December 2, 2015

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,

The American Society for Radiation Oncology is pleased to provide comments on the NCCN CNS guideline. Our experts reviewed the CNS guideline for gaps relative to radiation therapy (appropriate modality, dose, timing, etc.) and have offered recommendations supported by evidence-based rationales where applicable for your consideration when the NCCN CNS Guideline Panel convenes later this month.

ASTRO is in the process of finalizing our glioblastoma (GBM) guideline, so we have not shared comments on GBM at this time. We will share our GBM guideline once it is published and may provide additional feedback at that time. Instead, at this time we have focused our comments on the following sections:

- Treatment Principles;
- Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma;
- Adult Ependymomas (excluding myxopapillary);
- Leptomeningeal disease;
- Primary Spinal Cord Tumors; and
- Meningioma.

We hope these recommendations are of interest to your panel as you review and update the 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

Treatment Principles #1

Our concern is related to use of RT therapist rather than radiation oncologist. In the principles of treatment, the guideline states: "The involvement of an interdisciplinary team, including neurosurgeons, RT therapists, oncologists, neurologists, or neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain lesions, the NCCN Panel encourages thorough multidisciplinary review of each patient case once the pathology is available" (page MS-3).

The term "RT therapist" has a very specific meaning in the field of radiation oncology and refers to the technicians who help to operate and deliver radiation treatments. The appropriate terminology for a physician that specializes in the use of radiation therapy in the management of cancer and other diseases is "Radiation Oncologist".

Recommendation: Revise page MS-3 to state: "The involvement of an interdisciplinary team, including neurosurgeons, radiation oncologists, medical oncologists, neurologists, or neuroradiologists, is a key factor in the appropriate management of these patients. For any subtype of malignant brain lesions, the NCCN Panel encourages thorough multidisciplinary review of each patient case once the pathology is available."

Rationale: Appropriate terminology.

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma #1

Our concern is that the recommendation for MRI within 72 hours after surgery is essential to optimal management and is only stated in a footnote (Page ASTR-1, footnote f).

Recommendation: Move the recommendation for MRI within 72 hours after surgery out of footnote into main flow chart to highlight its importance in management decisions.

Rationale: Many facilities are reluctant to perform MRI within hours after surgery for a variety of reasons including concerns about the lack of reimbursement for in-house MRIs. Recent data demonstrate a survival benefit with the use of adjuvant chemoradiation for patients with any residual disease on post-operative MRI. In addition, the current algorithm recommends adjuvant chemoradiation for any patient with less than gross total resection which is best determined on MRI within 72 hours after surgery. Thus a reluctance to perform MRI within 72 hours after surgery, and associated delay beyond 72 hours when granulation tissue may confound MRI assessment of completeness of surgical resection is no longer acceptable and this aspect of management needs to be emphasized.

References:

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. IntJ Radiat Oncol Biol Phys. 2015:91(3):497–504.

Karim A.B, Afra D, Cornu P, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. Int Radiat Oncol Biol Phys. 2002;52(2): 316–324.

Shaw EG, Wang M, Coons SW, et al. Randomized Trial of Radiation Therapy Plus Procarbazine, Lomustine, and Vincristine Chemotherapy for Supratentorial Adult Low-Grade Glioma: Initial Results of RTOG 9802. JClin Oncol. 2012;30(25):3065–3070.

van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005;366(9490):985–990.

Adult Low-Grade Infiltrative Supratentorial Astrocytoma/ Oligodendroglioma #2

Our concern is that in the algorithm regarding adjuvant treatment options for low risk, low grade glioma include observation, fractionated RT, or chemotherapy, but do not include adjuvant chemoradiation (page ASTR-1).

Recommendation: If adjuvant therapy is considered for select patients with low grade glioma then chemoradiation should be an option. Conversely, if any adjuvant therapy is felt to be inappropriate for these patients then only observation should be listed.

Rationale: Observation is appropriately listed. However, radiation or chemotherapy are also listed as options but not chemoradiation. To be consistent, if adjuvant therapy is felt to be an appropriate consideration for these patients then chemoradiation should be included. Conversely, if chemoradiation is not felt to be an appropriate consideration for these patients then perhaps only observation should be recommended as the currently listed single modality therapies are infrequently utilized and may compromise the ability to provide chemoradiation in the event of high grade recurrence when chemoradiation is the standard of care.

Adult Ependymomas (excluding myxopapillary) #1

Our concern is that there are no recommendations regarding treatment techniques and recent studies show that conformal therapy is effective while reducing dose to surrounding critical structures and toxicity (page BRAIN-C, 1 of 3).

Recommendation: Add the bolded to the current guideline text:
"Limited Fields: Intracranial tumor volumes are best defined using pre- and postoperative imaging, usually enhanced T1 and or FLAIR/T2. Anatomic area that are touched by preoperative tumor volume plus postoperative signal abnormality on MRI for GTV, CTV (GTV plus 1-2 cm margin) should receive 54-59.4 Gy in 1.8-2.0 Gy fractions. Conformal radiation therapy (3D, IMRT, VMAT, etc.) is recommended to spare critical structures."

Rationale: A prospective phase II trial (RT-1) of 153 patients (median age 2.9 years; range 0.9-22.9 months) with localized ependymoma conducted at St. Jude Children's Research Hospital (SJCRH) from 1997 to 2001 using 3D-conformal RT had a 3-year progression-free survival (PFS) of 75% and the 3-year cumulative incidence of local failure was 15% while maintaining good cognitive function.

The ACNS0121 protocol, which was based on the concepts of conformal therapy developed at St. Jude had a 7-year event-free survival of 69%, with an overall survival (OS) of 81% and local control rate of 87% after a median follow-up of 62 months from the initiation of RT.

References:
Merchant TE, Mulhern RK, Krasin MJ, et al. Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. J Clin Oncol. 2004;22:3156–62.

Merchant TE, Kiehna EN, Li C, et al. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. Int J Radiat Oncol Biol Phys. 2005;63:1546–54.

Merchant TE, Li C, Xiong X, et al. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol. 2009;10:258–66.

Netson KL, Conklin HM, Wu S, et al. A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma. Int J Radiat Oncol Biol Phys. 2012: 84(1):217-223.

Landau E, Boop FA, Conklin HM, et al. Supratentorial ependymoma: disease control, complications, and functional outcomes after irradiation. Int J Radiat Oncol Biol Phys. 2013;85(4):e193-9.

Adult Ependymomas (excluding myxopapillary) #2

Our concern is that there is no mention of consideration for boosting gross metastatic disease in the spine or brain which should be considered (page BRAIN-C, 1 of 3).

Recommendation: Add the bolded to the current guideline text:
"Craniospinal: Whole brain and spine (to bottom of thecal sac) receive 36 Gy in 1.8 Gy fractions, followed by limited field to spine lesions for 45 Gy (Gross metastatic lesions below the conus could receive higher doses). Primary intracranial site should receive total dose of 54-59.4 Gy in 1.8-2.0 Gy fractions. Consider boosting any gross intracranial metastatic sites to a higher dose while respecting normal tissue tolerances."

Rationale: Areas of gross disease will need doses higher than 36 Gy for local control. Tolerance of cauda equina is in the range of 54-60 Gy so higher doses could be delivered to this area.

References:
Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation Int J of Radiat Oncol Biol Phys 1991; 21(1): 109–122.

Pieters RS1, Niemierko A, Fullerton BC, et al. Cauda equina tolerance to high-dose fractionated irradiation. Int J Radiat Oncol Biol Phys.2006; 64(1):251-7.

Adult Ependymomas (excluding myxopapillary) #3

Our concern is that there is no recommendation regarding treatment techniques or mention of consideration for boosting gross metastatic disease in the spine or brain which should be considered (page MS-13).

Recommendation: Add the bolded to the current guideline text:
"Typical craniospinal irradiation scheme includes 36 Gy in 1.8 Gy fractions to the whole brain and spine followed by limited field irradiation to the spine lesions to 45 Gy. Gross metastatic lesions below the conus and gross intracranial metastases may be boosted to higher doses while respecting normal tissue tolerances. For intracranial ependymomas, the primary brain site should receive a total of 54 to 59.4 Gy in 1.8 to 2.0 Gy fractions. For spinal ependymomas, patients should receive 45 to 50.4 Gy in 1.8 Gy fractions. Higher doses up to 60 Gy are reasonable for spinal tumors below the conus medullaris. Conformal radiation therapy (3D-CRT, IMRT, VMAT, etc.) is recommended to spare critical structures and uninvolved tissue. Proton beam craniospinal irradiation may be considered when toxicity is a concern."

Rationale: Consistency with recommended changes above.

Leptomeningeal disease #1

Our concern is that MRI of the brain and spine is also required to define tumor extent and guide radiation treatment planning and this should be completed for all patients who are considering radiotherapy (Page MS-30).

Recommendation: Add bolded text:
"MRI of the brain and spine should also be performed if intra-CSF chemotherapy and/or radiotherapy are being considered."

Rationale: MRI is the gold standard for the definition of tumor extent in the CNS. Unless not able to be performed, MRI should be performed for all patients who will receive radiation for leptomeningeal disease to allow for optimal definition of treatment volume and sparing of non-target tissue. In addition, page LEPT-1 states: "Brain and spine MRI if patient is a candidate for radiotherapy and/or intra-CSF chemotherapy." This change will achieve internal consistency with page LEPT-1.

Leptomeningeal disease #2

Our concern is found in the treatment algorithm for good risk patients. "Involved field RT to bulky disease, symptomatic sites" is followed only by "CSF flow scan (LEPT-3)," which then essentially describes the algorithm for intrathecal chemotherapy on pages LEPT-3 and then LEPT-4, with no mention of organ-specific systemic agents. That said, both the Principles of Systemic Therapy on page BRAIN-D, 3 of 7, and the narrative section on pages MS-29 and MS-30, describe the use of organ-specific, systemic drugs with CNS penetration. This widely utilized, generally less morbid approach after involved field RT, is not included in the current treatment algorithm on pages LEPT-2, LEPT-3, and LEPT-4.

Recommendation: On page LEPT-2, in the algorithm for good risk patients, following "involved field RT to bulky disease, symptomatic sites" include two options for drug therapy. The first option should state: "Consider the use of organ-specific, systemic agents with CNS activity" followed by an arrow to "If evidence for progression of leptomeningeal disease then consider switching systemic drug or intra-CSF chemotherapyi,j,k, see CSF flow scan (LEPT-3)." The second option should state: "Consider intra-CSF chemotherapyi,j,k, see CSF flow scan (LEPT-3)." Both options would ultimately flow to LEPT-3, maintaining the overall structure of the algorithm while incorporating this common treatment strategy at the appropriate place in the algorithm.

With this change the existing footnotes are unchanged but ordered differently, see below, and as a result of the change: "CSF flow study" is only "strongly recommended" for patients who will receive intra-CSF chemotherapy, which is more appropriate and consistent with standard practice.

Footnote "i" now refers to "Principles of Brain and Spine Cord Tumor Systemic Therapy (BRAIN-D)".

Footnote "j" now refers to "Induction intra-CSF chemotherapy can start with radiation (concomitant) or high-dose methotrexate for lymphoma or CSI."

Footnote "k" now refers to "Highly recommended to ensure patency of CSF flow if intraventricular catheter was placed."

Rationale: Treatment strategies for LMD that employ systemic agents, many of which are often organ-specific, that are known to achieve CNS penetration and activity, are generally favored in current clinical practice over IT chemotherapy due to reduced toxicity. Therefore, we recommend the guideline specifically include and highlight these strategies, which have become more commonly utilized than intra-CSF chemotherapy in practice. In addition, the use of these systemic agents is discussed in the Principles and Narrative sections, and inclusion in the algorithm is needed for internal consistency.

Leptomeningeal disease #3

Our concern is with craniospinal irradiation which is listed as a treatment option on page LEPT-3. This treatment is associated with substantial toxicity and is rarely used in clinical practice.

Recommendation: Craniospinal irradiation is highly toxic and is rarely recommended in the setting of leptomeningeal disease. Add footnote "l" to both instances of "Craniospinal irradiationl" on page LEPT-3. Footnote "l" should state: "CSI is associated with substantial toxicity and should only be considered for highly select patients."

Rationale: Craniospinal irradiation is associated with substantial toxicity and is therefore rarely, if ever, appropriate for a patient with limited prognosis, as in LMD. This is almost never performed in clinical practice and it should be clear to the audience that this should only be considered in highly select patients.

Leptomeningeal disease #4

Our concern is related to the narrative section on page MS-31 that states: "Patients with breast cancer, leukemia, or lymphoma may receive craniospinal RT as an alternative." This treatment is associated with substantial toxicity and is rarely used in clinical practice.

Recommendation: Add the bolded:
"Patients with breast cancer, leukemia, or lymphoma may receive craniospinal RT as an alternative. CSI is associated with substantial toxicity and should only be considered for highly select patients."

Rationale: Craniospinal irradiation is associated with substantial toxicity and is therefore rarely, if ever, appropriate for a patient with limited prognosis, as in LMD. This is almost never performed in clinical practice and it should be clear to the audience that this should only be considered in highly select patients.

Primary Spinal Cord Tumors #1

Our concern is that the only recommendation provided is for doses of 45-54 Gy using 1.8 Gy per fraction, and that for tumors below the conus medullaris higher doses up to 60 Gy can be delivered. No mention is made of other radiation techniques, in particular SRS and SBRT, commonly prescribed treatments for these tumors, are not included (page BRAIN-C, 2 of 3).

Recommendation: Add the bolded text:

- Doses of 45–54 Gy are recommended using fractions of 1.8 Gy. In tumors below the conus medullaris higher doses up to 60 Gy can be delivered
- In select patients, or recurrences after prior radiation, stereotactic radiation techniques (SRS, SBRT) are appropriate
- It is critical to consider tolerance of the spinal cord and/or spinal nerve roots, and conformal radiation therapy (3D-CRT, IMRT, VMAT, etc.) is recommended to spare critical structures

Rationale: Primary spinal cord tumors constitute 2% to 4% of all central nervous system neoplasms and are characterized based on their location as intramedullary, intradural extramedullary, and extradural. Among intramedullary tumors, ependymomas are more common and often can be surgically resected. Astrocytomas infiltrate the spinal cord and complete resection is rare. Intradural extramedullary tumors include schwannomas, neurofibromas, and meningiomas. These are usually amenable to surgical resection. If they are not amenable to resection then SRS or SBRT are treatment options.

Gerszten et al. have reported on 73 intradural lesions treated with CyberKnife, using a single fraction of 12–20 Gy. With 37 months median follow up, local control was 100 %, and there was long term improvement in pain scores in 73 % of the patients. Late spinal cord toxicity is one of the major concerns when planning radiotherapy to spinal lesions. In the largest published retrospective review, 1,075 patients with primary or metastatic tumors were treated with CyberKnife at Stanford or Pittsburgh Universities between 1996 and 2005. Six patients developed radiation induced late myelopathy at 2–9 months after treatment. In three of these patients, symptoms improved with intervention, and one patient progressed to paraplegia. Specific dosimetric factors associated with development of myelopathy could not be identified.

References:

Chamberlain MC, Tredway TL. Adult Primary Intradural Spinal Cord Tumors: A Review. Curr Neurol Neurosci Rep. 2011;11:320-328.

Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for benign intradural spinal tumors. Neurosurgery. 2008; 62(4):887–96.

Benzil DL, Saboori M, Mogilner AY, Rocchio R, Moorthy CR. Safety and efficacy of stereotactic radiosurgery for tumors of the spine. J Neurosurg. 2004;101:413-418.

Degen JW, Gagnon GJ, Voyadzis JM, et al. CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. J Neurosurg Spine. 2005;2:540-549.

Dodd RL, Ryu MR, Kamnerdsupaphon P, Gibbs IC, Chang SD Jr, Adler JR. CyberKnife radiosurgery for benign intradural extramedullary spinal tumors. Neurosurgery. 2006;58:674-685.

Lo SS, Chang EL, Yamada Y, Sloan AE, Suh JH, Mendel E. Stereotactic radiosurgery and radiation therapy for spinal tumors. Expert Rev Neurother. 2007;7:85-93.

Kukreja S, Ambekar S, Sin AH, Nanda A. Cumulative survival analysis of patients with spinal myxopapillary ependymomas in the first 2 decades of life. J Neurosurg Pediatr. 2014;13(4):400-407.

Gibbs IC, Patil C, Gerszten PC, et al. Delayed radiation induced myelopathy after spinal radiosurgery. Neurosurgery. 2009;64(2 Suppl):A67–72.

Meningiomas #1

Our concern is that the algorithm does not recommend consideration for radiation after resection of symptomatic small grade II and incomplete resection of symptomatic small grade I meningiomas (age MENI-1).

Recommendation: In the treatment column, add the bolded:
"Surgery if potential neurologic consequences and if accessible, followed by RT if WHO Grade III and consider RT for resected or incompletely resected WHO grade II or incompletely resected WHO Grade 1."

Rationale: Radiation offers improved local control for grade II meningiomas and incompletely resected grade I meningiomas. It should be considered to reduce risk of recurrence or progression, especially in a location that was initially symptomatic and not amenable to complete resection, where recurrence may not be resectable and can cause morbidity that may not be reversible by radiation at that point.

References:
Goldsmith B, Wara W, Wilson C, Larson D. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. J Neurosurg. 1994;80(2):195-201.

Meningiomas #2

Our concern is related to the discussion of RT dose and technique. Based on the published literature, a dose greater than 50 Gy is recommended for incompletely resected or unresectable disease. It is important to consider the tolerance of critical intracranial structures. Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures. Conformal radiation therapy (3D-CRT, IMRT, VMAT, etc.) is recommended to spare critical structures and uninvolved tissue (page BRAIN-C, 2 of 3)

Recommendation: Add the bolded:

- WHO grade I meningiomas may be treated by fractionated conformal radiotherapy with doses of 45-54 Gy in 1.8 Gy fractions. A dose of greater than 50 Gy is recommended for incompletely resected or unresectable disease.
- Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures. Conformal radiation therapy (3D-CRT, IMRT, VMAT, etc.) is recommended to spare critical structures and uninvolved tissue."

Rationale: Goldsmith et al. found doses above 52 Gy resulted in improved local control. Several studies also showed excellent local control with fractionated stereotactic and IMRT approaches.

References:

Uy NW, Woo SY, The BS, et al. Intensity modulated radiation therapy (IMRT) for meningioma. Int J Radiat Oncol Biol Phys. 2002;53(5):1265-70.

Debus J, Wuendrich M, Pirzkall A, et al. High efficacy of fractionated stereotactic radiotherapy of large base-of-skull meningiomas: long-term results. J Clin Oncol. 2001;19(15):3547-53.

Pirzkall A, Debus J, Haering P, et al. Intensity modulated radiotherapy (IMRT) for recurrent, residual, or untreated skull-base meningiomas: preliminary clinical experience. Int J Radiat Oncol Biol Phys. 2003;55(2):362-72, 2003.

Selch MT, Ahn E, Laskari A, et al. Stereotactic radiotherapy for treatment of cavernous sinus meningiomas. Int J Radiat Oncol Biol Phys. 2004;59(1):101-1.