4.

Central nervous system (CNS) tumours

Background

Three important considerations underpin the choice of treatment fractionation in neuro-oncology. First, the results of treatment vary widely and, second, the brain and spinal cord are susceptible to late radiation damage which is strongly dependent on radiation dose per fraction. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) papers published in 2010 provide details of normal tissue tolerances for brain, brainstem, optic nerves and chiasm, hearing and spinal cord.[1–9] Patients with a life expectancy of more than 12–18 months are rarely treated with doses per fraction greater than 2 Gray (Gy). With increased use of inverse planned intensity-modulated radiotherapy (IMRT), consideration must be given to appropriate dose constraints to serial structures, balancing tumour control against risk of toxicity. Finally, our understanding of tumours, in particular the gliomas, has changed substantially recently, and there is clearly a key role for isocitrate dehydrogenase (IDH) mutations and chromosomal (1p/19q) codeletions. This is likely to further evolve over time.

High-grade glioma

Radical treatment

Retrospective analyses and one randomised trial have demonstrated a dose–response relationship for high-grade glioma up to, but not beyond, 60 Gy in 30 fractions.[10–12] This has led to the adoption of the dose regimen of 60–65 Gy delivered in 1.8–2.0 Gy fractions as standard in the therapy of better prognosis patients with high-grade malignant glioma. Further attempts to improve response through hyperfractionation or accelerated fractionation have not demonstrated a significant survival benefit.[13,14] The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma has been shown to improve overall and progression-free survival.[15] The first trial only included patients under the age of 70. However, a subsequent study included older patients and found similar benefits from the addition of temozolomide.[16]

For World Health Organization (WHO) grade III gliomas with 1p and 19q chromosomal co-deletion, the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy, either before or after radiotherapy, has recently been shown to improve overall survival.[17,18] The addition of temozolomide after radiotherapy has been shown to improve survival in patients with grade III non-1p 19q co-deleted tumours and final results of this trial are still awaited. Recent trials for grade III glioma (anaplastic oligodendroglioma and oligoastrocytoma, and non-1p19q co-deleted WHO grade III glioma) have all used a radiotherapy dose of 59.4 Gy in 33 fractions, providing Level 2a evidence for this regimen in WHO grade III glioma.[19–22] Previous dose determination studies in high-grade gliomas used a dose of 60 Gy in 30 fractions for grade III gliomas.[11,20]

Recommendations

For patients of good performance status:

WHO Grade IV glioma (GBM)
60 Gy in 30 daily fractions over 6 weeks (Grade A)

WHO Grade III glioma
59.4 Gy in 33 fractions over 6.5 weeks (Grade A)
60 Gy in 30 fractions over 6 weeks (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.[19]

Palliative treatment

Increasing age is a significant negative prognostic factor for patients with glioblastoma. Several trials in older patients have evaluated shorter courses of radiotherapy. One randomised trial which recruited patients aged ≥60 of Karnofsky Performance Status (KPS) ≥50 showed similar survival for 40 Gy in 15 fractions over three weeks compared to 60 Gy in 30 fractions.[21] In another randomised trial in patients aged ≥60 principally of WHO performance status 0–2, 34 Gy in ten fractions appeared to have similar survival rates in patients over 60 and better survival in patients over 70 than 60 Gy in 30 fractions of radiotherapy alone.[23] Shorter fractionations are therefore an option in elderly patients unsuitable for chemo-radiotherapy. The recent results using 40 Gy in 15 fractions in older patients combined with concurrent and adjuvant temozolomide suggest that this may be the best option in fit, older patients.[16]

For patients with high-grade glioma and poor performance status, when treatment is indiciated, hypofractionated treatments are used.[24,25] The most commonly adopted regimen in the UK is 30 Gy in six fractions over two weeks.

Recommendations

Elderly patients with glioblastoma unsuitable for chemo-radiotherapy:

40 Gy in 15 fractions over 3 weeks (Grade A)
34 Gy in 10 fractions over 2 weeks (Grade B)
30 Gy in 6 fractions over 2 weeks (Grade C)

For patients of poor performance status being treated for high-grade glioma:

30 Gy in 6 fractions over 2 weeks (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.[19]

Low-grade glioma

For low-grade glioma, two prospective randomised dose comparison trials have demonstrated no difference in outcome between 45 Gy in 25 fractions and 59.4 Gy in 33 fractions and between 50.4 Gy in 28 fractions and 64.8 Gy in 36 fractions.[26,27] As a result, a standard dose of 50.4 Gy in 28 fractions of 1.8 Gy is accepted practice in the UK and internationally. A dose of 54 Gy in 30 fractions over six weeks was used in a randomised study of the timing of radiotherapy and also in the Radiation Therapy Oncology Group (RTOG) 9802 randomised trial which showed an overall survival benefit for the addition of adjuvant procarbazine, lomustine and vincristine (PCV) chemotherapy after radiotherapy for high-risk low-grade glioma (age 18–39 and incompletely resected, or age ≥40 with any extent of resection).[28,29] This provides Level 2b evidence for this regimen.[19]

Recommendations

50.4 Gy in 28 daily fractions over 5.5 weeks (Grade A)
54 Gy in 30 daily fractions over 6 weeks (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.[19]

Finally, data from molecular pathology are likely to further refine these guidelines.

Meningioma

For benign meningioma (WHO grade I), radiotherapy may be used as radical treatment or postoperatively after incomplete resection or recurrence. Radiological surveillance is often an appropriate option for benign meningioma, depending on tumour growth, location and the risk to the patient from further tumour growth. Randomised clinical trial evidence is lacking, but generally excellent rates of local control are reported with radiotherapy doses of 50–54 Gy in 25–30 fractions. Small-volume benign tumours away from critical structures (for example, optic apparatus) may also be treated with stereotactic radiosurgery (SRS). Multiple series confirm long-term local control rates in excess of 80% using both fractionation and SRS. Lower doses have been used in more recent series with similar local control rates.

Radiotherapy should be considered for recurrent or incompletely resected meningioma of atypical histology. As for other benign intracranial tumours, fractionation has been governed by tolerance of local structures and adjacent brain tissue. There is an absence of prospective randomised clinical trial evidence for the use of adjuvant radiation therapy. However, multiple institutional series have demonstrated an improvement in local control and overall survival with adjuvant radiotherapy doses of 50.4–59.4 Gy in 28–33 fractions.[30–33] There is some evidence to suggest that local control is enhanced at doses greater than 52 Gy.[30–33]

Patients with grade 2 meningiomas are at higher risk of relapse, and standard practice has historically been to give radiotherapy. The role of adjuvant radiotherapy, balanced against the neuro-cognitive side-effects, in patients with completely resected meningioma are being explored in the ROAM study (EORTC 1308). In patients who have incompletely resected tumours, radiotherapy has been offered at a dose of 60 Gy in 30 fractions. Attempts at dose escalation using radiosurgery boost and accelerated hyperfractionation have failed to achieve improved local control.[32] The EORTC 26021-22021 phase II trial (NCT00626730) of postoperative radiotherapy for atypical and malignant meningiomas which treated Simpson stage 1–3 to 60 Gy and Simpson stages 4–5 to 70 Gy closed in 2013 and is in follow-up.[34]

Special consideration should be given to meningioma of the optic nerve sheath. There is now evidence from multiple institutional series that radiotherapy should be considered as a primary treatment option to achieve tumour control and consequentially prevent visual deterioration and symptomatic proptosis.[35,36]

Recommendations

Tumour grade 1:

50.4–54 Gy in 28–30 fractions over 5.5–6 weeks (Grade C)
50–55 Gy in 30–33 fractions over 6–6.5 weeks (Grade C)

Grade 2:

54–60 Gy in 30 fractions over 6 weeks (Grade D)

Grade 3:

60 Gy in 30 fractions over 6 weeks (Grade D)

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.[19]

Pituitary tumours

Fractionation has been governed by tolerance of the local structures and prospective data is lacking. There are consistent reports of high local control when using 45 Gy in 25 fractions for non-functioning pituitary adenomas.[37] This is commonly accepted as the standard dose for tumours without adverse features including suprasellar extension. There is data to suggest that the dose response may increase up to about 50 Gy, however, higher doses are generally reserved for tumours with adverse features.[38] Small inoperable pituitary tumours away from optic apparatus may be suitable for single fraction stereotactic treatment which offers a similar local control rate.[39]

Although radiological control rates are high, biochemical remission rates for functional tumours vary considerably using conventional doses of 45–54 Gy (1.8–2 Gy per fraction). No clear dose response has been defined using fractionated treatment, however, higher marginal doses are used when using single fraction stereotactic treatment.

Recommendation

45 Gy in 25 fractions over 5 weeks (Grade D)

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.[19]

Craniopharyngioma

Radiation therapy is typically used as an adjunct to surgery after maximal tumour resection. Doses between 50–60 Gy in 30 fractions have been used. Historical studies of postoperative radiotherapy showed a dose of 55 Gy to be a threshold dose in terms of local disease control, though concern over the risk of radiation induced optic neuropathy has resulted in median doses of 50–52.2 Gy in more recently published series.[40–42]

Recommendations

50–55 Gy in 30–33 fractions over 6–6.5 weeks (Grade D)
52.2–54 Gy in 27–28 fractions over 5.5 weeks (Grade D)

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.[19]

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