educational session

Brain tumors

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Radiotherapy in malignant glioma

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introduction

Management of patients with high-grade glioma is essentially care of patients with incurable malignancy. While the primary measure of efficacy of treatment remains survival, the palliative value of treatment and the issues of care are equally important but poorly studied end points. The treatment modality tested in randomised trials, which has shown the largest magnitude of survival benefit, is radiation therapy. Modern radiation therapy to tolerance doses is rarely associated with structural damage in the form of necrosis. The cause of functional impairment such as cognitive dysfunction is usually multifactorial with radiation merely a contributing factor. The most onerous side-effect of radiation is tiredness, which may persist for weeks or months after radiotherapy and may adversely affect quality of life.

effectiveness of radiotherapy

Two large randomised studies performed in the 1970s have compared radiotherapy with supportive care alone. They demonstrated a 6-month survival benefit at a median time point for the whole population of patients studied [1, 2]. The two by two design in the study of Walker et al. also compared chemotherapy alone with no specific treatment without radiotherapy; chemotherapy with carmustine (BCNU) also showed little impact on survival [1]. The studies showing benefit for radiotherapy were carried out at a time when quality of life assessment was not routinely performed. However, they reported improvement or stabilisation of performance status using a Karnofsky performance status (KPS) scale in patients who received radiotherapy. On this basis, radiotherapy has become accepted as the treatment of choice in patients with histologically verified malignant glioma. On present evidence, of all treatments tested, radiotherapy offers the greatest magnitude of survival benefit.

radiation parameters

volume of irradiation

The question of the radiotherapy volume has only been tested in one randomised study, which did not demonstrate a survival difference between whole brain radiotherapy throughout and whole brain radiotherapy followed by a localised boost to the same total radiation dose [3]. This data has largely been superseded by a universally adopted policy of localised radiotherapy attempting to avoid irradiating normal brain. The rationale is based on a well-documented recurrence pattern where the majority of malignant gliomas recur as a direct extension of the enhancing primary tumour mass. The usual practice is to treat with high dose, the region of enhancement and a 2–5 cm margin.

radiation dose

Initial sequential dose-finding studies suggested survival benefit for increasing the radiotherapy dose from 50 to 60 Gray (Gy) [4]. The dose–response relationship was confirmed in a Medical Research Council (MRC) randomised trial, in which patients randomised to receive 60 Gy in 30 fractions had a median survival benefit of 3 months compared with patients receiving 45 Gy in 20 fractions [5]. A randomised Radiation Therapy Oncology Group (RTOG) study demonstrated no further survival benefit for an additional 10 Gy boost following 60 Gy whole brain irradiation [6]. The current practice in high-grade glioma is, therefore, fractionated external beam radiotherapy to a dose of 60 Gy in 30 daily fractions given to a localised volume encompassing the enhancing tumour mass and a 2–5 cm margin.

advances in radiation therapy technology

The principal development in the technology of radiotherapy in the last two decades can be broadly classified as conformal radiotherapy (CRT) and, more recently, image-guided radiotherapy (IGRT). In modern CRT, computer tomography (CT) and magnetic resonance imaging (MRI) are used routinely for delineation of the tumour. Modern functional imaging such as positron emission tomography (PET) is being investigated for biological planning and functional MRI and tractography may be used, as in neurosurgery, to aid avoidance of critical structures.

Conformal techniques of delivery include beam shaping with multi-leaf collimator (MLC), the use of intensity modulated radiotherapy (IMRT) and the use of charged particles such as protons and heavy ions. While IMRT and particle therapy are being explored, their application in the treatment of gliomas is currently limited. They do not show a clear benefit in terms of improved delivery of radiation to the tumour and better avoidance of normal brain. IMRT can be explored in biological treatment planning to selectively increase the dose to more critical structures.
biologically active areas of the tumour and to deliver defined doses to areas of presumed microscopic disease while maintaining the full dose to the main tumour mass and avoiding critical normal structures.

IGRT adds further precision to treatment delivery with real time imaging of the target during treatment. The potential impact of IGRT on the radiotherapy of glioma is not clear.

The developments in cranial irradiation in the last decade, which add precision to treatment delivery, include stereotactic radiotherapy, which can be given either in a fractionated manner or as single fraction stereotactic radiosurgery. Stereotactic radiotherapy techniques are in routine use for the treatment of localized benign tumours but their role in the treatment of infiltrating malignant gliomas is limited [7].

palliative radiotherapy

The median survival of patients with malignant glioma ranges from less than 6 months to over 4 years [8, 9]. It may, therefore, be appropriate to avoid prolonged intensive irradiation in patients with limited prognosis and reserve more radical treatment for those with more favourable prognosis. A number of phase II studies suggest little or no survival detriment with lower dose irradiation in patients with poor prognosis identified by poor performance status, glioblastoma histology and old age [10, 11]. The recommended regimens range from 30 Gy in six to 10 fractions to 45 Gy in 20 fractions. Two randomised studies confirmed no detriment of using shorter radiotherapy in older patients [12, 13].

intensification of radiotherapy

radiation sensitizers

The limitation to brain tumour radiotherapy is radiation tolerance of the normal brain. Increasing radiation dose intensity could, theoretically, lead to improved tumour control although at a cost of higher morbidity and therefore no improvement in therapeutic ratio.

Increase in radiation intensity confined to the tumour alone can be achieved with radiation sensitizers, with altered fractionation or by more localised delivery of radiation. The presumed radiation resistance of gliomas has been assumed to be due, at least in part, to hypoxia and many trials tested the efficacy of hypoxic radiation sensitizers [14, 15]. While individual randomised trials have not demonstrated benefit, a meta-analysis suggested a 5% improvement in survival for misonidazole as hypoxic cell sensitizer [16]. Studies of hyperbaric oxygen, neutrons and particle radiotherapy (pions) have not shown a benefit but studies of hyperbaric oxygen and neutrons were underpowered [17–19]. Bromodeoxy Uridine (BudR), which preferentially sensitizes proliferating tissues, while found to be promising in phase II studies, did not demonstrate survival benefit in a randomised study [20].

altered fractionation

Higher radiation doses can be given without increasing toxicity by multiple small fractions per day (hyperfractionation). Dose intensity can also be increased by shortening the treatment time giving multiple treatments a day to the same overall dose (acceleration). With the exception of one small trial, randomised studies have failed to demonstrate a survival benefit for either high-dose treatment (72 Gy hyperfractionated versus 60 Gy CRT) [21] or for accelerated treatment. Nevertheless accelerating treatment was not found to be detrimental and shortened the treatment period [22].

increasing dose with modern radiation techniques

Higher radiation doses to the tumour can be given by more localised delivery either by insertion of radiation sources directly into the tumour (interstitial radiotherapy/brachytherapy) or by high precision localised external beam conformal or stereotactic radiotherapy. Differential doses with a central boost can also be given with IMRT. The higher radiation doses given with any of the techniques increase the incidence of necrosis within the high-dose region. While numerous phase II studies suggested a benefit for increased local dose, all such studies are subject to selection bias [23]. It has been possible to increase the dose with CRT although the benefit is not clear [24]. A randomised study of interstitial radiotherapy boost showed no survival benefit with additional irradiation [25]. The addition of stereotactic radiotherapy boost in patients with small tumours has also not improved survival [26]. Phase II studies of IMRT giving high central doses have also, so far, not shown survival benefit [27].

chemotherapy

Chemotherapy has been given concurrently with irradiation as a potential radiosensitizer. The success of temozolomide given as concomitant and adjuvant treatment with radiotherapy in patients with glioblastoma is assumed to be due, in part, to the concomitant component of treatment. It is not clear if this represents radiosensitization or simply an additive effect.

molecular targeting

Radiation response may be modified through molecular targeting of pathways involved in radiation damage and repair and in pathways known to be altered in gliomas. Inhibition of epidermal growth factor receptor (EGFR) signalling with tyrosine kinase (TK) inhibitors (gefitinib and erlotinib) has demonstrated in vitro and in vivo enhancement of cytotoxicity of radiation. Early phase II studies of combined TK inhibitors and radiation have not demonstrated clear survival benefit [28]. Based on the paradigm of concomitant radiotherapy and temozolomide, where the combination of treatment may have been responsible for the survival benefit seen in the randomised trial, other agents are increasingly tested in this setting and this includes both conventional chemotherapeutic agents, molecular targeting agents and angiogenesis inhibitors.

conclusion

Radiotherapy remains the most effective treatment in the management of patients with high-grade glioma. The optimum treatment is 60 Gy given in daily fractions over a period of 6 weeks to a localised volume including the tumour and a margin. Patients with short predicted life expectancy can be offered less intensive treatment or symptomatic care alone.
There is currently no evidence that intensification of irradiation with radiotherapy sensitizers, altered fractionation or with more localised irradiation, improve survival or quality of life in patients with malignant glioma. Studies which attempt to modify radiotherapy intensity through new radiotherapy techniques and by novel biological modulation through targeted therapy continue with the hope of improving the therapeutic ratio. However, the potential of any new therapy will require evidence for benefit in randomised trials.

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references


