

REVIEW ARTICLE

## The evolving roles and controversies of radiotherapy in the treatment of glioblastoma

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### Abstract

Numerous randomised controlled trials have demonstrated the benefit of radiation therapy in patients with newly diagnosed glioblastoma and it has been the cornerstone of treatment for decades. The aims of this review are to (1) Briefly outline the historical studies which resulted in radiation being the current standard of care as used in the Stupp et al. trial (2) Discuss the evolving role of radiation therapy in the management of elderly patients (3) Review the current evidence and ongoing studies of radiation use in the recurrent/salvage setting and (4) Discuss the continuing controversies of volume delineation in the planning of radiation delivery.

## Introduction

The benefit of radiation therapy in patients with newly diagnosed glioblastoma has been demonstrated in numerous randomised trials and has been the cornerstone of treatment for decades. In attempts to improve the very poor outcomes associated with this disease, numerous therapeutics have been added to radiation though with very little success until the landmark study by Stupp et al.<sup>1,2</sup> which established gross surgical excision followed by concurrent temozolomide and radiation being the standard of care.

Despite the long history of radiation use in glioblastoma, there are continuing controversies over

tumour volume delineations and its role in the recurrent/salvage setting. Furthermore, multiple recent studies of elderly patients with glioblastoma suggest that the role and dose/fractionation of radiation delivery to this increasing population will continue to evolve. The aims of this review are to (1) Briefly outline the historical studies which resulted in radiation being the current standard of care as used in the Stupp et al. trial<sup>1,2</sup> (2) Discuss the evolving role of radiation therapy in the management of elderly patients (3) Review the current evidence and ongoing studies of radiation use in the recurrent/salvage setting and (4) Discuss the continuing controversies of volume delineation in the planning of radiation delivery.

## Methodology

The authors have identified a number of evolving and controversial issues facing the practicing radiation oncologist in the management of high-grade gliomas (HGG). The range of topics is not exhaustive but is representative of what the authors perceive as areas where the management is evolving. Searches using the terms 'glioblastoma', 'high grade glioma', 'recurrence', 'radiotherapy', 'radiation therapy' 'elderly' and 'stereotactic' were used in various combination to search Medline and PubMed databases without any date limits. In addition, the references of published papers were searched manually for relevant articles. Abstracts from the Society of Neuro-Oncology conferences held in 2013 and 2014 were also manually searched.

## Radiation therapy in the management of newly diagnosed glioblastoma

There is level 1 evidence for the use of radiation therapy in the treatment of patients with glioblastoma with numerous randomised controlled trials showing a clear survival benefit. The majority of the trials have combined grade 3 and 4 gliomas though the majority of the patients had grade 4 disease. In one of the earliest randomised trials of radiation in HGG, Reagan et al.<sup>3</sup> randomised 63 patients in 1970 from the Mayo Clinic to the arms of (1) whole brain radiation to a dose of 50 Gy in 25–28 fractions, (2) CCNU (lomustine) alone and (3) combination of CCNU and radiation. Median survival was 11 months in the radiation alone and 12 months in the combination arms compared to only 6 months in the CCNU alone arm. Numerous other randomised trials have confirmed the survival advantage of radiation therapy in newly diagnosed disease and a pooled analysis<sup>4</sup> of six randomised trials have shown a risk ratio for 1 year mortality of 0.81 favouring post-operative radiation versus none (Table 1).

The standard radiation dose of 60 Gy in 30 fractions is based on retrospective analysis of three prospective clinical trials which suggested a dose–response relationship between 50 and 60 Gy<sup>5</sup> and attempts at dose escalation using conventional radiation,<sup>6</sup> intensity modulated radiotherapy,<sup>7</sup> brachytherapy<sup>8,9</sup> and radiosurgery<sup>10</sup> found no additional benefit resulting in 60 Gy being the standard of care as used in the Stupp trial.<sup>1,2</sup> However, a study using dose escalation with protons to 90 cobalt gray equivalent and accelerated treatment did reduce the central pattern of recurrence and was associated with improved survival compared with historical controls.<sup>11</sup>

**Table 1.** Randomised studies of radiation therapy in the management of newly diagnosed glioblastoma

Study	Arm 1	Arm 1 outcome	Arm 2	Arm 2 outcome	Arm 3	Arm 3 outcome	Arm 4	Arm 4 Outcome
Reagan et al <sup>3</sup>	Whole brain radiation 50Gy in 25-28#	MS = 11 months	CCNU + radiation	MS = 12 months	CCNU alone	MS = 6 months	NA	NA
Walker et al <sup>67</sup>	Whole brain radiation 50Gy-60Gy	MS = 35 weeks	BCNU + radiation	MS = 34.5 weeks	BCNU alone	MS = 18.5 weeks	Best supportive care	MS = 14 weeks
Kristiansen et al <sup>68</sup>	Whole brain radiation 45Gy in 25#	MS = 10.8 months	Radiation + IV bleomycin	MS = 10.8 months	No radiation or chemotherapy	MS = 5.2 months	NA	NA
Walker et al <sup>69</sup>	Whole brain 60Gy in 30-35#	MS = 367weeks	BCNU + radiation	MS = 49 weeks	Semustine + radiation	MS = 43 weeks	Semustine alone	31 weeks
Andersen et al <sup>70</sup>	Radiation alone	1 yr survival 19%	No radiation	1 year survival 0%	NA	NA	NA	NA
Sandberg-Wollheim <sup>71</sup>	Radiation to 58Gy + PVC	MS = 62 weeks	PVC alone	MS = 42 weeks	NA	NA	NA	NA

BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea (Carmustine); CCNU, lomustine; PVC, procarbazine, vincristine, and lomustine; MS, median survival

## Role of radiation in elderly patients

The most significant prognostic factor in patients with glioblastoma is age, followed by Karnofsky performance status, and mental status.<sup>12</sup> There has been continuing controversy regarding the optimal management of elderly patients as their survival tends to be short yet the standard treatment is lengthy. Questions therefore arise as to whether the benefit of the standard 6 week course of chemoradiation is justified in this population and outweigh the potential inconvenience and higher morbidity of treatment.<sup>13</sup>

The role of radiation in the elderly population has been demonstrated in a French randomised trial by Keime-Guibert *et al.* in which patients aged 70 years and over, a dose of 50 Gy in 1.8 Gy per fraction has been shown to increase median survival over best supportive care alone (29.1 vs. 16.9 weeks) with a hazard ratio (HR) of death of 0.47 (95% CI 0.29–0.76). This was achieved without any associated decrement in quality of life or cognitive function.<sup>14</sup> Using shorter courses of radiation therapy, a Canadian study by Roa *et al.* has excluded a greater than 14% difference in the proportion of patients  $\geq 60$  years of age surviving at 6 months between the standard adjuvant dose of 60 Gy in 30 fractions versus a hypofractionated dose of 40 Gy in 15 fractions over 3 weeks alone without chemotherapy.<sup>15</sup> In the subgroup of 45 patients aged 60 or older, another study which randomised patients between 60 Gy in 30 fractions versus 45 Gy in 20 fractions found that the survival HR was 1.0 (95% CI, 0.54–1.89)<sup>16</sup>, suggesting that a shorter course of radiation may be appropriate for this cohort of patients.

More recently, the NOA-08 study<sup>17</sup> randomised 412 patients to standard radiation alone of 60 Gy in 30 fractions versus temozolomide administered using a 1 week on, 1 week off schedule. The study showed that temozolomide was non-inferior to radiation alone with a HR 1.09 (95% CI 0.84–1.42) and a trend for improved overall survival in the group with *MGMT* (*O*<sup>6</sup>-methylguanine–DNA methyltransferase) promoter methylation status. This temozolomide schedule however was associated with a significantly higher risk of haematological, liver function derangement, infective and thromboembolic toxicity.

The Nordic Clinical Brain Tumor Study Group<sup>18</sup> randomised 342 patients into (1) temozolomide alone arm at a dose of 200 mg/m<sup>2</sup> on days 1–5 of every 28 days; (2) standard radiation to 60 Gy in 30 fractions and (3) hypofractionated radiation to a dose of 34 Gy in 10 fractions. The temozolomide only group had longer median overall survival compared to the long course radiation group (8.3 vs. 6 months,) but not against short course radiation (median survival 7.5 months). For all

patients who received temozolomide or hypofractionated radiation, the overall survival was similar (8.4 vs. 7.4 months). A subgroup analysis of patients older than 70 years showed survival was better with temozolomide or with hypofractionated radiotherapy compared with standard radiation, HR 0.35 and 0.59 respectively. A recent meta-analysis<sup>19</sup> including both these randomised trials in addition to 3 non-randomised comparative studies<sup>20–22</sup> demonstrated that temozolomide alone may be non-inferior to radiation alone but is not necessarily a straight-forward solution for elderly glioblastoma patients because of an increased risk of toxicities, especially when given using a dose dense schedule. These studies also suggest that *MGMT* promoter methylation may be a useful predictive biomarker to stratify elderly glioblastoma patients for radiation versus alkylating agent chemotherapy.<sup>23,24</sup>

Currently there are no randomised studies on combined therapy in the elderly population but a meta-analysis of non-randomised studies showed that chemoradiation with temozolomide conferred a clear survival benefit on a selection of elderly glioblastoma patients who had a favourable prognosis, for example, extensive resection, favourable KPS.<sup>25</sup> A randomised joint study of the National Cancer Institute of Canada (NCIC)/EORTC (European Organisation for Research and Treatment of Cancer)/TROG (Trans Tasman Radiation Oncology Group) is exploring the efficacy of hypofractionated radiation with and without temozolomide (NCT00482677) and will be needed to confirm these results. This study is now closed to accrual.

Based on current evidence, patients not suitable for the Stupp *et al.*<sup>1,2</sup> protocol of chemo-radiation to a dose of 60 Gy in 30 fractions include alternative hypofractionated regimes such as 40 Gy in 15 fractions, 45 Gy in 20 fractions and 34 Gy in 10 fractions. For elderly patients who are not suitable for radiation therapy and have *MGMT* methylated tumours, temozolomide alone may be a suitable treatment option.

## Role of radiation in recurrent disease

Patients with glioblastoma invariably recur despite optimal upfront treatment with the majority of recurrences occurring within the first year.<sup>26</sup> Local recurrences are the major contributor to patient mortality and are difficult to manage, given the morbidity of surgical re-excision,<sup>27–29</sup> the large volume of re-irradiation often required and the limited effective systemic options.<sup>30</sup> The outcome following recurrence is very poor with a 6-month progression free survival (PFS) of 15%, median PFS of only 9 weeks and median overall survival of 25 weeks.<sup>31</sup>

Several case series, retrospective and prospective studies have shown the potential efficacy and acceptable toxicity of radiosurgery for this disease.<sup>32–37</sup>

In a large series of 147 patients treated to a median dose of 35 Gy in 10 fractions prescribed to the 85–90% isodose either alone or in addition to repeat craniotomy or concomitant chemotherapy, similar outcomes were obtained with median survival of 10 and 11 months for patients with Grade 3 and 4 tumours respectively. There was also no demonstrated clinically significant acute morbidity.<sup>37</sup> In another large-single institution series, Combs *et al.*<sup>38</sup> investigated the role of re-irradiation in 172 patients ( $n = 42$  WHO grade 3;  $n = 59$  WHO grade 4). The median dose was 36 Gy in 2 Gy per fraction using the fractionated stereotactic approach. Median survival after re-irradiation was 8 months for patients with glioblastoma and 16 months for patients with grade 3 tumours.

Bevacizumab is a human recombinant monoclonal antibody to vascular endothelial growth factor (VEGF), which was approved in 2009 by the FDA in the United States for the treatment of recurrent glioblastoma based on durable responses relative to historical controls from non-comparative phase II trials.<sup>39,40</sup> To this end, Gutin *et al.*<sup>41</sup> reported on a series of 25 patients with recurrent HGGs treated with a stereotactic dose of 30 Gy in 5 fractions prescribed to the 100% isodose with bevacizumab. The reported 6 month PFS and median PFS were 65% and 7.3 months for glioblastoma with a median survival of 12.5 months. There were no reported cases of radiation necrosis and the majority of the toxicity was associated with bevacizumab, but was in line with other reports of bevacizumab use. In a more recent study, Cuneo *et al.*<sup>42</sup> reported the 1 year overall survival for patients with glioblastoma who received adjuvant (concurrent with or after radiosurgery) bevacizumab was 50% vs. 22% for patients not receiving adjuvant bevacizumab ( $P = 0.005$ ). Other studies have suggested that a combination of bevacizumab and radiosurgery or hypofractionated stereotactic radiation therapy for recurrent malignant glioma confers improved survival and acceptable toxicity. Furthermore, in a small study of 15 patients with recurrent high grade glioma treated with stereotactic radiosurgery (SRS) where lesions <3 cm in diameter were treated in a single fraction with either 18 Gy or 24 Gy, and those 3–5 cm in diameter received 5 × 5-Gy fractions with bevacizumab; no changes in neurocognition, quality of life and Karnofsky performance status were detected.<sup>43</sup>

The Radiation Therapy Oncology Group (RTOG) has opened a randomised phase II trial (RTOG 1205) of concurrent bevacizumab and radiation therapy versus bevacizumab alone in previously irradiated, bevacizumab-

naïve patients with recurrent glioblastoma. Unifocal lesions with a maximum diameter <5 cm will be treated with a stereotactic approach to a dose of 35 Gy in 10 fractions.

For patients with recurrent disease, there is a select group who may benefit from re-irradiation using the stereotactic approach. These include patients with a greater than 6-month period since previous high dose radiation, smaller tumours (e.g., <5 cm), reasonable performance status (e.g., Karnofsky performance status  $\geq 60$ ) and absence of leptomeningeal disease.

### Optimal radiation target volume in glioblastoma

All of the early trials demonstrating a survival benefit of radiation therapy have utilised whole brain irradiation but multiple studies investigating the patterns of recurrence showed that 70–90% occurred within 2–3 cm of the original tumour.<sup>44–50</sup> Lee *et al.*<sup>51</sup> investigated 36 patients treated to 70 Gy or 80 Gy using a planning target volume (PTV) of tumour +2–3 cm finding that 89% of recurrences were central or in-field. A study performed by Shapiro *et al.*<sup>52</sup> investigated the possibility of delivering at least part of the radiation to only part of the brain. Patients recruited between 1980 and 1981 were offered whole brain radiation to a dose of 60.2 Gy in 35 fractions while those accrued between 1982 and 1983 were randomised to whole brain radiation as described or 43 Gy in 25 fractions of whole-brain radiotherapy plus 17.20 Gy coned down to the tumour volume. Survival differences between the radiotherapy groups were small and not statistically significant suggesting that giving part of the radiotherapy by coned-down boost is as effective as full whole-brain radiation. Other studies have shown that despite utilising partial brain radiation, most of the recurrences are in close proximity to the original tumour<sup>53</sup> despite dose escalations up to 90 Gy.<sup>7</sup>

However, continuing controversy and variability lies in the method in which the ‘at risk’ tumour volumes are delineated. A recent multi-centre study investigating dose dense temozolomide in newly diagnosed glioblastomas used the RTOG approach for North American centres and the EORTC approach for European centres,<sup>54</sup> reflecting the continued variability in practices around the world. Current RTOG protocols use a two phase approach which encompasses the peritumoral oedema as these areas are believed to contain high concentrations of tumour cells<sup>55–57</sup> (Table 2). The disadvantage to such an approach is that this may lead to larger radiation treatment fields, especially when there is significant oedema, with resulting increased risk of neurotoxicity.<sup>58</sup> However, as discussed above, published series found that

**Table 2.** Examples of the variability in radiation volume delineation in glioblastoma.

Technique	Chemotherapy	Pre- versus post-op MRI	Phase 1	Phase 2
Minniti <i>et al</i> <sup>60</sup>	Yes, concurrent and adjuvant TMZ	Post-op	GTV = resection cavity + residual volume on contrast enhancing T1 images. CTV = GTV + 2 cm. Dose = 60 Gy/30#. For CTV > 250 cm <sup>3</sup> Phase I treated to dose = 50 Gy/25#. PTV = CTV + 0.3 cm	For CTV > 250 cm <sup>3</sup> . GTV as described. CTV = GTV + 1 cm. Dose = 10 Gy/5#. PTV = CTV + 0.3 cm
RTOG 0837	Yes, concurrent and adjuvant TMZ	Post-op but use pre-op for correlation	GTV1 = T2 or FLAIR abnormality including post-operative enhancement and resection cavity. CTV1 = GTV1 + 2 cm limited to natural barriers to tumour growth. If no oedema then PTV = Contrast enhanced lesion + surgical cavity + 2.5 cm margin. PTV1 = CTV1 + 3–5 mm. Dose = 46 Gy/23#	GTV2 = contrast enhancing T1 lesion and surgical cavity. CTV2 = GTV2 + 2 cm limited to natural barriers of tumour growth. PTV2 = CTV2 + 3–5 mm. Dose = 14 Gy/7#
MD Anderson <sup>59</sup>	44% had some form of systemic therapy. Only 1 patient concurrent TMZ	Post-op	GTV = resection cavity and T1 contrast enhancement. CTV = GTV + 2 cm. PTV = CTV + 0.5 cm. Dose = 50 Gy/25#	PTV = GTV + 0.5 cm. Dose = 10 Gy/5#
NABTT <sup>62–64</sup>	Yes	Post-op	GTV1 = T1 enhancing and non-enhancing tumour volume (T2 or FLAIR). CTV1 = GTV1 plus a margin of 5 mm. PTV1 = CTV1 plus a margin of 3–5 mm. Dose = 46 Gy in 23 #	GTV2 = T1 enhancing tumour volume. CTV2 = GTV2 + 5 mm. PTV2 = CTV2 + 3–5 mm. Dose = 14 Gy/7#
Jansen <i>et al</i> <sup>72</sup>	No	Pre- and post-op	CTV = T2 high signal and contrast enhancing on CT. PTV = CTV + 5 mm. 60 Gy in 30# in single phase	If CTV > 250 cm <sup>3</sup> then 2nd target volume for boost after 40–50 Gy
Stupp <i>et al</i> <sup>1,2</sup>	Yes	Pre-op	CTV = GTV + 2–3 cm. 1 phase 60 Gy in 30 #	Nil
Clinical Practice Guidelines for the management of adult gliomas: Astrocytomas and Oligodendrogliomas <sup>73,74</sup>	Yes	Post-op	GTV = contrast enhancing area on CT or T1 weighted MRI. CTV = GTV + high signal area on T2 weighted MRI or perifocal hypodense zone on CT. PTV = CTV + 5 mm. Dose = 60 Gy in 30#	No recommendations given

GTV, gross tumour volume; CTV, clinical target volume; PTV, planning target volume; RTOG, radiation therapy oncology group; NABTT, new approaches to brain treatment therapy.

the majority of recurrences occurred within 2 cm of tumour margins, suggesting that the proximity to the tumour rather than the zone of peritumoral oedema is correlated with tumour recurrence.

Since 1981, the University of Texas MD Anderson Cancer Center (MDACC) has defined the gross tumour volume (GTV) to include the resection cavity and any residual contrast enhancing resection cavity with a 2 cm margin to form the clinical target volume (CTV), excluding the peritumoral oedema. An additional 5 mm was used for the PTV. This was treated to a dose of 50 Gy in 25 fractions and an additional 10 Gy in 5

fraction boost was delivered to the above defined GTV with a 0.5 cm PTV margin. A planning study by Chang *et al.*<sup>59</sup> was conducted in 48 patients comparing this approach with that of the RTOG 97-10 trial. Only a minority of 17 patients received some form of chemotherapy. They found that with either technique, 90% of the failures were central and in-field and that there was no correlation between the recurrence and oedema volume. However, for the patients who had large volumes of peritumoral oedema of >75 cm<sup>3</sup>, the volume of normal brain irradiated was smaller using the MDACC approach.<sup>59</sup>

The EORTC approach is to also not deliberately include the peri-tumoral oedema as used in the landmark Stupp et al.<sup>1,2</sup> trial but to encompass the contrast enhancing T1 disease as the GTV which is subsequently expanded by 2 cm to form the CTV. In a planning study of 105 patients comparing the EORTC and the RTOG approach of including the peritumoral oedema, no difference in recurrence patterns was evident, with more than 80% of patient tumours occurring within the high dose volume. All the patients received concurrent followed by adjuvant temozolomide. Dosimetric analysis showed that the median percent volume of normal brain irradiated to high doses was significantly higher for the RTOG, especially if the peritumoral oedema was  $>50 \text{ cm}^3$ .<sup>60</sup> The MDACC method is further supported by a small randomised trial of 50 patients comparing the two approaches. It was found that using the MDACC technique resulted in a smaller PTV but no significant difference in the recurrence patterns. Furthermore, the group receiving the MDACC approach was associated with higher median overall survival (13 months vs. not reached in MDACC arm) as well as quality of life compared to the RTOG group.<sup>61</sup>

Several studies have utilised even smaller margins still and the New Approaches to Brain Tumor Therapy (NABTT) consortium have used margins as small as 5 mm. Three phase II studies conducted by NABTT testing novel agents in addition to temozolomide and radiation<sup>62</sup> have shown significant improvement in survival over the chemoradiation arm of the Stupp trial.<sup>2</sup> Although there are several reasons accounting for the improvement, it is possible that using these more limited margins may not compromise the outcomes.

Series from NABTT<sup>63–65</sup> institutions assessing patterns of failure following chemo-radiation with CTV margins as small as 5 mm have found that the predominant local pattern of treatment failure remains unchanged with the use of these smaller CTV margins. For example, in the study by Paulsson et al.<sup>65</sup> patients treated at Wake Forrester University Comprehensive Cancer Centre had no statistically significant difference in failures within the 60 Gy volume whether a 5, 10 or a 15–20 mm CTV margin was used.

Some of the above studies however were performed either before concurrent and adjuvant temozolomide chemotherapy became the standard of care or did not have *MGMT* status for the majority of patients. Based on the volumes defined in the Stupp trial,<sup>2</sup> overall recurrence occurred inside the radiation field in 72.2%, outside in 21.5%, and at radiotherapy margin in 6.3% of patients. Out-of-field failures were especially more frequent in those patients with *MGMT* methylated tumours with only 57.9% in field and marginal failures compared to those with *MGMT* unmethylated tumours where the

corresponding rates were 85%.<sup>66</sup> This finding was also seen in a separate study which showed only 64% of recurrences were central/in-field in methylated versus 91% in the unmethylated patients.<sup>60</sup> These are interesting findings but more studies are required before changes in tumour volume delineations are based on *MGMT* status of the tumours.

Our recommended treatment dose/fractionation and volumes, consistent with the recently published guidelines in *eviQ*<sup>75</sup> are detailed in Tables 3–5. The *eviQ* guidelines

**Table 3.** Suggested dose/fractionation for glioblastoma.

Technique	Phase	Dose	Fractionation	Fractions per fortnight
3D Conformal Technique		60 Gy	30	10
3D Conformal Technique				
2 phase	Phase 1	46 Gy	23	10
	Phase 2	14 Gy	7	10
Intensity modulated simultaneous integrated boost				
	Phase 1	50 Gy	30	10
	Phase 2	60 Gy	30	10

Guidelines are consistent with that published by *eviQ*.<sup>75</sup>

**Table 4.** Suggested delineation method for glioblastoma using single phase technique.

GTV	Where tumour has been biopsied (open biopsy only, stereotactic biopsy excluded) - GTV consists of the region of enhancement without oedema on the pre-operative CT/MRI
	Where the tumour has been resected – GTV consists of the surgical tumour bed plus any residual enhancing tumour as seen on the planning scan
CTV	
GTV + 10–15 mm	The CTV should account for the new position of the abnormality/ tumour bed shift on the planning scan and any post-operative imaging whilst respecting anatomical boundaries
	The CTV extends to the contralateral hemisphere only when a midline structure as the corpus callosum is invaded by tumour as visualised on T2 weighted MRI
	The tentorium and meninges should be considered as anatomical borders and therefore a margin of 5 mm is sufficient to encompass the microscopic spread at these borders
PTV	
CTV + 3–5 mm	For all PTV expansions, a smaller CTV-PTV expansion may be appropriate in departments which have quantified their set-up errors

Guidelines are consistent with that published by *eviQ*.<sup>75</sup>

**Table 5.** Suggested delineation method for glioblastoma using 2 phase technique.

Phase 1	
Phase 1 GTV	Where tumour has been <i>biopsied</i> <ul style="list-style-type: none"> <li>• GTV consists of the region of enhancement without oedema on the pre-operative CT/MRI where the tumour has been <i>resected</i></li> <li>• GTV consists of the surgical tumour bed plus any residual enhancing tumour as seen on the planning scan</li> </ul>
Phase 1 CTV	<ul style="list-style-type: none"> <li>• GTV + 10–15 mm (consider inclusion of any oedema on the CT/MRI scans)</li> <li>• The CTV should account for the new position of the abnormality/tumour bed shift on the planning scan and any post-operative imaging whilst respecting anatomical boundaries</li> </ul>
Phase 1 PTV	CTV + 3–5 mm margin plus additional margin to account for department setup accuracy
Phase 2	
Phase 2 GTV	GTV consists of region of enhancement without oedema on the pre-operative CT/MRI
Phase 2 CTV	GTV + 5 mm (respecting OAR tolerances)
Phase 2 PTV	CTV + 3–5 mm margin plus additional margin to account for department setup accuracy

Guidelines are consistent with that published by eviQ.<sup>75</sup> GTV, gross tumour volume; CTV, clinical target volume; PTV, planning target volume.

were obtained after extensive literature review and consensus panel discussion of radiation oncologists with a sub-speciality interest in neuro-oncology across several Australian states.

The guidelines take into account the recent advancements in imaging, treatment verification and immobilisation since many of the above reports have been published. The recommendations are to encompass the post-operative resection bed (as delineated on post-operative magnetic resonance imaging within 24–48 h of surgery) and residual tumour volume without inclusion of the surrounding oedema on contrast enhancing T1 images as the GTV with a 1.5 cm expansion to form the CTV which is limited to normal, uninvolved anatomical structures. An expansion for PTV should take into account daily set-up uncertainties and is department specific but should be between 0.3 and 0.5 cm. The above volume should be treated to a dose of 60 Gy in 30 fractions. For larger tumour volumes, where meeting dosimetric constraints may be an issue, a two phase approach is recommended or alternatively an intensity modulated radiotherapy technique with a simultaneous integrated boost may be employed (Tables 3–5).

## Conclusions

Following maximal safe surgical resection, radiation is the most important adjuvant treatment modality for patients with newly diagnosed glioblastoma with multiple randomized controlled trials demonstrating a clear survival advantage. There is recent data which suggests that in elderly patients, a shorter hypofractionated treatment regimen may be appropriate and in those with *MGMT* methylated tumours, temozolomide alone may also be considered in those who are not suitable for radiation therapy. The NCIC/EORTC study will address

the question of adding temozolomide to hypofractionated radiation in the elderly population.

There is an increasing role of re-irradiation in the recurrent setting and this may be considered for a select group of patients, given the promising results of patient series, although further studies are ongoing and will more adequately assess the safety and efficacy of such an approach.

There are continuing controversies regarding the optimal volume delineation though there is data to suggest that proximity to the gross tumour rather than the presence of peritumoral oedema may be a more important factor in predicting the initial site of recurrence. Target volumes should therefore take this into account to reduce the volume of normal brain irradiated.

Despite radiation having a central role in the management of patients with glioblastoma for several decades, its role and details are continuing to evolve and results of studies over the next few years will no doubt continue to refine the way radiation is delivered to patients diagnosed with this devastating disease.

## Conflict of Interest

The authors declare no conflict of interest.

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