19.
Brain metastases

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. As such, it is helpful to classify patients according to a simplified system. The recursive partitioning analysis (RPA) based system of the Radiation Therapy Oncology Group (RTOG) is simple and robust.[1]

Patients can be divided into three groups according to:

- Karnofsky Performance Status (KPS) (at least 70)
- Control of the primary tumour
- Brain as the only site of disease.

Patients have the worst outlook in group 3 with a KPS <70.[2] This system has been validated on a separate data set. It has been pointed out that group three includes a substantial majority of patients therefore it may be difficult to identify those unlikely to gain palliative benefit from radiotherapy.[3] It has been suggested that further subdivision of group 3 may assist in advising on treatment.[4]

The more recently developed Diagnosis-specific Graded Prognostic Assessment (DS-GPA) is primary cancer specific.[5] The data used to develop survival estimates according to DS-GPA score still do not fully reflect the latest systemic therapies and may be subject to selection biases, however, some independent validation has been reported.[5–9]

The regimens most commonly used for the whole-brain radiotherapy (WBRT) treatment of cerebral metastases are 30 Gy in ten fractions over two weeks or 20 Gy in five fractions over one week. For patients with limited disease, other approaches, including gamma knife or stereotactic radiosurgery (SRS) and intraoperative radiotherapy are feasible. The following discussion draws heavily on a systematic review performed as part of the Cancer Care Ontario programme in evidence-based care.[10]

Solitary or oligo-metastases

The evidence from one systematic review and three randomised trials suggests benefit from adding surgery to WBRT for patients of good performance status with a solitary metastasis (Level 1a).[10–13] SRS added to WBRT offers a survival benefit for selected patients with a solitary metastasis, as well as for patients of RPA Class I with up to three metastases.[14] In patients with up to three brain metastases and KPS ≥70, adding SRS to WBRT improves functional independence and reduces steroid requirements at six months (Level 1b).[14,15]

Patients with more than three brain metastases were not included in these trials. Moreover, it is recognised that the number of brain metastases detected on magnetic resonance imaging (MRI) is technique dependent. For small-volume disease, a prospective observational study (Level 2+) in patients with up to ten metastases (largest <10 centimetres^3 [cm^3] , total volume ≤15 cm^3) has suggested that overall survival is equivalent for patients with 5–10 as compared to 2–4 metastases and therefore the number of metastases treated using SRS without WBRT may not correlate with outcome.[15,16] Several retrospective studies (Level 3) have shown that the total volume of brain metastases correlates better with outcomes, including local control, distant intracranial relapse and overall survival after SRS than number of brain metastases.[7,15,17–19]

Recommendations

Solitary metastases:

Surgery or SRS:

Lesion diameter
<20 millimetres (mm) – 24 Gy single dose (Grade B)
21–30 mm – 18 Gy single dose (Grade B)
31–40 mm – 15 Gy single dose (Grade B)

Multiple metastases up to total volume of 20 cm^3 with good performance status (Karnofsky Performance Status ≥70) and controlled extra-cranial disease:[2]

SRS:

Lesion diameter
<20 mm – 24 Gy single dose (Grade C)
21–30 mm – 18 Gy single dose (Grade C)
31–40 mm – 15 Gy single dose (Grade 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.[15]

Whole-brain radiotherapy with SRS

While WBRT was part of the initial treatment of patients in the above-mentioned trials of surgery or SRS, three randomised trials have now investigated the addition of WBRT to surgery or SRS for patients with 1–4 brain metastases.[20–23] A meta-analysis of these trials has also been published.[24] Adding WBRT to local therapy by surgery or SRS appears to improve intracranial control and reduce neurological deaths without influencing overall survival (Level 1a).[15] However, the addition of WBRT to SRS has been shown in one small randomised trial to result in a significantly greater risk of neurocognitive deficits at three months, and for this reason many groups now choose to defer WBRT.[25] Post-treatment MRI surveillance was used in all three trials and is recommended by some expert groups, but high-level evidence about the value of MRI surveillance is lacking.[26] Avoidance of the hippocampus has been suggested as a method to limit the neurocognitive effects of WBRT. The forthcoming HIPPO study is a randomised clinical trial of conventional versus hippocampal sparing WBRT in patients with oligometastatic disease, which uses 30 Gy in ten fractions in both arms of the study.

Recommendation

WBRT with SRS:

30 Gy in 10 fractions over 2 weeks (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.[15]

Whole-brain radiotherapy for multiple metastases

Background

Several randomised trials have compared different radiotherapy regimens for patients with multiple cerebral metastases. Most have used 30 Gy in ten fractions as the control arm and have compared this regimen to either higher or lower doses.[27–30] Only one small study of 70 patients has compared the six-month survival rate after 30 Gy in ten fractions to that after 20 Gy in five fractions. There was no significant difference.[25] An RTOG study reported in 1980 compared three regimens: 40 Gy in 15 fractions; 30 Gy in ten fractions; and 20 Gy in five fractions.[31] 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 five fractions is inferior to, or better than, 30 Gy in ten fractions (Level 1b).[15]

Other regimens assessed in RTOG randomised trials included: 10 Gy single-dose and 30–40 Gy in 10–20 fractions; 40 Gy in 20 fractions; 40 Gy in 15 fractions; 30 Gy in 15 fractions and 30 Gy in ten fractions.[31,32] There was no statistically significant difference in median survival. The trial results suggest that regimens using only one or two fractions are inferior to 30 Gy in ten fractions, but that there is no improvement in survival when dose is increased beyond 30 Gy in ten fractions (Level 1b).[15]

Patients in RPA Class III have such a poor prognosis that it may be difficult to justify any radiation treatment at all. Careful consideration should be given to patients with non-small cell lung cancer. The Medical Research Council (MRC) QUARTZ study shows no significant benefit in terms of survival or quality adjusted life years for WBRT over optimal supportive care.[33]

Recommendation

Multiple cerebral metastases:

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.[15]

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