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Background

This is a heterogeneous population of patients with diverse underlying histologies, differences in disease burden outside the central nervous system (CNS) and differing systemic therapy options. Prognostic scores including the disease-specific graded prognostic assessment (dsGPA) may assist in predicting prognosis but are often not in routine clinical use.[1] The management of these patients continues to be variable and individualised and should be coordinated within multidisciplinary teams.

Prognosis from brain metastases has improved in recent years, likely driven by advances in systemic therapy, but continues to be poor for a subgroup of patients.[1] Three important criteria when deciding on management of patients with brain metastases are:

- Prognosis of at least 6 months
- Controlled or treatable extracranial disease
- Karnofsky performance status of at least 70.

Patients who fail to meet these criteria have worse outcomes following irradiation of their intracranial metastatic disease and so may not benefit from treatment. Age may not be a significant prognostic indicator, and older patients may benefit from aggressive treatment of their brain metastases.[2]

For the purposes of this guidance, stereotactic radiosurgery (SRS) is considered equivalent across the commonly used stereotactic platforms of linear accelerators, Gamma Knife and CyberKnife. Though studies exist describing dosimetric differences between these platforms, there is no definitive evidence of a difference in clinical outcomes. The use of systemic therapies with intracranial penetrance is increasing, but their role in the place of, or in conjunction with, radiation therapy is yet to be fully established[3] and is outside the scope of this document.

SRS for solitary metastases

Radiation therapy of brain metastases has evolved from whole-brain radiotherapy (WBRT), to SRS with adjuvant WBRT, to SRS alone. Studies have shown SRS alone results in similar overall survival rates and so adjuvant WBRT is typically omitted to avoid associated neurocognitive side-effects.[4] Lesions larger than 4 cm in diameter are unlikely to be suitable for SRS due to an unacceptable dose of irradiated normal brain tissue and subsequent risk of radionecrosis, although the latest ASTRO guidelines recommend a maximum diameter of no more than 6 cm.[5] The recently published HyTEC report found that metastases treated in a single fraction with a normal tissue volume (excluding gross tumour volume) receiving more than 12 Gy (V12 Gy) to 5 cm^3, 10 cm^3 or >15 cm^3 resulted in radionecrosis rates of approximately 10%, 15% and 20% respectively.[6] Therefore, lesions larger than 2–3 cm in diameter, lesions in close proximity to a critical organ at risk or lesions where the V12 Gy is greater than 10 cm^3 should be considered for fractionated or staged radiosurgery. One study found improved local control and less radiation necrosis for metastases larger than 2 cm in diameter when treated with a fractionated regimen of 27 Gy in 3 daily fractions compared with a single fraction.[7]

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30 Gy in 5 daily fractions is another commonly used hypofractionated regimen,[8,9] while 35 Gy in 5 daily fractions has also been prospectively evaluated and is sometimes used.[10] Staged radiosurgery is an adaptive approach where large lesions are reimaged, planned and treated at 2- or 3-weekly intervals and is used in place of fractionation at some centres.[11]

SRS for multiple metastases

Early trials of SRS in brain metastases included patients with up to 3 lesions.[12] Prospective, randomised data now exist to support the use of SRS alone for up to 4 metastases[13] and prospective, observational data support the use of SRS alone for up to 10 metastases.[14] The use of SRS alone for more than 10 metastases is controversial and not supported by international guidelines due to a lack of evidence.[5] Trials are currently recruiting to compare overall survival outcomes for patients including those with more than 10 metastases treated with SRS versus hippocampal-sparing WBRT, and results are awaited (trial identifiers NCT03550391, NCT01592968, NCT03075072 and NCT03775330). However NHS clinical commissioning criteria for the use of SRS in brain metastases do not specify a maximum number and instead specify a total intracranial disease volume limit of 20 cm^3, [15] while the European Association of Neuro-Oncology (EANO) recommends a stricter limit of 15 cm^3. [16]

Recommendations

Single-fraction SRS:

Lesion diameter:

- <20 mm – 21–24 Gy single dose (Grade B)
- 21–30 mm – 18 Gy single dose (Grade B)
- 31–40 mm – 15 Gy single dose (Grade B) (consider hypofractionated SRS)

Hypofractionated SRS:

- 24–27 Gy in 3 daily fractions (Grade B)
- 30 Gy in 5 daily fractions (Grade B)
- 35 Gy in 5 daily fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[17]

WBRT for single or multiple metastases

Patients not suitable for SRS can be considered for WBRT, although certain patient subgroups may not benefit. The Medical Research Council (MRC) QUARTZ trial found those with non-small cell lung cancer (NSCLC) and a limited prognosis had no overall survival or quality-of-life benefit with WBRT over best supportive care.[18] Several randomised trials have compared different radiotherapy regimens for patients with multiple cerebral metastases. Most have used 30 Gy in 10 fractions as the control arm and have compared this regimen with either higher or lower doses.[19–22] Only one small study of 70 patients has compared the 6-month survival rate after 30 Gy in 10 fractions with that after 20 Gy in 5 fractions, and this found no significant difference.[23] A Radiation Therapy Oncology Group (RTOG) study reported in

1980 compared three regimens: 40 Gy in 15 fractions, 30 Gy in 10 fractions and 20 Gy in 5 fractions.[24] The median survival in all three groups was between 3.2 months and 3.5 months ($p>0.05$). There is, therefore, no clear evidence that 20 Gy in 5 fractions is inferior to, or better than, 30 Gy in 10 fractions (Level 1b). No improvement in survival has been shown when dose is increased beyond 30 Gy in 10 fractions (Level 1b).

Methods to reduce the risk of neurocognitive decline associated with WBRT include hippocampal sparing, provided no lesion is within close proximity of the hippocampus.[25] A randomised controlled study of the concurrent use of the glutamate receptor antagonist memantine did not reach the primary endpoint of reduced decline in cognitive function and so has not received approval from the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[26]

Recommendations

Whole-brain radiotherapy ± hippocampal sparing:

- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 20 Gy in 5 fractions over 1 week (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[17]

Postoperative radiotherapy

Evidence from two randomised trials suggests an overall survival benefit from adding surgery to WBRT for patients of good performance status with a solitary metastasis (Level 1a).[27,28] Though a third trial did not show an overall survival benefit, this may have been due to the high proportion of poor-performance status patients included.[29] Surgical resection without adjuvant WBRT carries twice the risk of cavity recurrence.[30] SRS to the surgical cavity has shown similar overall survival rates and less neurocognitive decline than adjuvant WBRT and so is generally preferred.[31] Preoperative SRS looks to mitigate against the issues of difficulty contouring the surgical cavity and relatively high subsequent focal leptomeningeal rates, and trials have opened in some centres internationally to compare outcomes with adjuvant SRS. Results from these trials are awaited (trial identifiers NCT03741673, NCT04503772).

Currently, SRS to the surgical cavity following complete resection of cerebral metastases is not recommended by NHS England due to a lack of evidence of improvement in overall survival compared with observation alone. However, where there is evidence of residual or recurrent disease, SRS should be considered.

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Recommendations

Adjuvant SRS, adapted from various studies:[5,32,33]

Cavity volume (cm3)	Equivalent sphere diameter (cm)	Single-fraction SRS dose (Gy)	Level of evidence
<4.2	<2.0	20 Gy	B
≥4.2 to <8.0	≥2.0 to <2.5	18 Gy	B
≥8.0 to <14.4	≥2.5 to <3	17 Gy	B
≥14.4 to <20	≥3 to <3.5	15 Gy (or fractionated SRS)	C
≥20 to <30	≥3.5 to <4	For fractionated SRS	C

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[17]

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