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National Cancer Institute Collaborative Workshop on Shaping the Landscape of Brain Metastases Research: challenges and recommended priorities

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Abstract

Brain metastases are an increasing global public health concern, even as survival rates improve for patients with metastatic disease. Both metastases and the sequelae of their treatment are key determinants of the inter-related priorities of patient survival, function, and quality of life, mandating a multidimensional approach to clinical care and research. At a virtual National Cancer Institute Workshop in September, 2022, key stakeholders convened to define research priorities to address the crucial areas of unmet need for patients with brain metastases to achieve meaningful advances in patient outcomes. This Policy Review outlines existing knowledge gaps, collaborative opportunities, and specific recommendations regarding consensus priorities and future directions in brain metastases research. Achieving major advances in research will require enhanced coordination between the ongoing efforts of individual organisations and consortia. Importantly, the continual and active engagement of patients and patient advocates will be necessary to ensure that the directionality of all efforts reflects what is most meaningful in the context of patient care.

Introduction

As survival rates for patients with cancer improve, brain metastases and the sequelae of their treatment are an increasing public health concern affecting growing numbers of patients with cancer. Management requires balancing inter-related priorities of patient survival, function, and quality of life, mandating a multidimensional approach to clinical care and research. Challenges specific to brain metastases stem from the unique and inadequately characterised brain tumour microenvironment, which modulates the initiation and progression of disease, and the subsequent adverse sequelae of therapy. Alteration of brain homoeostasis by the presence of brain metastases and the therapy needed to treat them directly contributes to patient survivorship and quality of life—more than in any other metastatic organ site.

Since the earliest seminal studies establishing the benefit of surgical resection in certain patients with limited intracranial disease,[1] survival outcomes for particular subsets of patients have improved, but still remain suboptimal. Given the complexity of the metastatic continuum, the unique brain microenvironment, and the clinical challenges of obtaining tissue specimens, progress in the research and treatment of brain metastases has been slow. As outlined in the landmark US Food and Drug Administration (FDA) guidance in 2020,[2] patients with brain metastases have historically been excluded from clinical trials given concerns around their shortened life expectancy and poor performance status with associated risks of toxicity. Moreover, few US federal funding resources and funding mechanisms have been specifically devoted to brain metastases research. This limited funding allocation might be related, in part, to the low number of funding applications focused on brain metastases;

in the fiscal year 2022, new application submissions for brain metastases research comprised only 1·5% of all applications to the National Cancer Institute (NCI), reflecting a paucity of submissions despite the high incidence and impact of brain metastases. Among the NCI research awards reviewed between 2012 and 2023, the number of proposals submitted with a focus on brain metastases was approximately 60% lower than the number of proposals for glioblastoma, despite the substantially higher incidence of brain metastases. Although the success rate of funding appears to be similar on average between both groups (figure 1), why so few proposals are submitted for this area of unmet need is unclear.

At the virtual NCI Workshop on Shaping the Landscape of Brain Metastases Research (Sept 29–30, 2022), key stakeholders convened to define research priorities addressing crucial areas of unmet need in brain metastases research, and to propose new collaborations to address these priorities. These stakeholders included patients and patient advocates, clinicians and translational scientists, leaders from NCI-funded clinical trial networks, advocacy and foundation partners, academic societies, the FDA, and NCI leadership (panel 1). At the outset, in a discussion led by survivors of brain metastases, the often-used phrase of a meaningful advance was defined as "expedient discovery towards the cure or prevention of brain metastases that would enable patients to maintain maximal function, cognition and quality of life". With this foundation, key challenges (panel 2) and recommended priorities for brain metastases research emerged.

Key challenges and knowledge gaps

Do research priorities align with patient-defined meaningful advances?

In a survey of patients with cancer conducted before the workshop by a participating patient advocate (CH), a key identified priority was gaining control of or curing brain metastases while maintaining a good quality of life. Among the phase 2 and 3 clinical trials conducted over the past decade that have defined new standard therapies for patients with brain metastases,[3,4] only a small number have directly incorporated primary and secondary endpoints addressing durable disease control in conjunction with the maintenance of patient's neurological function and quality of life. Given the rapid pace of drug development, whether common endpoints, such as radiographic response indicating activity in the CNS, are of substantial long-term or meaningful significance to patients is unclear. Moreover, how patient function and quality of life are affected by newer systemic agents with CNS activity in combination with, or in lieu of, surgery and radiotherapy is largely unknown. This knowledge gap is anticipated to grow with the rapid pace of drug development and the increasing number of trials without a backbone of standard-of-care local therapies.

As indicated by the patients and patient advocates represented at this workshop, novel approaches are needed not only for the treatment of established brain metastases, but also for their earlier detection and prevention.[5,6] At present, the available guidelines[7–14] for screening asymptomatic patients with cancer for brain metastases are not optimally tailored to the individual patient or to the subsets of patients who are at risk of developing brain metastases, whether on the basis of clinical or molecular predictors. Earlier detection is preferred over identifying advanced metastases after symptom onset, given the potentially

higher toxicity of local therapies at later stages of CNS involvement.[15,16] Yet neither a standard MRI protocol nor a clear identification of the subsets of patients who are at high risk for brain metastases has been established for each primary cancer subtype. This knowledge gap is partly related to limitations in the collection of epidemiological data and the absence of mandated reporting of brain metastases to local and federal registries such as the Central Brain Tumor Registry of the United States.[17] As a result, the true population-based incidence of brain metastases and rate of neurological death due to intracranial disease by histological or molecular subtype are unknown. More importantly, the absence of these data limits our ability to construct models identifying patients who are at greatest risk of developing brain metastases.

Very few clinical trials[18] have addressed the prevention of brain metastases for several possible reasons. Focused trials with key goals of primary and secondary prevention are rare, in part due to inadequate knowledge of which patients to recruit and to the anticipated lengthy duration, size, and cost of such trials. Insufficient emphasis on the development of agents and drug classes that affect the tumour microenvironment and modulate metastatic initiation is underscored by scarce funding for both preclinical and clinical investigations in this line of research. To our knowledge, no primary or secondary prevention studies for brain metastases have been conducted through the Experimental Therapeutics Clinical Trials Network or the National Clinical Trials Network of the United States. Many recent and developing trials over the past 5–7 years have been limited to available, industry-driven drug candidates primarily designed for systemic efficacy, with secondary evaluation of their activity in established brain metastases, and very little to no emphasis on the prevention of brain metastases. Many positive clinical trials of these therapies have produced only months of improvement in progression-free survival, with attendant adverse effects.

Can the spectrum of patient experience be adequately characterised to target areas for improvement?

Although instruments to assess patients' brain tumour symptoms, neuropsychology, and quality of life are commonly used in clinical trials,[19] no standardised toolkit has been established to measure these domains in patients with brain metastases.[20] Among the practice-changing phase 2 and 3 trials in brain metastases treatment published over the past 5 years that evaluated neuroprotective strategies with radiation, or drug therapy regimens in lieu of radiation, substantial variation exists in the extent and type of the functional assessments undertaken.[3,4] Approaches have ranged from no specific functional evaluation, to estimating global (non-brain-specific) health status, and implementing brain-specific batteries assessing patients' neurocognition,[21] symptoms, and quality of life. An even greater unmet need is the identification of instruments specific for brain metastases that could be feasibly implemented across organisations for integration into routine clinical care, outside of the rigour of prospective clinical trials. The unique trajectory of the disease course often includes repeated and combined methods of treatment over months to years, with the potential need for supportive medications (eg, steroids), and poorly understood interactions between therapies. Adequately profiling the longitudinal trajectory of patients with brain metastases both in clinical trials and in clinical practice is imperative.[22–24] Moreover, understanding the extent and effect of interactions between newer systemic therapy agents

and standard-of-care therapies (ie, radiotherapy) is crucial. These data are not captured in brain metastases trials designed to assess the benefit of systemic therapy regimens without a backbone of radiation treatment and must, therefore, be assessed with real-world data. A major limitation of this method of data collection includes the potential for bias (known and unknown), precluding definitive conclusions regarding the comparative efficacy and toxicity of single or combined methods of therapy.

Integrating patient-reported outcomes in the care of patients with metastatic cancer has been shown to reduce emergency room visits, increase patients' adherence to treatment, and improve patients' quality of life and overall survival.[25] Although progress is being made in incorporating patient-reported and objective function assessments as primary and secondary objectives in NCI-funded clinical trials, optimising the large-scale integration of instruments specific to brain metastases into routine clinical practice will substantially increase the available data for analysis and action. Leveraging big data and technology platforms from non-medical industry stalwarts with artificial intelligence-powered informatics analyses could ultimately power predictive models that accurately estimate clinical outcomes. A focus on easy-to-use toolkits via online and electronic applications might enhance patient participation, potentially allowing patients to provide their own clinical data. Optimal integration across organisations' electronic medical records and demonstration of the value and medical necessity of acquiring this data in routine care will be important in aiding widespread adoption in clinical practice as a communication tool and platform for shared decision making.

Can functional determinants be identified to mitigate risk factors for neurological injury?

Although neurological injury from cancer therapy is a multifactorial process with evidence for the centrality of dysregulated inflammation,[26–28] the intraindividual and interindividual risk factors for clinically meaningful functional and cognitive impairments are poorly understood. Identification of modifiable and protective factors is crucially needed. Although individual patients have differing genetics, cofactors, and exposures that influence their susceptibility to toxicity, precisely how different patients experience greater injury (or impaired recovery) after exposure to therapies for brain metastases is unknown. A substantial number of patients still require whole-brain radiotherapy, and the consequences of repeated stereotactic radiosurgery and the under-studied effect of newer CNS-active systemic agents on neurological function underscore the importance of identifying modifiable risk factors for neurological injury. The potential benefits of enhancing patients' resilience to injury through cognitive or physical exercise[29] or of addressing concurrent mood related symptoms (eg, depression and anxiety) are yet to be fully explored.

At present, no validated screening tools exist to identify which patients are at highest risk for delayed, irreversible structural and functional neurological injury. Specific tools to assess mechanisms underlying neurological function (eg, neurotransmission, synaptic plasticity, glial homoeostasis, and neurogenesis) have not been translated to patient studies and should be developed and studied alongside the broader functional assessments currently in clinical use.

How therapy might most effectively be individualised to maximise safety, or whether patients who are at higher risk for neurological injury should be considered for de-intensified treatment strategies (without compromising disease control or survival), as opposed to offering intensified therapies to patients at lower neurological risk, is unknown. As a result, most therapies for brain metastases follow a one-size-fits-all approach. Understanding which specific impairments are most crucial to patients and understanding their dynamics in the treatment and survivorship timeline is imperative to improve the therapeutic ratio of standard and investigational therapies.

Which tumour and microenvironmental factors determine brain tropism, metastatic initiation, and progression?

The primary determinants of brain tropism, the initiation of micrometastases, and the progression to macrometastases are not well understood. Although a wide variety of primary tumour types metastasise to the brain, the unknown common denominator (if present) could involve a unique mutational[30] and epigenetic evolutionary profile, promoting brain tropism and tumour cell survival through adaptation to the microenvironmental niche or construction of a new brain microenvironment. Better identification of the relationships between cells in the tumour microenvironment (eg, astrocytes, neurons, microglia, and immune cells) and tumour cells during the development of brain micrometastases[31,32] is crucial for the design of new and innovative prevention trials. Further development of haematogenous or patient-derived xenograft preclinical models[33] with an emphasis on understanding the relationship between novel therapies and standard-of-care treatments is needed. Preclinical models can efficiently facilitate the prioritisation of targets and therapies for clinical testing and validation. The development and testing of agents with blood–tumour barrier permeability that modulate the role of the tumour microenvironment in the formation and progression of metastases should be emphasised.

Biomarkers to predict the development, progression, and treatment resistance of brain metastases are scarce.[34] Key unanswered questions, including which subsets of patients could safely defer radiation and surgery in lieu of newer CNS-active systemic agents, will require the identification of biomarkers to individualise care. Molecular, cellular, imaging, and even digital biomarkers should be explored through the prospective collection of multimodality datasets. Advances in mechanistic understanding of brain metastatic colonisation will lead to new, potentially brain-specific preventive therapies with subsequent improvements in disease control, quality of life, and potentially survival.

How should clinical trials be conducted to efficiently test promising therapies?

At present, the necessary coordination to support the efficient conduct of high-risk, high-impact brain metastases trials is poorly executed across organisations. The development and implementation of clinical trial concepts is opportunistic and focused on the priorities of an individual organisation, rather than on promoting a coordinated and unified series of trials on the basis of a well defined national vision and strategy. A collaborative and unified approach is required to move beyond incremental advances to major breakthroughs in the field.

Survival as an endpoint is an insufficient measure of a meaningful outcome in this patient population with a substantial competing risk of systemic disease progression. Endpoints that sufficiently capture elements of patient function should be routinely incorporated into trials specific for brain metastases. Novel and composite endpoints including survival, free of the development of initial or additional brain metastases, neuro progression-free survival (including neurological and neurocognitive function), intracranial progression-free survival (freedom from salvage therapies), freedom from neurological death, and survival with equal or less cognitive and functional decline should be implemented and tailored to the expected effect of the intervention under study.

Given the pace of drug discovery, novel trial designs should be encouraged that permit the rapid opening and closing of arms, with an emphasis on combinatorial drug–radiotherapy approaches based on sound biological rationale. Although novel trial designs are being implemented for rapid assessment of drug therapies, including in select patient populations with brain metastases, these streamlined trials should incorporate standard-of-care therapies (ie, radiotherapy and surgery) in rational combination or sequence with newer drug therapies. As most patients with brain metastases will require radiotherapy,[4] prospective, comparative data characterising the potential synergy or toxicity of drug–radiotherapy combinations are crucial. Consideration of planned subset accrual for patients with known brain metastases in clinical trials evaluating systemic agents with CNS penetrance should be incorporated early in the clinical trial design process.[35] Importantly, multidisciplinary team engagement including neurosurgeons, radiation oncologists, medical oncologists, and neuro-oncologists is necessary for patient recruitment and the successful conduct of high-impact clinical trials.

What barriers should be addressed to ensure adequate inclusion and representation in research?

As expressed by the patients and patient advocates at this workshop, involving patients early in the study development process will enhance study participation and enrolment in brain metastases trials. Patient input in trial design and the development of a dissemination plan and outreach materials is important for the successful conduct of clinical trials. Investigators should share data showing why the trial might be beneficial and help patients to understand why their responses and participation matter. During this process, investigators often discover patient willingness to engage in high-risk, high-reward research studies, especially when enabled by open communication regarding the valuable knowledge gained by their participation.

In the process of scientific research, ensuring adequate representation of diverse patient populations is crucial to ensure the generalisability of the results and to maximise the safety and efficacy of interventions.[36] Challenges with travel, childcare, or access to electronic technologies might limit the participation of some patient populations. Disparities in access to advanced treatments, coordinated care at academic centres, and supportive therapies must be effectively addressed to mitigate persistent disparities in cancer outcomes.[36]

Major effort should be devoted to minimising delays and barriers in access to clinical trials for brain metastases.[36–38] Lowering the barriers to entry includes reducing the minimum

size criteria of measurable disease, optimising the classification of leptomeningeal disease (which might exclude patients from some trials), opening a separate trial group to include patients with leptomeningeal disease, and incorporating cohorts of patients with brain metastases in phase 1 or phase 2 trials when no major safety signals emerge in dose-finding studies.

Ultimately, the infrastructure of routine clinical care should be optimised through the development of multidisciplinary, patient-centric brain metastases clinics[39–41] and CNS metastases care coordination programmes.[42] Best practices from these programmes streamline multidisciplinary care and decrease time to initiation of CNS-directed therapies.[43,44] Such multidisciplinary clinics can facilitate substantially higher enrolment onto clinical trials.[39,41,42] As therapies continue to develop for molecular subgroups, agnostic to primary cancer type, greater coordination across disease sites and specialties will be increasingly paramount to ensure timely treatments and optimal patient accrual onto clinical trials.

How should common priorities be defined to enable collaborative national and international data sharing and accelerated discovery?

At present, numerous databanks incorporating clinical, treatment, and follow-up data of varying scope and magnitude have been established for patients with brain metastases across individual institutions, co-operative groups, and consortia. No common set of data elements has been established across these efforts, nor has standardised data entry been achieved to allow the required scale of analysis necessary to inform next-generation clinical trials.

Given the vast quantity of multidimensional, longitudinal data types required, public–private–academic partnerships with advanced artificial intelligence and machine learning algorithms will be needed to analyse digitalised real-world data. Multimodality data should include imaging; pathology; molecular, patient-reported, and objective function measures; social determinants of health; toxicity; and disease control and survival outcomes. Data collection must be modular, interoperable across vendors and organisations, and responsive to the rapidly changing landscape of therapies.

This NCI workshop was the first of its kind to convene the breadth of relevant stakeholders to reach a consensus on these key challenges and knowledge gaps and to define recommended priorities (figure 2) for future brain metastases research.

Recommended priorities for collaborative brain metastases research

Priority 1: identify subsets of patients who are at high risk for brain metastases

An unmet need is that patient populations who are at high risk of developing brain metastases are not well defined.

To advance the areas of enhanced screening and early intervention, and primary and secondary prevention of brain metastases, the specific subsets of patients who are at high risk for developing brain metastases should be identified through an inclusive and representative multidimensional data collection process. Understudied opportunities exist for

screening before and disease monitoring after the development of brain metastases. These opportunities include low-burden, standardised MRI with the potential for rapid, automated assessment; liquid screening detection tools for molecular profiling of cerebrospinal fluid and blood; cognitive and symptom measures with online or app-based platforms for ease of patient and provider use; and wearable biometric technologies.

We recommend the development of a consensus for a minimum standardised set of data elements with the flexibility to incorporate advances in knowledge that permit multisite data collaboration on a global scale. A standardised imaging protocol to allow rapid screening for brain metastases in subsets of patients who are at high risk should also be developed, and the cost-effectiveness of its implementation across these patient subsets should be shown.

Priority 2: identify subsets of patients who are at high risk for functional or cognitive impairment from treatment

An unmet need is that standard therapies are not specifically tailored to mitigate the risk of functional or cognitive impairment for individual patients or subsets of patients who are at risk of these sequelae.

Numerous reporting and performance tools tailored to patients with primary brain tumours have been implemented across clinical trials. These tools measure multiple aspects of patients' quality of life, including their neurocognition, ability to complete daily tasks, and psychosocial wellbeing, and present a unique opportunity to longitudinally characterise dysfunction and identify potential risk factors. Developing tools to best assess real-world performance among patients with brain metastases would help accelerate the development of interventions to prevent or mitigate functional and cognitive impairment from cancer therapy.

We recommend the development of a standardised, accessible, convenient, and clinically meaningful battery of patient-reported and objective measures of function, symptoms, and quality of life that are specific to brain metastases and implementable in routine clinical care across institutions. This standardised tool should be developed in collaboration with patients and patient advocates, to maximise patient participation and benefit.

Priority 3: align preclinical and clinical research priorities

An unmet need is that although many in vivo preclinical models for brain metastases evaluate the prevention of brain metastases, most clinical trials evaluate the treatment of established brain metastases. The interaction between cancer cells and the brain microenvironment that leads to reprogramming allowing for the establishment and initiation of metastatic growth might be distinct from the microenvironment of an established lesion. Thus, therapies developed in a preventive, preclinical setting might not be applicable in therapeutic clinical trials.

Expanding beyond the existing systemic therapy pipeline, an avenue is needed to develop and test preventive and therapeutic interventions that target the tumour microenvironment. Multiple existing haematogenous or patient-derived xenograft preclinical models can be used to efficiently prioritise preventives and therapeutics for clinical testing. These models

should be improved on to facilitate the rapid credentialling of promising interventions with preplanned stopping rules for futility. Preclinical models should also include clinically relevant endpoints and explore the relationship between novel therapies and standard-of-care radiotherapy and surgery.

We recommend the establishment of a nexus for preclinical to clinical investigations with close collaboration between scientists and clinical trialists to enable the rapid translation of promising candidate preventives and therapeutics to clinical trials and patient care. In conjunction with preclinical models, greater emphasis on window-of-opportunity trials and obtaining both pre-treatment and on-treatment biospecimens is crucial to elucidate biological mechanisms and to develop biomarkers to predict the development of metastases and treatment resistance.

Priority 4: optimise the framework for the design and conduct of brain metastases-specific trials

An unmet need is that traditional endpoints for brain metastases clinical trials, such as response rate and survival, do not adequately capture what is most meaningful to patients. Moreover, unduly restrictive eligibility criteria hindering clinical trial enrolment, inefficiencies in the process to start protocol therapy, and barriers to access exclude patients from timely treatment with promising interventions. Inadequate intergroup collaborations underscore the absence of a pipeline of executable clinical trials framed to promote a well defined, overarching vision to advance the field.

Expanded clinical trial initiatives, including brain metastases-specific basket trials with innovative, practical design and targeted incorporation of informative endpoints, might enable assessment of the optimal sequencing of radiotherapy plus drug combinations and accelerate clinical translation to specific patient populations.

We recommend the development of a consensus for reproducible clinical trial endpoints that are reflective of benefits specific to patients with brain metastases, the phase of the trial, and the category of intervention. Ultimately, coalescing behind a national vision to collaboratively address areas of unmet need through a series of coordinated clinical trials will be required for major advances in brain metastases research and treatment.

Conclusion

Cancer research is typically organised around the cell of origin or anatomical site of the primary tumour. Therefore, a structural nexus to understand the brain metastases continuum that spans tropisms, unique brain-specific niche construction, points of treatment interventions, and quality of life is a persistent unmet need. Meaningful advances in treatment and outcomes will require an integrative, systems-level approach that builds on innovative programmes, such as the NCI Metastasis Research Network, aimed at characterising mechanisms across the metastatic continuum and therapeutic response.

Achieving meaningful large-scale advancement in brain metastases research will require enhanced collaboration and coordination between the ongoing efforts of individual groups

and institutions. Convening the many varied stakeholders to coalesce as a community for the purpose of collectively enumerating the top priorities to shape future brain metastases research efforts was the first crucial step and intention of this workshop. Next, focused working groups with multidisciplinary expertise will be assembled from these stakeholder groups to specifically address the key challenges of each priority. Progress will be benchmarked and recalibrated moving forward with guidance from the NCI and, importantly, the working groups will continually and actively engage with patient advocates to ensure that the directionality of all efforts reflects what is most meaningful in the context of patient care. Successful output from these working groups will require continued collaboration with the advocacy groups, professional societies, and organisations represented at this workshop and others, whose ongoing efforts might now more effectively converge on these key priorities.

Translating promising treatment options to clinical practice requires multidisciplinary coordination. Partnerships with community providers and patient advocates to promote education and the dissemination of knowledge and to localise patient access to optimal care for brain metastases will help to ensure that the impact of these collective scientific endeavours will equitably and inclusively benefit all patients.

Acknowledgments

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Panel 1:

Organisations and societies represented by the experts at the NCI Collaborative Workshop on Shaping the Landscape of Brain Metastases Research

- Alliance for Clinical Trials in Oncology

- American Association for Cancer Research

- American Brain Tumor Association

- American Society of Clinical Oncology

- American Society for Radiation Oncology

- Consortium for Intracranial Metastasis Academic Research

- Department of Health and Human Services Food and Drug Administration

- Guiding Researchers & Advocates to Scientific Partnerships (GRASP)

- Living Beyond Breast Cancer

- LUNGevity Foundation

- Melanoma Research Foundation

- Metastatic Breast Cancer Alliance

- National Brain Tumor Society

- National Cancer Institute Center for Cancer Research

- National Cancer Institute Division of Cancer Biology

- National Cancer Institute Division of Cancer Treatment and Diagnosis

- National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and the Gynecologic Oncology Group (NRG) Oncology

- The Radiosurgery Society

- Society for Immunotherapy of Cancer

- The Society for Neuro-Oncology

- Touch4Life

Panel 2:

Key questions specific to research on and treatment for brain metastases and their associated knowledge gaps and challenges

Do research priorities align with patient-defined meaningful advances?

Knowledge gap

- Whether common endpoints in brain metastases clinical trials (eg, radiographic response) constitute meaningful advances for patients is unknown

- With the rapid pace of drug discovery, how CNS-active systemic agents affect patient function, quality of life, and long-term disease control in combination with, or compared with, radiotherapy is largely unknown

- Although earlier detection of brain metastases is a stated priority of patients and patient advocacy groups, subsets of patients who are at high risk of developing brain metastases have not been clearly defined, and no standardised screening tool exists

- Although primary and secondary prevention of brain metastases remain an ultimate goal to improve patient outcomes, very few trials have been designed to answer this question

Challenges and barriers

- Few brain metastases trials have emphasised functional or quality-of-life endpoints along with metrics of disease control and survival

- Accurate population-based estimates of the incidence and outcomes of brain metastases in the USA are unavailable due to the absence of mandated reporting of cases to local and federal US registries and non-uniform data collection across institutions

- Inadequate emphasis on prevention trials relates to poor knowledge of which patients to recruit, the prohibitive cost and duration of trials, and insufficient emphasis on the research and development of this therapeutic class

Can the spectrum of patient experience from CNS metastases treatment and survivorship be adequately characterised to target areas for improvement?

Knowledge gap

- Patients with brain metastases have a unique disease trajectory, including combined methods of treatment for systemic and CNS disease; however, no standardised brain metastases-specific instruments have been developed and uniformly implemented to adequately measure patient symptoms, performance, toxicities, or quality of life and their dynamics over time

- Most modern systemic therapy clinical trials do not capture the effect of delayed toxicities and interactions with standard-of-care treatment, such as radiotherapy

- Real-world data are also scarce, as most centres do not incorporate patient-reported outcomes or functional assessments of patients with brain metastases into routine clinical practice

Challenges and barriers

- The optimal integration of patient-reported and objective functional assessment tools into the electronic medical record across organisations must be established

- The value of collecting patient-reported and objective performance measures as a clinical communication tool and platform for shared decision making should be shown

- Simple and automated electronic data collection platforms supplemented with traditional methods of data collection might allow patients to provide their own clinical data and help overcome barriers to access for all patients

Can key determinants of function be identified to address modifiable risk factors for neurological injury from therapies for brain metastases?

Knowledge gap

- The specific impairments that are most important to patients and their dynamics during the timeline of cancer treatment and survivorship are not well characterised

- Intraindividual and interindividual risk factors for functional and cognitive impairments from therapies for brain metastases are poorly understood

- The benefits of addressing psychological distress and enhancing patients' resilience to neurological injury through exercise and rehabilitative interventions have not been well explored

Challenges and barriers

- Validated screening tools must be developed to identify which patients are at the highest risk of delayed, irreversible structural and functional neurological injury

- Specific tools assessing the factors underlying neurological impairment (eg, neurotransmission, synaptic plasticity, glial homeostasis, and neurogenesis) should be translated from the preclinical to the clinical arena

- Standard and investigational therapies must be tailored to the neurological risk of the individual patient

Which tumour and microenvironmental factors determine brain tropism, metastatic initiation, and progression?

Knowledge gap

- The primary determinants of brain tropism, the initiation of micrometastases, and their progression to macrometastases are unknown

- Insufficient emphasis has been placed on elucidating the role of the tumour microenvironment in the metastatic cascade and developing agents that modulate the role of the tumour microenvironment

- Biomarkers to predict brain metastases development, progression, and treatment resistance are scarce

Challenges and barriers

- Further development of preclinical models with an emphasis on understanding the relationship of novel therapies to standard-of-care radiotherapy and surgery is needed

- An avenue is needed to develop and test preventive and therapeutic interventions that target the tumour microenvironment and expand beyond the industry-driven systemic therapy pipeline

- Streamlined workflows are needed to collect multidomain molecular, cellular, imaging, and digital data to identify and validate biomarkers for the development of brain metastases and treatment resistance

How should clinical trials for CNS metastases be conducted to efficiently test promising therapies?

Knowledge gap

- Beyond survival and radiographic response, a standardised set of composite endpoints that capture meaningful elements of patient function, quality of life, freedom from new brain metastases, or salvage therapies should be routinely incorporated into therapeutic clinical trials for brain metastases

- Novel trial designs for rapid assessment of newer drug therapies should incorporate standard-of-care treatment (eg, radiotherapy or surgery) in rational combination or sequencing with newer drug therapies

Challenges and barriers

- Clinical trial concept development and implementation is opportunistic, and focused on the priorities of an individual organisation, rather than on promoting a coordinated and unified series of trials on the basis of a well defined national vision and strategy

- A poor framework or familiarity with novel composite endpoints (disease control plus function) could hinder the development of beneficial trials for patients with brain metastases

- Multidisciplinary team engagement including neurosurgeons, radiation oncologists, medical oncologists, and neuro-oncologists is crucial for patient recruitment and the successful conduct of high-impact clinical trials.

What barriers should be addressed to ensure adequate inclusion and representation of all patients in brain metastases research?

Knowledge gap

- Insufficient early communication and feedback to patients regarding study rationale or output from research, participation could hinder patient willingness to engage in research activities

- Inadequate peer education and partnership with community providers could limit patient access to clinical trials or timely, coordinated care

- Overly restrictive entry criteria for brain metastases clinical trials limit available therapies and progress in areas of greatest need

Challenges and barriers

- Inadequate representation of diverse patient populations limits the generalisability of results

- Disparities in access to advanced treatment methods, coordinated care at academic centres, and supportive therapies must be effectively addressed to mitigate persistent disparities in cancer outcomes

- Implementation of multidisciplinary, patient-centric clinics and care coordination programmes for brain metastases will be paramount to optimise clinical care and accrual onto clinical trials for this patient population

How should common priorities be defined to enable collaborative data sharing and accelerated discovery on a national and international scale?

Knowledge gap

- No consensus regarding standardised, minimum data elements for brain metastases registries has been defined to allow for the national or international pooling of data

- Public–private–academic partnerships to develop longitudinal, multimodality, real-world databases designed to advance discovery for brain metastases have not been realised on a large scale

Challenges and barriers

- Individual efforts of institutions, consortia, research organisations, and professional societies should be coordinated to expand the impact of shared knowledge and research

- Data collection must be modular, interoperable across vendors and organisations, and responsive to the rapidly changing landscape of cancer therapies

- Digitalisation of a vast quantity of data types will be required to use artificial intelligence and machine learning platforms capable of addressing unanswered questions that will inform next-generation clinical trials

Search strategy and selection criteria

No formal literature search was performed. Consensus guidelines for brain metastases management from 2018 to 2023 were reviewed, and additional literature was identified through a review of guideline bibliographies and reference lists cross-referenced by searching PubMed from database inception to April 1, 2023, with the terms "brain metastases" and "guidelines". Only full-text articles published in English were reviewed. The final reference list was generated on the basis of the relevance of the papers to the scope of this Policy Review.
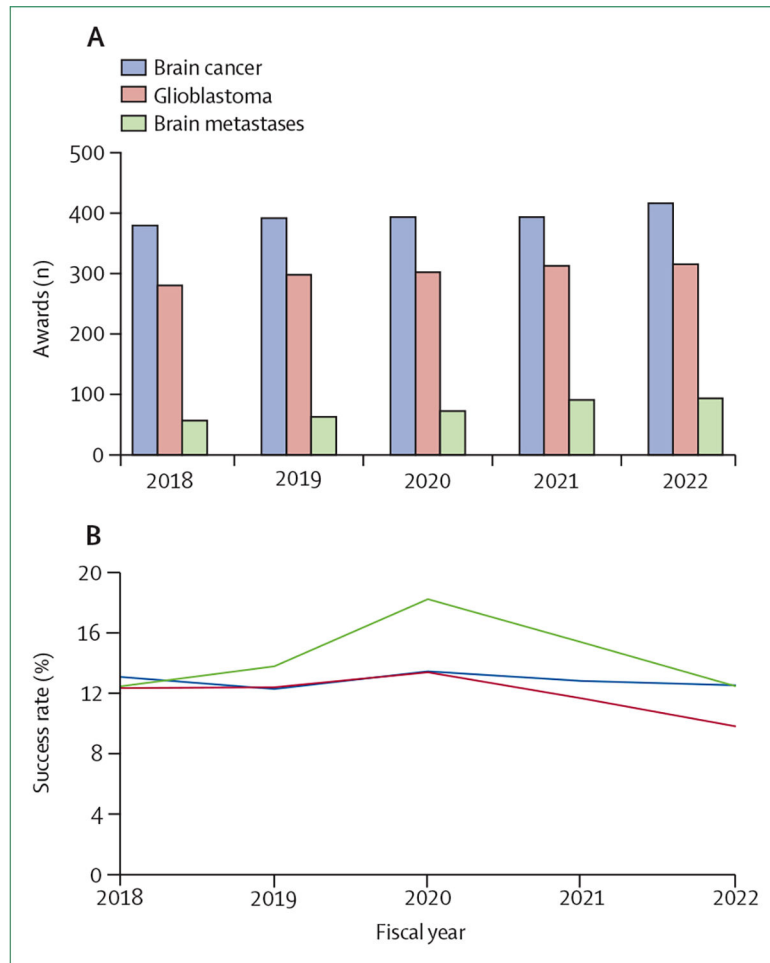
Figure 1:
National Cancer Institute awards (A) and success rates (B) for brain cancer, including brain metastases, for the fiscal years 2018–22
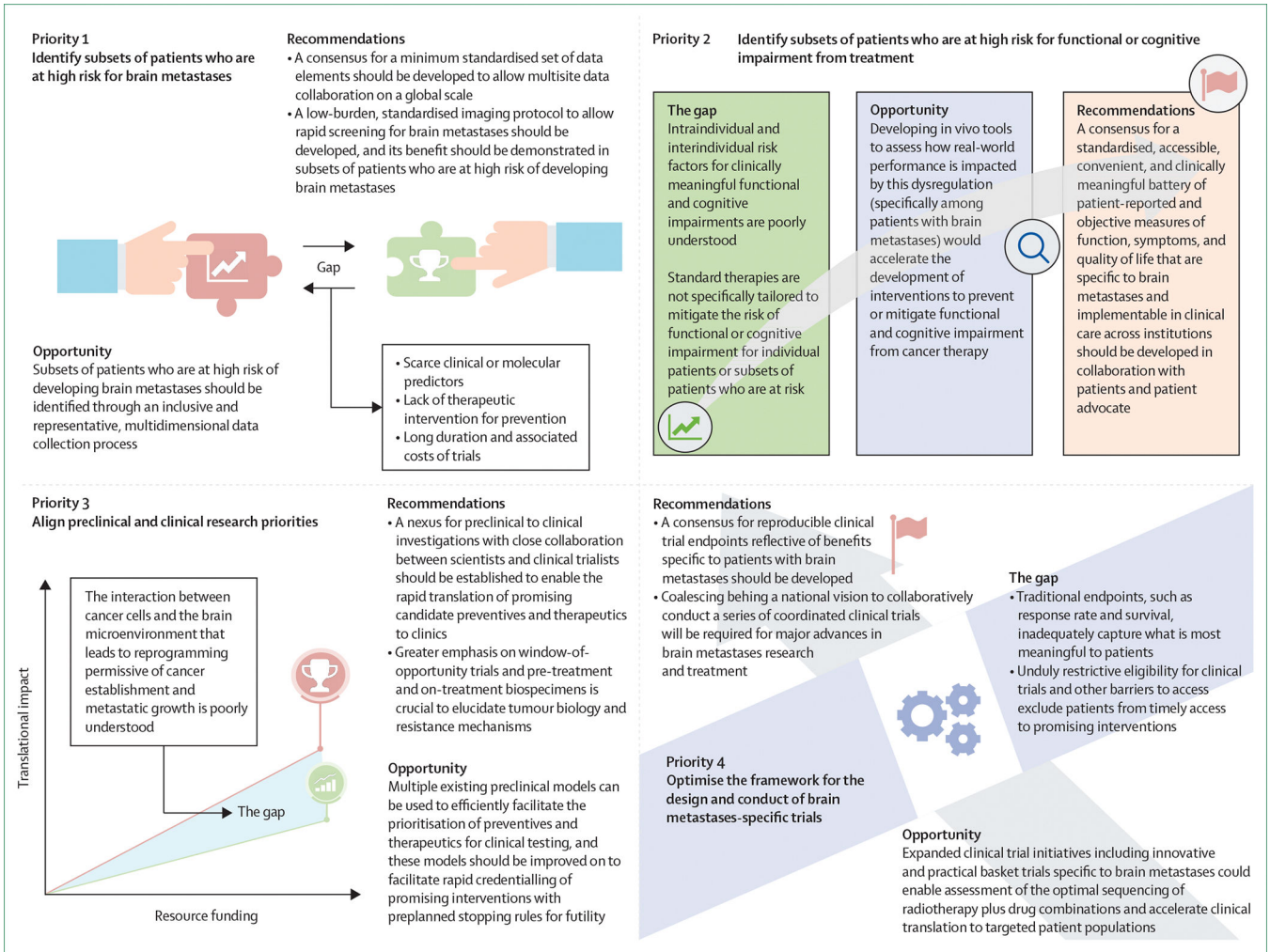
Priority 1
Identify subsets of patients who are at high risk for brain metastases

Recommendations
- A consensus for a minimum standardised set of data elements should be developed to allow multisite data collaboration on a global scale
- A low-burden, standardised imaging protocol to allow rapid screening for brain metastases should be developed, and its benefit should be demonstrated in subsets of patients who are at high risk of developing brain metastases

Gap

Opportunity
Subsets of patients who are at high risk of developing brain metastases should be identified through an inclusive and representative, multidimensional data collection process

- Scarce clinical or molecular predictors
- Lack of therapeutic intervention for prevention
- Long duration and associated costs of trials

Priority 2   **Identify subsets of patients who are at high risk for functional or cognitive impairment from treatment**

The gap
Intraindividual and interindividual risk factors for clinically meaningful functional and cognitive impairments are poorly understood

Standard therapies are not specifically tailored to mitigate the risk of functional or cognitive impairment for individual patients or subsets of patients who are at risk

Opportunity
Developing in vivo tools to assess how real-world performance is impacted by this dysregulation (specifically among patients with brain metastases) would accelerate the development of interventions to prevent or mitigate functional and cognitive impairment from cancer therapy

Recommendations
A consensus for a standardised, accessible, convenient, and clinically meaningful battery of patient-reported and objective measures of function, symptoms, and quality of life that are specific to brain metastases and implementable in clinical care across institutions should be developed in collaboration with patients and patient advocate

Priority 3
Align preclinical and clinical research priorities

The interaction between cancer cells and the brain microenvironment that leads to reprogramming permissive of cancer establishment and metastatic growth is poorly understood

Translational impact

The gap

Resource funding

Recommendations
- A nexus for preclinical to clinical investigations with close collaboration between scientists and clinical trialists should be established to enable the rapid translation of promising candidate preventives and therapeutics to clinics
- Greater emphasis on window-of-opportunity trials and pre-treatment and on-treatment biospecimens is crucial to elucidate tumour biology and resistance mechanisms

Opportunity
Multiple existing preclinical models can be used to efficiently facilitate the prioritisation of preventives and therapeutics for clinical testing, and these models should be improved on to facilitate rapid credentialling of promising interventions with preplanned stopping rules for futility

Recommendations
- A consensus for reproducible clinical trial endpoints reflective of benefits specific to patients with brain metastases should be developed
- Coalescing behing a national vision to collaboratively conduct a series of coordinated clinical trials will be required for major advances in brain metastases research and treatment

The gap
- Traditional endpoints, such as response rate and survival, inadequately capture what is most meaningful to patients
- Unduly restrictive eligibility for clinical trials and other barriers to access exclude patients from timely access to promising interventions

Priority 4
Optimise the framework for the design and conduct of brain metastases-specific trials

Opportunity
Expanded clinical trial initiatives including innovative and practical basket trials specific to brain metastases could enable assessment of the optimal sequencing of radiotherapy plus drug combinations and accelerate clinical translation to targeted patient populations

Figure 2:
Recommended priorities for collaborative research on brain metastases