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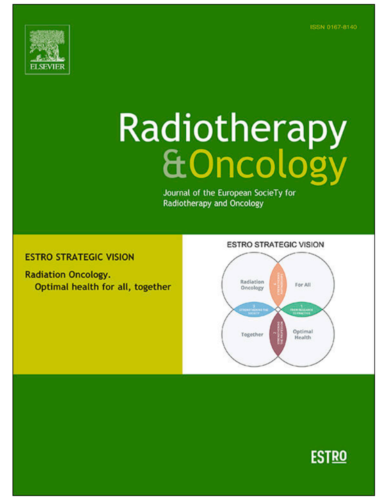

Original Article

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ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma

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Running head: ESTRO-EANO glioblastoma target delineation guideline

Keywords: glioblastoma; target volume; delineation; radiotherapy; EORTC; consensus; ESTRO; EANO

Highlights:

- The present ESTRO-EANO guideline reports the novel standard for target delineation of glioblastoma and refines the ESTRO-ACROP/EORTC standard
- GTV is defined on MRI as T1 contrast-enhancing tumour (for biopsy only patients) and/or resection cavity plus residual contrast-enhancing tumour, if present
- A 15 mm margin around the GTV should be applied to generate the CTV, edited to take account of anatomical barriers to tumour spread
- Inclusion of oedema within CTV is not advised, whereas T2/FLAIR signal abnormalities may represent non-enhancing tumour and should be considered for inclusion within the CTV

Abstract

Background and Purpose: Target delineation in glioblastoma is still a matter of extensive research and debate. This guideline aims to update the existing joint European consensus on delineation of the clinical target volume (CTV) in adult glioblastoma patients.

Material and Methods: The ESTRO Guidelines Committee identified 14 European experts in close interaction with the ESTRO clinical committee and EANO who discussed and analysed the body of evidence concerning contemporary glioblastoma target delineation, then took part in a two-step modified Delphi process to address open questions.

Results: Several key issues were identified and are discussed including i) pre-treatment steps and immobilisation, ii) target delineation and the use of standard and novel imaging techniques, and iii) technical aspects of treatment including planning techniques and fractionation. Based on the EORTC recommendation focusing on the resection cavity and residual enhancing regions on T1-sequences with the addition of a reduced 15 mm margin, special situations are presented with corresponding potential adaptations depending on the specific clinical situation.

Conclusions: The EORTC consensus recommends a single clinical target volume definition based on postoperative contrast-enhanced T1 abnormalities, using isotropic margins without the need to cone down. A PTV margin based on the individual mask system and IGRT procedures available is advised; this should usually be no greater than 3 mm when using IGRT.

Background and Purpose

Radiotherapy is a core treatment modality in the management of glioblastomas [1]; several studies have demonstrated that it provides improved overall survival compared to supportive care alone [2-4]. These studies used simple 2D and 3D radiotherapy techniques that expose sizeable volumes of normal brain to moderate to high doses of radiation, thus increasing the risk of acute and late neurotoxicity [5].

More sophisticated radiotherapy planning and delivery approaches have been widely adopted over the past decade, principally intensity-modulated radiotherapy (IMRT) especially using volumetric modulated arc therapy (VMAT). These enable the volume of normal brain receiving moderate to high radiation doses to be minimised [6] thus reducing the adverse effects of treatment. Modern radiotherapy techniques also enable dose distributions to be sculpted around critical brain structures such as optic chiasm and brainstem. Hence, accurate delineation of tumour volumes and organs at risk is crucial.

Along with the development of more accurate radiotherapy (RT) planning and delivery methods, imaging techniques have been developing which can aid target delineation. Amongst these, magnetic resonance imaging (MRI) has become mandatory while functional imaging using a variety of positron emission tomography (PET) tracers remains under investigation.

These guidelines present current ‘best practice’ with regard to target delineation and RT delivery for glioblastoma with the aim of standardised management in both routine clinical practice and clinical trials.

Methods and Materials

A systematic literature search was conducted in MEDLINE PubMed that evaluated adults with glioblastoma. The search focused on randomised, prospective and retrospective trials published in English (all sample sizes were considered). Both MeSH terms and text words were used and the following search strategy was applied: ("Glioblastoma/radiotherapy" [MeSH] OR "glioblastoma" OR "malignant glioma" OR high-grade glioma) AND ((delineation) OR (target volume) OR (CTV) OR (PTV) OR (margin) OR (recurrence pattern) OR (contouring) OR (organs at risk)).

The final literature review was conducted in April 2022 and 1,013 abstracts were retrieved, from which 51 studies providing data on target delineation and radiation therapy details for glioblastoma were selected for evaluation. In parallel, abstracts presented at the ESTRO and ASTRO conferences between 2015 and 2021 were analysed separately. These sources were not included within this guideline, but were reviewed to ensure that no practice changing trials had been conducted in the meantime.

The ESTRO Guidelines Committee identified 14 European experts who discussed and analysed the body of evidence concerning glioblastoma target delineation. Subgroups were defined who contributed sections to the overall guideline. The results of the literature search were included if appropriate. Open questions were identified and decisions made according to a modified Delphi process – 11 out of 14 experts took part in two predefined rounds in which 65% agreement was defined as 'consensus' and 80% as 'strong consensus'; three additional experts were invited from EANO (MvdB, MW and NG) to participate in drafting the manuscript.

Results

Preparation

To ensure accurate re-positioning, the patient's head should be immobilised using an individually adapted 3-point single layer thermoplastic mask system. This is the most widely used system, and enables masks to be prepared at the same appointment as the planning CT. In centres using surface guided systems, open-face mask immobilisation may be considered to improve patient comfort and positioning accuracy, especially in claustrophobic patients. A flat position with the head in neutral is the most widely accepted practice as it is the most comfortable for the patient. A CT scan should be obtained with a maximum of 2 mm slice thickness from the vertex to the lower border of the C3 vertebral body. The CT simulation is then fused with post-operative contrast-enhanced MRI to aid target delineation. Postoperative MRI scans are generally obtained within 72 hours of surgery so an additional scan is required around the time of CT simulation usually applying a limited MR protocol (see next section). For all patients, a new MRI is recommended within 2 weeks prior to the RT start date due to the high risk of tumor increase or resection cavity volume changes. A new MRI is mandatory for patients who underwent subtotal or partial resection. If MRI cannot be obtained or is contra-indicated, intravenous contrast should be administered during the planning CT scan to help identify residual disease. If amino acid PET/CT or PET/MRI is used to provide additional information for target definition, the same maximum interval of two weeks between imaging and RT start date is advised.

Image registration is an important step of the treatment planning process. Performing MRI in the treatment position with an immobilisation mask could reduce errors due to non-rigid tissue deformation and uncertainties related to image registration; however, similar high registration accuracy can be obtained using planning CT and MR images with a thin (1 mm) slice thickness while maintaining the head and neck in a neutral position. Registration between MRI and CT should be carefully reviewed; in the presence of different degrees of head extension, registration accuracy can be increased by using the region of interest instead of the whole head. Alternatively, if treatment is to be delivered on a hybrid MR linear accelerator, an MRI-only process may be considered [6].

Imaging techniques

Target delineation should be performed using contrast-enhanced 3D T1-weighted and T2/FLAIR sequences (3D sequences can be useful in cases of residual non-enhancing tumor). The MRI protocol should provide adequate image quality and spatial resolution [7]. However, caution should be advocated when using T2/FLAIR sequences for planning purposes. First, these signals are not specific, and may represent oedema, inflammation, postoperative ischemic changes or gliosis, rather than tumour infiltration. They can also fluctuate substantially over short time periods depending on tumour mass-effect, postoperative oedema and steroid dose. Second, using the entire T2/FLAIR hyperintense signal to define the CTV (if not using a sequential reduced boost volume) often translates into a large target volume that might exceed the tolerance of the normal brain. Nevertheless, T2/FLAIR signal changes may be helpful in identifying regions of suspected tumour infiltration. T2/FLAIR signal abnormalities associated with tumour infiltration include infiltration of the cortex or deep grey nuclei, mass effect (as determined by gyral thickening and sulcal effacement), ventricular compression and/or thickening of the corpus callosum. Oedema, in contrast, tends to follow natural white matter tracts, respects the cortex and is closer to CSF signal than tumour, which is more compact [8].

While the use of conventional MRI sequences (T1, T2, and FLAIR) permits definition of the volumetric boundaries of the tumour (i.e., structural imaging), perfusion- and diffusion-weighted MRI can add information about regional blood volume and microstructural architecture. MR spectroscopy may provide additional molecular and metabolic information. However, the roles of functional and metabolic MR imaging in target delineation of glioblastoma remain ill-defined and currently these modalities should only be used within the framework of prospective trials and are not recommended for routine delineation of glioblastoma.

In addition to MRI, metabolic PET imaging is increasingly entering clinical practice. In contrast to [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG), which is frequently used for staging of extracranial cancers, radiolabeled amino acids exhibit low uptake in normal brain, enabling improved delineation of brain tumours, particularly gliomas. Frequently used amino acid tracers are [^{11}C-methyl]-L-methionine (MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET), 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), and anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (fluciclovine). An important feature of these tracers is their ability to cross the intact blood-brain barrier, mostly via the transport system L for large neutral amino acids; this is particularly helpful for delineation of glioma regions that are non-enhancing on MRI [9]. These tracers may therefore be suitable for RT planning. The panel agreed that the current evidence supports the use of FET PET as a valuable additional tool for target delineation (Delphi consensus, 73%) while acknowledging that it is still under investigation and that logistical and financial factors may limit its use in routine practice.

In terms of their ability to define metabolically active tumour volumes, the amino acid PET tracers MET, FET, and FDOPA appear to be similar [10-12]. Furthermore, previous reports provide additional evidence for the value of FET PET [13-18] and MET PET [11] in target volume delineation and as prognostic biomarkers [19].

If used, the GTV (PET) should be auto-contoured in three dimensions, with tumour tissue defined by uptake above a threshold of 1.6-1.8 of mean SUV (standardized uptake value) in the background region-of-interest (ROI) (Delphi agreement 90%). The recommended threshold value is derived from a biopsy-controlled study in glioma patients in which a lesion-to-brain ratio of 1.6 provided the best separation of tumoural from peritumoural tissue [20]. Other centres use a threshold of 1.8 × background activity for estimation of the biological tumour volume (BTV) [21]. To increase specificity, PET scans should be obtained at least two weeks after neurosurgery (Delphi agreement, 90%). Review and manual editing with respect to the MRI is required and should be performed by a physician with nuclear medicine experience.

The advent of hybrid PET/MR scanners allows simultaneous acquisition such that amino acid PET, conventional and advanced MRI sequences (e.g., perfusion-weighted MRI) can easily be acquired in a single session. Besides optimizing co-registration of brain images, this technique increases convenience for patients by reducing scanning time and avoiding exposure to the additional radiation doses associated with PET/CT. Of note, however, MRI-based attenuation correction may be challenging [22].

General target delineation strategy

Although the European Organization for Research and Treatment of Cancer (EORTC) and the Radiotherapy and Oncology Group (RTOG) have adopted different approaches to delineating target volumes in glioblastoma, both groups have previously recommended a volumetric GTV expansion of 2 cm to generate the CTV. This margin was applied to encompass areas of potential microscopic tumour infiltration, and was adjusted to respect anatomical borders, as reported in our previous glioblastoma target delineation guideline [23]. In Europe, where RT is typically delivered in a single phase and the GTV was defined as the resection cavity plus any residual enhancing tumour on contrast-enhanced T1-weighted MRI, this approach is based largely on data showing that more than 80% of tumour recurrences occur within 2 cm of the GTV [24-31].

More recently, retrospective and prospective studies using reduced GTV-to-CTV margins of 0.5-1.5 cm to treat glioblastoma with either conventionally fractionated or hypofractionated radiation schedules have shown overall survival, progression-free survival times and recurrence patterns similar to those observed in studies applying current target delineation recommendations [32-38]. Table 1 provides a summary of analyses of recurrence patterns. Indeed, one small randomised trial (N = 50) suggested improved survival and reduced toxicity when smaller margins were applied [39], although imbalances in patient characteristics and missing molecular information severely limits its interpretation. With the aim of maintaining treatment efficacy while limiting the risk of treatment-related neurocognitive toxicity, a reduction of GTV-to-CTV margin to 1.5 cm is recommended (90% agreement on Delphi) and the following target volume approach is proposed:

- In resected tumours, GTV delineation should be based on the resection cavity (if present) plus any residual enhancing tumour on contrast-enhanced T1 weighted MRI, without inclusion of peri-tumoural oedema. GTV should include all postoperative contrast-enhancing areas; however, some regions of contrast enhancement may represent post-surgical infarction or gliosis. These areas may be excluded from the GTV after careful review of pre- and immediate post-resection MRI scans.
- Although there are no data to suggest that inclusion of perifocal oedema in the target volume improves outcomes, T2/FLAIR changes may represent areas of tumour infiltration, as described in the imaging section and the latest 'RANO resect' report [40]. Preoperative T2/FLAIR can also help to distinguish residual tumour margins from postoperative vascular changes or oedema (Figure 2). Distinguishing infiltrating non-enhancing tumour from oedema on T2/FLAIR can be challenging. The expert panel agreed that it is not necessary to include all T2/FLAIR signal abnormality where these are felt to represent oedema. It was agreed that if changes were felt to represent non-enhancing tumour they should be encompassed in the CTV. However, based on currently available evidence, no consensus could be reached regarding the margin that should be added to the T2/FLAIR volume. Experts on the panel recommended margins ranging from 0 – 15 mm.
- The use of perfusion- and diffusion-weighted MRI and amino acid PET tracers MET, FET, and FDOPA may help to identify areas of tumour infiltration beyond conventional MRI, and may specifically be helpful to define suspected non-enhancing tumour [41]. Although PET is not part of standard imaging for target delineation of glioblastoma, its use is recommended based on results from some early phase clinical trials, and the available data support its use to improve target delineation. While there was insufficient agreement to recommend changes in margins when amino acid PET is used (Delphi:

64% agreement), it was agreed that FET PET may in the future prove to be useful in reducing CTV margins [42]. As an example, the WHO 2021 classification identifies a subgroup of diffuse gliomas that should be treated as glioblastomas according to their molecular profile, even in the absence of typical histological characteristics, such as microvascular proliferation or necrosis [43, 44]. Specifically, IDH-wildtype diffuse astrocytic tumours without mutations in histone H3 genes that exhibit one or more of three genetic markers (*TERT* promoter mutation, *EGFR* gene amplification, combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/−10]) should now be classified as glioblastoma [45]. Because most of these tumours appear as non-enhancing lesions on MRI, GTV should include the resection cavity plus any residual tumour visible as either contrast-enhancing on T1-weighted or hyperintense on T2/FLAIR MRI.

- The Clinical Target Volume (CTV) is defined as the GTV plus a margin to account for microscopic spread. Based on studies of recurrence pattern and tumour infiltration (see above), 15 mm is the recommended margin to be applied in all directions of likely tumour spread. While preliminary studies have suggested that inclusion within the CTV of glioma stem cell niches in the subventricular zones might improve outcomes [46], additional clinical studies are needed to validate this hypothesis. There is currently consensus that the subventricular zone should not be intentionally included in the CTV (Delphi: 82% voted against inclusion). Margins should be reduced at anatomical barriers such as the skull (0 mm, using bone window), ventricles (5 mm), falx (0 mm), tentorium cerebelli (0 mm), visual pathways/optic chiasm and brainstem (each 0 mm), provided the tumour is distant from the white matter tracts extending to these regions (e. g. midbrain) (Delphi consensus: 91%; Fig. 1). No margin reduction should be applied at the corpus callosum, cerebral and cerebellar peduncles. In 'molecularly defined' glioblastomas, similar margins should be applied in the range of 10-15mm; however, the optimal GTV-to-CTV margin strategy for these tumours needs to be better defined in future studies.

Organs at risk

Critical organs at risk (OAR) that should be delineated as a minimum requirement include the optic nerves, optic chiasm, eyes, lenses, brain and brainstem, all of which should be taken into consideration during the planning process and might result in compromised PTV coverage. Non-critical OARs may include the cochleas, lacrimal glands, pituitary gland, hypothalamus and hippocampi. For these latter structures, dose constraints may be used as guidance during

plan optimisation, but explicit PTV compromise is discouraged unless critical dose constraints cannot otherwise be met, such as for the brainstem or optical system.
Hippocampal sparing has received considerable attention recently, but neurocognition data to support its use when planning radiotherapy for glioblastoma patients is currently lacking. Bilateral dose-sparing of uninvolved hippocampi was reported to be safe in a large cohort study [47]. In a small prospective observational study of 18 adult patients with benign or low-grade brain tumours treated with conventionally fractionated stereotactic radiotherapy, Gondi and colleagues [15] produced a dose-response model where 2Gy per fraction equivalent doses greater than 7.3Gy to 40% of the bilateral hippocampi volume were associated with long-term memory impairment when comparing formal neurocognitive testing at 18 months follow-up to baseline. The model was rather uncertain, however, and interpreting 7.3Gy as a 'hard' threshold is not supported. Nonetheless, a consensus was reached in the group that, while ipsilateral sparing should be discouraged, contralateral hippocampal dose reduction was acknowledged as being of potential value as long as target coverage was preserved (level of agreement: 91%).

Contouring of OAR should follow the Global Harmonisation Group (GHG) consensus guidelines [48]. In addition to the GHG delineation guidance for the brain, it is recommended to subtract the GTV from the brain OAR contour for proper dosimetric assessment (level of agreement: 91%). Although no evidence based recommendation for a brain dose constraint exists, the use of dose objectives for treatment plan optimization and assessment is encouraged, e.g. mean brain dose, V30/40/45Gy or equivalent uniform dose (EUD) with parameter a=9 [49]. For large or multifocal lesions, margins or prescription dose may be reduced according to experience and cumulative brain exposure, for example if V45Gy(brain) is ≥ 50% [50] or CTV volume exceeds 350 cc (personal communication within expert panel, level of agreement: 80%). Some specific OAR considerations may be appropriate for the few patients treated with proton beam therapy [51].

Expansion of OARs to create a planning risk volume (PRV) for each OAR is encouraged, especially for the optic system and brainstem (level of agreement: 91%) and the margin should reflect the accuracy of daily set-up. Nevertheless, there is no robust data to transfer current OAR constraints directly to their respective PRV, i.e. the experts would accept higher doses to the PRV as compared to the OAR hard constraint.

PTV margin concepts

The PTV should take into account geometric uncertainties of treatment delivery, CT-slice thickness including CT-MRI fusion, patient setup, IGRT and radiation delivery precision.

Thermoplastic mask systems in combination with daily IGRT are recommended, along with 6D corrections (translations and rotations) if available. Surface imaging has shown promise as a tool for replacing closed-faced masks with open-faced masks, both for improved patient comfort and real-time motion monitoring of the patient to ensure treatment accuracy. Surface-guided radiotherapy in combination with X-ray imaging has shown sub-millimetric accuracy in several studies [52]. The definitive CTV-PTV margin should be based on the institutional fixation technique and local quality assurance measurements [53, 54]. Ideally, each department should audit their set up results and apply the margin indicated by the data. As a guide, daily IGRT and modern treatment machines enable PTV margin reduction in order to spare surrounding normal tissue. A PTV margin of 3 mm is recommended (Delphi: strong consensus, 100%), but 2-5 mm is acceptable depending on the respective IGRT program. Use of a 2 mm PTV margin, daily IGRT and VMAT produced similar progression-free (PFS) and overall survival (OS) to 3D-CRT and wide margins in a large cohort of glioblastoma patients, suggesting that a margin of 2 mm may be adequate at some institutions [47].

Planning details and treatment delivery

While 3D-CRT has for many years been a standard technique for glioblastoma treatments, IMRT/VMAT is increasingly being used to achieve superior high-dose conformity around the PTV. IMRT/VMAT can provide superior solutions for tumours in close proximity to critical OARs such as the brainstem or optic system (e.g. temporal or insular tumours), or which have irregular shapes [55, 56]. VMAT is generally preferred to fixed-field IMRT techniques because it combines similar or better conformality with faster planning and delivery. GTV and CTV target delineation should not be influenced by the radiation technique used (3D-CRT, fixed-field IMRT or VMAT), the type of fractionation (standard versus hypofractionation), or the use of concurrent chemotherapy. Since particle therapy has not been proven to be superior to IMRT, the panel does not recommend its use in primary glioblastoma treatment (agreement 100%) [57].

Radiation dose prescription and planning should be performed according to ICRU guidelines (ICRU50, 62 and 83 reports). Prescription to the reference point should ensure that at least 95% of the PTV is encompassed by the 95% isodose surface, that the median dose to the PTV is close to the prescription dose, and that the D2% should be less than 107% (Delphi: strong agreement, 90%). Meeting hard constraints for critical OARs (e.g. brainstem and chiasm) necessitates compromise of the PTV dose coverage. In terms of radiation exposure of OAR, the recommendations from the current best-practice parameters should be followed (see Table 2). The best dosimetry is usually achieved with at least two coplanar or (often preferably) non-coplanar VMAT arcs [58]. There may be a future role for online MR-guided radiotherapy which enables detection of anatomical changes during therapy and may enable the use of protocols with adapted fractionation and/or margins, but evidence on these issues is currently insufficient and it remains an area of research [59-61].

Fractionation

The gold standard fractionation scheme for fit, younger patients is a dose of 60 Gy delivered in 30 fractions of 2 Gy each with concurrent daily oral temozolomide [62]. In the NORDIC trial [63] of patients aged 60 years and above, those treated with 60 Gy experienced inferior outcomes than those treated with a shorter, hypofractionated regimen. In frail/elderly patients (>65-70 years) or those with poor prognosis, hypofractionated schedules are appropriate, such as 40.05 Gy delivered in 15 fractions of 2.67 Gy [36, 64] or 34 Gy in 10 fractions of 3.4 Gy [63, 64], with the goal of completing treatment in 2-3 weeks. Alternatively, a shorter fractionation schedule of 25 Gy in 5 fractions may be considered for elderly and/or frail patients with smaller tumours [62].

Conclusions

More accurate and precise target delineation guidelines for glioblastoma should help to promote standardisation and uniformity (see Figs. 1 and 2 for two example cases, with additional images within the supplementary material and a flowchart in Fig. 3). Currently, while some aspects of the delineation technique are evidence based [65, 66], many arise from consensus practice. Alternative research methods, including the use of large image data sets and machine learning technologies, are currently being explored with a view to optimising target delineation. These methods require validation in prospective trials before being adopted into clinical practice [67].

While recognising that there is a range of approaches to defining the target volume in glioblastoma patients, the ESTRO-EANO guideline committee proposes the following pragmatic algorithm. Changes from the previous ESTRO-ACROP guideline [23] are listed in Table 3:

- Immobilisation with a thermoplastic mask system; planning CT with 1-2 mm slice thickness
- Fusion with postoperative MRI (+/- novel MRI sequences) acquired within two weeks of the RT start date; postoperative MRI within 72 h after surgery can be used for assessment of extent of resection and preoperative MRI may help with interpretation of postoperative images and provide information on pre-operative tumour extent.

- GTV defined as T1 contrast-enhancing tumour (for biopsy only patients) and/or resection cavity plus residual contrast-enhancing tumour, if present
- A 15 mm margin around the GTV should be applied in three dimensions to generate the CTV, edited to take account of anatomical barriers to tumour spread
- Inclusion of T2 abnormalities (oedema) within CTV is not advised
- Non-enhancing areas may represent a component of glioblastoma, as defined in the new WHO brain tumour classification; in such cases, consideration should be given to including regions of high T2/FLAIR signal intensity within the GTV in addition to contrast enhancing tumour, and to adapting or decreasing GTV to CTV margins
- CTV to PTV margin is department-specific based on measured patient relocation accuracy and other unavoidable errors. It is determined by the accuracy of the fixation system and setup verification. In the absence of department values, 3 mm is advised and this can be reduced if regular, high precision IGRT techniques are employed.
- The standard dose in good performance adult patients is 60 Gy in 2 Gy fractions; for elderly patients a hypofractionated schedule should be regarded as current standard (using the same CTV/PTV definitions).

Table 1: Selected publications relevant to target delineation of glioblastoma with focus on progression-free survival and/or recurrence pattern analyses.

Authors	**No pts**	**Study**	**GTV**	**CTV**	**PTV**	**Dose [Gy]/fx**	**Recurrence pattern**	**mPFS, 95% CI [months]**	**mOS, 95% CI [months]**
Gebhart BJ [32]	95	retrospective	first phase: T1 enhancing and non-enhancing tumour volume (T2 or FLAIR) boost: T1 enhancing tumour volume	$GTV_{1,2}$+5 mm	$CTV_{1,2}$+3-5mm	46/23 14/7	81% in-field 6% marginal 28% distant	8 (3-46)	NR
Azoulay M [34]	30	ph 1/2	tumour resection cavity, residual enhancing tumour, and nodular non-enhancing tumour	GTV+5mm	CTV+0 mm	25/5 30/5 35/5 40/5	NR	8.2 (4.6-10.5)	14.8 (10.9-19.9)
Navarria P [33]	164	PSM	tumour resection cavity + residual enhancing tumour	GTV+0mm	CTV+5mm	60/15 60/30	NR	10 (8.2-11.8) 12.3 (8.7-15.9)	16.7 (14.5-18.9) 17.9 (16-19.9)
Kumar N [39]	50	rand ph 2	RTOG protocol tumour resection cavity + residual enhancing tumour	Initial phase GTV+oedema + 20mm boost GTV+25mm	CTV+5mm CTV+5mm	40/20 20/10	87% in-field* 12.5% marginal 0% distant	6.1	12
			MDACC protocol tumour resection cavity + residual enhancing tumour	initial phase GTV+20mm boost phase GTV+5mm	CTV+5mm CTV+5mm	40/20 20/10	87% in field* 6.2% marginal 6.2% distant	8.8	17
Brown PD [57]	67	rand ph 2	tumour cavity and any residual T1 tumour enhancement	GTV+20mm	CTV+3-5mm GTV+3-5mm	50/60 /30 IMRT	NR	8.9	21.2
						50/60 /30 protons		6.6	24.5
Tu Z [68]	68	retrospective	tumour resection cavity + residual enhancing tumour	GTV+20mm	CTV+5mm	60/30	100% within 2cm from GTV, 94.8% within 1cm	7 (1-78)	13 (3-92)

Authors	No pts	Study	GTV	CTV	PTV	Dose [Gy]/fx	Recurrence pattern	mPFS [months]	mOS [months], 95% CI
Zheng L [69]	55	retrospective	tumour resection cavity + residual enhancing tumour	GTV+10mm GTV+20mm	CTV1+3mm CTV2+3mm	60/30 54/30	44pts central 2pts in-field 1pt marginal 1pt distant	7	17.7
Perry JR [36]	562 (elderly)	rand ph 3	tumour resection cavity + residual enhancing tumour	GTV+15mm	CTV+5mm	40/15	NR	5.3 RT+TMZ 3.9 RT	9.3 RT+TMZ 7.6 RT
Guram K [35]	267	retrospective	first phase: T1 enhancing and non-enhancing tumour volume (T2 or FLAIR) boost: T1 enhancing tumour volume		$GTV_{1,2}$+10mm $GTV_{1,2}$+4mm GTV+2-3cm	45/25 16.2/9	NR	10.7 10.2	19.1 19.3
Amino acid PET guided approaches									
Fleischmann DF [42]	36	retrospective	Tumour cavity and any residual T1 enhancement/ FET-PET based biological tumour volume	GTV+BTV+15mm	CTV+3mm	60/30	34 in-field* 2 out of field 0 marginal		
				GTV+20mm	CTV+3mm	60/30	34 in-field* 2 out of field 0 marginal	NR	NR
Laack NN [70]	75	ph 2	surgical cavity plus any residual CE, metabolic target volume (MTV) on DOPA-PET	GTV+10mm	CTV+3mm GTV+3mm	60/30 76/30	NR	8.8	16
Pessina F [71]	93	ph 2	surgical cavity plus the residual tumour and MET-PET uptake	GTV+0mm	GTV+5mm	60/15	NR	10	16

Legend
*including central recurrences
#recurrence patterns evaluation
** ^{18}F-FET-PET employed for recurrence pattern analysis
PSM=propensity score matched analysis
NR=not reported
fx=fraction
ph=phase
rand=randomised
TMZ=temozolomide

Table 2: Selected OAR dose limits for glioblastoma patients receiving conventional dose and fractionation RT - individual adaptation may be necessary according to the clinical situation. Some experts advocate the use of PRVs (mainly in critical serial structures such as chiasm or brainstem) applying the constraints mentioned below, others do not. *Most protocols allow ipsilateral cochlea to receive 60Gy rather than compromise dose. **according to the EORTC 1709 trial https://clinicaltrials.gov/ct2/show/NCT03345095 and respective RTQA recommendations. ***more than 1 cc rather discouraged. ALARA – as low as reasonably achievable.

OAR	Objective(s)
BRAINSTEM	D ≤ 54 Gy [72] $D_{0.03cc}$ ≤ 56 Gy** 1-10cc*** < 59 Gy (periphery) [72] Surface $D_{0.03cc}$ ≤ 60 Gy [73]** Interior $D_{0.03cc}$ ≤ 54 Gy [73]
CHIASM	D_{max} < 55 Gy [72] $D_{0.03cc}$ ≤ 55 Gy [73]**
COCHLEA	Ideally one side mean <45 Gy [74] ALARA
EYES	Macula <45 Gy [75] Eye balls D_{max} ≤ 40 Gy** (low priority)
LACRIMAL GLANDS	D_{max} < 40 Gy [76] Mean ≤ 25Gy [73] ALARA
LENS	Ideally <6 Gy Max 10 Gy [76]
OPTIC NERVES	D_{max} ≤ 54 Gy [77] D_{max} < 55 Gy [72] $D_{0.03cc}$ ≤ 56 Gy**
PITUITARY	D_{max} < 50 Gy [78] ALARA

Table 3: Changes from previous guideline

Topic	Guideline 2016	Current guideline
GTV	Cavity + contrast-enhanced T1	Cavity + T1 contrast enhancement, optionally PET-based BTV, or FLAIR alteration clearly visualized as tumour
Role of FLAIR	Optional inclusion of oedema	Exclude vasogenic oedema, if FLAIR indicates presence of non contrast-enhancing tumour, include with variable/no margin
Role of PET	Lack of definite evidence	Amino acid PET is a valuable tool for target delineation
CTV margin	20 mm	15 mm
PTV margin	3-5 mm, audit own IGRT capabilities	3 mm advised
Anatomical adaptations	falx/tentorium 5 mm	falx/tentorium 0 mm
Histology	Classical glioblastoma	Novel WHO 2021 classification, molecular types considered as well

Figure 1A-F: 65 year old patient with a right frontal glioblastoma. The GTV (red contour) was expanded by 1.5 cm to generate the CTV (blue contour) and constrained at anatomical barriers (bone, falx), whereas no correction was applied at the genu corporis callosi. No further CTV expansion was applied and the FLAIR abnormalities visible in the right frontal lobe were not included (panels E, F). The PTV (orange) was generated by a 3 mm geometric expansion of the CTV (orange).

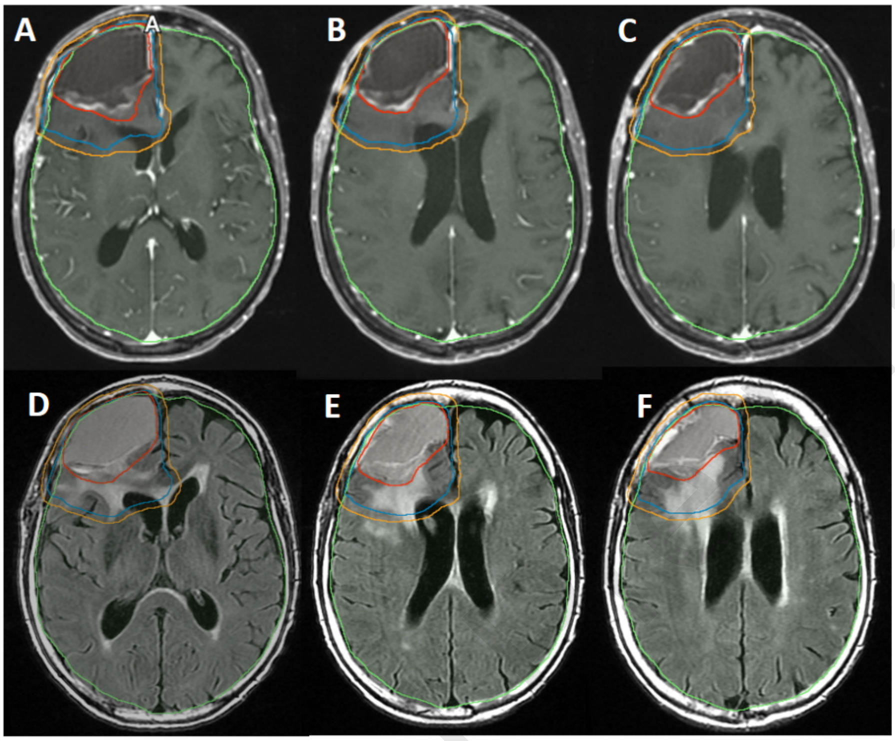


Figure 2A-F: 56 year old patient with a left occipito-parietal glioblastoma. The GTV (red contour) was expanded by 1.5 cm to generate the CTV and constrained at anatomical barriers (bone, falx). The CTV (blue contour) was enlarged to include the abnormalities of the splenium corporis callosi (thickening and hyperintensity in FLAIR sequence) that were suspicious of tumour infiltration (panels E, F). The PTV (orange) was generated by a 3 mm geometric expansion of CTV (blue). No further margins were applied after inclusion of FLAIR abnormalities.

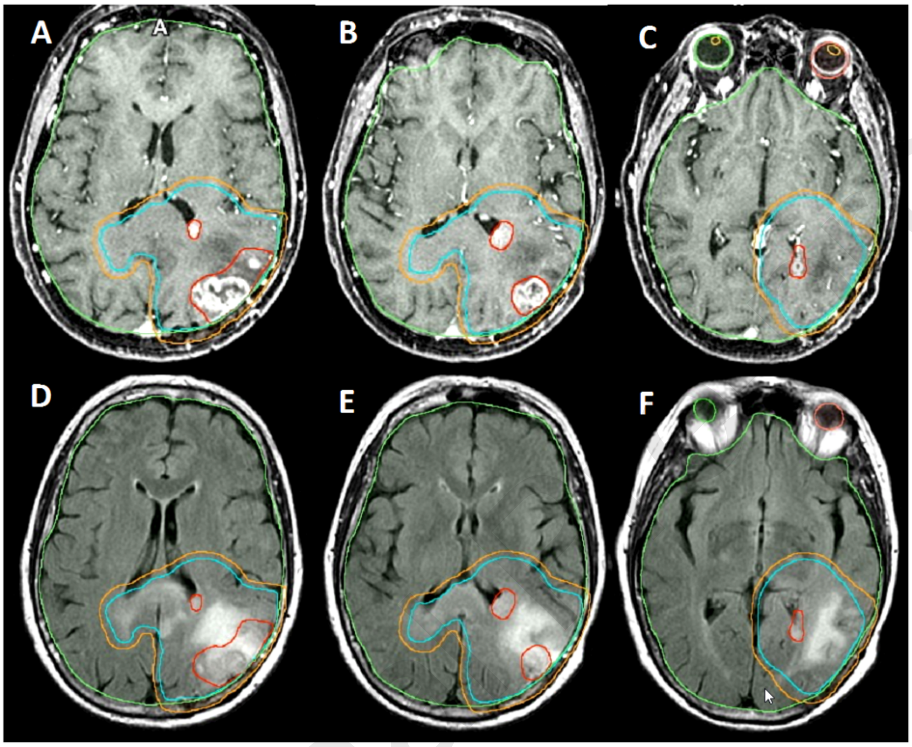
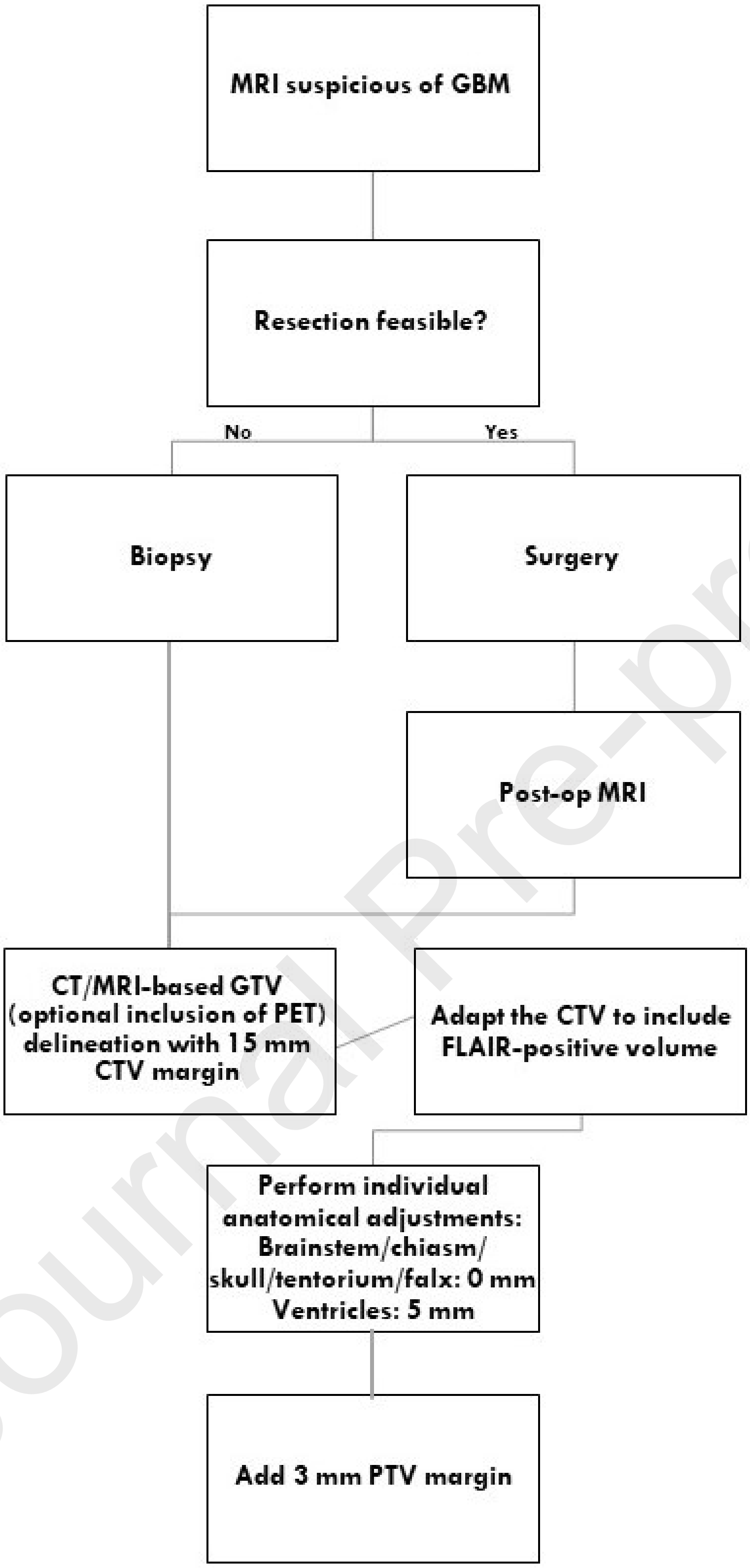


Figure 3: Flowchart illustrating how to delineate CTV and PTV: FLAIR-positive tumour should be distinguished from vasogenic oedema, and should be included with a variable margin (no consensus has been reached, dependent on clinical case and whether differentiation from oedema feasible).


MRI suspicious of GBM
Resection feasible?
No
Yes
Biopsy
Surgery
Post-op MRI
CT/MRI-based GTV (optional inclusion of PET) delineation with 15 mm CTV margin
Adapt the CTV to include FLAIR-positive volume
Perform individual anatomical adjustments: Brainstem/chiasm/ skull/tentorium/falx: 0 mm Ventricles: 5 mm
Add 3 mm PTV margin

Abbreviations

3D-CRT	3-dimensional conformal radiotherapy
ACROP	(ESTRO)-Advisory Committee on Radiation Oncology Practice
ADC	Apparent diffusion coefficient (ADC)
BTV	Biological tumour volume
CTV	Clinical target volume
CSF	Cerebrospinal fluid
DWI/DTI	Diffusion-weighted/diffusion tensor imaging
EORTC	European Organisation for Research and Treatment of Cancer
ESTRO	European SocieTy for Radiotherapy & Oncology
EUD	Equivalent uniform dose
FDG	[^{18}F]-2-fluoro-2-deoxy-D-glucose
FET	O-(2-[^{18}F]-fluoroethyl)-L-tyrosine
FLAIR	Fluid-attenuated inversion recovery
FDOPA	3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine
GHG	Global harmonisation group
GTV	Gross tumour volume
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
MET	[^{11}C-methyl]-L-methionine
MRI	Magnetic resonance imaging
OS	Overall survival
PET	Positron-emission tomography
PFS	Progression-free survival
PTV	Planning tumour volume
PRV	Planning organ at risk volume
ROI	Region-of-interest
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SIB	Simultaneous integrated boost
TBR	Tumour-to-background ratio
VMAT	Volumetric intensity-modulated arc therapy

Preparation of the guideline

The guideline was prepared following the ESTRO SOP for guidelines and is an expert guideline. The writing committee consisted of the following experts: MN and GM coordinated the guideline panel and drafted the manuscript. NA, CB, MB, AC, SCE, FJL, PN, PMAR and UR were part of the expert panel, took part in the modified Delphi process and participated in the preparation of the manuscript. NG, MvdB and MW were EANO liaison persons and contributed neuro-oncological input/imaging paragraphs. All authors read and approved the final manuscript. The reviewing of the guideline was performed by Neil Burnet, Vinai Gondi, and Jonathan Yang - their advice is highly appreciated.

Guideline update

This guideline is planned to be updated within a 4 years-time frame unless there are fundamental scientific changes which require an earlier update. Amendments will be made if changes are minor but of clinical significance.

DISCLAIMER

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Highlights:

- The present ESTRO-EANO guideline reports the novel standard for target delineation of glioblastoma and refines the ESTRO-ACROP/EORTC standard
- GTV is defined on MRI as T1 contrast-enhancing tumour (for biopsy only patients) and/or resection cavity plus residual contrast-enhancing tumour, if present
- A 15 mm margin around the GTV should be applied to generate the CTV, edited to take account of anatomical barriers to tumour spread
- Inclusion of oedema within CTV is not advised, whereas T2/FLAIR signal abnormalities may represent non-enhancing tumour and should be considered for inclusion within the CTV

Conflict of interest statement

The authors declare that they have no competing interests.

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) of this work.