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Review

The evolving clinical management of cerebral metastases

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Abstract

Concepts in the management of brain metastases are evolving. Until recently, brain metastases have been considered as a homogenous condition, managed with whole brain radiotherapy, surgical resection for large lesions and stereotactic radiosurgery for smaller lesions. Increasingly, specific systemic medical therapies are being used to treat brain metastases based on the primary site of disease. This disease specific management is causing a change in perspective about brain metastases and has led to improved survival for patients with primary disease subtypes amenable to tailored medical therapies. We review the recent literature to present evidence for the use of subtype specific medical therapies, advances in surgical resection techniques and stereotactic radiosurgery as the primary treatment modalities. The decline in use of whole brain radiotherapy as first line treatment is also discussed. Based on the recent literature, we propose a new management algorithm to reflect the progress in available options for tailoring disease specific treatments and support the change in paradigm to consider brain metastases as separate disease states based on the primary site of cancer rather than as a homogenous entity.

Keywords: Cerebral metastases; Neurosurgery; Stereotactic radiosurgery; Radiotherapy; Chemotherapy

Introduction

Malignancy can spread to the brain from numerous primary sites resulting in metastases being the most common intracranial tumour, occurring in 15–40% of cancer patients.[1] With the development of more aggressive treatments of primary tumours, resulting in prolonged survival, alongside the development of improved imaging techniques; the incidence of cerebral metastases is increasing.[1,2] The most common primary sites of spread to the CNS are lung, breast and melanoma, accounting for 67–80% of all brain metastases, and less commonly genitourinary and gastrointestinal tumours.[3] Table 1 shows the relative frequencies of primary cancers that develop brain metastases.[3–6]

The majority of tumours metastasize to the brain via haematogenous spread. This results in tumours localising to watershed areas of arterial circulation within the brain at the grey-white matter junction; hence 90% of intracranial metastases arise above the tentorium.[1,7] The brain has previously been seen as a sanctuary site in terms of metastatic disease. This was thought to be due to the presence of the blood brain barrier (BBB).[1] This epithelial layer, when intact, limits penetration of systemic therapies into the brain. Neoangiogenesis within tumours results in new blood vessels that lack a competent BBB permitting some tumour penetration by modern chemotherapeutic agents.[8]

Location and number of metastases is dependent on disease biology; lung cancer and melanoma have a tendency to present with multiple lesions, whereas breast and renal cancers often present with single lesions.[8,9] Location also impacts presentation, median time from initial diagnosis to presentation of the intracranial disease ranging from 3 to 12 months.[6] The majority of brain metastases develop in the presence of a known primary cancer.[9] If large enough to be symptomatic common signs and symptoms of metastatic

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Table 1
Incidence of cerebral metastases by primary site.

Primary site	Proportion of all cerebral metastases by primary site (%)	Incidence of primary site cancers with cerebral metastases (%)
Lung	41–56	16.3–19.9
NSCLC	24–44	
SCLC	6–15	
Breast	13–30	5.0–5.1
Melanoma	6–11	6.8–7.4
Renal	2–6	6.5–9.8
GI	6–9	1.2–1.8
Unknown	2–14	

disease includes headaches, focal neurological deficits, seizures or abnormalities of higher mental functioning.[10]

Brain metastases historically have been regarded to have a very poor prognosis. Median survival, in unstratified cohorts, is quoted to be in the region of 1–2 months without treatment, dependent on number of lesions and primary site.[11–13] Progressive neurological deterioration, both cognitive and physical, impact on quality of life and poorer performance status; limiting options for both surgical and systemic therapies. Prognostic factors in patients with intracranial metastases vary by diagnosis but include performance status, age, control of primary tumour, extent of extracranial metastases, and volume of intracranial lesions.[14,15] Given treatment decisions rely on these factors, diagnosis specific prognostic assessments, such as the diagnosis specific graded prognostic assessment[16] exist to estimate survival (Table 2)[17] and aid management selection in this heterogeneous group of patients.

With improved survival from targeted systemic therapies and the development of surgical techniques alongside newer treatment modalities such as stereotactic radiosurgery attitudes towards the management cerebral metastases is changing. Decision making in such a heterogeneous population remains a therapeutic challenge. Here we review the current evidence in the evolving management of metastatic intracranial tumours.

Diagnosis

The majority of patients with brain metastases will develop neurological symptoms at some stage in their illness.[18] In most patients the brain metastases develop after the primary tumour is diagnosed.[10] Detection and imaging of metastases is important not only in initial staging of malignancy but also in guiding treatment strategies and measuring treatment response.

First line imaging for both groups of patients is usually non-enhanced CT. It is well tolerated and easily accessible. Complications such as haemorrhage, mass effect and hydrocephalus can be ascertained. Following this contrast CT or MRI are indicated to further evaluate any lesion identified. MRI is more sensitive than CT at identifying cerebral metastases and is the imaging modality of choice. Gadolinium contrast is used to detect small metastases not apparent on non-contrast imaging.[19]

For patients where the presentation is neurological in nature and the primary tumour is unknown imaging studies provide a means of identifying potential primary sites. In a majority of cases a CT chest, abdomen and pelvis is indicated and the yield for detecting a primary tumour is high, identifying a primary tumour in 30–35% of cases.[20] PET and PET/CT have also been suggested as possible accurate and cost-effective method of detecting an unknown primary[20] but remain challenging to use in mainstream clinical practice.[21]

Serum tumour markers rarely offer diagnostic value in those with an undiagnosed primary as these patients often have nonspecific over expression[22]; a caveat to this is intracranial germ cell tumours in which alpha-fetoprotein and human chorionic gonadotropin can aid diagnosis and be used to assess treatment response.[23]

An evolving approach to non-invasive diagnosis and monitoring tool is circulating tumour DNA, this method allows for genomic characterisation of tumours. Although it has shown promise in the diagnosis and monitoring of other tumours cell-free circulating DNA shows low levels in the serum of those with intracranial tumours. Higher levels of circulating DNA can be seen in the CSF of those with metastatic brain tumours and is currently more representative of brain tumour genomic alterations. In the future these may provide an opportunity for 'liquid diagnosis' and offer a potential strategy for monitoring disease progression.[24–26]

More specific techniques such as endoscopy are reserved for when signs and symptoms and clinical findings reveal a possible primary site.[20]

Management

Surgery

Compared with primary intracranial tumours such as gliomas, brain metastases have a more distinct boundary and often a capsule separating them from the surrounding brain parenchyma. This allows for gross total surgical resection in selected patients using microsurgical techniques to dissect the tumour free from adjacent parenchyma. Since the first RCT to demonstrate the survival advantage of adding surgical resection of a solitary metastases to whole brain radiotherapy by Patchell et al. (1990),[27] surgery has consistently been used in the multimodality treatment of brain metastases. Surgery is especially important in patients with large (>3 cm diameter) lesions causing mass effect/neurological symptoms and in whom the underlying primary diagnosis is unknown. Table 3[27–33] summarizes the results of the prospective RCTs of surgery for brain metastases. It is important to note that these trials comprised a heterogeneous mix of metastases from different primary sites.

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