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Long-term survivors in 976 supratentorial glioblastoma, *IDH*-wildtype patients

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OBJECTIVE Glioblastoma, isocitrate dehydrogenase (*IDH*)–wildtype is the most aggressive glioma with poor outcomes. The authors explored survival rates and factors associated with long-term survival in patients harboring a glioblastoma, *IDH*-wildtype.

METHODS In an observational, retrospective, single-center study, the authors examined the medical records of 976 adults newly diagnosed with supratentorial glioblastomas, *IDH*-wildtype between January 2000 and January 2021. They analyzed clinical-, imaging-, and treatment-related factors associated with 2-year and 5-year survival.

RESULTS The median overall survival was 11.2 months (12.2 months for patients included after 2005 and the introduction of standard combined chemoradiotherapy). The median progression-free survival was 9.4 months (10.0 months for patients included after 2005). Overall, 17.6% of patients reached a 2-year overall survival, while 2.2% of patients reached a 5-year overall survival. Furthermore, 6.6% of patients survived 2 years without progression, while 1.1% of patients survived 5 years without progression. Two factors that were consistently associated with 2-year and 5-year survival were first-line oncological treatment with standard combined chemoradiotherapy and methylated O^6-methylguanine-DNA methyltransferase promoter. Other factors that were significantly associated with 2-year or 5-year survival were age at diagnosis ≤ 60 years, headaches or signs of raised intracranial pressure at diagnosis, cortical contact of contrast enhancement, no contrast enhancement crossing the midline on initial imaging, total or subtotal tumor resection, and a second line of oncological treatment at recurrence. Within 21 cases of 5-year survival, 18 were confirmed to be glioblastomas, *IDH*-wildtype, and 7 of the 5-year survivors (38.9%) had additional genetic alterations: 3 cases had an *FGFR* mutation or fusion, 3 cases had a *PIK3CA* mutation, 1 case had a *PTPN11* mutation, and 1 case had a *PMS2* mutation in the context of constitutional mismatch repair deficiency syndrome.

CONCLUSIONS Five-year overall survival in patients with glioblastoma, *IDH*-wildtype is extremely low. Predictors of a longer survival are mostly treatment factors, emphasizing the importance of a complete oncological treatment plan, when achievable. Glioblastoma, *IDH*-wildtype 5-year survivors could be screened for actionable targets in case of recurrence.

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KEYWORDS glioblastoma; isocitrate dehydrogenase; overall survival; surgery; survival analysis; oncology; tumor

ABBREVIATIONS aOR = adjusted OR; CMMRD = constitutional mismatch repair deficiency; KPS = Karnofsky Performance Status.

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Glioblastoma accounts for 15% of all brain tumors and is the most common primary malignant brain tumor in adults, with an incidence rate of 3.22 per 100,000 person-years.[1]

It also happens to be the most aggressive form of glioma as it is an incurable disease associated with a dismal prognosis. Since 2005, the addition of concurrent and adjuvant temozolomide to a radiation schedule—now referred to as standard combined chemoradiotherapy—produced better overall survival than radiation therapy alone in newly diagnosed glioblastoma patients[2] and extended 5-year survival rates from 5% to 13%.[3]

Despite improvements in standard of care, survival rates for patients with glioblastoma remain low, and there has been minimal progress in extending them since 2005. Several studies have analyzed factors associated with longer survival. Many difficulties come with the subject of glioblastoma survival, the first being the definition of long-term survival, which varies from 2 to 5 years depending on the study.[4–9] Some publications also refer to glioblastoma patients surviving more than 5 years as extreme survivors.[4] Another main issue is the definition of glioblastoma, which has changed since the cIMPACT-NOW 2020 update[47] and later the 2021 WHO classification of CNS tumors.[14] The current definition only includes isocitrate dehydrogenase (*IDH*)–wildtype diffuse astrocytoma with histological or molecular features of glioblastoma. It no longer includes grade 4 astrocytoma, *IDH*-mutant, which has been associated with greater survival rates.[4,7,9–11]

The aim of this study was to measure survival rates and identify clinical-, imaging-, and treatment-related factors associated with prolonged survival in a large and homogeneous group of glioblastoma, *IDH*-wildtype adult patients.

Methods

Study Design and Setting

This retrospective, observational, monocentric study was conducted at a tertiary referral neuro-oncology surgical center between January 2000 and January 2021. The paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[12]

Study Ethics

The local institutional review board approved the study protocol. The requirement to obtain informed consent was waived for this observational retrospective study.

Participants

Inclusion criteria were 1) patients older than 18 years of age at diagnosis; 2) histomolecular diagnosis of glioblastoma, *IDH*-wildtype according to the current WHO classification; 3) supratentorial hemispheric location; and 4) available follow-up data.

We included 976 of the 1027 screened patients, corresponding to 95.1% of all eligible patients. All patients were diagnosed at our institution, through their initial surgery, and documented in a consecutive manner. The study flowchart is detailed in Fig. 1.

Data Collection

Patient- and tumor-related characteristics included sex, age, presenting symptom, headaches or signs of raised intracranial pressure, epileptic seizures, neurological focal deficit, Karnofsky Performance Status (KPS) score, Radiation Therapy Oncology Group recursive partitioning analysis class, tumor side, tumor volume, cortex involvement of contrast enhancement, contrast enhancement crossing the midline, and O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status.

Treatment-related and follow-up characteristics included type of surgical treatment and extent of resection (biopsy, partial removal, subtotal removal, or total removal including supramarginal removal), adjuvant first-line oncological treatment, tumor progression, oncological treatment at progression, and death.

Tumor volume (in cm^3) comprised rim of enhancement and central necrosis and was calculated using segmentation of abnormal signal on preoperative postcontrast T1-weighted sequences, as previously described.[13] The extent of resection was quantified on early (< 48 hours) postoperative postcontrast T1-weighted sequences and was defined as follows: total when no residual abnormality was present, subtotal when a residual abnormality < 10% of the volume of the tumor was present, partial when a residual abnormality > 10% of the volume of the tumor was present, or biopsy.

Histomolecular Diagnosis

The diagnosis of glioblastoma was made according to French guidelines.[15] When faced with a diffuse glioma with astrocytic features, with high rates of cell division, and either microvascular proliferation or central areas of tumor necrosis, systematic screening for *IDH* mutations was carried out using immunohistochemistry targeting *IDH1R132H* since 2008 and was performed retrospectively for earlier cases. For all patients younger than 55 years of age, a sequencing of *IDH1/2* had additionally been performed to identify minor *IDH* mutations. For patients with an *IDH*-wildtype diffuse astrocytoma lacking histological features of glioblastoma, further molecular analyses were performed to identify molecular signatures of glioblastoma.[14] *H3K27M* mutations were tested for and

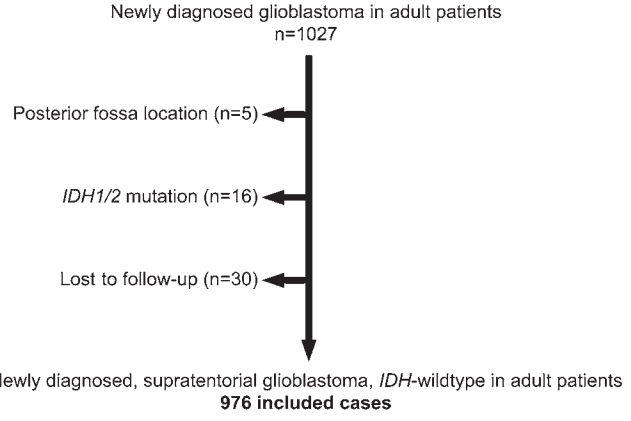

FIG. 1. Flowchart of the study design.

excluded when location (midline), histological morphology, or age (younger) pointed toward the possibility of this differential diagnosis. *MGMT* promoter methylation status analysis was performed using pyrosequencing on clinical request based on practical recommendations (cutoff at 10%).[15]

To explore the possibility that 5-year survivors were initially misdiagnosed with glioblastoma, *IDH*-wildtype, expert neuropathologists (A.T.E. and P.V.) specifically examined these cases and enriched the diagnosis with additional molecular information through DNA sequencing, RNA sequencing, and methylation analyses.

Oncological Treatment

The decision as to whether to perform a particular surgical procedure was decided by the treating senior neurosurgeon based on individual clinical findings, according to his own surgical preferences and to the guidelines from the French Neurosurgical Society.[16–18] Postoperative oncological treatments were decided individually according to practical recommendations[15] during systematic multidisciplinary meetings involving neurosurgeons, neuropathologists, radiologists, oncologists, and radiotherapists.

Outcomes

Overall survival was measured from the date of histomolecular diagnosis to the date of death from any cause. Progression-free survival was measured from the date of histomolecular diagnosis to the date of tumor progression defined according to the Response Assessment in Neuro-Oncology criteria.[19] For surviving patients, these intervals were censored at the date of last follow-up.

The purpose of this study was to identify parameters associated with 2-year and 5-year survival in glioblastoma, *IDH*-wildtype patients.[4–9]

Statistical Analysis

To determine factors impacting 2-year progression-free survival and 2- and 5-year overall survival, univariate analyses were carried out using the chi-square or Fisher's exact test for comparing categorical variables, and the unpaired t-test or Mann-Whitney rank-sum test for continuous variables, as appropriate. Variables associated with a p value < 0.05 in unadjusted analysis were then entered into multivariate logistic regression models. Unadjusted survival curves for overall survival were plotted using the Kaplan-Meier method, using log-rank tests to assess significance for group comparison. Cox proportional hazards models were constructed using a backward stepwise approach, adjusting for predictors previously associated with mortality in univariate analysis, with the final model retaining only the variables significant at the $p < 0.05$ level. Considering the mostly exploratory nature of this study investigating several different outcomes and predictors of various nature, no power calculation had previously been performed and no correction for multiple statistical comparisons was made.

Analyses were performed using JMP software (version 16.2.0, SAS Institute Inc.).

Results

Characteristics of the Patient Cohort

A total of 976 adult patients harboring a newly diagnosed glioblastoma, *IDH*-wildtype (57.8% men; mean age 62 years, range 19–83 years) were included. Two hundred four patients (20.9%) included in this cohort were diagnosed before the standard combined chemoradiotherapy era (2000–2005). The main characteristics of the study sample are detailed in Table 1.

The *IDH*-wildtype mutation status was defined using immunohistochemistry targeting *IDH1R132H* and required *IDH1/2* sequencing for the 254 remaining patients. An *MGMT* promoter methylated status was uncovered in 138 of 324 screened patients (42.6%). The diagnosis was ascertained following biopsy in 428 patients (43.9%) or resection in 548 patients (56.1%). After surgery, 816 patients (83.6%) received an adjuvant first-line oncological treatment: 510 of 976 patients (52.3%) received combined chemoradiotherapy, with 498 of 772 patients (64.5%) diagnosed during the standard combined chemoradiotherapy era (after 2005) receiving combined chemoradiotherapy. In total, 542 of 976 patients (55.5%) were treated with a radiation dose of 60 Gy, while 167 of 976 (17.1%) received between 40 and 59.9 Gy.

Only 1 patient in our cohort received tumor treating fields, as reimbursement for and use of this treatment only became available in France in 2023.

Progression-Free and Overall Survival

During follow-up (mean 14.9 ± 15.5 months), 670 patients (68.6%) experienced a first tumor recurrence. The median progression-free survival was 9.4 months in the whole series (Fig. 2A), improving from 8.3 months to 10.0 months during the combined chemoradiotherapy era (Fig. 2C). Treatments used at recurrence are detailed in Supplementary Table 1.

Of these patients, 398 (40.8%) received a second line of treatment at first recurrence (resection in 70 cases, chemotherapy in 371 cases, and radiotherapy in 56 cases). In total, 189 patients received targeted therapy or immunotherapy as part of second-line treatment (mainly anti-VEGF therapy). Of the 670 patients with a first tumor progression, 199 (30%) had a second tumor recurrence, and 132 of them (20%) received a third line of treatment. Of the 199 patients with a second tumor recurrence, 57 (29%) had a third tumor recurrence, and 30 of them (15%) received a fourth line of treatment. Eleven patients (1.1%) never experienced a tumor recurrence and were alive without progression at a mean of 93.2 ± 20.1 months after histomolecular diagnosis.

During follow-up, 850 patients died from an oncological cause; the remaining patients were still alive at last follow-up. The median overall survival was 11.2 months in the whole series (Fig. 2B) and improved from 9.0 months to 12.2 months during the combined chemoradiotherapy era (Fig. 2D).

Two-Year Overall Survival

Of the 976 patients, 172 (17.6%) were alive 2 years postsurgery. Predictors of 2-year survival are detailed in

TABLE 1. Main characteristics of the study sample (n = 976)

Parameter	Value
Clinical parameters	
Sex	
Male	564 (57.8)
Female	412 (42.2)
Age at Dx, yrs	
Median	63
Mean ± SD	61.67 ± 12.29
Range	19–93
≤60	417 (42.7)
>60	559 (57.3)
Presenting symptom	
Asymptomatic	15 (0.15)
Epileptic seizures	264 (27.0)
Headaches or signs of raised ICP	210 (21.5)
Neurological deficit	487 (49.9)
Headaches or signs of raised ICP at Dx	
No	600 (61.5)
Yes	376 (38.5)
Epileptic seizures at Dx	
No	649 (66.5)
Yes	327 (33.5)
Neurological focal deficit at Dx	
No	266 (27.3)
Yes	710 (72.7)
KPS score at Dx	
Median	80
Mean ± SD	74.87 ± 15.98
Range	0–100
>70	538 (55.1)
70	214 (21.9)
<70	224 (23.0)
RTOG-RPA class	
Median	5
Mean ± SD	4.62 ± 0.81
Range	3–6
3 or 4	440 (45.1)
5 or 6	536 (54.9)
Imaging & histopathological parameters at histological Dx	
Side	
Rt	415 (42.5)
Lt	414 (42.4)
Bilat	147 (15.1)
Tumor vol, cm^3	
Median	29.05
Mean ± SD	41.30 ± 43.55
Range	0–397.12
<30	494 (50.6)
≥30	476 (48.8)
Data missing	6 (0.6)
Imaging & histopathological parameters at histological Dx (*continued*)	
Cortex involvement of CE	
No	226 (23.2)
Yes	731 (74.9)
No CE	19 (1.9)
CE crossing the midline	
No	793 (81.3)
Yes	165 (16.9)
No CE	18 (1.8)
MGMT promoter methylation status	
Unknown	652 (66.8)
Methylated	138 (14.1)
Unmethylated	186 (19.1)
Oncological treatment parameters	
Resection	
Yes	548 (56.1)
No	428 (43.9)
EOR	
Partial	520 (53.3)
Total & subtotal	456 (46.7)
Standard combined CRT as 1st-line treatment	
Yes	510 (52.3)
No	466 (47.7)
2nd line of treatment	
No	252 (25.8)
Yes	398 (40.8)
Died before recurrence	326 (33.4)

CE = contrast enhancement; CRT = chemoradiotherapy; Dx = diagnosis; EOR = extent of resection; ICP = intracranial pressure; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group.
Values are given as number of patients (%) unless otherwise indicated.

Table 2. In multivariable analyses, age at diagnosis ≤ 60 years (adjusted OR [aOR] 1.67, 95% CI 1.08–2.56; p = 0.0214), cortex involvement (aOR 2.51, 95% CI 1.36–4.63; p = 0.0032), no tumor crossing the midline (aOR 11.05, 95% CI 2.57–47.54; p = 0.0012), methylated *MGMT* (aOR 4.74, 95% CI 2.52–8.89; p < 0.0001), subtotal and total resection (aOR 1.86, 95% CI 1.16–2.96; p = 0.0091), first-line treatment with combined chemoradiotherapy (aOR 5.78, 95% CI 3.32–10.40; p < 0.0001), and second line of oncological treatment at tumor recurrence (aOR 1.68, 95% CI 1.03–2.74; p = 0.0357) were independently associated with 2-year survival.

Two-Year Progression-Free Survival

Of the 976 patients, 64 (6.6%) were alive without tumor progression 2 years postsurgery. Predictors of 2-year progression-free survival are detailed in Supplementary Table 2. In multivariable analyses, the presence of headaches or signs of raised intracranial pressure (aOR 1.99, 95% CI

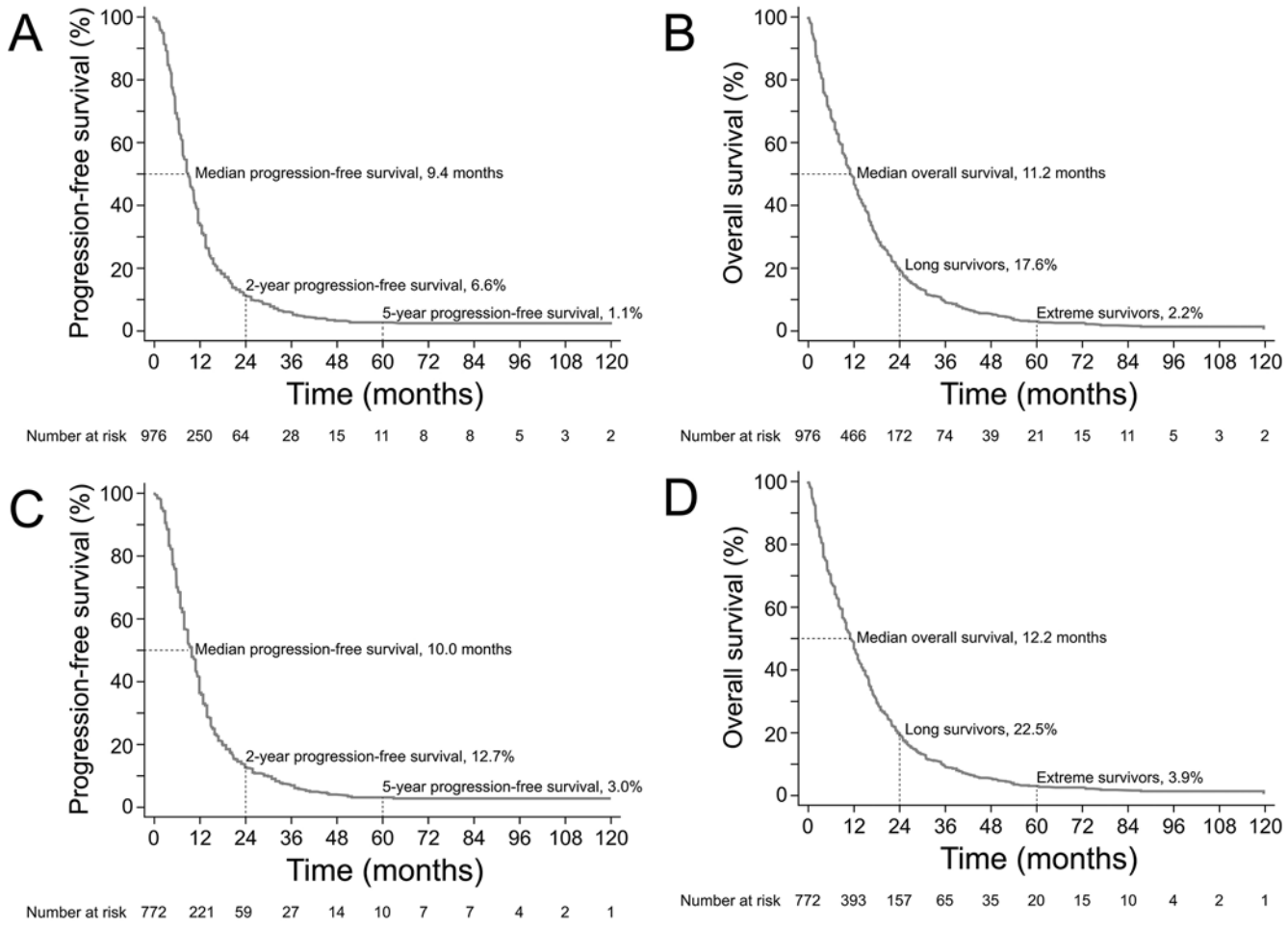

FIG. 2. Kaplan-Meier curves showing progression-free survival (**A**) and overall survival (**B**) in the whole series (n = 976). Kaplan-Meier curves showing progression-free survival (**C**) and overall survival (**D**) in the subset of patients diagnosed during the standard combined chemoradiotherapy era (after 2005) (n = 772).

1.13–3.49; p = 0.0157), cortex involvement (aOR 3.59, 95% CI 1.24–10.36; p = 0.0179), methylated *MGMT* (aOR 6.06, 95% CI 2.47–14.81; p < 0.0001), subtotal and total resection (aOR 3.87, 95% CI 1.81–8.26; p = 0.0005), and first-line treatment with combined chemoradiotherapy (aOR 15.43, 95% CI 4.66–51.09; p < 0.0001) were independently associated with 2-year progression-free survival.

Five-Year Overall Survival

Of the 976 patients, 21 (2.2%) were alive 5 years postsurgery. Eleven were alive without tumor progression, 2 were alive despite tumor progression, and 8 patients died after tumor progression. Characteristics of alive patients 5 years postsurgery are detailed in Table 3. Predictors associated with 5-year overall survival are detailed in Table 4. In multivariable analyses, the presence of headaches or signs of raised intracranial pressure (aOR 4.01, 95% CI 1.50–10.69; p = 0.0056), methylated *MGMT* (aOR 5.24, 95% CI 1.41–19.47; p = 0.0134), and first-line treatment with combined chemoradiotherapy (aOR 15.01, 95% CI 1.92–117.13; p = 0.0097) were independently associated with 5-year survival.

Five-Year Progression-Free Survival

Of the 976 patients, 11 (1.1%) diagnosed were alive without tumor progression at 5 years postsurgery. At last follow-up, their KPS score ranged from 80 to 100. Among the 7 patients employed at the time of diagnosis, all resumed their employment (6 full time, 1 part time). The remaining 4 patients were retired at the time of diagnosis. Characteristics of the alive patients without tumor progression at last follow-up are detailed in Table 3.

Genetic Alterations in Glioblastoma, *IDH*-Wildtype 5-Year Survivors

Complementary histomolecular analyses (targeted DNA sequencing, RNA sequencing, and DNA methylation analysis) were performed on the 21 patients who survived 5 years. Eighteen of 21 cases (85.7%) were confirmed to have glioblastoma, *IDH*-wildtype: 2 of 21 were reclassified as diffuse hemispheric glioma, *H3 G34R*–mutant and 1 of 21 was reclassified as a supratentorial ependymoma, *ZFTA* fusion–positive. Among the 5-year survivors, 7 of 18 (38.9%) harbored additional genetic alterations: 3 had

TABLE 2. Clinical, imaging, and treatment factors of 2-year overall survival (n = 172)

Parameter	No. of Pts (%)	Logistic Regression Model					
		Unadjusted OR			aOR		
		OR	95% CI	p Value	OR	95% CI	p Value
Initial clinical parameters							
Sex							
Female	77 (44.8)	1 (ref)					
Male	95 (55.2)	0.83	0.61–1.15	0.2665			
Age at Dx, yrs							
>60	102 (59.3)	1 (ref)			1 (ref)		
≤60	70 (40.7)	2.26	1.62–3.16	**<0.0001**	1.67	1.08–2.56	**0.0214***
Headaches or signs of raised ICP at Dx							
No	99 (57.6)	1 (ref)					
Yes	73 (42.4)	1.30	0.94–1.79	0.1100			
Epileptic seizures at Dx							
No	92 (53.5)	1 (ref)					
Yes	80 (46.5)	1.92	1.39–2.65	**<0.0001**			
Neurological focal deficit at Dx							
No	69 (40.1)	1 (ref)					
Yes	103 (59.9)	0.47	0.34–0.65	**<0.0001**			
Presenting symptom							
Asymptomatic	4 (2.3)	1 (ref)					
Epileptic seizures	64 (37.2)	1.01	0.31–3.23	0.9870			
Signs of raised ICP	43 (25.0)	0.87	0.27–2.81	0.8118			
Neurological deficit	61 (35.5)	0.42	0.13–1.37	0.1517			
KPS score at Dx							
≥70	156 (90.7)	1 (ref)					
<70	16 (9.3)	0.29	0.17–0.49	**<0.0001**			
RTOG-RPA class							
3 or 4	121 (70.3)	1 (ref)					
5 or 6	51 (29.7)	0.25	0.18–0.36	**<0.0001**			
Imaging parameters							
Side							
Rt	83 (48.3)	1 (ref)					
Lt	85 (49.4)	1.01	0.73–1.40	0.9337			
Bilat	4 (2.3)	0.10	0.04–0.28	**<0.0001**			
Tumor vol, cm^3							
<30	108 (62.8)	1 (ref)					
≥30	64 (37.2)	0.56	0.41–0.78	**0.0006**			
Unknown	0 (0.0)						
CE involving the cortex							
No	16 (9.3)	1 (ref)			1 (ref)		
Yes	151 (87.8)	2.89	1.77–4.72	**<0.0001**	2.51	1.36–4.63	**0.0032***
No CE	5 (2.9)						
CE crossing the midline							
Yes	165 (95.9)	1 (ref)			1 (ref)		
No	2 (1.2)	21.41	5.25–67.26	**<0.0001**	11.05	2.57–47.54	**0.0012***
No CE	5 (2.9)						

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TABLE 2. Clinical, imaging, and treatment factors of 2-year overall survival (n = 172)

Parameter	No. of Pts (%)	Logistic Regression Model					
		Unadjusted OR			aOR		
		OR	95% CI	p Value	OR	95% CI	p Value
Treatment parameters							
Resection							
No	31 (18.0)	1 (ref)					
Yes	141 (82.0)	4.72	3.17–7.04	**<0.0001**			
EOR							
Partial	41 (23.8)	1 (ref)			1 (ref)		
Total & subtotal	131 (76.2)	4.91	3.41–7.08	**<0.0001**	1.86	1.16–2.96	**0.0091***
Standard combined CRT as 1st-line treatment							
No	19 (11.0)	1 (ref)			1 (ref)		
Yes	153 (89.0)	9.40	5.90–14.98	**<0.0001**	5.78	3.22–10.40	**<0.0001***
MGMT promoter methylation status							
Unmethylated	28 (16.3)	1 (ref)			1 (ref)		
Methylated	55 (32.0)	3.89	2.33–6.52	**<0.0001**	4.74	2.52–8.89	**<0.0001***
Unknown	89 (51.7)	0.68	0.58–1.43	0.6819			
2nd line of treatment at recurrence							
No	35 (23.3)	1 (ref)			1 (ref)		
Yes	115 76.7)	2.59	1.72–3.89	**<0.0001**	1.68	1.03–2.74	**0.0357***

Pts = patients.
Boldface type indicates statistical significance.
* Variable entered in the multivariable backward stepwise logistic regression model.

FGFR alterations (case 17 had an *FGFR3::STK4* fusion, case 18 had an *FGFR3::TACC3* fusion, and case 6 had an *FGFR1* mutation). Additionally, 3 cases (cases 5, 11, and 12) had a *PIK3CA* mutation, 1 (case 12) had a *PTPN11* mutation, and 1 (case 2) held a *PMS2* inactivating mutation in the context of constitutional mismatch repair deficiency (CMMRD) syndrome.

Discussion

Key Results

In this retrospective, monocentric cohort of 976 adult patients harboring a newly diagnosed supratentorial glioblastoma, *IDH*-wildtype, we showed that 1) median progression-free and overall survival were 9.4 and 11.2 months, respectively; 2) 2-year progression-free and overall survival rates were 6.6% and 17.6%, respectively; 3) 5-year progression-free and overall survival rates were 1.1% and 2.2%, respectively; 4) independent predictors of 2-year overall survival were younger age at diagnosis, cortex involvement, absence of tumor crossing the midline, methylated *MGMT*, subtotal or total resection, first-line treatment with combined chemoradiotherapy, and second line of oncological treatment at tumor recurrence; 5) independent predictors of 2-year progression-free survival were presence of headaches or signs of raised intracranial pressure, cortex involvement, methylated *MGMT*, subtotal or total resection, and first-line treatment with combined chemoradiotherapy; 6) independent predictors of 5-year survival were presence of headaches or signs of raised intracranial pressure, methylated *MGMT*, and first-line treatment with combined chemoradiotherapy; 7) and 7 of 18 (38.9%) 5-year survivors harbored additional genetic alterations (*FGFR* alterations, *PIK3CA* mutations, *PTPN11* mutation, and *PMS2* mutation).

Interpretation

Prolonged survival in glioblastoma has been previously reported.[20–31] The assessment of survival rates and the identification of predictors for prolonged survival are essential and require studies based on large series of patients using the 2021 WHO classification criteria. Previous studies have reported median overall survival ranging from 12 to 14 months and 2-year overall survival rates ranging from 13% to 32%, aligning with the present median overall survival of 11.2 months and 2-year overall survival rate of 17.6%.[4,6,8,32,33] Contrarily, we report a 5-year overall survival rate of only 2.2%, whereas previous studies have reported a 5-year overall survival rate ranging from 4% to 26%.[6,8,32] The available literature, although comprised of well-conducted and interesting work, is limited by the fact that most studies included grade 4 astrocytoma, *IDH*-mutant patients in their analyses. Because this group of patients has longer survival rates, their exclusion in our study could explain the lower proportion of 5-year survivors we observed in our glioblastoma, *IDH*-wildtype cohort. The exclusion of *IDH*-mutant cases would also suggest that the overall prognosis for glioblastoma, *IDH*-wildtype, including untreated and treated patients, is worse than what has

TABLE 3. Clinical, imaging, histomolecular, and treatment characteristics of 5-year survivors without (n = 11) or despite (n = 10) tumor progression

Case No.	Sex	Age at Dx, yrs	KPS Score at Dx	RTOG-RPA Class at Dx	Tumor Location	Midline Crossing	Cortex Involvement	Tumor Vol, cm^3	EOR	*MGMT* Promoter Methylation Status (%)	Standard Combined CRT (no. of cycles)	KPS Score at Last FU	Employment at Last FU	Tumor Progression	Time to Progression, mos	OS, mos	WHO 2021 Reclassification
Alive w/o tumor progression																	
1	M	21	80	4	Rt temporal	No	Yes	67.0	Total	Methylated (38)	Yes (6)	100	Full time	No	—	63.0	HGG *H3 G34R*
2	F	22	90	3	Lt frontal	No	Yes	81.0	Total	NA	Yes (6)	90	Full time	No	—	119.8	GBM, *IDH*-WT
3	M	26	90	3	Rt parietal	No	Yes	103.0	Total	Unmethylated (2)	Yes (6)	90	Full time	No	—	90.0	ST EPN, *ZFTA* fused
4	F	27	90	3	Lt frontal	No	Yes	0.5	Partial	NA	Yes (6)	90	Full time	No	—	65.0	HGG *H3 G34R*
5	F	29	90	3	Rt frontal	No	Yes	37.1	Total	NA	Yes (6)	100	Full time	No	—	94.0	GBM, *IDH*-WT
6	M	32	100	3	Rt frontal	No	Yes	53.5	Total	Unmethylated (7)	Yes (10)	100	Full time	No	—	125.0	GBM, *IDH*-WT
7	M	59	70	4	Rt parietal	No	Yes	113.4	Subtotal	NA	Yes (12)	80	Retired	No	—	66.0	GBM, *IDH*-WT
8	F	60	80	4	Rt occipital	No	Yes	16.9	Subtotal	Methylated (22)	Yes (12)	90	Part time	No	—	105.0	GBM, *IDH*-WT
9	F	65	90	4	Lt temporal	No	Yes	32.7	Subtotal	Methylated (18)	Yes (12)	90	Retired	No	—	106.0	GBM, *IDH*-WT
10	F	67	90	4	Rt parietal	No	Yes	58.8	Total	Methylated (22)	Yes (6)	90	Retired	No	—	96.0	GBM, *IDH*-WT
11	F	72	90	5	Lt temporal	No	Yes	1.2	Biopsy	Methylated (33)	Yes (9)	90	Retired	No	—	85.5	GBM, *IDH*-WT
Alive despite tumor progression																	
12	M	32	80	4	Lt occipital	No	Yes	32.0	Subtotal	Methylated (14)	Yes (36)	90	—*	Yes	37.0	74.9	GBM, *IDH*-WT
13	F	48	90	3	Rt frontal	No	Yes	25.3	Total	Unmethylated (2)	Yes (6)	90	—*	Yes	51.0	77.0	GBM, *IDH*-WT
14	F	52	90	4	Rt occipital	No	Yes	130.9	Total	Methylated (34)	Yes (6)	80	Sick leave	Yes	9.0	92.0	GBM, *IDH*-WT
15	M	52	90	5	Rt temporal	No	No	111.2	Biopsy	NA	Yes (5)	90	—*	Yes	12.5	63.4	GBM, *IDH*-WT

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TABLE 3. Clinical, imaging, histomolecular, and treatment characteristics of 5-year survivors without (n = 11) or despite (n = 10) tumor progression

Case No.	Sex	Age at Dx, yrs	KPS Score at Dx	RTOG-RPA Class at Dx	Tumor Location	Midline Crossing	Cortex Involvement	Tumor Vol, cm^3	EOR	*MGMT* Promoter Methylation Status (%)	Standard Combined CRT (no. of cycles)	KPS Score at Last FU	Employment at Last FU	Tumor Progression	Time to Progression, mos	OS, mos	WHO 2021 Reclassification
16	M	53	80	5	Lt temporal	No	Yes	1.2	Biopsy	NA	Yes (NA)	80	—*	Yes	16.0	72.5	GBM, *IDH*-WT
17	F	57	90	4	Rt frontal	No	Yes	9.1	Partial	Methylated (28)	Yes (3)	70	Sick leave	Yes	26.0	63.5	GBM, *IDH*-WT
18	F	58	100	5	Lt insular	No	Yes	5.6	Biopsy	NA	Yes (3)	70	—*	Yes	7.0	87.5	GBM, *IDH*-WT
19	M	59	90	4	Rt frontal	No	No	17.9	Total	Methylated (16)	Yes (16)	90	—*	Yes	52.0	81.2	GBM, *IDH*-WT
20	F	64	80	4	Rt frontal	No	Yes	226.8	Total	Methylated (20)	Yes (11)	80	—*	Yes	24.4	60.7	GBM, *IDH*-WT
21	M	77	90	4	Rt temporal	No	No	3.8	Total	Methylated (25)	Yes (12)	90	—*	Yes	38.4	60.5	GBM, *IDH*-WT

GBM = glioblastoma; FU = follow-up; HGG = high-grade glioma; NA = not available; OS = overall survival; ST EPN = supratentorial ependymoma; WT = wildtype; — = not applicable.
* Patient died.

been previously reported and that 5-year survival is an exception in these patients.

Previous studies have identified younger age, female sex, higher KPS score, gross-total resection with adjuvant combined chemoradiotherapy, and methylated *MGMT* promoter as being associated with longer survival.[4,6,8,10,34–36] In 2023, the European Organization for Research and Treatment of Cancer published the first results of a registry study of patients with glioblastoma surviving at least 5 years and found that patients without any recurrence experienced longer median overall survival than patients with one or more recurrences and that they had a high rate of unmethylated *MGMT* promoter.[37]

Consistent with previous reports, younger age was a significant predictor of long-term survival in our cohort, but sex and KPS score were not. Interestingly, in the present series, patients presenting with headaches at diagnosis tended to have higher survival rates, possibly because such patients had tumors that were diagnosed early, less frequently located in eloquent brain regions, and more likely to receive extensive resection. Regarding tumor characteristics, the unilateral aspect, but not the side or tumor volume, was a predictor of prolonged survival. Cortex involvement and absence of midline crossing, both suggesting the superficial aspect of the tumor, were significant predictors of prolonged survival. This finding is in accordance with a previous study that reported the lack of subventricular zone involvement as a predictor for longer survival.[8] Oncological treatments, including extent of resection and combined chemoradiotherapy, were predictors of prolonged survival independent of increased temozolomide sensitivity linked to methylated *MGMT*. Unlike clinical and radiological factors, treatment factors and methylated *MGMT* were significantly associated with both progression-free and overall survival in all analyses. This finding suggests the positive impact of the therapeutic management: maximal resection plus combined chemoradiotherapy should be intended, whenever feasible, for each patient harboring a supratentorial glioblastoma, *IDH*-wildtype, whatever the *MGMT* promoter methylation status. Regarding predictors associated with dismal outcomes, it seems important to acknowledge that several patients with such unfavorable prognostic factors were among long-term survivors: 70 of the 2-year survivors (n =172) and 5 of the 5-year survivors (n = 21) were older than 60 years of age at diagnosis; 31 of the 2-year survivors and 4 of the 5-year survivors only had a biopsy; and 28 of the 2-year survivors and 3 of the 5-year survivors had an identified unmethylated *MGMT*. These findings support the approach of offering aggressive, maximal treatment to all patients when feasible, regardless of their clinical, radiological, or molecular tumor characteristics. This is especially relevant for elderly patients, who tend to be offered less aggressive options of first-line treatment and also receive oncological treatments less frequently at recurrence.[38]

The 21 long-term survivors, harboring an overall survival ≥ 5 years, were investigated for particular molecular profiles. Two patients were reclassified as having diffuse hemispheric glioma, *H3 G34R*–mutant and 1 patient was reclassified as having a supratentorial ependymoma, *ZFTA* fusion–positive. This finding was surprising given

TABLE 4. Clinical, imaging, and treatment factors of 5-year overall survival (n = 21)

Parameter	No. of Pts (%)	Logistic Regression Model					
		Unadjusted OR			aOR		
		OR	95% CI	p Value	OR	95% CI	p Value
Initial clinical parameters							
Sex							
Female	12 (57.1)	1 (ref)					
Male	9 (42.9)	0.44	0.19–1.19	0.0555			
Age at Dx, yrs							
>60	16 (76.2)	1 (ref)					
≤60	5 (23.8)	4.42	1.61–12.17	**0.0011**			
Headaches or signs of raised ICP							
No	6 (28.6)	1 (ref)			1 (ref)		
Yes	15 (71.4)	3.97	1.63–9.67	**0.0024**	4.01	1.50–10.69	**0.0056***
Epileptic seizures							
No	13 (61.9)	1 (ref)					
Yes	8 (38.1)	1.22	0.53–2.82	0.6389			
Neurological focal deficit							
No	9 (42.9)	1 (ref)					
Yes	12 (57.1)	0.52	0.23–1.18	0.1157			
Presenting symptom							
Asymptomatic	0 (0)	1 (ref)					
Epileptic seizures	5 (23.8)						
Signs of raised ICP	12 (57.1)						
Neurological deficit	4 (19.0)						
KPS score at Dx							
≥70	21 (100)	1 (ref)					
<70	0 (0)						
RTOG-RPA class							
3 or 4	17 (81.0)	1 (ref)					
5 or 6	4 (19.0)	0.16	0.05–0.46				
Imaging parameters							
Side							
Rt	14 (66.7)	1 (ref)					
Lt	7 (33.3)	0.49	0.21–1.16				
Bilat	0 (0)						
Tumor vol, cm^3							
<30	9 (42.9)	1 (ref)					
≥30	12 (57.1)	1.24	0.55–2.79	0.6036			
Unknown	0 (0)						
CE involving the cortex							
No	3 (14.3)	1 (ref)					
Yes	18 (85.7)	1.57	0.53–4.65	0.4112			
CE crossing the midline							
Yes	0 (0)						
No	21 (100)						
Treatment parameters							
Resection							
No	4 (19.0)	1 (ref)					
Yes	17 (81.0)	4.09	1.39–12.06	**0.0106**			

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TABLE 4. Clinical, imaging, and treatment factors of 5-year overall survival (n = 21)

Parameter	No. of Pts (%)	Logistic Regression Model					
		Unadjusted OR			aOR		
		OR	95% CI	p Value	OR	95% CI	p Value
Treatment parameters (*continued*)							
EOR							
Partial	6 (28.6)	1 (ref)					
Total & subtotal	15 (71.4)	3.55	1.40–9.01	**0.0077**			
Standard combined CRT as 1st-line treatment							
No	1 (4.8)	1 (ref)			1 (ref)		
Yes	20 (95.2)	21.62	2.91–160.75	**0.0027**	15.01	1.92–117.13	**0.0097***
MGMT promoter methylation status							
Unmethylated	3 (14.3)	1 (ref)			1 (ref)		
Methylated	11 (52.4)	5.59	1.55–20.22	**0.0086**	5.24	1.41–19.47	**0.0134***
Unknown	7 (33.3)	0.82	0.22–3.05	0.7635			
2nd line of treatment at recurrence							
No	4 (36.4)	1 (ref)					
Yes	7 (63.6)	1.40	0.43–4.59	0.5789			

Boldface type indicates statistical significance.
* Variable entered in the multivariable backward stepwise logistic regression model.

that both diagnoses are also associated with a poor prognosis.[39] The remaining 18 long-term survivors were confirmed to have glioblastoma, *IDH*-wildtype. Three cases harbored *FGFR* alterations, 3 held a *PIK3CA* mutation, 1 had a *PTPN11* mutation, and 1 case had a *PMS2* mutation in the context of CMMRD syndrome. Because we do not have access to the same molecular information for the short-term survivors in our cohort, we attempted to compare our glioblastoma 5-year survivors with glioblastoma patients within The Cancer Genome Atlas database.[40] We noted that a *PIK3CA* mutation was commonly found in 9% of a dataset of 291 glioblastoma[41] patients, but < 1% had an *FGFR1* mutation, 3% had a genetic alteration of *FGFR3*, and < 1% had a *PTPN11* mutation. Additionally, the oncogenic *FGFR3::TACC3* fusion has been previously described in a subset of glioblastoma cases, and several studies have suggested that it provides a survival benefit.[42–45] Similarly, *PTPN11* is a gene promoting MAPK signaling, and mutations in this gene have been shown to be enriched in recurrent glioblastoma responding to anti-PD-1 immunotherapy.[46]

Additional reports in short- and long-term survivors are necessary to make conclusions regarding the diagnostic and therapeutic implications of these alterations, but these findings suggest a more frequent representation of genetic variants in 5-year survivors, which is of practical importance because these patients could be screened for an actionable target in case of tumor recurrence.

Generalizability

The strengths of this study include 1) the homogeneous collection of data on glioblastoma, *IDH*-wildtype in adults with a central histomolecular review and a dedicated comprehensive analysis of 5-year survivors; 2) the exclusion of grade 4 astrocytoma, *IDH*-mutant associated with higher survival; 3) the large study sample of 976 patients, one of the largest cohorts ever studied on glioblastoma, *IDH*-wildtype; 4) the long-term follow-up with minor loss to follow-up, allowing survival analyses with inclusion of multiple variables of interest and confounders; and 5) the concomitant search for clinical, radiological, molecular, and treatment factors associated with prolonged survival.

Limitations

Limitations arose from the observational, retrospective, monocentric nature of the study and the exploratory design of statistical analyses. Potential biases resulted from the fact that this study relied heavily on documentation and from missing data, particularly regarding *MGMT* promoter methylation status. Missing data were controlled by their systematic incorporation in statistical analyses as a specific category. The large time span for case inclusion induced biases in survival analyses due to the evolution of therapeutic management over time (standard combined chemoradiotherapy since 2005), but the varying standards of care over time were incorporated in statistical models. The absence of assessment for additional genetic alterations in non–5-year survivors is also a limitation in this study. By focusing on newly diagnosed supratentorial glioblastoma, *IDH*-wildtype in adults, the present results cannot be extrapolated to the pediatric population or to the posterior fossa and spinal locations. Therefore, these findings should be interpreted with full consideration of the retrospective and exploratory nature of the analyses and thus should be validated within prospective large databases.

Conclusions

Prolonged survival in adult patients with glioblastoma, *IDH*-wildtype is an exception, with a 5-year overall survival rate of 2.2%. Predictors of prolonged survival are mostly treatment factors, emphasizing the importance of maximal resection followed by combined chemoradiotherapy, when achievable. Additionally, glioblastoma, *IDH*-wildtype 5-year survivors could be screened for actionable targets in case of tumor recurrence.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Pallud, Aboubakr, Roux. Acquisition of data: Pallud, Aboubakr, Moiraghi, Elia, Roux, Bedioui, Parraga, Benevello, Dezamis, Oppenheim, Varlet. Analysis and interpretation of data: Pallud, Aboubakr, Moiraghi, Tauziede-Espariat, Roux, Simboli, Fathallah, Oppenheim, Zanello. Drafting the article: Pallud, Aboubakr, Elia, Roux, Simboli, Muto, Zanello. Critically revising the article: Pallud, Aboubakr, Moiraghi, Elia, Roux, Leclerc, Planet, Bedioui, Simboli, Dhermain, Fathallah, Chrétien, Dezamis, Oppenheim, Varlet, Zanello. Reviewed submitted version of manuscript: Pallud, Aboubakr, Moiraghi, Roux, Simboli, Dhermain, Fathallah, Muto, Oppenheim, Zanello. Approved the final version of the manuscript on behalf of all authors: Pallud. Statistical analysis: Pallud, Aboubakr. Administrative/technical/material support: Pallud, Elia. Study supervision: Pallud.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables 1 and 2. https://thejns.org/doi/suppl/10.3171/2024.5.JNS24393.

Data Availability

We support data sharing within the restrictions of the ethical approval permissions. Requests can be made to the corresponding author.

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