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Personal View

Rethinking metastatic brain cancer as a CNS disease

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Summary

Advances in molecular biology, genetics, and epigenetics have refined our understanding of metastatic brain cancer and underscored the need for better classification and targeted approaches. The heterogeneity of brain metastases highlights the differences from their primary source of origin and contributes to therapeutic resistance. Before colonising the brain, tumour cells acquire specialised proficiencies that enable them to capitalise on the unique microenvironment of the brain. The tumour cells further orchestrate key adaptations to adjust to the brain microenvironment by manipulating the blood–brain barrier, evading immune surveillance, rewiring metabolic profiles, and reprogramming astrocytes. These adaptations facilitate tumour survival, growth, and treatment resistance. Recognising metastatic brain cancer

as a distinctive CNS disease, rather than an extension of the primary cancer, would support the development of rational approaches that target its molecular and genetic features and improve research funding in this area. Here, we delve into the distinct genetic and phenotypic characteristics of metastatic brain cancer, and reflect on how a change in the perception of this disease could accelerate the development of more effective therapies and drive continued progress in the field of neuro-oncology.

Introduction

Metastatic brain cancer, or brain metastases, is a major cause of cancer-related mortality. It is much more common than primary brain tumours and spreads mostly from primary malignancies in the lung, breast, and skin.[1] In the USA, more than 200 000 cases are diagnosed each year. Treatment includes surgery for large parenchymal brain metastases causing mass effect, stereotactic radiosurgery for limited brain metastases and local control in resected brain metastases, hippocampal avoidance whole-brain radiotherapy, upfront local therapy for symptomatic metastases, and palliative care.2, 3 Some subsets of patients with asymptomatic brain metastases might benefit from targeted therapies, cytotoxic agents, and immunotherapy.[3]

Symptomatology of brain metastases is directly linked to their location; they are often asymptomatic until their volume increases, compresses, or invades a crucial structure.[4] Clinically, they manifest with symptoms that either localise to the neuroanatomy involved or are consistent with increased intracranial pressure.[5] They lower quality of life and portend poor prognosis, with a median overall survival that ranges from 4 months to 21 months depending on a number of factors, including performance status and the status of extracranial disease.[6]

Brain metastases have traditionally been perceived as secondary manifestations originating from a primary source. However, the realm of cancer understanding has been profoundly affected by progress in molecular biology, genetics, and epigenetics, leading to a more intricate grasp of the nature of cancer itself. It is now acknowledged that cancers previously perceived as singular entities encompass a multitude of distinct cancer subtypes. This shift in perspective has been accompanied by a parallel surge in the exploration of molecular foundations, consequently fostering the emergence of targeted therapies. As a direct result, there has been a noticeable upswing in the use of tumour sequencing,[7] a practice that has now become an integral aspect of contemporary oncology research and clinical applications.

In this Personal View, we propose rethinking metastatic brain cancer as a distinctive CNS disorder. We emphasise genetic and phenotypic distinctions between brain metastatic and primary cancer cells. Additionally, we delve into tumour cell interactions within the CNS microenvironment, encompassing the immune milieu. An assessment of the efficacy of existing systemic therapies in the context of metastatic brain cancer follows. We acknowledge that our exploration of these topics is not exhaustive; rather, it is designed to stimulate discussion and encourage critical thinking about the status of metastatic brain cancer. Finally, we advocate increased funding and advancement of therapeutic strategies specific to brain metastases as unique CNS manifestations, differing from their primary origin.

Section snippets

Genetic and epigenetic profile

Brain metastases possess unique biological features that distinguish them from primary tumours. They exhibit branched evolution by accumulating genetic abnormalities, enhancing their ability to migrate to, survive in, and thrive in the CNS.[8] This ability supports Paget's century-old seed and soil hypothesis, which suggests that metastases preferentially grow in specific organs.[9] Early evidence from mouse melanoma studies showed organotropism, with melanoma cells favouring the lungs and ovaries …

Microenvironmental adaptations of metastatic brain cancer

Establishing a protumoral niche in the brain parenchyma requires metastatic brain cancer cells to adjust and interact with other cellular components that are present in the tumour microenvironment. These adaptations promote the survival and growth of cancer cells in the brain, while allowing them to evade the immune system and resist therapies. …

Metabolic alterations

Metastatic brain cancer cells develop new metabolic profiles to support their growth and survival. The upregulation of HIF-1 signalling regulates cellular responses to low oxygen concentrations, or hypoxia. Hypoxia is a common feature of solid tumours, including brain metastases, and HIF-1 helps cancer cells to adapt to this environment by promoting angiogenesis, metabolic reprogramming, and the evasion of immune surveillance.[52] Co-expression of HIF-1α with other proteins, such as TWIST, …

The neuronal niche

The brain has a cellular composition unique to the CNS where the majority of cancer cells that infiltrate the brain do not survive. Metastatic brain cancer cells undergo distinct physiological adaptations,[59] differing from those observed in extracranial sites, to endure and propagate within the brain parenchyma. Conversely, extracranial metastases exhibit similarities in cellular and metabolic traits with their primary tumors.59, 60

Tumoral–glial interactions in the setting of metastatic brain …

Targeting metastatic brain cancer

Improved screening techniques for metastatic brain cancer have led to the detection of more cases of brain metastases. Although many lesions require neurosurgical intervention to alleviate effects, less symptomatic intracranial lesions or lesions in inoperable locations have permitted

trials of radiotherapies, targeted therapies, and immunotherapies to help patients. …

Conclusions

A change in how we approach metastatic brain cancer is needed to better diagnose and treat this disease. Brain metastases are currently seen as secondary to primary extracranial cancers, which could hinder the understanding of their unique biology, such as tumour microenvironment changes, immune evasion, and specific molecular pathways. Viewing metastatic brain cancer as a CNS disease would enable focused research funding and the development of precise, targeted therapies for clinical use (…

Declaration of interests

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