Brain metastases

RADIATION ONCOLOGY

The changing management of brain metastases requires a multidisciplinary approach.

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Incidence, presenting symptoms, prognosis

BRAIN metastases occur in up to one in five patients with cancer, with solid malignancies originating outside of the central nervous system.

Lung, breast, melanoma, renal and colorectal primary tumours are most commonly involved. Patients may present with symptoms relating to raised intracranial pressure (such as early morning headaches and vomiting) or focal, location-dependent sequelae due to mass effect, oedema, bleeding or seizure activity.

Asymptomatic disease is increasingly common due to increased rates of screening MRI, which has greater resolution than CT for detecting small lesions.

Survival relates to the number and location of brain metastases, age, functional status, primary tumour type and burden of disease elsewhere.

Prognostic tools that incorporate these factors can be used to inform clinicians and patients in shared decision-making.[1]

For example, the predicted median survival for a fit, 62-year-old man with non-small cell lung cancer and a solitary brain metastasis is over nine months, compared with only three months for a similar patient with multiple brain metastases and uncontrolled extracranial disease. Clearly the treatment priorities for these two patients will differ.

Initial management

At diagnosis, patients with symptomatic brain metastases should commence a corticosteroid to reduce the effect of peritumour oedema. A common regimen is oral dexamethasone at 4-8mg once or twice daily, depending on severity.

A proton pump inhibitor should also be prescribed to lessen the risk of gastric irritation.

Late afternoon or evening steroid doses impair sleep quality and thus morning doses are preferred. Monitoring for steroid-induced hyperglycaemia is recommended in at-risk individuals, especially including those with established diabetes.

Patients should be advised not to drive a motor vehicle, which is mandated by law. GPs can access further guidance regarding assessing fitness to drive online from Austroads and the Neurosurgical Society of Australasia.[2,3]

Antiepileptic medication is indicated in those with seizure activity. Levetiracetam or valproic acid are preferred agents, based on efficacy, tolerability and fewer interactions with other drugs and chemotherapy.

Subsequent management

In recent years, the management of brain metastases has changed because new therapeutic options are available. Importantly, patients with advanced malignancy have competing risks for survival — only one in four patients have a neurological death. Therefore, treatment recommendations are best made within the context of a specialist multidisciplinary team (comprising neuroradiologist, neurosurgeon, radiation oncologist, medical oncologist, palliative care physician, nursing and allied health professionals, with the GP being notified of the consensus treatment recommendation).

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Adjustments to ongoing systemic therapy may be required because concurrent use during brain radiotherapy might lead to increased toxicity.

Whole-brain radiotherapy

This has been a standard treatment for many patients for decades. The intent is to improve symptoms and neurological signs by inducing regression or restraining growth of metastases.

The entire brain is treated using two large lateral radiation fields (figure 1). Whole brain radiotherapy is usually delivered as a course of daily treatments over one or two weeks. However, when local therapy is possible, it is now employed up-front in relatively few patients.

Local therapies

1. Stereotactic radiosurgery

Stereotactic radiosurgery is a non-invasive, outpatient alternative to neurosurgery. It allows the precise delivery of a single high dose of radiation to the tumour to maximise local control and minimise dose to the surrounding normal tissues (see figure 2).

2. Stereotactic radiotherapy

Stereotactic radiotherapy is an alternative technique that also delivers a biologically high cumulative dose, spreading it over 2-5 treatments (known as fractions).

The efficacy of stereotactic radiosurgery and stereotactic radiotherapy is probably comparable in some instances, although high-quality data are lacking. Importantly, access to these modern technologies is improving across Australia, but there is still progress to be made compared with availability in other countries.

Randomised trials have

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clarified optimal treatment combinations in patients with brain metastases. The addition of surgery or stereotactic radiosurgery to whole brain radiotherapy improves outcomes in patients with limited (four or fewer) brain metastases, and also improves survival in those with a single lesion.[4,5,6]

Surgery and stereotactic radiosurgery are generally considered equally effective, although one may be favoured over the other in certain situations. Surgery may be preferred for a larger lesion (more than 3-4cm in diameter) or when histopathology is required.

However, this type of radiosurgery may be recommended to treat multiple lesions or those located in areas of the brain that are surgically inaccessible.

Stereotactic radiosurgery may enable the treatment of inoperable lesions too large for whole brain radiotherapy, based on the theoretical advantage that it reduces risk of injury to normal tissues by treating over multiple, rather than a single, fractions.

Conversely, giving whole brain radiotherapy after surgery or stereotactic radiosurgery improves control of CNS disease, but does not improve survival or duration of functional independence.[7,8]

In trials that have evaluated this further, patients not receiving whole brain radiotherapy reported superior memory function and quality of life overall, despite experiencing greater rates of recurrent disease.[9,10]

For these reasons, stereotactic radiosurgery without whole brain radiotherapy is a common approach initially, but close monitoring with serial MRI is required to identify recurrences at an early stage.

Salvage treatment may include local therapies and/or whole brain radiotherapy, and will depend on the clinical status of the patient at that stage.

Lastly, after surgery, stereotactic radiosurgery or stereotactic radiotherapy to the resection cavity (avoiding dose to the remainder of the brain) may be considered as an alternative to observation when whole brain radiotherapy is withheld. This is based on the observation that the risk of recurrence is greatest in and around the surgical cavity, rather than elsewhere in the brain.

Figure 1

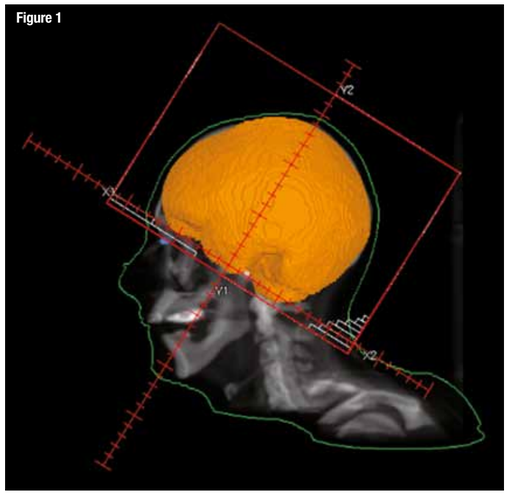

Figure 2

Figure 1. Lateral view demonstrating whole brain radiotherapy field arrangement. The brain (orange) is included in its entirety within the red rectangle that defines the field edges. Shielding is used inferiorly to exclude the lenses (blue) and reduce the risk of cataracts. This image has been acquired with the patient lying supine.

Figure 2. Stereotactic radiosurgery treatment plan in axial (top pane), sagittal (left) and coronal (right) planes. The patient has previously undergone surgery for a right occipital lesion (*) and now represents with a new metastasis in the left thalamus. Stereotactic radiosurgery delivers 18Gy (yellow line) to the target and dose beyond this drops quickly, as illustrated by 12Gy (green) and 6Gy (blue) isodose lines.

Side effects of brain radiotherapy

Stereotactic radiosurgery and stereotactic radiotherapy are generally well -tolerated treatments. Side effects can occur, due to radiotherapy-induced increasing peritumour oedema in the days after treatment. Typically, a short course of corticosteroids is prescribed by the treating specialist to minimise this effect.

Radionecrosis is characterised by an intense inflammatory response to radiotherapy-induced injury that relates to the total dose and volume treated. It occurs in about 5% of patients many months after treatment, and can be difficult to distinguish from progression clinically and/or radiologically.

Initial management is with corticosteroids and surgery is considered in refractory cases.

Side effects from whole brain radiotherapy differ to those after stereotactic radiosurgery and or stereotactic radiotherapy.

Fatigue and alopecia of the scalp are common side effects towards the end of treatment and for a number of weeks after.

Concerns regarding potential adverse late effects on memory function must be balanced against the risk of uncontrolled progressive CNS disease. For this reason, whole brain radiotherapy remains a valuable treatment option when local therapy up-front, or at recurrence, is not appropriate or possible.

Hippocampal-sparing whole brain radiotherapy is an advanced radiotherapy technique that limits dose to the areas of the temporal lobes suspected to be associated with radiotherapy-related memory impairment. Early data are encouraging, but further work is needed to assess whether the increased resources required are justified.[11]

As a possible alternative, recently the drugs memantine and donepezil have been shown to yield small, but statistically significant, gains in some aspects of cognitive function after this radiotherapy.[12,13]

So far, their use has not been widely adopted, but might be useful to consider on an individualised basis.

Targeted agents

Generally, chemotherapy is not useful to treat brain metastases. A number of targeted agents are emerging in molecular subtypes of lung, breast, melanoma and renal cancers that can penetrate the blood–brain barrier and may represent new treatment options.

Work is ongoing to assess efficacy and optimal sequencing with existing treatments.

Currently, potentially effective agents are sometimes used to treat multiple, low-volume, asymptomatic brain metastases, thus reserving stereotactic radiosurgery and/or whole brain radiotherapy for progression.

Summary

The management of brain metastases is changing and multidisciplinary expertise is essential to individualise patient care. Treatments, including surgery, stereotactic radiosurgery, stereotactic radiotherapy and whole brain radiotherapy, all play key roles in appropriately selected individuals.

For patients with a limited number of metastases and a reasonable functional status, stereotactic radiosurgery or surgery is a common approach, as long as surveillance MRI is possible to detect recurrent disease at an early stage.

The utility of targeted therapies is growing. Drug and technological developments may help to maximise the quality of survival in some patients. ●

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References

1. *Journal of Clinical Oncology* 2012; 30:419-25.
2. Austroads. Assessing Fitness to Drive. See: bit.ly/1OqUktD
3. Neurosurgical Society of Australia driving guide for clinicians. See: bit.ly/1LsnPta
4. *New England Journal of Medicine* 1990; 322:494-500.
5. *International Journal of Radiation Oncology Biology Physics* 1994; 29:711-17.
6. *Lancet* 2004; 363:1665-72.
7. *Journal of the American Medical Association* 2006; 295:2483-91.
8. *Journal of Clinical Oncology* 2011; 29:134-41.
9. *Journal of Clinical Oncology* 2013; 31:65-72.
10. *Journal of Cliniclal Oncology* 2015; 33:suppl; abstr LBA4.
11. *Journal of Clinical Oncology* 2014; 32:3810-16.
12. *Neuro-Oncology* 2013; 15:1429-37.
13. *Journal of Clinical Oncology* 2015; 33:1653-59.