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Clinical practice guidelines

Radiotherapy guidelines for gliomas: 2025 update☆

Radiothérapie des gliomes : mise à jour 2025

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ABSTRACT

Gliomas are the most frequent malignant primary brain tumours in adults. The proximity of organs at risk, the infiltrating nature, and the radioresistance of gliomas have to be taken into account in the choice of prescribed dose and technique of radiotherapy. The management of glioma patients is based on clinical factors (age, Karnofsky performance status) and tumour characteristics (histology, molecular biology, tumour location), and strongly depends on available and associated treatments, such as surgery, radiotherapy, and chemotherapy. The knowledge of molecular biomarkers is currently essential; they are increasingly evolving as additional factors that facilitate diagnostics and therapeutic decision-making. We present the update of the recommendations of the Société française de radiothérapie oncologique (the French Society for Radiation Oncology) on the indications and the technical procedures for performing radiotherapy in patients with gliomas.

RÉSUMÉ

Les gliomes sont les tumeurs cérébrales malignes primitives les plus fréquentes de l'adulte. La proximité des organes à risque, leur nature infiltrante et leur faible radiosensibilité sont des facteurs à prendre en compte dans le choix des doses et techniques d'irradiation. La prise en charge des patients atteints de gliome repose sur les caractéristiques cliniques du patient, et de la tumeur (histologie, biologie moléculaire, localisation anatomique), ainsi que sur la nature des traitements disponibles et associés. La connaissance des marqueurs moléculaires tumoraux est devenue essentielle ces dernières années. La multitude de facteurs a rendu complexe les stratégies thérapeutiques pour ces patients au pronostic très variable. La radiothérapie constitue toujours un pilier majeur du traitement des gliomes. Nous présentons la mise à jour des recommandations de la Société française de radiothérapie oncologique sur les indications et les modalités techniques de réalisation de la radiothérapie pour les patients atteints de gliome.

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1. Introduction

Gliomas are the most common malignant primary brain tumour in adults accounting for an estimated 2000 new cases each year in France [1,2]. The incidence of glioblastomas increases in a linear and aged-related manner until the age of 75 years and then decreases thereafter. Median age is around 64 years [3]. Gliomas can be difficult to treat since they are located close to organs at risk, are infiltrative and little radiosensitive. Prognosis and treatment will depend on features such as histological grade, molecular biology data, age and general status of the patient. This article provides updated radiotherapy indications and technical recommendations for the treatment of grade 2 to 4 gliomas.

2. Radiotherapy of grade 4 gliomas

The description of glioblastoma treatments differs according to the age of the patient (under 70 years and over 70 years) and their general state of health evaluated by the Karnofsky performance status. These criteria are arbitrary and vary according to the publications (ranging from 60, 65, to 70 years) [4–8]. Naturally, the physiological age of the patient takes precedence over their chronological age and although a geriatric oncology assessment may be useful, its prognostic or predictive value has not been demonstrated [9,10].

2.1. Radiotherapy indications

Randomised trials have demonstrated the value of systematic radiotherapy after neurosurgery. Radiotherapy should begin within 4 to 6 weeks after surgical resection and can start more rapidly, as early as 2 weeks, in the case of a simple biopsy [11–14].

2.1.1. Subjects under the age of 70 years in good general health (WHO performance index 0, 1, 2 or Karnofsky performance status of 70 to 100 %)

Standard treatment after surgery (excision or biopsy) is radiotherapy of 60 Gy in 30 fractions for six weeks combined with concomitant chemotherapy of 75 mg/m^2, D1-42, and adjuvant temozolomide (six cycles of 150 to 200 mg/m^2, day one to five, starting every 28 days) based on the trial regimen of the National Cancer Institute of Canada (NCIC) and the European Organisation for Research and Treatment of Cancer (EORTC) [15–17].

Tumour treating fields is recommended in patients who received standard chemoradiotherapy, since the addition of this technique to maintenance temozolomide has demonstrated a gain in progression-free- and overall survival [18]. Tumour treating fields is a non-invasive technique delivering an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumour.

Since magnetic resonance spectroscopic imaging has been shown to predict the site of relapse, the effect of magnetic resonance spectroscopic imaging-guided dose escalation on overall survival of patients with newly diagnosed glioblastoma has been evaluated but no improvement in overall survival has been demonstrated yet [19]. Therefore, dose escalation in radiotherapy guided by metabolic imaging should remain within the framework of clinical trials.

2.1.2. Subjects over the age of 70 years in good general health (Karnofsky performance status of 50 to 100 %)

Standard treatment after surgery (excision or biopsy) is radiotherapy, which offers a benefit compared to supportive care alone [4,6,20,21]. Combining radiotherapy and temozolomide is an option [8,16]. The EORTC 26062-22061 and NCIC studies evaluating hypofractionated brain radiotherapy (40.5 Gy delivered in 15 fractions) with or without temozolomide in patients at least 65 years reported the benefit of combining concomitant and adjuvant temozolomide with hypofractionated radiotherapy versus radiotherapy alone: with overall survival of 9.3 versus 7.6 months (hazard ratio [HR]: 0.37; $p < 0.0001$) and median progression-free survival of 5.3 months versus 3.9 months (HR: 0.50; $p < 0.0001$) [22]. Chemotherapy is administered during the three weeks of hypofractionated radiotherapy. temozolomide alone is also an option in the presence of O6-methylguanine-DNA-methyltransferase promoter methylation (MGMT) [5,7,23].

2.1.3. Subjects over the age of 70 years in poor general health (KPS of less than 50 %)

Hypofractionated treatment can be balanced against palliative care or temozolomide [23]. The Association des neuro-oncologues d'expression française (Anocef, the French-speaking Association of Neuro-oncologists) suggests that in elderly subjects (over 70 years of age) or in poor clinical functional condition (Karnofsky performance status of less than 70 %), an accelerated hypofractionated radiotherapy regimen can be administered delivering 34 to 50 Gy in ten to 20 fractions [24].

2.2. Total dose and fractionation

2.2.1. Subjects under the age of 70 years in good general health (WHO performance index 0, 1, 2 or Karnofsky performance status of 70 to 100 %)

The recommended total dose, determined on the basis of three randomised trials, delivered to the International Commission on Radiation Units and Measurements (ICRU) reference point is 60 Gy in 30 fractions of 2 Gy, over six weeks [16,25–27].

2.2.2. Subjects over the age of 70 years in good general health (Karnofsky performance status at least 50 or 60 %)

The recommended and most commonly used regimen in France is as follows: a total dose of 40.05 Gy delivered to the International Commission on Radiation Units and Measurements (ICRU) reference point in 15 fractions of 2.67 Gy, over 3 weeks [28].

Other regimens have been proposed: a total dose delivered to the ICRU point of 50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks, or a total dose delivered to the ICRU point of 34 Gy in ten fractions of 3.4 Gy, over 2 weeks; these two regimens have only been evaluated in one randomised trial [5,6]. Or a total dose of 60 Gy is delivered to the ICRU point in 30 fractions of 2 Gy over 6 weeks [29]. This latter regimen is no longer recommended as it is considered inferior in terms of overall survival compared to hypofractionated regimens [5].

2.3. Delineation of target volumes

No clear-cut recommendations are available on the delineation of target volumes [30].

2.3.1. Subjects under the age of 70 years in good general health (WHO performance index 0, 1, 2 or Karnofsky performance status of 70 to 100 %)

There are several schools of thought regarding the definition of target volumes.

2.3.1.1. European regimen. The European regimen according to the EORTC/European Society for Radiotherapy and Oncology (ESTRO)/European Association of Neuro-Oncology (EANO) consensus that has been recently published suggests a single volume treated at a dose of 60 Gy defined hereafter [31].

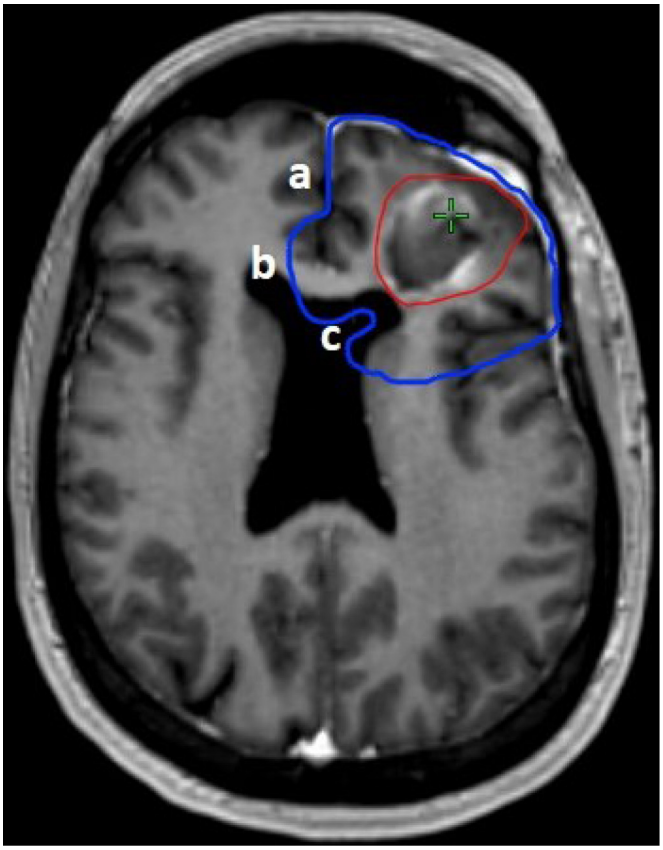

Fig. 1. Illustration of the clinical target volume construction for glioblastoma radiotherapy: the gross tumour volume (red contour) was expanded by 1.5 cm to generate the clinical target volume (blue contour) and constrained at anatomical barriers (bone, falx) (a) with a 5 mm strips at ventricle level (c), whereas no correction was applied at the genu corporis callosi (b).

2.3.1.1.1. Gross tumour volume. The gross tumour volume (GTV) is defined by the contrast enhancement on dosimetric magnetic resonance MRI or surgical cavity in the case of tumour resection (whose margins may be considered as the clinical target volume if no contrast enhancement) and residual contrast enhancement on postoperative T1 MRI sequence with gadolinium injection. Non-enhancing areas may represent a component of the tumour, especially for molecular glioblastomas; in such cases, regions of high T2/fluid-attenuated inversion recovery (FLAIR) signal intensity (corresponding to tumour and not to vasogenic oedema) should be included within the gross tumour volume.

2.3.1.1.2. Clinical target volume. The clinical target volume (CTV) is defined by a 15 mm margin around the gross tumour volume. Inclusion of T2 abnormalities within the clinical target volume is not advised if it corresponds to vasogenic oedema. If the FLAIR sequence indicates the presence of non-contrast-enhancing tumour (molecular glioblastomas), it should be included in the target volume. Margins should be reduced to anatomical barriers such as the skull (0 mm, using bone window), ventricles (5 mm), falx (0 mm), tentorium cerebelli (0 mm), visual pathways/optic chiasm and brainstem (each 0 mm), provided the tumour is distant from the white matter tracts extending to these regions (e.g., midbrain) (Fig. 1). However, attention should be paid to the routes of anatomic extension (corpus callosum with crossing to the contralateral hemisphere, cerebral peduncles to the brainstem, anterior white commissure).

2.3.1.1.3. Planning target volume. Clinical target volume to planning target volume (PTV) margins is department-specific based on measured patient relocation accuracy and other unavoidable errors and can be adapted by the centre (generally comprised between 2 and 5 mm).

2.3.1.2. American regimen. The American Radiotherapy Oncology Group (RTOG) regimen suggests an initial volume treated at a dose of 46 Gy followed by a further dose of 14 Gy (RTOG study 0825) [32]:

- GTV 1: T2 or FLAIR abnormalities including surgical cavity and residual contrast enhancement;
- CTV 1: 20 mm margin around GTV 1;
- if there is no oedema, PTV1 is defined by the contrast enhancement with a margin of 25 mm;
- GTV 2: surgical cavity and residual contrast on T1 MRI after gadolinium injection;
- CTV 2: 20 mm margin around GTV 2.

No difference in terms of outcome or toxicity has been reported between the use of RTOG or EORTC guidelines for the delineation of grade 3-4 glioma, including in the subgroup of patients with isocitrate dehydrogenase wildtype glioblastoma [33].

2.3.2. Subjects over the age of 70 years in good general health (Karnofsky performance status at least 50 %)

The same rules apply but the clinical target volume margin is reduced to 15 mm. For cases with FLAIR hypersignal, the same considerations (vasogenic oedema versus non-enhancing tumour), previously detailed, should be consider in case of inclusion or not in the target volume. Equally, in this area there are several schools of thought, presented hereafter.

2.3.2.1. EORTC. The EORTC suggests treating a single volume (EORTC study 26062-22061). The gross tumour volume is defined as contrast enhancement and/or surgical cavity on the postoperative T1 MRI after gadolinium injection. The clinical target volume is defined by a 15 mm margin around the gross tumour volume adapted to anatomical barriers (such as bone, cerebellar tentorium, cerebral falx). However, attention should be paid to the routes of anatomic extension such as the corpus callosum with crossing to the contralateral hemisphere, or cerebral peduncles to the brainstem).

2.3.2.2. RTOG. The RTOG suggests treating a single volume [4]:

- GTV 1: T2 or FLAIR abnormalities including surgical cavity and residual contrast enhancement;
- CTV 1: 20 mm margin around GTV 1;
- PTV 1: 46 Gy;
- if there is no oedema, PTV1 is defined by the contrast enhancement with a margin of 25 mm.

2.4. Description of radiation techniques

2.4.1. Intensity-modulated conformal radiotherapy

Intensity-modulated radiotherapy is currently the main radiation technique used for glioma treatment and allows a better sparing of organs at risk [34,35].

2.4.2. Stereotactic radiotherapy

First-line stereotactic radiotherapy for high-grade gliomas is not an option outside of therapeutic trials, since no randomised or prospective study has demonstrated benefit in terms of overall survival [34–36]. For recurrent high-grade gliomas, stereotactic reirradiation can be considered after individual discussion by multidisciplinary team. Several factors need to be considered,

including the interval between the initial radiotherapy and reirradiation (generally more than 6 months), Karnofsky performance status, tumour grade and volume, patient age [37].

The optimal reirradiation regimen (dose and fractionation) remains to be defined but the most frequent schedules used are doses of 30 to 35 Gy delivered in ten fractions, 25 Gy delivered in five fractions and 36 Gy delivered in 18 fractions [38–40]. The benefit of a concomitant systemic treatment is also controversial (temozolomide or lomustine [CCNU] or bevacizumab). In the National Research Group (NRG) Oncology/RTOG1205 study, the adjunction of bevacizumab to reirradiation (35 Gy delivered in ten fractions) was associated with a benefit in progression-free survival but not in overall survival [41]. The benefit of reirradiation plus CCNU is currently tested in the LEGATO trial (NCT05904119). Practice guidelines of stereotactic reirradiation are discussed in the corresponding upcoming article (Escande A, et al. General technical considerations and reirradiation of brain and head and neck tumours. Suggestions from the Société française de radiothérapie Guidelines Group. Submitted for publication).

2.4.3. Protontherapy

Proton beam radiotherapy is not recommended for glioblastoma outside of a clinical trial. A phase II randomized trial comparing proton beam radiotherapy and intensity-modulated radiotherapy for glioblastoma has failed to show a benefit of the former in terms of delay in time to cognitive failure with similar progression-free survival and overall survival [42].

2.5. Isocitrate dehydrogenase-mutant grade 4 astrocytoma

There is no available randomized evidence specifically in patients with isocitrate dehydrogenase (IDH)-mutant grade 4 astrocytoma, but it is important to note that survival in this population is nearly double that of IDH-wildtype glioblastoma. In the absence of other evidence this population could be treated like IDH-mutant anaplastic astrocytoma (grade 3) with radiotherapy and adjuvant temozolomide, or like IDH-wildtype glioblastoma with radiotherapy plus concurrent and adjuvant temozolomide [43].

3. Radiotherapy of anaplastic grade 3 gliomas

Histological grade 3 gliomas are now classified into three subgroups after mandatory molecular analysis according to the World Health Organisation (WHO) 2021 central nervous system classification [44]:

- IDH-mutant grade 3 astrocytoma;
- IDH-mutant and 1p/19q codeleted grade 3 oligodendroglioma [45–48];
- formerly called “IDH wildtype astrocytoma”, corresponding to molecular glioblastoma in the 2021 classification.

3.1. Radiotherapy indications

It is important to note that most randomized trials in this population were conducted prior to the 2021 molecular classification.

3.1.1. Anaplasic oligodendrogliomas

Standard treatment after surgery (excision or biopsy) is radiotherapy combined with procarbazine–CCNU–vincristine (PCV) chemotherapy delivered either before or after radiotherapy, in line with the findings of two major randomised trials (RTOG 9402 and EORTC 26951) [45,49,50]. No difference in terms of efficacy or toxicity was observed whatever the sequence (chemotherapy delivered either before or after radiotherapy. The results of final report of EORTC 26951 and RTOG 9402 estimated progression-free- and overall survival probabilities at 20 years from random assignment of 30 % and 35 %, respectively [50].

POLCA is a phase III trial in France with two arms: PCV chemotherapy alone and radiotherapy followed by PCV chemotherapy, for patients with anaplastic oligodendroglioma. The trial is closed to inclusions.

In the randomised phase III trial of the Neuro-Oncology Working Group of the German Cancer Society (NOA-04) comparing adjuvant radiotherapy and chemotherapy with PCV or temozolomide in 274 patients with grade III gliomas, 71.9 % were oligodendrogliomas [51]. No significant difference in progression-free survival and overall survival was observed between the three treatment groups. Despite the lack of data comparing monochemotherapy to chemoradiation, clinical data seem to highlight the benefit of multimodal treatment combining chemotherapy and radiotherapy [52].

In a recent publication of the results from a retrospective cohort study enrolling 305 newly diagnosed patients with grade 3 oligodendrogliomas receiving radiotherapy and chemotherapy between 2008 and 2022, of which 67.9 % of patients ($n = 207$) were received PCV, and 32.1 % with temozolomide ($n = 98$), first-line PCV chemoradiation was associated with better overall survival outcomes compared to temozolomide chemoradiation after a median follow-up of 78.4 months [53]. It suggests that the improved safety profile associated with temozolomide comes at the cost of inferior efficacy in this population. Further investigation using prospective and randomized studies is warranted.

3.1.2. Anaplasic astrocytomas

The EORTC 26053-26054 CATNON (NCT00626990) trial investigating 1p19q non-codeleted anaplastic gliomas has four treatment arms: radiotherapy alone (59.4 Gy delivered in 33 fractions of 1.8 Gy), radiotherapy followed by adjuvant temozolomide (12 cycles), and chemoradiotherapy, i.e. radiotherapy and concurrent temozolomide with or without adjuvant temozolomide. Final results have been published and showed that adjuvant temozolomide improved overall survival compared with no adjuvant temozolomide (median overall survival: 82.3 months, 95 % confidence interval [CI]: 67.2–116.6 months versus 46.9 months, 95 % CI: 37.9–56.9 months; HR: 0.64, 95 % CI: 0.52–0.79, $p < 0.0001$), whereas there was no benefit of concomitant temozolomide [54]. Clinical benefit was dependent on *IDH* mutational status. That is why radiotherapy followed by 12 cycles of adjuvant temozolomide is the standard treatment in IDH-mutant grade 3 astrocytomas.

In a post hoc analysis of the CATNON trial, exploring whether adding temozolomide to radiotherapy improves outcome in patients with wildtype IDH1/2 anaplastic astrocytomas with molecular features of glioblastoma (redesignated as glioblastoma wildtype IDH in the 2021 classification), temozolomide treatment did not add benefit beyond that observed from radiotherapy, regardless of MGMT promoter status. These findings require a new well-powered prospective clinical study to explore the efficacy of temozolomide treatment in this patient population [55].

3.1.3. Subjects over the age of 70 years in poor general health (Karnofsky performance status of less than 50 %)

The value of hypofractionated treatment can be balanced against palliative care alone or chemotherapy [56]. Anocef suggests administering an accelerated hypofractionated radiotherapy regimen in elderly subjects (over 70 years of age) or in poor clinical functional condition (Karnofsky performance status of less than 70 %) delivering 40 to 50 Gy in 15 to 20 fractions [25].

3.2. Total dose and fractionation

The recommended total dose delivered at the ICRU point is 59.4 Gy in 33 fractions of 1.8 Gy, over 6.5 weeks, regardless of 1p19q and IDH status [45–48,54,57].

3.3. Delineation of target volumes

3.3.1. ESTRO-EANO guidelines

The ESTRO-EANO guidelines are summarised hereafter [58].

3.3.1.1. Gross tumour volume. The gross tumour volume includes 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. 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 gross tumour volume. The delineation of the gross tumour volume can be informed by additional MRI and/or functional imaging. If available, aminoacid positron-emission tomography (PET) and perfusion/diffusion MRI can be valuable tools to improve the differentiation between oedema and tumour.

3.3.1.2. Clinical target volume. The clinical target volume consists in an expansion of the gross tumour volume with a margin of 15 mm. The clinical target volume 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). The clinical target volume should not be edited for areas where tumour spread is possible, such as hippocampus or corpus callosum.

3.3.2. American Society for Radiation Oncology guidelines

The American Society for Radiation Oncology (ASTRO) guidelines define the gross tumour volume as residual FLAIR changes, resection cavity and any residual enhancement on T1 postcontrast, and the clinical target volume as the gross tumour volume with a 10 to 15 mm expansion [59].

3.4. Description of radiotherapy techniques

3.4.1. Intensity-modulated radiotherapy

Intensity-modulated radiotherapy is the main radiation technique in this indication. Its value in terms of survival has not yet been demonstrated compared to three-dimensional (3D) radiotherapy but since it protects healthy tissues its use should be considered for patients with a good prognosis and a long life expectancy (i.e., patients with IDH1 mutated oligodendrogliomas and astrocytomas) [45,48,49,60–62]. Intensity-modulated radiotherapy is the preferable option in such cases, especially since it improves the conformation and protection of organs at risk without increasing the integral dose in healthy tissues and their exposure to low doses [63].

3.4.2. Stereotactic radiotherapy

Refer to Section 2.4.2.

3.4.3. Proton beam radiotherapy

Photon radiotherapy is the current standard of care for oligodendroglioma radiotherapy, but it can cause long-term side effects in a population of long survivors. These can develop years after radiotherapy and can include memory problems and difficulties in processing information, which can have a negative impact on quality of life. Proton beam therapy potentially improves quality of life by sparing more healthy brain tissue than photon radiotherapy [64]. Currently, there are no published randomised trials in adults, but the NRGBN005, 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.

4. Radiotherapy of grade 2 gliomas

Grade 2 gliomas in adults account for 15 % of gliomas. Surgery with complete or partial excision is the first therapeutic option in full knowledge of the fact that another treatment (chemotherapy or radiotherapy) will be required at some point, given the inevitable progressive potential of these tumours over the longer term [62,65]. The following questions arise: (i) what sort of treatment should be offered (radiotherapy or chemotherapy)? And (ii) in what sequence, i.e. immediately after surgery or after a certain delay?

Up to now only five randomised trials have analysed the role of radiotherapy when modern techniques such as intensity modulation were not used [66–70]. These studies were based on the older versions of the WHO brain tumour classification, which did not consider molecular biology data. The role of radiotherapy is still being debated. A randomised trial has shown that early postoperative radiotherapy delayed symptomatic recurrence without impacting overall survival [71,72]. However, the trial did not adequately evaluate the long-term consequences on cognitive functions [73]. Due to this fact, delaying or postponing radiotherapy, especially in younger patients helps delay or avoid long-term cognitive effects that are particularly relevant in patients with an estimated life expectancy of ten years or longer. One ongoing French clinical trial evaluates delayed radiotherapy in patients with 1p/19q codeleted low grade 2 oligodendrogliomas (POLO trial).

The main risk factors to be considered when determining the most appropriate postoperative strategy are: type of resection, initial tumour size, presence or absence of neurological deficits, medically uncontrolled seizures, performance status, IDH mutation status and presence of 1p/19q codeletion [74]. In IDH mutant gliomas, selective IDH inhibitors (vorasidenib) have shown efficacy and safety, and may allow to differ the use of radiotherapy. The INDIGO trial tested vorasidenib versus a placebo in patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone no previous treatment other than surgery. Progression-free survival and the time to the next intervention in the group receiving vorasidenib were significantly improved compared to the placebo group [75]. However the place of this new treatment remains to be defined, there is no indication to concomitant administration with radiotherapy (outside a clinical trial).

4.1. Radiotherapy indications

Radiotherapy is indicated for low-grade gliomas in cases of:

- non-removable tumour;
- recurrent removable tumour;
- tumour with an unfavourable prognosis (midline extension, diameter greater than 6 cm, preoperative neurological symptoms, partial resection, uncontrolled epilepsy);
- progressive tumour after chemotherapy [76–80];
- low-grade gliomas described as triple negative (no IDH mutation, no P53 mutation, no 1p19q codeletion) with a poor prognosis (now frequently reclassified as molecular glioblastoma) [81].

It should be noted that some authors suggest chemotherapy as a first step for large sized gliomas, although limits-thresholds have not been clearly established [82].

Two recent studies have highlighted the value of initial supplementary treatment to improve overall survival, particularly in cases with IDH1-mutation. RTOG 9802 is a randomised phase III trial comparing radiotherapy alone with radiotherapy followed by PCV chemotherapy in patients with grade 2 glioma (including oligodendroglioma and astrocytoma) considered as high risk (i.e. aged over 40, or 18 to 39 years with surgical resection considered as incomplete). Progression-free survival and overall survival were significantly prolonged in patients receiving the combination therapy (13.3 years versus 7.8 years, $p = 0.003$). A secondary analysis revealed that IDH1-mutation glioma patients benefited the most from the combination therapy [83,84].

The EORTC 22033-26033 study compared in high-risk patients with grade 2 glioma (i.e. aged over 40 years, progressive disease, tumour size greater than 5 cm, tumour crossing the midline, or neurological symptoms) radiotherapy of 50.4 Gy and temozolomide chemotherapy (75 mg/m^2). No difference in progression-free survival was observed between the two groups. A subgroup analysis showed a progression-free survival benefit for IDH1-mutated glioma patients without 1p/19q codeletion in the "radiotherapy alone" group [83]. Moreover, no significant differences in quality of life or cognitive function were observed between the two treatment groups [85].

The results of these two trials favour the combination of radiotherapy and chemotherapy for patients with high-risk grade 2 glioma, with a median progression-free survival of 4 years and 10.4 years, respectively, in patients treated with radiation alone and those receiving the combined treatments [86].

4.2. Total dose and fractionation

According to EORTC guidelines, a dose of 50.4 Gy delivered in 28 fractions, as used in the EORTC 22033 trial, is recommended [70]. As 54 Gy delivered in 30 fractions was used in several trials including the RTOG 9802, the committee agreed that this dose level is also acceptable [87].

4.3. Delineation of target volumes

4.3.1. ESTRO-EANO guidelines

The ESTRO-EANO guidelines are summarised hereafter [58].

4.3.1.1. Gross tumour volume. The gross tumour volume includes 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. T2/FLAIR abnormalities that are thought to represent tumour should be included in the gross tumour volume. The delineation of the gross tumour volume 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.

4.3.1.2. Clinical target volume. The clinical target volume consists in an expansion of the gross tumour volume with a margin of 10 mm. The clinical target volume 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). The clinical target volume should not be edited for areas where tumour spread is possible, such as hippocampus or corpus callosum.

4.3.2. American Society for Radiation Oncology guidelines

The ASTRO guidelines define the gross tumour volume as the residual FLAIR changes, resection cavity and any residual enhancement on T1 postcontrast and the clinical target volume as the gross tumour volume with a 10 to 15 mm expansion [59].

4.4. Description of the standard technique

4.4.1. Intensity-modulated conformal radiotherapy

Intensity-modulated radiotherapy is the first-line technique mainly to protect organs at risk. Since intensity-modulated radiotherapy protects healthy tissues, its use should be considered for patients with a good prognosis and a long life expectancy. Intensity-modulated radiotherapy is the preferable option in such cases, especially since it improves the conformation and protection of organs at risk without increasing the integral dose in healthy tissues and their exposure to low doses [63,88].

4.4.2. Stereotactic radiotherapy

Due to a lack of data on low-grade gliomas, no recommendations or options are proposed.

4.4.3. Proton beam radiotherapy

This high-precision technique likely to improve the healthy tissue sparing is under assessment in grade 2 glioma patients. Two ongoing randomised trials (one European, PROGLIO; one in North America) compare proton beam radiotherapy to intensity-modulated radiotherapy using X-ray beams.

5. Follow-up

The first MRI scan after radiation is performed between 1 and 3 months, according to the histomolecular grade, in the absence of recent progressive clinical signs that do not improve with corticosteroids. MRI monitoring is continued every 2 to 3 months. An increase or change in the contrast enhancement on the T1-gadolinium sequence may occur within 12 weeks following radiation; however, this phenomenon may correspond to "pseudo progression" [89,90]. Pseudo progression can be retained as a diagnosis when there are no clinical symptoms, and no new lesions appear outside the areas corresponding to 80 % of the radiotherapy isodose. Multimodal MRI or PET-CT (with fluorodopa) or PET-MRI provide useful guidance for the differential diagnosis of actual progression compared to pseudo progression.

6. Technical preparation for radiotherapy of gliomas

6.1. Work-up required when preparing radiotherapy

A dosimetric CT scan and delineation MRI should be performed as close as possible to the first radiotherapy session (not later than 15 days).

6.1.1. CT scan

A planning CT should be obtained with a maximum of 2 mm slice thickness from the vertex to the lower border of the C5 vertebral body. In most cases, the injection of an iodine contrast product is not necessary. However, an injection should be offered if an MRI is contraindicated.

6.1.2. MRI prior to radiotherapy

A dosimetric MRI is mandatory unless contraindicated; no immobilisation system is required. Images (axial, coronal, sagittal) must be adapted to the requirements and registration potential of the treatment planning systems. The rate of deformation is lower with a 1.5T MRI [91]. The required sequences are as follows: T1, T2 FLAIR and T1 with injection of gadolinium and axial

Table 1
Summary of recommendations on radiotherapy for gliomas.

Indications	Target volume, total dose, fractionation	Recommended technique	Possible or acceptable techniques	Techniques not recommended	Techniques currently being assessed
Glioblastoma					
Systematic external irradiation after surgery (biopsy or excision) Subjects under the age of 70 years in good general health (WHO status 0, 1, 2 or Karnofsky performance status ≥ 70 %)	Single-phase irradiation Volumes GTV: contrast enhancement (T1 gadolinium sequence) CTV (EORTC): GTV + 15 mm PTV: depending on the centre Doses PTV: 60 Gy/30 fractions/5 times/week OR Two-phase irradiation (RTOG) Volumes GTV1: FLAIR hypersignal and contrast enhancement (T1 gadolinium sequence) GTV2: contrast enhancement (T1 gadolinium sequence) CTV1: GTV1 + 20 mm CTV2: GTV2 + 20 mm PTV1 and 2: depending on the centre Doses PTV1: 46 Gy/23 fractions/5 times/week PTV2: 60 Gy/30 fractions/5 times/week	Intensity-modulated radiotherapy	3D radiotherapy with portal imaging	Stereotactic radiotherapy Proton	
Systematic external irradiation after surgery (biopsy or excision) Subjects over the age of 70 years in good general health (Karnofsky performance status ≥ 50 %)	Single-phase irradiation Volumes GTV: contrast enhancement (T1 gadolinium sequence) CTV (EORTC): GTV + 15 mm PTV: depending on the centre Doses PTV: 40.05 Gy/15 fractions/5 times/week	Intensity-modulated radiotherapy	3D radiotherapy with portal imaging	Stereotactic radiotherapy	Intensity-modulated radiotherapy
External irradiation after surgery (biopsy or excision) Subjects over the age of 70 years in poor general health (Karnofsky performance status < 50%) If radiotherapy indication retained	Single-phase irradiation Volumes GTV: contrast enhancement (T1 gadolinium sequence) CTV (EORTC): GTV + 15 mm PTV: depending on the centre Doses PTV: 40.05 Gy/15 fractions/5 times/week Otherwise NORDIC trial, PTV: 34 Gy/10 fractions/5 times/week	Intensity-modulated radiotherapy	3D radiotherapy with portal imaging	Stereotactic radiotherapy	Intensity-modulated radiotherapy
Grade 3 gliomas					
Systematic external irradiation after surgery (biopsy or excision) Subjects in good general condition (Karnofsky performance status ≥ 50 %)	Volumes GTV: FLAIR hypersignal and contrast enhancement (T1 gadolinium sequence) CTV (EORTC): GTV + 15 mm PTV: depending on the centre Doses PTV: 59.4/33 fractions/5 times/week	Intensity-modulated radiotherapy	3D conformal radiotherapy with portal imaging	Stereotactic radiotherapy	Proton
Grade 2 gliomas					
External irradiation after surgery (biopsy or excision) IF RADIOTHERAPY INDICATION RETAINED	Single-phase irradiation Volumes GTV: FLAIR hypersignal (and contrast enhancement (T1 gadolinium sequence) if appropriate) CTV (EORTC): GTV + 10 mm PTV: depending on the centre Doses PTV: 50.4 Gy/28 fractions/5 times/week	Intensity-modulated radiotherapy	Proton	Stereotactic radiotherapy	Proton

3D: three-dimensional; CTV: clinical target volume; EORTC: European Organisation for Research and Treatment of Cancer; FLAIR: fluid attenuated inversion recovery; GTV: gross (macroscopic) tumour volume; PTV: planning target volume; RTOG: Radiation Therapy Oncology Group; WHO: World Health Organisation.

image acquisition. When using treating planning systems, to optimise the registration and fusion of images between the CT and MRI, it is important to plan a 3D T1 whole skull sequence with injection (spoiled gradient-recalled [SPGR] or CUBE neuronavigation). Spin echo sequence imaging enhances tumour visualisation. For grade 2 and 3 gliomas, and molecular glioblastoma especially without contrast enhancement, a T2 FLAIR 3D axial sequence (with or without injection of a contrast product) of the entire skull is required. The quality of the MRI must be controlled to minimise distortion phenomena [87].

6.1.3. Preoperative MRI

A preopertive MRI is not systematically indicated but can be used to accurately define contours in the event of the total excision of a small lesion. In fact, identifying the surgical bed can be difficult in the absence of contrast enhancement and abnormalities on the T2 FLAIR sequence.

6.1.4. Immediate postoperative MRI

An immediate postoperative MRI (24 to 48 h after surgery), if performed, can be useful for assessing any residual tumour volume and presence of haematoma; however, it should not be considered as a substitute for the delineation/dosimetry MRI.

6.1.5. PET imaging

If available, aminoacid PET can be valuable tools to improve the differentiation between oedema and tumour in specific cases (reirradiation) and for target delineation.

6.1.6. Image registration/fusion

The registration/fusion of images is always performed, manually, either semi-automatically or automatically. The quality of the registration should always be controlled. In this context, it is recommended that the brainstem, cochlea and internal auditory meatus should be delineated on both the planning CT and MRI. Checks must be carried out to ensure that the structures delineated on the MRI are correctly projected onto the contours on the CT scan. The projection of the cerebral falx and ventricles should also be checked. An automatic delineation software can be used for consistency and reproducibility of delineations.

6.2. Description of treatment position and immobilisation system

6.2.1. Treatment position

Patients are placed in a supine position, aligned with a wedge under their neck and head moulded to the morphology of the patient, with a knee cushion, with their arms alongside their body. For temporal lesions, a mobile immobilisation headrest can be used.

6.2.2. Head immobilisation systems

Traditional thermoformed plastic masks for the head or head/necks are indicated for standard radiation. Dedicated stereotactic masks are used for stereotactic radiotherapy.

6.3. Definition of organs at risk and dose constraints

For the delineation of organs at risk, the RecoRad^{TM} guidelines issued in 2016 and 2020 are easy to consult and include references to the relevant delineation atlases, as those in the current issue and upcoming update (Noël G., et al. Organs at risk radiation dose-constraints: 2025 update. Submitted for publication) [92–95].

6.3.1. Subventricular zones

In animal models it has been shown that gliomas develop from stem cells in the subventricular zones [96]. High doses delivered (above 59.4 Gy) in these zones provide superior tumour control by destroying cancer stem cells [97,98]. Adeberg et al. reported that survival outcomes were lower for tumours located near to the subventricular zone [99]. However, the benefit of this approach remains controversial, especially since this type of irradiation appears to damage cognitive functions in long-term survivors. Outside of studies, these volumes cannot be considered as specific targets in routine practice. Therefore, undercoverage of the planning target volume should not be considered under any circumstances to protect subventricular zones.

6.3.2. Hippocampus

The limbic system plays a major role in a number of functions including concentration, planning, visual/spatial orientation, memory acquisition and consolidation, and complex event-based and long-term memory. A significant portion of radiation-induced cognitive impairment is connected to hippocampus irradiation. During glioma irradiation, the clinical benefit of hippocampal sparing remains a matter of debate, but some studies seem to find a neurocognitive benefit in sparing the contralateral hippocampus [28,100–102]. Also, particular attention could be paid to the mean dose delivered to the left hippocampus. Indeed, in a prospective study with 133 glioblastomas treated with chemoradiotherapy, the mean left hippocampus dose was significantly associated with postradiation decline in Mini-Mental State Examination (MMSE) scores ($p = 0.005$), while the right hippocampus mean dose did not reach statistical significance [103]. RTOG provides a useful delineation atlas for the hippocampus for routine clinical practice (http://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx).

7. Conclusion

The recommendations on radiotherapy for gliomas are summarised in Table 1.

Author contributions

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Appendix A. Useful links

https://www.anocef.org/
http://www.imaios.com/en/e-Anatomy
http://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx

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