Peer Review File

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Reviewer Comments

Reviewer A

Comment: The provide a review of the treatment various treatment options available for brain metastases and leptomeningeal disease.

The review covers all of the appropriate treatment modalities, including surgery, radiation, and medical therapies, which are broken down by pathology of the brain metastases.

Although this review focuses on the 'emergent' use of radiation for BM and LM, there is not an extensive discussion of comparisons of surgery versus WBRT vs SRS, which adds to a thorough discussion of the different treatment modalities.

The author's criteria for emergent RT essentially eliminates all true emergent situations, which is treated by surgical intervention/decompression/CSF diversion. Although the authors suggest situations where there is an urgency to treat patients that cannot tolerate the true emergent interventions, these are essentially situations where RT is used for palliation. There is little evidence of response of the RT strategies that the authors note in this review. Therefore, these RT strategies are more treatment strategies that can be used when true emergent treatment cannot be provided.

Reply: Thank you for this review. We agree that there is little evidence guiding RT strategies in this situation, and thus our work is reliant upon expert commentary.

Reviewer B

Thank you for the opportunity to review this manuscript. It is an excellent summary and will be a helpful resource to many clinicians.

Comment 1The systemic therapy section could be shortened.
Reply 1 Given the diversity of malignant histologies that can cause brain metastases, and growing list of targeted agents with CNS activity, we have kept this section to the current 5 paragraphs. We feel this space is well spent to help clarify the current state of systemic therapies that may be considered, due to the evolving landscape of systemic options with CNS activity.

Comment 2 Line 12: Define emergent
Reply 2 Within the manuscript text we define emergent within the introduction section as follows: “We define emergent as requiring treatment initiation within 24-48 hours of symptomatic presentation, including a need to initiate treatment after typical clinical hours or on a weekend or clinic holiday. Thus, a patient with minimal-to-no symptoms while medically managed (e.g., corticosteroids), may not require emergent

initiation of RT." We hesitate to reiterate this definition in the abstract for the sake of manuscript length

Comment 3 Line 16: Suggest change chemotherapy to systemic therapy
Reply 3 We have updated the text with this suggestion, replacing 'chemotherapy' with 'systemic anti-cancer therapy'

Comment 4 Line 18: What disciplines are the expert authors? Just Radiation Oncologists? Are there medical oncologists and neurosurgeons involved?
Reply 4 We assume that the blinded nature of manuscript review led to this question, as author affiliations include their specialty department. The authors include radiation oncologists and medical/neuro-oncologists.

Comment 5 Line 20: See Line 16
Reply 5 We have updated the text with this suggestion, replacing 'chemotherapy' with 'systemic anti-cancer therapy'

Comment 6 Line 45: Over what time period did the patients have a symptomatic improvement?
Reply 6 Unfortunately, the reference in question (PMID 17851852 Christian 2008) does not provide data regarding time-course of symptomatic improvement.

Comment 7 Line 46: Please reference the rising incidence of CNS metastases
Reply 7 Our current text reads: "As the incidence of central nervous system (CNS) metastases is thought to be rising due to improved systemic therapies prolonging patient survival…" This statement is supported by two references. A third reference (#6: PMID 22012633 Nayak 2012 'Epidemiology of Brain Metastases') has been added.

Comment 8 Line 72/Methods Section: Is this a systematic review, or was it a somewhat targeted approach via PubMed and Google Scholar? Suggest a slight expansion of this section. Was it just published manuscripts or abstracts as well?
Reply 8 Per the manuscript's title, this is a narrative review. We have updated the methods section to clearly state that this is a narrative review, while also describing that full manuscripts and abstracts were considered

Comment 9 Line 95: Should there be a mention of the need for contrast MRI?
Reply 9 Just prior to the referenced line, we state: "…contrast-enhanced magnetic resonance imaging (MRI) are the most valuable…"

Comment 10 Line 99: It might be worthwhile to mention advanced imaging techniques such as MRI perfusion/amino acid PETs etc

Reply 10 We have considered including reference to such advanced techniques. However, they are unlikely to be broadly employed in the emergent setting, and we therefore did not include discussion of their use

Comment 11 Line 121: Should steroids be given immediately if the diagnosis is potentially lymphoma but unknown?
Reply 11 We have added the text: “If an etiology of undiagnosed lymphoma is suspected, the clinician and medical oncologist should discuss the benefit of prompt corticosteroid initiation versus risk of obfuscating diagnosis.”

Comment 12 Line 147: Please clarify/expand "additional surgical consideration"- do you mean that it should be encouraged?
Reply 12 We have updated the text to read: “We recommend surgery be strongly considered for tumors in the posterior fossa…”

Comment 13 Line 152: Suggest briefly mention alternative treatment modalities
Reply 13 We have updated to text to clarify that we were stating that radiotherapy or chemotherapy should be considered for highly radiosensitive or chemoresponsive histologies, as an alternative to surgery.

Comment 14 Line 155: Can also have a change of receptor subtype. e.g. seen in breast cancer
Reply 14 We have updated the text to add “…change in receptor subtype…”

Comment 15 Line 159: "in the non-emergent setting": perhaps need to clarify as post-op SRS is recommended whether patients undergo surgery in the emergent or non-emergent setting
Reply 15 Within this section, we state a typical recommendation for adjuvant radiotherapy following surgical resection of solitary brain metastasis. We have added text to the end of this section to reinforce the consideration of adjuvant radiotherapy after the emergent period.

Comment 16 Line 176: 3-8 weeks is probably a little long (3-4 reasonable). See Minniti Radiat Oncol 2021 Table 1
Reply 16 We have updated this text to read: “adjuvant radiotherapy is preferably given 3-4 weeks post-operatively, but is occasionally delayed up to 8 weeks due to patient-specific factors.”

Comment 17 Line 180: Suggest adding brief mention of pre-op radiosurgery (can ref PMID 35751740 and 35234410)
Reply 17 We have included the reviewer’s recommended reference PMID 35751740 (Palmer 2022) and referenced PMID 33383817 (Gutschenritter 2020) for further context on the topic. We have revised the manuscript with the following text: “Pre-operative radiosurgery has also been studied, but is typically employed in

patients in whom symptoms improve on steroids or anti-epileptic medication to allow radiosurgery planning."

Comment 18 Line 204: Suggest this section on systemic therapy is made significantly more concise. Particularly as there is a limited role in the emergent setting
Reply 18 Please see our previous reply to the first comment by Reviewer B.

Comment 19 Line 212: Suggest correction/clarification. TKIs are not commonly used in melanoma
Reply 19 The word 'tyrosine' has been removed. Text updated to reflect our reference to "kinase inhibitors".

Comment 20 Line 271: Suggest clarifying patient population (e.g. limited brain mets, all <2cm, asymptomatic)
Reply 20 There are multiple studies cited through the manuscript that could be clarified by adding information on patient inclusion criteria. However, adding such information for each referenced study would add substantial length to the manuscript.

Comment 21 Line 290/297: Is WBRT the only emergent RT option available? GK SRS can be delivered very quickly. MSKCC team is doing a webinar this week on same day linac-based SRS as well.
Reply 21 The reviewer raises a valid point regarding the relative speed of GammaKnife treatment design and delivery, as well as the emergence of rapid LINAC-based SRS planning. However, patients who require emergent radiotherapy for brain metastases typically have significant neurologic symptoms. Stereotactic radiosurgery is generally inappropriate in the emergency setting given the risk of acutely worsening symptoms. We have edited the text to reflect this.