04 Central nervous system (CNS) tumours

Treatment of brain and spinal cord tumours presents specific challenges as radiation toxicity can have deleterious effects on a patient's function and cognition. The choice of dose, fractionation and technique needs to take into account the risk of neurological sequelae as well as tumour control.[1] The acute and late toxicities relate to the maximum or mean doses to structures such as optic chiasm, optic nerves, brainstem, cochlea, eyes, and the volume and location of brain parenchyma irradiated. Studies have shown that one of the principal factors determining late cognitive impairment is fraction size,[2] so for patients with longer life expectancy (over 12–18 months), fraction sizes of 1.8–2.0 Gy are usually recommended. In order to minimise dose to adjacent organs at risk, patients are standardly treated using advanced radiotherapy techniques.

Intracranial glioma

In 2021, WHO published a new classification of brain tumours that incorporates molecular and genetic features.[3] One of the main changes is to separate glial series tumours into IDH wildtype and IDH mutated. While many tumours can be classified as wildtype on immunohistochemistry, for younger patients or if there are any unusual features, sequencing is required as some mutations are otherwise missed.

IDH wildtype glioma

The majority of these are Grade 4 lesions and termed glioblastoma, IDH wildtype (GBM IDH WT).

If a tumour has the morphology of a Grade 2 or 3 glioma but is IDH wildtype on sequencing then additional analysis is required. If there is evidence of one or more of telomerase reverse transcriptase (TERT) promotor mutation, epidermal growth factor receptor (EGFR) gene amplification or gain of entire chromosome 7 and low entire chromosome 10 (7+/10–) then the tumour is managed as a GBM IDH WT. If these features are not present, particularly in a younger person, then this may be a rare lower-grade glioma subtype and needs to be managed accordingly.

GBM IDH WT is further subclassified into those with O6-methylguanine-DNA methyl-transferase (MGMT) promotor methylation and those without. MGMT methylation is both predictive of likelihood of response to temozolomide chemotherapy, but also prognostic, independent of use of temozolomide. However, it is important to note which testing technique has been utilised (pyrosequencing or PCR are recommended), and that the underlying biological mechanisms are complex, so recommendation based on MGMT methylation alone on the use or not of temozolomide is not clear cut.[4]

Factors that also need to be considered when assessing the optimum dose and fractionation for patients with GBM IDH WT include performance status, age, cognitive impairments, volume of residual disease (and surrogate of steroid dose), location of tumour, and co-morbidities.[5]

Several trials have been conducted examining dose escalation and none have identified an improvement in overall survival with doses more than 60 Gy using 2 Gy per fraction.

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Several studies have compared this schedule with hypofractionated schedules; a Canadian trial looked at 40 Gy in 15 fractions in older patients or less fit younger patients and showed equivalence.[6] A Swedish study looked at a shorter schedule of 34 Gy in 10 fractions compared with 60 Gy in 30 fractions, and those patients over the age of 70 years had a detrimental survival with the prolonged course.[7] Consequently, shorter-course schedules are recommended for those over the age of 70 years. Some trials have used 65 years of age as the cut-off for 'elderly', whereas others have used 70 years of age. Consequently, the optimal management of people between 65 and 70 years of age needs to be assessed on a case-by-case basis.

Concurrent and adjuvant temozolomide has been shown to improve overall survival in patients with methylated GBM IDH WT when added to 60 Gy in 30 fractions,[8] and for older patients with 40 Gy in 15 fractions.[9] The addition of temozolomide may be considered in patients with unmethylated tumours, but the survival gain is more marginal.

For less fit patients, short-course treatments such as the Swedish 34 Gy in 10 fractions[7] or the UK schedule of 30 Gy in 6 fractions on alternative days over 2 weeks[10,11] may be considered, but in this group the survival gain may be minimal.

Recommendations

Glioblastoma, IDH wildtype:

Good performance status (KPS 80–100) and aged <70 with minimal residual tumour:

• 60 Gy in 30 daily fractions over 6 weeks ± temozolomide (Grade A)

Moderate performance status (KPS 60–70), or aged over 70:

• 40 Gy in 15 fractions over 3 weeks ± temozolomide (Grade A)

Poor performance (KPS 50–60) may be considered for shorter-course treatments such as:

• 34 Gy in 10 fractions (Grade B) or 30 Gy in 6 fractions on alternate days (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.[12]

IDH mutated glioma

The IDH mutated tumours are further subdivided into those with 1p19q codeletion (previously called oligodendroglioma) or without 1p19q codeletion (astrocytoma).

Non-codeleted IDH mutated glioma

These tumours are Grade 2, 3 or 4 depending on morphology.

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Grade 2

Grade 2 non-codeleted IDH mutated gliomas (diffuse astrocytoma) have a good survival. Previous studies (conducted prior to recognition of IDH) comparing immediate with deferred radiotherapy showed that, for many patients, initial active surveillance is a reasonable option.[13] However, certain features (age >40 years, tumour >4 cm, crossing midline and neurological deficit) are associated with a poorer prognosis, so those patients may be considered for earlier treatment.[14]

The European Organisation for Research and Treatment of Cancer (EORTC) looked at initial radiotherapy (using 50.4 Gy in 28 fractions) compared with chemotherapy (temozolomide) and showed superior progression-free survival for patients with non-codeleted tumours managed with radiotherapy.[15]

There have been two studies examining dose escalation in patients with Grade 2 glioma (EORTC 45 Gy in 25 fractions[16] versus 60 Gy 30 in fractions, and Radiation Therapy Oncology Group (RTOG) 50.4 Gy in 28 fractions versus 64.8 Gy in 36 fractions).[17] Both studies failed to demonstrate an improvement in survival, and the toxicity was increased in the dose escalation arms. Consequently, the lower doses are recommended, though recent trials have used 50.4 Gy in 28 fractions.[15,18]

If there are some concerning features on the pathology (eg higher proliferation) or imaging (increased perfusion) dose escalation (eg to 54 Gy in 30 fractions[19] or using an integrated boost) may be considered.

Analysis of the long-term results of a trial of patients with Grade 2 glioma either >40 years or with >2 cc residual disease comparing radiotherapy alone (54 Gy in 30 fractions) with or without adjuvant PCV (procarbazine, CCNU and vincristine) demonstrated marked increase in overall survival with the addition of adjuvant PCV (for IDH mutated tumours with or without 1p19q).[19] Consequently, there is a trend for patients who meet these criteria to consider radiotherapy and adjuvant chemotherapy earlier.

Whether or not PCV is the optimal chemotherapy for non-codeleted tumours remains debated as there has not been a trial of adjuvant temozolomide in this group.

Grade 3

The management of Grade 3 IDH mutated non-codeleted gliomas (anaplastic astrocytoma) has been assessed in the CATNON trial. This study gave 59.4 Gy in 33 fractions and then assessed use of concurrent and/or adjuvant temozolomide. Though the final analysis is awaited, initial analysis of the data demonstrates significant improvement in overall survival with the use of adjuvant temozolomide, but to date there is no survival gain from the use of concurrent temozolomide.[20]

For some patients, particularly if there are logistical issues or the radiotherapy volume is small, 60 Gy in 30 fractions may be considered.[21]

Grade 4

Grade 4 IDH mutated gliomas were previously classified as glioblastoma but were given a new classification in WHO 21 in recognition that they have a better prognosis (median survival around 36 months compared with 14 months for GBM IDH wildtype).[22,23]

The optimal management of this new subgroup has not been tested in clinical trials, but as they were included in prior glioblastoma trials they are managed according to these protocols.

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Most Grade 4 IDH mutated gliomas have MGMT methylation and, as they occur mainly in younger age groups, the majority are treated with 60 Gy in 30 fractions with concurrent and adjuvant temozolomide.[8] If the patient is older, has poor performance status or very large tumour volume then the schedules used for IDH wildtype tumours may be considered.

Recommendations

IDH mutated non-codeleted:

Grade 2:

- 50.4 Gy in 28 fractions (or 45 Gy in 25 fractions or 54 Gy in 30 fractions) with adjuvant PCV (Grade A) or adjuvant temozolomide (Grade D)

Grade 3:

- 59.4 Gy in 33 daily fractions over 6.5 weeks with adjuvant temozolomide (Grade A)

Grade 4:

- 60 Gy in 30 daily fractions over 6 weeks with or without concurrent and adjuvant temozolomide (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.[12]

Codeleted IDH mutated glioma

Though these are graded into Grade 2 (oligodendroglioma) and Grade 3 (anaplastic oligodendroglioma), this distinction appears to have minimal impact on overall survival, with a median survival of 13 to 15 years), so it is important to consider late effects when managing these patients.[24]

Grade 2

These patients were included in the RTOG 9802 Grade 2 trial mentioned above, which used 54 Gy in 30 fractions with and without adjuvant PCV.[19] This group of IDH mutated and codeleted gliomas had the greatest gain from the addition of PCV.[25]

However, many of these tumours are slow growing and occur in younger patients, so for many with minimal residual postoperative tumour, active surveillance is often the initial management approach, with radiotherapy and PCV utilised when there is evidence of radiological or symptomatic (eg increasing seizure frequency) progression.[5]

Grade 3

Two trials examined radiotherapy giving 59.4 Gy in 33 fractions with or without adjuvant/neoadjuvant PCV,[26,27] and both demonstrated an improvement in overall survival with the addition of chemotherapy.

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For most patients with Grade 3 codeleted gliomas, immediate postoperative radiotherapy and chemotherapy is recommended, though for some with minimal residual disease and only foci of anaplasia, active surveillance may be an appropriate management strategy.

As with non-codeleted Grade 3 gliomas, if there are logistical issues or the radiotherapy volume is small then 60 Gy in 30 fractions may be considered.

Recommendations

IDH mutated codeleted:

Grade 2:

- 50.4 Gy in 28 fractions (or 45 Gy in 25 fractions or 54 Gy in 30 fractions) with adjuvant PCV (Grade A)

Grade 3:

- 59.4 Gy in 33 daily fractions over 6.5 weeks with adjuvant PCV (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.[12]

Protons

Protons are not routinely recommended for patients with Grade 3 or 4 gliomas, or for people over the age of 25 with a Grade 2 glioma. However, they may be considered in those under the age of 25 with an IDH-mutant, 1p19q codeleted Grade 2 glioma to try to minimise the volume of normal tissue receiving medium or low doses.[28]

Studies comparing the impact on quality of life and cognition between photons and protons in good-prognosis patients are due to start recruitment soon.

Reirradiation

There is increased interest in the use of reirradiation, particularly in patients who have relapsed after a reasonable interval of local control (usually >12 months). Schedules utilised vary depending on tumour biology, interval from initial presentation and tumour volume.[29]

There is one randomised phase II trial in glioblastoma (RTOG 1205[30]), which randomised patients to bevacizumab with or without reirradiation giving 35 Gy in 10 fractions. Although there was no improvement in overall survival, the proportion of patients with progression-free survival at 6 months was significantly higher in the reirradiation arm. In the UK a schedule of 35 Gy in 10 fractions is being increasingly used, particularly for glioblastoma. A UK trial is under way comparing reirradiation with palliative chemotherapy (BRIOCHE), which will hopefully provide more evidence on the impact of reirradiation on survival.

For patients with a lower-grade glioma without possible transformation, schedules using 1.8 Gy per fraction should be considered (eg 45–50.4 Gy in 25 to 28 fractions).

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Spinal cord glioma

Gliomas of the spinal cord are rare lesions with a wide range of clinical behaviour.[31,32] Though pathological confirmation is recommended in most cases, due to the risks of increasing neurological deficits, some are treated empirically with radiotherapy. The dose of radiotherapy must balance maximising odds of tumour control with risk of spinal cord injury.

Recommendation

- 54 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.[12]

Meningioma

Meningiomas are graded 1, 2 (atypical) and 3 (anaplastic). Grading historically has been based on morphological features, but it has been long recognised that there are lesions where the behaviour was not accurately reflected by this approach alone. Consequently, the new WHO 2021 grading incorporates some molecular markers. For example, lesions with TERT promotor mutation and/or CDKN2A/B homozygous deletion are now classified as Grade 3 due to their much higher rate of local recurrence.

Many meningiomas are picked up as incidental findings on magnetic resonance imaging (MRI) for another symptom and often require surveillance alone. For lesions that are causing symptoms and/or are enlarging, surgery remains the mainstay of treatment, but for some locations, particularly around the base of the skull, surgery can have a high risk of complications. Therefore, following multidisciplinary discussion,[33] radiotherapy is sometimes recommended without pathological confirmation.

Grade 1 or no pathological conformation

Radiotherapy may be used as radical treatment if inoperable or postoperatively after incomplete resection or on recurrence.[34,35] There are three types of radiotherapy utilised for meningiomas: conventionally fractionated (1.8–2.0 Gy per day) using VMAT or fractionated stereotactic radiotherapy (fSRT), single-fraction stereotactic radiosurgery (SRS) or hypofractionated SRS (fraction size >5 Gy). The choice of modality depends on lesion location and volume.

Lesions in close proximity to critical structures, particularly the optic nerves and chiasm, are more commonly treated with conventionally fractionated radiotherapy due to the dose limitations when giving single fractions (eg chiasm tolerance is <10 Gy in 1 fraction or <25 Gy in 5 fractions).[36,37] Respective case series suggest that single-fraction SRS is less effective in larger tumours than 7.5–10 cc.[38–40] The risk of toxicity (particularly oedema) increases with volume of lesion so conventional fractionation is usually used for lesions >3 cm.[41]

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Conventionally fractionated radiotherapy

Randomised clinical trial evidence is lacking, but generally excellent rates of local control (80–100%) are reported with radiotherapy doses of 50–54 Gy in 25–30 fractions.[33] A combined photon/proton trial showed no benefit from escalating the dose to 63 Gy relative biological effectiveness (RBE).[42]

Radiosurgery

Small-volume (<7.5–10 cc) meningiomas away from critical structures (eg >5 mm from optic apparatus such as optic nerves, chiasm and tracts) may also be treated with single-fraction SRS. Doses utilised range from 12 to 16 Gy. One large retrospective series suggests that local control appears to be inferior for doses less than 13.5 Gy[43] and another showed no gain from doses over 15 Gy,[38] so it appears 14–15 Gy is the optimal dose range.

Hypofractionated SRS can also be used for smaller meningiomas (<3 cm max diameter) that are close (<5 mm) to critical structures such as the brainstem. There are a wide range of schedules and prescription isodoses used in the retrospective series. However, the most commonly used schedule is 25 Gy in 5 daily fractions.[44–46]

Grade 2 (atypical)

Patients with Grade 2 meningiomas are at higher risk of relapse, even after complete (Simpson I–III) resection, but the use of adjuvant radiotherapy must be balanced against potential long-term side-effects such as neuro-cognitive toxicity.[47]

Practice has varied internationally; the ROAM trial (EORTC 1308) has been conducted in which patients with completely resected Grade 2 meningiomas were randomised between 60 Gy in 30 fractions and surveillance alone.[48] Recruitment is complete, but the results have not yet been reported.

RTOG 0539 was a non-randomised phase II study delivering 54 Gy in 30 fractions for patients with Grade 2 meningioma with gross total resection (Simpson I–III),[49] and 54 Gy with integrated boost to 60 Gy if there was a subtotal resection (Simpson IV–V).[50] The 3-year progression-free survival was 93.8% and 57.1%, respectively.

The EORTC conducted a non-randomised phase II trial (22042) delivering 60 Gy in 30 fractions in those with Simpson I–III, with a 10 Gy boost if Simpson IV–V. The vast majority (82%) had gross total resection, and 3-year progression-free survival was 88.7%, which exceeded the predicted 70%.[51]

The use of radiosurgery for Grade 2 meningioma remains controversial due to the margins required (most standard radiotherapy trials use 1 cm margin from gross tumour volume [GTV] to clinical target volume [CTV]) to reduce local recurrence. The dose margins and fraction have not yet been established.[47]

Grade 3 (anaplastic)

Anaplastic meningiomas are rare (<3% of meningiomas, though this will increase with new molecular classification) so data on optimal management are limited. They were included in the RTOG 0539 high-risk arm and EORTC 22042, but the numbers in each study are small: 17 and 9, respectively.[50,51]

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Retrospective studies show that, though reduced after adjuvant radiotherapy, the risk of recurrence both locally and in other areas of the meninges remains high, and though dose escalation has been considered, whether this approach is beneficial is yet to be established.[47]

Recommendations

Grade 1:

- VMAT 50–54 Gy in 25–30 fractions over 5–6 weeks (Grade C)
- SRS 13–15 Gy in a single fraction (Grade C)
- SRS 25 Gy in 5 fractions (Grade D)

Grade 2:

- VMAT 54–60 Gy in 30 fractions over 6 weeks (Grade B)

Grade 3:

- VMAT 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.[12]

Pituitary adenoma

Pituitary lesions account for 15% of intracranial tumours and the majority are benign adenomas, but around a third invade local structures.[52]

They are categorised into functioning (hormone-secreting – ACTH, growth hormone, prolactin, TSH or gonadotrophins) or non-functioning lesions.

They may require treatment due to their hormone secretion or due to pressure on surrounding structures such as the optic chiasm.

The primary treatment is usually surgery (or dopamine agonists for prolactinomas) with radiotherapy reserved for:

- Recurrent or progressive non-secreting tumours following surgical excision, residual disease close to optic apparatus with the concern of threat to vision
- Lesions with adverse pathological features such as Ki 67 >3%[52]
- Secretory tumours with persistent hormone elevation despite maximal hormone blockade
- Patients not medically fit for surgery.

Prevention of further enlargement following radiotherapy is achieved in over 90%[53,54] at 10 years with the majority of patients treated using 45 Gy in 25 fractions.[55,56] However, if there are adverse features, such as large size or marked local invasion then dose escalation to 50.4–54 Gy using 1.8 Gy per fraction may be considered.[52,56] Advanced planning and set-up techniques should be utilised to minimise doses to adjacent organs at risk, particularly the chiasm.

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The rate of biochemical cure for functioning lesions is, however, much lower, with most conventionally fractionated series quoting 35–50%. To try to increase biochemical cure, there has been interest in utilising SRS for lesions >3 mm from optic apparatus and <3 cm in size. However, there are no randomised studies, just single-centre series with minimal data on lesion size and varying length of follow-up.[57]

The NHS England commissioning guidelines also state that hypofractionated SRT (2–5 fractions) can be considered in patients with non-functional adenomas where the optic apparatus is involved (eg 25 Gy in 5 fractions). This was restricted to non-functional lesions due to lack of evidence in functional lesions.[58]

The use of proton treatment for pituitary tumours is still under investigation. Currently in the UK, patients <25 years with pituitary adenomas are eligible based on theoretical reduction in late effects in surrounding structures.

Recommendation

• 45–54 Gy in 25–30 fractions over 5–6 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.[12]

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