Foundations of Neuro-Oncology: A Multidisciplinary Approach

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Neuro-oncology is a branch of medicine focused on the diagnosis and treatment of primary and secondary tumors of the nervous system as well as the neurologic complications of cancer and cancer treatments. In practice, neuro-oncologists require an intimate knowledge of the neurologic presentation and management of central nervous system tumors, including gliomas, meningiomas, primary central nervous system lymphoma, metastases to the nervous system, and others. The mainstays of treatment for most nervous system tumors include surgical intervention, radiation therapy, and medical treatment with chemotherapy, immunotherapy, and/or targeted therapy. Interdisciplinary collaboration is thus critical to neuro-oncology. The prognosis for many central nervous system tumors, including gliomas and brain metastases, is often poor despite the advent of novel medical therapies. Efforts to develop more effective therapies are ongoing, and patient enrollment in clinical trials assessing the efficacy of new treatments is crucial to improve outcomes.

INTRODUCTION

Neuro-oncology is a rapidly evolving field that exists at a crossroads of multiple disciplines. Management of primary and metastatic tumors of the central nervous system (CNS) involves coordination of medical and surgical treatment of these conditions as well as associated complications, including complications of the therapies themselves. Frequent communication and collaboration across medical specialties is required.

This review focuses on the foundations of neuro-oncology, including the role of neuro-oncologists in clinical practice, their training, and their operation within a multidisciplinary team that includes neurosurgeons, radiation oncologists, medical oncologists, neuroradiologists, and neuropathologists. We also discuss the complex decision making required for the management of common CNS tumors.

ROLE OF NEURO-ONCOLOGISTS IN CLINICAL PRACTICE

The practice of neuro-oncology is multifaceted and involves diagnosis and treatment of primary and metastatic tumors affecting the CNS. In addition, neuro-oncologists are involved in diagnosing and managing neurologic complications of cancer and associated treatments. Accordingly, neuro-oncology uniquely requires close and frequent collaboration with representatives of multiple disciplines, including neurosurgery, neuroradiology, neuropathology, radiation oncology, medical oncology, palliative care, and rehabilitation medicine. Historically, neuro-oncology mostly involved treatment of gliomas and other primary brain tumors, typically through use of surgery, radiation, and a few cytotoxic chemotherapies. However, neuro-oncology has rapidly evolved with the advent of safer neurosurgical techniques, new neuroimaging modalities, new therapeutic options for brain

Key words
- Brain metastases
- Brain tumors
- Gliomas
- Meningiomas
- Neuro-oncology
- Primary CNS lymphoma
- Tumor boards

Abbreviations and Acronyms
BCNU: Carmustine
CCNU: Lomustine
CNS: Central nervous system
CSF: Cerebrospinal fluid
FDA: Food and Drug Administration
GBM: Glioblastoma
IDH: Isocitrate dehydrogenase
KPS: Karnofsky Performance Status
MRI: Magnetic resonance imaging
PCNSL: Primary central nervous system lymphoma
PCV: Procarbazine, lomustine, and vincristine
SRS: Stereotactic radiosurgery
TTF: Tumor treating field
UCNS: United Council for Neurologic Subspecialties
VEGF: Vascular endothelial growth factor
VTE: Venous thromboembolism
WBRT: Whole-brain radiotherapy
WHO: World Health Organization

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metastases, and inclusion of molecular profiling in the diagnosis and treatment of brain tumors.[1,2] The 2016 update to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System incorporated molecular parameters, in addition to histology, into the diagnosis of CNS tumors for the first time,[3,4] which has affected clinical practice substantially. The bulk of neuro-oncologic practice, including therapeutic decision making and implementation of treatment strategies, occurs in the outpatient setting, although neuro-oncologists may also offer opinions regarding neuro-oncologic diagnoses and treatment plans in consultation in the inpatient setting, particularly regarding acute presentations of neurologic complications of cancer and cancer therapies. Further, neuro-oncologists are playing a larger role in the management of brain metastases from systemic malignancies.

Patients with primary CNS tumors (tumors that arise within the brain or spinal cord) represent a substantial proportion of clinical practice in neuro-oncology because many medical oncologists deal on their own with the secondary complications of systemic cancer in their own patients. Gliomas are the most common primary brain tumors in adults, and the bulk of clinical practice in adult neuro-oncology involves treatment of both high-grade gliomas (including glioblastoma [GBM]) and low-grade gliomas. However, neuro-oncologists also care for patients with other CNS tumors, such as meningiomas, primary CNS lymphoma (PCNSL), and medulloblastoma. After diagnosis, neuro-oncologists must assess the need for chemotherapy and/or radiation therapy, which must be coordinated with radiation oncology. If chemotherapy is indicated, the appropriate chemotherapeutic regimen depends on the specific histopathologic/molecular diagnosis (discussed in further detail in the section on "Epidemiology and Management of Common CNS Tumors"). For example, for high-grade gliomas of astrocytic differentiation, including GBM, the mainstay of initial postoperative treatment consists of a regimen of radiation therapy and concurrent chemotherapy with temozolomide followed by adjuvant temozolomide.[5] Patients must be monitored closely for toxicities such as nausea, constipation, and bone marrow suppression. Certain primary CNS tumors (e.g., meningiomas), may not require cytotoxic chemotherapy, and management after resection involves active surveillance for recurrence and consideration of radiation therapy depending on the histologic grade. Because effective treatment options remain limited for many brain tumors, clinical trials of experimental therapies may be considered on initial diagnosis or at recurrence.

Neuro-oncologists are responsible for monitoring for recurrence of all primary CNS tumors with serial neuroimaging (typically magnetic resonance imaging [MRI] of the brain or spine with and without contrast depending on the location of initial disease) and determining the frequency with which neuroimaging is needed. In patients with recurrent primary CNS tumors, neuro-oncologists coordinate the treatment strategy via a multidisciplinary approach, coordinating care with neurosurgeons and radiation oncologists to determine whether surgical intervention and/or radiation are required and deciding appropriate next steps in medical therapy if indicated, including chemotherapy, immunotherapy, and targeted therapy based on the molecular profile of the tumor. In patients with severe tumor-related symptoms and poor prognosis, the neuro-oncologist often engages with palliative care specialists for aid in managing symptoms at end of life. The prognosis for GBM, the most common adult brain tumor encountered by neuro-oncologists, is grim, with a median survival of 14.6 months even with treatment with radiation and temozolomide,[5] highlighting the importance of palliative care and hospice discussions to maintain quality of life and manage caregivers' concerns.

Neuro-oncology has expanded to include the management of systemic tumors metastatic to the CNS as well. The mainstay of treatment for brain metastases includes resection of symptomatic, surgically accessible lesions and radiation therapy, requiring collaboration across neurosurgery, radiation oncology, and medical oncology. Neuro-oncologists may also be consulted to provide input regarding potential systemic therapies that may penetrate the blood-brain barrier and treat CNS disease.

The neuro-oncologist must be familiar with the diagnosis and treatment of common neurologic and medical complications of primary CNS tumors as well as neurologic complications of systemic cancers and tumor-directed therapies, including chemotherapy, immunotherapy (e.g., chimeric antigen receptor T cells and checkpoint inhibitors), radiation therapy, and targeted molecular therapies. Patients with CNS disease may experience neurologic sequelae such as seizures, headaches, cerebral edema, encephalopathy, strokes, and peripheral neuropathy, either as a direct result of the tumor itself or as a result of cancer treatments. The neuro-oncologist must also determine the need for imaging and additional diagnostic testing, such as cerebrospinal fluid (CSF) sampling, in patients suspected to have metastatic leptomeningeal dissemination, whether from a systemic or primary CNS malignancy. In addition, paraneoplastic neurologic syndromes have unique neurologic presentations and require specific diagnostic workups and treatments, including immunomodulatory therapies, such as intravenous administration of immunoglobulin, plasmapheresis, and treatment with immunosuppressive medication.

Ancillary treatments, such as corticosteroid therapy, may be necessary to treat peritumoral edema and radiation necrosis, which often cause headaches and focal neurologic deficits, and neuro-oncologists must determine the appropriate timing and dosing of corticosteroid therapy. Patients with brain tumor at times require chronic treatment with high-dose corticosteroids, leading to several medical complications that must be managed by neuro-oncologists, including hyperglycemia, hypertension, immune suppression, and mood changes. Further, all malignancies, including and particularly brain tumors, are associated with hypercoagulability with increased risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. Neuro-oncologists must have a low threshold to pursue diagnostic evaluations for VTE and must weigh the risks and benefits of treating VTE with therapeutic anticoagulation, which can lead to bleeding complications such as intracranial hemorrhage.

NEURO-ONCOLOGY TRAINING

Given the specialized nature of neuro-oncology, dedicated subspecialty training is required. Such training is typically achieved through completion of a fellowship training program in neuro-oncology accredited by the United Council for Neurologic

Subspecialties (UCNS) followed by board certification through a written examination administered by the UCNS.[6,7]

The UCNS is a nonprofit organization created with the mission of accrediting neurologic subspecialty training programs and certifying physician competence. The purpose of UCNS-accredited fellowship training programs in neuro-oncology is to prepare trainees for independent practice in neuro-oncology based on supervised clinical work with increasing patient care responsibilities and transition to independent practice.[8,9] All programs must allow fellows to obtain competencies in the 6 core competency areas defined by the Accreditation Council for Graduate Medical Education: patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice.[8,9] UCNS-accredited fellowship training programs in neuro-oncology must show that they meet standards of graduate medical education excellence set by the UCNS and subspecialty experts in neuro-oncology.[10] The accreditation process is peer-reviewed and is overseen by the Accreditation Council, which is a standing committee reporting to the UCNS Board of Directors. The Accreditation Council is responsible for preparing subspecialty-specific program requirements, common program requirements applicable to all UCNS subspecialties, and periodic revisions to reflect current educational practice. Program requirements must be approved by the UCNS Board of Directors. The Accreditation Council reviews completed applications and related correspondence to determine whether a program is in compliance with the program requirements and designates an accreditation status for each program, identifying points of partial compliance and/or noncompliance with its standards if necessary.[11] Applications for accreditation may be submitted at any time of year and are reviewed twice per year in the autumn and spring. Periodic reviews of program requirements occur at least every 5 years, at which time the Accreditation Council works with subspecialty-recommended consultants.

To be eligible to participate in neuro-oncology fellowship programs, trainees must have a current valid unrestricted license to practice medicine in the United States or Canada or its territories. In addition, trainees must have graduated from an Accreditation Council for Graduate Medical Education—accredited residency program in neurology, child neurology, neurologic surgery, internal medicine and medical oncology, or pediatrics and pediatric hematology/oncology.[9] All fellows must be board-certified or eligible for certification in a primary American Board of Medical Specialties or Royal College of Physicians and Surgeons of Canada specialty: neurology, neurosurgery, medical or pediatric oncology, radiation oncology, or neuropathology. The minimum duration of clinical training must be 12 months, whereas the maximum duration is 36 months.

After fellowship training, neuro-oncology providers must sit for a written board certification examination. The Certification Council sets certification policy and oversees physician committees that develop the certification examination.[12] Certification examinations are developed by a committee of physician experts identified by the sponsoring organizations of the specific subspecialty. UCNS staff and the Certification Council review submitted applications for the certification examination to verify eligibility and application compliance.[13] All applicants for board certification must be diplomates in good standing of the American Board of Medical Specialties, American Osteopathic Association, or Royal College of Physicians and Surgeons of Canada in neurology, child neurology, neurologic surgery, internal medicine and medical oncology, pediatrics and pediatric hematology/oncology, or radiation oncology.[7] In addition, all applicants must hold a current active valid unrestricted and unqualified license to practice medicine in at least 1 jurisdiction in the United States, its territories, or Canada. UCNS certification is time-limited, and recertification is required after 10 years.[14]

UCNS-accredited neuro-oncology fellowship programs in the United States are primarily based at large urban academic medical centers. The geographic distribution of neuro-oncology fellowship programs is reflective of the locations with the highest concentrations of practicing neuro-oncologists. Patients living in rural areas may have limited access to neuro-oncology providers, clinical trials, and advanced neuroimaging and surgical techniques.

INTERDISCIPLINARY COLLABORATION

Caring for patients with CNS tumors requires a multidisciplinary approach, and neuro-oncologists regularly collaborate with providers from a variety of medical fields. Dedicated neuroradiologists are integral to the care of patients with CNS tumors. Most patients with CNS tumors initially present with neurologic symptoms that warrant neuroimaging, often MRI of the brain and/or spine. The neuroradiologist renders a radiographic differential diagnosis for the lesion in question, which helps to dictate whether surgical intervention for tissue sampling and diagnosis is warranted.

Decisions regarding whether to pursue surgical intervention to establish a tissue diagnosis and/or allow surgical decompression to relieve neurologic symptoms rely on radiographic characteristics and close collaboration with neurosurgery. For example, if imaging suggests an aggressive high-grade malignant process (e.g., the heterogeneous enhancement and surrounding vasogenic edema commonly seen with high-grade gliomas), biopsy with maximal safe resection would be indicated. However, if the radiographic appearance is consistent with a low-grade process or if the risks of surgery would potentially outweigh the benefit, monitoring with serial neuroimaging may be considered. The standard of care for gliomas includes maximal safe tumor removal.[15,16] However, the anatomic location of the tumor may prohibit resection because of the risk of precipitating neurologic deficits, particularly if lesions infiltrate eloquent brain and/or deep structures such as the corpus callosum and thalamus. In these cases, surgical biopsy is pursued to establish a tissue diagnosis and minimize the risk of neurologic dysfunction. After tissue sampling by a neurosurgeon, tissue must be analyzed by a neuropathologist to obtain a diagnosis.

After the establishment of a pathologic diagnosis for a CNS neoplasm, an interdisciplinary treatment strategy is formulated based on that diagnosis. In treating patients with CNS neoplasms, neuro-oncologists must frequently collaborate with radiation oncologists, because a variety of CNS neoplasms (including gliomas, CNS metastases, and some meningiomas) require radiation therapy. Decisions regarding the most appropriate radiation

technique, such as intensity-modulated radiation therapy, whole-brain radiotherapy (WBRT), or stereotactic radiosurgery (SRS), as well as the total dose of radiation and duration of treatment, are made by the treating radiation oncologist.[17]

For patients with primary brain tumors, the neuro-oncologist typically guides medical management of the disease process and coordinates care across disciplines. However, for patients with metastatic CNS tumors, the primary medical oncologist typically formulates and implements the medical treatment plan for the patient's malignancy (including chemotherapy, immunotherapy, and targeted therapies), whereas the neuro-oncologist usually plays a consulting role in helping manage CNS metastases and resultant neurologic symptoms. Brain metastases often require extensive multidisciplinary discussions regarding appropriate CNS-penetrating systemic therapy in addition to the potential role of surgery and radiation therapy.[18]

Given the multidisciplinary nature of CNS tumor management, tumor boards are a key component of neuro-oncology practice. Representatives from neuro-oncology, neurosurgery, radiology, pathology, medical oncology, and/or radiation oncology meet regularly to review neuroimaging and pathology, discuss clinical decision making, and help educate trainees.[19-21] These conferences allow for open and confidential communication among providers from various disciplines and permit the formation of customized, cohesive treatment plans.

EPIDEMIOLOGY AND MANAGEMENT OF COMMON CNS TUMORS

Gliomas

Gliomas are the most common primary brain tumors in adults and account for 80% of malignant primary CNS tumors.[22] Historically, gliomas have been classified into 4 histologic grades: grade I and II tumors are considered low-grade gliomas and grade III and IV tumors are considered high-grade gliomas. WHO grade I gliomas include pilocytic astrocytomas, which are most common in children and are not considered diffuse infiltrating gliomas (as WHO grade II, III, and IV tumors are). WHO grade II gliomas include diffuse infiltrating gliomas of both astrocytic (diffuse astrocytoma) and oligodendroglial (oligodendroglioma) differentiation. WHO grade III tumors include anaplastic astrocytomas and anaplastic oligodendrogliomas, and WHO grade IV tumors include GBM. Histologically, high-grade tumors are characterized by increased cellularity, nuclear atypia, and mitotic activity compared with low-grade tumors. The histologic hallmarks of GBM include microvascular or endothelial proliferation and necrosis, which are not present in WHO grade II or III tumors.

Classification of CNS tumors has recently shifted to incorporate molecular profiling with histology, as delineated in the 2016 WHO Classification of Central Nervous System Tumors.[4] This WHO classification update separated gliomas according to mutations in the genes for isocitrate dehydrogenase (*IDH1* or *IDH2*). When present, *IDH* mutation confers a more favorable prognosis and response to treatment.[23,24] Thus, the entity previously deemed "glioblastoma" is now divided into "glioblastoma, *IDH*-mutant" and "glioblastoma, *IDH*-wild-type." Similarly, WHO grade II and III astrocytomas are divided into *IDH*-mutant and *IDH*-wild-type entities. Further, oligodendrogliomas (both WHO grade II oligodendrogliomas and WHO grade III anaplastic oligodendrogliomas) are defined by the presence of both *IDH* mutation and loss of chromosomes 1p and 19q (1p/19q codeletion), both of which confer a favorable prognosis.[25]

With respect to high-grade gliomas, GBM is the most common malignant brain tumor in adults and most often occurs in the fifth to seventh decades of life; the incidence of high-grade gliomas increases with age.[26] The presenting symptoms depend on the anatomic location of the lesion and include focal neurologic deficits, such as weakness and sensory changes; seizures; and signs and symptoms of increased intracranial pressure, such as headaches. Workup for all gliomas, including high-grade gliomas, includes MRI with gadolinium contrast; high-grade gliomas typically enhance heterogeneously with contrast and cause associated T2/fluid-attenuated inversion recovery signal abnormalities.

Treatment for high-grade gliomas begins with maximal safe resection. Resective surgery offers several potential benefits, including pathologic confirmation of the diagnosis; tissue sampling for molecular testing, which informs prognosis and treatment; and reduction of mass effect, which may improve neurologic symptoms.[26] Extent of resection is associated with improved survival,[27,28] although it has never been prospectively shown in randomized clinical trials that more aggressive surgical resection results in longer duration of survival. When resection is not feasible based on the anatomic location of the tumor, surgical biopsy may be pursued to obtain tissue for diagnosis and molecular testing.

Surgery is typically followed by a combination of radiation therapy and chemotherapy. In patients with GBM, fractionated radiation therapy is most often given to a total of approximately 60 Gy in 30 fractions over a period of 6 weeks[5] to the gross tumor volume with a 2-cm to 3-cm margin. Radiation is given concomitantly with temozolomide, an oral alkylating agent that has been shown to improve survival of patients with GBM.[5] Temozolomide is administered concurrently with radiation therapy for 6 weeks, followed by a 1-month treatment break, after which a new baseline MRI is obtained. Adjuvant temozolomide is then administered in cycles in which the drug is taken on days 1–5 of each 28-day cycle, for a goal of 6–12 cycles. In patients ≥60 years of age, a hypofractionated course of radiation therapy (40 Gy in 15 fractions) is associated with no difference in overall survival and fewer adverse effects compared with the standard 6-week course.[29] One study[30] found that in patients who are elderly (age ≥65 years and Karnofsky Performance Status [KPS] >70), frail (age ≥50 years and KPS 50–0), or elderly and frail (age ≥65 years and KPS 50–0), a hypofractionated regimen of 25 Gy in 5 fractions was noninferior to 40 Gy in 15 fractions. Thus, for patients with poor functional status, including those who are elderly, for whom a more lengthy course of radiation may be burdensome to the patient and caregivers, a rationale can be made for a 5-day course of radiation.

Initial treatment for newly diagnosed GBM may also involve use of tumor treating fields (TTFs). TTFs are low-intensity alternating electric fields shown to induce cell cycle arrest and apoptosis at the cellular level and are delivered through transducer arrays on the scalp that are connected to a portable device.[26] Use of TTFs has been associated with improved progression-free and overall survival in patients with newly diagnosed GBM when used concomitantly with adjuvant temozolomide after completion of

radiation,[31] and TTFs are approved by the U.S. Food and Drug Administration (FDA) for treatment of newly diagnosed GBM. However, the results of these studies remain controversial, especially with the lack of sham device in the control arm and no definitive efficacy in early clinical trials with recurrent GBM. Compliance with the device is associated with better clinical outcomes, and TTFs should be worn on the scalp uninterrupted for ≥18 hours per day. Use of TTFs may be limited by patient preference given the need to wear the device nearly continuously, the need to shave one's hair to wear the device, and the potential associated scalp irritation.

In addition, biodegradable copolymers impregnated with carmustine (BCNU), an alkylating agent, may be used in the treatment of newly diagnosed high-grade gliomas, including GBM. These BCNU implants, also known as Gliadel wafers, are placed in the resection cavity and are FDA approved for treatment of newly diagnosed high-grade gliomas as an adjunct to surgery and radiation as well as for recurrent GBM as an adjunct to surgery. Although Gliadel wafers have been associated with some improvement in median survival in newly diagnosed high-grade gliomas,[32] they are not widely used in clinical practice given associated toxicities (including cerebral edema, seizures, and infection) and given that they have not been compared directly with standard treatment with radiation and temozolomide.[33]

In patients with anaplastic astrocytoma, initial treatment is essentially identical to treatment for GBM. However, patients with anaplastic oligodendroglioma are typically treated with radiation therapy followed by a 3-drug chemotherapy regimen known as PCV (consisting of procarbazine, lomustine [CCNU], and vincristine), which has been shown to improve overall survival in patients with 1p/19q codeleted anaplastic oligodendroglioma compared with radiation alone.[34] However, PCV is notably more toxic than temozolomide and is more poorly tolerated by patients. Therefore, some neuro-oncologists favor use of temozolomide over PCV, although temozolomide has not yet been shown to be equally as effective as PCV in treatment of oligodendrogliomas, and long-term data from phase 3 clinical trials have thus far only supported the efficacy of PCV. A study comparing the efficacy of temozolomide compared with PCV in 1p/19q codeleted gliomas is being conducted.[35]

Treatment for recurrent high-grade gliomas is individualized and depends largely on the anatomic location of the recurrence. Repeat resection can be considered in surgically accessible lesions, as can repeat irradiation, depending on the location of the recurrence with respect to field, timing, and dosing of the previous radiation course. Systemic treatment options include cytotoxic chemotherapies such as CCNU, BCNU, or carboplatin. Antiangiogenic therapy (often with the vascular endothelial growth factor [VEGF] inhibitor bevacizumab) is used for the treatment of recurrent high-grade gliomas. Although bevacizumab has been shown to produce a radiographic response in GBM[36,37] and often functions to reduce peritumoral edema and improve neurologic symptoms, it has not been shown to improve overall survival.[38] Studies are ongoing regarding the role of immunotherapy (i.e., immune checkpoint inhibitors) in the treatment of recurrent high-grade gliomas, but preliminary studies indicate minimal efficacy as monotherapy. Patients often have repeat surgery to both relieve neurologic symptoms and obtain updated molecular profiling of a rapidly evolving malignancy in cases of new targetable mutations, although there are no prospective data establishing that targeted therapy results in extended survival. Although neuro-oncologists choose among the treatment options for recurrent GBM based on each patient's unique clinical situation, only temozolomide, nitrosoureas such as CCNU and BCNU, and bevacizumab are FDA approved for treatment of recurrent GBM.

Initial treatment is more variable for low-grade gliomas. Radiographically, low-grade gliomas are typically hyperintense on T2 sequences and nonenhancing. Decisions regarding surgical management (either biopsy or maximal safe resection) are largely dependent on patient preference and prognostic factors, including age, tumor size, and anatomic location as well as the presence or absence of neurologic deficits.[39] In a patient at high surgical risk, it may be reasonable to monitor the lesion in question with serial imaging and pursue only a tissue diagnosis in the setting of clinical or radiographic progression. Management of low-grade gliomas after surgical intervention is also highly variable, and the optimal timing of initiation of treatment is not entirely clear. In 1 prospective study of observation in patients younger than 40 years who had gross total resection of their lesion,[40] disease recurrence occurred within 5 years of surgery in approximately 50% of patients. If the decision is made to observe, active surveillance with regular MRI studies is required to detect disease recurrence. If and when treatment is pursued, it may consist of a combination of radiation therapy and chemotherapy or radiation therapy alone. For astrocytic tumors, initial treatment often involves a combination of concurrent radiation and temozolomide followed by adjuvant temozolomide as with GBM. Oligodendrogliomas are often treated with radiation therapy followed by PCV chemotherapy; as stated earlier, studies are under way to determine the efficacy of temozolomide compared with PCV in 1p/19q codeleted gliomas.[35] The total dose of radiation administered for treatment of low-grade gliomas is often lower than the dose used for high-grade gliomas, typically 50–54 Gy; it has previously been shown that there is no significant difference in 5-year overall or progression-free survival between a 50.4-Gy regimen and a 64.8-Gy regimen in adult patients with low-grade gliomas.[41,42] Regardless of initial treatment, low-grade gliomas will recur and have the potential to transform into higher-grade tumors.

All systemic therapies for gliomas, whether in the initial or recurrent setting, require monitoring for toxicities. Potential side effects of temozolomide include nausea, bone marrow suppression, and hepatotoxicity. During initial treatment with concurrent radiation and temozolomide or adjuvant temozolomide for gliomas of any histologic grade, routine monitoring of complete blood counts and comprehensive metabolic panels are required. Potential toxic effects of PCV include bone marrow suppression, pulmonary toxicity, peripheral neuropathy, and the possibility of precipitating a hypertensive crisis if taken with tyramine-containing foods, because procarbazine is a weak monoamine oxidase inhibitor. Thus, patients must undergo routine monitoring of blood counts and pulmonary function testing as well as avoid tyramine-containing foods. There is also an increased risk for the development of secondary malignancies such as myelodysplastic syndrome and acute myelogenous leukemia years after exposure to alkylating agents. Patients on platinum-based

chemotherapies must undergo routine monitoring of blood counts given the risk of bone marrow suppression. For patients on bevacizumab, renal function and urinalyses must be monitored (proteinuria is a potential side effect); hematologic parameters are also watched closely in the setting of increased risk of coagulopathy. All targeted therapies require routine monitoring for toxicities associated with each individual therapy.

For all gliomas, prognosis is dependent on a variety of clinical, histologic, and molecular factors. Overall, the prognosis for high-grade gliomas is poor, with a median survival of 16–18 months for GBM, 2–5 years for anaplastic astrocytoma, and 15 years for anaplastic oligodendroglioma.[26] However, molecular factors are becoming increasingly crucial in prognostication for gliomas, even within a specific histologic diagnosis. As noted previously, both *IDH* mutation and 1p/19q codeletion are associated with a more favorable prognosis and treatment response. For example, an *IDH*-mutant anaplastic astrocytoma has a more favorable prognosis than an *IDH*-wild-type anaplastic astrocytoma, and oligodendrogliomas have a better prognosis than astrocytomas. In addition, methylation of the *MGMT* (O-6-methylguanine-DNA methyltransferase) gene has been shown to confer a survival benefit and improved response to treatment in patients with GBM,[5,43] because *MGMT* promoter methylation results in silencing of this DNA repair gene, thus reducing the ability of tumor cells to repair DNA damaged by alkylating agents such as temozolomide. Both age and performance status have been independently associated with prognosis in high-grade gliomas, with increasing age and poorer performance status associated with worse prognosis.[44,45] In addition to *IDH* mutation and 1p/19q codeletion, age <40 years, presentation with isolated seizures, and smaller tumor size are associated with more favorable prognosis in low-grade gliomas.[39]

Meningiomas

Meningiomas are dura-based tumors that arise from arachnoid cap cells of the intracranial or spinal dural surface. These lesions account for approximately 36.6% of all primary CNS tumors,[46,47] and their incidence increases with age. Common anatomic locations for meningiomas include the cerebral convexities, falx cerebri, and skull base. Risk factors for developing meningiomas include exposure to ionizing radiation, hormone exposure, and certain genetic syndromes, such as neurofibromatosis type 2. On MRI, meningiomas appear as dura-based mass lesions that enhance homogeneously with gadolinium contrast, often with a contrast-enhancing dural tail. On computed tomography, meningiomas may harbor calcifications, with associated hyperostosis of the overlying skull.

Meningiomas are divided into 3 histologic grades according to WHO: WHO grade I (typical) meningiomas represent 81.1%, WHO grade II (atypical) meningiomas 16.9%, and WHO grade III (anaplastic or malignant) meningiomas 1.7% of meningiomas.[46,47] WHO grade I meningiomas are characterized by a low mitotic rate, whereas WHO grade II meningiomas are characterized by a higher mitotic rate, brain invasion, or certain pathologic characteristics such as necrosis. WHO grade III meningiomas are characterized by the highest mitotic rate or certain specific histologic features (i.e., papillary or rhabdoid histology). The 10-year survival for patients with meningioma ranges from 57.1% to 77.7%,[46] although WHO grade II and WHO grade III meningiomas are more aggressive, with a poorer prognosis than WHO grade I meningiomas. Approximately 50% of WHO grade II meningiomas and 90% of WHO grade III meningiomas recur 5 years after initial diagnosis.[47] Historically, histologic grade has been used for the prognosis of meningiomas, as stated earlier. However, in recent years, studies have shown that epigenetic factors (such as DNA methylation profiles) may be helpful in predicting recurrence risk and outcomes.[48]

Meningiomas are often discovered incidentally. For small asymptomatic tumors, observation with serial imaging may be pursued.[46,49] However, for growing tumors and/or tumors causing neurologic symptoms, resective surgery is the mainstay of treatment for meningiomas of all histologic grades. Rates of recurrence depend on extent of resection, which is characterized by the Simpson grade. Simpson grade 1 resection involves gross total resection of tumor, dural attachment, and involved bone. Simpson grade 2 describes gross total resection of tumor with coagulation of dural attachment, and Simpson grade 3 gross total resection without removal or coagulation of the associated dura. Simpson grade 4 resection denotes a subtotal resection, and Simpson grade 5 biopsy only. Recurrence is more likely in patients in whom tumors have been incompletely resected, and recurrence risk increases with Simpson grade.

For WHO grade I tumors that have been surgically resected, surveillance with serial imaging is often pursued to monitor for recurrence. However, for WHO II tumors that have been incompletely resected and for WHO grade III tumors, adjuvant treatment is required to delay recurrence. Radiation therapy is often used postoperatively, and both SRS and external beam radiotherapy have been used depending on the size and location of the treatment area.[46,49] Adjuvant radiation therapy has been shown to improve progression-free and overall survival in grade III tumors[50,51] and subtotally resected grade II tumors.[52] However, the benefit of adjuvant radiation therapy for WHO grade II gross totally resected tumors has not been established.

Systemic therapies have not been found to provide significant benefit in the treatment of meningiomas. VEGF inhibitors, such as bevacizumab and sunitinib, have been associated with only mild improvements in progression-free survival in some patients with meningioma,[53,54] and this may represent only imaging artifact secondary to the vascular stabilizing effects of VEGF inhibitors. Cytotoxic chemotherapies have not shown efficacy. Studies examining the role of immunotherapy and targeted therapies based on tumor genetics are ongoing.

PCNSL

PCNSL is an extranodal non-Hodgkin lymphoma arising in the brain, spinal cord, leptomeninges, and/or eyes without systemic disease. PCNSL represents approximately 2% of all CNS tumors.[55,56] Immunocompromise, such as in patients with human immunodeficiency virus/AIDS and those with solid organ transplants requiring immunosuppression, is a risk factor for PCNSL, likely related to concomitant Epstein-Barr virus infection. In immunocompetent patients, PCNSL is not associated with Epstein-Barr virus and typically occurs in older individuals, with a median age at diagnosis of 66 years.[56] The incidence of PCNSL in immunocompetent patients older than 65 years is increasing.[56,57]

The clinical and radiographic characteristics of PCNSL are often protean. In immunocompetent patients, PCNSL occurs as a solitary intracranial lesion in up to 70% of patients and most commonly involves the periventricular white matter, basal ganglia, thalamus, and corpus callosum.[56] However, multifocal disease can be seen as well. Lesions are usually homogeneously enhancing with associated restricted diffusion. Histopathologically, >90% of PCNSL is diffuse large B-cell lymphoma, with fewer cases of T-cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, and low-grade lymphomas.[58]

If untreated, PCNSL has a poor prognosis, with overall survival of approximately 1.5 months.[56] Expedited tissue diagnosis, usually with stereotactic biopsy, is thus critical to establish a histopathologic diagnosis. Unlike in glioma, resection is not associated with survival benefit in PCNSL.[59] In addition to stereotactic biopsy, medical evaluation to establish extent of disease is necessary. Patients undergoing workup for PCNSL should undergo CSF analysis including flow cytometry as well as contrast-enhanced total spine MRI to evaluate for leptomeningeal spread. Ophthalmologic examination, including slit-lamp examination, should be performed to evaluate for ocular disease. In addition, computed tomography scans of the chest, abdomen, and pelvis (with or without positron emission tomography) and a bone marrow biopsy are recommended as part of the staging workup. Testicular ultrasonography should be performed in men to evaluate for testicular lymphoma.

PCNSL is radiosensitive, and WBRT was historically the mainstay of treatment, producing response rates (although not necessarily durable). However, WBRT is associated with substantial long-term consequences, including delayed neurotoxicity. Patient who receive WBRT, particularly those older than 60 years, are at risk of developing long-term neurologic sequelae, such as cognitive impairment, gait disturbance, and urinary incontinence. Chemotherapeutic regimens, most importantly with high-dose intravenous methotrexate, have shown substantial efficacy in PCNSL and are now standard of care. Studies have found that monotherapy with high-dose methotrexate is associated with overall response rates of 35%–74%, median progression-free survival of 10–12.8 months, and overall survival 25–55 months,[60-62] with improved outcomes when combined with other systemic agents. Initial treatment, or induction therapy, for PCNSL involves a methotrexate-based regimen, although there is no consensus on the optimal exact regimen of other drugs. The purpose of induction therapy is to produce a complete radiographic response. Induction therapy is followed by consolidation therapy, which aims to eliminate residual disease. Consolidation therapy can be achieved through use of additional chemotherapy, such as cytarabine, as well as nonchemotherapeutic strategies such as WBRT or autologous stem cell transplantation.

Although methotrexate-based chemotherapy is associated with high response rates, relapse is common and occurs in approximately half of patients who initially respond to treatment.[56] The optimal treatment regimen for recurrent disease is not well established. A variety of strategies may be used in the setting of PCNSL relapse, including rechallenge with high-dose intravenous methotrexate or other chemotherapy, immune checkpoint inhibitors, targeted therapies such as ibrutinib, and WBRT.

With treatment, long-term survival can be seen in 15%–20% of patients with PCNSL,[56] particularly in young patients with good performance status. Advanced age and poor performance status are poor prognostic factors. Approximately one fourth of patients with newly diagnosed PCNSL do not respond to initial treatment. Relapse in PCNSL is common, with 5-year survival as low as 33%,[55] and prognosis for refractory PCNSL remains poor.

CNS Metastases

Metastases from systemic malignancies are the most common brain tumors in adults and are seen in up to 30% of adult patients with cancer.[63] Systemic malignancies can metastasize to the brain parenchyma, the meninges (including the dura and leptomeninges/CSF space), the spinal cord, and the peripheral nervous system. Common causes of intraparenchymal brain metastases are small-cell and non-small-cell lung cancer, breast cancer, melanoma, and renal cell carcinoma.[63] Prostate cancer tends to metastasize to the dura rather than the brain parenchyma, whereas breast cancer, melanoma, lymphoma, and leukemia are the most common causes of leptomeningeal carcinomatosis.

The radiographic appearance of brain metastases is heterogeneous. Brain metastases can appear as solitary or multiple lesions. Most characteristically, brain metastases appear as contrast-enhancing lesions at the gray–white junction. Some systemic malignancies, such as melanoma and renal cell carcinoma, tend to produce hemorrhagic metastases.

The optimal treatment strategy for brain metastases depends on the size and number of brain metastases, the histologic tumor type, the genetic profile of that tumor, the state of the patient's systemic disease, and the patient's overall performance status. Potential treatment options include tumor resection, radiation therapy, and systemic therapies, including CNS-penetrating chemotherapy or targeted therapies based on genetic profiling. For large (diameter ≥3 cm),[64] accessible lesions causing neurologic symptoms, resective surgery may be considered, because resection may reduce mass effect and improve neurologic symptoms. Surgery has the added benefit of providing a tissue diagnosis in patients in whom the primary malignancy is unknown. Resection is a mainstay of treatment for patients with a single brain metastasis, and patients with multiple metastases may also benefit from resection if a dominant symptomatic metastasis is present.[64,65] In patients with widespread systemic disease and/or poor performance status, surgery is less likely to provide substantial clinical benefit, and other treatment strategies should be considered.

With respect to radiation therapy, both SRS and WBRT are used in the treatment of brain metastases.[63-65] SRS uses multiple convergent beams to deliver a large dose of radiation to a small tumor volume. Both SRS and WBRT can be performed postoperatively if surgery is pursued, and SRS to the resection cavity is a common treatment strategy. Typically, SRS is used when <4 brain metastases are present, although, more recently, SRS is being considered in patients with a higher CNS metastatic disease burden.[63] SRS may also be considered in patients with classically radioresistant tumors, such as melanoma. However, in patients with >4 or 5 metastases and/or with few systemic treatment options available, WBRT is still considered the mainstay of

therapy. Cognitive side effects of WBRT may be mitigated by a hippocampal avoidance strategy when feasible and, possibly, by the use of memantine.[66,67] WBRT must also be considered in the setting of leptomeningeal carcinomatosis, given diffuse spread of malignant cells through the CSF spaces.

Systemic therapies for CNS metastases are largely dependent on the primary malignancy and the presence of actionable mutations as well as the availability of therapeutic options that penetrate the CNS. For example, patients with non-small-cell lung cancer harboring mutations in the EGFR (epidermal growth factor receptor) tyrosine kinase domain or ALK rearrangement, EGFR tyrosine kinase inhibitors such as osimertinib or ALK inhibitors such as alectinib may be of benefit. In patients with metastatic melanoma and BRAF mutations, BRAF inhibitors such as dabrafenib may be considered. In addition, immune checkpoint inhibitors, such as PD-1 (programmed cell death protein 1) and PD-L1 (programmed death-ligand 1) inhibitors, have been shown to improve prognosis in patients with brain metastases in several cancers, including both lung cancer and melanoma.[63] CNS-penetrating cytotoxic chemotherapies may also be considered.

CLINICAL TRIALS

As per the National Institutes of Health, clinical trials are research studies in which 1 or more human participants are prospectively assigned to 1 or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.[68] Because many neuro-oncologic conditions, particularly high-grade gliomas, have poor prognoses and limited treatment options, clinical trials are essential to identify novel, safe, and effective therapies. In addition, clinical trials are needed to clarify appropriate treatment pathways; for example, it is not known whether postoperative radiation therapy is beneficial compared with observation for patients with gross totally resected WHO grade II meningiomas. There are several barriers to enrolling neuro-oncologic patients in clinical trials. Clinical trials are often available only at large academic medical centers, and providers may have difficulty finding open studies in an individual patient's geographic area.[69] In addition, trials can require strict monitoring schedules and potential toxicity. Providers also may believe that their patients are concerned about the experimental nature of the trial or about being placed in placebo or control groups, which may result in reduced referrals for clinical trials.[69] Concerted efforts are required at both provider and institutional levels to increase enrollment in neuro-oncology clinical trials.

CONCLUSIONS

Neuro-oncology is a continuously evolving field that involves the diagnosis and management of primary and metastatic tumors of the nervous system as well as management of neurologic complications of cancer and oncologic treatments. Neuro-oncology requires extensive multidisciplinary cooperation with colleagues from neurosurgery, radiation oncology, medical oncology, neuroradiology, and neuropathology. Tumor boards allow regular communication and the development of collaborative treatment plans. Common CNS tumors (e.g., gliomas, meningiomas, PCNSL, and CNS metastases) are managed with a combination of systemic therapies, including chemotherapy and targeted therapies, as well as surgery and radiation therapy. The prognosis for many neuro-oncologic conditions remains poor despite ongoing advances in treatment regimens. Increased enrollment of neuro-oncologic patients in clinical trials is necessary to establish the safety and efficacy of new treatment paradigms.

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