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RESEARCH

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Proton therapy for adult type *IDH*-mutated glioma: Proglío-1, a multicenter retrospective study

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Abstract

Background Gliomas with isocitrate dehydrogenase (*IDH*) mutation affect young adults with a long-life expectancy. While radiotherapy is effective, studies have shown its detrimental effects on cognition and quality of life. Unlike photon radiotherapy, proton therapy better spares healthy tissue. This study aimed to report mid-term survival and toxicities of proton therapy in a multicentric cohort of adults with *IDH*-mutant gliomas.

Methods We retrospectively analyzed 90 patients treated with proton therapy in France since 2016, including 60 with *IDH*-mutated astrocytomas and 30 with oligodendrogliomas. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier and compared with the log-rank test. Prognostic factors were assessed using univariate Cox models. Toxicities, radiation-induced-contrast-enhancement (RICE) and patterns of recurrence were evaluated.

Results At the time of proton therapy, World Health Organization (WHO) pathology grades 2, 3, and 4 were observed in 42%, 54%, and 3% of patients, respectively. Protons were delivered as upfront therapy in 41 patients and after recurrence in 49. After a median follow-up of 27.3 months, median OS was not reached, and median PFS was 42.5 months for the whole cohort. WHO grades 3–4 had lower PFS than WHO grade 2 ($p=0.044$). Patterns of recurrence were in-field (79%), out-of-field (7%), borderline (4%), and mixed (11%). Proton therapy was well tolerated, with only three grade > 2 toxicities. RICE occurred in 23 patients, but 74% of them did not require any treatment.

Conclusions Proton therapy in *IDH*-mutated gliomas shows a favorable mid-term tolerance and efficacy profile.

Keywords Proton therapy, Glioma, *IDH*-mutated, Astrocytoma, Oligodendroglioma

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Background

Diffuse gliomas are the most common primary malignant tumors of the central nervous system in adults. Since the last update of the World Health Organization (WHO) classification, published in 2021, several subtypes and grades of gliomas are defined according to histological and molecular criteria [1]. Among several recurrent molecular alterations, *IDH*-mutation and 1p19q codeletion have emerged as the most important diagnostic and prognostic molecular markers [2, 3].

For patients with oligodendrogliomas (*IDH*-mutated gliomas with 1p19q codeletion) or grade 2 astrocytomas (*IDH*-mutated gliomas without 1p19q codeletion), a median overall survival of approximately 10 years with standard of care (surgery followed by adjuvant or delayed chemotherapy and radiotherapy (RT)) is expected. In comparison, patients with *IDH*-wild-type gliomas, have a median survival of only 1.9 years [4–7].

Oligodendrogliomas and *IDH*-mutated astrocytomas, generally affect healthy young adults, with a professional activity and a long-life expectancy [8]. These tumors exhibit a tendency to progress to higher grades of malignancy and may result to death if untreated [9, 10]. Therefore, the main objective of treatments is to achieve the most durable response possible, while avoiding late disabling toxicities.

The management of these tumors is multimodal, and primarily relies on surgery, which should be as complete as possible, but often limited to partial resection or biopsy for anatomical and functional reasons. Most patients will undergo RT (or chemo-radiotherapy) during their disease, either as post-operative adjuvant in accordance with guidelines or following tumor progression. Standard photon RT aims to deliver a total dose of 50–60 Gy (according to the grade of the tumor: 50–54 Gy for grade 2 glioma, and 60 Gy for grade 3–4 glioma) in fractions of 1.8–2.0 Gy, using conformal techniques such as Intensity-Modulated RadioTherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Tomotherapy [11].

Despite the efficiency of RT in this population, several studies have shown deleterious effects of radiations on cognitive functions and quality of life [12–14]. Others studies highlighted the increased risk of cerebrovascular events after brain irradiation [15], as well as an increased risk of secondary radiation-induced cancer [16].

Therefore, a major concern should be avoiding long-term side effects of irradiation in this population. Quality of life and neurocognitive functions preservation should be prioritized.

Even though progress in photonic RT has been significant during last years (VMAT, IMRT, radiosurgery), there is, due to the multiplicity of irradiation beams and entry ports, a pool of low and intermediate doses throughout the brain, which may contribute to mid or long-term side

effects [17–20]. One of the strategies to avoid these late side effects is to improve dose discrimination between the target volume and the organs at risk.

Proton therapy (PT) is an appealing technique due to its ballistic and physical properties. The depth dose distribution of a proton beam, characterized by the Bragg peak, makes it an attractive modality of irradiation. Unlike photon therapy, protons minimize the exposure of healthy tissues to intermediate and low doses (see Fig. 1) which is particularly beneficial for reducing late radiation-induced toxicities.

To date, no prospective clinical trial has compared front-line RT using photon therapy versus PT in terms of survival and cognitive impact. However, some studies are currently ongoing, and the first results are expected in the coming years [21–23].

In France, PT is currently used for the treatment of pediatric cancers, skull base tumors (chordomas, chondrosarcomas), paraspinal chordomas, and ocular melanomas. PT is being investigated for several other potential indications. *IDH*-mutated gliomas are among the potentially relevant indications, so as to maintain local control while reducing cognitive impairment [24].

Our study, the first of this kind in France, aims to report mid-term survival and toxicities of PT in adult patients population with oligodendrogliomas and *IDH*-mutant astrocytomas.

Materials and methods

Study characteristics

We conducted a retrospective multicenter study in the three French PT centers (Caen, Nice and Orsay). The study was conducted following the Declaration of Helsinki and approved by the Ethics Committee of the François Baclesse Comprehensive Cancer Center. It was conducted in compliance with the French Research Standard MR-004 “*Research not involving Human participants*” and is registered in the French Health Data Hub under the reference F20230911115941. All patients received written information, and none of them expressed opposition to the use of their data.

Patient and treatment characteristics

All patients included were older than 18 years at the time of PT with a histological proven diagnosis of oligodendroglioma or *IDH*-mutated astrocytoma, whatever the grade.

Proton therapy was administered at the Proton Therapy Center of Normandy (Cyclhad), the Curie Institute in Orsay (ICPO), and the Mediterranean Institute of Proton Therapy. In these centers, the standard practice is to treat all patients with *IDH*-mutant gliomas using PT. However, in some cases — particularly due to treatment delays or excessive tumor size (> 10 cm) — conventional

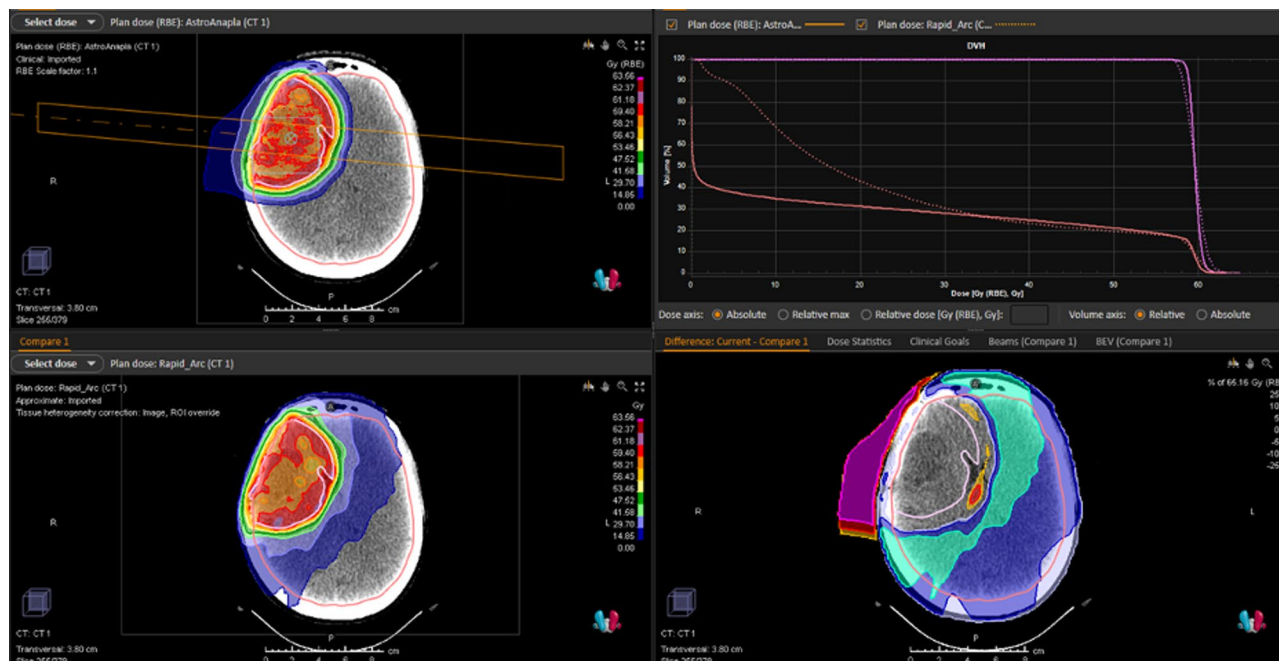


Fig. 1 Dosimetric comparison of proton therapy (SFUD) versus VMAT for *IDH1*-mutated astrocytoma. Legend: Dosimetric comparison of Single-Field Uniform Dose (SFUD) proton therapy irradiation (upper left) with a photonic VMAT plan (lower left) for the treatment of *IDH1*-mutated anaplastic astrocytoma. Illustration of the benefit of proton therapy on the Dose Volume Histogram (upper right); difference in dose distribution (lower right)

radiotherapy was used instead. In all cases, indication of proton therapy was approved by a multidisciplinary tumor board.

All patients were treated with PT between 2016 and 2024 and were centrally followed after PT and all adverse effects were monitored. The gross tumor volume (GTV) was defined as the area of contrast enhancement on T1-weighted MRI or hyperintensity on T2 FLAIR sequences. The clinical target volume (CTV) was generated by expanding the GTV or the postoperative residual cavity by 10–15 mm, modified with respect to anatomical boundaries. A 95% prescription isodose line was used to ensure coverage of the robust CTV. According to standard recommendations, patients underwent regular clinical examinations and regular Magnetic Resonance Imaging (MRI) [11]. Patients were excluded if they had undergone irradiation with any modality other than PT, or if they received previous RT.

Data collection

Data were retrospectively collected from medical and imaging records.

The histological diagnosis were reclassified according to the WHO 2021 classification [1].

The quality of surgical resection was based on the resection procedure report and postoperative MRI. Gross-total resection (GTR) was defined as a macroscopically complete resection with no residual T1 contrast enhancement or FLAIR hyperintensity. Sub-total

resection (STR) was defined as a macroscopically incomplete resection with visible tumor residue as T1 contrast enhancement and/or FLAIR hyperintensity. Biopsies were defined as simple diagnostic samples.

Toxicities were collected from the first day of PT until the last day of follow-up.

Based on reports and analysis of follow-up MRIs, we defined radiation-induced contrast enhancement (RICE) as T1-weighted contrast enhancement (T1w-Gd) within the irradiated field, mimicking tumor progression, but not consistent with true progression based on the complete set of follow-up imaging. We classified them into pseudoprogression (if occurred <6 months after PT) or radionecrosis (if occurred >6 months after PT) [25, 26].

Endpoints definition

The primary outcome of the study was progression-free survival (PFS), defined as the time between the first day of PT and iconographic progression according to Response Assessment in Neuro-Oncology (RANO) criteria [27].

Secondary outcomes were: overall survival (OS) defined as the time between the first day of PT and death from any cause; cumulative incidence of RICE; acute (<6 months) and late (>6 months) toxicities according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0); receiving antiepileptic drug therapy after PT; delay between the end of PT and the next anti neoplastic treatment; and localisation recurrence (in field, borderline, out-of-field) defined as progression

disease according to RANO criteria, occurring within the isodose prescription of 95%, 50–95%, and less than 50%, respectively.

Statistical analysis

Patients characteristics were described using mean and standard deviation or median and range (in case of non-normal distribution) for quantitative variables and using frequencies and proportions for qualitative variables. Survivals were estimated from the first day of PT using

the Kaplan-Meier method and compared between groups using the Log-Rank test. Prognostics factors of survival were assessed using univariate Cox models (age at diagnosis, type of last surgery, WHO grade at the time of PT, histology, timing of PT, occurrence of radionecrosis, number of surgical procedures, and number of chemotherapy lines). A P-value < 0.05 was considered as statistically significant. Statistical analysis were performed using R software, version 4.3.2.

Results

Characteristics of the patients

A total of ninety patients were enrolled in this study. The median age at the time of the initial diagnostic was 36 years (range: 21–65 years). Most patients presented with *IDH1*-mutated gliomas ($n=85$, 94%), while 5 patients (6%) had *IDH2*-mutated gliomas. Sixty patients (67%) were diagnosed with astrocytoma *IDH*-mutant, including 25 (28%) with astrocytoma *IDH*-mutant WHO grade 2, 32 (26%) with astrocytoma *IDH*-mutant WHO grade 3 and 3 (3%) with astrocytoma *IDH*-mutant WHO grade 4. Oligodendrogliomas were identified in 30 patients (33%), with 13 (14%) presenting oligodendroglioma WHO grade 2 and 17 (10%) with oligodendroglioma WHO grade 3.

At the time of PT, WHO grades 2, 3, and 4 were observed in 42%, 54%, and 3% of patients, respectively.

Detailed demographic and clinical characteristics of the study population are presented in Table 1 (see Table 1).

Characteristics of the treatment

According to guidelines, the majority of patients with WHO grade 2 glioma (87%) received a total dose of 50.4–54 Gy (RBE) delivered in 27–30 fractions. Similarly, most patients with WHO grade 3–4 glioma (83%) received 59.4–60 Gy (RBE) in 30–33 fractions. At the clinician's discretion, 13% of patients with WHO grade 2 received a higher dose than 54 Gy (RBE), while 17% of patients with WHO grade 3 received a lower dose than 60 Gy (RBE). The relative biological effectiveness (RBE) of PT was uniformly considered being 1.1.

The Pencil Beam Scanning (PBS) was employed for the majority of patients ($n=70$, 78%), including 63 patients treated with Single-Field Uniform Dose (SFUD) and 7 patients with Intensity-Modulated Proton Therapy (IMPT).

Forty-one patients (46%) received PT as upfront therapy (first line with or without surgery), including 12 (13%) after biopsy, 20 (22%) after STR, and 9 (10%) after GTR. Forty-nine patients (54%) received PT following recurrence, either exclusively ($n=38$, 42%) or after additional surgery ($n=11$, 12%).

Among patients treated in the upfront setting, 17 (41%) received chemotherapy prior to the initiation of PT. Among patients treated after recurrence, 57%, 18%, and

Table 1 Characteristics of the population

	Overall ($n=90$)
Age at diagnostic – median (range)	36.0 (21.0–65.0)
Gender – n (%)	
Female	38 (42)
Male	52 (58)
KPS – n (%)	
100%	43 (48)
90%	47 (52)
Histology – n (%)	
Oligodendroglioma, WHO grade 2	13 (14)
Oligodendroglioma, WHO grade 3	17 (19)
Astrocytoma, <i>IDH</i> -mutant, WHO grade 2	25 (28)
Astrocytoma, <i>IDH</i> -mutant, WHO grade 3	32 (36)
Astrocytoma, <i>IDH</i> -mutant, WHO grade 4	3 (3)
WHO Grade – n (%)	
2	38 (42)
3	49 (54)
4	3 (3)
<i>IDH1_2</i> – n (%)	
<i>IDH1</i> mutated	85 (94)
<i>IDH2</i> mutated	5 (6)
1p/19q codeletion – n (%)	30 (39)
Localisation – n (%)	
Frontal	37 (41)
Fronto-parietal	4 (5)
Fronto-temporal	15 (17)
Parietal	11 (12)
Temporal	19 (21)
Brainstem	3 (3)
Missing	1 (1)
Tumor size (major axis) – n (%)	
<5 cm	30 (45)
≥5 cm	37 (55)
Missing	23 (28)
Contrast enhancement at the time of PT - n (%)	23 (37)
Initial clinical presentation - n (%)	
Headaches	14 (16)
HTIC	6 (7)
Focal epilepsy	18 (20)
Generalized epilepsy	40 (44)
Neurological deficit	15 (17)
Incidental	4 (4)

8% had received one, two, and three lines of chemotherapy, respectively.

The detailed treatment characteristics are presented in Table 2 (see Table 2).

Survival outcomes

The median follow-up for the cohort was 27.3 months (range: 1.54–97.1 months) after the completion of PT.

The median PFS was 42.5 months. PFS was 90% at one year, 75% at two years, and 62% at three years post-PT (Fig. 2A). No significant differences in PFS were observed based on histology subtype with a median PFS of 42.5 months for astrocytoma and 54 months for oligodendroglioma (Fig. 2B). WHO grades 3–4 were associated with a significantly shorter median PFS compared to WHO grade 2 (37.3 months vs. not reached; $p=0.044$) (Fig. 2C). No significant differences in PFS were observed based on the timing of PT; however, the two-year PFS rate was higher in the upfront group (82%) compared to the recurrence group (68%) (Fig. 2D).

The median OS was not reached. OS rates were 98%, 92%, and 88% at one, two-, and three-years post-PT, respectively (Fig. 2E). No significant differences in OS were observed based on histology subtype, although there was a trend favouring oligodendroglioma (2-year OS rates: 88% for astrocytoma vs. 100% for oligodendroglioma; $p=0.058$) (Fig. 2F). Similarly, no significant differences in OS were observed between WHO grade 2 and grades 3–4, with a 2-year OS rates of 92% in both group (Fig. 2G). Patients who received PT as upfront treatment had significantly better OS than those who received PT after recurrence ($p=0.017$) (Fig. 2H). At two- and three-years post-PT, overall survival rates in the recurrence subgroup were 85% and 78%, respectively, compared to 100% at both time points in the upfront group.

In univariate analysis, prior chemotherapy lines were the only factor significantly associated with worse PFS (0 vs. ≥ 1 line: HR=2.72, 95% CI [1.17–6.32], $p=0.02$). However, patients who underwent PT as upfront treatment had significantly higher OS than those receiving PT at recurrence (upfront vs. recurrence: HR=5.25, 95% CI [1.14–24.1], $p=0.033$). No other factors significantly influenced OS or PFS, though a trend was observed toward better OS for oligodendroglioma (astrocytoma vs. oligodendroglioma: HR=0.25, 95% CI [0.05–1.16], $p=0.077$) (see Table 3).

Patterns of recurrence

A total of 28 patients (31%) experienced progression after PT. The analysis of recurrence patterns revealed that the vast majority of patients with progression relapsed in-field ($n=22$, 79%), meaning within the 95% isodose prescription area. Two patients (7%) exhibited out-of-field progression (<50% isodose), and one patient (4%)

experienced a borderline relapse (50–95% isodose). Additionally, three patients (11%) presented mixed progression patterns: one (4%) with in-field and borderline relapse, and two (7%) with in-field and out-of-field progression.

From the end of the PT, the mean delay before initiation of a new treatment was 21 months. Post-relapse treatments were administered as follows: 23 patients (82%) received chemotherapy or targeted therapies alone or in combination with surgery or irradiation, 5 patients (18%) underwent surgery, 2 patients (7%) received additional PT for out of field progression and 1 patient (4%) underwent stereotactic radiation therapy.

Among patients who underwent surgery after relapse, 4 had histologically confirmed recurrence, including 2 whose tumors progressed to a higher WHO grade of malignancy (WHO grade 4). In the remaining 2 patients, the tumor histology was unchanged compared to the time of PT. For one patient, the histopathological report was missing.

Toxicities outcomes

Proton therapy was relatively well tolerated. Acute toxicities (within <6 months) were primarily grade 1 (66%) or grade 2 (28%). The most commonly reported symptoms included alopecia (80%), radiation dermatitis (46%), asthenia (39%), nausea/vomiting (39%), and headache (33%). Three grade 3 toxicities (3%) were reported, all of which were cases of nausea/vomiting.

Late toxicities (after 6 months) were uncommon and consisted only of grade 1–2 events. The most frequently reported late toxicities were asthenia (24%) and alopecia (16%).

Neurocognitive side effects were observed in 6 patients (7%) within the first six months after PT, including 5 patients with grade 1 and 1 patient with grade 2 effects. After six months post-PT, neurocognitive side effects were observed in 14 patients (16%), with 12 (13%) experiencing grade 1 and 2 (2%) experiencing grade 2 effects.

No grade 4 or 5 acute or late toxicities were observed.

The adverse effects of PT were reported in the Table 4 (see Table 4).

One year after the end of PT, 36 patients were on anti-epileptic treatment, and two years after PT, 24 patients remained on antiepileptic treatment.

Radiation-induced contrast enhancement (RICE)

During follow-up, RICE was observed in 23 patients (26%), with a median onset of 11 months post-PT (range: 1–35). Seven cases occurred within 6 months (pseudoprogression), and 16 beyond 6 months (radionecrosis). No differences in the incidence of RICE were observed based on tumor histology, radiation dose, or timing of PT (Fig. 3).

Table 2 Characteristics of the treatment

	Overall (n = 90)
Number of surgeries before PT - n (%)	
Upfront therapy (1st line with or without surgery)	
1	41 (100)
Recurrence	
1	32 (65)
2	12 (24)
3	5 (10)
Extent of resection - n (%)	
Biopsy	25 (28)
GTR	17 (19)
STR	47 (53)
Missing	1 (1)
Total dose (Gy RBE) / Number of fractions - n (%)	
WHO grade 2	
50,4 / 28	13 (34)
54 / 27–30	20 (53)
59,4–60 / 33–30	5 (13)
WHO grade 3–4	
50,4 / 28	1 (2)
54 / 27–30	8 (15)
59,4–60 / 33–30	43 (83)
Timing of proton therapy - n (%)	
Upfront therapy (1st line with or without surgery)	41 (46)
<i>Biopsy + PT</i>	12 (13)
<i>STR + PT</i>	20 (22)
<i>GTR + PT</i>	9 (10)
Recurrence	49 (54)
<i>Surgery + PT</i>	11 (12)
<i>PT only</i>	38 (42)
Time between diagnosis and the start of PT (months) – median (range)	15.5 (1.00–218)
Time between the last surgery and the start of PT (months) – median (range)	11.0 (1.00–185)
PT technique – n (%)	
Double Scattering	20 (22)
Pencil Beam Scanning	
<i>SFUD</i>	63 (70)
<i>IMPT</i>	7 (8)
Corticosteroid therapy at the start of PT – n (%)	2 (2)
Corticosteroid therapy at the end of PT – n (%)	23 (28)
Number of chemotherapy lines before PT – n (%)	
Upfront therapy (1st line with or without surgery)	
0	24 (59)
1	17 (41)
Recurrence	
0	8 (16)
1	28 (57)
2	9 (18)
3	4 (8)
Concomitant chemotherapy – n (%)	
Temozolomide	15 (17)
Maintenance chemotherapy – n (%)	
PCV	16 (18)
Temozolomide	24 (27)

Table 2 (continued)

	Overall (n = 90)
None	47 (52)
Time between the last chemotherapy and the start of PT (months) – median (range)	5 (1.00–1470)

Most were asymptomatic ($n = 20$, 87%), while 3 patients (13%) had symptoms (seizures, neuro-sensory deficits). No treatment was needed in 17 cases (74%), while 4 (17%) required corticosteroids and 2 (9%) received both corticosteroids and bevacizumab. All treated patients had radionecrosis, while none with pseudoprogression required treatment. Evolution was favourable in most cases: complete response ($n = 8$), partial response ($n = 7$), and stable disease ($n = 6$). RICE typically occurred in the periventricular area and/or at the distal edge of the proton path where the linear energy transfer (LET) is the highest (Fig. 4).

Discussion

This is the first study in France to assess the safety and clinical outcomes of PT in adult type *IDH*-mutated glioma. After a median follow-up of 27.3 months, we observed a median PFS of 42.5 months, while the median OS was not reached for the entire cohort. The number of chemotherapy lines administered prior to PT, as well as the timing of PT, were both associated with poorer survival outcomes in the univariate analysis. Most progressions (79%) occurred within the 95% prescription isodose. PT exhibited a favorable safety profile. During follow-up, RICE was observed in 26% (30% pseudoprogression; 70% radionecrosis) of patients mostly asymptomatic (87%) and sometimes required treatment (26%).

The data on PT for this indication remain limited, with most studies being retrospective and involving a limited number of patients. Our survival results align with previous reports. Qiu et al. observed a 2-year PFS rate of 78% in *IDH*-mutated diffuse gliomas (WHO grades 2–4) [28]. Similarly, Willman et al. reported a 3-year PFS rate of 77%, though their cohort included predominantly favourable cases (WHO grade 1/2 gliomas, most without prior chemotherapy) [29]. A larger analysis of 184 WHO grade 2/3 gliomas revealed a median PFS of 2.2 years for WHO grade 3, while median PFS for WHO grade 2 was not reached after a median follow-up of 5.1 years [30]. Lastly, Tabrizi et al. observed a median PFS of 4.5 years in a cohort of exclusively WHO grade 2 glioma where nearly all patients were chemotherapy-naïve, suggesting less advanced disease [31].

Direct comparison with conventional RT is challenging due to the heterogeneity of patient populations, tumor types, and treatment protocols. The RTOG 9402 and EORTC 26,951 trials reported median PFS and OS

of 9.8–13.1 years and 13.2–14.2 years, respectively, for anaplastic oligodendrogliomas treated with RT and PCV chemotherapy [6]. The CATNON study demonstrated a median OS of 9.7 years in patients with anaplastic astrocytomas treated with photon RT and temozolomide, with a 5-year OS rate of 81.6% [7]. There is no comparative arm with photon therapy in our study, which limits the ability to draw firm conclusions about the relative benefit of PT in this indication. Large-scale randomized controlled trial designed to compare the two irradiation modalities in terms of survival outcomes, quality of life, and neurocognitive toxicities in patients with *IDH*-mutated WHO grade 2–3 gliomas, as NCT05190172, APPROACH and NRG-BN005 are expected to address these questions [21–23]. However, the first results will not be available for several years. Until then, the findings of our study should be considered.

Survival rates observed in our study are lower. As the timing of PT was inhomogeneous in our cohort with 54% of patients starting after recurrence, it has obviously shifted the survival data in our study. Additionally, the absence of OS differences by grade may reflect the natural evolution of these tumors toward higher malignancy, as observed in two patients who experienced a WHO grade 4 transformation, histopathologically confirmed after relapse. In routinely practice, repeated biopsies at the time of progression are rare, making tumor transformation difficult to rule out. Moreover, a longer follow-up is necessary to determine whether the PFS benefit observed in WHO grade 2 gliomas and oligodendrogliomas translates into an OS advantage.

One concern with PT is the risk of out-of-field relapse due to the low dose deposited beyond tumor. However, our findings indicate that 79% of relapses occurred within the 95% prescription isodose, suggesting effective tumor coverage. Comparing these findings with literature is challenging due to the limited data on recurrence patterns post-PT in this indication and the lack of consensus on their definition in *IDH*-mutated gliomas. Our in-field recurrence definition align with Kamran et al. who reported 74% of failures occurring in-field after PT [32]. Similarly, Willman et al. observed that 66% of failures within the high-dose field (80% isodose) though 33% of patterns were undetermined [29]. In conventional RT, Im et al. found most relapses for *IDH*-mutated gliomas occurred within the clinical target volume (CTV) [33]. In a mixed *IDH*-wildtype (25%) and *IDH*-mutated (75%)

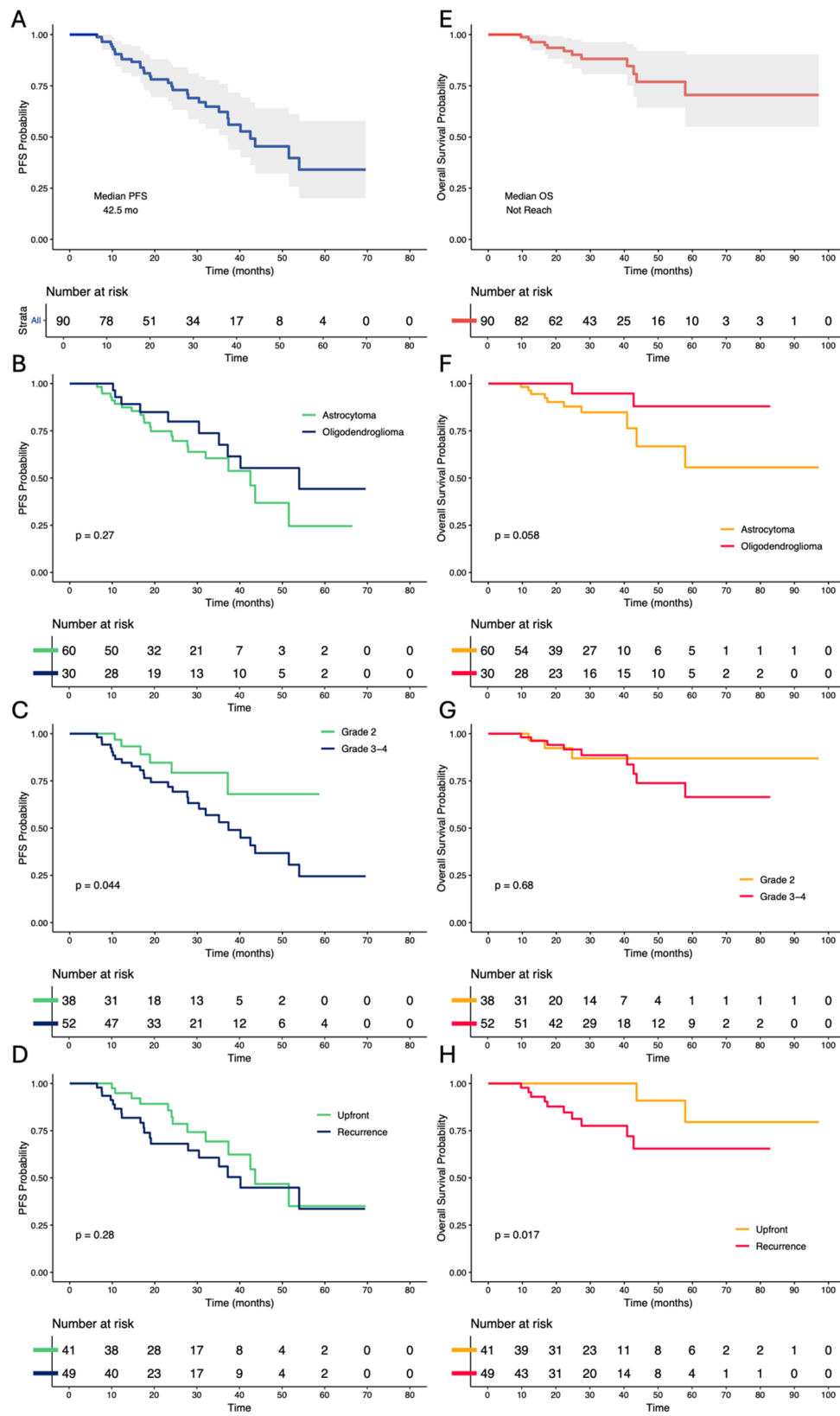


Fig. 2 Kaplan-Meier curves of PFS and OS for total cohort and clinical subgroups. Legend: Progression-free survival (PFS) for the entire cohort (**A**); stratified by histology (**B**), WHO grade (**C**), and timing of PT (**D**). Overall survival (OS) for the entire cohort (**E**); stratified by histology (**F**), WHO grade (**G**), and timing of PT (**H**)

Table 3 Prognostic factors of survival and progression-free survival – Univariate Cox models

Characteristic	Overall survival		Progression-free survival	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis				
<40 [Ref.]	-	-	-	-
≥40	0.85 (0.25, 2.90)	0.8	1.34 (0.65, 2.76)	0.4
Type of last surgery before PT				
B [Ref.]	-	-	-	-
GTR	0.36 (0.04, 3.22)	0.4	0.41 (0.11, 1.51)	0.2
STR	0.74 (0.21, 2.63)	0.6	0.90 (0.40, 2.00)	0.8
Number of lines of chemotherapy				
0 [Ref.]	-	-	-	-
1+	3.49 (0.76, 16.1)	0.11	2.72 (1.17, 6.32)	0.020
WHO grade at PT				
2 [Ref.]	-	-	-	-
3–4	1.32 (0.35, 4.91)	0.7	2.42 (0.99, 5.90)	0.052
Histology				
Astrocytoma [Ref.]	-	-	-	-
Oligodendroglioma	0.25 (0.05, 1.16)	0.077	0.65 (0.30, 1.40)	0.3
Timing of PT				
Upfront [Ref.]	-	-	-	-
Recurrence	5.25 (1.14, 24.1)	0.033	1.47 (0.72, 2.97)	0.3
RICE				
No [Ref.]	-	-	-	-
Yes	0.54 (0.12, 2.48)	0.4	1.14 (0.54, 2.41)	0.7
Number of surgeries before PT				
1 [Ref.]	-	-	-	-
2–3	2.20 (0.66, 7.31)	0.2	1.10 (0.45, 2.68)	0.8

Table 4 Acute (< 6 months) and late (> 6 months) toxicities associated with proton therapy

Type	Acute toxicities		Late toxicities	
	Grade 1–2	Grade > 2	Grade 1–2	Grade > 2
Alopecia	72 (80%)	N/A	14 (16%)	0
Asthenia	35 (39%)	0	22 (24%)	0
Epilepsy	12 (13%)	0	11 (12%)	0
Headache	30 (33%)	0	13 (14%)	0
High Intracranial Pressure (HICP)	4 (4%)	0	0	0
Nausea/Vomiting	19 (21%)	3 (3%)	2 (2%)	0
Neurological deficit	20 (22%)	0	13 (14%)	0
Radiation Dermatitis	41 (46%)	0	0	0
Cognitive disorders	6 (7%)	0	14 (16%)	0

glioma cohort treated with RT, Back et al. reported 63% local relapse [34]. They noted *IDH*-mutated tumors had more frequent distant relapses within two years (45% vs. 26%, $p=0.005$) and higher rates of ventricular/subependymal relapses (30% vs. 18%, $p=0.047$) compared to *IDH*-wildtype tumor. Their use of GTV as a reference may have overestimated distant relapses compared to our study.

The predominantly in-field recurrence pattern post-PT highlights its effectiveness in tumor coverage while

facilitating reirradiation for out-of-field recurrences, as observed in two patients from our study. Furthermore, a future advantage of PT could be dose escalation within the GTV-CTV to maximize local control while preserving healthy tissues.

We observed RICE in 26% of patients, comprising 30% of pseudoprogression and 70% of radionecrosis, with a median onset of 11 months post-PT.

This phenomenon is widely reported in the literature, with a median incidence of 23% (range: 12–55%) and in a median time to onset from 1 to 15 months, consistent with our findings [30, 35–43]. However, the terminology used to define it remains inconsistent. Terms such as radionecrosis, pseudoprogression, or RICE are commonly used to describe T1w-Gd occurring near the irradiated field leading to heterogeneous interpretations. These events pose a significant challenge in patient management for two main issues:

First, distinguishing RICE from tumor progression based solely on imaging is difficult, as they share overlapping radiological features. Eichkorn et al. reported that 39% of RICE cases were misinterpreted as tumor progression [37]. Several risk factors for RICE have been identified, primarily through retrospective analyses, including radiation dose and volume [35, 42], fractionation schedule [35], proton therapy [36], re-irradiation [35, 37], age

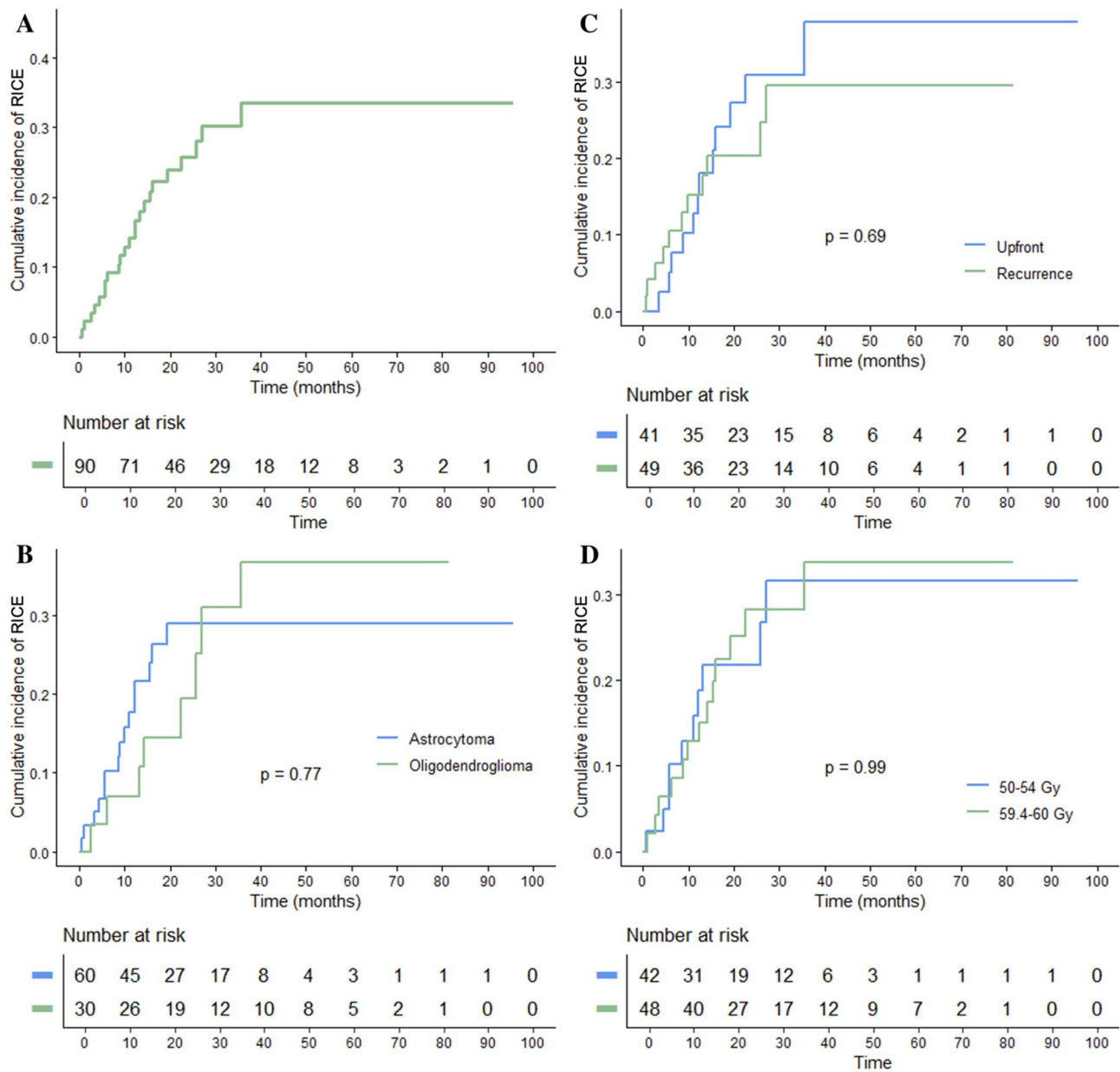


Fig. 3 Cumulative incidence of RICE for the total cohort and clinical subgroups. Legend: Cumulative incidence of RICE for Entire cohort (A); Stratified by tumor histology (B); Stratified by timing of proton therapy (C); Stratified by radiation dose (D)

[30], concurrent chemotherapy [37, 38], diabetes [35], oligodendroglioma histology [42] and periventricular location [43, 44]. According to Winter et al. [26], radionecrosis is a late-onset lesion typically occurring more than six months post-irradiation. It may cause symptoms and is often associated with a progressive and irreversible course. In contrast, pseudoprogression is a transient phenomenon without clinical consequences occurring within the first 6 months post-PT. Several radiological features have been proposed to support the diagnosis of pseudoprogression, including contrast enhancement that is often patchy (<1 cm), multifocal, located in white

matter, periventricularly distributed, or positioned at the terminal ends of the proton beam [41]. Our findings met these criteria, as none of the patients with pseudoprogression required specific treatment.

The second issue is the risk of severe symptoms. Among the 23 cases of RICE observed in our study, only 3 were symptomatic (seizures, neuro-sensory deficits), and 6 required specific treatments (corticosteroids and/or bevacizumab) due to symptoms or as a “diagnostic test” with corticosteroids, at the clinicians’ discretion. Our findings are reassuring regarding symptom severity. Similarly, literature reports indicate that the vast majority

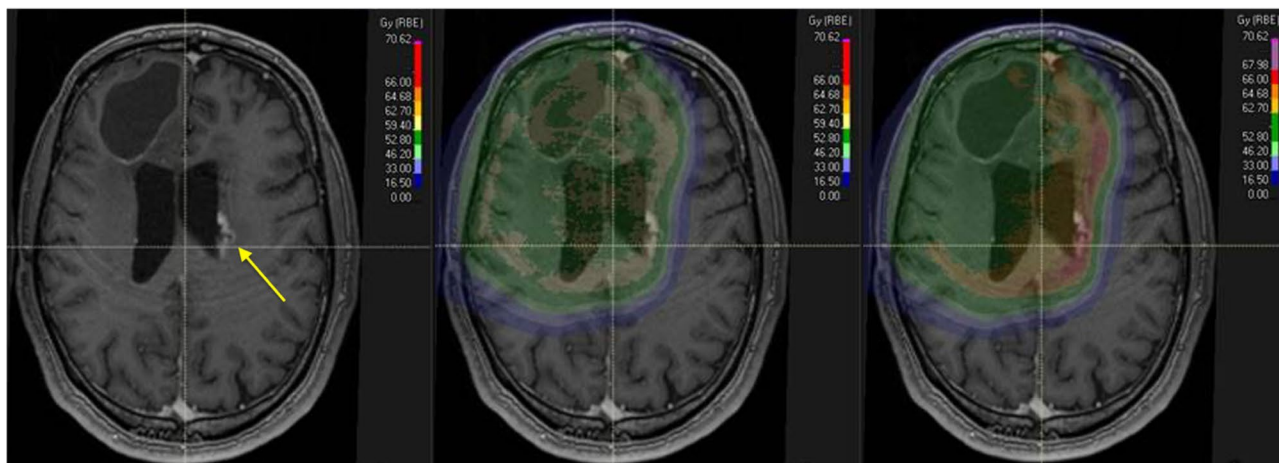


Fig. 4 Imaging and dose distribution of radionecrosis under fixed and variable RBE models. Legend: Typical imaging characteristics of radionecrosis (yellow arrow on the left) with a periventricular distribution. Dose distribution based on a fixed relative biological effect (RBE = 1.1) (middle) and a variable RBE (McNamara, $\alpha/\beta = 3.76$, right)

(>80%) of RICE cases are grade 0–2 events [30, 35, 37, 42] with approximately one-third requiring specific treatment such as surgery, corticosteroids, or bevacizumab [30, 36, 37]. Acharaya et al. reported a grade 5 radionecrosis case in a patient who had received PCV after PT [42]. As highlighted by Eichkorn et al., chemotherapy has been associated with both the development and severity of RICE [37]. This underscores the importance of distinguishing tumor progression from RICE.

The pathophysiological mechanisms underlying radionecrosis remain poorly understood. However, variations in LET and RBE in PT, particularly at the distal end of the proton beam path, is suspected to play a role [44].

Proton therapy, due to its limited dose deposition in healthy tissue, appears to be a promising approach for reducing neurocognitive toxicities and preserving quality of life [45].

The tolerance profile of PT in our cohort was excellent, consistent with the literature [46]. *IDH*-mutated gliomas primarily affect young adults, often without associated comorbidities, who are fully engaged in professional and social life. Therefore, assessing return to work and quality of life is critical for this indication, but it is not yet fully integrated into current clinical practice. Efforts should be made to encourage further evaluations in this area.

Similarly, we reported neurocognitive side effects based on physicians' consultation notes; however, most patients did not undergo a comprehensive neuropsychological examination, which remains a challenge in routine clinical practice.

In the literature, assessments of cognitive functions are often limited to pediatric studies. Lassaleta et al. demonstrated in a meta-analysis of pediatric brain tumor patients that those treated with PT achieved significantly higher scores across most neurocognitive outcomes

compared to those treated with photon-based radiation therapy [47]. In adults, Tabrizi et al. observed that most low-grade glioma patients retained normal neurocognitive function at 5 years after PT [31]. Such studies require long-term follow-up and should be strongly encouraged in *IDH*-mutated gliomas.

The limitations of this study are inherent to its retrospective assessment of oncological outcomes and toxicities, which may introduce uncertainties. We attempted to standardize the histological classification of patients according to the 2021 WHO criteria; however, the lack of centralized pathology review may have led to classification bias. Our limited follow-up period may be insufficient to assess long-term disease control and late toxicities including neurocognitive side effects. Furthermore, the heterogeneity of our cohort introduces a treatment bias that affect survival outcomes. Future studies with long-term follow-up and a randomized controlled design are warranted [21–23].

Conclusion

To conclude, the retrospective multicentric analysis conducted on a cohort of adult patients with *IDH*-mutated gliomas suggests a satisfactory mid-term tolerance and efficacy profile. WHO grade remained the most important factors influencing PFS. However, the timing of proton therapy did not influence the PFS. RICE is not a rare phenomenon observed after proton therapy being mostly asymptomatic and often difficult to distinguish from true tumor progression. Prospective studies with longer follow-up and comprehensive neuropsychological assessments are needed to fully evaluate the potential of proton therapy in reducing long-term and neurocognitive toxicities. Given the dosimetric profile of proton therapy and the predominantly in-field recurrence pattern, future

studies on dose escalation strategies could also be relevant to optimizing local control while preserving healthy tissues.

Abbreviations

CTV	Clinical target volume
GTR	Gross-total resection
GTV	Gross tumor volume
IDH	Isocitrate dehydrogenase
IMPT	Intensity-Modulated Proton Therapy
IMRT	Intensity-Modulated RadioTherapy
LET	Linear energy transfer
MRI	Magnetic Resonance Imaging
OS	Overall survival
PBS	Pencil Beam Scanning
PFS	Progression-free survival
PT	Proton therapy
RANO	Response Assessment in Neuro-Oncology
RBE	Relative biological effect
RICE	Radiation-induced contrast enhancement
RT	Radiotherapy
SFUD	Single-Field Uniform Dose
STR	Sub-total resection
T1w-Gd	T1-weighted contrast enhancement
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

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Author contributions

The conceptualization of the study was carried out by N.G. and P.L. Formal analysis was conducted by F.C. and N.G. Investigation was performed by N.G., E.J., J.J., E.S., R.S., S.D., R.S., S.M., and J.D. Methodology was developed by N.G. and P.L. Resources were provided by E.J., J.J., R.S., S.D., D.S., A.L., E.E., J.R., F.M., M.F., J.D., and P.L. Supervision was ensured by J.B. and P.L. Visualization was handled by N.G., F.C., C.M., and P.L. The original draft was written by N.G. and P.L., and the review and editing were carried out by N.G., E.J., J.J., F.C., E.S., R.S., S.D., S.M., D.S., A.L., E.E., C.M., J.R., F.M., M.F., S.V., J.B., J.D., and P.L. All authors have read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki and approved by the Ethics Committee of the François Baclesse Comprehensive Cancer Center. It was conducted in compliance with the French Research Standard MR-004 "Research not involving Human participants" and is registered in the French Health Data Hub under the reference F20230911115941. All patients received written information and none objected to the use of their data. The ethics committee waived the requirement for individual informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

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