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Guidelines

ESTRO/EANO recommendation on reirradiation of glioblastoma

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ABSTRACT

Background and Purpose: Although reirradiation of glioblastoma has a long history of clinical practice, guidance on how to perform it in the context of recent technological advances, modern imaging modalities or systemic therapy is scarce. This joint ESTRO/EANO guideline aims to collect the existing evidence to produce recommendations for safe reirradiation of glioblastoma.

Methods: The basis of this ESTRO/EANO clinical practice guideline are nine key questions (KQ) which were formulated by a consortium of radiation-oncologists, radiologists, medical oncologists, neurooncologists, medical physicists and radiation therapists. A systematic review was conducted and the KQ were addressed based on this evidence and expert opinion to draft recommendations and statements which were then voted on in a modified DELPHI process.

Results: The DELPHI consensus process resulted in 18 recommendations and nine statements of which all achieved group consensus. Thirteen (48%) were based on available prospective evidence and 14 (52%) on expert opinion. Level of evidence did not exceed "moderate", reflecting the scarcity of prospective randomized evidence

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for most aspects of reirradiation. Consensus recommendations and statements reflected aspects of patient selection, imaging for recurrence assessment, target volume delineation, treatment planning, combined modality treatment, and follow-up.

Conclusions: Currently, based on the ESTRO/EANO consensus, reirradiation may be considered in selected patients with glioblastoma. GTV definition is based on T1-weighted MR-sequences, while a GTV to CTV margin is not mandatory. A PTV margin of maximum 3 mm is recommended based on the individual mask system and IGRT procedures. A biological effective dose greater than 36 Gy in 2 Gy fractions is recommended. A careful assessment of prognostic factors on survival such as age, interval from initial radiation, large treatment volumes, poor KPS, and poor neurologic/neurocognitive status is essential for making a clinical recommendation.

Introduction

Reirradiation of brain tumors has a long history of preclinical and clinical studies especially with regards to effectiveness and safety in the recurrent setting. Clinical benefit for reirradiation of brain tumors with data from individual case series dates back more than 80 years [1]. In a recent systematic review by the European Society of Radiotherapy and Oncology (ESTRO) and the European Organization for Research and Treatment of Cancer (EORTC) of 439 studies conducted from 2000 to 2020 on reirradiation, 117 (24 %) involved the brain, and most of them included patients with high-grade gliomas [2]. Using a large array of dose and fractionation regimens, several retrospective studies report clinical benefit in patients with recurrent glioblastoma receiving a second course of radiotherapy showing variable overall survival (OS) times of 7–12 months (Minniti review 2021). More recently, prospective clinical trials have confirmed that reirradiation is feasible although without an obvious benefit in terms of OS or quality of life compared to systemic treatment alone. Systematic reviews for endpoints like progression-free (PFS) or OS, and treatment specific aspects like the use of stereotactic radiotherapy and radiosurgery have indicated a benefit with regards to PFS, but not on OS [3–7].

Data on tolerance and recovery of CNS structures supporting safety of reirradiation come from both preclinical and clinical studies [8–11]. Groundbreaking reirradiation experiments performed by Wong, van der Kogel and Ang in the 1990 s with reirradiation of the spinal cord of rats and rhesus monkeys revealed a significant dose-dependent recovery after a latent period of three months, which increased over the subsequent two years [12–14]. Published clinical results are consistent with the observations of post-radiation repair observed in the animal models, suggesting that cord tolerance appears to increase at least 25 % 6 months after the initial course of RT [9–11,15]. The tolerance of sensitive brain structures to reirradiation has been evaluated in few retrospective studies. A systematic review on reirradiation of diffuse brainstem gliomas including seven studies with a total of 90 patients, [16] showed that a second course of radiation was associated with clinical improvement and radiological response without significant toxicity employing doses of 20–24 Gy given in 2 Gy fractions. An analysis found no relevant long-term toxicity in a series of 58 patients who received reirradiation for a malignant glioma using maximum EQD2 values of 80.3 Gy, 79.4 and 95.2 Gy to the optic chiasm, optic nerves and brainstem, respectively, considering an α/β ratio of 2 Gy for these structures [17].

Despite these data on tolerance of reirradiation of brain and spinal cord, the evidence for the clinical benefit of reirradiation for glioblastoma has been regarded as controversial. In this regard, reirradiation should be always recommended in a multi-disciplinary tumor (MDT) board after careful evaluation of all prognostic factors for tumor control, radiation-induced neurotoxicity, and/or overall survival. Therefore, this multi-disciplinary EANO/ESTRO consensus-based guideline was developed to provide guidance on how to safely perform CNS reirradiation of glioblastoma with the respective technical feasibility and quality. The guidance focuses on patient selection, including clinical and diagnostic criteria for recurrence, target volume definition, dose and fractionation, treatment planning and delivery, as well as combined therapy options, and follow up.

Materials and methods

The consensus is based on the ASTRO Clinical Practice Guidelines Methodology Guide and endorsed by the ESTRO and EANO Guideline Committees. The ESTRO Guidelines Committee identified 20 European experts who in close interaction with the ESTRO clinical committee and EANO scientific committee discussed and analyzed the body of evidence concerning contemporary glioblastoma reirradiation patterns-of-practice, then participated in a two-step modified Delphi process to address open questions. Subgroups were defined who contributed sections to the overall guideline. Details on the consensus process can be found in the supplement.

The specialists (which included all authors, except AH) were selected to represent different specialties involved in reirradiation (including radiation oncology, medical physics, medical oncology, nuclear medicine, neuro-radiology and radiation therapists). The panellists have a broad clinical background and established scientific knowledge regarding management of glioma in general, radiotherapy techniques, imaging, salvage treatment and reirradiation in particular.

The Delphi process was accompanied by a systematic review. Further details on the methodology and the results of the systematic review can be found in the supplement.

Discussion of key questions and recommendations

The role of reirradiation for patients with gliomas has been assessed in a few prospective and several retrospective patient cohorts. Three prospective randomized trials evaluating reirradiation with or without the addition of systemic treatment demonstrated an improvement in PFS, but not in OS (statement 1) [3,6,7]. The NRG Oncology/Radiation Therapy Oncology Group (RTOG)1205 prospective randomized phase II trial was designed to evaluate the safety and efficacy of reirradiation for recurrent GB with modern radiation techniques. It demonstrated a similar median survival time of 10.1 months following hypofractionated SRT (35 Gy/10 fractions) plus bevacizumab or bevacizumab alone; however, 6-months PFS)rate improved significantly from 29 % to 54 % in combined group. In another small randomized trial of 91 patients with recurrent GB receiving the recombinant glycosylated fusion protein Asunercept/APG 101, the median OS was 11.5 months for both groups, whereas median PFS was 4.5 months after combined treatment and 2.5 months after reirradiation alone ($P = 0.016$) [7]. Although prospective and randomized, this study does not readily inform on the role of irradiation in this setting because the irradiation was given in both arms.

KQ1: Which patients should be considered for reirradiation?

KPS has emerged a strong predictor of OS, as it appears as the single most common factor in multivariate analysis of prospective trials or in prognostic model development of large retrospective cohorts [6,18]. It is also the first guiding parameter in a recent SNO/EANO consensus recommendation [19].

In contrast, the impact of other factors including tumor volume, repeat surgery, interval of time to the second radiotherapy, MGMT promoter methylation, and concurrent systemic therapy remains unclear. A minimum interval from the previous radiotherapy course of six months is recommended, as it reflects radiobiological aspects of

potential recovery [10,12] and prognosis/ efficacy of the previous treatment, and is in line with a recent pattern of care survey (Table 1; recommendation 2; [20]).

Reirradiation after prior resection may be considered in patients with favorable prognostic factors, i.e. minimal postoperative deficits and good KPS (Table 1; recommendation 3; [4,6]).

Although clinical trial inclusion criteria can be used as a guidance for clinical routine, decision making will still rely on individual patient and tumor characteristics and should thus be based on a multi-disciplinary tumor discussion (Table 1; recommendation 1; [2]).

KQ2: What imaging is required to assess recurrence after primary treatment of GB?

Post-contrast enhanced T1-weighted imaging is required to assess recurrence of GB (recommendation 4). Additionally, T2-weighted/T2-weighted-FLAIR imaging is important for the identification of progressive abnormalities indicating non-enhancing tumor progression. However, assessment of recurrence after primary treatment of GB is complicated by treatment induced changes (pseudoprogression/radiation necrosis) which are indistinguishable on conventional MRI (contrast-enhanced T1-weighted, T2-weighted/T2-weighted-FLAIR imaging), in particular when these occur in-field (Table 2; recommendation 4). Consequently, to assess recurrence and differentiate it from pseudoprogression, contrast-enhanced T1-weighted MRI in itself is insufficient. Several advanced imaging techniques (i.e., perfusion MRI, MR spectroscopy, AA-PET) more accurately detect tumor-associated processes (neovascularisation, metabolic changes, cell proliferation) and may help to better differentiate tumor recurrence from pseudoprogression/radiation necrosis than conventional MRI alone (Table 2; recommendation 4; [21–24]). Accuracies to make this differentiation are reported to be around 85–90 %, but these are predominantly based on retrospective and/or selected patient populations [25].

Studies comparing advanced imaging techniques to each other directly (i.e., being performed within the same patient) are limited, but have not indicated one technique that is clearly superior to the other (Table 2; statement 2, [21,22,24,26,27]). In addition, no clear evidence exists that combining techniques improves diagnostic accuracy [28]. Given that these techniques require substantial expertise to be performed and correctly interpreted, and that not all techniques are available at all sites, it is recommended to use one or more advanced imaging technique(s) (advanced MRI and/or PET) [29], but the choice should be based on the available local expertise (Table 2; statement 2).

Most studies on reirradiation report findings based on contrast-enhanced T1-weighted imaging alone. Thus, while it makes sense that a differentiation between recurrence and pseudoprogression should be made prior to reirradiation, there is still no evidence that determining recurrence prior to reirradiation based on this distinction would change treatment planning or outcome.

Re-imaging after an interval of four to eight weeks may elucidate the underlying pathology (stable/subsiding changes indicating pseudoprogression/radiation necrosis versus continued increase indicating recurrence).

In addition, the imaging finding should be correlated with the previously irradiated volume and may help in the differentiation: in case of a distant CNS recurrence (no geometric overlap with previous irradiation volume, i.e. repeat organ irradiation), pseudoprogression/ radiation necrosis can readily be excluded, whereas in case of Type I/II reirradiation [2] the prior radiation dose distribution and dosimetry can serve as a guidance in addition to imaging to decide for or against tumor progression [21,30–32].

The final confirmation of recurrent GB versus pseudoprogression/ radionecrosis should be based on clinical and imaging features with the MDT board.

KQ3: What are requirements for optimal target definition?

This key question was addressed with the aspects of recommended imaging and optimal target definition including GTV and CTV delineation in mind.

Simulation CT (slices in thickness and spacing of 1–3 mm) should be performed using an individualised immobilisation thermoplastic mask and images should be acquired encompassing the entire cranium. It is advisable to acquire MRI images for planning purposes similar to simulation CT (1 mm slice thickness, orthogonal plane). According to the expert consensus survey, pre-treatment images should be registered to the treatment planning scan for target delineation, using an automatic fusion algorithm for rigid registration (Table 3; recommendation 5, [21]). Careful visual control of the registration accuracy is advised as a manual consistency check for quality control. As panel, we recommend that appropriate target selection should include lesions not exceeding 5–6 cm in largest diameter, while larger lesions, multi-focal and leptomeningeal disease should be excluded from reirradiation. Critical organs at risk should be contoured, especially the brain, brainstem, optic nerves, chiasm, and eyes.

GTV is typically defined as the visible lesion on MRI contrast-enhanced T1-weighted sequences [7,30,33,34] as well as suspected

Table 1
Key question 1 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ1: Which patients should be considered for reirradiation?	Strength of recommendation	Level of evidence
Recommendations		
1. Reirradiation of patients with recurrent glioblastoma should be based on individual decision making and should only be recommended after careful discussion in an MDT balancing risks, benefits, and treatment alternatives (100 %; 19/19).	*Strong*	*Expert opinion*
2. Reirradiation of patients with recurrent glioblastoma may be considered with a KPS >=60 and an interval > 6 months from the previous radiotherapy independent of age or MGMT methylation status (89 %; 17/19).	*Conditional*	*Moderate*
3. After gross total resection of recurrent glioblastoma reirradiation may be considered in patients with favorable prognostic factors (84 %; 16/19).	*Conditional*	*Low*
Statement		
1. Although reirradiation has not yet been shown to provide an OS benefit, a prolongation of progression-free survival can be expected after careful patient selection (84 %; 16/19).	–	*Moderate*

Table 2
Key question 2 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ2: What imaging is required to assess recurrence after primary treatment of GB?	Strength of recommendation	Level of evidence
Recommendations		
4. To assess recurrence, particularly in-field, contrast-enhanced T1-weighted imaging is required, and the addition of advanced MRI or AA-PET is recommended for its differentiation from pseudoprogression/ radiation necrosis (95 %; 19/20).	*Strong*	*Low*
Statement		
2. Advanced imaging techniques (i.e., perfusion MRI, MR spectroscopy, AA-PET) increase diagnostic accuracy for differentiation of recurrence from pseudoprogression, but no technique, nor combination of techniques, is clearly superior to the other (95 %; 19/20).	–	*Low*

Table 3
Key question 3 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ3: What are requirements for optimal target definition?	Strength of recommendation	Level of evidence
Recommendations		
5. Rigid image registration for target volume definition and dose accumulation is recommended (89 %; 17/19).	*Strong*	*Moderate*
6. CE-T1-weighted contrast enhancing lesions, new or progressive T2-weighted/T2-weighted FLAIR abnormalities, and AA-PET-avid regions should be included in the GTV (80 %; 16/20).	*Strong*	*Expert opinion*
7. A CTV margin is not mandatory, but a GTV to CTV margin of 3–5 mm can be added optionally (depending on overall volume, dose/fractionation and pattern of recurrence), while a maximum CTV to PTV of 3 mm is recommended (80 %; 16/20).	*Strong*	*Expert opinion*
Statement		
3. If functional imaging is considered, both AA-PET as well as advanced MRI are valid options, although no consensus could be reached to whether or not to include perfusion suspect regions into the GTV (80 %; 16/20).	–	*Expert opinion*

new / progressing T2-weighted/T2-weighted FLAIR abnormalities [35–38] or AA-PET avid regions (Table 3; recommendation 6). AA-PET imaging could be [^{11}C]Methionine (MET) PET [22,39,40], [^{18}F]fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) PET [21,41], or [^{18}F]fluoroethyltyrosine (FET) PET [23,24,27,42]. Based on the recently presented results of the GLIAA trial (ESTRO 2024; abstract only) which compared MR-only to FET-PET based target volume definition, the additional value of PET for target volume delineation needs to be revisited and cannot be unequivocally recommended at present (for study details see [43]).

No consensus could be reached on whether to include or not to include perfusion suspect regions into the GTV (Table 3; statement 3).

According to the survey a CTV margin is not mandatory, but a GTV-CTV margin of 3–5 mm can optionally be added (Table 3; recommendation 7). In the published literature there is no standard GTV to CTV margin; in the majority of studies the GTV corresponds to the CTV [21,22,34,37,44–49], but others used margins ranging from 3 to 5 mm [7,33,38,50].

A PTV margin should be created by a geometrical expansion of the CTV using a margin of up to 3 mm [21,22,34,45–48].

KQ4: What is the recommended dose and fractionation for reirradiation?

Several prospective trials and retrospective analysis of clinical data sets suggest the safe use of conventional (36 Gy in 18 fractions) and moderately hypo-fractionated (35 Gy in 10 fractions) reirradiation for the treatment of recurring high-grade gliomas [6,33,38,50–53]. Similarly, hypo-fractionation was shown to be well tolerated in several reports where a common regime used was 30 Gy in 5–6 fractions to tumor size of typically 3–3.5 cm or less [31,46,48,51,54–56]. One prospective dose-escalation trial reports that the safe upper dose tolerance in a 3 fraction schedule was 11 Gy x 3 with concomitant bevacizumab for tumors of smaller size (median 2.6 cm, range 1.8–5.4 cm) [57]. In a recent review reporting the outcome of hypofractionated SRT for 995 patients with recurrent glioblastoma included in 17 studies, a similar median OS time of 9.2 months (ranging from 7.5 to 12.5 months) has been observed in patients treated with SRT using doses of 30–45 Gy in 2.5–4.0 Gy fractions and those receiving 25–35 Gy in 5–7 Gy fractions [58]. The safe use of single dose SRS to 16–24 Gy with prescription to the 50–80 % isodose line to smaller tumors has also been reported with a reported OS in the range of 7.5 to 13 months [44,51,59–62]. Frequently, retrospectively collected datasets include a wide range of prescription practices which have been employed in analysis to find potential influence of dosimetry on survival outcomes. Selection-bias within such datasets may risk over-interpretation of the impact of dosimetry. Data suggests improved PFS with doses above BED10 of 40 Gy for SRS and BED10 of 45 Gy for conventional fractionation [63]. Similarly, Shen et al suggest OS benefit of doses above 41.4 Gy in 2-Gy-equivalent fractions. Further, it has been demonstrated that 46 Gy in 2-Gy fractions were beneficial vs. lower doses in terms of OS, although interpretation of the data needs to take into account that 33.2 % of the tumors were grade III or less [64]. The evidence for any additional gains of increasing the biologically effective dose much beyond 40–55 Gy appears rather weak. Finally, there is no clear evidence for an advantage or a disadvantage of an inhomogeneous dose, such as a very high central dose often employed to treat intracranial metastatic disease, compared to a homogeneous dose distribution within the defined target. In the GLIAA trial [43] patients with a diameter between 1–6 cm on PET and CET1 MRI were treated with 39 Gy in 3 Gy/d which appeared to be tolerable and safe.

Our preference is hypofractionated SRT for moderate-to-large size lesions, given as moderate hypofractionation (35 Gy in 10 fractions of 3.5 Gy each) or as high-dose hypofractionation (27–30 Gy in 3–5 fractions). Conventionally fractionated schedules may represent an alternative to hypofractionation for larger targets, although longer courses should be reserved for patients with longer expected OS. Single-fraction SRS can be used for smaller lesions.

Assessing local control after reirradiation of brain tumors is difficult and has only been reported in very few reports [3,7,21–23,44,61,65]. Thus, the panel could only draw conclusions and make recommendations on the safe use of SRS (Table 4; recommendation 9), the maximum size of the tumor volume where prospective evidence exists (Table 4; statement 4) and the minimally effective dose based on available prospective PFS data (in EQD2Gy; Table 4; recommendation 8).

Taken together, and considering the poor prognosis of the patient group, the limited evidence available, in the clinical treatment of selected patients with recurring high-grade glioma we recommend the following principles regarding dose-prescription:

(1) use of a regime delivering a biologically equivalent dose above 36 Gy in 18 fractions to the target (corresponding to a EQD2Gy of 36 Gy; Table 4; recommendation 8; using an a/b value of 3 Gy).

(2) use of as few treatment fractions as possible, and the preferred use of radiosurgery (single fraction or hypofractionated) for smaller tumors (Table 4; recommendation 9).

As the target size was restricted to a maximum diameter of 6 cm, no recommendation on the use of hypofractionated radiotherapy can be given for larger recurrences with regards to safety and efficacy. The panel was aware that this might not always reflect clinical practice given

Table 4
Key question 4 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ4: What is the recommended dose and fractionation for reirradiation?	Strength of recommendation	Level of evidence
Recommendations		
8. A treatment in which a sufficient dose is delivered is preferred, and therefore, the biologically equieffective dose measured in EQD2 should be no less than 36 Gy in 2 Gy fractions (84 %; 16/19).	*Strong*	*Moderate*
9. Single fraction radiosurgery can be used for smaller lesions (e.g. GTV size up to 3 cm) (100 %; 18/18).	*Strong*	*Expert opinion*
Statement		
4. Prospective evidence with regards to safety and efficacy only exists for lesion sizes up to 6 cm (100 %; 18/18).	–	*Expert opinion*

the irregular shape of recurrences exceeding 6 cm which still may exhibit an overall safe volume to treat.

KQ 5: What is the preferred treatment planning and delivery method?

As one major goal of reirradiation is the safe delivery of radiotherapy in a previously treated area with significant dose exposure to organs at risk (OARs), most prominently the brain itself, the overall aim should be the reduction of this unnecessary exposure. Although reirradiation has been performed with conventional 3D conformal radiotherapy without IMRT and advanced imaging [66], the panelists advocated for advanced IGRT planning and delivery techniques to achieve the recommended PTV margins of maximum 3 mm, as these are standard of care nowadays and have been employed in virtually all recent reirradiation trials or reports [3,6,61,67]; (Table 5; recommendation 10). Advanced IGRT may include SRS, VMAT / IMRT / DCA planning techniques and stereoscopic x-ray, CBCT or surface based technology for delivery and where available careful consideration to the use of proton therapy should be given [68].

Table 5
Key question 5 and 6 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ5: What is the preferred treatment planning and delivery method? *KQ6: How should cumulative doses be assessed with regards to safety?*	Strength of recommendation	Level of evidence
Recommendations		
10. Advanced IGRT techniques should be employed for high dose reirradiation (95 %; 18/19).	*Strong*	*Low*
11. EQD2 dose recalculation is preferred (over BED and EUD) and should be used for dose accumulation, as it is most commonly used in the literature and easy to interpret (89 %, 16/18).		*Moderate*
12. PTV prescription and compromise should follow the following cascading steps: 1) No PTV compromise if cumulative OAR doses are deemed safe and/ or acceptable. 2) PTV compromise allowed to keep cumulative OAR doses safe and/ or acceptable. 3) If a reasonable CTV / GTV dose coverage is not to be achieved, dose prescription may be adapted to reach safe or acceptable OAR doses. (88 %; 15/17)	*Strong*	*Expert opinion*
13. Recovery from previous irradiation has only consistently been described for brain tissue and spinal cord and thus, should only be considered for assessing cumulative doses in these organs (88 %; 16/17).	*Strong*	*Low*
Statement		
5. The minimum set of OAR to evaluate after biological dose accumulation include: brain, brain stem, optic chiasm, optic nerves/ tract, cranial nerves in close proximity to PTV (89 %; 16/18).	–	*Expert opinion*
6. Both methods of dose accumulation are considered valid when assessing cumulative doses to brain tissue: a) Same OAR constraints as for first course; dose discount for first course considered. b) Cumulative OAR constraints used. (100 %; 17/17)	–	*Expert opinion*
7. As there is considerable uncertainty about recovery of optic chiasm and optic nerves' function, allowance of cumulative doses should be carefully assessed (100 %; 18/18).	–	*Expert opinion*

PTV prescription for reirradiation should follow similar principles as for a primary course of radiotherapy with the primary goal of respecting safe or acceptable OAR dose limits (Table 5, recommendation 12). Thus, a PTV compromise is reasonable to keep OAR safe or acceptable and PTV prescription should only be adjusted if this is not achieved even with a significant PTV compromise.

KQ6: How should cumulative doses be assessed with regards to safety?

Although BED and less frequently EUD based biological dose recalculation has been used in CNS reirradiation, most published literature on reirradiation uses EQD2Gy recalculation [10,69] and thus, has been recommended by the panellists as method of choice for biological recalculation (Table 5, recommendation 11; using an a/b of 3 Gy). As serious adverse events with major impact on QoL or life threatening outcome are of major concern a minimum set of OAR for delineation and consideration in treatment planning and dose / toxicity assessment was agreed (expert opinion; Table 5; statement 5). As no standard for reirradiation currently exists, the set of OAR was selected from ESTRO-EANO GBM guidelines [70].

As there does not yet exist a clear recommendation for dose accumulation including the necessity for biological dose recalculation and appropriateness of recovery assumption, consensus was reached reached on two dose accumulation methods that can be employed: a) Same OAR constraints are used for reirradiation as were for the first course with dose discount for first course [9,11], b) Cumulative OAR constraints are used.

Of note, tissue recovery is still a matter of debate and subject to investigation. Consistent recovery has been described for brain and spinal cord and thus should be considered when assessing cumulative doses to these organs (Table 5; recommendation 13).

In contrast, recovery of other sensitive brain structures remains to be better characterized. Although clinical studies assessing the efficacy and toxicity of a second course of radiation for brainstem and optic pathways suggest potential tissue recovery [16,17,71], available data are too limited to model tissue complication probability risks based on interval period between radiation therapy courses. Therefore, the panelists were unable to reach consensus regarding dose recovery recommendations for these structures.

KQ 7: What is the evidence for combined modality reirradiation?

KQ 8: What is the role of maintenance systemic therapy after reirradiation?

The use of combined reirradiation and systemic treatments, mainly alkylating agents and bevacizumab given concurrently and/or as maintenance therapy, has been evaluated in several studies reporting OS and PFS times of around 9–12 months and 4–7 months, respectively [GM1] [6,31,34,42,55,61,72–75]. In a few retrospective studies, the combination of RT, given as either conventionally- or hypo-fractionated schedules, with alkylating agents has been associated with longer OS and PFS times compared with RT alone, but this benefit seems to be more pronounced in MGMT methylated tumors [31,34,73,74,76], raising the question whether the same outcome could have been achieved with alkylators alone. Temozolomide may be the most commonly used alkylating agent for combinations with RT, yet, lomustine is commonly considered the standard chemotherapy in recurrent glioblastoma and by consensus is the control arm in large phase III trials such as REGAL, EORTC 26101 or AGILE [77]. The reported toxicity following reirradiation and temozolomide is similar to that observed following reirradiation alone, with the rates of grade 3 toxicity < 10 %. Similar survival advantages of combination as with alkylators have also been reported following bevacizumab and SRS/SRT compared to reirradiation alone [42,55,75], but it is impossible to control for selection bias unless patients are randomized. In contrast, other series failed to show significant survival benefit with the addition of systemic agents to RT [33,52,61,72]. In a retrospective study of 161 patients with recurrent malignant gliomas receiving 36 Gy in 2 Gy fractions and concurrent bevacizumab with or without maintenance therapy, Fleischmann et al.

observed a similar median OS and PFS of 9 months and 5 months for patients receiving reirradiation alone or reirradiation with either concomitant or concomitant and maintenance bevacizumab. Expectedly, combined treatment was associated with reduced risk of symptomatic radionecrosis. In the NRG Oncology/RTOG 1205 trial, 182 patients with recurrent GB who were randomized to receive combined SRT (35 Gy in 3.5 Gy fractions) and bevacizumab or bevacizumab alone, similar median OS times of 10.1 and 9.7 months have been observed between the groups [6]. However, the combined treatment was associated with better 6-months PFS (54 % versus 29 %, $p < 0.001$). The treatment was well tolerated with low rates of acute (5 %) and no delayed grade ≥ 3 toxicity.

Most studies reporting on combined modality reirradiation use conventional (36 Gy in 18 fractions) and moderately hypo-fractionated (35 Gy in 10 fractions) treatment and show that the addition of either alkylating agents or bevacizumab is well tolerated [6,42,72,74,75]. As for studies of reirradiation alone, treatment volumes are delineated using MRI with a GTV-CTV margin up to 5 mm [6,31,34,42,44,61,73–76]. Thus, the panelists recommend that there is no need to change target definition, dose and fractionation when considering combined modality treatment (Table 6, Recommendation 14*)*.(See Table 7).

As yet, no prospective data indicate that reirradiation in combination with systemic therapy, including alkylating agents or bevacizumab, is superior to reirradiation alone and this panel cannot make a clear recommendation for this approach, especially with respect to a specific drug combination (Table 6, statement 8). Combining different radiotherapy schedules with systemic agents active against recurrent gliomas remains a research priority and should be further explored in prospective clinical trials (Table 6; recommendation 15*)*. Combined SRT and bevacizumab offers longer PFS compared with bevacizumab alone in 1205 RTOG trial [6]. Although this may represent an important clinical benefit in such patients with unfavourable prognosis, current limited data are insufficient to support the routine use of concurrent or maintenance systemic therapy after reirradiation (Table 6,statement 9).

KQ 9: What follow-up schedule is recommended and what should be assessed?

So far, prospective clinical studies have examined different therapeutic options for recurrent disease rather than research questions related to post-treatment follow-up. The study protocols have included slightly different follow-up strategies that reflected institutional or cooperative group practice at that time. For example, the randomized phase II study RTOG 1205 (concurrent bevacizumab and reirradiation versus bevacizumab alone) included optional MR diffusion and perfusion weighted imaging at 8 and 24 weeks post-treatment start as strongly recommended examinations [6]. Repeat MR diffusion and perfusion weighted imaging at progression was also optional but strongly recommended as further confirmation of true tumor progression. Due to possible radiation effects, the initial scan six weeks following reirradiation should not be used to declare progression. The patients should consistently be followed with the same diagnostic imaging study. Follow-up after treatment discontinuation or progression was scheduled: q8 weeks for 1 year, then q6 months for 1 year, then annually ($\pm$ 2 weeks). A single-arm phase II study by evaluated outcomes by MR imaging at 1 month, and every 3 months thereafter [61]. Thus, the expert panel reached consensus on a follow-up recommendation derived from the available evidence consisting of clinical assessment and conventional MRI every 3 months (Table 7; recommendation 16, [19,22,23,32,46,60,78].

An early clinical assessment for toxicity at six weeks after reirradiation is recommended In case of further tumor progression and after exclusion of pseudoprogression/radiation necrosis if there are no further reasonable treatments options transition to best supportive care should be considered and further imaging follow-up is not beneficial and should be halted (recommendation 17).

In a retrospective study (n = 111), post-treatment changes were seen in 33 (30 %) patients on follow-up imaging, with higher cumulative dose (EQD2 $\geq$ 104.3 Gy) being associated with increased risk of post-reirradiation pseudoprogression [78]. A prospective dose- and volume-escalation study evaluation comprised MRI, ^{18}F-FET PET/CT, clinical evaluation, QOL questionnaires and neurocognitive testing [23]. Both imaging modalities were used for each evaluation at follow-up, but the time of tumor progression was determined using the MRI-based RANO criteria. Recent reviews [79–81] have provided in-depth discussion of PET contribution in different scenarios. Thus, If conventional diagnostic MRI reveals suspicious finding, further imaging with AA-PET or advanced MRI (perfusion, spectroscopy) can help to distinguish tumor progression from radiation necrosis and should be considered if it impacts treatment relevant decision making (recommendation 18, [22,27,60,61]. Recently, consensus recommendations for structured implementation of AA-PET into follow-up and response assessment of gliomas have been published and may facilitate disease monitoring [82]. Early recognition of imaging findings of radiation necrosis is important to initiate treatment in order to minimize the morbidity and mortality

Table 6
Key question 7 and 8 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ7: What is the evidence for combined modality reirradiation? *KQ8: What is the role of maintenance systemic therapy after reirradiation?*	Strength of recommendation	Level of evidence
Recommendations		
14. When considering combined modality treatment, there is no need to change target definition, dose and fractionation (94 %; 17/18).	*Strong*	*Expert opinion*
15. The use of systemic treatment together with reirradiation of recurrent glioblastoma should be further explored in prospective clinical trials (95 %; 18/19).	*Strong*	*Expert opinion*
Statement		
8. A clear recommendation for this approach, especially with respect to a specific drug combination, cannot be given (94 %; 17/18).	–	*Moderate*
9. Currently, data are insufficient to support the routine use of concurrent or maintenance systemic therapy after reirradiation (89 %; 16/18).	–	*Expert opinion*

Table 7
Key question 9 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

KQ9: What follow-up schedule is recommended and what should be assessed?	Strength of recommendation	Level of evidence
Recommendations		
16. Follow-up should be assessed every 3 months including standard diagnostic MRI with early clinical assessment of acute toxicity after 6 weeks (100 %; 20/20).	*Strong*	*Moderate*
17. When in transition to optimal supportive care (lack of further therapeutic options) further follow-up is not beneficial and not recommended (85 %, 17/20).	*Strong*	*Moderate*
18. Following suspicious findings in standard FU MRI the combined use of AA-PET and advanced MRI (perfusion, spectroscopy) should be considered to differentiate radiation necrosis from true progression (95 %; 19/20).	*Strong*	*Low*

associated with this condition.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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