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► To cite this version:

Vincent Harlay, Romain Appay, Celine Bequet, Gregorio Petreirena, Chantal Campello, et al.. Radio-chemotherapy feasibility for biopsy-only unresectable IDH wild-type glioblastomas (BO-GBM). *Neuro-Oncology Practice*, 2023, 10 (6), pp.536-543. 10.1093/nop/npad028 . hal-04254204

HAL Id: hal-04254204

<https://amu.hal.science/hal-04254204v1>

Submitted on 19 Feb 2024

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Radio-chemotherapy feasibility for biopsy-only unresectable *IDH* wild-type glioblastomas (BO-GBM)

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Abstract

Background. “Biopsy-only” glioblastoma (BO-GBM) is a heterogeneous, understudied group of patients associated with a poor outcome. Our objective was to explore the pattern of care and prognosis associated with BO-GBM in our center.

Methods. Patients with *IDH* wild-type BO-GBM included in a prospective regional cohort initiated in 2014 and closed in 2017 were retrospectively reviewed for patient characteristics, MRI findings, treatment allocation, and delivery.

Results. Of 535 patients included in the cohort, 137 patients were included in the present analysis. The median age was 66 years old and the median KPS was 70. Forty-six patients (33.6%) were referred to radiotherapy and chemotherapy (RT-TMZ) regimen, 75 (54.7%), considered unfitted for RT, received chemotherapy upfront (CT) and 16 (11.7%) were referred to palliative care (PC). Regarding the first group, 91% of patients completed the RT-TMZ. In the CT group, 11 of 75 patients (14.7%) underwent radiotherapy after chemotherapy upfront. Median overall survival was 12.3 months (95% CI, 15.30–24.16), 5.7 months (95% CI, 6.22–9.20), and 1.9 months (95% CI, 1.43–5.08) in RT-TMZ, CT, and PC groups, respectively. In multivariate analyses, progression-free survival was impacted by baseline KPS ($P < .001$) and *MGMT* status ($P = .004$). Overall survival was impacted by baseline KPS ($P < .001$) and age ($P = .030$).

Conclusion. BO-GBM constitute a large and heterogeneous population in which one-third of patients is amenable to the standard of care, with survival outcome close to one of the patients who underwent surgery. Reliable criteria are needed to help select patients for adequate treatment while new strategies are warranted for BO-GBM unfit for RT.

Keywords:

biopsy-only | glioblastoma | treatments | unresectable

Isocitrate dehydrogenase (IDH) wild-type (wt) glioblastoma (GBM) is the most common primary tumor of the central nervous system in adults (except for meningiomas and adenomas).^{1–4} They represent 80% of primary CNS tumors diagnosed in the United States.⁵ Tumor progression is associated with a loss of neuro-cognitive functions,^{6,7} a loss of functional independence,⁸ and a decrease in quality of life.^{9,10} Nowadays, there is no curative treatment available. Treatment with maximal surgical resection followed by radiotherapy–chemotherapy using temozolomide (RT-TMZ)

has become the standard since the publication of the EORTC (European Organisation for Research and Treatment of Cancer) 22981/26981 trial.¹¹ Numerous therapeutic trials have taken place since 2005, some of which have improved progression-free survival (PFS) of newly diagnosed GBM patients.^{12,13} However, no improvement in overall survival (OS) was observed compared to the current standard^{14–16} with the recent exception of the TTF device.¹⁷ The median overall survival remains short, between 14 and 16 months for these patients. At relapse, chemotherapy is associated with a low response

rate,^{18,19} while the use of bevacizumab is associated with improved PFS but no modification of OS.²⁰ Immunotherapy to date has failed to improve GBM patient outcome.²¹

BO-GBM is an understudied group of patients associated with a poorer outcome, which has been reported to represent up to 25% of newly diagnosed GBM.² Feasibility and completion of the RT-TMZ regimen are not clearly established in this population. In the US National Cancer Data Base (NCDB) of patients diagnosed with GBM from 2006 to 2011, only 15% of biopsy-only patients were referred to the RT-TMZ regimen. More recently, in a monocentric cohort (2005–2019) 53 out of 95 (56%) patients with BO-GBM were referred to RT-TMZ, of whom only 18 patients (19%) completed the regimen.²² Therapeutic management of BO-GBM patients remains challenging with no current recommendation. Dedicated clinical trials are missing and physicians are frequently helpless to take care of these patients.

Then, our objective was to explore the pattern of care and predictive factors of newly diagnosed BO-GBM patients to develop adapted therapeutic options.

Methods

Patient Cohort

For this single-institution study, we prospectively included 447 patients with histologically-confirmed newly diagnosed *IDH* wild-type glioblastoma followed in the neuro-oncology department of CHU La Timone in Marseille, France, between January 2014 and December 2017. Among them, 158 patients had biopsy only (35%). Among these 158 patients, 21 patients were excluded for missing data leaving 137 patients with BO-GBM for the present analysis (Supplementary Fig. 1). The following clinical data were collected at diagnosis: age, gender, KPS, headache, seizures, neuro-somatic symptoms (motor impairment, sensory impairment, ataxia, cranial nerve involvement, and vesico-sphincter disorders) and cognitive impairment (dysexecutive syndrome, temporo-spatial disorientation, ideomotor slowness, attentional disorders, memory disorders, language disorders, apraxia, psychiatric disorders, excessive somnolence, and hemineglect). This study was approved by our local ethics committee and was in accordance with the Declaration of Helsinki (SIRIC cohort no. 2014-A00585-42).

Brain MRI

Tumor localization corresponded to the involvement of cerebral lobes and deep anatomical structures. The topography of the tumor considered the presence of unilateral, bilateral, or midline crossing lesions. The number of tumor foci at diagnosis was studied: a unifocal tumor had only 1 FLAIR hyper signal range and could be associated with 1 enhancement spot maximum. A multifocal tumor was defined by the presence of a single FLAIR hyper signal range associated with at least 2 different contrast spots within the tumor. A multicentric tumor had at least 2 noncontiguous FLAIR hyper signal ranges, each of which may include one or more contrast spots. We also studied

the products of the 2 largest perpendicular diameters of the lesions.²³ The measurements were performed using the Centricity™ Universal Viewer (GE Healthcare) imaging processing software. We collected the presence of a mass effect on the midline and ventricles, the midline crossing, an initial intra-tumoral hemorrhage or an initial hydrocephalus by obstruction of the natural cerebrospinal fluid (CSF) pathways.

Pathological and Molecular Analysis

Pathological tissue was obtained after stereotaxic biopsy or open biopsy.

For pathological analysis, the tumor tissues were fixed in 10% formalin and embedded in paraffin wax. Paraffin blocks were cut into slices at 3.5 μm . Samples were stained with haematoxylin–phloxine–safron (HPS) according to standard protocols. All samples were reviewed by 2 experienced neuropathologists (DFB and RA). All diffuse gliomas were graded, according to the 2016 WHO classification, as WHO grade IV (high-grade glioma, HGG).²⁴ Immunohistochemistry was performed on Benchmark Ventana autostainer (Ventana Medical Systems SA) for *IDH1* R132H (Dianova, H09) and *EGFR* (3C6, Roche). The *EGFR* expression was quantified as the percentage of cells at different staining intensities as previously studied by Hirsch et al.^{25,26} When the results of *IDH1* R132H immunohistochemistry were negative or unreliable, the status of *IDH1* and *IDH2* mutations was addressed by direct sequencing using the Sanger method and primers, as described previously.²⁷ For *MGMT* promoter methylation status determination, DNA extraction was performed from 5 slides from FFPE tumoral fragments using the QIAamp DNA kit (Qiagen, Courtaboeuf, France). Only samples containing at least 60% of tumor cells were processed (neuropathologist confirmation). Twenty to 200 ng of DNAs were treated with sodium bisulfite using the EpiJET Bisulfite Conversion kit and purified according to the specified protocol (Thermo Fischer Scientific Inc.). Bisulfite-modified DNA was amplified using *ampliTaq Gold 360* Master mix (Applied Biosystems) with a forward primer and a biotinylated reverse primer (Pyromark Q96 CpG *MGMT*, Qiagen). Pyrosequencing was performed using PyroMark-Q48 advanced CpG Reagents and the sequencing primer (Pyromark Q96 CpG *MGMT*, Qiagen) using the Pyromark Q48 Autoprep software on a PyroMark Q48 pyrosequencer (Qiagen). Full details for CpG location and the validation method can be found in the study by Quillien et al.²⁸

Treatments Data

Treatment options include radiotherapy–temozolomide and/or systemic treatment including alkylating agents (temozolomide without or with carmustine) and bevacizumab. Temozolomide was administered alone at the dose of 150 $\text{mg}/\text{m}^2/\text{day}$ for 5 consecutive days out of 28 for the first cycle, and from the second cycle at the dose of 200 $\text{mg}/\text{m}^2/\text{d}$ for 5 days out of 28. Temozolomide could also be administered in association with carmustine. In this case, temozolomide was administered for 5 days every 6 weeks and carmustine was administered with the unique

dose of 130 mg/m² in a perfusion every 6 weeks. Tolerance using CTCAE criteria v5.0 and clinical efficacy of treatment were evaluated each month by physicians. Treatment response was assessed by MRI every 2 months according to the RANO criteria.²⁹

Statistical Analysis

Categorical variables are presented as numbers and percentages, and the quantitative results are as a median with minimum and maximum range or a mean with standard error as an index of dispersion. Comparisons were made with Student's *t*-test, Chi² or Fisher tests for qualitative data and *t*-test or Mann–Whitney for quantitative data, as appropriate. Progression-free survival (PFS) was defined as the time from the biopsy to documented progression or death, censored at the date of the last documented disease evaluation for alive patients without progression. Overall survival (OS) was defined as the time from the biopsy to death from any cause, censored at the date of last contact. The survival rate was estimated using the Kaplan–Meier method, and differences between curves were compared by a log-rank test. Cox proportional hazard regression models were used in multivariate analyses. Significant factors in univariate analyses were included in the multivariate analyses. Both univariate and multivariate survival analyses were conducted to identify prognostic factors. All tests were two-sided, and a *P*-value < .05 was considered statistically significant. Analyses were performed with SPSS software v22.

Results

Patients (Tables 1 and 2, Supplementary Fig. 1)

Our population included 84 men (61.3%) and 53 women (38.7%). The median age at diagnosis was 66.0 years (range, 17.4–89.6). The median KPS at diagnosis was 70 (range, 30–90). Forty patients (29.2%) presented with seizures at diagnosis. Concerning neuro-somatic signs, we noted that 65 patients (47.4%) had motor impairment. Concerning neuro-cognitive signs, 46 patients presented with language disorder (33.6%). Concerning histologic and molecular features, 45 patients (32.8%) presented with a methylated *MGMT* promoter and 52 patients (38%) with an unmethylated promoter. *MGMT* status couldn't be analyzed for 29.2% of patients. Ninety complete MRI were available for analysis at diagnosis. The tumor was unifocal for 47 patients (34.3%), multifocal for 21 patients (15.3%) and multicentric for 22 patients (16.1%). The tumor involved the right hemisphere for 28 patients (31.2%), and the left hemisphere for 39 patients (42.7%). There was bilateral involvement for 16 patients (18.2%). The main involved cortical regions were the frontal and temporal lobes (55.5% and 36.5%, respectively). The mean products of perpendicular diameters were 1202.5 mm² (median 869.8 ± 113.6). Eighteen patients presented with initial bleeding (13.1%). Seventy-five patients (54.7%) underwent stereotaxic biopsy and 62 patients (45.3%) underwent open biopsy.

Table 1. Patient characteristics at diagnosis. Number of patients (%)

Clinical features	N	%
Age at diagnosis (median, range)	66 (17.4–89.6)	
Gender (W/M)	53/84	38.7/61.3
KPS (median, range)	70 (30–90)	
KPS < 60	36	25.9
KPS = 60	29	20.9
KPS ≥ 70	72	52.6
Symptoms at diagnosis		
Headache	15	10.9
Seizures	40	29.2
Neuro-somatic signs		
Motor impairment	65	47.4
Sensory impairment	10	7.3
Ataxia	27	19.7
Cranial nerve involvement	37	27.0
Vesico-sphincter disorders	8	5.8
Any cognitive/language impairment	110	80.3
Dysexecutive syndrome	18	13.1
Temporo-spatial disorientation	38	27.7
Ideomotor slowing	43	31.4
Attentional disorders	16	11.7
Memory disorders	36	26.3
Language disorders	46	33.6
Apraxia	5	3.6
Psychiatric disorders	7	5.1
Excessive somnolence	12	8.8
Hemineglect	5	3.6
Histological and molecular characteristics		
<i>MGMT</i> promoter	97	70.8
methylated	45	32.8
unmethylated	52	38.0
Hirsch score (median, range)	200 (15–400)	
Biopsy		
Stereotaxic biopsy	75	54.7
Surgical biopsy	62	45.3

Numbers in bold and italic are for percentages of patients for each characteristic.

Treatment Feasibility (Table 3, Fig. 1, Supplementary Tables 1 and 2)

Concerning treatment allocation, we identified 3 groups of patients. Patients treated with concomitant radio-chemotherapy (RT–TMZ) followed by adjuvant temozolomide according to the Stupp or Perry protocol^{11,30} (according to the patient age), those treated with chemotherapy upfront (CT), and those who received palliative care (Supplementary Table 1).

Table 2. Radiological features of biopsy-only glioblastoma patients at diagnosis

Radiological features	N	%
Number of patients with available complete baseline neuro-imaging	90	65.7
Lesions		
Unifocal	47	34.3
Multifocal	21	15.3
Multicentric	22	16.1
Topography		
Restrict to right hemisphere	28	31.2
Restrict to left hemisphere	39	42.7
Bilateral	16	18.2
Midline	7	7.9
Distribution within cortical regions		
Frontal lobe	50	55.5
Temporal lobe	33	36.5
Parietal lobe	31	34.3
Occipital lobe	14	16.1
Insular lobe	12	13.1
Tumor cross-sectional area (mm²)		
Mean	1202.5	
Median ± SD; range	869.8 ± 113.6; 65–4515.4	
Mass effect	64	46.7
Midline crossing	48	35
Bleeding	18	13.1
Hydrocephalus	12	8.8

Regarding the first group, 42 of 46 patients completed RT–TMZ (91%). Four patients interrupted RT–TMZ (8.7%), 2 because of progression and 2 because of toxicity (Supplementary Table 2). Regarding the CT group, 7 patients were treated with carmustine. Eleven of 75 patients (14.7%) received radiotherapy protocol after chemotherapy upfront and 10 patients completed radiotherapy (7.3%). Only one patient interrupted chemotherapy because of toxicity (Supplementary Table 2).

Regarding treatment tolerance, grade 3–4 toxicities using CTCAE criteria v5.0 were collected including thrombocytopenia (23.2%), lymphopenia (14.6%), and neutropenia (6.8%). Intense fatigue related to treatment was reported for 9 patients (8.7%) (Table 3).

Patient Outcome (Fig. 2)

The best treatment responses in the whole cohort were complete response (CR), partial responses (PR), stable disease (SD), or progressive disease (PD) in 2%, 9%, 42%, and 47%, respectively. In the RT–TMZ group, responses, assessed at least 3 months apart from the end of RT, and compared to preradiotherapy imaging, were CR 7%, PR 15%, SD 54% and PD 24%. In the CT group, treatment responses included PR 7%, SD 43%, and PD 51%.

In the whole cohort, the median OS was 7.6 months (IC95%: 6.0–9.2) and the median PFS was 3.7 months (IC95%: 2.9–4.8). In the RT–TMZ group, median OS and PFS were 12.3 months (IC95%: 7.9–16.7) and 7.6 months (IC95%: 6.4–8.7), respectively. In the CT group, median OS and PFS were 5.7 months (IC95%: 4.3–7.1) and 2.6 months (IC95%: 1.5–3.8), respectively. In the palliative care group, median OS and PFS were 1.9 months (IC95%: 0–3.7) and 0.5 months (IC95%: 0.4–0.6), respectively. PFS-6 months rates were 61% and 28% in the RT–TMZ and CT groups,

Table 3. Therapeutic adverse events during first-line treatment, using CTCAE criteria v5.0

Adverse events	N	Grade 1–2	Grade 3–4	%
Vertebral collapse	4	4		3.9
Fractured rib	1	1		1
Intracranial bleeding	6	5	1	5.8
Other location bleeding	5	5		4.9
Wound dehiscence	1	1		1
Venous thromboembolic events	8	6	2	7.8
Thrombocytopenia ≥ grade 3	24	0	24	23.2
Neutropenia ≥ grade 3	7	0	7	6.8
Lymphopenia ≥ grade 3	15	0	15	14.6
Anemia	3	2	1	2.9
Infection without agranulocytosis	17	15	2	16.5
Arterial hypertension	2	1	1	1.9
Fatigue grade ≥ 3	9		9	8.7
Cognitive impairment	1	1		1

Values in italic are for percentages of patients for each adverse event.

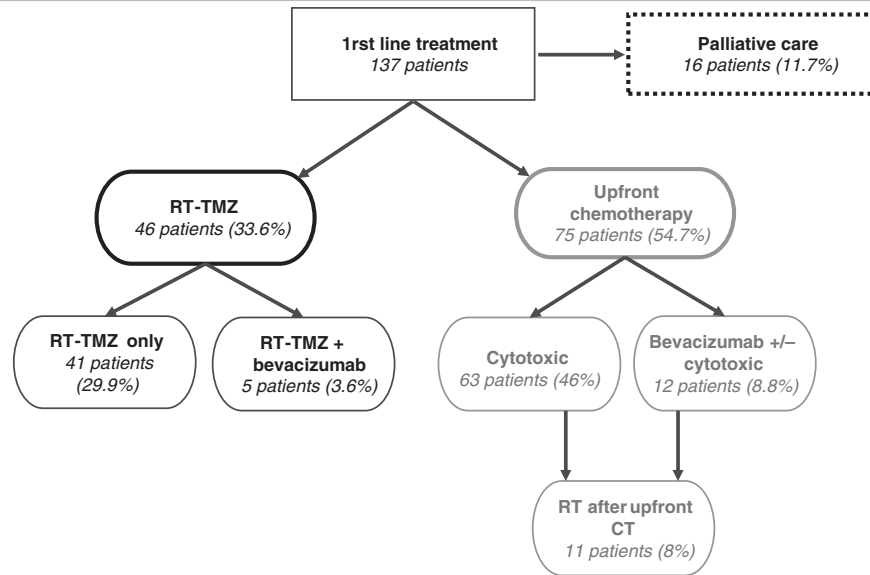


Fig. 1. Therapeutic strategies: radiotherapy–temozolomide (RT–TMZ), chemotherapy upfront (CT) or palliative care (PC).

Table 4. Prognostic factors. HR: hazard ratio; CI: confidence interval. $P = P$ -value

Factors	Progression-free survival		Overall survival	
	P univariate	P multivariate (HR; 95%CI)	P univariate	P multivariate (HR ; 95%CI)
Age at diagnosis (cutoff: 66)	.098	.105	.011	.030 (1.767; [1.057–2.953])
KPS (lower versus higher than 70)	<.001	<.001 (4.022; [2.063–7.841])	<.001	<.001 (3.037; [1.715–5.380])
Topography (midline or bilateral versus unilateral)	.002	.762	<.001	.178
Corticosteroids (cutoff: 60)	.106		.016	.345
Hirsch score (cutoff: 200)	.068		.021	.093
Bleeding on neuro-imaging (yes/no)	.001	.105	.092	
<i>MGMT</i> promoter methylation status (no/yes)	.014	.004 (2.546; [1.355–4.787])	.142	

respectively. OS-12 months rates were 57% and 20% in the RT–TMZ and CT groups, respectively.

Prognostic and Predictive Factors (Table 4, Fig. 2, Supplementary Figs. 2 and 3)

In univariate analyses, PFS was negatively impacted by a low KPS ($P < .001$), bilateral or midline crossing lesions ($P = .002$), initial bleeding ($P = .001$) and unmethylated *MGMT* status ($P = .014$). Overall survival was negatively impacted by higher age at diagnosis ($P = .011$), low KPS ($P < .001$), bilateral or midline crossing lesions ($P < .001$), high prednisolone equivalent dose ($P = .016$), and a high Hirsch score^{25,26} ($P = .021$).

In multivariate analyses, PFS remained impacted by KPS ($P < .001$) and *MGMT* status ($P = .004$). Overall survival remained impacted by KPS ($P < .001$) and age at diagnosis ($P = .030$).

In the RT–TMZ group, we identified a specific population with an overall survival longer than 9 months. The predictive factor associated with this population was a younger

age ($P = .013$). Interestingly, the KPS was not predictive for longer OS in this group.

In the chemotherapy upfront group, *MGMT* methylation status was significantly associated with patient PFS ($P < .001$) and OS ($P = .009$, Supplementary Fig. 3). Finally, predictive factors of radiotherapy completion at the end of upfront chemotherapy (CT group) were higher KPS ($P = .001$, Supplementary Fig. 2) and unilateral tumors ($P = .023$).

Discussion

Glioblastoma is one of the most common primary tumor of the central nervous system. Its prognosis remains poor. Surgical tumor resection, if possible, followed by concomitant and adjuvant RT–TMZ (Stupp protocol) has rapidly become the standard of care as it has been able to show a benefit in terms of overall survival in selected patients with preserved autonomy (KPS ≥ 70).¹¹ In elderly patients (>65 years) with a good KPS, the RT–TMZ combination (with an adapted RT schedule, 40 Gy in 15 fractions) appear superior

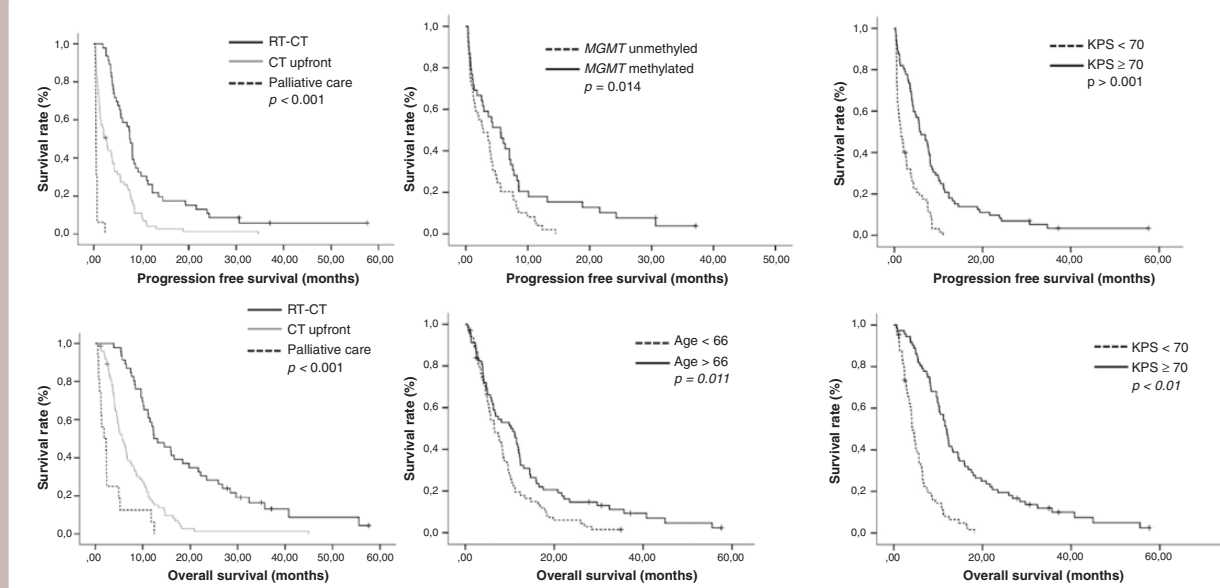


Fig. 2. PFS and OS according to treatment groups. Prognostic factors for PFS and OS.

to RT only even in patients with unmethylated MGMT tumor.³⁰ However, patients with BO-GBM, who often have impaired autonomy, constitute a significant subset of patients who are not always amenable to RT-TMZ combination. In the present study, based on a prospective cohort, we observed that BO-GBM patients constitute a large and heterogeneous population in which one-third of them is amenable to the standard of care, with survival outcome close to one of the patients who underwent surgery. Patients considered unfit for RT-TMZ at diagnosis fail frequently to be referred subsequently to RT after upfront CT and exhibit a poor survival outcome. Thus, reliable criteria are needed to help select patients for adequate treatment while new strategies are warranted for BO-GBM unfit for RT.

BO-GBM represent a variable but significant subset of patients, between 5% and 21% in previous literature reports,^{22,31} and up to 35% in our study. The variability between these cohorts is probably explained by selection bias with a distinct median age at diagnosis (61 years in the study of Kole³² versus 66 for our cohort) and variable functional status.

Nevertheless, this population is understudied: there are few dedicated cohorts in literature and BO-GBM patients are frequently underrepresented in therapeutic clinical trials, leading to limited strong recommendations for patient management. Thus, BO-GBM is frequently considered unfit for RT-TMZ or RT: in the US database,² only 1325 (15%) out of 8781 BO-GBM are referred to RT-TMZ versus 33% in our cohort. Moreover, the completion of RT is poorly documented but remains critical for its efficiency. In Lober et al., 55% of BO-GBM patients were referred to RT-TMZ but only 34% completed regimen.²² In the TEMAVIR clinical trial³³ dedicated to BO-GBM, 24% of patients failed to complete radio-chemotherapy, while in another French clinical trial³⁴ evaluating the combination of BCNU and temozolomide in the neoadjuvant

setting for BO-GBM, radiotherapy was completed in 78% of patients. In our study, we noted that only 4 patients out of 46 interrupted RT-TMZ (8.7%) including 2 of them because of progression (4.3%). This observation reinforces the feasibility of patient selection for first-line treatment by RT-TMZ in this population. Indeed, it was up to physicians to decide whether patients could benefit from radiotherapy or chemotherapy upfront. We also noticed in our study that patients that we considered to be unable to receive RT-TMZ at diagnosis can rarely be irradiated afterwards. Indeed, among 75 patients who started with CT upfront, only 11 were able to undergo RT-TMZ afterwards. We then tried to identify predictive factors of radiotherapy completion after upfront chemotherapy in this subgroup. We observed that patients with higher KPS and unilateral tumors were associated with radiotherapy success, opening a new perspective in terms of patient selection. Of note, we observed a higher proportion of grade 3–4 thrombocytopenia than usually reported with temozolomide, which could be related to the advanced age of our population. We observed grade 3–4 thrombocytopenia ($n = 24$), for 21 patients treated by RT-TMZ or maintenance temozolomide and for 3 patients treated with the combination of temozolomide and carmustine. Concerning grade 3–4 neutropenia ($n = 7$), 5 patients received RT-TMZ and 2 patients received carmustine. Grade 3–4 lymphopenia ($n = 15$) was found in patients treated with RT-TMZ. Finally, palliative care remained an option; variable according to culture and health system.

Classical prognostic factors for GBM patients include patient age, performance status and extent of surgical resection.^{35–38} In particular, a recursive partitioning analysis (RPA) undertaken by the RTOG^{37,38} (Radiation Therapy Oncology Group) highlighted 4 prognostic groups for glioblastoma patients (classes III–VI) based on patient age, KPS, neurological function, presence of cognitive

impairment and extent of surgery.⁷ In our study, focusing on BO-GBM, we confirmed the prognostic impact of age and functional status (KPS) in this specific population, as well as the *MGMT* methylation status for progression-free survival. Moreover, we were able to identify a favorable group of patients after RT-TMZ. Interestingly, the KPS was not predictive for longer OS in this sub-group.

Our study has some limitations and the results we found need to be confirmed by other studies. It should be noted that our collection is monocentric, which leads us to interpret the results with caution. However, these first results highlight the need to more focus and include these patients in prospective studies to refine their management and optimize their outcomes.

Conclusion

In conclusion, we studied the characteristics at diagnosis and during follow-up of a population of 137 patients with BO-GBM. This group constitutes a large and heterogeneous population in which one-third of them is amenable to standard of care, with survival outcomes close to one of the patients who underwent surgery. In this study, most patients who have started RT-TMZ are able to complete it. Patients considered unfit for RT-TMZ at diagnosis and treated with chemotherapy upfront may rarely be amenable to RT-TMZ. Although age, functional status, steroid intake, and tumor size contribute to influence the feasibility of RT-TMZ, further works are needed to improve treatment decisions and explore new strategies for patients with BO-GBM.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

Acknowledgments

We thank the ARTC-Sud patients' association (*Association pour le Recherche sur les Tumeurs Cérébrales*). We thank the Cancéropôle PACA.

Conflict of interest statement.

No conflict.

Funding

This work was supported by ARTC-Sud.

Competing interests:

None.

Authors Contributions

Conceptualization (O.C. and E.T.); data curation (V.H., R.A., C.B., G.P., C.C., M.B., D.A., S.B., T.G., D.F.B., I.N., and O.C.); formal analysis (V.H. and E.T.); methodology (O.C. and E.T.); supervision (O.C. and E.T.); writing—original draft (V.H., E.T., and O.C.); writing—review and editing (All authors).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

The study was approved by our local ethics committee in accordance with the Declaration of Helsinki.

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