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Original article

ESTRO-ACROP guideline "target delineation of glioblastomas"

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ABSTRACT

Background and purpose: Target delineation in glioblastoma (GBM) varies substantially between different institutions and several consensus statements are available. This guideline aims to develop a joint European consensus on the delineation of the clinical target volume in patients with a glioblastoma (GBM).

Material and methods: A literature search was conducted in PubMed that evaluated adults with GBM. 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)). In parallel, abstracts from ESTRO and ASTRO 2010–2015 were analysed and separately reviewed. The ACROP committee identified 14 European experts in close interaction with the ESTRO clinical committee who discussed and analysed the body of evidence concerning GBM target delineation.

Results: Several key issues were identified and are discussed including (i) pre-treatment steps and immobilization, (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 20 mm margin, special situations are presented with corresponding potential adaptations depending on the specific clinical situation.

Conclusions: Currently, based on the EORTC consensus, a single clinical target volume definition based on postoperative T1/T2 FLAIR abnormalities is recommended, using isotropic margins without the need to cone down. A PTV margin based on the individual mask system and IGRT procedures available is advised, usually of the order of 3–5 mm.

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Radiotherapy has been the mainstay of treatment for glioma since the 1980's when it was established that post-operative treatment improves survival [22,23,45–47]. It remains the most effective non-surgical treatment for the majority of patients, with or without chemotherapy, although primary chemotherapy with temozolomide (TMZ) may benefit a subset of older patients [27,50]. The gold standard treatment for glioblastoma (GBM) is based on a multidisciplinary approach employing surgery followed by radiotherapy with or without concurrent and adjuvant chemotherapy [43,44]. Ideally, a maximal safe resection of the enhancing tumour should be performed; however, if resection is

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; ACROP, (ESTRO)-Advisory Committee on Radiation Oncology Practice; ADC, Apparent diffusion coefficient (ADC); CTV, Clinical target volume; DWI/DTI, Diffusion-weighted/diffusion tensor imaging; EORTC, European Organisation for Research and Treatment of Cancer; ESTRO, European SocieTy for Radiotherapy & Oncology; GBM, Glioblastoma; GTV, Gross tumour volume; IGRT, Image-guided radiotherapy; IMRT, Intensity-modulated radiotherapy; 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; PWI, Perfusion-weighted imaging; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; SIB, Simultaneous integrated boost; TMZ, Temozolomide; VMAT, Volumetric intensity-modulated arc therapy; WBRT, Whole-brain radiotherapy.

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likely to result in major functional impairment, then an open or stereotactic biopsy should be performed [41]. Pathological confirmation of GBM should be obtained prior to high-dose (chemo)radiotherapy, however in exceptional circumstances this may be waived, for example in elderly patients unfit for diagnostic procedures in whom there is no realistic differential diagnosis based on advanced MR imaging.

Historically, GBM patients were treated with whole-brain radiotherapy (WBRT) alone or followed by a cone down boost to the tumour, but high doses were needed to maximise local control [45–47]. Close proximity to radiosensitive organs at risk (OARs) and recognition of the impact of high dose RT on cognition have motivated radiation oncologists to evolve the planning process over the past 20 years [7,39]. Initially, two phase partial brain irradiation was introduced, followed by the development of focal radiotherapy in the form of 3-dimensional conformal radiotherapy (3D-CRT) and more recently techniques such as intensity-modulated radiotherapy (IMRT), and volumetric intensity-modulated arc therapy (VMAT).

As modern radiation techniques have become more conformal to the Planning Target Volume (PTV) with respect to the high-dose region, an accurate delineation of target volumes has become increasingly important. The experience with individual case review of the EORTC/NCIC trial showed that more rigorous definition of volumes, OARs and techniques is required [2].

This guideline article aims to provide an overview of existing delineation strategies, their therapeutic value to date and recurrence pattern analyses. The ultimate aim is to define the optimal strategy for target delineation in GBM.

Methods and materials

A literature search was conducted in MEDLINE PubMed that evaluated adults with GBM. 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 September 2015 and a total of 692 abstracts was retrieved. In parallel, abstracts from ESTRO and ASTRO 2010–2015 were analysed and separately reviewed; these were not included within this guideline but were used to ensure that no practice changing trials had been conducted in the meantime.

The ACROP clinical committee identified 14 European experts who discussed and analysed the body of evidence concerning GBM target delineation. Subgroups were defined who contributed partial sections to the whole guideline. The results of the literature research were used and included if appropriate. Open questions were identified and decisions were met according to majority view.

Results

Preparation

To ensure accurate re-positioning the patient's head should be immobilized using an individually adapted mask system. Thermoplastic systems are the most widely used and can be prepared at the same appointment as the planning CT scan. A flat position with the head in neutral is the most widely accepted practice as it is most comfortable for the patient. A CT scan should be obtained using 1–3 mm slice thickness from the vertex to the lower border of C3. As GBM can grow rapidly an up-to-date (ideally $\leqslant$2 weeks old) contrast enhanced MRI scan should be fused with the planning CT to aid target delineation. If a recent MRI is not available, for example if MRI is contra-indicated, then intravenous contrast should be administered during the planning CT scan to help identification of residual disease.

Imaging techniques

Target delineation should be performed using contrast enhanced T1 + T2/FLAIR sequences. Caution should however be advocated when using the latter for planning purposes. Firstly, T2/FLAIR signals can substantially fluctuate depending on tumour mass-effect and postoperative oedema. Secondly, using the entirety of T2/FLAIR hyper-intensity signals to define the CTV (if not using a sequential decreased boost volume), will often translate into a target volume associated with an irradiation dose/volume beyond the tolerance of the normal brain (TD5/5 60 Gy to one third, [9], though estimates rather conservative, see QUANTEC [24], but less volumetric data given).

While the use of conventional MRI sequences (i.e. T1, T2 and FLAIR) permits definition of the volumetric boundaries of the tumour (i.e. structural imaging), perfusion- and diffusion-weighted MRI potentially add information about the regional blood volume and microstructural architecture of the high-grade glioma. However, the role of functional imaging for target delineation in the treatment of GBM remains ill-defined. The use of perfusion- and diffusion-weighted MRI, with or without spectroscopy, should only be used in the framework of prospective trials and not in routine delineation during the planning process of a GBM patient.

Similarly there is no definitive role for PET imaging. Although previous reports have shown an impact of techniques such as FET-PET [12,30,35,49] and MET-PET [14] on target volume delineation, without a clear "gold standard" for comparison and in the absence of prospective randomised studies using these modalities to define GTV or CTV cannot currently be recommended. It has been suggested that PET imaging (MET or FET), may be useful in the context of re-irradiation because of the extensive post-therapeutic imaging changes which might be differentiated more accurately by PET. This role has not been fully validated, however.

General target delineation strategy

Although the addition of TMZ to radiotherapy has improved outcomes, almost all patients develop tumour recurrence at the primary tumour site [4,20,48]. In patients with residual tumour post surgery, recurrence occurs predominantly at the site of the tumour. In macroscopically resected tumours, recurrence tends to occur in regions of tumour infiltration along white matter tracts [15]. It is suggested that glioblastoma may not be a focal tumour, but an infiltrative disease of the entire brain, since tumour cells may be found in varying densities throughout the whole brain [38]. Recurrences may thus be due to inadequate therapeutic doses limited by the tolerance of normal tissue to irradiation [8]. The development of a tumourigenic microenvironment in areas with higher densities of residual cells may also contribute to the risk of recurrence [18]. Most authors use a 1.5–2 cm volumetric expansion of the GTV to generate the CTV, adjusted to anatomical borders. This is based on data demonstrating over 80% of recurrences within a 2 cm margin of the contrast enhanced lesion on CT- or MRI scans [3,6,10,16,17,25,31,48].

Based on the limited volume irradiation studies, different consensus guidelines have been established. There are two major approaches to delineating the clinical tumour volume (CTV) (NCCTG/Alliance and ABTC approaches will not be discussed). The recommendation of the European Organization for Research and Treatment of Cancer (EORTC) is to deliver RT in a single phase

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(60 Gy, 2 Gy per fraction) while the Radiotherapy and Oncology Group (RTOG) recommends two phases starting with a larger volume that receives 46 Gy before "coning down" for the additional 14 Gy. Both recommendations are embedded within trial protocols developed by the respective groups (Table 1). There has been no randomised comparison of the different consensus practices, but both approaches were permitted in two recent multicenter trials (CENTRIC and RTOG 0525), with randomisation stratified according to radiotherapy technique, and no difference in progression-free or overall survival was observed [11,42]. Other retrospective studies compared the EORTC consensus with that used by the RTOG and confirmed that larger PTVs failed to produce a significant reduction in marginal or distant recurrences [6,29].

Therefore, in Europe single phase treatment is advocated. The two-phase technique results in a larger volume of brain receiving high to moderate doses with a potentially increased risk of cognitive impairment [13]. The single volume approach is also more convenient as only one planning phase is necessary.

Defining the optimal target volume for GBM represents a balance between minimising treatment-related toxicity while maintaining efficacy in terms of tumour control. The use of postoperative MRI fused with the planning CT is required for accurate target identification and delineation. Although an early postoperative MRI scan (e.g., within 48 h) is recommended to assess the presence and extent of residual tumour following surgery, use of this scan alone for radiotherapy planning may underrepresent the extent of disease at the time of treatment planning due to shifting of the brain and the potential for tumour regrowth. Ideally an MRI scan less than two weeks old should be used. In general, contrast-enhanced thin-slice (3 mm or less) T1-weighted and FLAIR sequences should be fused with the planning CT. The use of 1-mm isotropic MPRAGE images may improve delineation of grey and white matter and small anatomical structures (hippocampi, optic pathway), significantly reduce flow artifacts and provide more accurate CT/MRI co-registration; however it is less sensitive to enhancement as compared to SE or TSE T1-weighted sequences. Despite some promising data, the use of advanced functional MRI techniques, including perfusion-weighted imaging (PWI), diffusion-weighted and diffusion tensor imaging (DWI/DTI), and PET-CT remains investigational.

1) In macroscopically resected tumours Gross Tumour Volume (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. In general, GTV should include all postoperative contrast-enhancing areas; however, some regions of contrast enhancement may represent post-surgical infarction or gliosis. Comparing planning MRI with preoperative scans and postoperative diffusion-weighted imaging (DWI) may help to discern postoperative vascular changes from residual tumour, providing more precise GTV delineation. For patients with a secondary glioblastoma, nonenhancing areas may be a component of the tumour; in such
cases, consideration may be given to include hyperintensity on T2/FLAIR in the GTV in addition to the contrast enhanced tumour, and use adapted/decreased GTV to CTV margins.
2) 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) 20 mm is the recommended margin applied in all directions of likely tumour spread along the white matter tracts but reduced at anatomical barriers such as the skull (0 mm, using bone window), ventricles (5 mm), falx (5 mm), tentorium cerebelli (5 mm), visual pathway/optic chiasm and brainstem (each 0 mm), provided the tumour is distant from the white matter tracts extending to these regions (e.g. midbrain). Although some reports suggest that the CTV should be modified to include all regions of abnormal T2/FLAIR MRI signal considered to represent peritumoural oedema, there are no definite data to suggest that their inclusion alters outcome. If the high signal regions are to be included, particularly if they are considered to represent regions of low grade tumour, comparisons of T2 and FLAIR sequences indicate that FLAIR derived target volumes are larger than their T2 based counterparts [19], so the recommendation is that regions of abnormal FLAIR signal should be used for delineation.
3) Distinguishing between oedema and residual tumour may be difficult if not impossible. A pre-existing history of a lower-grade tumour, the presence of IDH1 mutation, or an increased cerebral blood volume ratio at dynamic susceptibility-weighted contrast-enhanced perfusion images all increase the likelihood that FLAIR hyperintense regions represent a component of the tumour, as for secondary glioblastoma.

Organs at risk

The OARs including the optic nerves, optic chiasm, eyes, lenses, brain and brainstem should be contoured. Other potential OARs include the cochleas, lacrimal glands, pituitary gland and hypothalamus – although these are considered 'relative OARs' since few oncologists would compromise dose to PTV in order to reduce dose to these organs. Some radiation oncologists also contour the

Table 1
Guidelines for target delineation of glioblastoma, according to the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG).

EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)	RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)
Phase 1 (to 60 Gy in 30 fractions)	Phase 1 (to 46 Gy in 23 fractions)
GTV = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans).	GTV1 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).
CTV = GTV plus a margin of 2 cm*	CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm.
PTV = CTV plus a margin of 3–5 mm	PTV1 = CTV1 plus a margin of 3–5 mm
	Phase 2 (14 Gy boost in 7 fractions)
	GTV2 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans)
	CTV2 = GTV2 plus a margin of 2 cm
	PTV2 = CTV2 plus a margin of 3–5 mm

GTV = gross tumour volume; CTV = clinical target volumes; PTV = planning target volume.
MRI = magnetic resonance imaging.
* Margins up to 3 cm were allowed in 22981/22961 trial, and 1.5 cm in 26981–22981 trial.

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Table 2
OAR definitions and dose limits in GBM patients - individual adaptation necessary according to the clinical situation. *Most protocols allow ipsilateral cochlea to receive 60 Gy rather than compromise dose.

OAR	If contouring on MRI always double check on CT in case of misalignment	Objective(s)
Brainstem	The foramen magnum to the point where the optic tract passes lateral to the midbrain (this upper limit is arbitrary but easy to define and ensures consistency). Again, for consistency, the quadrigeminal (tectal) plate should be included	$D \leqslant 54$ Gy [28] 1–10 cc < 59 Gy (periphery) [28]
Chiasm	Sits above and behind the anterior clinoids and runs backwards above the sella turcica. For consistency, the anterior and posterior 'limbs' should extend 5 mm to include the start of the optic nerves anteriorly and optic tracts posteriorly. The chiasm can sometimes only be seen on a single slice as it is about 3 mm thick in cranio-caudal direction. It is often easiest to identify in the coronal plane	D_{max} <55 Gy [28]
Cochlea	Sit just anterior to the lateral aspect of the internal auditory canal. They are most easily identified on the CT bone windows as small caves in the bone measuring 4–6 mm. Contour on 3 slices otherwise too small for dose calculation algorithms	Ideally one side mean <45 Gy [33]
Eyes	The whole of the outside of the globe should be contoured to include sclera and cornea. The macula lies opposite the lens	Macula <45 Gy [34]
Lacrimal glands	These can be difficult (sometimes impossible!) to see – but they lie on the superior and lateral aspect of the globe with the inferior border at the (axial) equator of the globe and wrap around superiorly about 30 degrees (i.e. face on – left eye from 1 to 3 o'clock and right eye 9 to 11 o'clock). They sit anterior to the (coronal) equator of the globe. Dose limits should not be used to compromise PTV dose	D_{max} <40 Gy [21]
Lens	Usually easy to see on the CT scan. However as cataracts are easily treatable the dose limits should never compromise PTV dose	Ideally <6 Gy Max 10 Gy [21]
Optic nerves	From the back of the globe to the optic chiasm passing through the optic canal to enter the skull anterior and inferior to the anterior clinoid. To help identify the exact path through the orbit change to CT bone windows. Ensure they join up with optic chiasm. It may be useful to check the structure in the sagittal plane to ensure the outlined structure is not an extra-ocular muscle	$D_{max} \leqslant 54$ Gy [19] D_{max} <55 Gy [28]
Pituitary	Within the sella turcica with chiasm lying superior and anterior to the stalk. As hypopituitarism is easily treatable the dose limits should never compromise PTV dose	D_{max} <50 Gy [32]

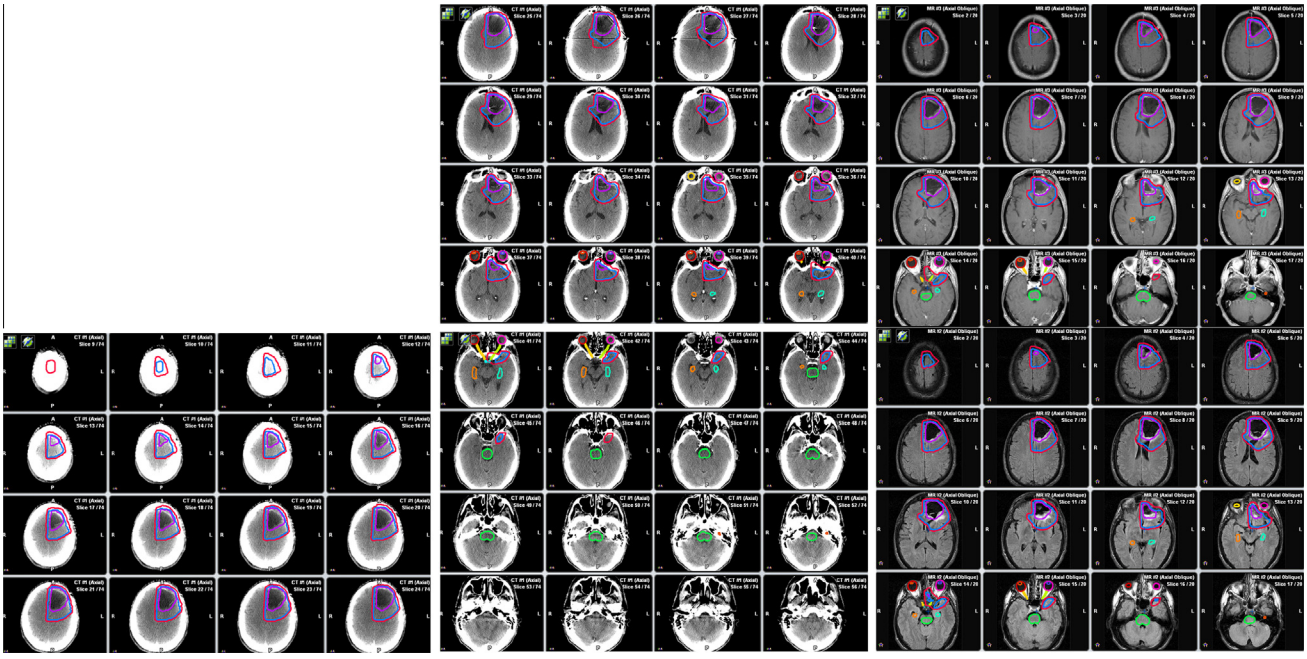

Fig. 1. Left frontal lobe glioblastoma (subsequently delineated in CT/CE T1/FLAIR slices), GTV (purple): surgical cavity, CTV (blue): GTV + 2 cm constrained at anatomical sites; falx (5 mm) (CT slices 10–40, T1 slices 2–13, FLAIR slices 2–13), cavernous sinus, optic chiasm (0 mm) (CT slices 40–41, T1 slices 13–14, FLAIR slices 13–14), bone (0 mm) (all slices and series). PTV (red): CTV + 3 mm. Organs at risk: Brainstem (light green), optic chiasm (sky blue), left optic nerve (lime green), right optic nerve (yellow), left eye (pink), right eye (red), left lens (slate blue), right lens (dark orange), right hippocampus (orange), left cochlea (brown).

contralateral hippocampus when the tumour is in a location that will allow sparing without compromising dose to the target; the principle of this approach is acknowledged but there is currently insufficient evidence to support recommendations on hippocampal sparing.

Expansion of OARs to create a planning risk volume (PRV) for each OAR is frequently applied; the margin should reflect the accuracy of daily set-up. Overlaps between PRVs and PTV should be considered and may necessitate reducing PTV dose adjacent to OARs.

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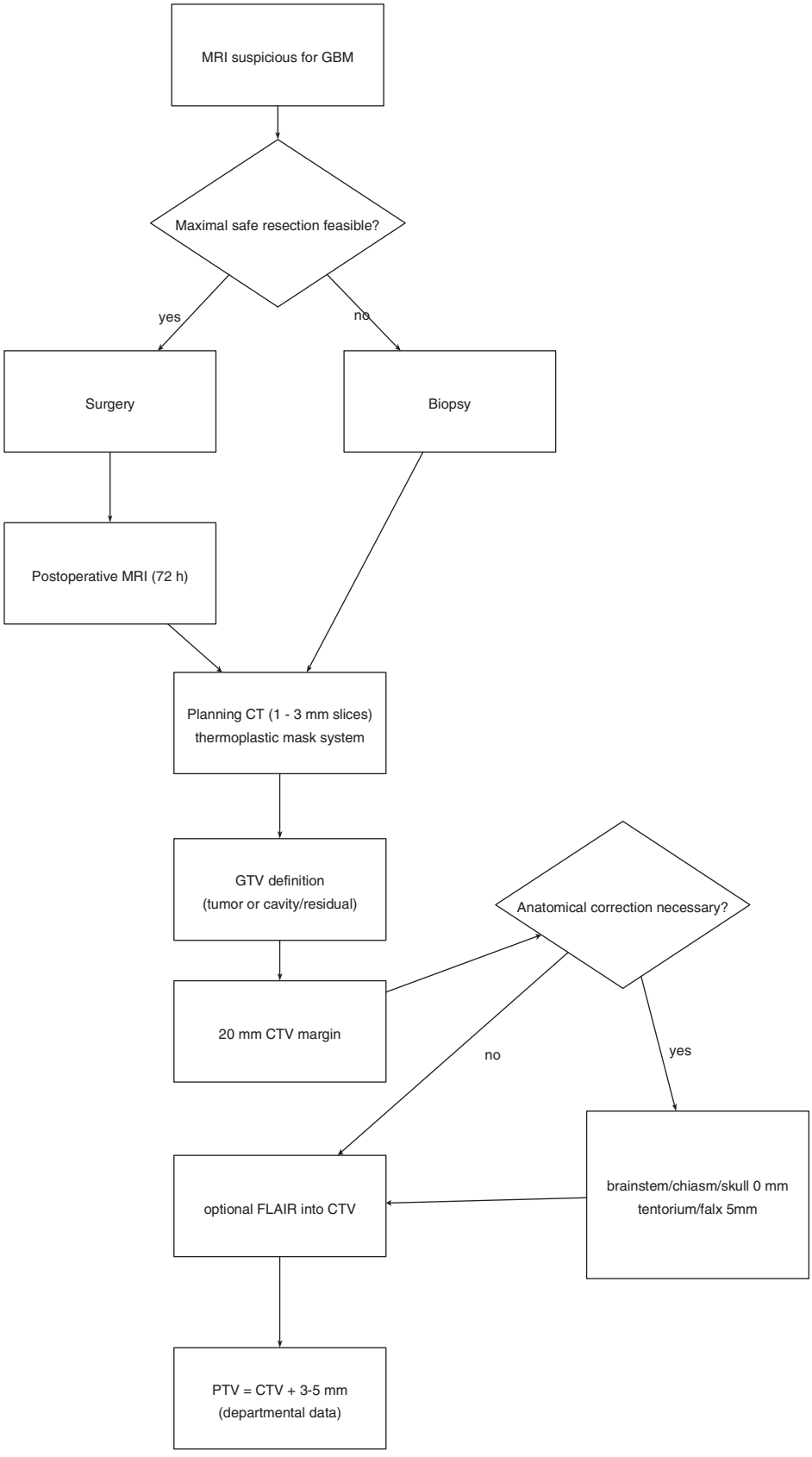

Fig. 2. Flowchart how to delineate the CTV/PTV.

PTV margin concepts

The PTV should take into account uncertainties of planning, including those arising from CT-MRI fusion and patient setup. Restricting the CTV to PTV margin to a maximum value around 3–5 mm is recommended to limit the dose to surrounding normal tissue. This should be feasible with current thermoplastic mask systems in combination with on- or offline imaging options on modern linear accelerators. The definite margin should be based on the institutional fixation technique and quality assurance measurements [5,37]. Ideally each department should audit their set up results and apply the margin indicated by the data.

Treatment technique

While 3D-CRT remains standard for the majority of GBM, IMRT/VMAT is increasingly being used for some locations and for volumetrically or spatially challenging tumours. For smaller, spherical frontal and/or parietal tumours 3D-CRT is often sufficient, whereas IMRT/VMAT can provide superior solutions for tumours (e. g. temporal, insular) that are in close proximity to the brainstem or orbit, or which have irregular shapes [1,26]. VMAT is more often used than IMRT due to its similar conformality and faster planning and delivery.

GTV and CTV target delineation should not be influenced by the radiation technique used for treating GBM (3D-CRT, IMRT or VMAT), the type of fractionation (standard versus hypofractionation), or the use of concurrent chemotherapy. While for the majority of patients treated with short courses of palliative radiotherapy 3D-CRT is likely to be adequate, there is growing realisation that prolonged survival can be achieved in a subpopulation of patients who have undergone (near-) complete resection followed by high-dose chemo-radiotherapy. This group of patients is at risk of long-term radiation-induced neurocognitive toxicity and may benefit from intensity modulated techniques that reduce high (biological) dose regions at the cost of low-dose bath, and achieve steep dose gradients adjacent to critical structures. Several VMAT techniques are in clinical use that allow for superior high-dose conformity and increased speed of treatment delivery.

Planning details

The radiation dose is prescribed according to ICRU guidelines (ICRU50 & 62 reports) to 100% at the isocentre, ensuring that the 95% isodose surface covers at least 95% of the PTV. Meeting constraints for critical OARs (e.g. brainstem and chiasm) may necessitate a compromise in terms of local under-dosage to the PTV. For radiation exposure of OAR, the recommendations from the QUANTEC DVH parameters should be followed (see Table 2), a detailed report on contouring issues is given by Scoccianti and colleagues [40]; specific planning issues concerning IMRT/VMAT are beyond the scope of this guideline and therefore we refer to the ICRU83 report.

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 TMZ.

In elderly patients (>70 years) or those with poor performance status (KPS < 70) hypofractionated schedules are appropriate, such as 40 Gy delivered in 15 fractions of 2.67 Gy [36] or 34 Gy in 10 fractions of 3.4 Gy [27]. Based on phase II data, 30 Gy in 5/6 Gy per fraction delivered on alternate days is frequently used in the UK and other European countries. In the Scandinavian trial of elderly patients those treated with 60 Gy over six weeks experienced inferior outcomes than those treated with a shorter hypofractionated regimen.

Conclusions

More accurate and precise target delineation guidelines for GBM should help to promote standardisation and uniformity (see Fig. 1 for a sample case and a flowchart in Fig. 2). Currently, while a number of aspects of the delineation technique are evidence based, many arise from consensus practice.

While recognising that there is a range of approaches to defining the target volume in GBM patients, the ACROP guideline committee proposes the following pragmatic algorithm:

- Immobilisation with a thermoplastic mask system; planning CT with 1–3 mm slice thickness.
- Fusion with postoperative MRI, obtained within the preceding two weeks; postoperative MRI within 72 h after surgery can be used for assessment of extent of resection and preoperative MRI helps with interpretation of postoperative images and provides information on the extent of preoperative tumour.
- GTV defined as T1 contrast-enhancing tumour (for biopsy only patients) and/or resection cavity plus residual contrast-enhancing tumour, if present.
- A 20 mm margin around the GTV should be applied to generate the CTV, edited to take into account anatomical barriers to tumour spread.
- Inclusion of T2/FLAIR abnormalities within CTV is optional though not recommended as routine.
- For patients with a secondary glioblastoma, non-enhancing areas may be a component of the tumour; in such cases, consideration should be given to include high signal intensity on T2/FLAIR in the GTV in addition to the contrast enhanced tumour, and to use adapted/decreased GTV to CTV margins.
- CTV to PTV margin is department specific based on measured patient relocation accuracy and other inevitable errors. It is determined by the accuracy of the fixation system and setup verification. In the absence of department values 3–5 mm is advised and this can be at the lower limit or less if regular high precision IGRT techniques are employed.
- 3D-CRT/IMRT/VMAT can be selected on the basis of complexity of target volume and proximity of critical OARs.
- The standard dose in good performance adult patients is 60 Gy in 2 Gy fractions in combination with TMZ; for elderly patients a hypofractionated schedule should be regarded as current standard (using the same CTV/PTV definition).

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: M.N. coordinated the guideline panel and drafted the manuscript. M.B., A.C., S.E.C., S.C.E., A.F., A.L.G., F. J.L., G.M., R.M., U.R., S.C.S. and D.C.W. were part of the expert panel and participated in the preparation of the manuscript. C.B. initiated the guideline, participated in its conception as well as the preparation of the manuscript. All authors read and approved the final manuscript. The reviewing of the guideline was performed by Arnab Chakravarti and Brigitta Baumert – their advice is highly appreciated.

Guideline update

This guideline is planned to be updated within a 2 year-time frame unless there are fundamental scientific changes which

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require an earlier update. Amendments will be made if changes are minor but of clinical significance.

Conflicts of interest

The authors declare that they have no competing interests.

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