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June 13, 2016

Joan S. McClure, MS
Senior Vice President, Clinical Information and Publications
NCCN
275 Commerce Drive, Suite 300
Fort Washington, PA 19034

Re: CNS Guidelines

Dear Ms. McClure,

ASTRO is pleased to share our recently published glioblastoma (GBM) guideline (attached). Given our new guideline recommendations and evaluation of the literature regarding GBM, we have provided some comments on the Anaplastic Glioma/Glioblastoma section of the NCCN CNS guideline. Additionally, we have also included comments on the following sections of the NCCN guideline:

- Adult Medulloblastoma and Supratentorial PNET;
- Primary CNS Lymphoma; and
- Metastatic Spine Tumors.

Our experts reviewed the CNS guideline for gaps relative to radiation therapy (appropriate modality, dose, timing, etc.) and have offered these recommendations supported by evidence-based rationales where applicable for your consideration when the NCCN CNS Guideline Panel next convenes. We hope these recommendations are of interest to your panel as you review and update your guidelines. For ease of use of your panel, we have each recommended revision on a separate page. Where there are multiple requests for revisions within a disease site, they are numbered.

The NCCN guidelines are well regarded and influential, and we are excited about the prospect of enriching the radiation therapy recommendations so the quality of and access to cancer care of patients with CNS cancers improves. In the meantime, if you have any questions or concerns, please contact Emily Wilson, Executive Vice President, at 703-839-7364 or emily.wilson@astro.org.

Sincerely,

Laura Thevenot

Laura I. Thevenot
CEO

Anaplastic Glioma/Glioblastoma #1

Our concern is with the options currently included for good performance status patients > 70 years, which are given in the following order: 1) hypofractionated focal brain RT alone (category 1), 2) standard focal brain RT + concurrent and adjuvant temozolomide, 3) hypofractionated focal brain RT + concurrent and adjuvant temozolomide, and 4) temozolomide (page GLIO-3).

Recommendations: Consider listing "hypofractionated RT + concurrent and adjuvant temozolomide" on pages MS-11 and GLIO-3 ahead of "standard focal brain RT + concurrent and adjuvant temozolomide."

Rationale: We favor hypofractionated RT with or without concurrent and adjuvant temozolomide as the preferred approach for good performance status, elderly patients for the following reasons:

1. While EORTC/NCIC 26981-22981 (NCCN ref 76) established six weeks of radiotherapy with concomitant and adjuvant TMZ as the standard of care for patients under 70 with good performance status, patients older than 70 were excluded from the study.

2. Category 1 evidence supports the efficacy of hypofractionated RT in the elderly (NCCN ref 61).

3. As already stated on page MS-9, the Nordic trial showed better survival with hypofractionation than with standard radiation.

4. The Canadian trial (NCCN ref 62) showed no difference in survival between hypofractionation and standard radiation, while hypofractionated radiation was better tolerated, with lesser corticosteroid requirements. The Nordic trial also suggested that hypofractionation is better tolerated, with more patients completing therapy.

5. Prospective phase II data demonstrate that hypofractionated radiotherapy with concomitant and adjuvant TMZ is safe and efficacious, with stable or improved quality of life until the time of disease progression (NCCN refs 85 & 86).

6. Randomized data comparing hypofractionated chemoradiation (40 Gy in 15 fractions with 3 weeks of TMZ) to standard chemoradiation (60 Gy in 30 fractions with 6 weeks of TMZ) are not yet available, but one propensity-matched analysis found similar median overall and progression free survival times between the two groups. Standard chemoradiation was associated, however, with increased grade 2-3 neurologic toxicity, worsened performance status, and higher corticosteroid requirements. Another recently published propensity-matched analysis also showed no difference in survival between hypofractionated and standard chemoradiation. Multivariate analysis did suggest that radiation alone was associated with decreased overall survival compared to chemoradiation.

7. Hypofractionated radiation with or without temozolomide can be delivered in a much shorter period of time than standard chemoradiation, which is more convenient, easier logistically, and important for this population of patients with limited life expectancy.

References:

Minniti G, Scaringi C, Baldoni A, et al. Health-related quality of life in elderly patients with newly diagnosed glioblastoma treated with short-course radiation therapy plus concomitant and adjuvant temozolomide. *Int J Radiat Oncol Biol Phys.* 2013;86(2):285-291.

Minniti G, Scaringi C, Lanzetta G, et al. Standard (60 Gy) or Short-Course (40 Gy) Irradiation Plus Concomitant and Adjuvant Temozolomide for Elderly Patients With Glioblastoma: A Propensity-Matched Analysis. *Int J Radiat Oncol Biol Phys.* 2015;91(1):109-115.

Arvold ND, Tanguturi SK, Aizer AA, et al. Hypofractionated versus standard radiation therapy with or without temozolomide for older glioblastoma patients. *Int J Radiat Oncol Biol Phys.* 2015;92(2):384-349.

Anaplastic Glioma/Glioblastoma #2

Our concern is that the algorithm for "resectable" local recurrences indicates that they should always be resected (page GLIO-4). This should be revised as the overall benefit of reoperation in this setting remains unclear and the potential advantages of surgery in facilitating pathologic confirmation of recurrence and/or tumor decompression must be weighed against the significant risks associated with reoperation in this population. In addition, there is no mention of age, performance status, or level of neurological impairment in guiding decisions in this algorithm.

Recommendation: Revise the algorithm on GLIO-4 to include an additional arrow from "Resectable" that extends directly to the list of non-surgical treatment options listed on the right. An alternative solution for this finding is to revise "Unresectable" to read," Unresectable or Resection Not Recommended/Elected."

Include a footnote on GLIO-4 indicating that, "Patient age, performance status, and clinical indication for pathologic confirmation of recurrence and/or tumor decompression should guide the decision for reoperation."

Rationale: Surgery may relieve symptomatic mass effect. Reoperation may, however, be complicated by impaired wound healing related to prior irradiation and/or anti-angiogenic agents, and since many patients have previously undergone maximal safe resection, additional surgery could encroach on eloquent areas, leaving neurologic deficits. The suggested revision is consistent with the recommendations from an expert panel that has recently convened to author an evidence-based guideline on the management of glioblastoma.

References:

Brandes AA, Bartolotti M, Franceschi E. Second surgery for recurrent glioblastoma: advantages and pitfalls. *Expert Rev Anticancer Ther.* 2013;13(5):583-587.

Bose D, Meric-Bernstam F, Hofstetter W, Reardon DA, Flaherty KT, Ellis LM. Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care. *Lancet Oncol.* 2010;11(4):373-382.

Chaichana KL, Zadnik P, Weingart JD, et al. Multiple resections for patients with glioblastoma: prolonging survival. *J Neurosurg.* 2013;118(4):812-820.

Hoover JM, Nwojo M, Puffer R, Mandrekar J, Meyer FB, Parney IF. Surgical outcomes in recurrent glioma: clinical article. *J Neurosurg.* 2013;118(6):1224-1231.

Anaplastic Glioma/Glioblastoma #3

Our concern is with the range of standard radiotherapy doses, which does not correspond with the fraction sizes given. (MS-7).

Recommendation: Revise to: "The typical dose is 59.4-60 Gy in 1.8-2.0 Gy fractions."

Rationale: When radiation is delivered in 1.8 Gy fractions, the total dose has to be 59.4 Gy; 60 Gy is not divisible by 1.8 Gy.

Anaplastic Glioma/Glioblastoma #4

Our concern is that the discussion on radiation therapy for recurrent glioblastomas understates the data available on re-irradiating recurrent gliomas (page MS-8).

Recommendation: Revise to state: "There are limited prospective data for re-irradiating recurrent gliomas."

Rationale: Many studies suggesting the safety and efficacy of re-irradiation are indeed retrospective, however there are data available (see below), and the same holds true for the other local treatment options in recurrent glioma such as surgery.

References:

Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* 2000;47(2):291-298.

Kong DS, Lee JI, Park K, Kim JH, Lim DH, Nam DH. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. *Cancer.* 2008;112(9):2046-2051.

Greenspoon JN, Sharieff W, Hirte H, et al. Fractionated stereotactic radiosurgery with concurrent temozolomide chemotherapy for locally recurrent glioblastoma multiforme: a prospective cohort study. *Onco Targets Ther.* 2014;7:485-490.

Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75(1):156-163.

Cabrera AR, Cuneo KC, Desjardins A, et al. Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: a prospective trial. *Int J Radiat Oncol Biol Phys.* 2013;86(5):873-879.

Anaplastic Glioma/Glioblastoma #5

Our concern is that the discussion of one of the trials of temozolomide in glioblastoma contains a typographic error (page MS-9).

Recommendations: Add the bolded text to read: "temozolomide or **hypo**fractionated RT compared to standard RT."

Rationale: Typographical error

Anaplastic Glioma/Glioblastoma #6

Our concern is with the recommendations for adjuvant therapy for patients >70 years omits the option of hypofractionated RT and temozolomide (page MS-11).

Recommendations: Add: "hypofractionated RT plus concurrent and adjuvant temozolomide" to the recommended options because evidence supports this approach and because the sentence should be consistent with the algorithm on GLIO-3.

List "hypofractionated RT" first on page MS-11, given that the level of evidence for hypofractionated RT is higher (category 1) than for the other options. This would also make the sentence more consistent with the algorithm on GLIO-3.

Consider listing "hypofractionated RT plus concurrent and adjuvant temozolomide" on page MS-11 ahead of "standard focal brain RT plus concurrent and adjuvant temozolomide."

In summary, revise MS-11 to read, "Options for those > 70 years include hypofractionated RT (category 1), hypofractionated RT plus concurrent and adjuvant temozolomide, standard fractionated RT plus concurrent and adjuvant temozolomide (category 2A for this group), or chemotherapy with deferred RT."

Rationale: See Anaplastic Glioma/Glioblastoma #1.

***References*:** See Anaplastic Glioma/Glioblastoma #1.

Anaplastic Glioma/Glioblastoma #7

Our concern is that the discussion of temozolomide for patients >70 years does not sufficiently discuss the potential toxicity (page MS-10).

Recommendation: We agree with this statement. However, it should be noted that temozolomide also confers adverse effects to which elderly patients are particularly susceptible, such as myelosuppression.

Indicate that, "Temozolomide also confers adverse effects distinct from those of radiotherapy and to which elderly patients are particularly susceptible, such as myelosuppression."

Rationale: In NOA-08, a phase III non-inferiority trial which randomized elderly patients to temozolomide vs standard radiotherapy, temozolomide conferred a higher risk of toxicity, with the most frequent grade 3-4 adverse events being neutropenia, lymphocytopenia, thrombocytopenia, elevated liver enzymes, infections, and thromboembolic events.

Reference:
Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol* 2012; 13:707-15.

Anaplastic Glioma/Glioblastoma #8

Our concern is that the recommendation for testing to assess for recurrence does not include biopsy (page GLIO-4 in the footnote and page MS-12).

Recommendation: Include "biopsy" as an option that should also be considered. The currently included imaging studies have significant limitations with respect to test accuracy.

Rationale: As stated in "Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group":

"Imaging modalities such as perfusion imaging, magnetic resonance spectroscopy, and positron emission tomography scans may sometimes be helpful in differentiating treatment effects from recurrent tumor. However, no imaging modality currently has sufficient specificity to conclusively differentiate recurrent tumor from treatment effects, and surgical sampling may occasionally be needed to obtain a definitive diagnosis."

Reference:

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. *J Clin Oncol*. 2010;28(11):1963-72.

Anaplastic Glioma/Glioblastoma #9

Our concern is that the outline of therapy for high-grade gliomas does not include all the reasonable approaches to target volume delineation (page BRAIN-C, 1 of 3).

Recommendation: Acknowledge that a wider variety of approaches with respect to target volume delineation are acceptable by revising to, "The GTV is best defined using pre- and postoperative MRI imaging using enhanced T1 and FLAIR/T2. The GTV is expanded by 2-3 cm (CTV) to account for sub-diagnostic tumor infiltration. Strategies for GTV definition vary with respect to the inclusion of edema in an initial target volume. When edema is included in an initial phase of treatment, fields are usually reduced for the last phase of treatment. Both strategies appear to produce similar outcomes."

Rationale: For GBM, several strategies for target definition have produced similar outcomes, all with a high risk of local failure and a low risk of marginal or distant failure. EORTC protocols, for example, target enhancing tumor and resection cavity plus margin without specifically targeting edema. Various institutions have published data from treatment paradigms using margins smaller than 2 cm.

References:

Ghose A, Lim G, Husain S. Treatment for glioblastoma multiforme: current guidelines and Canadian practice. *Curr Oncol.* 2010;17(6):52-58.

Minniti G, Amelio D, Amichetti M, et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. *Radiother Oncol.* 2010;97(3):377-381.

Paulsson AK, McMullen KP, Peiffer AM, et al. Limited Margins Using Modern Radiotherapy Techniques Does Not Increase Marginal Failure Rate of Glioblastoma. *Am J Clin Oncol.* 2014;37(2):177-181.

Gebhardt BJ, Dobelbower MC, Ennis WH, Bag AK, Markert JM, Fiveash JB. Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. *Radiat Oncol.* 2014;9:130.

McDonald MW, Shu HK, Curran WJ, Jr., Crocker IR. Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. *Int J Radiat Oncol Biol Phys.* 2011;79(1):130-136.

Adult Medulloblastoma and Supratentorial PNET #1

Our concern is that the algorithm for high-risk disease is misleading as it suggests that craniospinal irradiation alone is recommended, followed by chemotherapy, when in fact it should read "craniospinal radiation with chemotherapy followed by post-radiation chemotherapy" (page AMED-2).

Recommendation: Revise the algorithm for high-risk disease to recommend "craniospinal radiation with chemotherapy followed by post-radiation chemotherapy."

Rationale: Most likely a typographical error.

Adult Medulloblastoma and Supratentorial PNET #2

Our concern is that in the Principles of Brain Tumor Radiation Therapy there is no discussion of radiation technique (BRAIN-C, page 1 of 3).

Recommendations: Add the bolded text to read:

- "Standard risk for recurrence:
    - Conventional dose: 30–36 Gy CSI[8,†] and boosting the primary brain site to 54–55.8 Gy with or without adjuvant chemotherapy
    - Reduced dose: For young adults, may consider reduced dose radiation with adjuvant chemotherapy: 23.4 Gy CSI[8,9, ††]and boosting the primary brain site to 54–55.8 Gy[1]
- High risk for recurrence: 36 Gy CSI[3,†] with boosting primary brain site to 54–55.8 Gy with adjuvant chemotherapy
- **Consider the use of intensity-modulated radiotherapy or protons if available**"

***Rationale*:** CSI plays an important role in the management of adults with medulloblastoma but has serious toxicity. There is evidence that advanced radiation technique can reduce toxicity associated with treatment.

Reference:

Brown AP, Barney LC, Grosshans DR, et al. Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86:277-284.

Primary CNS Lymphoma #1

Our concern is that in the narrative section on Primary CNS Lymphoma (page MS-17) it states: "The majority of studies demonstrated the limitation of high-dose RT and led to the currently recommended dose of 24 to 36 Gy in 1.8 to 2.0 Gy fractions to the whole brain, without a boost." In contrast in the section on Principle of Brain Tumor Radiation (page BRAIN-3, 1 of 3) it states: "WBRT may be withheld in the primary setting in patients treated with chemotherapy. When used, WBRT doses should be limited to 23.4 Gy in 1.8 Gy fractions following a CR to chemotherapy. For less than complete response (CR), consider the same WBRT dose followed by a limited field to gross disease to 45 Gy or focal radiation to residual disease only."

The statements are contradictory with regards to the application of a radiation boost for patients with less than a complete response to chemotherapy.

Recommendation: Revise page MS-17 to state: "The majority of studies demonstrated the limitation of high-dose RT and led to the currently recommended dose of 24 to 36 Gy in 1.8 to 2.0 Gy fractions to the whole brain, without a boost, in patients who achieve complete response to chemotherapy."

Rationale: Internal consistency.

Primary CNS Lymphoma #2

Our concern is that in the narrative section on Primary CNS Lymphoma (page MS-19 to MS-20) it states: "For patients who are treated with prior WBRT and ultimately relapse, they may consider further chemotherapy (systemic and/or intrathecal), reirradiation, or palliative/best supportive care. High-dose therapy with stem cell rescue can also be considered (category 2B)." In contrast, in the treatment algorithm for relapsed or refractory CNS lymphoma in patients who have received prior whole brain radiotherapy (page CNS-3) the options listed are: Consider chemotherapy (systemic and/or intra-CSF) or high-dose therapy with stem cell rescue (category 2B) or Palliative/Best supportive care." Consider

While reirradiation is listed as an option for relapse after prior WBRT in the narrative section, reirradiation is not listed as an option in the treatment algorithm.

Recommendation: List "Reirradiation" as an option for relapsed or refractory CNS lymphoma after prior WBRT in the treatment algorithm on page CNS-3.

Rationale: Internal consistency.

Metastatic Spine Tumors #1

Our concern is that this section would benefit from better definition of scope and treatment intent. Metastatic spine encompasses tumors metastasizing to the spine, with/without soft tissue or bony expansion into the epidural space, with/without cord compression, as well as intramedullary tumors. The extent of disease and treatment intent determine appropriate treatment options. In addition, the current wording on dose ranges is not clear and, for example, could lead a reader to believe that a dose such as 40 Gy in 1 fraction is appropriate.

Recommendations:

1. Modify the wording for this section on page BRAIN-C, 2 of 3, to:

"Doses to vertebral body metastases will depend on patient's PS, spine stability, location in relationship to spinal cord, primary histology, presence of epidural disease, and overall treatment intent (pain relief, long-term local control, or cure). In patients with uncomplicated spine metastases that are treated primarily for pain relief, 8 Gy in 1 fraction has been shown to provide equivalent pain control to longer fractionation schedules and is more convenient for patients, but may be associated with higher rates of retreatment, which may be a consideration when life expectancy exceeds 6 months.

When lower BED regimens are utilized upfront (i.e. BED ≤ 60 Gy_2, which includes up to 20 Gy in 5 fractions but does not include 30 Gy in 10 fractions), retreatment with similar BED regimens, such 20 Gy in 5 fractions or 8 Gy in 1 fraction, can safely be considered as early as 4 weeks from initial treatment for pain relief. In other cases, doses ranging from 15 Gy in 1 fraction to 40 Gy in 20 fractions have been utilized for tumor control, with careful consideration of tolerance of the spinal cord and/or nerve roots. In selected cases, or recurrences after previous radiation, stereotactic radiation (SRS or SBRT) is appropriate. In these instances it is generally recommended that 6 months or more of time between treatments is required."

2. Revise page MS-34 by adding the bolded:

"Where there is no compression, fracture, or instability, EBRT is effective in achieving local control as primary treatment. A mean 77% local control rate from seven retrospective studies including 885 patients was found in a systematic review by Gerszten and colleagues.[346] RT is also a mainstay of palliative treatment for patients with poor PS, significant comorbidities, and/or limited life expectancy (<3–4 months). **In patients with uncomplicated spine metastases that are treated primarily for pain relief, 8 Gy in 1 fraction has been shown to provide equivalent pain control to longer fractionation schedules and is more convenient for patients.**"

3. Revise page MS-35 by adding the bolded:

"Primary EBRT alone is appropriate for patients with radiosensitive cancers (hematologic malignancies) and without evidence of spinal instability. Many fractionation schemes are available (**8 Gy in 1 fraction to 40 Gy in 20 fractions over 1 day–4 weeks**); the most common is a total of 30 Gy in 3-Gy daily fractions for 10 days.[352,353] Tolerance at the spine and/or nerve route must be considered in determining dose. **In patients with uncomplicated spine metastases that are treated primarily for pain relief, 8 Gy in 1 fraction has been shown to provide equivalent pain control to longer fractionation schedules and is more convenient for patients, but may be associated with higher rates of**

retreatment which may be a consideration when life expectancy exceeds 6 months."
Rationale: There is high quality evidence that 8 Gy in 1 fraction provides equivalent pain response to longer, less convenient fractionation schedules. In terms of time to retreatment and efficacy of retreatment, the international retreatment trial for bone metastases demonstrated non-inferiority for 8 Gy in 1 fraction versus fractionated regimens (spine patients represented 28% of the study population) with more acute toxicity reported in the fractionated group. The time from date of last fraction to retreatment was approximately 110 days (the study allowed for retreatment in patients who were at least 4 weeks from their initial course of radiation), providing support that retreatment, has efficacy and can safely be done much earlier in patients who have received initial radiation courses with BED less than 60 Gy_2 (such as 8 Gy in 1 fraction or 20 Gy in 5 fractions, but not 30 Gy in 10 fractions), and where normal tissue tolerances permit.

References:
Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol*. 2014;15:164–71

Chow E, Meyer RM, Chen BE, et al. Impact of Reirradiation of Painful Osseous Metastases on Quality of Life and Function: A Secondary Analysis of the NCIC CTG SC.20 Randomized Trial. *J Clin Oncol*. 2014. 32:3867-3873.

Metastatic Spine Tumors #2

Our concern is that the use of the term stereotactic radiosurgery only may be incomplete and including the term stereotactic body radiotherapy should be considered.

Recommendation: Revise page MS-36 to include the bolded:
"Patients who underwent prior RT or surgery plus adjuvant RT may consider surgery or re-irradiation to the recurred area. Stereotactic RT **(SRS or SBRT)** may be appropriate for select patients."

Rationale: The term stereotactic radiosurgery, as defined by American Association of neurological surgeons refers specifically to the use of single fraction treatment (http://www.aans.org/~/media/Files/Legislative%20Activities/Reimbursement/AANS-CNS%20Statement%20on%20SRS%20Coding.ashx?la=en), and multi-fraction SBRT is widely utilized in this setting.