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Overview

Radiotherapy in Glioblastoma: the Past, the Present and the Future

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Abstract

The aim of this review is to explore the changing utility of radiotherapy in the treatment of patients with glioblastoma over the past 60 years. Together with surgery, radiotherapy has always been the cornerstone of treatment of glioblastoma, but techniques have significantly advanced over this time. The exploration of early two-dimensional techniques, investigation of dose escalation, concomitant chemotherapy and modern techniques, including intensity-modulated radiotherapy, image-guided radiotherapy, and volumetric-modulated arc therapy will be covered. In addition, current controversies including decreasing margin size, re-irradiation, treatment of elderly patients, and novel imaging tracers will be discussed. Future directions including immunotherapy and tumour treating fields are examined. Radiotherapy-based treatments cannot rely solely on advances in chemotherapy or immunotherapy to improve the overall survival of patients with glioblastoma. Radiation oncology needs to continue to develop and improve the delivery, target definition, and dose of radiotherapy to these patients to improve their survival and the toxicity associated with treatment.

Key words: GBM; glioblastoma; IMRT; radiotherapy; TTF; VMAT

Statement of Search Strategies Used and Sources of Information

A Pubmed search was carried out for the following areas of interest: radiotherapy/radiation therapy in glioblastoma; intensity-modulated radiation therapy/IMRT in glioblastoma; volumetric-modulated arc therapy/VMAT in glioblastoma; novel tracers in glioblastoma; FET-PET in glioblastoma; FLT-PET in glioblastoma; hypofractionation in glioblastoma; elderly patients glioblastoma; tumour treating fields in glioblastoma; immunotherapy in glioblastoma; nanoparticle delivery systems in glioblastoma; dose painting in glioblastoma; integrated boost technique in glioblastoma; dose escalation in glioblastoma; dose response relationship in glioblastoma; high linear energy transfer radiation in glioblastoma; chemotherapy in glioblastoma. Additional references from reference lists of articles recovered in the original searches were also examined.

Introduction

More than 1400 new cases of malignant brain tumours are diagnosed in Australia each year [1]. Glioblastoma multiforme (World Health Organization grade IV) remains the most common primary brain tumour in adults [2], with a median age at diagnosis of 61 years [3]. Since the addition of temozolomide (TMZ) to adjuvant radiotherapy there has been considerable improvement in survival of these patients [4]. However, survival beyond 5 years from diagnosis remains relatively elusive.

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In addition to surgery, radiotherapy remains the cornerstone of treatment [5–9]. With ongoing improvements in the technical delivery of radiotherapy we expect there to be a clinical benefit for patients with both reduced short and late toxicity. In addition, as patients are living longer and a greater proportion are remaining functionally well until late in the course of their disease, more patients are being offered re-irradiation as part of their salvage treatment.

This review explores the changing nature of radiotherapy delivery to these patients over the last 70 years.

The Past

Evolution of Radiotherapy Technique

Over the decades, morbidity and mortality associated with neurosurgical intervention in glioblastoma has decreased due to improving imaging and neurosurgical techniques, as well as better understanding of neurophysiology [5,10]. Similar gains have been made in the field of radiation oncology. From as early as the 1940s, clinicians have routinely used radiotherapy to treat brain tumours. Initially this was with kilovoltage X-rays [11,12], but by the 1960s treatment was with megavoltage X-rays or ^{60}Cobalt teletherapy to the whole brain to a dose of 45–60 Gy [6,13]. By the 1970s some sophistication was evident in the radiotherapy technique as there was a move away from whole brain radiotherapy for the entire course of treatment. Some centres reported using a two-phase technique with an initial phase of whole brain radiotherapy to 30–46 Gy followed by a boost to the tumour of an additional 20–30 Gy [14–18]. Although the imaging techniques and ability to accurately define and deliver this 'boost' phase would be unacceptable by modern standards, the initial gains in more targeted delivery were made at this time.

Also around this time, a dose-response relationship for glioblastoma was shown by Walker and colleagues [11]. Doses of 50–60 Gy were associated with improved survival compared with doses $\leq$45 Gy. They showed that 60 Gy radiotherapy was associated with a 2.3 times longer survival compared with patients who received no radiotherapy. 55 Gy was associated with a doubling of survival and 50 Gy was associated with a 1.6 times longer life expectancy compared with patients who received no radiotherapy. Patients who received best supportive care after surgery had a median survival of 14 weeks versus 35 weeks for those who received adjuvant whole brain radiotherapy to a dose of 50–60 Gy [8,19]. These increases in survival were not associated with significantly increased toxicity.

Role of Imaging in Radiotherapy

During the 1970s and 1980s computed tomography began to be incorporated into radiotherapy planning to define the boost or target volume for the second phase of the radiotherapy. By the mid-to-late 1980s, magnetic resonance imaging (MRI) began to be incorporated [20]. T1-weighted and T2-weighted image datasets with gadolinium contrast were fused with the radiotherapy planning computed tomography scan to allow better definition of the tumour target volume. Although the slice thickness of 5–10 mm [20] was greater than what we would use today, and the resolution (1.5 Tesla) was less than currently available (3 Tesla), the better imaging techniques allowed a move away from whole brain radiotherapy and to at least a two-phase targeted treatment plan. The initial phase included all enhancing tumour and all surrounding oedema defined by increased T2 signal with an additional 2 cm margin of expansion, with the boost phase limited to only the contrast-enhancing abnormality on T1-weighted images with a 1 cm expansion. Current Radiation Therapy Oncology Group (RTOG) trials still use this two-phase technique.

Dose Escalation of Radiotherapy

Despite (at times whole brain) doses of 60 Gy, local failure at death and an ongoing poor survival led researchers to attempt radiotherapy dose escalation via either interstitial brachytherapy or additional external beam radiotherapy dose. Interstitial brachytherapy had particular appeal as it has the ability to deliver a high dose of radiotherapy direct to the tumour while sparing normal surrounding brain tissue. In a study by the Northern California Oncology Group (NCOG) [21], additional ^{125}Iodine brachytherapy boost was added to the standard radiotherapy protocol with concurrent and adjuvant chemotherapy. In this study of 63 patients the median survival was 88 weeks. Toxicity associated with brachytherapy boost included increased seizure activity, worsening neurological deficit, infection, haemorrhage, pulmonary embolus, and radiation therapy necrosis. These events have been reported in up to 16% of patients with 1% being fatal [22,23]. In addition, a significant rate of re-operation due to radiation therapy necrosis and oedema was observed (up to 50%) [21].

Interstitial brachytherapy with combined hyperthermia to overcome hypoxia has also been explored [24]. Hyperthermia was delivered by means of inductively heated, thermally regulating ferromagnetic implants after-loaded into the stereotactically placed catheters. The study by Stea *et al.* [24] also showed improved survival over conventional radiotherapy with a median survival of 20.6 months. However, 50% of patients required a second craniotomy for worsening neurological symptoms, suggesting an unacceptable level of toxicity associated with this treatment regimen.

Dose escalation with three-dimensional conformal radiotherapy has also been investigated. Salazar and colleagues [8] conducted a retrospective review of patients treated to doses of 70–80 Gy. Although there was a lengthening of median survival measured in weeks, there was no increase in survival beyond 2 years, even for doses as high as 80 Gy. The RTOG 9305 study failed to show a prognostic improvement for patients treated with a stereotactic boost in addition to the standard 60 Gy fractionated conformal radiotherapy with the alkylating agent carmustine [25]. In addition, local failure at progression was

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