REVIEW

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What is the most appropriate clinical target volume for glioblastoma?

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Practice Points

- Traditionally, very large margins are included in the clinical target volume (CTV) for glioblastoma and, typically, edematous areas on T₂ or fluid-attenuated inversion recovery sequences are intentionally encompassed in the CTV.
- Data from the European Organisation for Research & Treatment of Cancer trial and various other studies show that, with the omission of edematous regions outside the surgical cavity and contrast-enhanced tumor, there was no increase in marginal recurrence.
- Exclusion of edematous regions outside the surgical cavity and contrast-enhanced tumor results in a much smaller volume of normal brain parenchyma being irradiated.
- Tumors with *MGMT* methylation have better local control but higher risk of distant failure compared with their nonmethylated counterparts, but whether CTV delineation should be affected by the tumor *MGMT* methylation status is undecided and is yet to be determined.
- Magnetic resonance spectroscopy and PET have been used to delineate CTV and target delineation based on these modalities can differ significantly from that based on MRI. However, the significance of this is yet to be determined.
- Preliminary research shows that stem cell niches in the subventricular zone could be a potential target to be included in the CTV to improve outcome, but more research is needed to validate this hypothesis.

SUMMARY Glioblastoma is one of the most common primary brain tumors in adults and the prognosis is very poor. The standard treatment is gross total resection and postoperative radiotherapy with concurrent and adjuvant chemotherapy with temozolomide. Given its propensity to spread to areas of brain parenchyma surrounding the gross tumor volume (GTV), a generous margin is typically created around the GTV. Peritumoral edema is frequently

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included in the GTV, especially in the USA. The margin of expansion from GTV to clinical target volume also varies widely among different institutions. There is a lack of consensus as to what constitutes the most appropriate clinical target volume for glioblastoma.

Glioblastoma is a highly lethal disease and the standard treatment is maximal safe resection followed by partial brain radiotherapy with 6 months of concurrent adjuvant temozolomide [1]. Historically, the clinical target volume (CTV) for glioblastoma was the whole brain, but subsequently, multiple investigators found that most tumors recurred within 2–3 cm of the contrast-enhanced tumor on computed tomography (CT) or MRI scans [2–4]. Halperin *et al.* from Duke University (NC, USA) found that peritumoral edema also harbored glioblastoma cells and a margin of 3 cm from edema would be needed to include microscopic disease [2]. While it is common knowledge that a wide margin around the contrast-enhanced tumor or gross tumor volume (GTV) is needed for CTV expansion, there is no consensus as to what amount is needed. Furthermore, it is controversial whether peritumoral edema needs to be intentionally included in the GTV. Although it is rare to encounter long-term survivors of glioblastoma, best efforts should be made to avoid treating a large volume of normal brain parenchyma if possible. The delineation of CTV varies significantly among different cooperative groups and institutions [4,5,101]. Based on literature reviews, we seek to determine the most appropriate CTV for glioblastoma.

Imaging modalities used for target delineation

For target delineation, MRI with gadolinium or CT with contrast (if MRI is not available or cannot be performed in patients with contraindications to MRI) are typically used; although the former is preferred given its better ability to delineate the tumor and surrounding edema. Most clinical trials have utilized the above modalities for target delineation [4,5,101]. The surgical cavity and the contrast-enhanced tumor are defined using an axial T₁ sequence with gadolinium. If peritumoral edema is included in the GTV, an axial T₂ sequence is used. Some institutions use axial fluid-attenuated inversion recovery (FLAIR) sequences for target delineation, but it has been demonstrated discordance between volumes created using T₂ and FLAIR sequences [6]. However, there is no difference in the percentage overlap of volumes created using either sequence with the recurrent tumor [6].

Radiation Therapy Oncology Group target delineation

In the USA, the Radiation Therapy Oncology Group (RTOG) target delineation method is frequently used. In older RTOG trials, the initial target volume included the contrast-enhancing tumor and surrounding edema based on preoperative CT/MRI plus a 2 cm margin. If there was no surrounding edema, the initial target volume would include the contrast-enhanced tumor plus a 2.5-cm margin [4,7]. The cone-down target volume included the contrast-enhanced tumor on preoperative CT/MRI plus a 2.5-cm margin. The initial target volume would be treated to 46.0 Gy in 23 fractions and the cone-down target volume would be treated to another 14 Gy in seven fractions (cumulative dose: 60 Gy in 30 fractions).

For the current RTOG trials for glioblastoma, there are two target volumes and they are both delineated based on postoperative MRI with preoperative imaging for correlation [101]. The initial GTV is defined either using T₂ or FLAIR abnormalities on the postoperative MRI scan with the inclusion of any postoperative MRI enhancement and surgical cavity on axial T1 with gadolinium. The initial CTV is generated by adding a 2-cm margin around the GTV (Figure 1), with a margin reduction to 0.5 cm around natural tissue planes such as the skull, ventricles, falx, brainstem and optic nerve/chiasm. In cases where there is no surrounding edema, the initial CTV includes the contrast-enhancing lesion and surgical cavity plus a 2.5-cm margin. The boost GTV is defined by the contrast-enhanced T₁ abnormality and any surgical cavity on the postoperative MRI. The boost CTV is generated by adding 2 cm to the boost GTV, with a margin reduction to 0.5 cm around natural tissue planes such as the skull, ventricles, falx, brainstem and optic nerve/chiasm. The initial and boost planning treatment volumes (PTVs) are generated by adding 3–5 mm, depending on the image-guidance method. The initial and boost PTVs will receive 46 Gy and an additional 14 Gy (cumulative dose: 60 Gy), respectively.

European Organisation for Research & Treatment of Cancer target delineation

In the landmark glioblastoma trial of the European Organisation for Research and Treatment

Figure 1. Target delineation for glioblastoma. (A) Signal intensity, surgical cavity and residual enhancement (initial gross tumor volume [GTV] using Radiation Therapy Oncology Group [RTOG] method) based on axial fluid-attenuated inversion recovery sequence are contoured in red (inner contour) and clinical target volume (CTV) is a 2-cm expansion in all directions minus regions with tissue planes (initial CTV using RTOG method) and is contoured in light green (outer contour); (B) surgical cavity and residual enhancement (GTV using European Organisation for Research & Treatment of Cancer [EORTC] method and boost GTV using RTOG method) based on the axial T_1 sequence with gadolinium are contoured in magenta (inner contour) and CTV is a 2-cm expansion in all directions minus regions with tissue planes (CTV using EORTC method and boost CTV using RTOG method) and is contoured in purple (outer contour); (C) initial CTV using RTOG method contoured in light green (outer contour) is significantly larger than CTV using EORTC method (also boost CTV using RTOG method) contoured in purple (inner contour). For colour images see online at www.futuremedicine.com/doi/full/10.2217/CNS.13.38.

of Cancer (EORTC) [102], where radiotherapy alone was compared with radiotherapy combined with concurrent and 6 months of adjuvant temozolomide, CTV was defined as a 2–3-cm margin added to GTV (Figure 1), defined as the entire contrast-enhancing lesion on CT or MRI of the brain, in all directions [1,5]. The eyes, nasopharynx, optic nerves, chiasm and ear canals were avoided. In the case of complete surgical resection, the definition of the tumor bed was left to the judgment of the local investigator and the same 2–3-cm margin was added.

In the randomized study comparing hypofractionated radiotherapy (40 Gy in 15 fractions in 3 weeks [103]) with and without temozolomide in elderly patients, the CTV was defined as the GTV with a margin of 1.5 cm, with no expansion outside of any natural barriers to tumor growth [8].

Patterns of failure relative to delineation of CTV

■ CTV delineation including peritumoral edema with reduced margins

In a study from Emory University (GA, USA), 62 patients with newly diagnosed glioblastoma

were treated with radiotherapy to a total dose of 60 Gy with concurrent temozolomide. The initial CTV included postoperative T_2 abnormalities with a median margin of 0.7 cm and the boost CTV included residual T_1 -enhancing tumor and resection cavity with a median margin of 0.5 cm. PTV margin expansion was 0.3–0.5 cm. The PTV boost margin was 1 cm or less from the boost GTV in 92% of patients [9]. The volume of recurrent tumor (new T_1 enhancement) was categorized by the percent within the 60-Gy isodose line as central (>95%), in-field (81–95%), marginal (20–80%) or distant (<20%). Radiographic tumor progression developed in 43 out of 62 patients at a median follow-up of 12 months. Among 41 evaluable patients, 38 (93%) had in-field failure, two (5%) had marginal failure and one (2%) had distant failure relative to the 60-Gy isodose line [9].

In a recent study from Wake Forest University (NC, USA), the patterns of failure in the treatment of glioblastoma based on CTV margin size were examined. A total of 161 patients were included in the study and they were treated with CTV expansions ranging from 5 to 20 mm around edema, the contrast-enhanced tumor

and surgical cavity for initial treatment, and around contrast-enhanced tumor and surgical cavity for cone-down. Patterns of failure, time to progression and overall survival were analyzed based on CTV margin. For patients treated with 5-, 10- and 15–20-mm CTV expansion, 79, 77 and 86% experienced failures in the 60 Gy volume, respectively [10]. Corresponding rates of failure in the 46 Gy volume were 48, 55 and 66%, respectively. No statistical differences were observed among patients treated with 5-, 10- and 15–20-mm CTV margins in terms of 60 Gy failure, 46 Gy failure or marginal failure [10].

■ CTV delineation without intentionally including peritumoral edema

There have been several studies reporting patterns of failure based on CTV that excluded peritumoral edema. In an early study from the University of Michigan (MI, USA), 36 patients with glioblastoma were treated with 70–80 Gy in conventional fractionation using shrinking margins (2.5 to 1.5 to 0.5 cm) around the contrast-enhanced tumor and surgical cavity, and developed recurrence [11]. When the patterns of failure were analyzed, 29 patients had solitary recurrences, of which 26 and three were central and marginal failures, respectively. Multiple recurrent lesions were observed in seven patients, of whom three had multiple central and/or in-field lesions only, three had central and/or in-field lesions with additional small marginal or outside lesions, and one had six outside and one central lesions [11]. In aggregate, 32 out of 36 patients (89%) developed central or in-field recurrences, three (8%) had a significant marginal component to the recurrence and only one (3%) could be clearly regarded as developing failure mainly outside the high-dose zone [11].

Chang *et al.* analyzed the patterns of recurrence in 48 glioblastoma patients whose CTV did not intentionally include peritumoral edema treated at the MD Anderson Cancer Center (TX, USA) [12]. The CTV was created by adding a 2-cm margin to the GTV, which was defined as the resection cavity, and any residual contrast-enhanced tumor and edema was not intentionally included except for edema existing within the 2-cm margin [12]. A 5-mm margin was added to the CTV and GTV to create the PTV and boost PTV, respectively. The PTV was created by adding 0.5 cm to the CTV and the boost PTV was created by adding 0.5 cm to the GTV [12]. A dose of 50 Gy in 25 fractions was prescribed to

the PTV and an additional dose of 10 Gy in five fractions was prescribed to the boost PTV. Separate theoretical treatment plans based on RTOG guideline, which included peritumoral edema in the GTV, were generated for all 48 patients. The recurrence volume and edema volume did not show a correlation by linear regression modeling. Forty three patients (90%) developed recurrences centrally and in-field for both MD Anderson Cancer Center (50 Gy) and RTOG (46 Gy) plans. Three marginal and two distant recurrences occurred and they failed to be covered by the RTOG 46 Gy isodose volume, which included peritumoral edema [12].

Minniti *et al.* studied the patterns of failure in 105 patients with glioblastoma who recurred after 3D conformal radiotherapy and concurrent and adjuvant temozolomide according to different CTV definitions [13]. For treatment, the GTV was defined as residual tumor and resection cavity plus a 2-cm margin, similar to the EORTC definition. MRI of the brain showing tumor recurrence of these patients were fused with their treatment planning CT and the patterns of failure were analyzed dosimetrically using dose–volume histograms. A theoretical plan was created for each patient based on the inclusion of postoperative edema plus a 2-cm margin according to current RTOG guidelines [13]. There were 79 central recurrences, six in-field recurrences, six marginal recurrences and 14 distant recurrences. Comparing the RTOG and EORTC methods of CTV delineation, there was no difference in patterns of failure, although the median volume percentage of brain irradiated to high doses was significantly smaller for the EORTC method [13]. The median overall survival and progression-free survival intervals were 14.2 months and 7.5 months, respectively. One interesting observation was that while the rate of central/in-field recurrence was lower for patients with tumors with *O*⁶-MGMT promoter methylation compared with those with tumors without *MGMT* methylation (64% compared with 91% for those with unmethylated tumors), there was a higher rate of out-of-field recurrence in patients who had tumors with *MGMT* methylation (31 vs 5.4% for those with unmethylated tumors) [13].

In a study from McGill University (QC, Canada), 20 patients with completely resected glioblastoma underwent external-beam radiotherapy with concurrent and adjuvant chemotherapy [14]. The methylation status of each

tumor was also recorded and seven of them were methylated. The CTV was defined as a 2-cm margin around the surgical cavity. Edema was not intentionally included. All patients were treated to 60 Gy in 30 fractions. Recurrence occurred only at the resection margin in 17 (85%) patients [14]. Two patients developed distant failure (beyond 2.5 cm from surgical cavity) and one developed failure at resection margin and a distant site within 2.5 cm of the surgical cavity [14]. Two out of the three tumors with distant failure were methylated.

Conclusion

Data in the literature seem to suggest that most of the treatment failures are central/in-field, based mostly on diagnostic imaging with or without a biopsy, regardless of whether peritumoral edema, as shown on MRI, is included [4,9–11,13,14]. The RTOG approach requires a generous CTV expansion around a GTV, including peritumoral edema. A typical CTV margin expansion is 2 cm from edema plus any tumor and surgical cavity. Using such an approach, the amount of normal brain parenchyma included in the CTV is, in most cases, very large. In the study by Minniti *et al.*, the median GTV for the RTOG approach was three-times as much as that for the EORTC approach and the median CTV for the RTOG approach, was 1.5-times as much as that for the EORTC approach [13]. The median percentage volume of normal brain irradiated to 46 Gy for the RTOG approach was 40% higher than that for the EORTC approach. Some centers, including Emory University and Wake Forest University have utilized a reduced CTV margin around the peritumoral edema without observing an increased risk of central/in-field failure [9,10].

Taking a step further to reduce the volume, some centers do not intentionally include the peritumoral edema in the CTV. The EORTC approach typically requires a 2–3-cm expansion around the surgical cavity and contrast-enhanced tumor (based on CT or preferably MRI) to generate a CTV [1,5]. The studies mentioned above that used a similar approach did not show an increased risk of marginal failure [1,4,5,11,12]. The main pattern of recurrence is still in-field.

Some studies use other additional imaging modalities for target delineation, such as PET and magnetic resonance spectroscopy (MRS), and show discordant geographic distribution of abnormalities. Pirzkall *et al.*, from the University of California, San Francisco (CA, USA),

discovered substantial variations in spatial relationships between MRI and MRS-defined GTVs [15]. The choline:*N*-acetyl-aspartate index and other metabolic indexes were used to define the MRS-based GTV. Of the ten patients without contrast enhancement on the T_1 sequence of MRI after surgical resection, MRS showed abnormal metabolic activity in eight of them, extending 11–36 mm beyond the resection cavity [15]. In the 20 patients with contrast enhancement, metabolic activity fell outside the contrast enhancement in 19 of them, extending 8–33 mm beyond the contrast enhancement [15]. Although the T_2 signal intensity encompassed most of the MRS abnormality for all patients, the MRS-defined GTV extended beyond the T_2 signal intensity in six out of ten patients without contrast enhancement and in 13 out of 20 patients with contrast enhancement [15]. The T_2 volume increased by a median of 13–14%. Interestingly, subsequent follow-up MRI showed new areas of contrast enhancement corresponding to initial MRS abnormalities in eight out of ten patients with noncontrast-enhanced tumors [15]. The MRS-defined volumes also inversely correlated with time to development of new contrast enhancement. Grosu *et al.* from the University of Munich (Munich, Germany) used L-(methyl- ^{11}C)-labeled methionine (MET) PET for target delineation for resected high-grade gliomas, and found that the region of MET uptake was larger than that of the gadolinium enhancement on T_1 -weighted MRI in 74% of the cases, and the gadolinium enhancement area extended beyond the MET enhancement in 27 cases [16]. MET uptake was identified up to 4.5 cm beyond the gadolinium on MRI. When comparing T_2 -weighted MRI from 18 patients with MET-CT, MET uptake did not correspond exactly with the hyperintense areas on MRI in any patient, and MET uptake extended beyond the hyperintense area on the T_2 -weighted MRI in 50% of patients. Some hyperintense areas on the T_2 -weighted MRI were located outside the area of MET uptake in all cases. There was MET uptake up to 4 cm beyond the hyperintense area on T_2 -weighted MRI [16]. In another study from Germany, there was a significant difference in the size and geometric location of GTV, and tumor volume defined by ^{18}F -fluoroethyltyrosine uptake on PET in the majority of patients with glioblastoma [17].

Based on the information available so far, when target delineation is performed based on MRI, it appears that a 2–3 cm expansion around

the surgical cavity and contrast-enhanced tumor (GTV for the EORTC approach and boost GTV for the RTOG approach) is adequate for encompassing the disease process in most cases. If peritumoral edema is included in the initial GTV, a 1- instead of 2-cm CTV expansion should suffice. The biggest advantage of using the EORTC approach is the significantly decreased volume of normal brain parenchyma irradiated, potentially reducing the risk of neurocognitive and memory deficits [13]. The role of additional modalities such as PET or MRS in CTV delineation is not well defined and is yet to be determined.

Future perspective

It has been demonstrated that the delineation of CTV using other novel imaging modalities such as PET and MRS has resulted in some discrepancies in target definition compared with using regular MRI [15–17]. Whether these discrepancies will translate into differences in clinical outcomes is yet to be determined.

It has been observed that patients with glioblastomas with *MGMT* promoter methylation have a higher tendency to develop distant failure despite better local control compared with those with tumors without methylation [13]. The exact reason is unknown and further research is needed to determine whether CTV delineation should be determined by *MGMT* methylation status of the tumor.

Recent research suggests that glioblastoma is organized hierarchically with a small number of cancer stem cells having the unique ability of self-renewal and exhibition of multilineage potency, while their progeny lacks these features [18]. In the human brain, the subventricular zone and the subgranular layer have been shown to harbor

normal brain stem cells [18–20]. These regions may harbor specific regions of stem cell niches that are responsible for supporting neuronal stem cells and keeping them in an undifferentiated state [18]. In a preclinical study, it was suggested that tumor suppressor gene deletion in normal neural stem cells would lead to brain tumor formation [18,21]. There may be specific niches in the brain also housing cancer stem cells, which are relatively resistant to radiotherapy and chemotherapy [18,21–23]. Based on the above speculations, all cancer stem cells have to be eradicated in order to prevent recurrence. Inclusion of areas harboring cancer stem cell niches in the CTV may improve survival in patients with glioblastoma. Recent studies provide evidence for a role of cancer stem cells in cancer recurrence [18,24,25]. A recent evaluation of 173 glioblastoma patients pooled from two academic centers confirmed that higher radiation therapy doses to the ipsilateral cancer stem cell niches were associated with improved progression-free survival [24]. If this concept proves to be correct, these cancer stem cell niches should be included in the CTV. One potential confounding factor is the location of the glioblastoma. Further validation in clinical trials is necessary.

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