4.4 CNS malignancy

Radiotherapy fractionation in the CNS

4.4.1 Two important considerations underpin choice of treatment fractionation in neuro-oncology. Firstly, the results of treatment vary widely and, secondly, the brain and spinal cord are susceptible to late radiation damage which is strongly dependent on radiation dose-per-fraction. The extensive (predominantly older) literature on CNS radiation damage (1-6 and 8) was updated and expanded in the "QUANTEC" papers (Quantitative Analysis of Normal Tissue Effects in the clinic) published in 2010. In this edition of the journal, an overview and introduction to these papers is provided [Marks 2010a]; a summary paper tabulates results for multiple organ sites [Marks 2010b] and individual papers in the same journal issue provide more detail of normal tissue tolerances for brain, brainstem, optic nerves and chiasm, hearing and spinal cord. Patients with a life expectancy of more than 12–18 months are rarely treated with doses-per-fraction greater than 2 Gy. With increased use of inverse planned IMRT, care must be given to appropriate dose constraints to serial structures, balancing tumour control against risk of toxicity. For optic nerves and the chiasm, radiation induced optic neuropathy is unusual with Dmax < 55Gy in 1.8-2Gy fractionation. It is recognised that in selected circumstances it may be necessary to judiciously exceed conventional safe limits to maximise tumour control. The risk of toxicity is predicted to increase markedly at doses >60 Gy at 1.8 Gy/fraction, or at >12 Gy for single-fraction radiosurgery. It is estimated to be in the region between 3-7% in doses between 55Gy - 60Gy. (Mayo 2010). For schedules treating at 2Gy per fraction, 5 and 10% incidence of radiation necrosis is predicted to occur at 60Gy (range 50-70Gy) and 75Gy (range 70-85Gy) respectively [Lawrence 2010].

High grade glioma

4.4.2 Retrospective analyses9 and one randomised trial10 have demonstrated a dose–response relationship for high-grade glioma up to, but not beyond, 60 Gy in 30 fractions.11 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 (level 1+). Further attempts to improve response through hyper-fractionation12 or accelerated fractionation13 have not demonstrated a significant survival benefit. The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma has been shown to improve overall and progression-free survival (level 1+, Grade B) [14, Stupp 2009].

For 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 [Cairncross 2013, van den Bent 2013]. In these trials for anaplastic oligodendroglioma and oligoastrocytoma, the radiotherapy dose was 59.4 Gy in 33 fractions, providing level 2+ evidence for this regimen in WHO grade III glioma with oligodendroglial component [Cairncross 2013, van den Bent 2013]. The ongoing EORTC 26053-22054 trial in non-1p19q co-deleted WHO grade III glioma also uses 59.4 Gy in 33 fractions [EORTC 26053-22054].

For patients of good performance status being treated for WHO grade IV glioma, a total dose in a single phase of 60 Gy in 30 daily fractions in 6 weeks is recommended (Grade A). For WHO grade III glioma, 59.4 Gy in 33 fractions in 6.5 weeks (Grade B) is recommended.

4.4.3 Several trials in elderly patients with glioblastoma have evaluated shorter courses of radiotherapy. One randomised trial [Roa 2004] which recruited patients aged ≥ 60 of Karnofsky Performance Status (KPS) ≥ 50 showed similar survival for 40 Gy in 15 fractions over 3 weeks compared to 60 Gy in 30 fractions (level 1+). In another randomised trial [Malmström 2012] in patients aged ≥ 60, principally of WHO performance status 0-2, 34 Gy in 10 fractions appeared to have similar survival in patients over 60 and better survival in patients over 70 than 60 Gy in 30 fractions of radiotherapy alone (level 1+). Shorter fractionations are therefore an option in elderly patients unsuitable for chemo-radiotherapy. Results are awaited from another randomised trial in patients 65 years and older of good performance status which compared 40 Gy in 15 fractions over 3 weeks with the same radiotherapy plus concurrent and adjuvant temozolomide [NCT00482677].

Treatment is not always appropriate for patients with high-grade glioma and poor performance status but, when it is, hypofractionated treatments may be beneficial.15,16 The most commonly adopted regimen in the UK is 30 Gy in 6 fractions over 2 weeks (level 2+).
Elderly patients with glioblastoma who are unsuitable for chemo-radiotherapy may be considered for shorter fractionations, such as 40 Gy in 15 fractions over 3 weeks (Grade B), 34 Gy in 10 fractions over 2 weeks (Grade B), or 30 Gy in 6 fractions over 2 weeks (Grade C).

For patients of poor performance status being treated for high-grade glioma, a total dose of 30 Gy in 6 fractions over 2 weeks is acceptable as a palliative treatment (Grade C).

**Low grade glioma**

4.4.4 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. As a result, a standard dose of 45–50.4 Gy in 25–28 fractions of 1.8 Gy is accepted practice in the UK and internationally (level 1++). A dose of 54 Gy in 30 fractions in 6 weeks was used in a randomised study of the timing of radiotherapy [19, van den Bent 2005] and also in the RTOG 9802 randomised trial which showed an overall survival benefit for the addition of adjuvant PCV chemotherapy after radiotherapy for high risk low grade glioma (age 18-39 and incompletely resected, or age ≥ 40 with any extent of resection). This provides level 2++ evidence for this regimen.

For patients with low-grade gliomas, a total dose of 45–50.4 Gy in 25–28 daily fractions of 1.8 Gy is recommended (Grade A).

There is evidence to recommend the use of 54 Gy in 30 daily fractions of 1.8 Gy (Grade B).

Finally, it should be noted that given the histological heterogeneity of gliomas, molecular pathology techniques are being used for tumour phenotyping and stratification of patients to appropriate adjuvant therapy. Allocation of treatment schedule in the future is unlikely to be made solely on the basis of histological grade as indicated above.

**Pituitary tumours**

4.4.5 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 (Erridge 2009). 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 50Gy however higher doses are generally reserved for tumours with adverse features (Grigsby 1989). Level 4, D. Small inoperable pituitary tumours away from optic apparatus may be suitable for single fraction stereotactic treatment which offers a similar local control rate (Sheehan JNS 13).

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

A dose of 45Gy in 25 fractions is adequate for most benign non functioning pituitary adenomas. (Grade C).

**Meningioma**

4.4.6 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 [Adeberg 2012, Aghi 2009,] and overall survival [Goldsmith 1994, Milosevic 1996] with adjuvant radiotherapy doses of 50.4-59.4Gy in 28-33 fractions. There is some evidence to suggest that local control is enhanced at doses greater than 52Gy.

Radiotherapy should always be considered in malignant meningioma, to a dose of 60Gy in 30 fractions. Attempts at dose escalation using radiosurgery boost, and accelerated hyperfractionation failed to achieve improved local control [Goldsmith 1994, Katz 2005].
Special consideration should be given to meningioma of the optic nerve sheath. Here is now evidence from multiple institutional series that radiotherapy should be considered as a primary treatment option in order to achieve tumour control and consequentially prevent visual deterioration and symptomatic proptosis [Brower 2012, Roser 2006].

A dose of 50.4-55Gy in 28-33 fractions is recommended for atypical meningioma, and 60Gy in 30f in malignant meningioma (Grade C).

References


