



HHS Public Access

Author manuscript

JAMA Oncol. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

JAMA Oncol. 2022 September 01; 8(9): 1252–1254. doi:10.1001/jamaoncol.2022.1928.

Brain metastasis is a distinct oncologic disease best served by an integrated multidisciplinary team approach

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MeSH key words:

brain neoplasms; delivery of health care; disease management; metastasis

Until recently, brain metastases were considered an end-stage progression of cancer best managed palliatively. However, more aggressive therapeutic approaches for brain metastases are increasingly warranted for several reasons including: (1) their incidence is increasing in tandem with improving cancer survival, (2) the CNS is increasingly an isolated site of refractory and life-limiting disease, and (3) outcomes are improving—making optimized long-term control necessary in an increasing proportion of patients. In issuing its landmark 2020 guidance on brain metastasis patient inclusion in clinical trials, the FDA cited an urgent mandate to direct “attention...to address this unmet clinical need” and effectively challenged the oncology community to stop excluding, and indeed extend its focus to this population.¹

The key driver of improved outcomes of many brain metastasis patients includes several CNS-active drug approvals including TKIs targeting EGFR-mutant, Her2-amplified and ALK-rearranged malignancies, plus checkpoint inhibition activity in CNS melanoma, on a background of broadly improving survival across cancers. In parallel, the field has shifted from whole-brain radiation regimens (WBRT) in favor of stereotactic radiosurgery (SRS), which is both highly effective and readily applied to multiple metastases in individual patients. With wider application of SRS, individual tumor outcomes are improved with reduced radiation-induced cognitive side effects commonly seen following WBRT.

Concurrently, decision-making is becoming ever-more complex. In addition to expanding menus of systemic cancer-directed treatments, novel and improved local-ablative therapies such as percutaneous laser ablation, microsurgical techniques and brachytherapy have introduced a new range of upfront and salvage options but also important interactions. For example, corticosteroid avoidance is now prioritized for melanoma patients with

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cerebral edema and requiring immunotherapy, at times lowering the threshold for surgical intervention.² Conversely, surgery for even large metastases is now sometimes avoidable, for example in tumors exquisitely sensitive to CNS-penetrant third-generation EGFR inhibitors. Newly-available MR-guided laser interstitial thermotherapy systems deliver ablative treatment to unresectable, previously-irradiated tumors, and in poor candidates for surgical resection.

As survival increases among patients with previous SRS, complex neuro-imaging studies (dynamic contrast-enhanced MRI and FDG-PET), and at times biopsy, are often required to attempt to distinguish radiation necrosis from true recurrence requiring creative salvage approaches. Radiographic screening and post-metastasis surveillance algorithms remain poorly defined across cancer types and stages, leading to relatively frequent presentation with larger, more difficult-to-treat symptomatic lesions. Finally, leptomeningeal metastasis palliation mainstays require appropriate selection: local therapies (wide-field radiation and CSF shunting for refractory hydrocephalus) and, increasingly, intrathecal-therapy trials are considered, though end-of-life planning is also an important element of a comprehensive approach at this stage of cancer progression.

It is thus clear that specialized attention and multidisciplinary coordination are essential for the best care of these patients. Unfortunately, brain metastasis care in the United States has historically been siloed to the unifocal realms of Neurosurgery and/or Radiation Oncology in isolation from each other and from Medical Oncologists who retain depth of expertise for individual patients and their diseases, and who increasingly offer CNS-active therapies. Integrated multidisciplinary programs are therefore critical to bring the breadth of necessary perspectives to the table on an individualized basis.

Multidisciplinary disease management teams (MDTs), recommended as best oncologic practice for 25 years, have a strong legacy of improving outcomes in several cancers. For example, breast cancer MDT introduction in Scotland was associated with significantly reduced cancer-associated mortality compared to neighboring regions.³ Similarly, we believe that teams organized around CNS involvement can transform outcomes given the unique ramifications of progression in this arena. A nascent but growing literature is documenting the advantages of brain metastasis tumor boards, with significant rates of practice-changing recommendations and guideline conformity.⁴ In one experience, fully 35% of plans were substantially modified, with 90% plan adherence; and brain metastasis and breast cancer-brain metastasis clinics have been well-received with patient satisfaction approximating 90%.^{5,6}

We advocate for the implementation of Brain Metastasis programs in service of two goals: (1) coordinated decision-making and (2) efficient care, in recognition that treatment gaps lead to worse oncologic outcomes and that quality of life is inextricably linked to time spent outside the healthcare setting.⁷

Such programs benefit from 4 interrelated elements, each of which is transferable to any center without significant new resource allocation: dedicated tumor boards, multidisciplinary outpatient clinics, inpatient service lines, and clinical trials workgroups. Brain metastasis

tumor boards serve as programmatic lynchpins bringing together individual patients' treatment teams. Full participation of Medical Oncologists is often a limiting factor, yet their engagement is critical to the group's ability to introduce innovative treatments given their command of the overall patient condition. To facilitate participation, specific patient discussions can be prescheduled on a video-conference platform; in 3 years since implementation, we have seen exceptional engagement from the many oncologists caring for these patients. Additional CNS-focused oncologists, standing representatives from relevant local-therapy disciplines (Neurosurgery, Radiation Neuro-Oncology, Neuro-Oncology) plus Neuroradiology, Neuropathology and Physiatry, are present for some 300 case discussions yearly. A coordinator is required to collect weekly presentation requests and invite providers, but joint reviews significantly reduce physician effort redundancy for these complex cases (e.g., 1:1 radiology review with multiple providers). Importantly, such tumor boards should be open to community providers: treatment resources including radiation or neurosurgical care are often locally-available, while decision-making is more challenging without Neuro-Oncologists or CNS-focused Radiation Oncologists. Hence, opening these meetings to outside Medical Oncologists can directly contribute to improved outcomes beyond large urban cancer centers.

Armed with tumor board decisions, staff can quickly design patients' outpatient schedules. Treatment considerations are presented to patients at multidisciplinary clinic visits with assurance that their full treatment team has provided input, fostering rapid implementation. SRS simulation and treatment, presurgical testing, and trial enrollment can all be organized for the same visit. Dedicated advanced-practice providers can additionally provide long-term surveillance, neurologic symptom management, and care coordination. Reallocation of existing personnel offsets the required organizational effort, with patients only seeing required consultants in clinic; indeed, early data suggest that such pre-clinic triage reduces unnecessary visits.

Similarly, inpatient MDT consult services offer rapid, coordinated decisions for hospitalized patients. This focused paradigm can spark workflow improvement across the inpatient-outpatient continuum, e.g. early-intervention programs to avoid ER referrals for asymptomatic metastases, and expedited adjuvant SRS models delivering earlier postoperative treatment, which is associated with lower recurrence risk. Such initiatives can reduce unnecessary hospitalizations for some patients who are then efficiently cared for as outpatients; and for surgical patients, it has reduced time to adjuvant SRS from 4 to 2 weeks, allowing earlier systemic-therapy resumption.

Finally, workgroups of key stakeholders can catalyze the necessarily collaborative (sometimes histology-agnostic) therapeutic and diagnostic trials which are impossible to conceive or execute without cross-disciplinary input and patient centralization. Frontiers in this domain include innovative window-of-opportunity approaches, and radiomic and liquid biopsy biomarkers of parenchymal relapse and leptomeningeal dissemination.

In recognizing that its management requires a unique level of expertise and coordination, we believe that outcomes can be improved, and that ecosystems created by identifying and treating brain metastasis as a distinct disease will yield considerable patient benefits.

Perhaps as importantly, such an approach can spur innovation and trainee interest, and offer patients hope that their disease is no longer an unbeatable, rapidly-disabling and fatal complication. More work is needed to optimize systems, identify best practices, and ultimately improve outcomes, but recognizing these unique challenges and opportunities is essential to further advance in the right direction.

Funding:

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Conflicts of Interest:

At the time of submission and publication, all authors are affiliated with Memorial Sloan Kettering Cancer Center. The authors of this research deny any conflicts of interest regarding this study and make the following disclosures: NSM: Consulting fees for advisory board participation: AstraZeneca; research funding (to institution): GT Medical Technologies.

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