical Complications in Brain Tumor Patients

Tyler Schmidt

The surgical management of brain tumor patients has dramatically evolved over the last 20 years. Neurosurgical adjuncts, such as the operating microscope, neuronavigation, intraoperative neuromonitoring, tumor-fluorescence (5-ALA), tractography, and cortical mapping have been successfully incorporated into the neurosurgical theater. These modalities have enhanced the safety profile of neurosurgical intervention. These technologies have allowed for improved preservation of neurologic function as well as mitigation of potential morbidities. Despite the continued advancement of radiation, chemotherapy, and immunotherapy, surgery remains the initial treatment modality in the majority of patients with brain tumors. The main objective of neuro-oncological surgery is to provide maximal cytoreduction, decrease the mass effect and associated complications, and establish the pathologic diagnosis. Studies have repeatedly shown the benefit of gross total resection of brain lesions, including most common high and low grade gliomas, solitary brain metastasis and meningiomas. This chapter will review the complications related to neurosurgical treatment of brain tumors and provide guidance on the management of those patients from pre- to post-operative care.

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There are generally two groups of complications related to brain tumor surgery—surgical and systemic [1]. Surgical complications arise as a direct result of the surgery and are usually specific to the neurosurgical site and procedure. They include neurologic complications, such as postoperative seizures and neurologic deficits, as well as postoperative cerebral edema, cerebral hemorrhage, infarction, hydrocephalus, and regional complications, such as CSF leak, wound infection or dehiscence. Systemic complications are not directly related to the neurosurgical site and procedure and include the following: pulmonary complications (e.g. pulmonary embolism, pneumonia, atelectasis), cardiac complications (e.g. myocardial infarction, arrhythmias, hypo/hypertension), renal complications (e.g. urinary tract infections, acute kidney injury) and others. The risk of both surgical and systemic complications can be reduced with preoperative planning, meticulous surgical technique and use of intra-operative adjuncts as well as proper post-operative management.

Preoperative Management

Every preoperative assessment should begin with obtaining thorough medical history and performing careful physical examination in order to identify any comorbidities that might affect the outcome of the tumor resection procedure. Common medical comorbidities to screen for include hypertension, diabetes, atrial fibrillation as well as other cardiac conditions which require anticoagulation and antiplatelet therapy. Therefore, all current medications need to be reviewed and adjusted according to the patient's status.

Perioperative Antiepileptic Therapy

There is little to no evidence on the efficacy of antiepileptic drugs (AED) in prevention of postoperative seizures in patients with brain tumors and no history of seizures [2, 3]. Thus, they should not be routinely prescribed unless a documented seizure has occurred. The patients who present with single or multiple seizures are at higher risk for recurrence in the presence of intracranial pathology. In these

patients, AED therapy should be continued or initiated before surgery. Potential interactions between AED and other medications (especially chemotherapy) need to be considered before choosing a specific AED. Levetiracetam at the loading dose of 20 mg/kg intravenously followed by 500–1000 mg twice a day is commonly prescribed for seizure prophylaxis due to its low side effect profile.

Steroids

Steroids in patients with both primary and metastatic brain tumors significantly alleviate the symptoms occurring due to vasogenic edema and increased intracranial pressure both pre- and postoperatively. Dexamethasone is a corticosteroid of choice in neuro-oncological patients and has been shown to improve outcomes postoperatively in those patients. The initial IV bolus of 10 mg is followed by administration of 16 mg/day in 2–4 divided doses. The initiation of therapy should occur at least 3 days before surgery for maximal effect. Dexamethasone may be tapered off gradually in 2–3 weeks after surgery or quickly—3 days after surgery, depending on the individual benefit and the duration of preoperative steroid therapy. In general, lowest possible doses and early taper are recommended to avoid unnecessary side-effects and comorbidities due to steroid use. Prevention of steroid-induced ulcers requires gastrointestinal prophylaxis, such as proton pump inhibitors. Monitoring of blood glucose levels is also recommended while on steroid therapy. Prophylaxis against Pneumocystis jirovecii should be considered for patients requiring prolonged used of steroids.

Antiplatelet and Anticoagulation Medications

The risk of hemorrhage for intracranial surgery is high. Antiplatelet and anticoagulation therapy, including chemical DVT prophylaxis, should be withheld before surgery unless there are specific circumstances that are discussed with the surgical team. In general antiplatelet/anticoagulant medications should be stopped 5–7 days before elective surgery. Patients with drug-eluting stents

(DES) need to be administered dual antiplatelet therapy for up to 12 months after DES surgery. Even brief cessation of the therapy drastically increases the chances of life-threatening stent thrombosis. Therefore, the decision concerning the continuation of therapy through brain tumor surgery should be based on consultation between the patient's neurosurgeon and cardiologist and the consensus should be balanced between risks and benefits. Anticoagulation drugs are stopped preoperatively (unfractionated heparin: stop full IV anticoagulation 4–6 hours before surgery, subcutanoueous dosig, stop 12 hours before surgery; low molecular weight heparin (LMW heparin): stop prophylactic dose 12 hours before surgery, stop full anticoagulation 24 hours before surgery; fondaparinux: stop 2 to 4 days prior to surgery; rivaroxaban: stop 48 hours before; apixaban: stop 48 hours before surgery). Patients who require constant anticoagulation therapy with vitamin K antagonists (VKA) (e.g. mechanical heart valves) need to be bridged with LMW heparin. VKA (warfarin, acenocoumarol) are stopped 5 days before surgery and LMW heparin is started, with the last dose administered subcutaneously no later than 12 h before surgery.

Hyperglycemia

Perioperative hyperglycemia is significantly associated with adverse effects in patients undergoing brain tumor resection [4]. Glucose levels should be maintained at <180 mg/dL and hypoglycemia should be avoided in all patients. Close surveillance for hyperglycemia is especially warranted in patients that receive corticosteroids. The target level of glycosylated hemoglobin (HbA1C) should be <7.0% before surgery in patients with diabetes. Antidiabetic drugs are withheld preoperatively (metformin and short-acting sulfonylureas: 24 hours before surgery; thiazolidinediones: 24 to 36 hours before surgery; long-acting sulfonylureas: 48 to 72 hours before surgery) and substituted with intravenous insulin infusion or sliding scale insulin. Postoperatively, IV or subcutaneous insulin is administered as appropriate with careful attention as corticosteroids are weaned and pre-procedure diabetic medications are restarted to prevent hypoglycemia.

Optimizing Other Medical Conditions

Decision to withhold or administer antihypertensives and other cardiac medications perioperatively needs to be determined after consultation with a cardiologist and/or anesthesiologist. Fluid status should be addressed and optimized accordingly to prevent post induction hypotension and acute kidney injury. Patients with a history of pulmonary disease are at greater risk for perioperative respiratory complications, therefore optimization of lung function should be completed preoperatively.

Preoperative Imaging

There are several neurosurgical adjuncts that aid the neurosurgeon with preoperative planning and intraoperative approaches that optimize the extent of resection and safety profile. Moreover, additional imaging technologies are used for tumors located in eloquent areas to mitigate potential neurologic deficits related to resection. Neuronavigation utilizes thin-sliced MRI and CT scans to form a 3D reconstruction of the lesion and its relationship with adjacent anatomy. It can be further supplemented with functional data, such as functional MRI (fMRI) or diffusion tensor imaging (DTI). fMRI data is particularly useful for preoperative planning of surgical approach and surgical corridor as well as intraoperative navigation for intra-axial lesions located in eloquent areas. DTI tractography allows for a visualization of white matter fibers, such as the visual pathway, arcuate fasciculus, corticospinal tract and others. Despite the usefulness of intraoperative MRI (iMRI), fMRI, and DTI tractography in identification of crucial anatomical structures and their relationship to the lesion, current research shows low quality evidence on their efficacy in maximizing the extent of resection, postoperative neurological status, progression-free survival and overall survival in patients with gliomas, when compared to traditional neuronavigation [5–7]. However further research is ongoing as these new techniques are integrated into the neurosurgical workflow.

Intraoperative Management

Patient Positioning

Proper patient positioning is essential in providing surgical corridor visualization while minimizing iatrogenic pressure or traction injury due to the lengthy nature of some neurosurgical procedures. Prevention of pressure ulcers relies both on crafted positioning and ample use of gel and foam padding. The patient should be placed in a physiological position to prevent brachial plexus and other peripheral nerve injuries. The position of the patient can also affect the risk of developing venous air embolism (VAE).

Venous Air Embolism

The incidence of VAE during intracranial procedures has been reported in up to 76% of cases [8], the majority of which are asymptomatic. The risk of VAE increases when the surgery is done in close proximity to dural sinuses. Elevation of the patients head above the heart (e.g. sitting position for posterior fossa tumors) creates an additional gravitational gradient. Other risk factors include blood loss and dehydration. In patients with preoperatively detected patent foramen ovale, decision to avoid sitting or semi-sitting position should be considered.

Any unexplained hypotension, decreases in end-tidal carbon dioxide, arterial oxygen saturation, hypercapnia, and/or increase in end-tidal nitrogen should immediately suggest the possibility of VAE during surgery. Precordial Doppler and transesophageal echocardiography can be used to screen for air emboli. Surgeons should immediately soak the surgical field with saline to prevent further emboli by blocking venous channels. The patient is then placed in partial left lateral decubitus position (Durant maneuver), nitrogen dioxide is discontinued (if being utilized) and the patient should receive 100% oxygen. Catheter aspiration can be considered in severe cases. Hemodynamic instability should be treated immediately and if not effective, the surgery should be aborted.

Skin Incision and Tissue Handling

Planning of the scalp incision parallel to the major scalp vessels allows for better perfused skin flaps than U-shaped incisions. The base of the flap should be wider than the height to maintain adequate blood supply. The initial skin incision should be well optimized for possible salvage opportunities in case of postoperative infection, treatment induced dehiscence, or possible reoperation for disease recurrence. Meticulous dissection and gentle tissue handling prevent maceration of tissues that can lead to infection or delayed wound healing.

Ensuring Gross Total Resection and Preventing New Neurologic Deficits

Ensuring gross total resection (GTR) relies on meticulous surgical technique and visualization of the tumor. Intraoperative microscope and intraoperative imaging modalities, such as traditional neuronavigation, DTI tractography, fMRI and iMRI allow for preservation of crucial adjacent anatomical structures and deep white matter tracts, and as such, prevention of new neurological deficits (see Sect. 2.3). Moreover, fluorescence guided surgery with 5-aminolevulinic acid (5-ALA) or sodium fluorescein can additionally aid in visualization of the tumor margins and in maximizing GTR. Studies on the 5-ALA guided resections with and without addition of iMRI showed significantly higher rates of GTR and progression-free survival than those using white light alone [9, 10]. Utilization of 5-ALA requires low light conditions for 48 hours postoperatively to prevent photosensitivity reactions. Other techniques and modalities, such as neuro-endoscopy or BrainPath allow for minimally-invasive transsulcal approaches to subcortical lesions sparing transcortical injury. Preservation of en-passage vessels to adjacent functional cortex is of utmost importance during tumor dissection.

Intraoperative Neurophysiological Monitoring

Somatosensory evoked potentials (SSEP), motor evoked potentials (MEP) and intraoperative electromyography (EMG) can be used to evaluate the functioning of sensory and motor pathways. Cortical and subcortical mapping allows for navigation around those regions and tracts during resection of lesions in eloquent brain. Cortical mapping is particularly useful to maximize safe resection in motor, language, and cognition related lesions. Sleep mapping (during anesthesia) is usually performed for lesions that do not directly infiltrate eloquent regions, while awake mapping is preferred for more infiltrating lesions as they allow for real time feedback. All techniques have been shown to mitigate the risk of postoperative neurologic deficit and are utilized extensively in modern neurosurgical oncology.

Closure

Ensuring proper watertight dural and galeal closure decreases the risk of cerebrospinal fluid (CSF) leak, CSF fistula, pseudomeningocele, delayed wound healing, and infection. Skin approximation can be completed with surgical staples, absorbable, or non-absorbable suture with alignment of the dermal edges being critical for proper wound healing. The use of subgaleal closed drainage systems can minimize hematoma formation and improve healing.

Postoperative Complications and Management

Hemorrhage

Postoperative intracranial hemorrhage is one of the most feared complications of brain tumor surgery with high morbidity and mortality. However, small hematomas in the tumor cavity are found on postoperative imaging in up to 30% of patients [11]. Major hemorrhage requiring reoperation accounts for 2% of brain tumor cases [12]. Risk factors include subtotal resection,

tumor type (hemangioblastoma, infratentorial tumors), older age, pre-existing conditions, such as hypertension or coagulopathy. Ensuring intraoperative hemostasis and perioperative normotension are essential in preventing postoperative hemorrhage.

Seizures

Seizures occur in up to 10% of patients after brain tumor surgery [13]. Seizures can result from the cortical irritation after tumor resection, idiopathic causes, brain manipulation, or prolonged retraction. In some cases, intracranial hemorrhage or cerebral edema can result in postoperative seizures. Therefore, early postoperative seizures warrant reimaging usually with a noncontrast CT head. In general, patients are managed with antiepileptic drugs (see Sect. 2.1).

Neurologic Deficit

There are a number of factors contributing to the risk of new neurologic deficit after brain tumor resection. Many of them might be anticipated secondary to location of the lesion and surgical corridor. Deep location of tumors, location in or near eloquent areas, and tumors encasing major vessels are risk factors for postoperative deficits. Arterial or venous infarcts due to vessel sacrifice or injury can lead to symptomatic deficits. Neurologic deficits are often transient and resolve over the ensuing days/weeks/months. Intraoperative imaging, neuronavigation, and neurophysiological monitoring can reduce the risk of iatrogenic injury and new neurologic deficits (see Sect. 3.4).

Patients with new neurologic deficits should be evaluated by a comprehensive therapy/rehab team consisting of physical, occupational, and speech therapy as clinically warranted. Modern rehabilitation techniques/devices improve the quality of life of patients with persistent deficits.

Postoperative delirium can occur. Environmental techniques that can improve or prevent postoperative delirium include orienting the patient towards time and surroundings (lights on during daytime, family members present), proper uninterrupted sleep protocol, proper nutrition, and early mobilization.

Hydrocephalus

The rates of postoperative hydrocephalus reach 6–8% [14] for the lesions located at the skull base in close proximity to the fourth ventricle. Other risk factors include metastatic disease, intraventricular lesions, and transventricular approaches. The etiology of postoperative hydrocephalus is multifactorial and case dependent, including obstructive hydrocephalus from obstruction of CSF flow pathways or nonobstructive hydrocephalus from protein or blood product buildup in the CSF inhibiting normal CSF reabsorption. In the cases of persistent hydrocephalus, permanent CSF diversion via shunt is necessary.

Infection

Infections after brain tumor resection occur in 2–4% of patients [15, 16]. Known risk factors include duration of surgery, male sex, postoperative CSF leak and length of preoperative stay of more than one day [15]. Presentation ranges from superficial skin infection to meningitis, subdural empyema, or abscess. Additional risk factors for meningitis include elderly age group, presence of lumbar drain, and enteral nutrition. Standard antibiotic therapy based on sensitivity patterns should be started if infection is suspected. Subdural empyema and abscess may require additional reoperation for source control. Preventive methods include administration of perioperative antibiotics before induction (cefazolin), meticulous technique, strict sterility practices, and proper dural, galeal, and skin closure.

Wound Healing Complications

Dehiscence and wound healing problems can be related to older age, frailty syndrome, diabetes, previous surgery, previous chemo and radiotherapy, angiogenesis inhibitor utilization (bevacizumab), and carmustine (Gliadel©) wafer use. In order to improve wound healing the management should include correcting hyperglycemia, optimizing nutrition, utilizing proper closure techniques, and decreasing the pressure on the incision.

Venous Thromboembolism

Patients who undergo surgery due to brain tumor are at increased risk for developing venous thromboembolism (VTE). Additional risk factors for VTE include presence of malignancy, leg weakness, duration of surgery, and absence of thromboprophylaxis. Previous studies have shown the efficacy of intra- and postoperative intermittent pneumatic compression (IPC) [17] and LMW heparin [18] in reducing the risk of VTE. The timing of the start of anticoagulation therapy seems to affect the risk of postoperative hemorrhage, with higher rates of bleeding detected if the therapy is started during or early after the craniotomy. Current ESA guidelines [19] recommend the initiation of IPC thromboprophylaxis before surgery in all patients undergoing intracranial procedures. Moreover, the addition of subcutaneous LMW heparin is advised no earlier than one day post-surgery in patients with evidence of postoperative intracranial hemorrhage [19].

Other Systemic Complications

Cardiac complications occur in 1.1% and 0.7% of patients undergoing surgery for benign tumors and gliomas, respectively [20]. The incidence of acute renal failure after tumor resection is between 1.3 and 1.5% [20]. The treatment of those patients

requires a multidisciplinary approach and management. Malnutrition results in poor wound healing and worse outcomes. Nutrition consultation is advised in those patients.

References

1. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery. 1998;42(5):1044–55; discussion 1055–6. https://doi.org/10.1097/00006123-199805000-00054.
2. Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database Syst Rev. 2020;4(4):CD007286. https://doi.org/10.1002/14651858.CD007286.pub5.
3. Chen CC, Rennert RC, Olson JJ. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the role of prophylactic anticonvulsants in the treatment of adults with metastatic brain tumors. Neurosurgery. 2019;84(3):E195–7. https://doi.org/10.1093/neuros/nyy545.
4. Hagan K, Bhavsar S, Arunkumar R, et al. Association between perioperative hyperglycemia and survival in patients with glioblastoma. J Neurosurg Anesthesiol. 2017;29(1):21–9. https://doi.org/10.1097/ANA.0000000000000339.
5. Jenkinson MD, Barone DG, Bryant A, et al. Intraoperative imaging technology to maximise extent of resection for glioma. Cochrane Database Syst Rev. 2018;1(1):CD012788. https://doi.org/10.1002/14651858.CD012788.pub2.
6. Li P, Qian R, Niu C, Fu X. Impact of intraoperative MRI-guided resection on resection and survival in patients with gliomas: a meta-analysis. Curr Med Res Opin. 2017;33(4):621–30. https://doi.org/10.1080/03007995.2016.1275935.
7. Caras A, Mugge L, Miller WK, Mansour TR, Schroeder J, Medhkour A. Usefulness and impact of intraoperative imaging for glioma resection on patient outcome and extent of resection: a systematic review and meta-analysis. World Neurosurg. 2020;134:98–110. https://doi.org/10.1016/j.wneu.2019.10.072.
8. Papadopoulos G, Kuhly P, Brock M, Rudolph KH, Link J, Eyrich K. Venous and paradoxical air embolism in the sitting position. A prospective study with transoesophageal echocardiography. Acta Neurochir. 1994;126(2–4):140–3. https://doi.org/10.1007/BF01476424.
9. Eyüpoglu IY, Hore N, Savaskan NE, et al. Improving the extent of malignant glioma resection by dual intraoperative visualization approach. PLoS One. 2012;7(9):e44885. https://doi.org/10.1371/journal.pone.0044885.

10. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7(5):392–401. https://doi.org/10.1016/S1470-2045(06)70665-9.
11. Fukamachi A, Koizumi H, Nukui H. Postoperative intracerebral hemorrhages: a survey of computed tomographic findings after 1074 intracranial operations. Surg Neurol. 1985;23(6):575–80. https://doi.org/10.1016/0090-3019(85)90006-0.
12. Wang C, Niu X, Ren Y, Lan Z, Zhang Y. Risk factors for postoperative intracranial hemorrhage after resection of intracranial tumor in 2259 consecutive patients. World Neurosurg. 2019;129:e663–8. https://doi.org/10.1016/j.wneu.2019.05.239.
13. Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. J Neurosurg. 2013;118(4):873–83. https://doi.org/10.3171/2012.12.JNS111970.
14. Burkhardt J-K, Zinn PO, Graenicher M, et al. Predicting postoperative hydrocephalus in 227 patients with skull base meningioma. Neurosurg Focus. 2011;30(5):E9. https://doi.org/10.3171/2011.3.FOCUS117.
15. Schipmann S, Akalin E, Doods J, Ewelt C, Stummer W, Suero Molina E. When the infection hits the wound: matched case-control study in a neurosurgical patient collective including systematic literature review and risk factors analysis. World Neurosurg. 2016;95:178–89. https://doi.org/10.1016/j.wneu.2016.07.093.
16. Uzuka T, Takahashi H, Nakasu Y, et al. Surgical site infection after malignant brain tumor resection: a multicenter study for induction of a basic care bundle. Neurol Med Chir (Tokyo). 2017;57(10):542–7. https://doi.org/10.2176/nmc.oa.2017-0034.
17. Frisius J, Ebeling M, Karst M, et al. Prevention of venous thromboembolic complications with and without intermittent pneumatic compression in neurosurgical cranial procedures using intraoperative magnetic resonance imaging. A retrospective analysis. Clin Neurol Neurosurg. 2015;133:46–54. https://doi.org/10.1016/j.clineuro.2015.03.005.
18. Hamilton MG, Yee WH, Hull RD, Ghali WA. Venous thromboembolism prophylaxis in patients undergoing cranial neurosurgery: a systematic review and meta-analysis. Neurosurgery. 2011;68(3):571–81. https://doi.org/10.1227/NEU.0b013e3182093145.
19. Faraoni D, Comes RF, Geerts W, Wiles MD. European guidelines on perioperative venous thromboembolism prophylaxis. Eur J Anaesthesiol. 2018;35(2):90–5. https://doi.org/10.1097/EJA.0000000000000710.
20. Bekelis K, Kalakoti P, Nanda A, Missios S. A predictive model of unfavorable outcomes after benign intracranial tumor resection. World Neurosurg. 2015;84(1):82–9. https://doi.org/10.1016/j.wneu.2015.02.032.

Management of Older Patients with Brain Tumors

16

Andrea Wasilewski

The incidence of malignant glioma, specifically glioblastoma (GBM), IDH-wild type, is increasing among older patients [1]. Increased age has been associated with decreased overall survival, with older patients often surviving less than 6 months [2]. The definition of an older adult is variable, although most often is defined as those age 65 or older. Currently, no consensus exists on how to treat older patients with GBM, who have traditionally been underrepresented in clinical trials and often have additional comorbidities and impaired performance status that limit their ability to tolerate standard therapy [3]. Treatment strategies for older patients with glioblastoma are largely physician and institution dependent with large disparities in care. Patients over the age of 70 comprise greater than 25% of the GBM population yet remain significantly under-treated, often receiving no treatment or significantly less than standard care [3]. These patients have unique risks and needs that require careful and often multidisciplinary consideration and care.

The diagnosis, evaluation and determination of appropriate treatment present particular challenges in older adults. Older patients are more likely to experience delays in diagnosis due to non-specific symptoms such as headache, personality or cognitive

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changes. They may be offered less aggressive diagnostic procedures (e.g. offered a diagnostic biopsy rather than resection) and abbreviated courses of treatment or no treatment at all. Additionally, older patients frequently have medical comorbidities which may affect the safety, tolerability and effectiveness of treatment. Though this chapter focuses on evidence-based treatment strategies for older patients with glioblastoma, it is important to do a thorough functional and geriatric assessment prior to embarking on tumor-directed treatment. Older patients with poor performance status, patients who are frail, or patients with a limited life expectancy may be best served with palliative care and early integration of hospice. This chapter highlights the limited existing evidence for treatment of glioblastoma in older adults, approaches for the evaluation and risk stratification of older patients with brain tumors and discusses critical supportive care interventions for this population.

Treatment Options for Older Patients with Malignant Gliomas

The balance between the benefit and risks of glioma treatment in older adults is difficult in the setting of minimal evidence specific to this population. The current standard of care for treatment of glioblastoma (GBM) includes maximally safe surgical resection followed by radiation and alkylating chemotherapy with temozolomide (TMZ), with a median survival of 14.6 months in patients under the age of 70 with good performance status [4]. Subsequently, a randomized trial studying the addition of tumor-treating fields (TTF) to this regimen demonstrated an improvement of median survival to 19.6 months. Patients up to the age of 83 were included in this study, although the median age was much younger at 57 [5]. Older patients have traditionally been underrepresented on glioma clinical trials, thus making it difficult to apply such results to this population. In the past two decades several prospective clinical trials focused specifically on older patients have been conducted, the results of which are summarized in Table 16.1. The majority of these trials included patients

Table 16.1 Prospective randomized clinical trials in older adults with malignant gliomas

Clinical trial	Age	No. of patients	Radiation: Dose/ fraction/Duration (weeks)	Chemotherapy	Median overall survival	Significance
Keime-Guibert et al. [6] Supportive care vs. Standard RT	70–85	42 GBM 39 GBM	50 Gy/1.8 Gy/6		16.9 weeks 29.1 weeks	RT prolongs survival compared to best supportive care
Roa et al. [7] Standard RT vs. HfRT	60+	47 GBM 48 GBM	60 Gy/2Gy/6 40 Gy/2.6 Gy7/3		5.1 months 5.6 months	Hypofractionated RT is non-inferior to standard RT
IAEA Trial [8] HfRT vs. 1 week HfRT	50+	50 GBM 48 GBM	40 Gy/2.67 Gy/3 25 Gy/5 Gy/1		6.4 months 7.9 months	1-week HfRT can be considered in the very elderly and/or frail
NOA-8 [9] TMZ alone vs. Standard RT	66–84	178 GBM 17 AA 153 GBM 23 AA	60 Gy/2 Gy/6	TMZ 100 mg/m^2, 7 days on, 7 days off	8.6 months 9.6 months	TMZ alone is non-inferior to RT alone (most benefit if MGMT methylated)

(continued)

Table 16.1 (continued)

Clinical trial	Age	No. of patients	Radiation: Dose/fraction/Duration (weeks)	Chemotherapy	Median overall survival	Significance
Perry et al. [10] HfRT vs. HfRT + TMZ	65–90	281 GBM 281 GBM	40 Gy/2.67 Gy/3	Concurrent TMZ 75 mg/m^2 for 21 days during RT Adjuvant TMZ 150–200 mg/m^2 for 5 days per 28-day cycles (up to 12 cycles)	7.6 months 9.3 months	HfRT+TMZ should be considered in all older patients with reasonable performance status, particularly if MGMT methylated
Nordic Trial [11] TMZ vs. HfRT vs. Standard RT	60–88	93 GBM 98 GBM 100 GBM	34 Gy/3.4 Gy/2 60 Gy/2 Gy/6	TMZ 200 mg/m^2 for 5 days per 18-day cycles (up to 6 cycles)	8.3 months 7.5 months 6 months	Older patients have better outcomes with HfRT than standard RT TMZ monotherapy can be considered in MGMT methylated patients

GBM Glioblastoma, *AA* anaplastic astrocytoma, *RT* Radiotherapy, *HfRT* hypofractionated radiotherapy, *TMZ* temozolomide

who were functionally able to perform self-care with a Karnofsky Performance Status (KPS) of 70 or above. Data is limited for frail older patients who have additional functional impairments.

Surgical Treatment

Many factors should be considered prior to neurosurgical intervention in older patients. Older patients are more likely to have additional medical comorbidities that may increase their risk of surgical complications, prolonged hospitalization or requirement of rehabilitation post-operatively. Biopsy alone has been shown to have an inferior survival to subtotal or gross total tumor resection, although may be appropriate in those with significantly impaired functional status, significant comorbidities or multifocal tumors [12]. Maximally safe resection should be considered in patients for diagnosis, symptom control and survival benefit whenever possible. Surgical decisions should be guided by the use of a geriatric assessment or screening tool, medical risk evaluation and input from a multidisciplinary tumor board.

Radiotherapy

Radiotherapy should be considered in older glioma patients with several available regimens that can be administered with or without temozolomide. Radiation schedule and dose need to be considered and weighed against risk of adverse effects of treatment such as fatigue, cognitive toxicities and effects on quality of life. A hypofractionated course of radiotherapy (40 Gy in 15 fractions) has been shown to be at least as effective as standard radiotherapy (60 Gy delivered in 30 fractions) and is a preferred regimen for older or frail patients given improved tolerability and convenience. A standard radiotherapy regimen carries an increased risk of fatigue and cognitive dysfunction, which may be persistent and impairing for older patients but may be considered in those patients with excellent functional status. Abbreviated radiotherapy schedules (such as 25 Gy in 5 frac-

tions) can be used for patients with significant frailty or barriers to daily radiotherapy. Whenever possible, hippocampal sparing should be employed to limit both acute and long-term effects on memory and cognition.

Adjuvant Therapy

Apart from TMZ, no other systemic antineoplastic agents have demonstrated a survival benefit for older patients with malignant gliomas [13]. For patients who are functionally independent and without major medical comorbidities, concurrent radiation and TMZ followed by adjuvant treatment with TMZ is recommended and results in prolonged survival over radiation or TMZ alone. Treatment with TMZ is often withheld in patients with impaired performance status or an unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter. Monotherapy with TMZ can be used for patients with MGMT-methylated tumors. While combined chemoradiotherapy confers the largest survival benefit, treatment with TMZ alone can be considered in MGMT-methylated patients with lower performance status (KPS 50–70), significant cognitive issues or barriers to radiotherapy. The use of adjuvant TTF is considered standard of care but requires several considerations in older patients. TTF should be used in patients with adequate support systems to manage skin care as well as the strength and mobility to carry a weighted battery pack.

Older patients are at increased risk of toxicities from treatment with TMZ particularly fatigue, constipation and hematologic adverse effects. TMZ causes thrombocytopenia and lymphopenia which may be dose or treatment limiting. It is reasonable to stop treatment with TMZ in older patients with unmethylated MGMT promoters if they experience significant hematologic toxicities, fatigue or impaired quality of life. Patients with MGMT methylated promoters should be considered for dose reductions or delays in treatment if adverse effects are manageable. Adequate supportive care interventions, such as effective management of constipation, are necessary to improve tolerability of TMZ.

Disease Recurrence

At time of disease recurrence patients often experience functional decline which limits the safety and tolerability of further treatment. Re-resection, re-irradiation and second line chemotherapeutic agents such as lomustine are rarely used in older patients given high risk of morbidity and systemic toxicities. Clinical trials are increasingly becoming more inclusive of older patients and should strongly be considered in the appropriate setting. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is commonly used for recurrent disease in older patients. There are serious toxicities of bevacizumab including nephrotic syndrome, gastrointestinal perforation, hypertension and thromboembolic events—which may occur more frequently in older patients. In patients with significant cerebral edema or those with steroid dependence, bevacizumab can be used for symptomatic control and to improve neurologic function [14, 15]. As there are no therapies which improve survival in recurrent disease, continual reassessment of the safety, tolerability and goals of treatment is recommended. TTF monotherapy, which has demonstrated non-inferiority to physician's choice of chemotherapy, can also be used for disease recurrence with significantly lower risks of systemic adverse effects [16].

Evaluation and Risk Stratification of Older Patients with Malignant Gliomas

In current practice, a patient's functional status is defined using a performance scale such as the Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status. These scales are neither sensitive or specific and are largely based on a physician assessment of a patient's abilities at a specific time point. Additionally, these scales have limitations when used in patients with malignant gliomas, may not accurately reflect the true functional abilities of patients with

neurologic symptoms and are unable to capture small changes in function [17]. Baseline evaluations such as the comprehensive geriatric assessment and screening tools such as the Geriatric-8 survey can be a powerful tool for identifying frailty and predicting treatment risk. The geriatric assessment uses multiple validated tools to assess the geriatric domains of comorbidities, functional and psychological status, cognition, physical performance, nutrition, medication reconciliation and social support [18]. GA has been shown to detect unsuspected condition that may affect cancer treatment in over 50% of older patients [19]. According to the National Comprehensive Cancer Network (NCCN) guidelines for Senior Adult Oncology and the International Society of Geriatric Oncology recommendations, the GA should be a key part of the treatment approach for all older patients with cancer [20]. While the GA has not yet been incorporated into the evaluation of patients of older patients with primary brain tumors it has been shown to assist in selecting those most appropriate for treatment [21]. GA has also been useful in identifying underlying medical, functional and psychosocial issues that may interfere or disrupt treatment and highlighting domains of vulnerability and allow for interventions that may improve outcomes in older cancer patients, such as reducing treatment toxicity [22] (Table 16.2).

When a comprehensive geriatric assessment cannot be completed, a brief screening tool such as the Geriatric-8 (G8) can be considered. The G8 is comprised of 8 questions regarding age, nutritional status, medications, cognition, presence of depression, mobility, and self-rated health metrics. Total scores range from 0 to 17 with a score of 14 or higher defined as normal. Poor scores on the G8 in elderly patients with glioblastoma has been shown to be an independent prognostic factor [23].

Table 16.2 Suggested components of the comprehensive geriatric assessment for older brain tumor patients

Domain	Tool	Score signifying impairment
Physical function	• Activities of daily living (ADL) • Independent activities of daily living (IADL) • Fall history	• Any impairment in ADL or IADL • Any history of falls
Objective physical performance	• Short physical performance battery (4 m walk, chair stands, balance test)	• < or =9
Comorbidity	• Average number of comorbid conditions	• >5 comorbidities
Nutrition	• Body mass index • Mini nutritional assessment	• BMI < 21
Social support	• OARS medical social support	• Any deficit
Polypharmacy	• Number of total medications • Medications on Beer's criteria list	• > or =5 medications • Any medications on Beer's criteria list
Psychological	• Geriatric depression scale	• > or =5
Cognition	• Montreal cognitive assessment	• <26

Supportive Care for Older Adults with Malignant Gliomas

While all brain tumor patients are at risk of treatment- and tumor-related complications, these issues are of particular importance for older patients. This population is at increased risk of polypharmacy, adverse effects from supportive care medications, falls, mood issues and sleep dysregulation which impact quality of life and survival. Supportive care interventions should begin early in the course of treatment and should be continually addressed and reassessed.

Corticosteroids

While the use of corticosteroids is often necessary to decrease cerebral edema and manage neurologic symptoms, older patients may be particularly sensitive to their side effects. Corticosteroids should be used at the lowest tolerated dose that manages neurologic symptoms in order to mitigate toxicities such as weight gain, diabetes, emotional lability, insomnia, proximal myopathy and osteopenia. Older patients are at high risk of developing a proximal myopathy and osteopenia, which increases their risk of falls and subsequent fractures. Skin fragility also occurs with prolonged corticosteroid use and predisposes to skin tears and impaired wound healing- an important consideration, especially in patients also receiving bevacizumab. Emotional lability is a common occurrence with corticosteroids and can manifest as irritability, abnormally elevated mood or hypoactive delirium in older adults. Additionally, corticosteroids increase appetite and result in weight gain which can be problematic and lead to impaired mobility.

Tumor-Associated Epilepsy

Approximately 50% of glioma patients will experience a seizure during their disease course and require treatment with anti-seizure medication (ASM) [24]. Newer generation ASMs are preferred given their lower risk of sedation, bone marrow suppression and hepatotoxicity which may interfere or limit treatment with temozolomide. As fatigue, falls and cognitive dysfunction may be more common in older glioma patients, close attention to drug choice and dosage are required. The lowest possible ASM dose that effectively controls seizures should be used. If possible, older generation drugs such as phenytoin, valproic acid and phenobarbital should be avoided given increased risk of toxicities and drug-drug interactions. Levetiracetam is one of the most commonly used ASMs and is an attractive choice given its renal clearance, minimal drug interactions and relative tolerability. Older

patients are at increased risk of irritability or personality changes with levetiracetam, which can be compounded by toxicities from corticosteroids. Commonly used second line agents include valproic acid and lacosamide. Older patients are also at increased risk of cardiac arrhythmias, therefore an electrocardiogram should be done prior to initiation of lacosamide, as it can cause PR interval prolongation and first-degree atrioventricular block [25].

Fall Prevention

Most older patients with malignant gliomas, particularly those with corticospinal tract dysfunction, ataxia, visual field deficits or pre-existing mobility issues are at risk for falls. A thorough fall history should be obtained at each visit with an older patient. Physical therapy, occupational therapy and home safety evaluations should be considered in any glioma patient with falls, or neurologic impairment putting that at risk for falls. The use of assistive devices or orthotics should also be considered when appropriate.

Cognition Dysfunction

Older patients are more likely than their younger counterparts to experience cognitive effects from the tumor itself, as a consequence of radiotherapy or from supportive care medications such as AEDs. Cognitive ability should be considered in all older patients to determine whether a patient has the decisional capacity to consent to treatment, adhere to medication instructions and understand the indications to seek medical attention [26]. Patients with cognitive impairments often require the involvement of caregivers to maintain their safety. Cholinesterase inhibitors such as donepezil and NMDA receptor antagonists such as memantine which are commonly used for the treatment of Alzheimer's dementia have not been effectively studied in glioma patients. Given the poor prognosis and risks of side effects including nausea, dizziness and increased risk of seizures, use of these medica-

tions for cognition enhancement is generally not recommended for older glioma patients. Social work support and occupational therapy should also be considered all older glioma patients with cognitive dysfunction. Comprehensive review of a patient's medications, metabolic status, mood and fatigue should be done to determine whether these factors may be affecting cognition.

Mood

Mood disorders, particularly major depressive disorder, are common in older brain tumor patients and often under-reported [27]. Older patients are more likely to present with anhedonia, significant fatigue or pseudodementia and their symptoms are often incorrectly ascribed to aging or effects of their tumors and treatments. All older brain tumor patients should be screened for depression at every visit and provided treatment when appropriate. Tricyclic antidepressants should generally be avoided in older patients given the risk of anticholinergic effects which increase the risk of urinary retention, orthostatic hypotension and falls. Bupropion lowers the seizure threshold and should also be avoided. Serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally well tolerated in older patients and should be considered first line for treating depression in older glioma patients. Conventional and atypical antipsychotics should be avoided in older patients given the increased risk of stroke and death in older patients (especially those with a history of dementia). If absolutely necessary for patient safety concerns, a low dose of an atypical antipsychotic can be used.

Fatigue and Sleep Disturbances

Fatigue is reported by 40–70% of brain tumor patients and may be functionally limiting for older adults [28]. The etiology of a patient's fatigue is often multifactorial encompassing the effects of chemotherapy, cranial irradiation, antiepileptic and analgesics,

metabolic derangements, mood disorders and sleep disturbances. It is critical to assess fatigue at every encounter and to complete a thorough assessment of possible contributing factors including all cancer directed treatments, medications, laboratory values, nutritional status, neuropsychiatric symptoms and sleep patterns. Laboratory evaluations of thyroid function, serum sodium, glucose, vitamin B12, urea, ammonia and hematocrit should be considered. Older patients are at significant risk of polypharmacy and dose adjustment or elimination of any sedating medications, in particular opiate and benzodiazepines should be considered.

Aerobic exercise should be recommended to all older patients if their functional status allows, as this has been shown to reduce cancer-associated fatigue [29]. While some patients may experience increased energy from corticosteroids, their use for treatment of fatigue is not recommended given the serious side effects associated with chronic use in older adults. In cases where fatigue is functionally limiting and refractory to medical and lifestyle management, neuro-stimulants such as modafinil and methylphenidate can be used. These drugs should be used with extreme caution in older patients given their increased sensitivity to central nervous stimulation and tachycardia.

Sleep dysregulation is common amongst all brain tumor patients and can be an important cause of fatigue in cancer patients [30]. Sleep disturbances in older patients tend to present as hypersomnia and can be difficult to differentiate from fatigue or depression. All patients should be educated on proper sleep hygiene and in older patients this frequently means limiting or shortening daytime naps. Work-up of excessive sleepiness is similar to the evaluation of fatigue described earlier and in older patients there should be a particular focus on polypharmacy and medication effects.

Insomnia is often reported by brain tumor patients, particularly in patients taking corticosteroids. To manage corticosteroid-induced insomnia, patients should be treated with the lowest possible dose of corticosteroids and evening doses should be avoided. Melatonin is generally safe and is the recommended sleep aid for older brain tumor patients. Antihistamines, benzodiazepines and non-benzodiazepine hypnotics (zolpidem, eszopiclone, zaleplon) appear on Beers Criteria Medication List and should be avoided in

older patients given the increased risk of delirium, ataxia, cognitive dysfunction and falls [31].

Polypharmacy

In patients with a cancer diagnosis, additional comorbidities and polypharmacy are associated with a poorer overall survival [32]. Older patients are at increased risk of drug-drug interactions and toxicities from many medications due to increased sensitivity and decreased metabolism. A thorough medication review should be completed after which medications appearing on the Beers Criteria Medication List should be adjusted or eliminated. Table 16.3 shows a list of medications commonly prescribed medications that should be avoided in older adults. Older brain tumor patients are more sensitive to the compounding effects of centrally acting medications, which may manifest as fatigue or confusion, often occurring at much lower doses than in younger patients. For older patients, discussions regarding limiting or stopping non-essential medications prescribed for other comorbidities may be valuable.

Advance Care Planning

Advance care planning in older brain tumor patients should begin as soon as possible. Given the poor prognosis and increased risk of cognitive and functional decline, treatment goals and advance directives should be discussed and documented prior to starting treatment. Older brain tumor patients often require increased support as their disease progresses. Active and early involvement of caretakers is crucial, as many may be elderly themselves and have limitations to the care they can provide. A multidisciplinary support team including nursing, social work, home care and/or hospice should be considered early in an older patient's disease course to better anticipate changing needs and home support.

Table 16.3 Commonly used medications to avoid in older brain tumor patients

Therapeutic medication class	Commonly prescribed medications	Risks in older patients
Antihistamines	• Diphenhydramine • Hydroxyzine	• Anticholinergic effects • Sedation • Falls
Antipsychotics	• Haloperidol[a] • Perphenazine[a] • Chlorpromazine[a] • Aripiprazole[b] • Olanzapine[b] • Quetiapine[b] • Risperidone[b] • Ziprasidone[b]	• Increased risk of stroke and mortality in older adults with dementia
Barbiturates	• Butalbital • Phenobarbital	• Sedation • Physical dependence • Risk of overdose at low doses
Tricyclic antidepressants	• Amitriptyline • Clomipramine • Doxepin • Imipramine • Nortriptyline • Maprotiline	• Anticholinergic effects • Orthostatic hypotension • Falls • Sedation
Benzodiazepines[c]	• Alprazolam • Lorazepam • Temazepam • Chlorazepate • Clonazepam • Diazepam • Flurazepam	• Cognitive impairment • Delirium • Sedation • Falls • Fractures • Paradoxical agitation
Non-benzodiazepine hypnotics	• Eszopiclone • Zolpidem • Zaleplon	• Delirium • Falls • Fractures • Confusion • Minimal effect on sleep latency or duration
Skeletal muscle relaxants	• Cyclobenzaprine • Tizanidine	• Anticholinergic effects • Sedation • Falls

[a] First generation antipsychotics
[b] Atypical antipsychotics
[c] Benzodiazepines may be appropriate for procedural sedation, seizure abortion or end-of-life care

References

1. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst. 2008;100(9):630–41.
2. Iwamoto FM, et al. Patterns of care in elderly glioblastoma patients. Ann Neurol. 2008;64(6):628–34.
3. Dressler EV, Liu M, Garcia CR, et al. Patterns and disparities of care in glioblastoma. Neurooncol Pract. 2019;6(1):37–46.
4. Stupp R, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96.
5. Stupp R, Wong E, Scott C, et al. Interim analysis of the EF-14 trial: a prospective, multi-center trial of Novo-TTF-100A together with temozolomide compared to temozolomide alone in newly diagnosed GBM. Neuro Oncol. 2014;16:167.
6. Keime-Guibert F. Radiotherapy for glioblastoma in the elderly. N Engl J Med. 2007;356(15):1527–35.
7. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol. 2004;22(9):1583–8.
8. Roa W, Kepka L, Kumar N, et al. International Atomic Energy Agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. J Clin Oncol. 2015;33(35):4145–50.
9. Wick W, Platten M, Meisner C. Temozolomide chemotherapy alone versus radiotherapy alone from malignant astrocytoma in the elderly: the NOA-08 randomised phase 3 trial. Lancet Oncol. 2012;13(7):707–15.
10. Perry JR, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med. 2017;376(11):1027–37.
11. Malmstrom A, Gronberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomized, phase 3 trial. Lancet Oncol. 2012;13(9):916–26.
12. Chaichana KI, Chaichana KK, Olivi A, et al. Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival. Clinical article. J Neurosurg. 2011;114(3):587–94.
13. Hanna C, Lawrie TA, Rogozinska E, et al. Treatment of newly diagnosed glioblastoma in the elderly: a network meta-analysis. Cochrane Database Syst Rev. 2020;3:CD013261.
14. Friedman HS, et al. Bevacizumab alone and in combination with irinotecan. J Clin Oncol. 2009;27(28):4733–40.
15. Gilbert MR, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699–708.

16. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48(14):2192–202.
17. Stark AM, Stepper W, Mehdorn HM. Outcome evaluation in glioblastoma patients using different ranking scores: KPS, GOC, mRS and MRC. Eur J Cancer Care. 2010;19:39–44.
18. Roa AV, Hsieh F, et al. Geriatric evaluation and management units the care of the frail elderly cancer patient. J Gerontol A Biol Sci Med Sci. 2005;60:798–803.
19. Rodin MB, Mohile SG. A practical approach to geriatric assessment in oncology. J Clin Oncol. 2007;25:1936–44.
20. NCCN Clinical practice guidelines in oncology. n.d.. https://www.nccn.org/professionals/physician_gls/default.aspx#age. Accessed 21 Mar 2020.
21. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595–603.
22. Puts MT, Hardt J, Monette J, et al. Use of geriatric assessment for older adults in the oncology setting: a systematic review. J Natl Cancer Inst. 2012;104:1133–64.
23. Deluche E, Leobon S, Lamarche F, et al. First validation of the G-8 geriatric screening tool in older patients with glioblastoma. J Geriatr Oncol. 2019;10:159–63.
24. Wychowski T, Wang H, Buniak L, et al. Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation of AEDs. Clin Neurol Neurosurg. 2013;115(11):2365–9.
25. Delaunois A, Colomar A, Depelchin BO, et al. Cardiac safety of lacosamide: the non-clinical perspective. Acta Neurol Scand. 2015;132(5):337–45.
26. Wadley VG, Okonkwo O, et al. Mild cognitive impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living. Am J Geriatr Psychiatry. 2008;16:416–24.
27. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. J Natl Cancer Inst. 2011;103(1):61–76.
28. Armstong TS, Gilbert MR. Practical strategies for management of fatigue and sleep disorders in people with brain tumors. Neuro Oncol. 2012;13(Suppl 4):iv65–72.
29. Cramp F, Byron-Daniel J. Exercise for the management of cancer-associated fatigue in adults. Cochrane Database Syst Rev. 2012;11:CD006145.
30. National Comprehensive Cancer Network. Cancer-related fatigue (Version 2.2015). 2015. https://jnccn.org/abstract/journals/jnccn/13/8/article-p1012.xml. Accessed 28 Mar 2020.

31. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227.
32. Maione P, Perrone F, Gallo C, et al. Pre-treatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol. 2005;23:6865–72.

Palliative Care in Neuro-oncology

17

Young-Bin Song and Lynne P. Taylor

Introduction

Palliative care is the active, total care of patients and families who are dealing with serious, life-threatening, illness which is not expected to be responsive to curative treatment. Palliate, derived from the Latin root *palliare*, or "to cloak," means to protect and comfort with the goal of preserving the best possible quality of life. Because the hospice movement began in the United States in 1985 with the establishment of the Medicare hospice benefit, and the National Hospice Organization renamed as the National Hospice and Palliative Care Organization (NHPCO) in 2000, the average American has always assumed that palliative care and hospice services are one and the same. It is our hope that palliative care becomes a normative part of the early care of our patients with primary brain tumors to allow adequate exploration of goals of care, and to improve communication and maximize treatment of all symptoms. The goal is to acknowledge dying as a natural process and to provide compassionate care by relieving physical, social, psychological, and spiritual suffering.

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Introduction of Palliative Care Throughout the Disease Course

What Should the Neuro-oncologist Be Addressing Themselves?

Studies of palliative care in cancer patients have recognized that early introduction of palliative care results in improved symptom management and quality of life and reduction in the use of aggressive therapies near death. The value of palliative care is increasingly recognized in nonmalignant neurologic diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson disease, multiple sclerosis, and Huntington disease, with a focus on expert treatment of physical symptoms, interdisciplinary communication and assisting with the formulation of advanced care plans.

The American Academy of Neurology (AAN) published a position paper in 2022 updating the appropriate palliative care for patients with disorders of consciousness. In addition, it tried to distinguish between palliative care provided by neurologists to all patients with neurologic diseases versus the sub-specialty Palliative care that is also often required to appropriately and aggressively manage troublesome symptoms [1]. Palliative care in neuro-oncology sits at the nexus between the two worlds of oncology and neurology. One study of symptom burden in patients with malignant glioma found a high incidence of mood issues, confusion, communication deficits, headaches, seizures, and decreased mobility from hemiparesis [2]. Because of these challenges our patients necessarily rely heavily on family members and caregivers to communicate their needs, which brings unique challenges to their care team.

Communication Skills

Communication within a neuro-oncology practice presents numerous challenges brought about by our patient's symptoms and varying degrees of caregiver support. Many of our patients suffer from slowed cognitive processing, aphasia, and difficulties with insight and judgment, and might not be fully able to participate in discussions about prognostication, goals of care, or

advance care planning. Family members are often forced to be proxy decision-makers, a role for which they feel unprepared.

Therefore, excellent communication requires an understanding of patient and family emotions when explaining complex medical facts and formulating treatment plans compatible with patients' wishes and goals [3]. This is a fluid situation that requires frequent re-evaluation throughout the disease course, and it is a challenge to determine when to introduce the concept of palliative care. The timing of advanced care planning [advanced directives and portable medical orders or physician orders for life-sustaining treatment (POLST)] and end-of-life/hospice care discussions in a studied neuro-oncology population was highly variable [4]. Determining whether to involve a specialist palliative care team for facilitating these conversations is both patient and disease specific. Patients may intuitively understand the benefits of palliative care consultation but still decline the option due to logistical and travel challenges.

Excellent communication can be practiced and there are strategies and guidelines [5] to help us navigate through often difficult conversations. Unfortunately, given the nature of our specialty, we are often giving information which will be interpreted as "bad news," even if it is just "uncertain news." We firmly believe that it is important that neuro-oncologists embrace the empathic communication of complex news as part of their sub-specialty expertise.

Delivering Bad News

The SPIKES protocol (Table 17.1) is designed for delivering unwelcome news to cancer patients. Its aim is to gather information from the patient, give medical information, provide support

Table 17.1 The SPIKES protocol for delivering bad news

S: SETTING UP the interview
P: Assessing the patient's PERCEPTION
I: Obtaining the patient's INVITATION
K: Giving KNOWLEDGE and information to the patient
E: Addressing the patient's EMOTIONS with empathic responses
S: STRATEGY AND SUMMARY

Baile et al. (2000) [6]

Table 17.2 The NURSE acronym

Naming	Name the emotion
Understanding	Acknowledge and explain their perspective
Respecting	Respect the patient by offering praise or reassurance
Supporting	Support the patient by offering your presence and expertise
Exploring	Explore the emotions further by using "Tell me more" statements

Back et al. (2009) [7]

to patients, and develop a treatment plan together consistent with the patient's goals.

Responding to Emotions

The NURSE acronym is a tool that can be used to help us identify emotions and respond in ways to help us understand the patient perspective more completely. See Table 17.2.

Prognostication

Discussion of prognosis should begin by first asking permission from the patient and family if they are ready to have the conversation while adjusting it in the moment to their emotional responses [8]. When symptom progression leads to re-addressing treatment plans or goals of care, prognostic discussions are vital. To help decision making, if asked about the likelihood of overall survival, instead of using a specific period, it is recommended to use terms like "months to years," "days to weeks," or "hours to days" [8].

When Do We Need to Involve a Palliative Care Expert?

We are inconsistent in how often our patients are referred to palliative care. Studies by Walbert [9, 10] have demonstrated that there is variability in utilization of specialty palliative care consultation from neuro-oncologists. Neuro-oncologists differ in their comfort level in dealing with end-of-life issues. One group of

neuro-oncologists adopted a "solo practice model" in which they used both their skills at providing tumor-directed therapies and palliative care as needed, whereas other neuro-oncologists referred their patients to the specialty palliative care service [9]. We know that having a perspective free from treatment decisions can prevent "folie à deux (folly of the two)," a condition where both the patient and the treating physician unconsciously tell each other that things are going better than they are, as a coping mechanism.

In addition, patients are referred to palliative care at different time points from close to diagnosis to near death. Referral to a specialist palliative care service typically occurs late in the trajectory of the disease and bridges to hospice care, which has been termed the "Traditional Approach" [9]. While studies have shown the benefit of the "Integrated Approach" for oncology patients, where early referral is made to palliative care, we still lack unambiguous evidence from randomized studies of the efficacy and benefit of this approach for brain tumor patients but, nonetheless, believe it is likely to be the best model based on data from patients with metastatic lung cancer [11].

Common Symptoms in Patients with Brain Tumors

Cognitive Dysfunction

Cognitive dysfunction is common among brain tumor patients, including deficits in memory, attention, and executive functioning, and can be caused by the tumor, seizures, and side effects of treatment [8] as well as energy levels, sleep quality, and medication side effects.

Managing cognitive dysfunction can be difficult. Setting short and long-term goals can be helpful for those who exhibit disorganization; cognitive rehabilitation can improve visual attention and verbal memory. Patients with attentional deficits might benefit from pharmacologic interventions such as methylphenidate (Ritalin) or modafinil (Provigil) though proof of efficacy in large studies does not exist. See Table 17.3.

Table 17.3 Pharmacologic management for fatigue

Condition	Medications	Dosing
Attention and fatigue	Methylphenidate IR (Ritalin) Methylphenidate SR (Concerta)	10 mg twice daily 18 mg q day
	Dextro/ amphetamine	5–10 mg in 1–2 divided doses
	Modafinil[a]	200 mg q a.m.
Insomnia	Melatonin	2–3 mg 30 min before bedtime
	Trazodone	50 mg 1 h before bedtime Range: 50–100 mg daily
Nighttime agitation and delirium	Quetiapine	Starting dose: 25 mg at bedtime Range: 25–75 mg daily
	Risperidone	Starting dose: 0.5–1 mg at bedtime Range: 0.5–2 mg daily
	Olanzapine	Starting dose: 2.5 mg at bedtime Range: 2.5–5 mg daily
	Lorazepam	Starting dose: 0.5 mg at bedtime Range: 2–3 mg per day divided 2–3 times a day
	Diazepam	Starting dose: 2–5 mg daily Range: 2–10 mg every 3–4 h a day
	Haloperidol	0.5 mg every 1–4 h, as needed per day

Walbert (2017) [12], Gehring et al. (2012) [13], Thomas and Carver (2015) [14]

[a] Porter et al. (2020) [15] study demonstrated no improvement in fatigue in high grade glioma population using armodafinil (Nuvigil)

Fatigue

Fatigue occurs commonly in our brain tumor patients and is multifactorial in etiology. It affects more than 80% of patients who are undergoing radiation therapy [12]. Fatigue can also result from chemotherapy, both directly as a drug side effect, and indirectly by anemia and metabolic deficiencies. Other contributing factors include anxiety and depression, seizure medications, steroid use, and decreased mobility.

Management strategies for fatigue should be specific and targeted. Fatigue due to medications should lead to a discussion of

risks verses benefits, and feasible alternative medications. For cancer-related fatigue, a nonpharmacologic intervention can be encouragement to increase physical exercise [16].

Psychostimulants are generally well tolerated and may be beneficial for improving cognitive functioning and mood in selected brain tumor patients. See Table 17.3.

Insomnia

Insomnia is a common symptom among primary glioma patients. In one study by Robertson et al. (2016) [17], 46.8% of 340 recurrent glioma patients had insomnia and 20% required the use of sleep medications. Causes of insomnia are multifactorial, including mood issues, disruption to circadian rhythm, and steroid use. The same study [17] found that use of corticosteroids was associated with insomnia. Treatments for insomnia include sleep hygiene education, evaluation for sleep apnea, and sleep aid medications. Pharmacologic sleep aids include melatonin, trazodone, and for those experiencing nighttime agitation or delirium, consider atypical psychotics, such as quetiapine or risperidone (Table 17.3).

Mood Issues

Mood issues are common in neuro-oncology patients and are caused by many varied factors, including past psychiatric illness and medication side effects (dexamethasone and antiepileptic drugs (AEDs). Among patients with primary brain tumors, the rates of depression can vary from 13 to 47% and rates of anxiety from 35 to 48% [18]. These negatively affect our patient's quality of life through decreased emotional well-being, which should be screened and addressed during clinic visits.

A meta-analysis [19] confirmed that physician-based assessment tools are reliable and consistent for diagnosing depression in a clinical setting. Different treatment options (see Table 17.4) for depression include medication, counseling, and therapy. SSRIs and SNRIs are generally well tolerated with minimal drug-to-drug interactions. Gabapentin, lamotrigine and valproic acid can all be used as mood stabilizers. Pseudobulbar affect (PBA) can be a very difficult problem in patients with either deep bihemispheric

Table 17.4 Depression and anxiety medications

Class	Medications	Dose range
Selective serotonin reuptake inhibitors (SSRI)	Citalopram	20–40 mg daily
	Escitalopram	10–20 mg daily
	Fluoxetine	20–80 mg daily
	Sertraline	50–200 mg daily
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20–30 mg twice a day
	Venlafaxine	37.5–75 mg twice a day
AEDs (off-label or adjunct)	Lamotrigine	Slow upward titration 25 mg daily to 200 mg daily in weekly increments
	Valproic acid	250–500 mg three times daily
	Gabapentin (anxiety)	300–900 mg three times daily

tumors or those in the brainstem. Dextromethorphan/quinidine (Neudexta) which comes in a 20 mg/10 mg capsule and is used in doses of 1 cap bid can lessen emotional incontinence and lead to improvement in quality of life.

Headache

Headaches in brain tumor patients often present in a similar fashion to migraines and will respond if treated as such, if not due to increased intra-cranial pressure [20]. Otherwise, of course, steroid therapy is the mainstay of treatment.

Steroid Use

Steroids are used to treat vasogenic edema and can rapidly alleviate focal neurologic symptoms. Dexamethasone is the steroid of choice, due to its long half-life and lack of mineralocorticoid activity. It has many side effects, however, including insomnia, irritability, psychosis, delirium, and anxiety, in addition to hyperglycemia and proximal muscle weakness. While dexamethasone is given 3–4 times a day in the hospital, it should be given only once or twice daily in the outpatient setting as it has an exception-

Table 17.5 Steroid tapering guideline

- Goal: "As little as possible, but much as you need"
- Most can safely taper down every 3–7 days to dexamethasone 2 mg daily. Once at 2 mg daily, long-term steroid users >3 weeks may require slow taper every 14 days
- If dexamethasone dosing is BID, second dosing should be no later than 2 p.m.
- For slow taper schedule, consider obtaining morning fasting cortisol level
  - Level < 10 μg/dL, further tapering likely necessary, consider switching to hydrocortisone or prednisone
  - Level > 10 μg/dL, dexamethasone can be discontinued
- Consider PJP (Pneumocystis Jirovecii Pneumonia) prophylaxis with trimethoprim/sulfamethoxazole at dexamethasone ≥3 mg daily for >1 month duration or lymphopenia (ALC < 500 or CD4 < 200)

Steroid Conversion Chart

Steroid	Equivalent dose (mg)	Duration of action
Dexamethasone	0.75	36–72 h
Hydrocortisone	20	8–12 h
Prednisone	5	8–12 h

Shimmer and Funder (2017) [21]

ally long serum half-life of 36–72 h, with the second dose early in the afternoon to mitigate against insomnia. Look for opportunities for dose tapering and give a clear schedule to patients and caregivers. See Table 17.5 for guidelines. Dexamethasone can usually be tapered quickly down to 2 mg daily, followed by a slower tapering plan.

Seizures: See Table 17.7. Most of our patients will have a well-defined anti-convulsant regimen by the time they are near the end of their lives. In an urgent situation, it is helpful to know that both midazolam and diazepam can be given intra-nasally. Both now have a pre-packaged device for administration but a small syringe, fitted with a mucosal atomization device (MAD) is much less expensive. One to two drops can also be dripped into the nasal cavity with seizure cessation at 4 min [23].

Approach to Advanced Care Planning

Discussions about a patient's goals and wishes should occur at the time of diagnosis and be re-evaluated throughout the disease course. These conversations will shape the discussion of potential future treatment planning. One helpful tool, called the "Ask, Tell, Ask" method is used to assess a patient's understanding regarding any issue they might face (Table 17.6).

Part of the goals of care discussions involve advance care planning (Table 17.7), which aims to encourage shared decision making with caregivers or family members regarding patients' wishes and preferences. This includes completing POLST forms, regarding the use of cardiopulmonary resuscitation and other medical interventions, and advance directives [22].

Five Wishes: This is an excellent resource to help people navigate their wishes regarding DPOA and other aspects of palliative care during a serious illness. It is legal in most states when signed by two individuals and can be accessed and stored online at: https://fivewishes.org/individuals-and-families.

Table 17.6 Ask, Tell, Ask Method

Ask: the patient to describe his/her current understanding of the issue
Tell: the patient in straightforward language what you need to communicate in small chunks
Ask: the patient if he/she understood what you just said

Back et al. (2005) [24]

Table 17.7 Advanced care planning

Legal documents	Medical orders
• Advance directives • Living wills, healthcare power of attorney	• Portable medical order; POLST and others • Do-not-resuscitate orders
• Surrogate appointment and statement of preferences	• Medical orders based on shared decision-making

POLST legislative Guide (2014) [22]

Family/Caregivers

Family members are important because they are also caregivers and bear significant physical and emotional loads of their own. Our patients rely on their caregivers to keep them safe around the house, transport them to clinic visits and therapies, and help them remain compliant with their medications. Family members often express distress at the fact that they feel unprepared to manage unexpected symptoms such as seizures and abrupt neurologic decline. It is important to identify and address any barriers for access to resources for social, emotional, and psychological needs, including counseling services and support groups.

Hospice and End of Life Care

During the end-of-life phase, the symptom burden is always high and can produce significant distress in patients, family members and caregivers. With progressive tumor growth, patients experience worsening neurologic and cognitive deficits and fatigue, often caused by increased vasogenic edema. Dexamethasone can be restarted or increased in dose for short-term symptom relief, though doses of 2–4 mg daily should be considered the maximum without further upward dose titration as that increases delirium and agitation (Table 17.8).

Seizures are common during this period, occurring in 45% of patients [25]. Seizure management can be further complicated by dysphagia, which has been observed in 70% of patients in their last month of life who have difficulty with nutritional, fluid, and medication intake. Alternative AED options are available; see Table 17.9. There is no medical justification for the use of fluids and nutrition via feeding tube for our patients. When there are no longer any treatments that will lead to the slowing of growth of a brain tumor, the use of fluids often worsens cerebral edema and delirium without providing any benefit.

Table 17.8 Symptoms during end-of-life phase

Symptoms	% of patients (N = 55)
Drowsiness/progressive loss of consciousness	48
Dysphagia	39
Progressive focal neurological deficits	28
Seizures	25
Incontinence	22
Progressive cognitive deficits	18
Headache	18
Confusion	16
Bodily pain	14
Fatigue	14
Nausea/vomiting	11
Dyspnea	9
Constipation	5
Anxiety/depressive symptoms	5

Adopted from Sizoo et al. (2010) [25]

Table 17.9 Pharmacologic therapies during the end-of-life

Condition	Medications	Route and dosing
Cerebral edema	Dexamethasone	2–4 mg daily with no further upward adjustments
Seizures	Phenobarbital	PO: 50–100 mg 2 or 3 times daily IM: 1–3 mg/kg/day SC: 1200 mg/day
	Diazepam	Rectal: 0.3 mg/kg, then 20 mg PR Intranasal: 5/7.5/10 mg per 0.1 mL
	Lorazepam	IM/SC: 0.1 mg/kg
	Midazolam	Intranasal: 0.2 mg/kg
	Clonazepam	IM/SC: 1 mg
Agitation and delirium	Haloperidol	PO: 0.5–2 mg 2–3 times daily IM: 2–5 mg every 4–8 h or up to hourly; max: 20 mg/day
	Quetiapine	25–100 mg daily, in divided doses
	Olanzapine	2.5–5 mg daily

Adapted from Krouwer et al. (2000) [26]

Delirium can be multi-factorial, produced by medications, organ failure and infection, and metabolic imbalance. Antipsychotics, such as quetiapine and olanzapine can be helpful for agitated delirium, and when a patient is unable to swallow, haloperidol can be administered via intramuscular route.

Unlike other patients with solid tumors, the end of life for brain tumor patients generally does not include much physical pain. Death is most often caused by brain herniation [25], although a more recent glioblastoma autopsy study demonstrated extensive brainstem infiltration showing that recent extensions of survival rates may be leading to a different root cause of death than historically described [27]. During the days to weeks before dying, symptoms of drowsiness and dysphagia increase significantly to 87% and 71% respectively [25]. Patients have more difficulty clearing their pharyngeal secretions and they develop a loud respiratory noise, known as the "death rattle." These symptoms can be alleviated with atropine drops, glycopyrrolate, or scopolamine patch [14]. Eventually, patients become less conscious and descend through drowsiness to somnolence, and then coma in the days before death, generally succumbing to dehydration over 10–14 days.

References

1. Taylor LP, Besbris JM, Graf WD, Rubin MA, Cruz-Flores S, Epstein LG, et al. Clinical Guidance in Neuropalliative Care: An AAN Position Statement. Neurology. 2022;98(10):409–16. https://doi.org/10.1212/wnl.0000000000200063.
2. Faithfull S, Cook K, Lucas C. Palliative care of patients with a primary malignant brain tumour: care review of service use and support provided. Palliat Med. 2005;19(7):545–50. https://doi.org/10.1191/0269216305pm1068oa.
3. McFarlin JM, Barclay JS. Communicating effectively. In: Creutzfeldt CJ, Kluger BM, Holloway RG, editors. Neuropalliative care. A guide to improving the lives of patients and families affected by neurologic disease. Cham: Springer; 2019. p. 151–60.
4. Gofton TE, Graber J, Carver A. Identifying the palliative care needs of patients living with cerebral tumors and metastases: a retrospective analysis. J Neurooncol. 2012;108(3):527–34. https://doi.org/10.1007/s11060-012-0855-y. Epub 2012 Mar 31.

5. Gilligan T, Coyle N, Frankel RM, Berry DL, Bohlke K, Epstein RM, et al. Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol. 2017;35(31):3618–32. https://doi.org/10.1200/JCO.2017.75.2311. Epub 2017 Sep 11.
6. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES—A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302–11. https://doi.org/10.1634/theoncologist.5-4-302.
7. Back AL, Arnold RM, Tulsky JA. Mastering communication with seriously ill patients: balancing honesty with empathy and hope. Cambridge: Cambridge University Press; 2009.
8. Sharma A, Taylor LP. Malignant brain tumors. In: Creutzfeldt CJ, Kluger BM, Holloway RG, editors. Neuropalliative care. A guide to improving the lives of patients and families affected by neurologic disease. Cham: Springer; 2019. p. 117–33.
9. Walbert T. Integration of palliative care into the neuro-oncology practice: patterns in the United States. Neurooncol Pract. 2014;1(1):3–7. https://doi.org/10.1093/nop/npt004.
10. Walbert T, Glantz M, Schultz L, Puduvalli VK. Impact of provider level, training, and gender on the utilization of palliative care and hospice in neuro-oncology: a North-American survey. J Neurooncol. 2016;126(2):337–45. https://doi.org/10.1007/s11060-015-1973-0. Epub 2015 Oct 30.
11. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. NEJM. 2010;363:733–42.
12. Walbert T. Palliative care, end-of-life care, and advance care planning in neuro-oncology. Continuum. 2017;23(6):1709–26. https://doi.org/10.1212/CON.0000000000000538.
13. Gehring K, Patwardhan SY, Collins R, Groves MD, Etzel CJ, Meyers CA, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. J Neurooncol. 2012;107(1):165–74. https://doi.org/10.1007/s11060-011-0723-1. Epub 2011 Oct 2.
14. Thomas AA, Carver A. Essential competencies in palliative medicine for neuro-oncologists. Neurooncol Pract. 2015;2(3):151–7. https://doi.org/10.1093/nop/npv011. Epub 2015 May 12.
15. Porter AB, Heshan L, Sadhna K, Cerhan JH, Sloan JA, McMurray R, et al. A phase III randomized, double-blind placebo-controlled study of armodafinil (Nuvigil) to reduce cancer-related fatigue in patients with high-grade glioma (Alliance A221101). J Clin Oncol. 2020;38:15. Epub 2020 May 25.
16. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012;11:CD006145. https://doi.org/10.1002/14651858.CD006145.pub3.

17. Robertson ME, McSherry F, Herndon JE, Peters KB. Insomnia and its associations in patients with recurrent glial neoplasms. Springerplus. 2016;5(1):823. https://doi.org/10.1186/s40064-016-2578-6. eCollection 2016.
18. Ford E, Catt S, Chalmers A, Fallowfield L. Systematic review of supportive care needs in patients with primary malignant brain tumors. Neuro Oncol. 2012;14(4):392–404. https://doi.org/10.1093/neuonc/nor229. Epub 2012 Feb 3.
19. Huang J, Zeng C, Xiao J, Zhao D, Tang H, Wu H, et al. Association between depression and brain tumor: a systematic review and meta-analysis. Oncotarget. 2017;8(55):94932–43. https://doi.org/10.18632/oncotarget.19843.
20. Nelson S, Taylor LP. Headaches in brain tumor patients: primary or secondary? Headache. 2014;54(4):776–85. https://doi.org/10.1111/head.12326.
21. Shimmer BP, Funder JW. Adrenocorticotropic hormone, adrenal steroids, and the adrenal cortex. In: Brunton LL, Knollmann BC, Hilal-Dandan R, editors. Goodman & Gilman's: the pharmacological basis of therapeutics, 13th ed. McGraw-Hill. 2017. https://accessmedicine-mhmedical-com.offcampus.lib.washington.edu/content.aspx?bookid=2189&sectionid=172482605. Accessed 24 Jan 2021.
22. National POLST Paradigm Task Force. POLST legislative guide. 2014. http://www.polst.org. Accessed 24 Jan 2021.
23. Mahmoudian T, Mohammadi Zadah M. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. Epilepsy Behav. 2004;5:253–5.
24. Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. CA Cancer J Clin. 2005;55(3):164–77. https://doi.org/10.3322/canjclin.55.3.164.
25. Sizoo EM, Braam L, Postma TJ, Pasman HRW, Heiman J, Klein M, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. Neuro Oncol. 2010;12(11):1162–6. https://doi.org/10.1093/neuonc/nop045. Epub 2010 Jan 27.
26. Krouwer HG, Pallagi JL, Graves NM. Management of seizures in brain tumor patients at the end of life. J Palliat Med. 2000;3(4):465–75. https://doi.org/10.1089/jpm.2000.3.4.465.
27. Drumm MR, Dixit KS, Grimm S, Kumthekar P, Lukas R, Raizer JJ, et al. Extensive brainstem infiltration, not mass effect, is a common feature of end-stage cerebral glioblastomas. Neuro Oncol. 2020;22(4):470–9. https://doi.org/10.1093/neuonc/noz216.

Correction to: Neurosurgical Complications in Brain Tumor Patients

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In the original publication of the book, the below listed errors have been corrected.

In chapter 15, on page 238, rivaroxaban: stop 24 hours before; apixaban: stop 8 hours before surgery has been corrected to rivaroxaban: stop 48 hours before; apixaban: stop 48 hours before surgery in the revised publication.

The updated version of this chapter can be found at
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