Overview
Irradiating the Subventricular Zone in Glioblastoma Patients: Is there a Case for a Clinical Trial?
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Abstract
Glioblastoma is the most common and aggressive adult brain tumour. Over the last 10 years it has emerged that the subventricular zone (SVZ), the largest adult neural stem cell niche, has an important role in the disease. Converging evidence has implicated transformation of adult neural stems in gliomagenesis and the permissive stem cell niche in disease recurrence. Concurrently, clinical studies have suggested that SVZ involvement is a negative prognostic marker. It would follow that irradiating the SVZ may improve outcomes in glioblastoma by directly targeting this putative sanctuary site. To investigate this potential strategy, 11 retrospective studies and 1 prospective study examined the relationship between dose to the SVZ and survival outcomes in glioblastoma patients. This review summarises the theoretical underpinning of this strategy, provides a critical evaluation of the existing evidence and discusses the rationale for a clinical trial.

Key words: Cancer stem cells; glioblastoma; neural stem cells; radiotherapy; subventricular zone

Statement of Search Strategies Used and Sources of Information
Computer-guided literature searches were used to identify relevant literature using two independent systems, namely PubMed and Web of Science.

Introduction
Glioblastoma (GBM), the most common and aggressive adult brain tumour, carries a very poor prognosis. This is despite standard of care therapy of maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapy. The poor treatment response, together with the origins, progression and aggressive, inexorable recurrence of this disease, are poorly understood.

There is growing evidence to implicate the subventricular zone (SVZ) in both the initiation and the recurrence of the disease. Preclinical findings, together with a number of retrospective studies correlating high incidental radiation dose to the SVZ with improved survival outcomes, have led to speculation that irradiating the SVZ may be a viable strategy to improve outcomes in GBM. This review will discuss the rationale for a clinical trial, offer a critique of the existing evidence and highlight some important design considerations.

Background
Cancer Stem Cells in Glioblastoma
The cancer stem cell (CSC) hypothesis proposes a cellular hierarchy in which tumours are initiated and propagated by a biologically distinct subpopulation of multipotent cells capable of self-renewal [1]. This is in contrast to the more
traditional stochastic model of tumour growth, in which all tumour cells are intrinsically identical and intratumoural heterogeneity is instead due to local microenvironmental influences.

Evidence has emerged over the last decade in support of the CSC hypothesis in GBM. Cells expressing the stem cell marker CD133 have been isolated from human tumours and shown to be capable of transferring a phenocopy of the patient’s original disease into mouse models, whereas the CD133-negative cell fraction cannot [2–4]. More recently it has been revealed that neither CD133 nor any other surface marker is an absolute marker of ‘stemness’ [5,6] and CD133-negative cells cannot only recapitulate tumours in mouse models but also give rise to CD133-positive cells [7]. Indeed, CD133-negative cells are capable of differentiation and this has led to speculation of a hierarchy with CD133-positive tumour-initiating cells giving rise to transit-amplifying CD133-negative cells still capable of disease transference [8]. Moreover, studies have shown that vascular niches [9] and hypoxic conditions [10,11] may induce and maintain CSCs, suggesting a degree of plasticity of CSC phenotype depending on microenvironmental cues [6]. Given the vast inter-patient heterogeneity in GBM, it is unlikely that any single model is universally applicable. Indeed, there is variability in the degree of apparent CSC involvement in different patients, and there are clinical data associating a high CSC fraction in GBM with poor prognosis: both increased stem cell-associated gene expression patterns and increased neurosphere formation in vitro are predictors of worse survival [12,13]. The role of stem cells in GBM has been more comprehensively reviewed elsewhere [14].

A Role for the Subventricular Zone in Tumour Initiation?

The origins of these putative CSCs are unclear. A strong possibility is that they are transformed neural stem cells. Indeed, it has been experimentally shown in mouse models that GBM may arise from genomic instability [15] or excessive platelet-derived growth factor (PDGF) signalling [16] in neural stem cells. Thus, neurogenic niches in the brain are candidate sites of transformation. There are two such niches in the adult mammalian brain: the SVZ [17,18] and the subgranular zone (SGZ) in the hippocampus [19]. There is some experimental evidence to support the former as a birthplace of GBM. In p53/NF1-inactivated mouse models, the SVZ is the earliest identifiable site of tumour formation [20]. Further mouse models have shown that tumour suppressor gene deletion in neural stem cells in the SVZ is both necessary and sufficient to induce gliomagenesis, whereas similar targeting of non-neurogenic regions of the brain is not [21]. More recently, phylogenetic reconstruction of tumour evolution revealed that in a proportion of human GBM, the SVZ harbours CSCs that gave rise to the GBM mass, the first direct evidence of a SVZ contribution to human gliomagenesis [22]. However, there are a number of other hypotheses regarding the origin of CSCs in GBM. Gene expression analysis has revealed that in some cases oligodendrocyte progenitor cells distant to the SVZ may give rise to glioma instead [23,24] and a further hypothesis proposes that mature glia dedifferentiate to acquire stem cell-like characteristics [25]. Again, it is plausible that all these hypotheses are correct in different disease subtypes. Thus, it is important to note that neural stem cells have not been definitively established as the single cell of origin in GBM. Indeed, recent results have identified molecular differences between SVZ-originating tumours and cortex-originating tumours, which may drive different behaviours [26].

A Role for the Subventricular Zone in Recurrence?

A complementary idea is that the SVZ contributes to recurrence, even if it is not the original source of the tumour. Mouse models have shown that GBM cells exhibit a tropism for the SVZ, where they acquire a stem cell phenotype and mimic neural precursor cell behaviour by migrating to the olfactory bulb. These cells were shown on transplantation to be highly tumourigenic [27]. A similar SVZ tropism has been suggested in a proportion of human GBM, with the tumour originating outside the SVZ and subsequently growing into it [22]. Additionally, analysis of the pattern of spread of GBM, particularly cases involving the SVZ, reveals that it recapitulates the migration patterns of neural precursor cells [28]. Thus, it is possible that the SVZ can attract and harbour GBM-initiating cells, which then act to drive recurrence both locally and distantly through the same migratory routes as neural precursor cells.

Despite uncertainty over its precise role, there is a substantial body of literature to suggest that the SVZ plays a clinically important role in at least a proportion of GBM. SVZ-contacting tumours have repeatedly been shown to be associated with more aggressive clinical behaviour, such as multifocality and distant recurrences [29–32] (albeit not universally [33]) as well as robustly associated with worse prognosis [26,31,34,35]. Recent results have shown that SVZ-involving tumours have increased blood volume in the non-enhancing lesion than cortex-involving tumours, potentially attributing poor survival to an aggressive vascular phenotype [26]. Additionally, it has recently been shown that both SVZ-contacting and non-contacting tumours have a propensity to recur near to the SVZ or the SGZ [32], further suggesting that neurogenic regions may be reservoirs of subclinical disease, which then drives recurrence (Figure 1).

Relevance to Radiation Therapy Treatment Planning

Traditionally, generous margins have been added to the gross tumour volume during radiotherapy treatment planning to allow for sub-clinical tumour infiltration into adjacent brain (Figure 2). A 2–3 cm margin for clinical target volume (CTV) is informed from radiological and pathological observations of disease recurrence [36]. Patterns of failure studies confirm that with such CTV margins, the pattern of failure is predominantly local, both with single modality radiation therapy and combined chemoradiation treatment [37,38]. Local failure patterns suggest that in
most cases, insufficient radiation dose has been delivered to control tumour within the planning target volume (PTV). Radioresistant populations of tumour cells within the PTV may be due to hypoxia-induced growth arrest in the necrotic core of the tumour cavity [39]. The role of the SVZ in harbouring radioresistant tumour clones within the PTV has not been confirmed in vivo, although the biological argument for such an observation remains compelling.

Review of Retrospective Clinical Studies

Given the potential clinical significance of the SVZ, it would seem logical to eliminate the population of CSCs by targeting the SVZ with radiotherapy. There is an evolving corpus of retrospective studies that have investigated this strategy by attempting to correlate incidental dose delivered to the SVZ through conventional radiotherapy planning with survival outcomes. The methodology of these studies is fundamentally similar: dichotomising the patient cohort into a low SVZ dose and a high SVZ dose arm and comparing survival with the metrics of progression-free survival (PFS) and/or overall survival (Table 1).

In the first such study, Evers et al. [40] evaluated 55 patients with either grade 3 or 4 glioma. The cut-off for inclusion in the high-dose group was 43 Gy or greater to the bilateral periventricular region, chosen as it was the median dose to this structure across the whole cohort. The patient groups were well-matched for most variables, including performance status, age and surgical intervention, with the exception of gender. O6-methylguanine-DNA-methyltransferase gene (MGMT) methylation status was not considered as the information was not available for all patients. The key finding was that the high-dose arm had a statistically significantly improved median PFS (15.0 versus 7.2 months, \( P = 0.03 \)). Furthermore, the high dose of radiation to the bilateral SVZ gave a hazard ratio of 0.73 (\( P = 0.019 \)) on multivariate analysis, leading the authors to surmise that a high dose of radiation of the SVZ is an independent predictor of survival in GBM. Notably, incidental dose to the hippocampal formation, where the SGZ is located, did not correlate with PFS, suggesting that benefit is not achieved from irradiating other neurogenic niches in the brain.

A subsequent study [41] aimed to replicate these results in a cohort of 40 patients restricted to GBM. They applied the same cut-off of 43 Gy to their cohort and found no correlation between bilateral, ipsilateral or contralateral SVZ dose and PFS or overall survival. However, they did note a correlation between low dose to the contralateral SVZ and increased distant recurrences (\( P = 0.016 \)).

A further study from Gupta et al. [42] analysed a group of 40 patients, dichotomised based on the cohort's median dose of 59.9 Gy to the ipsilateral SVZ. Unlike previous studies, they included most pertinent prognostic factors,
including MGMT methylation status, in their multivariate analysis. Their results showed that ipsilateral SVZ dose was an independent predictor of improved overall survival (hazard ratio = 0.87, 95% confidence interval 0.77–0.98; \( P = 0.025 \)) but not PFS. In this cohort a high contralateral SVZ dose (>57.9 Gy) was associated with a significantly worse PFS (\( P = 0.02 \)) and overall survival (\( P = 0.05 \)). The authors reasoned that the latter effect was related to a high contralateral dose being associated with a larger tumour burden but did not show this definitively. Indeed, there was no significant correlation between overall PTV and survival outcomes.

These discordant results prompted Lee et al. [43] to pool 173 patients from two large academic centres and carry out a similar analysis with a larger cohort. Rather than use the cohort’s median SVZ dose as a cut-off, they reasoned that a high dose would be required to kill radioresistant CSCs, and applied a threshold dose of 59.4 Gy, an accepted prescription dose for high grade glioma. They showed that a high dose to the ipsilateral SVZ was significantly associated with a higher median PFS (12.6 versus 9.9 months, \( P = 0.042 \)), which remained significant on multivariate analysis (\( P = 0.009 \); hazard ratio 0.45; 95% confidence interval 0.25–0.82). A high dose also trended to a higher overall survival although this did not reach statistical significance (25.8 versus 19.2 months, \( P = 0.173 \)). These data were reanalysed using different cut-offs for the high-dose group, including the group’s previous finding of 43 Gy, as well as 50 Gy and 55 Gy, but these cut-offs yielded no significant differences.

A further large study at Johns Hopkins University evaluated 116 patients [44]. Across the whole cohort, patients receiving a high dose (>40 Gy) to the ipsilateral SVZ did not have significantly different survival outcomes to the low-dose group. However, among the 41 patients who underwent gross total resection, the recipients of high-dose ipsilateral SVZ irradiation showed a significantly improved PFS (15.1 versus 10.3 months, \( P = 0.028 \)) and overall survival (17.5 versus 15.6 months, \( P = 0.027 \)). Recent re-analysis of 102 patients from this cohort did not find any significant correlation between increased SVZ radiation dose and decreased incidence of distant recurrence, although this analysis was not limited to the gross total resection group [32].

A subsequent study to correlate SVZ dose with outcomes produced more sobering results [45]. The cohort of 60 patients was analysed using different cut-off doses to the ipsilateral and contralateral SVZ based on the 25th, 50th and 75th percentile of SVZ dose. Univariate analysis showed that a contralateral SVZ dose of over 59.2 Gy was a significant prognostic factor for poor PFS (7.1 versus 10.3 months, \( P = 0.009 \)). This remained significant for certain subgroups: male gender; age over 54 years; subtotal resection or biopsy only; Karnofsky performance score > 90; SVZ-contacting. It

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Cut-off dose to SVZ (Gy)</th>
<th>Median PFS, high versus low dose (months)</th>
<th>P value</th>
<th>HR (95% CI)</th>
<th>Median OS, high versus low dose (months)</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[40]</td>
<td>55</td>
<td>BL SVZ: 43</td>
<td>15.0 versus 7.2</td>
<td>0.03</td>
<td>0.735 (0.567–0.951)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>[41]</td>
<td>40</td>
<td>IL SVZ: 43</td>
<td>NR</td>
<td>0.32</td>
<td>NR</td>
<td>NR</td>
<td>0.38</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 43</td>
<td>NR</td>
<td>0.41</td>
<td>NR</td>
<td>NR</td>
<td>0.31</td>
<td>NR</td>
</tr>
<tr>
<td>[42]</td>
<td>40</td>
<td>BL SVZ: 57.9</td>
<td>10 versus 14</td>
<td>0.06</td>
<td>1.06 (0.97–1.15)</td>
<td>14 versus NR</td>
<td>0.22</td>
<td>1.08 (0.97–1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 57.9</td>
<td>10 versus 11</td>
<td>0.920</td>
<td>0.91 (0.80–1.03)</td>
<td>17 versus 15</td>
<td>0.95</td>
<td>0.87 (0.77–0.98)</td>
</tr>
<tr>
<td>[43]</td>
<td>173</td>
<td>IL SVZ: 59.4</td>
<td>12.6 versus 9.9</td>
<td>0.042</td>
<td>0.45 (0.25–0.82)</td>
<td>25.8 versus 19.2</td>
<td>0.173</td>
<td>0.65 (0.35–1.21)</td>
</tr>
<tr>
<td>[44]</td>
<td>116</td>
<td>IL SVZ: 40</td>
<td>NR</td>
<td>0.434</td>
<td>0.749 (0.453–1.24)</td>
<td>NR</td>
<td>0.754</td>
<td>0.827 (0.502–1.36)</td>
</tr>
<tr>
<td></td>
<td>41 (GTR)</td>
<td>IL SVZ: 40</td>
<td>15.1 versus 10.3</td>
<td>0.028</td>
<td>0.385 (0.165–0.901)</td>
<td>17.5 versus 15.6</td>
<td>0.027</td>
<td>0.385 (0.165–0.895)</td>
</tr>
<tr>
<td>[45]</td>
<td>60</td>
<td>IL SVZ: 62.25</td>
<td>NR</td>
<td>0.018</td>
<td>NR</td>
<td>NR</td>
<td>0.268</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 59.2</td>
<td>7.1 versus 10.4</td>
<td>0.009</td>
<td>1.72 (0.80–3.53)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>[46]</td>
<td>50</td>
<td>IL SVZ: 50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>19.83 versus 6.07</td>
<td>0.031</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 37</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>19.83 versus 8.73</td>
<td>0.118</td>
<td>NR</td>
</tr>
<tr>
<td>[47]</td>
<td>88</td>
<td>IL SVZ: 56.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 33.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>[48]</td>
<td>53</td>
<td>BL: 47.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL: 52.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL: 51</td>
<td>NR</td>
<td>0.002</td>
<td>0.112 (0.029–0.439)</td>
<td>NR</td>
<td>0.012</td>
<td>0.195 (0.055–0.697)</td>
</tr>
<tr>
<td>[49]</td>
<td>58</td>
<td>IL: 58.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL: 44.1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>[50]</td>
<td>72</td>
<td>BL SVZ: 49.1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL SVZ: 60.6</td>
<td>NR</td>
<td>0.95</td>
<td>NR</td>
<td>NR</td>
<td>1.03</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL SVZ: 39.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; SVZ, subventricular zone; BL, bilateral; IL, ipsilateral; CL, contralateral; HR, hazard ratio (multivariate analysis); NR, not reported; CI, confidence interval.
was also significantly associated with a poor overall survival in the subtotal resection/biopsy group. Similarly, an ipsilateral SVZ dose over 62.25 Gy had a significantly worse PFS in patients with Karnofsky performance score > 90 and those with SVZ non-contacting tumours. Although this negative effect could be due to tumour burden, the CTV itself did not correlate with survival PFS or overall survival on univariate or multivariate analysis.

A number of recent abstracts have reported mixed results. Ravind et al. [46] reported that in a retrospective analysis of 50 GBM patients, those who received over 50 Gy to the ipsilateral SVZ had significantly improved overall survival (19.83 versus 6.07 months, \( P = 0.031 \)), whereas contralateral doses over 37 Gy achieved a non-significant overall survival improvement (19.83 months versus 8.73 months; \( P = 0.118 \)). Anker et al. [47] analysed a cohort of 88 patients to find reduced PFS, but not overall survival, associated with ipsilateral SVZ doses greater than 56.4 Gy on univariate analysis, although this effect disappeared on multivariate analysis. A study of 53 patients by Foro et al. [49] was the only report of a significant improvement in overall survival in patients receiving a high dose (>51 Gy) to the contralateral SVZ (hazard ratio = 0.195; 95% confidence interval = 0.055–0.697), with the same being true for PFS (hazard ratio = 0.112, 95% confidence interval = 0.029–0.439). Sakuramachi et al. [48] reported that in a cohort of 58 patients, a high ipsilateral SVZ dose greater than 58.4 Gy is associated with shorter PFS, with no significant effect on overall survival. Most recently, Iuchi et al. [50] reported no significant difference between ipsilateral SVZ dose and acute change in performance status. The largest study showing an effect [43] did not include MGMT methylation status in their multivariate analysis and no studies included isocitrate dehydrogenase 1 gene (IDH1) status. The largest study showing an effect [43] did not include performance status in their multivariate analysis. The prospective study shares these limitations and did not explore neurocognitive effects, as it readily acknowledged [51]. Furthermore, multifocal tumours were excluded only in three studies [42,43,45]. Tumour location was not standardised across high SVZ dose and low SVZ dose groups and lateral ventricle contact was considered only in three studies [44,45,47]. Additionally, there was significant variation in the shape and volume of the contoured SVZ between different studies. Notably, Lee et al. [43] showed that their SVZ contouring included more inferior aspects of the periventricular zone, whereas Gupta et al. [42] included more anterior parts, highlighting the lack of consensus in contouring the SVZ. There may be significant differences between the precise anatomical areas irradiated and the distribution of the dose therein between the different studies. This is particularly important because the cytoarchitecture of the SVZ is unlikely to be homogenous [62].

A key conclusion is that it is impossible to distinguish between a prognostic effect of tumour location relative to the SVZ and any therapeutic benefit from irradiating the SVZ to a threshold dose from these retrospective studies.

### Review of Prospective Clinical Study

A single uncontrolled clinical trial investigating planned neural stem cell niche irradiation in GBM has been published [51]. The 54 participants received maximal safe resection followed by chemoradiation, with the CTV expanded to include the ipsilateral periventricular zone (5 mm lateral expansion adjacent to the ventricles). Mean doses to ipsilateral SVZ, subgranular layer (SGL) and total periventricular zone were 52, 47 and 51 Gy, respectively. The results were encouraging, with a median survival of 14 months and a dose of 58 Gy or greater to the ipsilateral SVZ correlating positively with improved overall survival (16 months versus 14 months, \( P = 0.03 \)), although a higher dose to the SGZ was associated with improved survival without reaching statistical significance.

### Neurocognitive Effects

Learning and memory deficits have been strongly associated with cranial irradiation in head and neck cancer patients [52]. The pathogenesis of this effect is related to neural precursor cell dysfunction in the SGZ leading to reduced cell proliferation [53–56]. It has also been shown that sparing the hippocampus, where the SGZ is located, gives superior neurocognitive preservation in cranial radiotherapy patients [57]. Although not as well-documented in the SVZ, similar effects on cell proliferation have been observed in mouse models of SVZ irradiation [58]. Additionally, although the link to cognition is not as robust, neurogenesis in the SVZ has been implicated in central nervous system regeneration [59,60].

It is therefore critical to consider the toxicity of any strategy that deliberately targets neurogenic niches in the brain. Chen et al. [44] reported no significant correlation between ipsilateral SVZ dose and acute change in performance status before and after radiotherapy (\( P = 0.592 \)). However, Lucchi et al. [61] found that although high doses of radiation to the SVZ sufficient to cause radiologically identifiable necrosis correlated with significantly improved overall survival (36.2 versus 13.3 months, \( P = 0.0001 \)), performance status was consistently and progressively impaired in this group.

### Inconsistencies and Limitations

These studies collectively fail to provide consistent evidence that SVZ irradiation improves outcomes in GBM. Although a correlation between SVZ dose and effect was shown more often than not, the cut-off dose was not reproducible across studies. Cohort sizes were small and the studies carried the usual limitations of retrospective studies. In many studies, important prognostic factors were not considered: only two studies [42,48] included MGMT methylation status in their multivariate analysis and no studies included isocitrate dehydrogenase 1 gene (IDH1) status. The largest study showing an effect [43] did not include performance status in their multivariate analysis. The prospective study shares these limitations and did not explore neurocognitive effects, as it readily acknowledged [51]. Furthermore, multifocal tumours were excluded only in three studies [42,43,45]. Tumour location was not standardised across high SVZ dose and low SVZ dose groups and lateral ventricle contact was considered only in three studies [44,45,47]. Additionally, there was significant variation in the shape and volume of the contoured SVZ between different studies. Notably, Lee et al. [43] showed that their SVZ contouring included more inferior aspects of the periventricular zone, whereas Gupta et al. [42] included more anterior parts, highlighting the lack of consensus in contouring the SVZ. There may be significant differences between the precise anatomical areas irradiated and the distribution of the dose therein between the different studies. This is particularly important because the cytoarchitecture of the SVZ is unlikely to be homogenous [62].
Traditional treatment protocols with 2–3 cm CTV margins will typically include the region of the SVZ adjacent to the tumour in the high dose volume by default. We have confirmed this by serial analysis of 100 GBM patients treated with chemoradiation therapy in our own institution, where in only 3% of cases did the CTV margin not include the SVZ at all.

**Future Directions**

Although the limitations in the existing body of evidence preclude its premature adoption into routine clinical practice, there is sufficient evidence to generate a testable hypothesis that SVZ irradiation can improve outcomes in GBM, in the form of a prospective randomised clinical trial. With increased availability of intensity-modulated radiotherapy treatment it becomes feasible to target substructures in the brain to a uniform radiation dose.

Before an efficacy study can be developed, a clinical trial is needed to establish the safety and feasibility of targeted radiation to the whole ipsilateral SVZ. This is now possible due to evolving radiotherapy techniques that permit precise targeting of radiation dose to specific substructures in the brain. A number of practical factors need to be considered.

**Defining the Subventricular Zone**

No consensus guidelines have been established for contouring of the SVZ. The studies discussed here have defined it anatomically as a 3–5 mm area around the lateral ventricles. Computer assisted segmentation tools can be used to carry out automatic segmentation consistently [63]. Morphological segmentation of the SVZ may be possible by combining additional magnetic resonance image (MRI) techniques, such as perfusion MRI and diffusion tensor MRI.

**Minimising Deleterious Effects**

Given the lack of understanding regarding dose response and tumour control for SVZ irradiation, care must be taken to quantify and limit the risk of neurocognitive deficit that has been associated with high-dose SVZ irradiation [61].

The extent of acceptable neurocognitive decline in the context of improved survival is a matter for debate, particularly in adult brain tumours with poor prognosis. A clinical trial is currently ongoing exploring the effect of sparing neural stem cell (NSC)-containing regions in conventional radiotherapy planning for GBM (NCT01478854). The results should help to better understand the deleterious effects of irradiating the SVZ. Future studies must also consider whether the deleterious effects of SVZ irradiation can be avoided by shielding nearby structures, notably the fornix and hippocampus.

A further safety consideration is dose selection. The published data do not provide consistent evidence except that doses exceeding 62.25 Gy can be deleterious. It would be reasonable in a safety study to take the whole ipsilateral SVZ to a dose of 60 Gy, as this would happen clinically in patients with larger tumours in proximity to the SVZ.

The available evidence supports restricting this dose to the ipsilateral SVZ. Involvement of the SVZ is not a strong predictor of contralateral disease and contralateral SVZ irradiation is often correlated with poor prognosis [42,45], albeit one study reports a benefit [48]. Nevertheless, two trials are presently ongoing incorporating the bilateral SVZ (NCT02177578) and the ipsilateral SVZ only (NCT02039778) in the CTV. The results will help to better inform future directions.

**Case Selection and End Points**

Surgical resection should be optimised with 5-ALA fluorescence-guided resection [64] and outcomes stratified for gross-total resection versus subtotal resection based on postoperative MRI, as some data suggest a significant effect only in the former group [44]. Additionally, patients selected must have all significant prognostic information available, including age, gender, performance status, tumour location, lateral ventricular contact, MGMT promoter methylation and IDH1 status.

Pertinent end points include PFS and overall survival, neurocognitive metrics, performance status and quality of life. Other end points would be recurrence location, radiological progression, cytological markers (stem cell assays), SVZ relative cerebral blood volume (rCBV) [26]. These would be especially useful as surrogate end points if small sample size was a potential barrier to showing significant survival outcomes.

**Conclusion**

The existing literature generates a promising hypothesis that irradiating the SVZ may extend survival in GBM. Current evidence is limited by incomplete study design and inconsistent survival outcomes, effective dose and SVZ delineation. Additionally, it does not exclude deleterious neurocognitive effects that may offset survival benefits. Even if optimally designed, studies correlating incidental SVZ radiation dose to survival are limited by the inherent confounding factor that a higher incidental SVZ dose reflects closer proximity of the tumour to the SVZ. Therefore, a careful designed clinical trial taking the whole ipsilateral SVZ to a therapeutic dose of 60 Gy is needed to establish the safety and feasibility of this strategy.

**References**


