Clinical neuro-oncology for the neurologist

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Abstract

Purpose of review

Neuro-oncologic patients are routinely encountered in clinical practice. Neuro-oncology is a rapidly evolving field, so understanding the most classic paradigms and contemporary advances will optimize patient care.

Recent findings

We discuss the recent reclassification of tumors via molecular characteristics as it applies to direct clinical practice and review the contemporary standard of care for infiltrating gliomas, meningiomas, brain metastases, and CNS lymphoma.

Summary

We provide a straightforward primer on neuro-oncology with a focus on the brain tumors most commonly encountered by the adult neurologist and a clear emphasis on clinically relevant points including those which have recently become incorporated into our standard management. We cite key reviews to allow interested readers an opportunity to gain a more comprehensive understanding of specific topics.

Neuro-oncology is an expansive yet niche field to which clinical neurologists, particularly trainees, receive variable exposure. An urgent need for improvement in patient outcomes has fueled intense research leading to a continuous evolution in our knowledge. In this review, we provide an overview of the field of neuro-oncology for the busy neurology clinician to remain fully abreast of the state of the art in neuro-oncology advances.

Categorization and classification of CNS tumors

CNS tumors can be broadly categorized into primary and metastatic. Although definitive support is lacking, the incidence of CNS metastases is many fold higher than primary brain tumors.^{1,2} The Central Brain Tumor Registry of the United States (CBTRUS) serves as a reliable repository of information regarding the incidence of primary brain tumors in the United States. Per CBTRUS, meningiomas have the highest incidence with infiltrating gliomas composing the second largest group. Among infiltrating gliomas, glioblastoma (GBM) is the most common, representing greater than 50% of infiltrating gliomas.³ The clinical practice for many neuro-oncologists centers on GBM and other high-grade gliomas. However, the neurologist may consult on and be involved in the diagnosis and therapeutic management of patients with a range of neuro-oncologic disorders.

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CNS metastases

CNS metastases can be divided by the neuroanatomic location into parenchymal brain and spinal cord metastases, CSF metastases, and dural metastases. Brain metastases are the most common intracranial tumors. Histologies that frequently metastasize to the brain include lung cancer, breast cancer, and melanoma. However, almost any malignancy has the potential for brain metastases. The majority of brain metastases arrive in the brain via a hematogenous route. A complex multistep process is involved in tumor cells leaving the primary tumor, moving safely through the systemic vasculature, halting their movement often at branch points of smaller vessels, extravasating out of the vasculature, surviving in the perivascular niche, and then growing beyond micro-metastatic size. General themes for this process persist across all histologies; however, there are uniquely histology-specific aspects as well.⁴ As with primary tumors, the interaction between brain metastases and their microenvironment is essential for the tumors to survive and thrive. An understanding of these processes and interactions will help reveal weak points in the tumors, which will help guide therapeutic development.⁵ One of these aspects, termed branched evolution, is the differential mutational status of the brain metastases when compared with the primary tumor or non-CNS metastases.⁶

Brain metastases can present as single, oligo, or multiple lesions. They are often round in shape and enhance on postcontrast imaging. Often, but not always, a distinct border can be seen between the tumor and surrounding brain, which may or may not be afflicted with edema (figure 1A). All management decisions weigh aspects of efficacy against the potential toxicities, which include surgical morbidity, worsening cerebral edema, radiation necrosis, and neurotoxicity from radiation. If a lesion is single, particularly if it is large in size, symptomatic, or in a location that cannot tolerate much enlargement or surrounding edema (such as the posterior fossa), surgical resection is considered. This is based on the results of randomized trials, which demonstrated improvement in survival with surgical resection followed by radiation compared with radiation alone.^{7,8} Oligometastases are limited in number, but are not defined by a specific quantity. The term implies a state distinct from widespread metastatic disease, a state where the “facility for metastatic growth has not been fully developed” and which cure may still be feasible.⁹ For oligometastatic brain metastases, stereotactic radiosurgery (SRS) will often be used. This can be efficacious with respect to local control and limits exposure of the normal brain to radiation diminishing the risk of neurotoxicity. The data are strongest to support treatment of up to 4 brain metastases; however, treating substantially more within the context of specific clinical circumstances is reasonable.¹⁰ With multiple brain metastases, whole-brain radiation therapy (WBRT) is often used. Contemporary means to decrease the neurotoxicity include the addition of the

Surgical resection has both diagnostic and therapeutic benefit. It can confirm that the tumor is a meningioma, delineate its grade, and evaluate for mutations, which may guide therapeutic trial enrollment.

NMDA receptor antagonist memantine to help decrease excitotoxicity¹¹ and a hippocampal avoidance WBRT (HA-WBRT) technique to limit the toxicity to the neural stem cells in the hippocampal region.¹² The 2 techniques when used in combination have recently been shown to provide additive benefit.¹³ In the contemporary era, robust CNS responses comparable to rates of systemic response have been seen in some histologies treated with molecularly targeted therapies or immunotherapies. This has led to the utilization of systemic therapies before/in conjunction with/and in place of radiotherapy, particularly in patients with small asymptomatic metastases. The optimal utilization of systemic therapies for brain metastases has not yet been codified and is undergoing active investigation.¹⁴

Meningiomas

Meningiomas are tumors arising from the tissues surrounding the CNS. Meningiomas are predominantly intracranial but can also occur in the spinal region. They predominantly cause symptoms by compression of underlying structures. Contemporary grading criteria are summarized in table 1. As with gliomas, these tumors can further be subdivided by their molecular characteristics, although this aspect is not yet a component of the World Health Organization (WHO) classification.¹⁵ These molecular characteristics include both mutually exclusive neuroanatomically defined mutations¹⁶ and specific methylation profiles of the entire genome.¹⁷ At this point in time, these molecular characteristics do not substantially alter the standard clinical management of patients with these tumors. However, they can lend insight into prognosis and are currently undergoing investigation with regard to their utility in a cooperative group trial (Alliance A071401; NCT02523014) of targeted therapies.

Radiographically, they are most often homogeneously enhancing lesions that appear to be extra-axial and arise from the dura (figure 1B). A substantial amount of underlying cerebral edema, an indistinct tumor-brain interface, heterogeneous enhancement, a previous history of radiation,

Figure 1 MRI appearance of CNS tumors on axial T1 postcontrast sequences

(A) Images from a 48-year-old woman with triple-negative breast cancer. A large left frontal relatively well-circumscribed lesion with substantial surrounding edema is noted. Multiple additional similar smaller lesions were noted on other cuts. (B) A 76-year-old woman with a left temporal region meningioma. The extra-axial homogeneously enhancing lesion arises from the dura. (C) A 73-year-old woman with IDHwt glioblastoma. A large heterogeneous right temporal/insular lesion is seen. (D) A 52-year-old woman with an IDH-mutated anaplastic astrocytoma. A large right frontal area of decreased signal with small areas of enhancement is noted. (E) Images of a 57-year-old man with a progressive grade 2 oligodendroglioma who had initially presented with seizures a number of years prior. An area of increased FLAIR is noted in the subcortical right frontal lobe. (F) Image of an 84-year-old woman with primary CNS lymphoma. Image demonstrates classic deep location of tumor with homogenous contrast enhancement. FLAIR = fluid-attenuated inversion recovery; IDH = isocitrate dehydrogenase.

or rapid interval growth of tumor raises suspicion that the lesion may be higher grade (grade 2 or 3). At this time, there are no standard radiographic parameters, which are pathognomonic for specific grades of meningiomas. In addition, there are other tumors that can mimic the appearance of meningiomas including dural metastases (most frequently from breast and prostate cancer), solitary fibrous tumor of the CNS (formerly hemangiopericytoma before its renaming in the WHO 2016 classification), dural

lymphoma, and other lymphoproliferative processes such as Rosai-Dorfman syndrome and immunoglobulin G4-related hypertrophic pachymeningitis.

Management of meningiomas ranges from clinical and radiographic observation to multimodality therapy with surgery followed by radiation. A number of factors influence this decision making, including patient age, comorbid medical conditions, symptomatology, tumor size, tumor location,

Table 1 Meningioma grading

Grade	Histologic subtype	Mitoses	Brain invasion	Or
1	Meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte rich, and metaplastic	<4 in 10 consecutive high-power fields	Not present	<3 of the following: <ul style="list-style-type: none"> • Increased cellularity • Small cells with high nucleus to cytoplasm ratio • Prominent nucleoli • Sheeting and foci of spontaneous necrosis
2	Clear cell and chordoid	≥4 and <20 in 10 consecutive high-power fields	May be present	
3	Rhabdoid and papillary	≥20 in 10 consecutive high-power fields	May be present	>3 of the following: <ul style="list-style-type: none"> • Increased cellularity • Small cells with high nucleus to cytoplasm ratio • Prominent nucleoli • Sheeting and foci of spontaneous necrosis

tumor growth rate, concern regarding other etiologies, and concern for higher-grade (2 or 3) meningiomas.¹⁸ Surgical resection has both diagnostic and therapeutic benefit. It can confirm that the tumor is a meningioma, delineate its grade, and evaluate for mutations, which may guide therapeutic trial enrollment. It also removes the compressive mass potentially alleviating symptoms. The goal of meningioma surgery is often gross total resection. This, however, is not typically feasible when the tumor is invading the posterior portion of the superior sagittal sinus nor for many skull base locations.

Presumed grade 1 meningiomas, alternatively, can be treated (if treatment is necessary) with SRS.¹⁹ SRS is a means of delivering a high dose of focal radiation to a relatively small field often in a single fraction. It provides excellent long-term control of grade 1 meningiomas, however, that benefit diminishes as the tumors increase in grade. For grade 3 meningiomas, because of the extremely high rate of recurrence, postoperative radiation is typically recommended, even after gross total resection.²⁰ Most often fractionated radiation to a higher dose is used, as this is associated with a better local control rate. For patients with gross totally resected grade 2 meningiomas, there is approximately a 50% chance of recurrence. In turn, it is unclear whether observation or postoperative radiation offers the best overall outcomes. This question is currently under investigation in the NRG BN003 (NCT03180268) randomized clinical trial. Numerous trials have evaluated a range of systemic therapies including hydroxyurea, estrogen receptor antagonists, somatostatin receptor antagonists, antiangiogenic agents, and tyrosine kinase inhibitors.¹⁸ At this time, there is no single agent or combination of agents, which has demonstrated a clear benefit in a substantial percentage of patients. The role of systemic therapies continues to be explored and may yield successes, possibly within specifically defined subsets of patients.

Overview of infiltrating gliomas

It is of value for the clinician to be aware of a recent revision of the WHO classification system²¹ (figure 2). Previous systems relied exclusively on histologic characteristics. The current system adopted in 2016 uses a layered approach incorporating histology and molecular features (table 2). This is important for infiltrating glial tumors. Of note, this system includes the mutational status of isocitrate dehydrogenase (*IDH*), histone genes, and chromosomal rearrangement of 1p/19q. It helps categorize these tumors into 4 large groups: (1) *IDH* wild-type (wt) astrocytomas including GBM (WHO IV) and diffuse astrocytomas (WHO II+III), (2) *IDH*-mutated astrocytomas (WHO II-IV), (3) *IDH*-mutated and 1p19q codeleted oligodendroglioma (WHO II+III), and (4) histone 3 mutated (most frequently *H3K27M*) midline gliomas (WHO IV). A previous categorization based on histologic characteristics, oligoastrocytomas, is being phased out. It is clear that at the molecular level, tumors that appeared to be of mixed lineage are either oligodendroglial or astrocytic. In turn, this category is no longer valid and will not be used. The natural

history of *IDH*wt GBM and *IDH*wt astrocytomas is similar and resembles the clinical course attributed to “traditional” GBM.²² In contrast, oligodendrogliomas and *IDH*-mutated astrocytomas typically have a more indolent clinical course with more favorable overall survival.²³ Our current treatment paradigms, however, are built around studies, which relied on histologic grading with only partial incorporation of the molecular characteristics.²⁴

*IDH*wt astrocytomas (GBS)

GBM *IDH*wt (figure 1C) and *IDH*wt astrocytomas (grade 2–3) are viewed as a unified tumor entity, which benefits from a multimodality approach to treatment.²⁵ Their management entails surgical resection followed by radiation therapy (RT) with concurrent temozolomide followed by additional post-RT temozolomide.²⁶ Tumors with silencing via methylation of the gene promoter for the DNA repair enzyme methyl-guanine methyl transferase (MGMT) garner greater benefit from the utilization of temozolomide.²⁷ Questions remain regarding the optimal number of post-RT cycles of temozolomide, with many practitioners opting for 6.²⁸ Intensification of the regimen in MGMT-methylated tumors with the addition of the nitrosourea CCNU is suggestive of efficacy.^{29,30} The utilization of low voltage moderate-frequency (200 kHz) electrical fields delivered via arrays placed on the shaved scalp when added to standard chemoradiotherapy has been shown to prolong survival, progression-free survival, and landmark survival. These tumor-treating fields (TTFields) were approved by the US Food and Drug Administration for newly diagnosed GBM in 2015.³¹ The improvement in the percentage of patients alive at specific landmarks in time (2 or 5 years for example) is important in assessing the value of treatments such as TTFields and others, as it provides information about the long-term benefit of an intervention.

In older patients de-escalation of treatment intensity is used to improve tolerability. A number of options can be considered including RT alone, temozolomide alone, and shorter course RT with or without chemotherapy. Numerous factors are incorporated in that decision.^{32,33} One frequently used regimen involves shorter-course (3 weeks) RT with concurrent temozolomide followed by adjuvant temozolomide.³⁴

Means to further improve treatments are undergoing investigation. The promise of immuno-oncology seen in other difficult to treat malignancies has not yet born fruit in neuro-oncology.³⁵ It remains, however, an active area of investigation with a range of approaches, including combinatorial regimens, being studied.³⁶ As with temozolomide/MGMT, there is hope that a predictive biomarker for immunotherapeutic treatment of gliomas will be uncovered and prospectively validated.³⁷

IDH-mutated astrocytomas

IDH-mutated astrocytomas (figure 1D) are slower growing than their *IDH*wt counterparts, but data on how to optimally treat

Figure 2 Diagnostic classification scheme for infiltrating gliomas

these patients are lacking. To date, no prospective clinical trials incorporating current classification systems have been completed. In patients younger than 40 years who have undergone a complete resection of a grade 2 tumor, observation is recommended, similar to oligodendrogliomas. In all others, most evidence suggests maximal safe resection followed by RT and chemotherapy.³⁸ In grade 3 tumors, RT with concurrent temozolomide followed by adjuvant temozolomide is a frequently used regimen, but the best prospective, randomized evidence supports the use of procarbazine/CCNU/vincristine (PCV). The ongoing CATNON (NCT00626990) international cooperative group study is attempting to answer the questions regarding the optimal management of this patient population.

GBM with an IDH mutation is rare and represents only 5%–10% of GBM. This is what had been referred to as secondary GBM tumors that have arisen from a lower grade glioma. Although we treat these the same as “traditional” GBM, outcomes are notably better and median survival is in excess of 2 years. Specific novel therapeutics including IDH inhibitors, IDH targeting vaccine, and eflornithine are under investigation for these tumors.

Oligodendrogliomas

Oligodendrogliomas (figure 1E), characterized by IDH mutations and 1p19q codeletion, are typically associated with a favorable prognosis when compared with IDHwt and IDH-mutant astrocytomas and have long been known to be treatment responsive with radiographic responses and prolonged progression-free survival being frequently observed. Treatment includes maximum feasible surgical resection. In patients younger than 40 years who have undergone a complete resection of grade 2 tumor, observation is recommended. In contrast, treatment with RT and/or chemotherapy is typically recommended for “high-risk” patients characterized by the

presence of radiographically residual tumor or age >40 years. There continues to be debate regarding whether RT alone, chemotherapy alone, or the combination should be used. Recently, mature data from long-term therapeutic trials support the combination of RT and chemotherapy in high-risk patients.^{39,40} The optimal chemotherapy regimen for these patients remains unknown with PCV, PC (omitting the vincristine which is associated with peripheral neuropathy), or temozolomide viewed as legitimate options. The ongoing CODEL (NCT00887146) trial is comparing RT+PCV vs RT with concurrent temozolomide followed by additional temozolomide cycles. Results are eagerly awaited.

Histone-mutated astrocytomas (diffuse midline gliomas)

A subset of infiltrating gliomas harbor mutations of histone genes, most frequently H3K27M. These tumors typically occur in midline locations and are more often found in the pediatric and young adult patients.⁴¹ They encompass a range of entities including diffuse intrinsic pontine gliomas. In adults, they are more often present in the thalamus and spinal cord where they appear to follow a less aggressive course than their pediatric equivalents. Currently, there is no clear guidance on optimal management, and treatment paradigms similar to those for GBM are often used.

CNS lymphomas

Neoplasms of lymphoid cells have the potential to involve the CNS. These CNS lymphomas can be divided into 2 broad categories: primary CNS lymphoma (PCNSL) and systemic lymphoma with secondary CNS involvement. PCNSLs are rare primary CNS tumors, and secondary involvement of the CNS is an uncommon manifestation of systemic lymphomas.⁴² It is, however, important for the neurologist to have an understanding

of these diseases, as they may be involved in the initial diagnostic evaluation and the early management may affect subsequent clinical care in this aggressive but curable neoplasm. Of particular importance is the need to avoid steroids, as they may obfuscate the diagnosis.

The radiographic appearance typically consists of homogeneously enhancing lesion(s) often with a corresponding uniform restriction of diffusion in nonvascular distributions on diffusion-weighted imaging and apparent diffusion coefficient sequences (figure 1F). These lesions can rapidly diminish when exposed to steroids and even resolve completely leading to nondiagnostic biopsies and delays in diagnosis.⁴³ In turn, it is advantageous to avoid steroids if possible before diagnosis and to use other means to decrease intracranial pressure if needed. With CNS lymphoma, biopsy is typically preferred due to poorer survival in early therapeutic studies among patients who underwent resection.⁴⁴ There have been subsequent studies that have challenged this perspective; however, a resective approach while reasonable in some clinical scenarios would not be considered the standard of care at this time.^{45,46} After the diagnosis of CNS lymphoma is established or oftentimes in parallel to help expedite initiation of therapeutic treatment, patients undergo staging to evaluate for extra-CNS involvement of disease. This extra-CNS staging will often involve CT/PET of the body and an ophthalmologic slit-lamp examination to evaluate for ocular involvement. Additional studies that may

With CNS lymphoma, biopsy is typically preferred due to poorer survival in early therapeutic studies among patients who underwent resection.

be included and are of less certain value include bone marrow biopsy, CSF analysis, and testicular ultrasound. Often, studies that may influence prognosis such as serum lactate dehydrogenase and CSF protein levels may be sent. Finally, serum HIV testing is routinely performed as HIV-associated CNS lymphoma may have some differences in management distinct from its non-HIV-associated counterpart.⁴⁷

PCNSL treatment consists of an induction phase in which the goal is to rid the patient of radiographically visible disease followed by a consolidation phase aimed at destroying any resistant microscopic cells which remain. The induction phase of PCNSL is built around a high-dose (HD) methotrexate (MTX)-based regimen. HD-MTX is administered intravenously as an inpatient regimen requiring frequent hospitalizations. One of the primary concerns related to HD-MTX is potential renal

Table 2 Effect of molecular alterations on classification of diffuse astrocytic and oligodendroglial tumors

Molecular alterations	Histology	WHO 2016 integrated diagnosis	Clinical features
Diffuse astrocytic tumors			
IDH wild type	Nuclear atypia Nuclear atypia, focal anaplasia, and mitoses All of above + microvascular proliferation	<i>Diffuse astrocytoma, IDH wild type</i> <i>Anaplastic astrocytoma, IDH wild type</i> <i>GBS, IDH wild type</i>	Aggressive clinical behavior, "traditional" GBS. Median survival 15–23 mo
IDH mutation	Nuclear atypia Nuclear atypia, focal anaplasia, and mitoses All of above + microvascular proliferation	<i>Diffuse astrocytoma, IDH mutant</i> <i>Anaplastic astrocytoma, IDH mutant</i> <i>GBS, IDH mutant</i>	Slow growing with disease course over many years Intermediate between low grade and GBM Secondary GBM (5% of cases), longer survival than "traditional" GBM, median survival 31–112 mo
H3K27M mutation	Astrocytoma	<i>Diffuse midline glioma</i>	Brainstem and thalamic gliomas; aggressive behavior, median survival ~12 mo, although in adult patients, this may be longer
Oligodendroglial tumors			
IDH mutation and 1p/19q codeletion	Oligodendrocytes with rounded nuclei and clear surrounding cytoplasm Above features with anaplasia and/or microvascular proliferation	<i>Oligodendroglioma, IDH mutant, and 1p/19q codeleted</i> <i>Anaplastic oligodendroglioma, IDH mutant, and 1p/19q codeleted</i>	Slowest growing with excellent sensitivity to chemotherapy and radiotherapy, median survival 96–210 mo More aggressive than oligodendroglioma, but responsive to therapy, and many patients have long-term survival

Abbreviations: GBS = glioblastoma; IDH = isocitrate dehydrogenase; WHO = World Health Organization.

TAKE-HOME POINTS

- Our understanding of branched evolution with accumulation of new mutations as solid tumors metastasize from their primary site to the brain will influence the study of therapeutics for brain metastases, particularly within the context of clinical trials for these patients.
- The 2016 WHO classification system for CNS tumors incorporates molecular characteristics, including IDH and H3K27M mutational status and chromosome 1p19q codeletion, into the definition of many tumor types, as these often correlate more tightly with the natural history.
- The term oligoastrocytoma is being phased out.
- The addition of directly applied alternating electrical fields (tumor treating fields) when added to standard of care has been shown to improve survival in patients with newly diagnosed GBS.
- Promising new agents, including those targeting Btk, are undergoing early phase investigations in primary CNS lymphoma.

injury due to intraneuronal crystallization of MTX, which is cleared through the kidneys. This risk is reduced with IV fluids and alkalinization of the urine. The optimal dose of HD-MTX and the optimal regimen are uncertain, but most evidence suggests that multiagent approaches are superior. There is variable support for rituximab, a monoclonal antibody to the B-cell marker, CD20. There has been a strong movement away from the inclusion of intrathecal chemotherapy as a component of the induction regimen. The optimal consolidation regimen is even less clear. A number of reasonable options exist. These include other chemotherapies, WBRT, or HD chemotherapy with autologous stem cell transplant.^{48,49} Decision making often depends on patient age, preferences in relation to cranial radiotherapy, and ability to withstand aggressive chemotherapy and transplant regimens. Novel therapeutics, both for newly diagnosed and recurrent disease, are undergoing investigation. Of particular interest are regimens incorporating ibrutinib, an oral agent targeting Bruton tyrosine kinase.⁵⁰ Although not yet a component of the standard of care, the role of novel therapeutics in the management of this disease will likely increase in importance.

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References

- Barnholtz-Sloan JS, Sloan AE, Davis FG, Vignea FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan detroit cancer surveillance system. *J Clin Oncol* 2004;22:2865–2872.
- Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol* 2017;19:1511–1521.
- Ostrum QT, Gittleman H, Liao P, 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.
- Fidler IJ, Yano S, Zhang RD, Fujimaki T, Bucana CD. The seed and soil hypothesis: vascularization and brain metastases. *Lancet Oncol* 2002;3:53–57.
- Fidler IJ. The biology of brain metastasis: challenges for therapy. *Cancer J* 2015;21:284–293.
- Brastianos PK, Carter SL, Santagata S, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov* 2015;5:1164–1177.
- Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
- Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;33:583–590.
- Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8–10.
- Saghal A, Ruschin M, Ma L, Verbakel W, Larson D, Brown PD. Stereotactic radiotherapy alone for multiple brain metastases? A review of clinical and technical issues. *Neuro Oncol* 2017;19(suppl 2):ii2–ii15.
- Brown PD, Pugh S, Laack NN, 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;15:1429–1437.
- Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RT0933): a Phase II Multi-Institutional Trial. *J Clin Oncol* 2014;32:3810–3816.
- Gondi V, Deshmukh S, Brown PD, et al. NRG Oncology CC001: a phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). *J Clin Oncol* 2019;37(15 suppl):2009.

14. Kotecha R, Gondi V, Ahluwalia MS, Brastianos PK, Mehta MP. Recent advances in managing brain metastasis. *F1000Res* 2018;7:F1000 Faculty Rev-1772.
15. Suppliah S, Nassiri F, Bi WL, et al. Molecular and translational advances in meningiomas. *Neuro-oncology* 2019;21(suppl 1):i4-i17.
16. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet* 2013;45:285–289.
17. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. *Lancet Oncol* 2017;18:682–694.
18. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. *Future Oncol* 2018;14:2161–2177.
19. Pollock BE, Stafford SL, Utter A, Giannini C, Schreiner SA. Stereotactic radiosurgery provides equivalent tumor control to Simpson grade 1 resection for patients with small to medium-size meningiomas. *Int J Radiat Oncol Biol Phys* 2003;55:1000–1005.
20. 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;64:56–60.
21. 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;131:803–820.
22. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for “diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”. *Acta Neuropathol* 2018;136:805–810.
23. Molinaro AM, Taylor JW, Wiencke JK, Wrensch MR. Genetic and molecular epidemiology of adult diffuse glioma. *Nat Rev Neurol* 2019;15:405–417.
24. Horbinski C, Ligon KL, Brastianos P, et al. The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients. *Neuro Oncol Epub* 2019 Jul 4.
25. Lukas RV, Wainwright DA, Ladomersky E, Sachdev S, Sonabend AM, Stupp R. Newly diagnosed glioblastoma: a review on clinical management. *Oncology (Williston Park, NY)* 2019;33:91–100.
26. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–996.
27. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005;352:997–1003.
28. Blumenthal DT, Gorlia T, Gilbert MR, et al. Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG oncology/RTOG. *Neuro Oncol* 2017;19:1119–1126.
29. Herrlinger U, Tzaridis T, Mack F, et al. Phase III trial of CCNU/temozolomide (TMZ) combination therapy vs. standard TMZ therapy for newly diagnosed MGMT-methylated glioblastoma patients: the randomized, open-label CeTeG/NOA-09 trial. *Lancet* 2019;393:678–688.
30. Stupp R, Lukas RV, Hegi ME. Improving survival in molecularly selected glioblastoma. *Lancet* 2019;393:615–617.
31. 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;318:2306–2316.
32. Young JS, Chmura SJ, Wainwright DA, Yamini B, Peters KB, Lukas RV. Management of glioblastoma in elderly patients. *J Neurol Sci* 2017;380:250–255.
33. Minniti G, Lombardi G, Paolini S. Glioblastoma in elderly patients: current management and future perspectives. *Cancers (Basel)* 2019;11:E336.
34. Perry JR, Laperriere N, O’Callaghan CJ, et al. Short-course radiation plus temozolomide. *N Engl J Med* 2017;376:1027–1037.
35. Kurz SC, Cabrera LP, Hastie D, et al. PD-1 inhibition has only limited clinical benefit in patients with recurrent high-grade glioma. *Neuro Oncol* 2018;91:e1355-1359.
36. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, Checkmate-143: the game is not over yet. *Oncotarget* 2017;8:91779–91794.
37. Zhao J, Chen AX, Gartrell RD, et al. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nat Med* 2019;25:462–469.
38. Lukas RV, Mrugala MM. Pivotal therapeutic trials for infiltrating gliomas and how they affect clinical practice. *Neuro Oncol Pract* 2017;4:209–219.
39. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016;374:1344–1355.
40. 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.
41. Louis DN, Giannini C, Capper D, et al. cIMPACT-NOW update 2: diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant. *Acta Neuropathol* 2018;135:639–642.
42. Malecek MK, Petrich AM, Rozelle S, et al. Frequency, risk factors, and outcomes, of central nervous system relapse in lymphoma patients treated with dose-adjusted EPOCH plus rituximab. *Am J Hematol* 2017;92:1156–1162.
43. Lukas RV, Riedell P, Horowitz PM, Pytel P, Kamson DO. Diagnostic evaluation in primary CNS lymphoma. *Neurologist* 2018;23:53–54.
44. DeAngelis LM, Yahalom J, Heinemann MH, Cirincione C, Thaler HT, Krol G. Primary CNS lymphoma: combined treatment with chemotherapy and radiotherapy. *Neurology* 1990;40:80–86.
45. Weller M, Martus P, Roth P, et al. Surgery for primary CNS lymphoma? Challenging a paradigm. *Neuro Oncol* 2012;14:1481–1484.
46. Rae AJ, Mehta A, Cloney M, et al. Craniotomy and survival for primary central nervous system lymphoma. *Neurosurgery* 2019;84:935–944.
47. Lukas RV, Stupp R, Gondi V, Raizer JJ. Primary central nervous system lymphoma-PART 1: epidemiology, diagnosis, staging, and prognosis. *Oncology (Williston Park)* 2018;32:17–22.
48. Lukas RV, Gondi V, Stupp R, Raizer JJ. Primary central nervous system lymphoma-PART 2: modern therapeutic management and future directions. *Oncology (Williston Park)* 2018;32:e11-e19.
49. Patrick LB, Mohile NA. Advances in primary central nervous system lymphoma. *Curr Oncol Rep* 2015;17:60.
50. Grommes C, Nayak L, Tun HW, Batchelor TT. Introduction of novel agents in the treatment of primary CNS lymphoma. *Neuro Oncology* 2019;21:306–313.