



Original Article

ESTRO-EANO guideline on target delineation and radiotherapy for IDH-mutant WHO CNS grade 2 and 3 diffuse glioma



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ABSTRACT

Purpose: This guideline will discuss radiotherapeutic management of IDH-mutant grade 2 and grade 3 diffuse glioma, using the latest 2021 WHO (5th) classification of brain tumours focusing on: imaging modalities, tumour volume delineation, irradiation dose and fractionation.

Methods: The ESTRO Guidelines Committee, CNS subgroup, nominated 15 European experts who identified questions for this guideline. Four working groups were established addressing specific questions concerning imaging, target volume delineation, radiation techniques and fractionation. A literature search was performed, and available literature was discussed. A modified two-step Delphi process was used with majority voting resulted in a decision or highlighting areas of uncertainty.

Results: Key issues identified and discussed included imaging needed to define target definition, target delineation and the size of margins, and technical aspects of treatment including different planning techniques such as proton therapy.

Conclusions: The GTV should include any residual tumour volume after surgery, as well as the resection cavity. Enhancing lesions on T1 imaging should be included if they are indicative of residual tumour. In grade 2 tumours, T2/FLAIR abnormalities should be included in the GTV. In grade 3 tumours, T2/FLAIR abnormalities should also be included, except areas that are considered to be oedema which should be omitted from the GTV. A GTV to CTV expansion of 10 mm is recommended in grade 2 tumours and 15 mm in grade 3 tumours. A

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treatment dose of 50.4 Gy in 28 fractions is recommended in grade 2 tumours and 59.4 Gy in 33 fractions in grade 3 tumours. Radiation techniques with IMRT are the preferred approach.

Introduction

The 2016 and 2021 updates of the WHO Classification of Tumours of the Central Nervous System changed the diagnostic classification by the integration of molecular markers in the routine diagnostics of brain tumours [1,2]. IDH mutational status is now a key element in the classification of adult-type diffuse gliomas. IDH-mutant diffuse gliomas are then subdivided into those with 1p/19q codeletion (oligodendrogliomas) and without codeletion (astrocytomas). Tumours are then categorized into grades 2, 3 or 4 according to morphological and molecular features [3]. The change in classification introduces new challenges in translating results from past trials into present-day clinical care. In addition, new methods of radiotherapy dose-delivery, as well as the increased availability of advanced structural and functional imaging, warrant new consensus guidelines on radiotherapy for lower grade diffuse glioma. Therefore, the European Society for Radiotherapy and Oncology (ESTRO) together with the European Association of Neuro-Oncology (EANO) developed this guideline for radiotherapy of IDH-mutant, grade 2 and 3 diffuse gliomas in adults. High grade, WHO grade 4, gliomas (HGG) are addressed in a separate guideline [4].

Methods

The ESTRO Guidelines Committee, CNS subgroup, nominated 16 European experts who identified areas of clinical uncertainty to be answered in this guideline. Four areas were addressed: 1). Imaging, 2). Radiotherapy (RT) volumes, 3). Radiotherapy techniques, and 4). Radiotherapy dose and fractionation.

Timing and sequencing of treatment were not included as this has been discussed extensively elsewhere [5].

For each topic, a literature search was performed including literature from 1990 to 2022. Both MeSH terms and text words were used with the

following search terms: (“Low grade glioma/radiotherapy” [MeSH] OR “higher grade glioma” 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) OR (radiation technique /brachytherapy/protons). For the imaging section of this guideline, a separate search was performed including the terms “MRI” and “magnetic resonance imaging” and “CT”. Additionally, national guidelines from the Netherlands, USA and the UK, and trial protocols from the EORTC, were consulted. It was agreed upon that only literature-based 3D-conformal or more sophisticated radiotherapy should be included. The final literature review was conducted in July 2023.

The findings from the literature search were discussed in regular online meetings and are summarised in Tables 1 to 4. Decisions were made by a majority vote with at least a of 51 % agreement in case of open questions. Open questions were identified, and recommendations made according to a modified Delphi process – 13 out of 15 experts took part in two predefined rounds in which 65 % agreement was defined as ‘consensus’ and 80 % as ‘strong consensus’. Table 5.

Additional experts from the EANO (MvdB, RR) participated in reviewing and drafting the manuscript.

Results

Imaging

Currently, 3 Tesla (3 T) MRI is the desired clinical standard, while 1.5 T is also completely acceptable despite a lower signal-to-noise ratio [6] (Delphi: strong consensus [92.9 %]). There are also, promising studies suggesting that ultra-high field (starting at 7 T) may provide superior images for dose planning [7].

There is a widely accepted standardized imaging protocol for

Table 1
Trials investigating adjuvant chemotherapy in grade 2 and 3 diffuse gliomas.

Trial name	Inclusion	Astro		Oligo		“Oligo astro”	Randomisation	Radiotherapy	Conclusions
		2	3	2	3				
RTOG9802 [83]	1998–2002	x		x		x	PCV vs observation	30*1.8 Gy	PCV improved OS (13.3 vs 7.8y).
RTOG9402 [76]	1994–2002				x	x	PCV vs observation	33*1.8 Gy	PCV did not improve OS (4.6 vs 4.7y). However, significant OS benefit in 1p/19q codeleted tumours (14.7 vs 7.3y).
EORTC 26,951 [77]	1995–2002				x	x	PCV vs observation	33*1.8 Gy	PCV improved OS (3.5 vs 2.6 y).
RTOG0424 [84]	2005–2009	x		x		x	TMZ concurrent or adjuvant vs historical controls	30*1.8 Gy	Inclusion based on >3 Pignatti risk factors. OS 8.2 years was an improvement over historical controls.
CATNON [75]	2007–2015		x				TMZ concurrent vs TMZ adjuvant vs TMZ concurrent and adjuvant vs observation (2x2 design)	33*1.8 Gy	TMZ adjuvant improved OS (6.9 vs 3.9y). TMZ concurrent did not improve OS (5.6 vs 5.0y).
NOA04 [78]	1999–2005		x		x	(x)	Observation vs PCV vs TMZ (2–1-1 design)	No data	No OS benefit for chemotherapy (8.0 vs 6.5y)
RTOG9813 [85]	2002–2007		x				PCV vs TMZ	33*1.8 Gy	No difference in OS (3.9y vs 3.8y). TMZ was better tolerated.

primary brain tumours [8], but this is focused on reaching the correct diagnosis and is not optimized for postsurgical treatment planning. The imaging protocol for RT planning must optimally define tumour borders without geometric image distortions. Three-dimensional (3D) sequences applying gap-free isotropic voxels of 1 mm or less are advised to guarantee a spatial resolution of images with minimal geometric distortions [9]. Geometric distortions can compromise the accuracy of delineation and planning, and should be reduced. This can be accomplished using post-processing tools, which often occurs automatically during reconstruction. Infratentorial lesions show improved rigid CT co-registration if the head position on CT and MRI matches but mask immobilisation for RT planning MRI is not the clinical standard [10].

For RT planning, it is recommended to use a combination of a 3D T2-weighted fluid-attenuated inversion recovery sequence (FLAIR) and a 3D T1-weighted sequence with and without contrast. 3D T1-weighted sequences can differ in image contrast of grey and white matter [11]. Greater structure contrast can be achieved by use of intravenous gadolinium-based contrast agent administration, which identifies tumour regions showing blood-brain barrier disruption which can indicate areas of tumour transformation to a higher-grade lesion. Technically it is possible to delineate grade 2 and 3 diffuse glioma only on T2-weighted images without contrast-enhanced MRI sequences. The early post-operative MRI scan (<48–72 h after surgery) can have surgical cellular debris and infarctions which can disguise or mimic RT-relevant tumour, and perifocal tumour oedema may not have resolved or may even extend. So, for lower grade diffuse glioma, where growth is slow, there is the time to enable these changes to resolve (e.g., repeat scan 3–4 months after surgery) [12]. Consequently, a new MRI scan is recommended when RT is being planned to enable more precise target delineation.

Following radiotherapy, most guidelines recommend an initial interval between follow-up MRIs of 3 to 6 months, that can be extended to 9 to 12 months in stable patients. Additionally, a baseline MRI scan on completion of radiotherapy is recommended [13]. Of note, a substantial proportion of irradiated lower grade gliomas shows signs of pseudo-progression or other treatment related changes [14–17], which can trigger unnecessary interventions such as surgery as well as patient stress. Therefore, clinically stable patients should preferably receive follow-up with the lowest frequency acknowledged acceptable in their recommended interval range (Delphi: consensus [84.6 %]) with a full brain tumour imaging protocol [8].

A CT scan remains a crucial step in RT planning for two reasons; firstly, the images provide the geometric gold standard that the more distorted MRI images can be co-registered to and secondly it provides the electron density information necessary for dose planning. No specific technical prerequisites apply towards lower grade diffuse gliomas, and standard protocols can be found elsewhere [18]. However, at craniotomy metal clips are often used for skull plate fixation, and the use of

Table 2
Trials investigating radiotherapy dose and timing in grade 2 and 3 diffuse glioma.

Trial name	Inclusion	Astro		Oligo		“Oligo astro”	Randomisation	Radiotherapy	Conclusions
		2	3	2	3				
<i>Early vs late</i>									
EORTC 22,845 [38]	1986–1997	x		x		x	RT vs observation	28*1.8 Gy	No OS benefit (7.4 vs 7.2y) but PFS benefit (5.3 vs 3.4y) for early RT
Alliance N0577 (CODEL) [86]	2009–2011				x		RT vs RT + TMZ vs TMZ	33*1.8 Gy	PFS worse in TMZ only arm (5y PFS 56 % vs 33 %). Study design changed to RT + PCV vs RT + TMZ
<i>Dose escalation</i>									
EORTC 22,033 [47]	2005–2010	x					RT vs TMZ	28*1.8 Gy	No difference in PFS (3.8 vs 3.3y)
EORTC22844 [44]	1985–1991	x	x	x			RT vs dose-escalated RT	25*1.8 Gy vs 33*1.8 Gy	No OS benefit (5y OS 58 % vs 59 %) or PFS benefit (5y PFS 47 % vs 50 %) for high dose RT
Intergroup [73]	1986–1994	x	x	x			RT vs dose-escalated RT	28*1.8 Gy vs 36*1.8 Gy	No OS benefit (15y OS 22 % vs 25 %) or PFS benefit (15y PFS 15 % vs 10 %) for high dose RT

Table 3
Overview of target volume definitions from published trials (

Trial name	Procedure	Target	ICRU definition
Grade 2			
EORTC 22,844 [44]	CT enhancing lesion + 20 mm	Target volume	ICRU29
EORTC 22,845 [38]	CT edema + 10 mm MRI T2 abnormalities + 20 mm	Target volume	ICRU29
RTOG 9802 [83]	MRI T2 abnormalities + 20 mm	Field edge	ICRU29
Intergroup [73]	Lesion on CT or MRI + 20 mm	Target volume	ICRU29
EORTC 22,033 [47]	MRI T1 enhancement and T2 abnormalities + 15 mm	CTV	ICRU50
RTOG 0424 [84]	MRI T2 abnormalities + 15 mm	CTV	ICRU50
Grade 3			
RTOG 9402 [76]	MRI T2 abnormalities + 20 mm to 50.4 Gy MRI T1 enhancement + 10 mm to 59.4 Gy	Target volume	ICRU29
EORTC 26,951 [77]	CT edema OR MRI T2 abnormalities + 25 mm to 45 Gy CT enhancing lesion OR MRI T1 enhancement to 59.4 Gy	PTV	ICRU50
EORTC 26,053 (CATNON) [75]	MRI T2 abnormalities + 15 – 20 mm	CTV	ICRU50
NOA04 [78]	MRI abnormalities + 20 mm	CTV	ICRU50
Alliance N0577 [86]	MRI T2 abnormalities + 10 mm to 50.4 Gy* MRI T2 abnormalities + 0 mm to 59.4 Gy*	CTV	ICRU50

adapted from [40]).

metal-artifact suppression acquisition techniques is recommended to optimize the accuracy of Hounsfield (HU) calculations.

Radiolabelled amino acids are of particular interest for glioma imaging using PET as their increased uptake in neoplastic tissue but low uptake in the normal brain parenchyma results in an improved tumour-to-brain contrast [18]. Most frequently used amino acid tracers are [¹¹C-methyl]-L-methionine (MET), O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine (FET), and 3,4-dihydroxy-6-[¹⁸F]-fluoro-L-phenylalanine (FDOPA). Radiolabelled amino acids exhibit a sensitivity of more than 90 % for glioma, however only around 70 % of lower grade diffuse gliomas

Table 4
Overview of published series in grade 2 and 3 diffuse glioma with pattern of failure data (

	Margin	Number of recurrences	In field	Field edge	Out of field
Grade 2					
Pu, 1994 [36]	10 – 30 mm to target volume	11	100 %	0 %	0 %
Rudoler, 1998 [37]	20 mm to target volume	16	100 %	0 %	0 %
van den Bent, 2005 [38]	20 mm to target volume	94	90 %	5 %	4 %
Shaw, 2002 [39]	20 mm to target volume	65	92 %	3 %	5 %
Kamran, 2019 [40]	7–15 mm to CTV	41	76 %	12 %	12 %
Jaspers, 2021 [41]	10 – 15 mm to CTV	39	92 %	0 %	8 %
Grade 3					
Im, 2018 [43]	15–20 mm to CTV	31	61 %	19 %	16 %
Back, 2020 [42]	10 mm to CTV	68	51 %	9 %	22 %

* Proton therapy series, WHO grade 1 and 2 glioma.

** The data shown pertains to isolated local, marginal, and distant relapses. In the remaining 12 (18%) patients recurrence was classified as a combination of local, marginal and distant failure. adapted from [40]).

exhibit increased uptake [19–22]. Thus, 20–30 % of these gliomas are amino acid PET negative (i.e., no increased uptake compared to the reference region). Of note, a subgroup of patients with lesions without amino acid uptake on PET and MRI findings suspicious for low grade gliomas (i.e., hyperintense T2/FLAIR signal without contrast enhancement) may even show photopenic defects (i.e., uptake visually lower than the reference region) and harbour high grade gliomas [23,24]. Conventional MRI is limited in its ability to differentiate between oedema, ischaemia, inflammation, and non-enhancing gliomas. For PET, several studies have correlated histology obtained from tissue specimens with amino acid uptake and provide evidence that amino acid PET detects the most malignant tumour parts more reliably than conventional MRI [25–30] Therefore, amino acid PET appears highly valuable for

Table 5
Results of modified Delphi.

Question	Topic	Answer	Level of agreement (%)
Imaging	MRI	3 Tesla MRI is desired clinical standard	92.9
	Pseudo-progression	clinically stable patients should receive follow-up with the lowest frequency acknowledged acceptable	84.6
RT volumes	GTV – general	GTV should include resection cavity and any residual tumour volume after surgery.	100
		Amino-acid PET and perfusion/diffusion advanced MRI can be good tools to improve the differentiation between oedema and tumour	92.9
	GTV – grade 2	T2/FLAIR abnormalities that are thought to represent tumour should be included in the GTV	100
	GTV – grade 3	T2/FLAIR abnormalities could either be tumour or oedema, but areas which are thought to represent oedema do not need to be included in the GTV	85.7
	CTV – grade 2	CTV should be created with an expansion of the GTV with a margin of 10 mm	90.9
	CTV – grade 3	CTV should be created with an expansion of the GTV 15 mm	91.7
RT techniques	CTV – general	CTV margin should be edited to respect anatomical boundaries unless tumour invasion is explicitly suspected	100
	Hippocampal sparing	If uni- or bilateral hippocampal sparing is used, the original constraint (D40% of bilateral hippocampus < 7.3 Gy) is recommended	91.7
	Planning	IMRT and VMAT are preferred approach due to the improved target conformity with associated better sparing of OARs	100
	Set-up control	Daily image guidance, including MV and KV cone beam CT and orthogonal X-ray imaging systems, is recommended	100
Dose, fractionation	Brachytherapy	application of interstitial brachytherapy adds to the treatment portfolio if used in experienced hands and selected cases	50
		50.4 Gy in 28 fractions is recommended	100
		54 Gy in 30 fractions as also used in several trials including the RTOG 9802, is also acceptable	83.3
		A lower dose level such as 45 Gy in 25 fractions, is advised against	100
	60 Gy in 30 fractions should not be exceeded in WHO grade 3 tumours	100	

target delineation. A more recent publication by the Response Assessment in Neuro-Oncology Working Group for PET (PET/RANO), summarizes the data and concluded that in glioma patients (including non-enhancing gliomas) amino acid PET may improve the delineation of radiotherapy target volumes beyond conventional MRI and identify additional tumour parts that should be targeted by radiotherapy [31]. According to current guidelines for glioma imaging using amino acid PET, the threshold for FET uptake for the delineation of tumour extent is defined as a mean tumour-to-brain ratio of 1.6 [32].

Radiotherapy volumes

Almost all patients with grade 2 and 3 diffuse glioma will at some time point undergo disease progression, typically in close proximity to the resection cavity following surgery [33–35]. More than 80 % of patients with grade 2 tumours exhibit treatment failure within the original RT fields [36–41]. Data on grade 3 tumours is limited, but the available evidence suggests higher rates of marginal and out-field failure [42,43]. There has been gradual reduction of field size over the last three decades prompted by; a) the pattern of mainly in-field recurrences, b) ongoing improvements in imaging, RT planning and dose delivery, and c) the longer overall survival increases concerns about late side effects of radiotherapy resulting from large treatment volumes. For grade 2 glioma, the landmark trials of the 1990’s and 2000’s typically adopted margin concepts that would amount to a CTV margin of 15 to 20 mm [38,39,44,45] around the resection cavity and any residual lesion on imaging. Later trials recommended a CTV margin to 15 mm in all patients [46,47], and current ongoing trials prescribe a CTV margin of 10 mm (NRG BN005, Alliance N0557) or below (EORTC 1635)(Table 3) For grade 3 glioma the early studies used a similar or slightly larger margins, with an additional boost phase [48,49]. Currently most trials use a CTV margin of around 15 mm in a single-phase technique [50,51] Fig. 1. The PTV should take into account all possible geometric uncertainties of treatment delivery as well as measurements of each institute. For intracranial treatments, the use of a mask system and daily online image guidance with cone beam CT typically reduces both systematic and random errors to 1.5 mm or lower[52]. The working party agreed on the following target delineation guidance, considering published recurrence data and distances (Table 4).

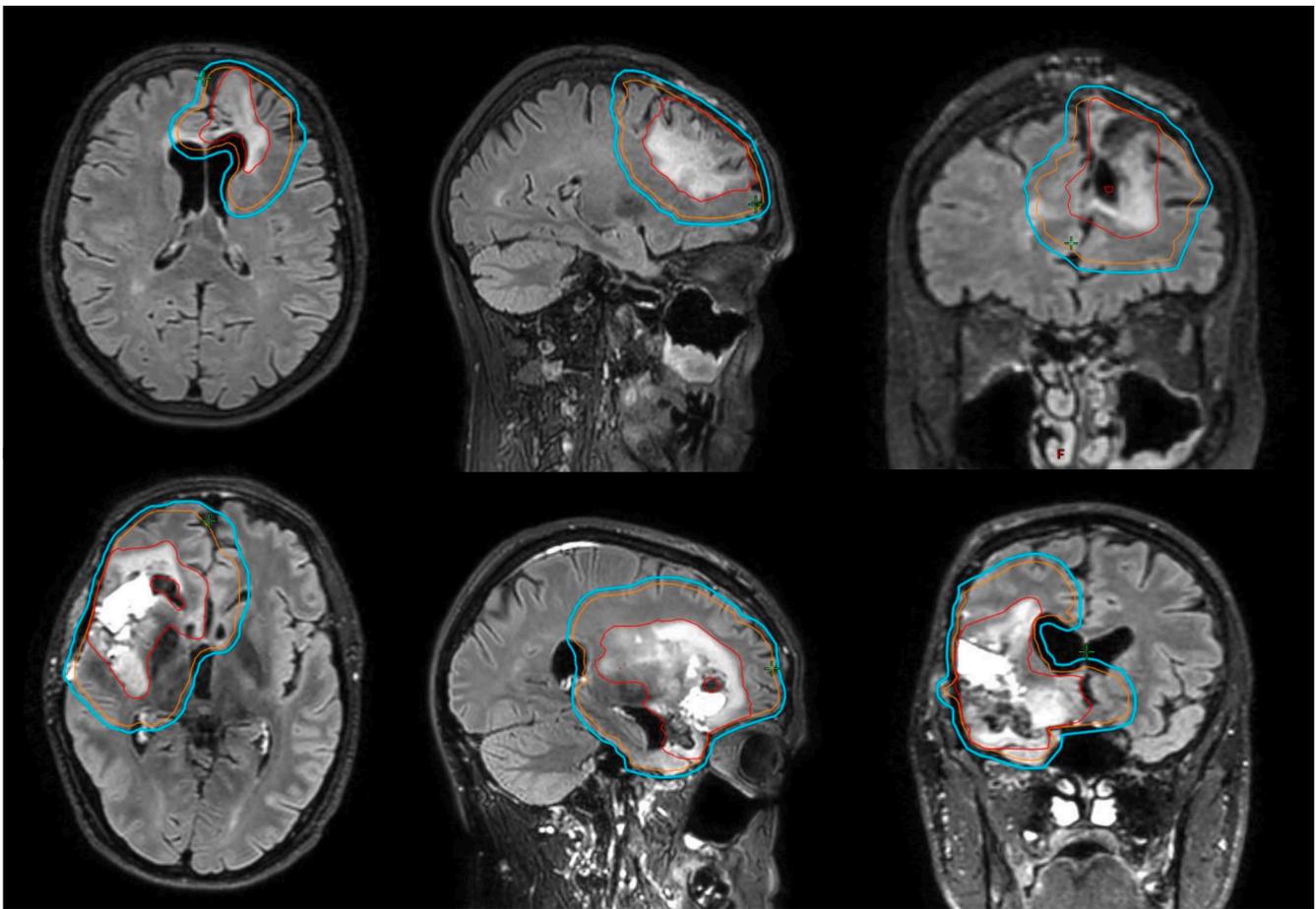


Fig. 1. Delineation of IDH-mutant lower grade glioma. GTV is in red, CTV in orange, PTV in blue. Top row: grade 2, CTV margin 10 mm, PTV margin 3 mm. Bottom row: grade 3, CTV margin 15 mm, PTV margin 3 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

GTV

- The GTV should include the resection cavity and any residual tumour volume after surgery (resection or biopsy). The same target delineation should be used for 1p/19q codeleted and non-codeleted glioma Enhancing lesions on T1 imaging should be included if they are indicative of residual tumour (Delphi: strong consensus [100 %]).
- In grade 2 tumours, T2/FLAIR abnormalities that are thought to represent tumour should be included in the GTV (Delphi: strong consensus [100 %]).
- In grade 3 tumours, T2/FLAIR abnormalities could either be tumour or oedema, but areas which are thought to represent oedema do not need to be included in the GTV (Delphi: strong consensus [85.7 %]).
- The delineation of the GTV can be informed by additional MRI and/or functional imaging. If available, amino acid PET and perfusion/diffusion MRI can be valuable tools to improve the differentiation between oedema and tumour (Delphi: strong consensus [92.9 %]).

CTV

- The CTV should be created with an expansion of the GTV with a margin of 10 mm for grade 2 tumours (Delphi: strong consensus [90.9 %]). and 15 mm for grade 3 tumours (Delphi: strong consensus [91.7 %]).
- The CTV margin should then be edited to respect anatomical boundaries, including the calvarium, tentorium, falx, and ventricles, and to exclude the optic nerves, chiasm, and pituitary gland (unless

tumour invasion is explicitly suspected) (Delphi: strong consensus [100 %]).

- The CTV should not be edited for areas where tumour spread is possible, such as hippocampus or corpus callosum.

PTV

- PTV is created using a margin of ≤ 3 mm depending on departmental set up policy.

Organs at risk

For organ-at-risk (OAR) delineation, the EPTN atlas contains definitions for the organs-at-risk used in CNS radiotherapy [53,54]. The atlas was developed for use in both photon and proton radiotherapy, its use is recommended in trials or multi-centre protocols. In photon radiotherapy the Intergroup atlas can be used as an alternative [55]. Preferably, all individual organs at risk should be contoured. Both atlases, as well as the ESTRO-EANO glioblastoma guideline, include OAR dose constraint guidance [4,56]. In addition to dose constraints, NTCP models can be used for both the purpose of patient selection and radiotherapy planning [57,58].

Although there is substantial interest in factors linked to late-onset neurocognitive decline in patients with grade 2 and 3 diffuse gliomas, demonstration of a direct relationship between RT dose parameters and cognitive outcome has so far been unsuccessful. The complex interplay between tumour location, baseline neurological functioning, along with the type and frequency of neurocognitive testing, make assessment of impact of RT dose for an individual patient challenging. The strongest

evidence exists for hippocampal avoidance, which has gained adoption in radiotherapy following the publication of RTOG 0933 [59]. If uni- or bilateral hippocampal sparing is used, the original constraint (D40% of bilateral hippocampus <7.3 Gy) is recommended (Delphi: strong consensus [91.7 %]). The mean dose to brain minus GTV (brain-GTV) can be considered as a planning objective and used to quickly compare plans with regards to dose in macroscopically uninvolved areas of the brain.

Radiotherapy techniques and dose-prescription

In view of the long survival of patients with IDH-mutant diffuse gliomas, it is important to keep doses to organs at risk and healthy normal brain as low as possible. Though no randomized trials have compared available radiation techniques, IMRT and VMAT are the preferred approach over 3D conformal RT due to the improved target conformity with associated better sparing of OARs (Delphi: strong consensus [100 %]). Daily image guidance, including MV and KV cone beam CT and orthogonal X-ray imaging systems, is recommended to enable set up margins to be minimised (Delphi: strong consensus [100 %]).

The physical characteristics of the proton beam offers the potential to reduce the volume of brain receiving low doses of radiotherapy. Also, intensity modulation of proton beams is now available, providing superior dose distributions in complex shaped target volumes when compared to older proton therapy techniques. The use of proton beam therapy may be particularly relevant in patients at young age with tumours that convey a favourable prognosis, such as IDH-mutant grade 2 diffuse gliomas. However, some reports suggest an increased rate of contrast-enhancing changes or pseudo-progression following proton radiotherapy, particularly when RT was combined with chemotherapy [60,61]. In contrast, a German and a Swedish study did not find an increased risk of pseudo-progression after proton beam therapy when compared to photon therapy data [62,63]. In proton therapy, global health as a domain of QoL has remained stable and similar to the normative reference [64]. Currently, there are no published randomised trials in adults, but the NRG005, NOA GLioProPh, and UK APPROACH trials are currently recruiting patients with IDH-mutant gliomas randomising them between photon-based IMRT or protons, with change in cognition as the primary endpoint. The results of these and other trials in set up phase will help decision making in future, though the potential reduction in late morbidity with protons will require many years to be fully evaluated.

Brachytherapy involves the use of radioactive isotopes to deliver ionizing radiation directly to the tumour offering an accurate dose distribution with steep dose gradient between tumour and normal tissue. It has a longstanding tradition being used since 1960 (¹⁹²Ir wires) and 1979 (¹²⁵I seeds) [65,66]. Its use has been suggested as a treatment option for patients with newly diagnosed non-resectable, small (≤ 4 cm), and circumscribed IDH-mutant grade 2 diffuse glioma in non-critical locations [67–71]. Temporary implants are typically preferred because of reduced risk of long-term toxicity compared to permanent implants [72]. The application of interstitial brachytherapy adds to the treatment portfolio if used in experienced hands and in selected cases (Delphi: no consensus [50 %]).

Dose, fractionation, toxicity

Tumour grade is still utilized for the choice of prescription dose, primarily because grade 2 and grade 3 diffuse glioma were treated within different trials.

In grade 2 tumours, several clinical trials have failed to show a clear dose response relationship [44,73]. Therefore, 50.4 Gy in 28 fractions, as used in the EORTC 22033 trial [47], is recommended (Delphi: strong consensus [100 %]). As 54 Gy in 30 fractions was used in several trials including the RTOG 9802, the committee agreed that this dose level is

also acceptable [74] (Delphi: consensus [83.3 %]). A lower dose level such as 45 Gy in 25 fractions, used by some practitioners in the treatment of large tumours, is advised against (Delphi: strong consensus [100 %]) as the historical trials that investigated this dose followed prescription conventions (ICRU 29) that would result in a biologically lower dose today.

In grade 3 tumours, 59.4 Gy in 33 fractions has been frequently used in trials. This is considered the standard for grade 3 1p/19q non-codeleted tumours [75]. This fractionation was also used in two clinical trials of grade 3 oligodendroglioma [76,77] but there are no randomised trials comparing different dose and fractionation schedules in this group of patients. The committee discussed the potential to reduce this dose level to minimize late effects, especially since patients with grade 3 1p/19q codeleted tumours have a better long-term survival. Alternative fractionation schedules, such as 56 Gy in 28 fractions, 54–57.6 Gy in 30–32 fractions, or simultaneous integrated boost (SIB) giving 54 Gy to non-enhancing and 60 Gy to enhancing disease in 30 fractions, could be used at the discretion of the treating physician. Historically, 60 Gy in 30 fractions was used in several high-grade glioma trials that included both grade 3 and grade 4 tumours (IDH wildtype and IDH-mutant). This dose should not be exceeded in grade 3 tumours [78] (Delphi: strong consensus [100 %]).

Discussion and future developments

Historically, trials investigating survival endpoints in lower grade diffuse glioma have taken ten years or more from trial initiation to yield clinically meaningful results. As such, basic concepts concerning target delineation and treatment dose have remained largely stable over the last decades. Use of response criteria such as those proposed by the Response Assessment in Neuro-Oncology group may allow for a faster introduction of new treatments into the clinic [13].

The number of imaging techniques, both from MRI and functional imaging, available for target delineation and response assessment is increasing and are likely to grow in importance in the coming years. As such, the complexity of target delineation may increase, and so will the added value of artificial intelligence assisted decision making. The successful application of targeted radionuclide therapy towards the treatment of extracranial tumours (such as neuroendocrine tumours and prostate cancer) has prompted efforts to translate this approach to neuro-oncology [79]. By exchanging the radionuclide, the same PET tracer can be used either for diagnostic purposes or therapy. For example, exchanging the positron emitter ⁶⁸Ga or ¹⁸F used in diagnostics with a β^- -emitter such as ¹⁷⁷Lu allows for targeted radionuclide therapy. A few clinical applications of targeted radionuclide therapy in glioma patients have passed the preclinical stage and are currently evaluated in clinical trials [80]. The outcomes of trials investigating survival, quality of life and neurocognitive function after proton beam therapy will determine its place in the radio therapeutic arsenal towards lower grade diffuse gliomas. In the future, ultra-high dose rate, or FLASH, radiotherapy may emerge as a treatment option. In high grade glioma, pre-clinical data suggests an opportunity for improving neurocognitive outcomes without compromising tumour control [81].

This guideline did not address the question of the optimal treatment sequence. The introduction of new systemic treatments may alter the timing of adjuvant radiotherapy after resection. For example, vorasidenib, an IDH1/2 inhibitor currently pending license approval, has been shown in a phase III trial to increase progression free survival in patients with grade 2 IDH-mutant diffuse glioma, which may delay the use of radiotherapy in patients [82]. Lastly, the increasing knowledge of biological markers has not yet been integrated into larger trials investigating dose and fractionation. The question whether the current dose levels are still necessary for good prognostic subgroups (like grade 3 IDH-mutant and 1p/19q codeleted tumours) therefore remains to be answered, and as such, it was felt that an allowance towards a dose reduction in such patients could be made in this guideline.

Conclusions and recommendations

This guideline provides recommendations for radiotherapy in *IDH-mutant* grade 2 and 3 diffuse glioma. Delineation should be informed by at least a directly acquired postoperative MRI. For grade 2 tumours, a 10 mm CTV margin and a dose of 50.4 Gy in 28 fractions is recommended. For grade 3 tumours, a 15 mm CTV and a dose of 59.4 Gy in 33 fractions is recommended. The guideline provides recommendations on OAR contouring, treatment planning, and discusses alternative methods of radiotherapy dose delivery.

CRedit authorship contribution statement

Brigitta G. Baumert: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Jaap P. M. Jaspers:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Vera C. Keil:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Norbert Galdiks:** Investigation, Writing – original draft, Writing – review & editing. **Ewa Izzycka-Swieszewska:** Investigation, Writing – original draft, Writing – review & editing. **Beate Timmermann:** Investigation, Writing – original draft, Writing – review & editing. **Anca L. Grosu:** Investigation, Writing – review & editing. **Giuseppe Minniti:** Investigation, Writing – original draft, Writing – review & editing. **Umberto Ricardi:** Investigation, Writing – review & editing. **Frédéric Dhermain:** Investigation, Writing – review & editing. **Damien C. Weber:** Investigation, Writing – review & editing. **Martin van den Bent:** Writing – review & editing. **Roberta Rudà:** Writing – review & editing. **Maximilian Niyazi:** Investigation, Writing – original draft, Writing – review & editing. **Sara Erridge:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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