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# BRAIN METASTASES: NEW TRENDS IN TREATMENT INDIVIDUALISATION

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## ABSTRACT
**Background:** Brain metastases (BM) are the most common neurological manifestation of cancer and a key cause of morbidity. In 2020, there were just under 150,000 cancer cases in Australia, of whom over 20% will develop BM. BM are increasing in frequency as a result of an ageing population, more sensitive methods of detection and a longer cancer patient life expectancy. Cancers of origin of BM include lung cancer, melanoma, breast, renal and colorectal cancers. Different molecular subtypes of cancers effects BM incidence, as well as guiding treatment selection. **Objectives:** Here, the clinical features and modern management of brain metastases, with an emphasis on treatment individualisation, are described. **Discussion:** Treatment of BM has matured from a one-size-fits-all approach, to individualised treatment. Steroids are often used initially. Definitive treatment options include surgery, radiotherapy (including stereotactic radiosurgery) and systemic therapies such as chemotherapy, targeted- and immuno-therapies.

**KEYWORDS:** brain; cerebral; metastases; surgery; radiotherapy.

## INTRODUCTION
Brain metastases (BM) are the commonest neurological manifestation of cancer and a major cause of cancer morbidity. In 2020, there were just under 150,000 cases of cancer in Australia.[1] Of these, over 20% will develop BM (>30,000 patients).[2] Their incidence is increasing due to improved cancer survival, earlier and more sensitive detection and an ageing population.

The incidence of BM depends on primary tumour type, in order: lung cancer, melanoma, renal, breast and colorectal cancers.[3] Patients with lung cancer and melanoma are most likely to have BM at diagnosis.[4] Molecular subtypes also influence BM incidence.

The most common sites for BM are the cerebral hemispheres (80%) and cerebellum (15%).[5] Most hemispheric lesions occur at the grey-white matter interface. The major differential diagnoses of BM include primary tumours and vascular / inflammatory lesions.

Prognosis is dependent on the site and number of lesions, performance status, age and the activity and extent of extracranial disease. Despite advances in surgery, radiotherapy and systemic therapies, prognosis remains poor, with median survivals of a few months to around a year.[4,6] Some subsets of patients do much better when selected for appropriate molecular therapies, where survival can be multiple years (eg, ref 7). Patients with BM are now considered heterogeneous, requiring treatment individualisation.

BM can manifest pleiotropic clinical features (Table 1). Some cancers may present with BM alone or synchronously with systemic disease (mostly lung cancer and melanoma). Usually a BM presentation follows within a couple of years of a new cancer diagnosis. A prior cancer diagnosis with new headaches or neurological symptoms or signs (Table 1) is suspicious for BM. The risk of seizures is approximately 20-25% and increases according to the number of BM.[8]; anticonvulsants should not be used routinely in the absence of seizure activity.[9] Focal weakness occurs not uncommonly and is usually due to a lesion in the opposite cerebral hemisphere or long tracts.

## RESULTS AND DISCUSSION
### Symptomatic treatments
In patients of poor performance status, best supportive care is often appropriate. The main symptomatic treatment for BM is steroids. Steroids (dexamethasone), usually improve cerebral oedema for weeks. Typical dosing is 16mg/day in divided doses, weaning to the lowest dose required to control symptoms.[10] This minimises the risk of steroid-related morbidities such as weight gain, poor glycaemic control, impaired wound healing, proximal myopathy and mood changes. The

efficacy of systemic immune checkpoint inhibitor therapies can be reduced by steroids.[11]

**Local therapies: surgery**

In fit BM patients (eg, Karnofsky Performance Score >=70)[12], surgery is usually carried out where there is a single large BM. Surgery can confirm the histopathological diagnosis, provide material for molecular analysis and rapidly relieve mass effect. Up to three BMs can be effectively treated with surgical resection.[13] However, even in contemporary series, surgery alone yields insufficient local BM control. Hence, resection of BM has often been followed by adjuvant RT. Two randomized trials of solitary BM indicate that surgery, when combined with adjuvant RT, prolongs survival.[14,15]

Tissue obtained from surgical resection can be used for molecular analysis to guide the selection of targeted therapies. It is important to test the BM itself as opposed to just the primary tumour or extracranial metastases, because major molecular differences may exist between the three ('molecular divergence').[16] To obtain tissue, minimally invasive surgery is increasingly used.

**Local therapies: WBRT**

Whole brain radiotherapy (WBRT) has been the cornerstone of treatment for BM for decades. It is a simple and cost-effective treatment, can extend survival and gives good palliation and symptom control.[5] Two randomised trials showed that WBRT increased control rates for BM.[17,18]

Toxicity of WBRT can be significant, with impairment of both neurocognitive function (NCF), and quality of life (QoL).[19-21] *Pharmacological* and *physical* approaches have been employed in an attempt to reduce the toxicity of WBRT. Memantine has neuroprotective properties and maintains NMDA receptors in a functional open state. For optimal neuronal health, a high ratio of NMDA receptors to GABA receptors is crucial. A Phase 3 trial randomised patients with BM receiving WBRT to memantine or placebo. The primary endpoint was memory preservation. There was a (non-significant) effect favouring the memantine arm (P=0.059). That arm also had better performance in verbal fluency and executive function. This study supports memantine use in WBRT patients with a reasonable life expectancy.

The hippocampus subserves memory and cognition function. Hippocampal neural stem cells are extremely sensitive to ionising radiation. Advanced radiotherapy techniques can be used to minimise hippocampal dose during WBRT.[22] (unpublished data, MJM). A large phase 2 study used hippocampal avoidance in WBRT delivered to BM patients.[23] Compared to historical controls, cognitive decline was statistically less. A randomised phase 3 trial is proceeding.

**Local therapies: stereotactic radiation**

Because of its toxicity, there has been a reduction in the use of WBRT for the treatment of patients with small numbers of BMs (eg, 3 or less)(Figure 1). SRS is a form of focussed RT, where multiple non-coplanar beams criss-cross the BM target, with extremely sharp dose gradients. To increase SRS tolerance, fractionated regimens are often employed for BM within or adjacent to especially sensitive brain regions (eg, brainstem)(Figure 2). SRS alone has a significant distant cerebral failure rate. Multiple randomised trials comparing the efficacy and safety of SRS alone vs SRS + WBRT demonstrated, in the WBRT arms, a decline in NCF and QoL (eg, refs 19,20,24). For these reasons, SRS alone has become standard-of-care for fit patients, with 3 or fewer BM. This is a major change in the last few years. In the circumstance of *resected* BM, where historically, WBRT has been used after surgery, BM cavity SRS reduces neurocognitive defects while improving local control. Two randomised studies support this approach as standard of care after resection of 1-3 BMs.[25,26] Ongoing SRS studies are also examining integration of SRS with targeted systemic therapies that cross, and are retained within, the blood-brain-barrier and/or which generate an immune response.

**Systemic therapies: chemotherapy**

Chemotherapy has been unsuccessful in BM management. The tight blood-brain barrier (BBB), blood-tumour barrier (BTB) and the presence of effective CNS drug efflux pumps (such as p-glycoprotein) are impediments to achieving effective intra-BM drug concentrations. Limited responses to chemotherapy do occur. For NSCLC and breast cancer BM patients, responses of the order of 10-15% in pretreated patients, are recorded.[27] However, chemotherapy is of little value in patients with melanoma BM.[27]

**Systemic therapies: targeted therapies**

Many molecular changes have now been characterised in BMs. Some of these changes are 'druggable targets', ie. drugs are available that mitigate against the molecular change. In cases where the molecular change is a driver of the carcinogenesis process (eg, 'molecular driver mutation'), there can be a dramatic antiproliferative effect. One issue with targeted drugs in BM therapy to date has been that although response rates are increasing, they tend to be short-lived.

First generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been used in NSCLC BM patients with EGFR mutations. They had response rates of 50-70%, associated with overall survivals of 15-22 months.[28] A third-generation TKI, Osimertinib, has better brain penetration and longer response durability.[29] Four to 5% of NSCLC BM patients also harbour ALK rearrangement in their tumours.[30] A number of ALK-inhibitor TKIs exist, including the later generation ALK-inhibitor

ceritinib. In a randomised trial, this drug had better activity that chemotherapy for BM.[31]

Trastuzumab has been a prototypical anti-HER2 therapy for systemic HER2+ breast cancer, but has minimal BBB penetration.[32] For HER2+ breast cancer BM patients, the TKI lapatinib has been utilised as dual therapy with capecitabine; in phase 2 trials, response rates of 20-66% are reported.[32,33]

For melanoma patients with BM, the BRAF inhibitors, vemurafenib and dabrafenib have cerebral response rates of 20-38%.[34,35] Targeted agent combination approaches have also been utilised in BM patients with melanoma: the mitogen-activated protein kinase (MAPK)- inhibitor, trametinib, combined with dabrafenib, had responses as high as 55%.[36] However, as seen in other tumour types, TKI responses are not durable, typically <6 months (summarised in ref 27).

**Systemic therapies: immunotherapy**

Successful immunotherapies are directed against various cell surface antigens. Some targets and agents are: PD-1 (eg, pembrolizumab and nivolumab); CTLA4 (eg, ipilumumab); anti-PD-L1 (eg, atezolizumab). Response rates to immunotherapies are considerably lower for those patients on steroids and should be considered separately for melanoma and non-melanoma tumours, since the former have higher response rates. With a two-drug approach, intracranial response rates have been shown to be over 55%, with 70% 2-year survivals[37], a marked improvement in BM outcomes since before immunotherapies were available.

**Table 1: Symptoms and signs of brain metastases.**

| **Symptoms** |
|---|
| Headache, nausea, vomiting |
| Behavioural and mental disturbance |
| Progressive focal weakness of sensory disturbance |
| Unstable gait |
| Seizures |
| |
| **Signs** |
| Progressive focal weakness or hemiparesis |
| Sensory disturbance |
| Unstable gait |
| Visual field loss |
| Papilloedema |
| Seizures |
| Cognitive disturbance |

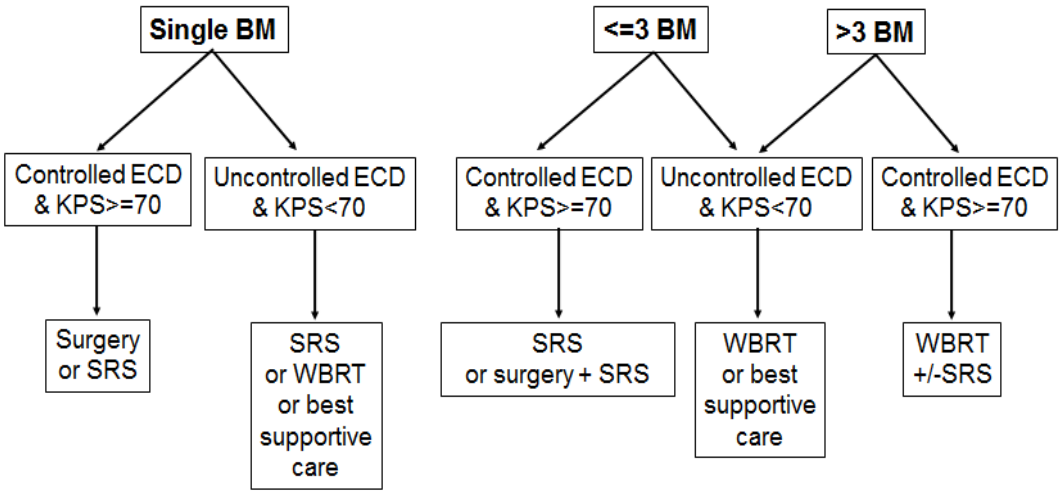


**Figure 1: Algorithm for BM treatment selection, depending on the number of BM. In the case of a single accessible BM in a fit patient, surgery is indicated, especially if there is mass effect or the BM is large, or histology is needed. As an alternative, SRS, either by itself or to the surgical bed, can be utilised. In patients with uncontrolled ECD or poor performance status, the options comprise SRS, WBRT or best supportive care. The latter is particularly relevant to the situation of a patient with a poor performance status (eg, KPS<70). For the situation of up to 3 BM in patients with controlled ECD and who are of an appropriately good performance status, SRS is the main option, but sometimes surgery is used, depending on the accessibility of the BM. If surgery is used it is usually followed up by cavity SRS. If the patient's performance status is low or ECD uncontrolled, best supportive care or WBRT is used. In patients with >3 BM, the cornerstone of treatment is WBRT. SRS in this patient group is currently being investigated in randomised trials. ECD: extracranial disease; KPS: Karnofsky performance score; WBRT: whole brain radiotherapy.SRS: stereotactic radiosurgery.**

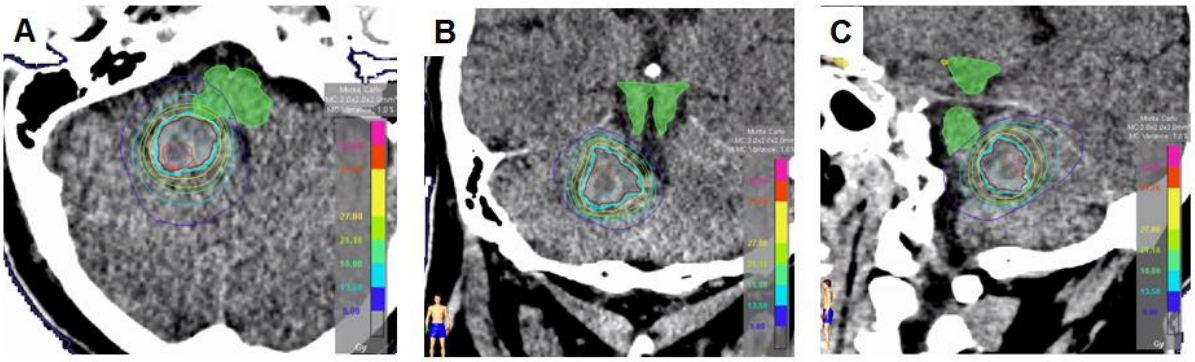


**Figure 2: Right cerebellar hemisphere BM. Example of SRS treatment. Radiation dose lines encompass the planning tumour volume (PTV). Because of its proximity to the brainstem (green shading), the lesion in this patient received fractionated SRS (ie, SRT).**

## CONCLUSION AND FUTURE

Despite improvements in surgery, radiotherapy and systemic therapies, the prognosis for BM remains guarded. Improved understanding of the biology of BM, including the brain- and BM- microenvironment[38] (reviewed in ref[39]), the blood-brain barrier and blood-tumour barrier[40] will aid the development of novel diagnostic and therapeutic approaches to BM. Minimally invasive surgery will be increasingly used for obtaining tissue for molecular BM classification. Integration of such knowledge into prognostic models should improve patient selection for precision medicine approaches to BM patients, reduce the toxicity of therapy and hopefully extend the current largely poor prognosis for this disease. Improved integration and sequencing of focal BM therapies with targeted and immunotherapies should also improve the therapeutic ratio.

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