

4. Central nervous system (CNS) tumours

Background

Two 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.

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 study only included patients under the age of 70, and therefore careful consideration should be taken before offering chemoradiation therapy to patients over 70.

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.^{16,17} In trials for anaplastic oligodendroglioma and oligoastrocytoma, the radiotherapy dose was 59.4 Gy in 33 fractions, providing Level 2a evidence for this regimen in WHO grade III glioma with oligodendroglial component.^{18–20} The ongoing European Organisation for Research and Treatment of Cancer (EORTC) 26053-22054 trial in non-1p19q co-deleted WHO grade III glioma also uses 59.4 Gy in 33 fractions (EORTC 26053-22054). Previous dose determination studies in high-grade gliomas used a dose of 60 Gy in 30 fractions for grade III gliomas.^{11,19}

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.¹⁸

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.²⁰ 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.²¹ Shorter fractionations are therefore an option in elderly patients unsuitable for chemo-radiotherapy. Results are awaited from another randomised trial in patients aged 65 years and older of good performance status, which compared 40 Gy in 15 fractions over three weeks with the same radiotherapy plus concurrent and adjuvant temozolomide.²²

For patients with high-grade glioma and poor performance status, when treatment is indicated, hypofractionated treatments are used.^{23,24} 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.¹⁸

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.^{25,26} 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 PCV chemotherapy after radiotherapy for high-risk low-grade glioma (age 18–39 and incompletely resected, or age ≥ 40 with any extent of resection).^{27,28} This provides Level 2b evidence for this regimen.¹⁸

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.¹⁸

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.

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.^{29–32} There is some evidence to suggest that local control is enhanced at doses greater than 52 Gy.^{29–32}

Radiotherapy should always be considered in malignant meningioma to a dose of 60 Gy in 30 fractions. Attempts at dose escalation using radiosurgery boost and accelerated hyperfractionation failed to achieve improved local control.³¹ 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.³³

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.^{34,35}

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.¹⁸

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.³⁶ 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.³⁷ Small inoperable pituitary tumours away from optic apparatus may be suitable for single fraction stereotactic treatment which offers a similar local control rate.³⁸

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.¹⁸

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.^{39–41}

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.¹⁸

References

1. Kramer S. The hazards of therapeutic irradiation of the central nervous system. *Clin Neurosurg* 1968; **15**: 301–318.
 2. Marks JE, Baglan RJ, Prassa SC, Blank WF. Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys* 1981; **7**(2): 243–252.
 3. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 1980; **6**(9): 1215–1228.
 4. Leibel SA, Sheline GE. Tolerance of the brain and spinal cord to conventional radiation. In: Gutin PH, Leibel SA, Sheline GE (eds). *Radiation Injury to the Nervous system*. New York: Raven Press, 1991: 239–256.
 5. Corn BW, Yousem DM, Scott CB *et al*. White matter changes are correlated significantly with radiation dose. Observations from a randomized dose-escalation trial for malignant glioma (Radiation Therapy Oncology Group 83-02). *Cancer* 1994; **74**(10): 2828–2835.
 6. Emami B, Lyman J, Brown A *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; **21**(1): 109–122.
 7. Berg G, Blomquist E, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in brain tumours. *Acta Oncologica* 2003; **42**(5–6): 582–588.
 8. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a users guide. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S1–S2.
 9. Marks LB, Yorke ED, Jackson A *et al*. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S10–9.
 10. Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys* 1979; **5**(10): 1725–1731.
 11. Bleehan NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. *Br J Cancer* 1991; **64**(4): 769–774.
 12. Salazar OM, Rubin P, McDonald JV, Feldstein ML. High dose radiation therapy in the treatment of glioblastoma multiforme: a preliminary report. *Int J Radiat Oncol Biol Phys* 1976; **1**(7–8): 717–727.
 13. Werner-Wasik M, Scott CB, Nelson DF *et al*. Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas: Radiation Therapy Oncology Group Study 83-02. *Cancer* 1996; **77**(8): 1535–1543.
 14. González DG, Menten J, Bosch DA *et al*. Accelerated radiotherapy in glioblastoma multiforme: a dose searching prospective study. *Radiother Oncol* 1994; **32**(2): 98–105.
 15. Stupp R, Hegi ME, Mason WP *et al*. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009; **10**(5): 459–466.
 16. Cairncross G, Wang M, Shaw E *et al*. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol* 2013; **31**(3): 337–343.
 17. van den Bent MJ, Brandes AA, Taphoorn MJ *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013; **31**(3): 344–350.
 18. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
-

19. Nelson DF, Diener-West M, Horton J, Chang CH, Schoenfeld D, Nelson JS. Combined modality approach to treatment of malignant gliomas--re-evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. *NCI Monogr* 1988; **1988**(6): 279–284.
20. Roa W, Brasher PM, Bauman G *et al*. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 2004; **22**(9): 1583–1588.
21. Malmström A, Grønberg BH, Marosi C *et al*. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol* 2012; **13**(9): 916–926.
22. <https://clinicaltrials.gov/ct2/show/NCT00482677> (last accessed 26/9/16)
23. McAleese JJ, Stenning SP, Ashley S *et al*. Hypofractionated radiotherapy for poor prognosis malignant glioma: matched pair survival analysis with MRC controls. *Radiother Oncol* 2003; **67**(2): 177–182.
24. Thomas R, James N, Guerrero D, Ashley S, Gregor A, Brada M. Hypofractionated radiotherapy as palliative treatment in poor prognosis patients with high grade glioma. *Radiother Oncol* 1994; **33**(2): 113–116.
25. Karim AB, Maat B, Hatlevoll R *et al*. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organisation for Research and Treatment of Cancer (EORTC) Study 22845. *Int J Radiat Oncol Biol Phys* 1996; **36**(3): 549–556.
26. Karim AB, Afra D, Cornu P *et al*. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organisation for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BR04: an interim analysis. *Int J Radiat Oncol Biol Phys* 2002; **52**(2): 316–324.
27. van den Bent MJ, Afra D, de Witte O *et al*. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005; **366**(9490): 985–990.
28. Shaw E, Arusell R, Scheithauer B *et al*. Prospective randomised trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/astern Cooperative Oncology Group Study. *J Clin Oncol* 2002; **20**(9): 2267–2276.
29. Adeberg S, Hartmann C, Welzel T *et al*. Long-term outcome after radiotherapy in patients with atypical and malignant meningiomas – clinical results in 85 patients treated in a single institution leading to optimized guidelines for early radiation therapy. *Int J Radiat Oncol Biol Phys* 2012; **83**(3): 859–864.
30. Aghi MK, Carter BS, Cosgrove GR *et al*. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. *Neurosurgery* 2009; **64**(1): 56–60; discussion 60.
31. Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *J Neurosurg* 1994; **80**(2): 195–201.
32. Milosevic MF, Frost PJ, Laperriere NJ, Wong CS, Simpson WJ. Radiotherapy for atypical or malignant intracranial meningioma. *Int J Radiat Oncol Biol Phys* 1996; **34**(4): 817–822.
33. <https://clinicaltrials.gov/ct2/show/NCT00626730> (last accessed 13/10/16)
34. Brower JV, Amdur RJ, Kirwan J, Mendenhall WM, Friedman W. Radiation therapy for optic nerve sheath meningioma. *Pract Radiat Oncol* 2013; **3**(3): 223–288.

References

35. Roser F, Nakamura M, Martini-Thomas R, Samii M, Tatagiba M. The role of surgery in meningiomas involving the optic nerve sheath. *Clin Neurol Neurosurg* 2006; **108**(5): 470–406.
 36. Erridge SC, Conkey DS, Stockton D *et al*. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. *Radiother Oncol* 2009; **93**(3): 597–601.
 37. Grigsby PW, Simpson JR, Emami BN, Fineberg BB, Schwartz HG. Prognostic factors and results of surgery and postoperative irradiation in the management of pituitary adenomas. *Int J Radiat Oncol Biol Phys* 1989; **16**(6): 1411–1417.
 38. Sheehan JP, Starke RM, Mathieu D *et al*. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg* 2013; **119**(2): 446–456.
 39. Varlotto JM, Flickinger JC, Kondsiolk D *et al*. External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. *Int J Radiat Oncol Biol Phys* 2002; **54**(2): 492–499.
 40. Masson-Cote L, Masucci GL, Atenafu EG *et al*. Long-term outcomes for adult craniopharyngioma following radiation therapy. *Acta Oncol* 2013; **52**(1): 153–158.
 41. Harrabi SB, Adeberg S, Welzel T *et al*. Long term results after fractionated stereotactic radiotherapy (FSRT) in patients with craniopharyngioma: maximal tumor control with minimal side effects. *Radiat Oncol* 2014; **9**: 203.
-