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TOPIC REVIEW

Guidelines in the management of CNS tumors

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Abstract

Introduction Evidence-based, clinical practice guidelines in the management of central nervous system tumors (CNS) continue to be developed and updated through the work of the Joint Section on Tumors of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS).

Methods The guidelines are created using the most current and clinically relevant evidence using systematic methodologies, which classify available data and provide recommendations for clinical practice.

Conclusion This update summarizes the Tumor Section Guidelines developed over the last five years for non-functioning pituitary adenomas, low grade gliomas, vestibular schwannomas, and metastatic brain tumors.

Keywords Brain tumor · Neuro-oncology · Gliomas · Vestibular schwannomas · Nonfunctioning pituitary adenomas · Metastatic brain cancer

Introduction

Commemorating its 35th anniversary, the Joint Section on Tumors of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS) continue to lead in the development of evidence-based, clinical practice guidelines summarizing the state of the art management of neurosurgical oncology. The explosion of publications and multidisciplinary nature of neurosurgical oncology requires clinicians to stay up to date and understand the presence and absence of evidence for practice. As such the CNS Guidelines serve to evaluate and translate medical knowledge into practical recommendations for patients and physicians [1].

Brain tumor management is multidisciplinary by nature, with approximately 25,000 new randomized control trials published every year of varying significance, strength of evidence, and accessibility [2]. Nevertheless, these trials may not include parameters or patient populations translatable to the masses affected by the specific pathology, and critical evaluation of these studies is mandatory [3]. Clinical practice guidelines (CPG) provide systemic assessments of publications needed in order to fully ascertain their efficacy in improving care while translating complex scientific research findings into recommendations for clinical practice and to potentially enhance the quality of health care and improve patient outcomes [2, 4, 5].

The CNS/AANS tumor guidelines adhere to a two-tiered methodology whereby levels of recommendation are always directly linked to levels of evidence with detailed evidentiary tables. Tumor Section guidelines have sought to reduce unexplained variability in care while, importantly, not restricting the ability of providers to deliver individualized

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care for any given patient. The group of physicians that participate in their development strictly follow the standards set by IOM. The CNS guidelines use strict systematic methodologies created to classify available evidence and provide recommendations for clinical practice, thus diminishing bias in the true quality of published knowledge. The following summarizes the Tumor Section Guidelines developed over the last 5 years for non-functioning pituitary adenomas, low grade gliomas, vestibular schwannomas, and metastatic brain tumors; key points will be highlighted.

Nonfunctioning pituitary adenomas

Pituitary adenomas are broadly categorized into micro- and macro-adenomas based on a 1 cm cut-off. The threshold is largely driven by the natural size of the sella, with lesions > 1 cm more likely to exert mass effect on surrounding critical anatomy. Micro- and macro-adenomas differ significantly in natural history. Microadenomas (< 1 cm) are often found incidentally and occur in at least 10% of autopsies or MRIs performed for unrelated indications, [6–8] in contrast to macroadenomas (> 1 cm) which occur in only 0.3% [9]. Tumor size has been consistently associated with tumor growth in multiple natural history studies, with an average volume growth rate of 0.34 mL per year, [10] though individual growth rates are quite variable. When managed conservatively, microadenomas progress in approximately 5–15% of cases, with a median time to tumor growth of > 4 years [11–14]. In contrast, a watch-and-wait approach for macroadenomas leads to growth in 39–60%, of which > 50% develop new or worsening visual deterioration. New hormone deficiency occurs in < 10% and apoplexy occurs in < 5% [11–14]. Non-functioning pituitary adenomas (NFPAs), the most common form of pituitary adenomas, do not secrete hormones, and vary clinically [15]. Their natural history, clinical evaluation, and management are summarized in the CNS guidelines [16]. (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

Initial evaluation and diagnosis

Neuroimaging

The gold standard imaging modality for pituitary adenomas is an MRI with fine sections through the sella, as MRI best (1) defines tumor anatomy relative to the pituitary gland, optic apparatus, and carotid arteries and (2) allows for the differentiation of NFPA from craniopharyngioma, meningioma, and other tumors that involve the sellar region (Level II) [17, 18]. CT and CT-angiogram are useful adjunctive tests [19] that facilitate neuronavigation, delineate sphenoid sinus anatomy and bony erosion by tumor, and aid in reconstruction planning if a CSF leak is anticipated (Level III) [20, 21]. Higher field strength MRI (3T) has a higher sensitivity for infiltration of the medial cavernous sinus wall and improved ability to visualize cranial nerves than conventional MRI (Level III) [22, 23]. While PET, spectroscopy, and intra-operative MRI (iMRI) have been explored as imaging platforms for NFPA, these modalities remain largely investigational [16].

Endocrinologic evaluation

Baseline assessment of anterior pituitary function is recommended in patients with pituitary adenomas (Level II). Serum prolactin level is an important first step to rule out a prolactinoma, for which medical management with a dopamine agonist is first-line treatment in the U.S [24–26]. Serum IGF-1 levels should be tested even in the absence of overt acromegaly, as 33–46% of clinically silent adenomas are immune-positive for GH on histology [27, 28] and exhibit higher recurrence [29]. In patients with NFPAs, partial hypopituitarism occurs at 25–85%, [30–40] with panhypopituitarism rates around 2–29% [34–37, 39]. These studies vary markedly with respect to which hormones are most commonly affected, however hypogonadism generally occurs in a range of 30–50%, and DI or SIADH are present in < 5%. Variability in hypopituitarism rates are at least in part due to differences in measurement techniques, limited sample sizes in the published studies, and heterogeneity in the definition of hypopituitarism. Replacement of adrenal insufficiency and hypothyroidism is recommended to prevent anesthesia complications and adrenal crisis (Level II) [41, 42]. Replacement is critical with pituitary apoplexy, since apoplexy is frequently associated with hypopituitarism (Level III) [43–45].

Visual system assessment

History of visual loss should be solicited as routine work-up for NFPA. Preoperative evaluation by an ophthalmologist is recommended for patients with pituitary adenomas (Level III), especially when the tumor makes contact with the optic apparatus or invades the cavernous sinus. Examination should include assessment of visual acuity, visual fields with static perimetry, the optic disc and retina, and extraocular muscle examination (Level III) [46–48]. Thorough examination allows for detection of subclinical defects [47], serves as a basis for follow-up or post-intervention comparison, evaluates for confounding comorbidities including cataracts and glaucoma, and is of prognostic value [49–52]. Rapid deterioration of visual

acuity or field and visual apparatus compression may warrant urgent surgery.

Management

Surgery is recommended for symptomatic NFPAs (Level II) [43, 53–65]. Gross total resection rates range from 65 to 80%, [43, 53, 55, 56, 58, 64, 65] vision improves in 40–93%, [31, 54–62, 64, 65] headaches improve in 56–90% [63], and hormone function improves in 14–51% [31, 54, 59, 64]. These benefits were balanced by an acceptably low adverse outcomes profile, including transient DI in 5–28%, [31, 54, 58, 60, 62, 64] permanent DI in 3–6%, [31, 54, 59, 60, 64] hormone function worsening in 7–31%, [60, 64], CSF leak in 2–4.7% [54, 60, 66, 67], epistaxis in 1.3–4%, [54, 60, 66] and carotid injury in 0.3–1% [54, 56, 60, 66, 67].

Endoscopic versus Microscopic endonasal approaches is often based on the training and experience of a surgeon (Level II) [68]. The multi-institutional, prospective, TRANSSPHER study, found no significant difference between gross total resection rates or volumetric extent of tumor resection between microscopic and endoscopic transsphenoidal approaches; even in subgroup analysis accounting for Knosp grade [68]. This study found that patients treated endoscopically had less new hormone deficiency but had longer surgical times [68]. A learning curve between microscopic and endoscopic endonasal approaches has been documented and is associated with shorter operative times and improved outcomes [69–71] A midline surgical corridor and adequate bony exposure facilitates surgical resection of NFPA (Level III) [72, 73]. There is insufficient evidence to recommend neuronavigation as a routine adjunct for NFPA resection [74, 75]. There is no evidence for the routine use of perioperative CSF diversion except in cases of large nonsellar defects ranging in size from 3.8 cm^2 (posterior fossa/clival) to 6.2 cm^2 (anterior fossa/cribriform) (Level II) [76]. There is insufficient evidence to recommend iMRI [77, 78].

NFPA patients who are not surgical candidates may undergo radiation or medical therapies. Radiosurgery can reduce tumor volume (40–80% cases), but cause pituitary hormone dysfunction in dose- and time-dependent fashion [79–81]. Medical therapy with dopamine agonists and somatostatin analogues have varied response. Monitoring for treatment failure, tumor progression, and side effects is critical [82–87].

Postoperative management

Imaging

The initial postoperative MRI should be done 3–4 months post-resection [58, 88–91] and continued indefinitely given tumor growth can occur even after a decade. (Level III) [91–94] Imaging sequences should include T1 pre-gadolinium, T1-post gadolinium, and T2 fast spin echo (Level III) [77]. Postoperative imaging of NFPA involving the sphenoid roof or sphenoid sinus is difficult to interpret since post-surgical changes may persist beyond 3 years after surgery [95, 96]. NFPA that are gross totally resected can be followed less frequently compared to a subtotal resection (Level III) [91, 97–99].

Endocrinologic and ophthalmologic follow-up

After surgical resection or radiation treatment, patients must continue endocrinologic follow-up (Level III) [88, 100–103]. Sodium levels and urine output should be carefully monitored in the peri-operative period (Level III), as life-threating hyponatremia and diabetes insipidus have been reported in the first 5–10 days postoperatively [101, 104]. Adrenal function should be monitored in the perioperative period, and then at 6 weeks and 12 months after surgery (Level III) [100]. Cortisol supplementation is indicated for patients with low morning serum cortisol (Level III) [100]. Hormonal axes can recover postoperatively, however, larger tumors are likely to have persistent endocrine dysfunction [92, 105]. Patients with gross total resection and normal pituitary function after 1 year may forego endocrine follow-up whereas subtotal resected or radiated tumors should be monitored at least annually (Level III) [103]. Ophthalmologic evaluation is recommended for patients who have undergone surgery or radiation therapy (Level III). Postoperatively, visual field defects may improve months after surgery but may plateau at 1 year [53, 61, 92]. Optimal timing for ophthalmologic follow-up is poorly defined.

Management of recurrent/residual tumor

Subtotal resection is associated with cavernous sinus invasion/high Knosp grade, large tumor size, vertical extension, irregular/multi-lobular geometry, previous surgery, and experience of the surgeon [60, 64, 68, 106, 107]. Progression of residual tumor and recurrence of NFPAs is more common with silent corticotropic and somatotropic adenomas and giant adenomas (> 4 cm) [29, 108–112]. Patients with known residual tumor or high-risk features may require adjuvant therapy to maintain tumor or symptomatic control. Re-resection is recommended for symptomatic residual/recurrent NFPAs if surgically accessible (Level III) [113–116]. Endoscopic resection for recurrent NFPA after a previous microscopic resection may improve the extent of resection [73, 114, 117]. For asymptomatic residual/recurrent NFPAs, radiation therapy or radiosurgery is recommended to mitigate tumor progression (Level II) [118, 119]. There is insufficient evidence to recommend early or late radiation, however the literature suggests that early radiosurgery can

improve progression-free survival with a variable tradeoff of late post-SRS endocrinopathy rates [97, 102, 103, 120–124]. Radiation demonstrates excellent control rates > 80% for recurrent or residual NFPA, though new hormone deficiency may occur (20–40%); thyroid and growth hormone deficiencies have a mean onset of 2 to 4 years [81, 123, 125, 126]. Optic pathway-sparing radiosurgery protocols achieve excellent tumor control without significant optic neuropathy in long follow-up for tumors abutting the optic apparatus [127].

Emerging therapies

Molecular analysis of pituitary tumors may yield subgroups which can risk-stratify patients and management strategies [128]. Given the explosion of new therapeutic targets, medical therapy for NFPA may become more efficacious with lower side effect similar to recent advances with craniopharygiomas [129, 130]. Surgical innovation such using fluorescence- and contrast dye-based visualization techniques may help differentiate normal pituitary gland from tumor, [131] and evaluate perfusion in reconstructive flaps [132] improving resection rates.

Low grade gliomas

Low grade glioma (LGG) management has evolved with recent advances in therapy, and better characterization of the term "low grade" which for the purpose of the published guidelines included the WHO Grade II glioma category specified as diffuse astrocytoma, oligodendroglioma, and mixed oligoastrocytoma (per the WHO definitions at the time of the publication) [133]. The LGG guidelines encompass eight guideline chapters reflecting the multidisciplinary nature and the complexity of neuro-oncologic management of LGG as follows: diagnostic imaging [134], biopsy [135], surgical resection [136], neuropathology [137], radiation therapy [138], chemotherapy [139], emerging/alternative therapies [140], and recurrence [141]. (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

The LGG Guidelines encompass forty-eight recommendations based on available evidence for the thirty-four questions were published in total. As subsequently discussed in further detail, the greatest proportion of level 1 and 2 recommendations were generated within the radiotherapy, imaging, and chemotherapy guidelines which seems to positively correlate with the means for conducting prospective, randomized studies or gold standard statistical assessments within these domains [142]. Guidelines for surgical intervention for LGG contained a majority of Level 3 recommendations; however, consideration must be given to the fact that Class 1 evidence in this domain is limited due to the ethical uncertainty of clinical equipoise presented by these studies [136]. Multiple clinical questions yielded insufficient evidence within the available literature, primarily within the Emerging Therapies guideline. Research on nutrition and alternative medicine continues to lack well-designed methodology, federal regulation, and funding interest [140]. As previously mentioned, the recommendation to use chemotherapy as an adjunct to radiotherapy for patients with unfavorable tumor characteristics was upgraded to a level 1 recommendation after results of the RTOG-9802 study became available in a peer-review format [142].

Initial evaluation and diagnosis

Low grade gliomas are slow growing tumors that ultimately progress to higher grade tumors in 2–10 years [143]. Appropriate management depends on accurate and timely diagnosis. Imaging of these tumors is critical in diagnosis, management, and follow up evaluation. For the purpose of creating guidelines to define the role of imaging in the management of adults with LGG, the authors reviewed 1297 citations [134]. After the review, 65 publications met the eligibility criteria set by the team to be included in creating these guidelines [134]. For a full discussion of the included studies and their classifications for all the guidelines chapters on LGG, the reader is encouraged to review the cited guideline articles. The MRI remains the best imaging modality for non-invasive diagnosis and evaluation of LGG. For patients with suspected LGG, anatomic imaging sequences necessary to make the diagnosis should include T1 and T2-weighted and Fluid Attenuation Inversion Recovery (FLAIR) imaging together with post-contrast administration T1-weighted sequences (Level II) [134]. The utility of computer tomography (CT) is limited to the presence of intratumoral calcification and hemorrhage and helps further narrow the differential diagnosis. Diffusion and perfusion weighted MR imaging can potentially help to discriminate between different tumor subtypes and identify areas of higher grade within the LGG (Level II and III) [134]. MR spectroscopy (MRS), positron emission tomography (PET), and single-photon emission CT imaging (SPECT) can offer additional diagnostic specificity, but their roles are less defined in clinical practice (Level III). Finally, the perfusion weighted imaging can play a role in prognostication (Level III).

With regard to histopathologic, and thus more definitive, diagnosis and evaluation of LGG, based on Level 1 evidence, the use of a representative surgical sample of the lesion for histopathological analysis of diffuse LGG is recommended [137]. Resection of the specimen is preferred over a biopsy specimen to minimize the potential for sampling error (Level III) [137]. A biopsy is recommended only when definitive surgical resection cannot be performed due to the location of the lesion, deep-seated and/or in eloquent

cortex, or when the patient cannot undergo craniotomy due to multiple medical co-morbidities (Level III) [135]. When planning the biopsy, it is suggested that surgeons use advanced imaging techniques such as MRI perfusion or spectroscopy to improve the diagnostic accuracy (Level III) [135].

Low grade glioma guidelines were published in 2015. Up until that time, there was Level II and III data to recommend the use of genetic and molecular markers for more accurate diagnosis, prognosis and assistance with some clinical decision-making. Assessment of IDH gene mutation via IDH1 R132H antibody and/or IDH1/2 mutation hotspot sequencing was suggested as an additional test for classification and prognosis of LGG due to its specificity [137]. There was Level III evidence for testing of 1p/19q loss by FISH array-CGH or PCR for suspected oligodendroglial cases to assist with prognosis and potential treatment planning [137]. Insufficient evidence existed to recommend routine methyl-guanin-methyl-transferase (MGMT) promoter methylation testing for LGG [137]. In the interim, new data on the role of genetic and molecular marker testing for LGG classification and prognosis has been published together with the new World Health Organization brain tumor classification [144–146]. These new developments warrant an update of our guidelines on LGG.

Management

Surgery

As previously mentioned, a surgically resected specimen is preferred over a biopsy specimen in order to improve diagnostic accuracy [136, 137] and is recommended over observation and/or biopsy to improve overall survival (Level III) and improve seizure control for patients presenting with seizures [136]. Data has shown that gross total resection (GTR) or subtotal resection (STR) is preferable to biopsy alone in order to decrease the rate of tumor progression to a higher grade (Level II) [136]. Further, a greater degree of resection can improve overall survival in patients with newly diagnosed LGG (Level III) [136]. In order to safely accomplish a greater degree of resection, the surgeon should utilize all the tools available in our armamentarium, including the acquisition of pre-operative diffusion tensor sequences and functional MR imaging (Level III), use of intraoperative MRI (Level III), and intraoperative mapping techniques for tumors in eloquent areas (Level III) [136].

Adjuvant therapy

As discussed by Aghi et al. the rate of progression and recurrence of LGG after surgical resection is high [136]. Hence, the role of adjuvant therapy after surgical resection was reviewed and discussed as part of the newly diagnosed LGG clinical practice guidelines. Radiotherapy is recommended as an alternative to observation as a means to preserve cognitive function in patients with LGG irrespective of extent of resection (Level II) [138]. There is Level I data to recommend radiotherapy for adult patients with LGG irrespective of the extent of resection to prolong progression free survival [138]. In patients that have undergone only subtotal resection radiotherapy is as well recommended to increase overall survival and seizure control (Level III) [138]. A lower dose of radiotherapy (45–50.4 Gy) is recommended instead of higher dose to reduce radiation therapy toxicity (Level I) [138]. Radiation therapy can be delayed until progression or recurrence; however, this may result in shorter time to progression (Level III) [138]. Regarding the field of radiotherapy, limited-field is recommended over whole-brain radiotherapy in management of these tumors (Level III) and stereotactic radiosurgery or brachytherapy is acceptable only in selected patients (Level III) [138]. Negative prognostic factors (Level III), when predicting response to radiotherapy, include older age, decreasing performance status, decreasing cognitive abilities and presence of astrocytic histological components [138]. Consideration, however, should be given when discussing with patients with LGG of radiation induced morbidity, including cognitive decline, metabolic dysfunction and malignant transformation (Level III) [138].

Due to this risks, chemotherapy is recommended as a treatment option to postpone the use of radiotherapy, to delay tumor growth and improve progression free survival, overall survival and clinical symptoms in adult patients with newly diagnosed LGG (Level III) [139]. Patients that would benefit the most from chemotherapy alone or in combination with radiotherapy as initial adjuvant therapy for LGG are specifically those that cannot undergo gross total resection (Level III). In addition, patients with residual tumor > 1 cm on post-operative MRI, those presenting with diameter of > 4 cm or patients older than 40 years of age irrespective of degree of resection should as well be considered for adjuvant chemotherapy (Level III) [139]. The addition of chemotherapy to radiotherapy is recommended in patients that carry IDH mutation, while temozolomide is recommended as treatment option in patients who harbor the 1p/19q co-deletion (Level III) [139]. Insufficient evidence exists to make a definitive recommendation on when to start chemotherapy; however, it is suggested that adjuvant chemotherapy begin no later than 12 weeks after the diagnosis of LGG has been confirmed. There is insufficient data to recommend one particular chemotherapy regimen over another and the same can be said regarding the duration of chemotherapy. At the time when the guidelines were published in 2015, there was Level II evidence to recommend that chemotherapy be

added to radiotherapy for patients with unfavorable LGG (all patients older than 40 years of age and patients younger but that had a residual of > 1 cm on post-operative MRI, presenting with tumor of > 4 cm in diameter). In 2016, the data from RTOG–9802 trials became available [147]. In light of this new data, our recommendation for chemotherapy to be added to radiotherapy in all patients with newly diagnosed LGG with unfavorable characteristics to improve survival was upgraded to a Level I recommendation [142].

Management of recurrence

Despite the 54 studies that specifically targeted management of recurrence of low-grade gliomas in adult patients and met the guideline criteria, the data was limited to Class III evidence. There were no clear- cut conclusions regarding the roles of chemotherapy, radiation therapy, and surgery at recurrence in said data [141]. The current purpose of repeat surgical resection is to provide symptomatic relief and improved diagnosis; there are no indications in the literature that fulfill criteria for progression or overall survival advantages. Radiation therapy at recurrence potentially improves survival in the radiation naïve patient with the caveat that future studies are necessary to confirm this conclusion [141]. Chemotherapy options are varied, and there are no prospective comparative studies on their benefits. However, in retrospective, uncontrolled studies of TMZ and PCV, these agents appear to induce an effective response rate and potentially beneficial outcomes [141]; further studies, however, are strongly warranted to substantiate the findings.

Emerging therapies

A paucity of literature exists with regards to the inclusion and assessment of emerging therapies in the treatment of LGG to the extent that only three publications met criteria for review [140]. Not only does research on nutrition and alternative medicine continue to lack well-designed methodology, federal regulation, and funding interest, but also the infrequency of LGG in relation to other neoplasms lowers the perceived impact of research efforts and adds to a study's expense and complexity. Nevertheless, these three studies provided minimal level III evidence [140]. One study retrospectively assessed the association of hyperglycemia with survival rates, recurrence, and malignant tumor degeneration. A lower survival rate and increased recurrence and malignant degeneration were associated with persistent hyperglycemia, even after patients with diabetes and those on continued post-operative steroids were excluded from the data. Nutrition was further evaluated as a means of alternative therapy via lycopene and folate intake which showed a greater survival rate with moderate folate intake as opposed to a poorer survival rate associated with moderate intake of fat soluble lycopene [140].

Finally, no level I–II evidence was contrived for the roles of immunotherapy, tumor vaccines, nutrition, or other various alternative therapies in the treatment of LGG [140]. Future directions in this field of research may stem from several scientific advancements within other oncology domains such as the acceptance of immunotherapy as a treatment for melanoma and renal cell carcinoma, or the use of nanoparticles in the diagnosis and treatment of high-grade gliomas. The implication of both patients' desire for alternative therapies and their utility in other oncology domains will serve as an impetus for continued research efforts as well as improvements in daily clinical practice with regard to assessing a patient's nutritional status and behaviors [140].

Vestibular schwannomas

Vestibular schwannomas (VS) originate from the vestibular division of the vestibulocochlear (VIII) nerve can present with hearing loss, vertigo, or symptoms from brainstem and/or cerebellar compression. The primary management for symptomatic or enlarging VS is surgical resection or radiotherapy, whereas asymptomatic and small lesions are followed with imaging. The CNS VS Guidelines encompassed a multi-disciplinary effort in summarizing the management of VS [148].

Initial evaluation and diagnosis

Patients with hearing loss, imbalance, or symptoms associated with brainstem/cerebellum compression undergo an MRI (high-resolution T2-weighted and contrast-enhanced T1-weighted MRI, standard T1, T2, FLAIR and DWI MR sequences) (Level III) [149–151]. Contrast-enhanced 3D T1 magnetization prepared rapid acquisition gradient echo (MPRAGE) or high-resolution T2 MR imaging is recommended and may provide better visualization of the facial nerve course and relationship to the internal auditory canal (IAC) [149]. In addition, preoperative hearing testing (BAERs) should be obtained [152–154]. VS found incidentally that are asymptomatic and small, should be monitored and followed with MRIs [150, 155–158].

Management

Surgical approaches for VS when serviceable hearing is present include microsurgical resection via the retrosigmoid (RS) or the middle fossa (MF) approach [148].There is insufficient evidence to suggest that one method is superior in achieving complete resection with facial nerve preservation [148].When serviceable hearing is not present, either

a RS or a translabrynthine approach can be used as there is insufficient evidence to suggest one method is superior. There are insufficient data to support a firm recommendation that surgery be the primary treatment instead of observation or radiation therapy for small intracanalicular tumors (< 1.5 cm) [148]. There is also no evidence to support that use of a multi-disciplinary team of a neurosurgeon and a neuro-otologist provides superior outcomes for cranial nerve preservation and complete resection, as compared to either subspecialist operating solely. Tumor size plays an important role in the probability of facial and vestibulocochlear nerve preservation. *Level III* [159] A larger tumor size correlates with a greater than average risk of loss of serviceable hearing [148]. Nimodipine (or with the inclusion of hydroxyethyl starch) can be used perioperatively to improve facial nerve outcomes and ameliorate hearing outcomes [160].

Postoperative management

Patients who undergo gross total resection (GTR) are recommended to undergo MRI [161] *Level II:* Postoperatively, post-contrast 3D T1 MPRAGE imaging should be obtained. Tumors which are subtotally resected are followed with MRIs [162], as nodular enhancement warrants a high index of suspicion for recurrence [163, 164]. If the tumor size remains stable, the interval at which imaging is obtained can be prolonged however there isn't sufficient evidence to comment on the interval and duration. With respect to the differences in the progression of solid versus cystic VS, patients with cystic tumors should be counseled that this type is associated with decreased rates of complete resection as well as rapid growth [149]. In the immediate postoperative setting, outcomes involving the facial nerve can be inferior when compared to their solid counterparts, but over time become similar [149]. In patients with NF2, more frequent imaging may be used due to variable growth rate; after the growth rate has been delineated, annual imaging may be sufficient [165, 166]. Patients with bilateral tumors, may have increased growth rate after resection of contralateral tumor and warrant more frequent imaging [149].

Radiosurgery and radiation therapy

Stereotactic radiosurgery (SRS) and stereotactic radiotherapy can play an important role in the management of patients with VS. (Level III) [167]Asymptomatic intracanalicular VSs and small VSs (< 2 cm) can be observed for growth. (Level III) [167] A single fraction SRS dose, < 13 (Gy), is recommended to enable hearing preservation and minimize cranial deficits [167–173]. There is insufficient evidence comparing number of fractionations and type of radiation (Gamma Knife (GK), Linear Accelerator (LINAC)-based and proton beam therapy. Post-SRS MRI to assess for recurrence is recommended but there is insufficient evidence as to the duration of interval imaging [174, 175]. With respect to the possibility of malignant transformation of VS post SRS treatment, patients should be advised that this risk is less than 0.5% [176].

Emerging therapies

The future directions of treatment in VS are centered around emerging medical therapies and novel surgical techniques. Bevacizumab prolongs tumor stability, improves hearing and delays time to hearing loss, and may reduce tumor size (Level III) [178] Lapatinib reduces VS size and improves hearing in patients with NF2 [179, 180]. Erlotinib and everolimus are both not recommended [178]. Aspirin use can be considered in patients undergoing observation which may reduce future risk of growth [178].Preoperatively, vestibular rehabilitation and gentamicin ablation of the vestibular apparatus should be considered to enhance postoperative mobility [178].

Brain metastases

The Guidelines for the Management of Brain Metastases comprises eight topics covered generated 26 specific questions and 46 specific recommendations [181–191]. Given the rapid evolvement of molecular targeted therapy, novel treatment paradigms have challenged traditional practices in the management of metastatic brain tumors. As guidelines reflect the published literature, there exists a limitations in the ability to incorporate these novel findings, some of which are presented but not included in the guidelines. The following are brief summaries of the most important level I & II guidelines.

Surgery

Surgical resection of metastatic brain tumors has focused on resection of a single solitary or symptomatic lesion, or a lesion exerting significant mass effect or brain compression. The guidelines encompassed 32 studies reflecting the literature, which recommended surgery plus whole brain therapy (WBRT) as first-line treatment in patients with single brain metastases with favorable performance status and limited extracranial disease to extend overall survival, median survival, and local control (Level 1) [182] It should be noted that the guidelines are based upon the published literature which has not reflected the change in practice to SRS or molecular therapy in place of WBRT.

Radiation therapy

Stereotactic radiosurgery (SRS) has largely replaced WBRT as first line therapy and postoperative therapy given it's efficacy and minimal side effect profile, however, the guidelines were limited to the 31 studies that met criterion for inclusion [185]. As such, there is level III evidence to support SRS as an alternative to open surgery for solitary lesions, particularly when they are deep or close to eloquent or potentially radiosensitive regions, as well as for the treatment of 2–4 lesions ($\leq$ 3 cm in diameter). SRS is also recommended to boost the resection cavity after resection of lesions, or for supportive, palliative care of patients with brain metastasis to improve symptoms and quality of life (Level III) [185].

Traditionally WBRT had been recommended in standard dose/fractionation (i.e., 30 Gy in 10 fractions or a biological equivalent dose (BED) of 39 Gy10). (Level I) [184] Given neurocognitive side effects with increasing total dose and dose per fraction of WBRT, doses exceeding 30 Gy given in 10 fractions, or similar biologically equivalent doses, are not recommended, except in patients with poor performance status or short predicted survival [184]. The guidelines also note that if prophylactic cranial irradiation (PCI) is given to prevent brain metastases for small cell lung cancer, the recommended WBRT dose/fractionation regimen is 25 Gy in 10 fractions, and because this can be associated with neurocognitive decline, patients should be told of this risk at the same time they are counseled about the possible survival benefits. (Level II) [184].

The addition of WBRT is not recommended in WHO performance status 0–2 patients with up to four brain metastases because compared to surgical resection or radiosurgery alone, the addition of WBRT improves intracranial progression-free survival but not overall survival. (Level II) [184] As such, WBRT has largely fallen from the standard postoperative regimen.

Chemotherapy

Traditional chemotherapy is not recommended as a standalone therapy nor in addition to SRS or WBRT (Level I) [186]. Newer emerging molecular targeted therapies have been associated with significant tumor responses and improvements in progression and overall survival and will likely change the guidelines on the use of medical therapy in future guidelines [192, 193].

Multiple brain metastases

Treatment of patients with multiple brain metastasis is rapidly evolving from radiation therapy ± surgical resection to include newer molecular therapies and surgery, followed by radiation in a more targeted role [192, 193]. No clear best practice has emerged and thus this approach hasn't yet been included in the guidelines. In patients with 2–3 brain metastases *not amenable to surgery* treatment with SRS in addition to WBRT is not indicated (Level I) [187] Conversely, WBRT boost after SRS for patients with WHO performance status of 0–2 with up to four brain metastasis is not recommended due both to the associated neuro-cognitive toxicity, as well as failure of WBRT to improved overall survival compared to SRS. (Level II) [184].

Emerging therapies

While use of conventional cytotoxic chemotherapy or more novel therapies (chloroquine, and afatinib) are not recommended for the treatment of brain metastasis (Level 1) [186–190], the recent emergence of novel molecular targeted therapy—particularly PD-1 checkpoint inhibitors has led to significant treatment response and outcome [192–194]. Metastatic intracranially melanoma and lung cancer have benefited from novel therapies which have changed the management paradigm and will undoubtedly improve the treatment and management of metastatic brain cancer and subsequent guidelines. In addition, laser interstitial thermotherapy (LITT) has emerged as an effective treatment for recurrent brain metastasis and or cerebral radiation necrosis after SRS [195].

Finally, three separate papers addressed the role of steroids, prophylactic anti-epileptic drugs (AEDs), and emerging and investigational therapies for the treatment of brain metastasis [188–190]. The studies on the use of steroids comprised 155 manuscripts, but no new studies were found since the 2010 guidelines [188, 196]. Five distinct clinical scenarios were addressed but only four were supported by level III evidence regarding the circumstance, type of steroid, dose and duration of the therapy, and the evidence was felt to be insufficient for the other scenarios [188]. Two specific clinical scenarios were posed to address the role of AEDs. 8167 papers were reviewed, but only five met criterion for full review, and only two met criteria for inclusion in the finding that AEDs were not routinely recommended in pre- or post-op patients with brain metastasis who had *not* suffered previous seizures [189].

Conclusion

Given the multidisciplinary nature of brain tumors, clinicians must incorporate state of the art and evidenced based management to improve patient care. The Joint Section on Tumors has recently published guidelines which encompass the best evidence with the obvious limitation that it is based upon published literature and may not reflect more contemporary therapies such as the case of metastatic brain cancer.

The Tumor Section is devoted to developing and updating brain tumor guidelines to establish systematic evidence practice recommendations and highlighting areas where there is a paucity of evidence to inspire future investigation. We look forward to the next 35 years of progress as the Tumor Section of AANS/CNS focuses on evidence-based approaches to create and update guidelines to provide the highest quality, effective and efficient neuro-oncologic care to our patients.

Disclaimer of liability

The information in these guidelines reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Compliance with ethical standards

Conflict of interest In each original guidelines document, all panel members provided full disclosure of conflicts of interest, if any, prior to establishing the recommendations contained within these guidelines. See original guidelines papers for details.

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