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.
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 neurological intervention in glioblastoma has decreased due to improving imaging and neurological 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 60Co 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 ≤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 125Iodine 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
found in >90% of patients. This randomised study confirmed other similar randomised results [26,27], suggesting that early findings of a radiotherapy boost improving survival were probably due to bias in patient selection rather than a true treatment effect (Table 1).

The Use of Radiation Sensitisers

Another mechanism explored by researchers to overcome the relative radioresistance of glioblastomas has been to use radiosensitisers. The theory behind the relative radioresistance was the presence of hypoxic, but potentially viable tumour cells, and the ability of tumour cells to accumulate sublethal damage [28]. In an attempt to overcome both of these factors, Kapp and colleagues [28] at Yale University Medical Centre used large doses per fraction radiotherapy (6 Gy weekly to a total dose of 42 Gy) with concomitant metronidazole, a hypoxic cell sensitiser. They reported on the initial 19 patients treated and found a median survival of 9.4 months with an acceptable toxicity profile. Urtasun and colleagues [29] also examined the use of metronidazole with radiotherapy in glioblastoma with promising early findings. However, in their follow-up study using misonidazole and hypofractionated radiotherapy [30] (the use of doses larger than 2 Gy per fraction, with shorter overall treatment time compared with standard fractionation) they failed to show an improvement in survival over conventionally fractionated radiotherapy.

The Use of High Linear Energy Transfer Radiation

Due to the theoretical advantage of high linear energy transfer radiation to overcome hypoxia (less oxygen dependent), fast neutron beam radiotherapy has been used in glioblastoma. Parker and colleagues [31] used 21 MeV deuterons on 21 patients with glioblastoma and found no increase in overall survival or improved quality of life. An American retrospective analysis of a Japanese study of boron neutron capture therapy [32] also failed to show a survival benefit compared with matched historical controls.

<table>
<thead>
<tr>
<th>Radiotherapy technique</th>
<th>Era</th>
<th>Median survival (months)</th>
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<tbody>
<tr>
<td>WBRT (kV) 40–45 Gy</td>
<td>1940s</td>
<td>4</td>
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<tr>
<td>WBRT (MV) 45–60 Gy</td>
<td>1960s</td>
<td>8–11</td>
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<td>WBRT (MV) + Boost 60 Gy</td>
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<tr>
<td>WBRT (MV) + Boost 60 Gy + nitrosoureas</td>
<td>1980s</td>
<td>10–12</td>
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<td>WBRT (MV) + Boost 75 Gy</td>
<td>1980s</td>
<td>14</td>
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<td>Two-phase PBRT (MV) 60 Gy</td>
<td>1980s &amp; 1990s</td>
<td>12</td>
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<td>Single-phase PBRT (MV)</td>
<td>2000s</td>
<td>14</td>
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<td>60 Gy + TMZ</td>
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<td>IMRT/VMAT (MV) 60 Gy + TMZ</td>
<td>2010s</td>
<td>19–22</td>
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WBRT, whole brain radiotherapy; PBRT, partial brain radiotherapy; MV, megavoltage X-rays; kV, kilovoltage X-rays; TMZ, temozolomide; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy.

The Addition of Chemotherapy to Adjuvant Radiotherapy

In ongoing attempts to improve the duration of survival, various chemotherapy regimens have been trialled concomitantly with adjuvant radiotherapy [13]. Agents trialled include: 5-fluorouracil, Carmustine, Lomustine (CCNU), semustine, cisplatinum, and procarbazine [5,7,13–16,33]. It was not until the addition of CCNU that a real survival advantage was seen [15]. The median survival of glioblastoma patients receiving CCNU and radiotherapy in the 1970s was about 11.5 months [14,15] versus about 5.8–8.3 months for those receiving adjuvant radiotherapy alone [15]. Once there was shown to be a clear advantage to the addition of nitrosoureas, particularly CCNU, attempts at combination chemotherapy with radiotherapy were made [7,17,33,34]. Eyre and colleagues [7] used a combination of CCNU and procarbazine with radiotherapy versus radiotherapy-CCNU alone but found no benefit to the combination. Similarly, Comella et al. [17] used a combination of BCNU, vincristine, and procarbazine with radiotherapy and found no survival advantage over single agent BCNU with radiotherapy.

It was not until the introduction of TMZ, an alkylating agent, initially in recurrent glioblastoma and subsequently in the newly diagnosed setting, that significant survival advantages were seen. The landmark study by Stupp and colleagues [35] published initially in 2002 investigated TMZ given concurrently with adjuvant radiotherapy followed by additional sequential treatment. In this initial phase II study they were able to show a median survival of 16 months with combined treatment. The subsequent randomised trial [4] of the above regimen versus standard adjuvant radiotherapy alone showed a 2 year survival of 27.2% with combined treatment (versus 10.9% for radiotherapy alone) and a median survival of 14.6 months (versus 12.1 months for radiotherapy alone). This remains the standard of care today for patients <65 years with glioblastoma. It should be clarified that the definition of ‘elderly’ patients in glioblastoma is not consistent as various studies have used different cut-offs — from 60 to 70 years. Currently most clinicians would consider 65 years as a cut-off point for elderly patients. The treatment of elderly patients will be discussed in more detail below.

The Present

Intensity-modulated Radiotherapy, Volumetric-modulated Arc Therapy and Image-guided Radiotherapy

Intensity-modulated radiotherapy (IMRT) allows delivery of a high dose of radiation to a target while sparing surrounding critical structures. It is produced by delivering multiple beamlets of radiation, from many angles incident on a target. These individual beamlets are dynamically shaped so that different areas within the target can receive different doses of radiation simultaneously. It far better achieves the standard goals of radiation therapy: to deliver a high dose of radiation to the target and spare the normal tissues, than conformal radiotherapy. As IMRT allows better...
target coverage and dose conformity with complex, irregular shapes, it is also able to reduce toxicity by achieving a better dose gradient between the target and normal tissues [9,36–39].

However, the benefits of IMRT can only be obtained with the use of accurate targeting by the use of image-guided radiotherapy (IGRT). Effective immobilisation with a thermoplastic mask or shell, or a relocatable frame system, is essential. IGRT increases the precision of treatment delivery and, in certain cases, allows the reduction in the planning target volume margin [36]. It ensures correction of both systematic (treatment planning) and random (set-up) errors. In practice, online IGRT is the most beneficial and is a process of daily pre-treatment imaging with, most frequently, an on-board cone beam computed tomography scan and correction of any positional errors before the delivery of radiotherapy. Although it has the potential to correct all observed translational errors (except possibly rotational errors), it replaces it with smaller potential errors in the IGRT process, such as matching error, couch position error and intra-fractional movement.

The benefits of using IMRT in central nervous system planning are particularly evident in difficult locations such as those close to the brainstem or orbit where it is almost impossible to achieve adequate dose coverage of the target while meeting organ dose constraints of the adjacent critical structure. The use of IMRT allows the production of plans with a variable dose, a graduated dose or simultaneous integrated boosts. IMRT permits the radiotherapy planner to specify dose limits to individual organs, including the hippocampus, potentially decreasing long-term toxicity. Figure 1 shows the ability of IMRT to better cover the planning target volume compared with three-dimensional conformal radiotherapy while still sparing critical structures such as the brainstem, optic chiasm and contralateral hippocampus.

The IMRT-simultaneous integrated boost technique allows delivery of a higher dose to the primary mass while simultaneously delivering a lower dose to the expanded margin. There are multiple ways to achieve this via either conventional or hypofractionated regimens [9,39]. Suzuki et al. [9] used a hypofractionated dose to the macroscopic tumour with a simultaneous conventional fractionation to the expanded margin. In a pilot study of six patients they delivered 70 Gy in 28 fractions (2.5 Gy per fraction) to the macroscopic tumour and 56 Gy in 28 fractions (2.0 Gy per fraction) to the expanded margin. With only a short follow-up (median 6.9 months) they found five of six patients progressed, with four patients progressing within the high-dose region. Unfortunately these results are in keeping with previous dose-escalation/hypofractionation failures [8,21–27].

Volumetric-modulated arc therapy (VMAT) is the innovative radiotherapy technique where the dose rate, gantry speed and field apertures (multileaf collimators) are dynamically changing while the treatment is being delivered. It overcomes the negative impact of IMRT treatment delivery time while allowing for comparable dosimetric conformity to IMRT [40]. It is increasingly being used in the treatment of glioblastoma due to the benefit of short treatment time over IMRT while retaining excellent dosimetry. However, there are limited studies at present exploring the use of VMAT in glioblastoma, although outcomes are expected to be similar to IMRT.

**Hypofractionation**

Recently there has been renewed interest in investigating a hypofractionated regimen of radiotherapy in newly diagnosed glioblastoma. Hypofractionation has certain desirable features: decreased overall treatment time for patients who have limited life expectancy, decreased cost to the patient and health system, and potential manipulation of radiobiological advantage — increased cell killing with higher dose per fraction and potentially reduced accelerated repopulation. Ammirati et al. [41] conducted a pilot

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**Fig 1.** Comparison of intensity-modulated radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3DCRT) dosimetry. (A) 60 Gy dose distribution using IMRT displaying excellent coverage of the planning target volume (PTV) outlined in red. (B) 40 Gy dose distribution using IMRT displaying sparing of half the brainstem/chiasm and no low dose wash in contralateral brain. (C) 40 Gy dose distribution using 3DCRT displaying significant underdosing of the PTV to spare the brainstem and chiasm and significant low dose wash to contralateral brain.
study assessing 52.5 Gy in 15 fractions with concurrent and 
adjuvant TMZ and found (with a median follow-up period 
of 10 months) a median survival of 12.7 months with 
acceptable toxicity. Similarly, Panet-Raymond and col-
leagues [42] retrospectively analysed 35 patients treated 
with an integrated boost hypofractionated regimen with 
concurrent and adjuvant TMZ. Their regimen consisted of 
60 Gy in 20 fractions to the gross tumour volume with 
concurrent 40 Gy in 20 fractions to the planning target 
volume. They reported a median survival of 14.4 months 
with no grade 3 or 4 toxicity. Interestingly, though, of the 23 
documented cases of progressive disease in this cohort, 21 
were central with only two patients progressing >2 cm 
from their initial gross tumour volume, suggesting that 
hypofractionated dose escalation does not change the 
pattern of failure of this disease.

Ultra-hypofractionated regimens, such as those in a 
study by Reddy et al. [43] of 60 Gy in 10 fractions, utilise 
decreased margins (5 mm) on the gross tumour volume on 
T1-weighted MRI imaging for their high-dose region and 
a lower simultaneous dose region (30 Gy in 10 fractions) to 
the larger T2-weighted radiological abnormality (clinical 
target volume). The aim of the reduced margins is to 
decrease potential toxicity and morbidity from such large 
fraction sizes (radiation necrosis) and the goal of the ultra-
hypofractionated regimens is to increase tumour cell kill. 
Unfortunately reported studies on hypofractionated regi-
mens have failed to improve survival in these patients 
[43,44]. At present there is still no benefit over standard 
conventional fractionation.

Decreased Margin Size

Due to historical patterns-of-failure data [45–55] large 
margins of expansion from the gross tumour volume to the 
clinical target volume have been incorporated. For example, 
the European Organisation for Research and Treatment of 
Cancer (EORTC) uses 2 cm dosimetric expansion margins 
around enhancing disease on MRI and the RTOG has used a 
two-phase technique with the initial phase incorporating a 
2 cm expansion beyond peritumoural oedema seen on T2-
FLAIR sequences on MRI, and the second phase utilising a 
2 cm margin beyond enhancing tumour (on T1-based 
contrast imaging alone, without the surrounding T2 signal 
alteration) [56]. Since the introduction of IMRT and VMAT, 
which display steeper dose gradients between target and 
surrounding tissue, and the introduction and routine use of 
TMZ, there has been no repeat of these earlier studies 
investigating patterns of failure and it is therefore unclear if 
these changes to practice have altered patterns of failure. 
The New Approaches to Brain Tumour Therapy consortium 
have adopted a reduced margin approach to the manage-
ment of glioblastoma. They use a 5 mm clinical target vol-
ume margin and have shown in several phase II studies no 
change in the pattern of failure compared with EORTC 
26981 [4] and in fact an improvement in overall survival 
(19.6 versus 14.6 months) [57].

Although the apparent improvement may be due to pa-
tient selection as well as the proportion of patients being 
treated with a novel systemic agent, and overall improve-
ment in patient care over the subsequent decades and 
improving salvage regimens, we can probably conclude that 
their margins are probably not inferior to larger margins 
utilised in the EORTC study. These results have been sup-
ported by a large retrospective series by Paulsson et al. [58], 
which analysed patterns of failure and survival for patients 
who had 5, 10 and 15–20 mm clinical target volume mar-
gins, and found no difference in patterns of failure or sur-
vival in patients receiving limited margins radiotherapy for 
glioblastoma. Optimal clinical target volume margins will 
probably continue to evolve in the future.

Elderly Patients

Optimal treatment regimens for elderly patients are yet 
to be determined. Although younger patients have shown 
 Improved survival since the addition of TMZ to standard 
60 Gy radiotherapy there remains concern over the toler-
ance of this regimen in the elderly as the landmark EORTC 
trial limited enrolment to patients under 70 years of age 
[59]. In addition to the potential increased toxicity of the 
combined chemoradiotherapy regimen in the elderly popu-
lation, it is unclear whether there is a survival benefit in 
this group, and what that magnitude of benefit might be.

Evidence to guide treatment in this age group remains 
limited and predominantly retrospective [59–64]. In 
Australia, most patients over the age of 65 years are offered 
short-course radiotherapy (40 Gy) in line with the pro-
spectively randomised trial by Roa et al. [65], which showed 
non-inferiority between 40 Gy adjuvant radiotherapy and 
60 Gy radiotherapy (median survival 5.6 versus 5.1 months, 
$P = 0.57$). Patients were not given TMZ. However, there is 
increasing retrospective evidence to support the use of 
long-course chemoradiotherapy in the elderly population 
[59,60,64,66,67].

The outcomes of the now closed NCIC/EORTC/TROG GBM 
Elderly trial in which patients were randomised to 40 Gy 
radiotherapy ± concurrent and adjuvant TMZ were recently 
presented at the 2016 American Society of Clinical Oncology 
annual meeting [68]. In total, 562 patients aged >65 years 
were enrolled in the study, with a median age of 73 years. 
The authors found that the addition of TMZ to short-course 
radiotherapy extended the median survival from 7.6 
months to 9.3 months. In addition, the 2 year survival rate 
was 10.4% for combined therapy versus only 2.8% for 
radiotherapy alone. Those patients who displayed O-6-
methylguanin-DNA methyltransferase (MGMT) pro-
moter methylation had a median survival of 13.5 months, 
approaching that seen in younger patient groups with long-
course chemoradiotherapy. Equally important to the dura-
tion of survival is the quality of survival in this age group. 
The study found that there was no difference in physical, 
cognitive, emotional and social functioning between the 
two treatment arms using standard EORTC QLQ-C30 and 
BN20 questionnaires.

A recently published prospective trial by Roa and col-
leagues [69] expands on their initial work by randomising 
elderly patients to 40 Gy in 15 fractions (standard) versus an
even shorter course of treatment — 25 Gy in five fractions over 1 week. They found that the shorter course was non-inferior, with a non-significant difference in median survival of 7.9 months versus 6.4 months (40 Gy arm).

Due to the shorter survival in the elderly cohort there has been interest in whether radiotherapy can be safely omitted and patients treated with TMZ alone. The NOA-08 trial by Wick and colleagues [70] was a prospective trial of long-course radiotherapy (60 Gy) versus TMZ alone in elderly patients with glioblastoma or grade III astrocytoma and showed non-inferiority of the TMZ alone arm. Similarly, the NORDIC study by Malmström and colleagues [71] showed similar median survival between TMZ alone and hypofractionated radiotherapy arms (median survival 8.4 versus 7.4 months, respectively). However, patients considered for this approach need to display MGMT methylation to achieve benefit from TMZ. MGMT testing is still not routine, with differing testing procedures in place, including immunohistochemistry, methylation-specific polymerase chain reaction, reverse transcriptase polymerase chain reaction, pyrosequencing and bisulphite sequencing, and no internationally agreed cut-off for positive (methylated) versus negative (unmethylated) results [72,73]. Testing is limited by sample quality and contamination. However, at present pyrosequencing shows the most promise.

This approach in the elderly population may be worth considering, particularly when patients are very elderly (>75 years), frail, or have had limited resection with considerable residual disease and probably require large-field radiotherapy as even short-course radiotherapy in this cohort of patients can be quite disabling, with lethargy that can be protracted and limits the efficacy of rehabilitation, and the patient’s ability to return to independence.

**Novel Imaging in Radiotherapy Planning**

Positron emission tomography (PET) scans have been commonly used in the management of cancer patients for at least two decades. The most commonly utilised radiolabelled tracer remains 18-fluorodeoxyglucose, but its utility in neuro- oncology is limited due to the high background uptake of the tracer in normal brain, making it difficult to distinguish any abnormality. Radiolabelled amino acid tracers are preferentially taken up by tumour cells due to an overexpression of amino acid transporters, with relatively low background uptake in normal brain tissue. This makes them an ideal imaging modality in gliomas. The two tracers most studied are [11C]-methionine (MET) and [18F]-flurodeoxy-o2-fluoroethyl-L-tyrosine (FET) [74]. Due to the short half-life of 11C-MET (20.4 min), FET has become the preferred amino acid tracer (18F half-life = 109.5 min). In the case of glioblastoma, the role of FET is primarily in the post-radiotherapy setting as it may aid differentiation between pseudoprogression and true tumour progression (particularly when pre- and post-radiotherapy scans are carried out), with reported sensitivity rates of 75–100% and specificity rates of 60–100% [74]. In the setting of re-irradiation for recurrence, FET has also been shown to better delineate tumour volume compared with MRI [74]. In early studies this has translated to an overall survival benefit [75]. MET has also been shown to correlate better with tumour delineation compared with MRI in the newly diagnosed setting [76].

**Re-irradiation**

Increasing experience has been gained in recent years with re-irradiation in the setting of recurrent glioblastoma. Initially this was with stereotactic radiosurgery/radiotherapy for small volume recurrences [77–84], but more recently with IMRT/VMAT [85] for diffuse recurrences. With increasing experience the concurrent use of bevacizumab with re-irradiation to reduce potential toxicity (radiation necrosis) has increasingly been utilised [86,87]. Similar to other salvage options for these patients, the median survival is in the order of 9–11 months [85] in carefully selected patients.

**The Future**

**Tractography and Functional Mapping in Radiotherapy Planning**

With respect to novel image tracers such as FET, limited spatial resolution remains a limitation. However, the advent of PET/MRI scanners may allow for improved diagnostic utility when both high resolution anatomical imaging (MRI) and functional imaging (PET) are combined in the one study. This should also result in a decrease in patient discomfort, time and cost. Diffusion tensor imaging tractography has been shown to differentiate between gross tumour and tumour infiltrative margins in a study by Price et al. [88]. Patients were imaged preoperatively then underwent image-guided biopsies along a single neural track that went into normal brain and diffusion tensor imaging and histology correlated. This study showed a sensitivity of 98% and a specificity of 81% of diffusion tensor imaging to accurately identify gross tumour, tumour infiltration and normal brain tissue. Utilising this or similar techniques may enable better target localisation and normal tissue avoidance.

**Dose Painting**

The heterogeneity of glioblastomas remains one of the key areas for research. As previously mentioned, there is a high preponderance of hypoxic, potentially viable tumour cells that may require a higher dose of radiation compared with the well-oxygenated cells in order to achieve cell death. [18F]-fluoromisonidazole ([18F]-FMISO) has the ability to identify hypoxic cells within tissue, and utilising this novel tracer in the planning process could allow ‘dose painting’, i.e. voxel-based dose targeting [74]. This could allow the radiation oncologist to specify different regions within the target volume to different doses via IMRT or VMAT integrated boost technique. In addition, the current proposed cut-off value for recurrence is a tumour to background uptake ratio for FET of 1.6. This could potentially be
incorporated into the radiotherapy planning process, allowing semi-automatic tumour delineation based on the threshold value of FET uptake.

Another way to achieve personalised radiotherapy plans may be via mathematical algorithms, such as those explored by Corwin et al. [89]. Their algorithm allowed for individual radiotherapy optimisation based on patient-specific tumour kinetics. These plans deliver the maximum dose to the proliferating rim of the tumour with less dose delivered to the centre and a decreasing gradient of dose on the periphery. However, the peak dose of these optimised plans was between 100 and 130 Gy, raising the risk of increased radiation necrosis. Further pre-clinical studies are required before this approach moves into clinical practice.

**Immunotherapy**

The role of immunotherapy in glioblastoma is rapidly expanding as the pharmaceutical industry develops drugs designed to exploit our innate immune mechanisms and vaccines are developed to directly target proteins involved in the immune cascade or direct tumour proteins. Drugs targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed death ligand 1 (PD1/PDL1) have shown significant early promise in a range of cancer types [90] and revitalised the field of immunotherapy and its potential role in the treatment of glioblastoma.

There are several current clinical trials investigating the role of immune checkpoint inhibitors, e.g. CTLA-4 and PD1/PDL1 inhibitors such as nivolumab, a PD1 inhibitor, in both the newly diagnosed and recurrent glioblastoma setting. If these early phase trials are positive, future directions will also probably involve combinations of these agents and incorporation into standard care protocols [91].

Epidermal growth factor receptor variant type III is a deletion mutation that is expressed in about 30% of primary glioblastomas [92]. A phase II trial of a peptide vaccine targeting this mutation, rindopepimut, delivered after the completion of radiation displayed an overall survival benefit compared with matched historical controls (26 versus 15 months, P = 0.0013) [93]. Unfortunately, the international phase III trial (ACT-IV) has recently been discontinued as the Data Safety and Monitoring Board reported after interim analysis that it was unlikely to meet the primary end point of difference in overall survival between the two arms of the study.

Another promising vaccine is the heat shock protein-96 targeted vaccine, which is currently being evaluated in a phase III clinical trial in recurrent glioblastoma [92]. Dendritic cell vaccines are also currently being investigated. One of the most promising that is currently being tested in newly diagnosed glioblastoma in a phase III clinical trial is DCvax-L. This dendritic cell vaccine uses autologous dendritic cells pulsed with a lysate derived from the patient’s own resected tumour [92].

**Tumour Treating Fields**

Tumour treating field (TTF) therapy uses alternating electric fields to disrupt tumour cell mitosis and is a novel therapy that has recently been approved by the Food and Drug Administration in the USA for use in recurrent glioblastoma [94]. A detailed overview of the radiobiological processes involved in TTF are beyond the scope of this review, but references are now available [94–100]. The initial phase III trial of TTF in recurrent glioblastoma compared it with physician’s choice chemotherapy [101]. The primary end point was overall survival and the trial failed to show a difference between the two arms, but did show an improvement in quality of life in the TTF arm. TTF is currently being investigated in newly diagnosed glioblastoma during the sequential TMZ phase after the completion of radiotherapy [94,102]. The interim analysis of the study by Stupp and colleagues [102] showed both improved progression-free survival and overall survival in the TTF/TMZ combined arm compared with TMZ maintenance alone (progression-free survival 7.1 versus 4.0 months, overall survival 20.5 versus 15.6 months). If the final results of this study support the initial findings then expanded research might include the potential role of TTF during radiotherapy for newly diagnosed glioblastoma. All results will better elucidate the feasibility and biological rationale for the use of TTF.

**Nanoparticle Delivery Systems**

There are numerous nanoparticle technologies of varying size and composition being developed for use as part of therapeutic strategies in cancer. In the treatment of glioblastoma nanoparticle delivery systems may enable cytotoxic chemotherapy access to tumour that would otherwise not cross the blood–brain barrier in therapeutic concentrations. A detailed analysis of these myriad systems is...
beyond the scope of this review, but references are available [103–110]. This area of neuro-oncological research will probably continue to grow and expand over the next decade (Figure 2).

Conclusion

The evolution and role of radiotherapy in the treatment of glioblastoma has certainly advanced significantly since the 1970s. The changes in chemotherapy and immunotherapy have also been substantial and will hopefully continue to make significant gains in the future. However, radiation-based treatments cannot rely solely on 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. This is the challenge faced over the next decade.

References

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