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The American Society for Radiation Oncology has reviewed the **2021 NCCN cutaneous melanoma guideline** for gaps relative to radiation therapy. We offer **two major recommendations** supported by evidence-based rationales and one minor recommendation for your consideration.

We hope you find these recommendations useful to your panel as you review and update the guidelines.

Sincerely,

Laura I. Thevenot
Chief Executive Officer, American Society for Radiation Oncology

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Major Recommendation 1: Treatment of Metastatic Disease

- We recommend removing on page ME-8 and ME-16 the "Resectable" after limited and the "unresectable" after disseminated.
- SBRT should be listed alongside resection for management of limited distant metastatic disease.

Rationale:
The cut point between widespread disease and limited metastatic disease is not solely at the discretion of the surgeon. Low-volume brain metastases and low-volume extracranial (even if unresectable) disease can be effectively managed by SBRT. SBRT should be listed alongside resection for management of limited distant metastatic disease, as there is randomized data supporting SBRT for oligometastatic disease, whereas there is no randomized data to this practice for surgical resection. Strictly speaking, SBRT should be the preferred option based on level of evidence, and this should be considered for the guidelines.

Randomized data now supports the use of stereotactic body radiotherapy (SBRT) for ablative treatment of oligometastatic disease (1-5 lesions) with a demonstrable benefits in progression-free survival and overall survival[1,2]. SABRT-COMET enrolled all histologies and demonstrated that SBRT was associated with a 5-year OS of 42.3%, versus 17.7% in patients managed with standard systemic therapies alone (p=0.006). As such this should be a standard consideration for all patients with oligometastatic disease. Furthermore, in line with intracranial control demonstrated with radiosurgery dosing, melanoma-specific data demonstrates that sufficient SBRT doses can achieve 100% of metastatic lesion control at 2 years, and approximately 93% at 5 years[3], countering the long-held belief that melanoma metastases are insensitive to radiotherapy. Additionally, SBRT has been modeled to be a more cost-effective strategy for melanoma pulmonary oligometastases than surgical resetion[4].

References:

1. Palma DA et al. J Clin Oncol. 2020 Sep 1;38(25):2830-2838. PMID: 32484754
2. Palma DA et all. Lancet. 2019 May 18;393(10185):2051-2058. PMID: 30982687
3. Youland RS et al. Adv Radiat Oncol . 2017 Feb 24;2(2):204-210. PMID: 28740933
4. Lester-Coll NH et al. Int J Radiat Oncol Biol Phys. 2016 Jun 1;95(2):663-72 PMDI: 27055395

Major Recommendation 2: ME-L

- We recommend removing the section titled "Selection of Initial Treatment Modality". Instead we propose listing "Best systemic therapy plus brain-directed therapy" as the first step under Principles of Brain Metastases Management. A bullet point under that heading should state "In highly select patients evaluated in a multidisciplinary setting, systemic therapy alone with close observation of intracranial response may be appropriate."

Rationale:
Neurosurgeons and radiation oncologists have no illusions about resection and/or SRS displacing the need for systemic therapy in the setting of intracranial metastases. It is not an either/or choice; any brain-directed therapy can and should be performed in the context of the best systemic therapy either ongoing or planned shortly thereafter. This framing as presented ("Selection of Initial Treatment Modality) however makes it seem as if systemic therapy is indicated (almost always) and that local therapy cannot be considered in parallel. Decades of brain metastases management clearly contradicts this presented dichotomy.

Furthermore, the presence or absence of symptoms is not a key determinant, as suggested by bullet points on this page. If a lesion becomes symptomatic, SRS is often not feasible, and craniotomy is required. This is to be avoided; the asymptomatic window is usually the ideal time to intervene. The randomized study[1] where Ipi/Nivo vs Nivo alone was studied for brain metastases resulted in a 60% intracranial progression rate, 6 craniotomies, and 9 deaths ascribed to intracranial progression in patients who were not offered upfront brain-directed therapy. This was not a study that supported omission of brain-directed therapy, rather a study that demonstrated the dangers of omitting brain-directed therapy for systemic therapy alone[2]. The randomized study for Braf/Mek inhibition in lieu of brain-directed therapy had similar concerning findings, with 10% of patients who were not afforded radiosurgery requiring craniotomy, as tucked away in the appendix[3].

Overall, we recommend strengthening the need for formal CNS specialist evaluation and weakening the option of systemic therapy alone. Practices of brain-directed therapy have been established as standards of care for brain metastatic management as per numerous radiation oncology and neurosurgical randomized studies, always in the context of best systemic therapy. Systemic therapy alone versus these standards have never been examined in a randomized fashion.

References:

1. Long GV et al. Lancet Oncol. 2018 May;19(5):672-681. PMID 29602646
2. Kruser TJ et al. Lancet Oncol. 2018 Aug;19(8):e366. PMID 30102217
3. Davies MA et al. Lancet Oncol. 2017 Jul:18(7):863-873. PMID 28592387

Minor Recommendation 1: ME-2 and ME-3

- We recommend a footnote describing the role of adjuvant RT for desmoplastic histologies. "For selected patients with positive margins after surgery…consider…RT"

Rationale: *We agree with the note on page ME-H page 1/7 that adjuvant RT may be considered for high-risk desmoplastic melanoma. However, there is no preceding footnote or pathway that would guide a surgeon or medical oncologist seeing a clinical patient to find this recommendation.*

References:
Included references #'s 8-11 in the "Principles of RT for Melanoma" on page 6 of 7, section ME-H nicely support this recommendation.