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Overview

Retreatment of Central Nervous System Tumours

B. Jones *, W. Grant †‡

* Gray Institute for Radiation Oncology and Biology, Department of Oncology, University of Oxford, Oxford, UK
† Gloucestershire Hospitals NHS Foundation Trust, Cheltenham General Hospital, Cheltenham, UK
‡ EORTC Headquarters, Brussels, Belgium

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Abstract

The purpose of this overview is to describe radiotherapy retreatment of primary central nervous system tumours from a practical clinical management perspective, including patient selection, choice of radiation technique, dose and fractionation. Useful relief of clinical symptoms and occasionally prolonged survival can follow retreatment. Further analysis of a previously published data set shows that the duration of remission after initial radiotherapy does not correlate with the duration of the remission after retreatment. Also there is no clear relationship between delivered tissue and tumour biological effective dose (BED) and duration of second remission. 'Recovery' of radiation tolerance with time is important and the radiobiological experiments that show this phenomenon have important limitations. To improve the decision as to how much recovery safely occurs with increasing time after radiotherapy, a new mathematical formulation is proposed. This is essentially conservative in its intent, compatible with experimental data sets, and provides a method for tentative calculation of retreatment dose and fractionation. Worked examples are provided of such calculations.

As an increasing number of relatively young patients are now retreated, it is important to extend the experimental and human evidence base. A nationally coordinated analysis of patients already retreated would be valuable, in order to make future retreatment as safe and effective as possible, with validation of the permissible retreatment schedules for the particular radiation technique used. A national register and task force is proposed to facilitate this.

Key words: Brain; glioma; radiotherapy; retreatment; spinal cord

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Introduction

Radiotherapy of primary brain tumours is itself a challenging subdiscipline of radiotherapeutics. Not only do patients have a tumour of various degrees of malignancy, but they may also have coexisting neurological deficits, epilepsy and personality changes. Their medical history inevitably includes one or more previous neurosurgical procedures, and most will be receiving drugs such as anticonvulsants, glucocorticoids and cytotoxic chemotherapy at different stages in their illness. Death usually follows failure of local tumour control, which results in raised intracerebral pressure from widespread tumour infiltration, cystic degeneration or intracerebral haemorrhage; others succumb to side-effects of treatment, such as steroid-related complications, including infection, or the effects of immobility, such as venous thrombosis and multiple pulmonary emboli.

The decision to offer a first course of radiation treatment can be difficult enough in terms of balancing risks and benefits alongside prognosis. Considerable judgement and often prolonged sympathetic conversations with patients and their families are required to ensure that the treatment goals (symptom relief, prolongation of life, reduction of steroid dependency and occasionally cure) are fully understood, while accepting that treatments can potentially reduce quality of life in both shorter and longer terms. Even more difficult are decisions regarding radiation retreatment,

Author for correspondence: B. Jones, Gray Institute for Radiation Oncology and Biology, Department of Oncology, University of Oxford, Oxford OX3 7DQ, UK.
E-mail address: Bleddyn.Jones@oncology.ox.ac.uk (B. Jones).

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as risks can be higher and benefits more uncertain. In most instances, retreatment is not advised, but it is important to determine which patients may be suitable for further radiotherapy, although they may be few in number.

Brain and spinal tumours are fortunately rare, and there are relatively few exemplary randomised controlled trials of their primary management. These facts imply that useful data on retreatments are more difficult to obtain, often in case report or retrospective form, including relatively few patients who have different tumour types and dose fractionation schedules, together with inevitable physician-related selection bias. Pleas for a national database of prospectively gathered data on certain rare conditions or treatment situations over a decade ago were not followed up in this area [1,2], and there seems to be no pan-European strategy on this.

The following overview refers to published series, but also includes personal experience, as well as the radiobiological rationale for allowing retreatment in certain situations. Some worked examples of retreatment dose calculation are given, using a new mathematical modelling approach to estimate available tolerance with time for recovery after the original treatment. The remit of this overview concerns the retreatment of gliomas in adults. The issues concerning more radiosensitive tumours, as in the paediatric and young adult practice, will follow similar principles.

Patient Assessment and Neural Tolerance

Details of the previous treatment notes and dose distribution plans must be scrutinised closely, with attention to the location of the highest dose regions, beam directions, dose and fractionation, as well as how the treatment was tolerated by the patient.

It is important to assess for radiation late effects. The central nervous system (CNS) is unfortunately inaccessible to direct inspection (with the exception of the optic nerve head) and palpation, but the scalp, bone flaps or other areas of irradiated skin should be examined for the presence of late radiation effects. Careful neurological examination is necessary and inspection of recent imaging studies should exclude major changes related to radiotherapy, surgery and degenerative processes, such as cerebral atrophy. The neurosurgical history of the patient is relevant and may adversely influence neural tolerance: repeated surgery, prolonged tissue retraction and localised obliterative procedures, such a lasering/diathermy can lead to tissue devascularisation, and such areas are more prone to radiation vascular effects. Inspection of the operation notes and dialogue with the neurosurgeon is advised, with planned avoidance of areas showing atrophy due to previous surgery. Significant atrophy in relation to radiation treatment is probably a contraindication.

Particular care is required in the regions of the optic nerves and chiasm, the temporal lobe and brainstem, which implies that retreatment of more superiorly located tumours can be pursued with less severe constraints. It is difficult to allocate a precise reduction in tolerance that will account for previous surgery, but this may amount to as much as 10 Gy in the case of the optic nerve and chiasm: these can tolerate up to 54–55 Gy in 30 fractions if there has been no previous surgery in that region, but only around 45 Gy in 25 fractions after significant surgery.

Sudden compressive changes and stretching of neural tissue can also cause some degree of devascularisation, although it is remarkable how far function (dependent on an intact vascular supply) can be preserved when tumour growth is slow.

The QUANTEC data sets [3] should be consulted with respect to the primary treatment and its own risks, but provide little useful guidance for retreatments. However, the primary treatment limits given in QUANTEC can be used for BED calculations that assume a certain degree of recovery of CNS tolerance with time. Those patients treated to very high initial doses should not necessarily be excluded from retreatments if these doses were confined to a tumour mass. Normal tissues that have exceeded the prescription dose will have received a higher dose per fraction as well as a higher dose, and will therefore be at increased risk.

Patient Characteristics

The patient should be medically robust, mentally alert and sufficiently co-operative to give consent and undertake retreatment, even if they may have neurological deficits that could potentially recover (Table 1). Performance status can be misleading, as many excellent responses have been achieved in patients with a hemiparesis, nominal and expressive dysphasia, etc. Longstanding severe neurological deficits, unresponsive to steroids, will probably not improve with radiation retreatment. Whereas age should not be a restriction, the increasing prevalence of cerebrovascular disease with age, or the presence of other serious concomitant medical conditions may influence the decision to retreat, as well as the choice of dose. A life expectancy of at least 12 months is a reasonable minimum requirement. Patients with longstanding high-dose steroid intake with associated severe Cushingoid side-effects are probably not suitable, as further dose increments may be required. Ideally, the patient should be capable of prolonged survival as far as non-neurological organ systems are concerned, with a history of a satisfactory response to the original treatment.

For those who develop neurological symptoms on relapse, improvements in their neurology with newly introduced steroid medication would support the use of

Table 1
The ideal patient profile

- Young (<50 years) and fit.
- Relapse over 3 years after primary radiotherapy for a low-grade glioma.
- Subradical dose received previously.
- Only partial retreatment of past high-dose volume required.
- Treatment volume smaller than in past.
- No evidence of brain atrophy or other severe late radiation changes.

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