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Original Research

Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY Brain Tumor Funders' Collaborative Consortium (EORTC 1419)

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Abstract ***Background:*** Median survival with glioblastoma remains in the range of 12 months on population levels. Only few patients survive for more than 5 years. Patient and disease features associated with long-term survival remain poorly defined.
Methods: European Organization for Research and Treatment of Cancer (EORTC) 1419 (ETERNITY) is a registry study supported by the Brain Tumor Funders Collaborative in the US and the EORTC Brain Tumor Group. Patients with glioblastoma surviving at least 5 years from diagnosis were identified at 24 sites in Europe, US, and Australia. In patients with isocitrate dehydrogenase (IDH) wildtype tumours, prognostic factors were analysed using the Kaplan-Meier method and the Cox proportional hazards model. A population-based reference cohort was obtained from the Cantonal cancer registry Zurich.
Results: At the database lock of July 2020, 280 patients with histologically centrally confirmed glioblastoma (189 IDH wildtype, 80 IDH mutant, 11 incompletely characterised) had been registered. In the IDH wildtype population, median age was 56 years (range 24–78 years), 96 patients (50.8%) were female, 139 patients (74.3%) had tumours with O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation. Median overall survival

was 9.9 years (95% confidence interval [95% CI] 7.9–11.9). Patients without recurrence experienced longer median survival (not reached) than patients with one or more recurrences (8.92 years) ($p < 0.001$) and had a high rate (48.8%) of MGMT promoter-unmethylated tumours.

Conclusions: Freedom from progression is a powerful predictor of overall survival in long-term survivors with glioblastoma. Patients without relapse often have *MGMT* promoter-unmethylated glioblastoma and may represent a distinct subtype of glioblastoma.

1. Introduction

Among primary brain tumours in adults, isocitrate dehydrogenase 1 or 2 (IDH) wildtype glioblastoma is the most malignant with one of the worst overall prognoses across cancer entities. The median overall survival at a population level remains in the range of 12 months despite multimodal therapy including surgery, radiotherapy and several approaches of pharmacotherapy [1,2]. Less than 5% of patients survive for more than five years [3] and many of these patients suffer from irreversible neurological impairment [4]. The true number of long-term survivors may be even lower since tumours of long-term surviving patients are often reclassified upon central histological and molecular diagnostic re-evaluation. The phenomenon of long-term survival with glioblastoma remains incompletely understood [5,6]. Factors usually associated with longer survival include young age, good Karnofsky performance status (KPS) at diagnosis, and O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation [1,2,7,8].

MGMT promoter methylation, a predictive marker of benefit from alkylating agents [7,9–11], became associated with longer survival with the introduction of temozolomide, although lack of *MGMT* promoter methylation does not exclude long-term survival. Yet, *MGMT* promoter methylation is significantly more common in long-term survivors of IDH wildtype glioblastoma than in unselected patient populations [12,6,13]. Overall, despite several attempts to define specific determinants of long-term survival in glioblastoma, no distinct constellation of characteristics has emerged so far beyond the factors summarised above that are uniformly associated with longer survival, but not distinctly linked to long-term survival.

The association of the IDH status with long-term survival has made the analyses of long-term survival with glioblastoma more complex. Patients with the former diagnosis of IDH mutant glioblastomas are known to survive longer than patients with IDH wildtype glioblastomas [14,15]. The rate of IDH mutations among five-year survivors of glioblastoma of 45% [13] was much higher than the rate of approximately 5% expected in an unselected glioblastoma population. With the 5th edition of the World Health Organization (WHO) classification of central nervous system tumors 2021 [16], IDH mutant astrocytic gliomas showing histological features of glioblastoma are no longer considered as 'glioblastoma, IDH mutant' but as 'astrocytoma, IDH mutant, CNS WHO grade 4' to indicate that these tumours are biologically and prognostically distinct from IDH wildtype glioblastoma [17,18]. Future studies on long-term survival will need to integrate new disease definitions, making comparisons with historical studies challenging. Therefore, in this study, we focused on IDH wildtype glioblastoma, with the aim to define and characterise clinical determinants of long-term survival in a patient population corresponding to the WHO 2021 definition of glioblastoma. For this purpose, a comprehensive multinational approach was undertaken to assemble clinical and molecular data from 189 IDH wildtype glioblastoma patients who survived for more than 5 years from diagnosis out of 273 patients originally diagnosed with IDH wildtype or IDH mutant glioblastoma according to WHO 2016 criteria [19]. To identify clinical prognostic features associated with long-term survival, these patients were compared with a population-based contemporary cohort of IDH wildtype glioblastoma patients [20,21].

2. Material and methods

2.1. Patient identification for the long-term survivor cohort

Patients aged 18 years or more at the time of diagnosis of glioblastoma, who survived for at least 5 years, were included. All tumours were centrally reviewed at the Institute of Neuropathology in Düsseldorf, Germany (G.R., J.F.). Patients without a centrally confirmed histological diagnosis of IDH wildtype glioblastoma or IDH mutant glioblastoma were excluded. Patients were registered and coded in the EORTC database. Patients alive at registration provided written informed consent. The study is registered at clinicaltrials.org (NCT03770468).

2.2. Central pathology review of the long-term survivor cohort

Tumours identified as glioblastoma according to the reports of the local pathology departments underwent central pathology review and were histologically and molecularly evaluated according to the criteria of the

WHO classification of central nervous system tumors 2016 [19]. IDH mutant tumours that fulfilled the WHO 2016 histopathological criteria of glioblastoma were included in the study. However, the correlative analyses reported here were conducted after stratification of the patient populations by IDH mutation status and restricted to the patients with centrally confirmed IDH wildtype glioblastomas. Formalin-fixed and paraffin-embedded (FFPE) tissue samples were available from all patients. For histological review, tumour tissue sections were routinely stained for hematoxylin-eosin and silver impregnation for reticulin fibres. In addition, immunohistochemical stainings were performed with antibodies detecting glial fibrillary acidic protein (GFAP, clone ZR356, ZETA Corporation, Arcadia, CA), IDH-R132H (clone H09, Dianova, Hamburg, Germany), and alpha-thalassaemia/mental retardation syndrome, X-linked protein (ATRX, clone ZR244, ZETA Corporation). Immunohistochemistry was carried out on the Dako autostainer link 48 (Agilent Technologies, Glostrup, Denmark) using the EnVision FLEX horseradish peroxidase-based detection system with 3.3-diaminobenzidine as chromogen (Agilent Technologies). Immunohistochemical sections were counterstained with hemalum and evaluated by two experienced neuropathologists (G.R., J.F.). All tumours that were IDH^{R132H}-negative upon immunohistochemistry were sequenced for mutations affecting the hotspot codons $IDH1^{R132}$ or $IDH2^{R172}$ [22,23]. The *MGMT* promoter methylation status was centrally determined by methylation-specific polymerase chain reaction (PCR) and/or DNA pyrosequencing [24,25].

2.3. Clinical data capture for the long-term survivor cohort

The following clinical information was collected: medical history, epidemiological factors, socio-economical, occupational and life style-associated factors, histological subtypes according to the WHO classification 2016 (classic glioblastoma, giant cell glioblastoma, gliosarcoma, epithelioid glioblastoma) [19], first-line treatment, and treatment at any recurrence. Recurrence was defined operationally as progression or recurrence as documented in the electronic case report form (eCRF) or a further therapeutic intervention since it was not feasible to centrally review progression.

2.4. Description of the reference cohort from the Canton of Zurich

Data of all patients aged 18 years or older diagnosed with glioblastoma in the years 2005–2014 who were inhabitants of the Canton of Zürich, Switzerland were retrieved from the cantonal cancer registry [20,21]. This cohort was used as a reference to compare baseline characteristics and outcomes of long-term survivors with a contemporary population-based cohort. Per WHO 2016 recommendations, patients aged younger than 55 years underwent sequencing for rare IDH mutations if $IDH1^{R132H}$ immunohistochemistry was negative. One hundred forty-nine patients aged 55 or more had the IDH status assessed by immunohistochemistry only. Clinical and treatment data were extracted from medical records. Thirteen patients surviving for 5 years or more were excluded from the control cohort; 8 of these patients are included in the long-term survivor cohort.

2.5. Ethics

The EORTC 1419 study was approved by the central Ethics Board of the Canton of Zurich (KEK 2014-0555) and locally at each participating site. The control cohort study was also approved by the Ethics Board of the Canton of Zurich (KEK-ZH-Nr. 2009-0135/1; KEK-ZH-Nr. 2015-0437) [20,21].

2.6. Data availability statement

Coded data will be made available upon reasonable request to other qualified investigators for purposes of replicating results.

2.7. Statistical analyses

Demographic, clinical, and molecular data are presented with descriptive statistics. The Chi-square test was performed for analysis of nominal variables, and the Mann-Whitney U test was used for the comparison of ordinal variables between groups. Progression-free survival was defined as the time between the date of diagnostic surgery and the date of first progression. Overall survival was defined as the time between the date of diagnostic surgery and the date of death. Kaplan-Meier curves were compared using the log-rank test. Patients without an event were censored at date of last follow-up before the database lock. Patients of the control cohort were also censored at last follow-up. Univariate and multivariate analyses were done using Cox regression. The multivariate model was applied to all patients who had complete information on all tested co-variables, that is, no missing data imputation technique was applied. For statistical analysis, SPSS Version 28 was used (SPSS IBM Corp., Armonk, NY, USA), and a p value of 0.05 was considered statistically significant.

3. Results

3.1. Patient and tumour characteristics of the long-term survivor cohort

At the cut-off date of June 24, 2020, 470 patients were registered, central reference histology was available for 347

patients (73.8%), and a total of 280 patients of these (82.4%) were confirmed as astrocytic gliomas corresponding to CNS WHO grade 4 upon central histology review, including 189 patients with glioblastoma, IDH wildtype, and 80 patients with glioblastoma, IDH mutant according to the WHO classification 2016 [19], now astrocytoma, IDH mutant, CNS WHO grade 4. Seven tumours were IDH^{R132H} wildtype by immunohistochemistry, but were not sequenced for lack of material, and 4 were tumours not otherwise specified according to the WHO classification 2021, also for lack of material [16]. The remaining 67 tumours were classified as astrocytoma, IDH mutant, CNS WHO grade 2 or 3 (n = 24), oligodendroglioma, IDH mutant and 1p/19q co-deleted, CNS WHO grade 2 or 3 (n = 16), or other less common diagnoses (n = 23); 4 samples were classified as non-neoplastic tissue, that is, lacked residual tumour tissue. For this report, only patients with centrally confirmed IDH wildtype glioblastoma were considered for most analyses, unless indicated otherwise.

Of the 189 patients with IDH wildtype glioblastoma diagnosed between 1999 and 2014 (Supplementary Fig. 1), 51 patients (27.0%) were younger than 50 years, 96 patients (50.8%) were female, and 134 patients (76.6%) had a gross total resection at first surgery. Histologically, this group included one epithelioid glioblastoma, two gliosarcomas, five giant cell glioblastomas, and 181 glioblastomas with classic histology. *MGMT* promoter methylation was noted in 139 tumours (74.3%). Compared with patients with IDH mutant astrocytoma, CNS WHO grade 4, patients with glioblastoma, IDH wildtype, were older, had more often received a gross total resection, and had tumours which were more frequently located in the temporal lobe and less frequently in the frontal lobe. Compared with the population-based cohort of IDH wildtype glioblastoma patients, the long-term survivors were younger, more often female, had a better KPS at diagnosis and had undergone a gross total resection more frequently. In addition, the tumours of long-term survivors more often showed *MGMT* promoter methylation (Table 1).

3.2. Personal and medical history

Among the long-term surviving patients with IDH wildtype glioblastoma, 125 of 153 evaluable patients (81.7%) were married at the time of diagnosis and 116 of 143 evaluable patients (81.1%) had children (Table S1). Inherited or autoimmune diseases were reported in 5 of 138 (3.6%) and 2 of 147 (1.4%) evaluable patients, respectively. Among the patients with the respective information being documented, 76 of 118 patients (64.4%) never smoked and 57 of 117 patients (48.7%) reportedly never consumed alcohol. The occurrence of other tumours before or after brain tumour diagnosis was reported in 16 of 155 evaluable patients (10.3%). Brain tumours in immediate kin were documented in 8 of 141 evaluable patients (5.7%). Seizures were a presenting symptom in 67 of 158 patients (42.4%), with 7 patients (4.4%) having experienced seizures more than 2 years before diagnosis. None of these factors was associated with recurrence (Tables S1 and S2).

3.3. Treatment regimens

Information on first-line treatment was documented for 174 of 189 patients with IDH wildtype glioblastoma (Table 2). Among these, 146 patients (83.9%) had received standard first-line therapy with temozolomide and radiotherapy followed by temozolomide maintenance therapy [26]. Repeat surgery and re-radiation were done in 76 patients (40.2%) and 54 patients (28.6%). More than half of patients were re-exposed to alkylating agents during the disease course, with 102 patients (54.0%) receiving temozolomide, and 68 patients (36.0%) receiving a nitrosourea compound. Bevacizumab was given to 61 patients (32.3%) (Table 2). Compared with the population-based IDH wildtype glioblastoma patient cohort, the long-term survivors more often received a focal treatment at recurrence, for example, surgery (40.2% versus 11.4%) or radiotherapy (28.6% versus 5.9%) (Table 2). Forty-one patients (22.8%) experienced no progression with a statistically unreached median survival. Fifty-five patients (29.1%) experienced 3 or more recurrences. Patients with any recurrence versus no recurrence did not differ by age, sex, KPS or extent of resection; however, *MGMT* promoter methylation was less frequent in patients with no recurrence (Table 3).

3.4. Outcome

Among the IDH wildtype glioblastoma long-term survivors, 135 patients (76.7%) experienced progression and 93 patients (49.2%) have died. Median progression-free survival was 4.6 years (95% confidence interval [95% CI] 3.9–5.3). It was 4.4 years (95% CI 3.7–5.1) for patients with *MGMT* promoter-methylated tumours and 5.3 years (95% CI 1.7–8.8) for patients with *MGMT* promoter-unmethylated tumours ($p = 0.005$). Indeed, unmethylated *MGMT* promoter methylation status remained associated with progression-free survival on multivariate analysis (Table S3).

Median overall survival for the entire IDH wildtype cohort was 9.9 years (95% CI 7.9–11.9). It was 9.8 years (95% CI 7.9–11.8) for patients with *MGMT* promoter-methylated tumours and 11.7 years (95% CI not defined) for patients with *MGMT* promoter-unmethylated tumours ($p = 0.536$). Fifty patients (26.5%) survived 10 years or longer, with 45 of them being alive at the time of data base lock. In the Canton of Zurich control cohort of IDH wildtype glioblastoma patients, the median progression-free survival was 4.7 months (95% CI 4.2–5.1), and the overall survival was 10.9 months (95% CI 9.1–12.7).

Table 1
Patient characteristics.

		Glioblastoma, IDH wildtype (N = 189) N (%)	Astrocytoma, IDH mutant, CNS WHO grade 4 (N = 80) N (%)	p-value[a]	Zurich cohort, glioblastoma IDH wildtype N = 341 N (%)	p-value[b]
Age	Median	56.0	40.0	< 0.001	66.0	< 0.001
	Range	24–78	21–64	–	29–90	
Age groups	< 50	51 (27.0)	68 (85.0)	< 0.001	33 (9.7)	< 0.001
	50–59	66 (34.9)	10 (12.5)		62 (18.2)	
	60–69	58 (30.7)	2 (2.5)		121 (35.5)	
	≥70	14 (7.4)	0 (0)		125 (36.7)	
Sex	Male	93 (49.2)	47 (60.3)	0.100	214 (62.8)	0.002
	Female	96 (50.8)	31 (39.7)		127 (37.2)	
	Missing	0 (–)	2 (–)	–	0 (–)	–
KPS post-operative (%)	80–100	63 (77.8)	29 (93.5)	0.146	116 (34.4)	< 0.001
	60–70	17 (21.0)	2 (6.5)		205 (60.8)	
	< 60	1 (1.2)	0 (0)		16 (4.7)	
	Missing	108 (–)	49 (–)	–	4 (–)	–
Extent of surgery (eCRF)	Gross total resection	134 (76.6)	40 (53.3)	0.001	104 (30.6)	< 0.001
	Partial resection	32 (18.3)	26 (34.7)		153 (45.0)	
	Biopsy	9 (5.1)	9 (12.0)		82 (24.1)	
	None, diagnosed at autopsy	0 (0)	0 (0)		1 (0.3)	
	Missing	14 (–)	5 (–)	–	1 (–)	–
MGMT promoter methylation status (%)	Unmethylated	48 (25.7)	13 (16.3)	0.093	128 (56.6)	< 0.001
	Methylated	139 (74.3)	67 (83.8)		98 (43.4)	
	Missing	2 (–)	0 (–)	–	115 (–)	–
Histological subtype	Glioblastoma	181 (95.8)	80 (100)	0.322	330 (96.8)	0.022
	Gliosarcoma	2 (1.1)	0 (0)		10 (2.9)	
	Giant cell glioblastoma	5 (2.6)	0 (0)		1 (0.3)	
	Epitheloid glioblastoma	1 (0.5)	0 (0)		0 (0)	
Tumour localisation (%)	Frontal	49 (26.9)	46 (59.7)	< 0.001	65 (19.3)	< 0.001
	Temporal	62 (34.1)	9 (11.7)		71 (21.1)	
	Parietal	36 (19.8)	8 (10.4)		45 (13.4)	
	Occipital	12 (6.6)	2 (2.6)		16 (4.8)	
	Multifocal	20 (11.0)	11 (14.3)		93 (27.7)	
	Deep structures	3 (1.6)	1 (1.3)		46 (13.7)	
	Missing	7 (–)	3 (–)	–	5 (–)	–
Survival	Median follow-up (95% CI)[c]	9.7 years (8.9–10.5)	10.7 years (9.9–11.2)	0.481	5.2 months (3.8–6.7)	< 0.001
	Median PFS (95% CI)	4.6 years (3.9–5.3)	5.1 years (3.6–6.6)	0.081	4.7 months (4.2–5.1)	< 0.001
	Median OS (95% CI)	9.9 years (7.9–11.9)	not reached	0.013	10.9 months (9.1–12.7)	< 0.001
	Events (progression)	135[d] (13 missing)	41 (14 missing)	0.035	308	< 0.001
	Events (death)	93	26	0.012	302	< 0.001
	Alive at last follow-up	96	54	0.012	39	< 0.001

N, number; MGMT, O^6-methylguanine DNA methyltransferase; KPS, Karnofsky performance status; eCRF, electronical case report form.
[a] Comparison between glioblastoma, IDH wildtype and astrocytoma, IDH mutant, CNS WHO grade 4.
[b] Comparison between glioblastoma, IDH wildtype and Zurich cohort, glioblastoma IDH wildtype.
[c] Of surviving patients.
[d] Of which N = 6 patients with confirmed progression, but without specific date of progression event, therefore N = 129 events included in median PFS.

Deceased patients in the IDH wildtype glioblastoma long-term survivor cohort died of glioblastoma except for 3 patients whose cause of death was documented as lung cancer (1), pneumonia (1) and unknown cause other than glioblastoma (1). There was no association with survival of the classic prognostic factors in glioblastoma of age, *MGMT* promoter methylation status, sex, extent of resection or KPS after first resection (Fig. 1A–E, Table 4). The only relevant prognostic factor in univariate analysis was the number of

Table 2
Treatment characteristics.

		Glioblastoma, IDH wildtype (N = 189) N (%)	Astrocytoma, IDH mutant, CNS WHO grade 4 (N = 80) N (%)	p-value[a]	Zurich cohort, glioblastoma IDH wildtype (N = 341) N (%)	p-value[b]
First-line treatment[c]	TMZ concomitant and maintenance	146 (83.9)	63 (84.0)	0.898	146 (43.6)	< 0.001
	TMZ monotherapy	7 (4.0)	4 (5.3)		24 (7.2)	
	TMZ plus other treatment	3 (1.7)	1 (1.3)		11 (3.3)	
	Nitrosourea monotherapy	3 (1.7)	0 (0)		1 (0.3)	
	Nitrosourea plus other	5 (2.9)	2 (2.7)		0 (0)	
	Other	10 (5.7)	5 (6.7)		13 (3.9)	
	No systemic treatment	0 (0)	0 (0)		140 (41.8)	
	Missing	15 (–)	5 (–)	–	6 (–)	–
Radiotherapy as part of first-line treatment	Yes	176 (93.1)	74 (92.5)	0.85	250 (74.6)	< 0.001
	No	13 (6.9)	6 (7.5)		85 (25.4)	
	Missing	0 (–)	0 (–)	–	6 (–)	–
Number of recurrences/ reinterventions (%)	0	41 (23.3)	28 (37.8)	0.114	0 (0)	< 0.001
	1	39 (22.2)	18 (24.3)		118 (36.4)	
	2	41 (23.3)	14 (18.9)		115 (35.5)	
	3	25 (14.2)	6 (8.1)		60 (18.5)	
	≥4	30 (17.0)	8 (10.8)		31 (9.6)	
	Missing	13 (–)	6 (–)	–	17 (–)	–
Surgery at any recurrence	Yes	76 (40.2)	29 (36.3)	0.543	39 (11.4)	< 0.001
	No	113 (59.8)	51 (63.7)		302 (88.6)	
Radiotherapy at any recurrence	Yes	54 (28.6)	21 (26.3)	0.698	20 (5.9)	< 0.001
	No	135 (71.4)	59 (73.8)		321 (94.1)	
TMZ at any recurrence	Yes	102 (54.0)	36 (45.0)	0.179	47 (13.8)	< 0.001
	No	87 (46.0)	44 (55.0)		294 (86.2)	
Nitrosourea at any recurrence	Yes	68 (36.0)	21 (26.3)	0.121	54 (15.8)	< 0.001
	No	121 (64.0)	59 (73.8)		287 (84.2)	
Bevacizumab at any recurrence	Yes	61 (32.3)	22 (27.5)	0.438	103 (30.2)	0.621
	No	128 (67.7)	58 (72.5)		238 (69.8)	
PCV at any recurrence	Yes	11 (5.8)	4 (5.0)	0.789	0 (0)	< 0.001
	No	178 (94.2)	76 (95.0)		341 (100)	
Platin-based therapy at any recurrence	Yes	10 (5.3)	3 (3.8)	0.590	5 (1.5)	0.011
	No	179 (94.7)	77 (96.3)		336 (98.5)	
Other at any recurrence[c]	Yes	24 (12.7)	10 (12.2)	0.964	21 (6.2)	0.010
	No	165 (87.3)	70 (87.8)		320 (93.8)	

N, number; IDH, isocitrate dehydrogenase; TMZ, temozolomide, PCV, procarbazin plus CCNU (lomustine) plus vincristine; eCRF, electronical case report form.

[a] Comparison between glioblastoma, IDH wildtype and astrocytoma, IDH mutant, CNS WHO grade 4.

[b] Comparison between glioblastoma, IDH wildtype and Zurich cohort, glioblastoma IDH wildtype.

[c] Others include any systemic or local treatment coded by the investigator in addition to treatments specifically mentioned in the table.

recurrences and the absence versus presence of any recurrence ($p < 0.001$) (Table 4, Fig. 1F and G). In multivariate analysis, the overall numbers became too low when all variables from the univariate analysis were included; however, multivariate analysis with higher overall numbers after omission of KPS would support the results from univariate analysis.

4. Discussion

The prognosis for patients with IDH wildtype glioblastoma has remained poor despite major medical advances and extensive scientific efforts [2]. Only a minority of patients experience survival beyond 5 years. Major favourable prognostic factors include younger age, gross total resection and *MGMT* promoter methylation. Originally, IDH mutation was considered as a strong prognostic factor in glioblastoma patients; however, tumours with IDH mutation are now no longer classified as glioblastoma but as astrocytoma, IDH mutant, CNS WHO grade 4 to distinguish between these biologically and clinically distinct tumour types [16,18].

Expectedly, the characterisation of the present EORTC 1419 ETERNITY cohort of patients with

Table 3
Group comparison by recurrence among IDH wildtype long-term survivors.

		Glioblastoma IDH wildtype (recurrence) (N = 135) N (%)	Glioblastoma IDH wildtype (no recurrence) (N = 41) N (%)	p-value
Age (years)	Median	55.0	59.0	0.198
	Range	24.0–78.0	33.0–78.0	
Age groups	< 50	36 (26.7)	12 (29.3)	0.131
	50–59	53 (39.3)	9 (22.0)	
	60–69	39 (28.9)	15 (36.6)	
	≥70	7 (5.2)	5 (12.2)	
Sex	Male	69 (51.1)	18 (43.9)	0.419
	Female	66 (48.9)	23 (56.1)	
KPS post-operative (%)	80–100	46 (74.2)	10 (90.9)	0.475
	60–70	15 (24.2)	1 (9.1)	
	< 60	1 (1.6)	0 (0)	
	Missing	73 (–)	30 (–)	–
Extent of surgery (eCRF)	Gross total resection	97 (75.8)	27 (71.1)	0.797
	Subtotal resection	24 (18.8)	8 (21.1)	
	Biopsy	7 (5.5)	3 (7.9)	
	Missing	7 (–)	3 (–)	–
MGMT promoter methylation status (%)	Unmethylated	24 (18.0)	20 (48.8)	< 0.001
	Methylated	109 (82.0)	21 (51.2)	
	Missing	2 (–)	0 (–)	–

N, number; IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine DNA methyltransferase, KPS, Karnofsky performance status; eCRF, electronical case report form.

centrally confirmed IDH wildtype glioblastoma surviving for 5 years or more showed a younger median age at diagnosis than the 65 years reported for the general glioblastoma population with or without IDH mutation [3], or compared to a population-based reference cohort of IDH wildtype glioblastoma [20] (Table 1). Interestingly, sex was balanced in the ETERNITY cohort whereas almost 2 of 3 patients are male on a population level [3,20] (Table 1). Further, we identified a much higher rate of tumours with *MGMT* promoter methylation in all age groups compared with the reference population (74.3% versus 43.4%) (Table 1, S2) which probably reflects the impact of alkylating agent chemotherapy on survival (Table 1). Most patients from the ETERNITY cohort underwent a gross total resection (76.6%) followed by standard first-line treatment with radiotherapy and concomitant and maintenance temozolomide (83.9%), reflecting a patient population eligible for standard of care treatment at diagnosis [1]. The apparent contradiction between more frequent location in the frontal lobe but less frequent gross total resection in IDH mutant tumours compared with IDH wildtype tumours in the long-term survivor cohort was noteworthy. However, extent of resection was not associated with tumour location in either IDH wildtype ($p = 0.189$) or mutant ($p = 0.224$) glioblastoma patients.

Next we examined prognostic factors within the cohort of patients who survived for 5 years. In contrast to the well-known prognostic value of sex, extent of resection and *MGMT* promoter methylation status in unselected patient populations, none of these factors remained prognostic in patients surviving more than 5 years, suggesting that these prognostic factors have already exerted, but also exhausted, their impact on the profile of the survivors.

The only factor that remained statistically significant in log-rank or Cox regression analysis was the number of recurrences ($p < 0.001$) (Fig. 1F and G) (Table 4). One may argue that this is a trivial observation because prolonged progression-free survival should translate into longer overall survival. Interestingly, as previously reported [27], glioblastoma patients without recurrence did not differ with regard to age, sex, KPS or extent of surgery from patients who experienced recurrence (Table 3). Intriguingly, the patients without recurrence showed a significantly higher proportion of *MGMT* promoter-unmethylated tumours. This observation suggests the existence of one or more currently unrecognised, but important molecular or other predictors of long-term survival.

Our findings also raise the question whether any patient who reaches the 5-year survival threshold without recurrence may have been cured. This should be viewed with caution since three patients of the historical monocentric Tübingen cohort experienced very late relapses after 118, 124 and 126 months [4]. Further, documented cause of death in the ETERNITY cohort was almost exclusively tumour progression.

Limitations of this study include the exclusion of the newly defined entity of 'molecular glioblastoma' [17] because these tumours are defined by the lack of histological features of glioblastoma. Further limitations include the lack of clinical source data verification including definition of progression and the challenge of

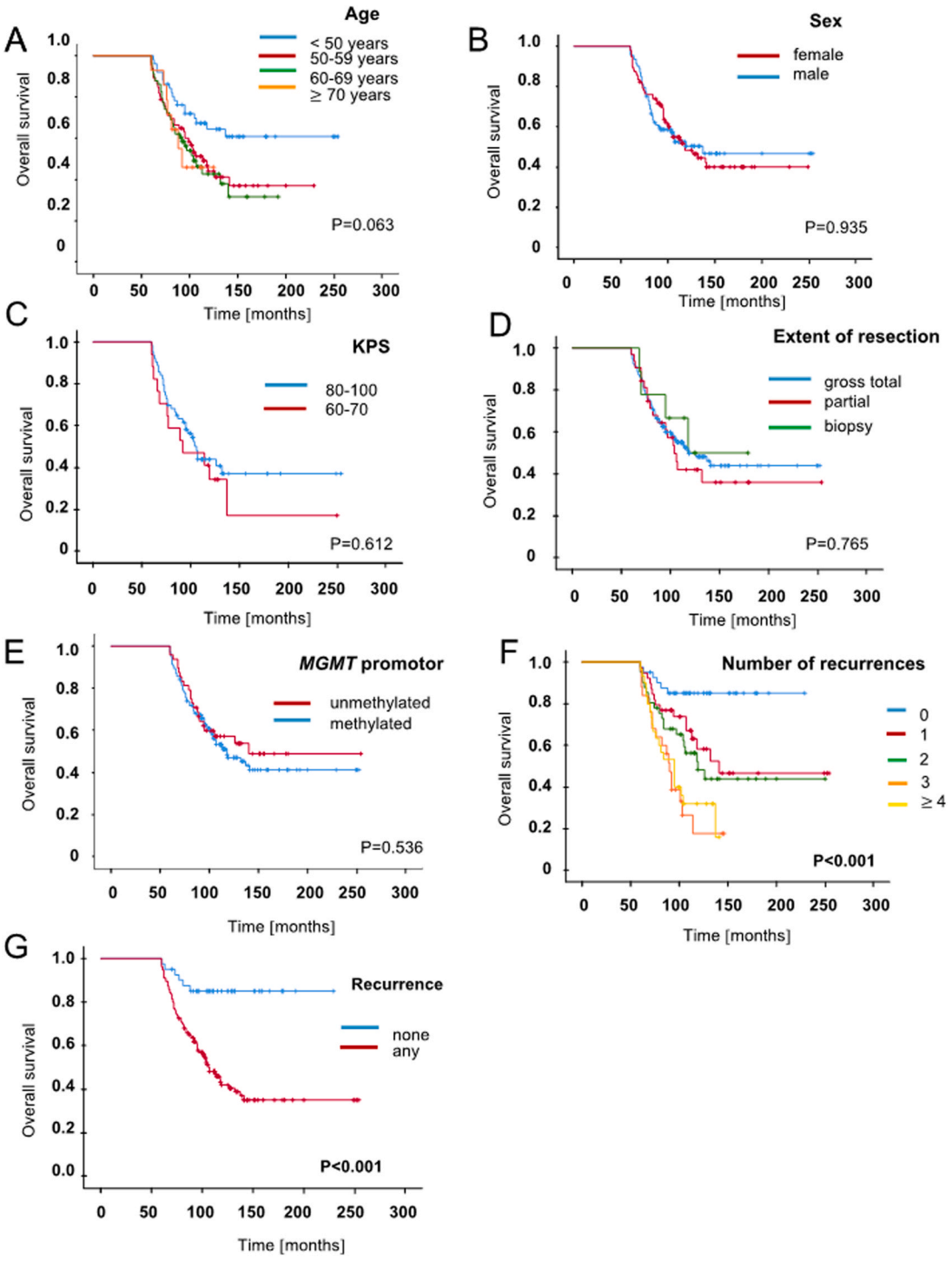

Fig. 1. Overall survival of the IDH wildtype glioblastoma long-term survivor cohort by age group (A), sex (B), Karnofsky performance status (C), extent of resection (D), *MGMT* promoter methylation status (E), number of recurrences (F) and stratified by either no recurrence or any recurrence (G). Note that six patients in the group of patients without recurrence either died from other causes or died without documented progression.

defining an appropriate contemporary reference group. Yet, we believe that our use of a well-established, population-based glioblastoma cohort as a comparison group is valuable to place our long-term survivor data in perspective. This control group does, however, differ from the long-term survivor cohort in some potentially important ways: the dates of patient accrual (2005 through 2014 versus 1998 through 2014), the treatments

Table 4
Univariate analysis with regards to death.

			Log-rank analysis			Cox regression analysis	
		N (events)	Median overall survival (years)	95% CI	p-value	HR (95% CI)	p-value
All patients		189 (93)	9.9	7.9–11.9	–	–	–
Age group	< 50	51 (18)	Not reached		0.063	0.48 (0.20–1.15)	0.099
	50–59	66 (36)	9.5	8.0–11.0		0.90 (0.40–2.03)	0.802
	60–69	58 (32)	8.7	7.2–10.2		0.99 (0.44–2.25)	0.980
	≥70	14 (7)	7.7	nd		1	ref
Sex	Male	93 (44)	11.4	nd	0.935	1	ref
	Female	96 (49)	9.8	7.6–12.0		1.02 (0.68–1.53)	0.935
KPS post-operative (%)	80–100	63 (35)	8.8	8.0–9.7	0.612	1	ref
	60–70	17 (12)	7.7	3.5–11.8		1.1 (0.60–2.00)	0.757
	< 60	1 (1)	7.9	nd		nd	nd
Extent of surgery (eCRF)	Gross total resection	134 (65)	9.9	7.5–12.3	0.765	1.21 (0.44–3.23)	0.712
	Partial resection	32 (18)	8.7	7.7–9.7		1.41 (0.48–4.18)	0.533
	Biopsy	9 (4)	9.8	nd		1	ref
	Missing	14 (–)	–	–	–	–	–
MGMT promoter methylation status	Methylated	139 (69)	9.8	7.9–11.8	0.536	1.16 (0.72–1.88)	0.538
	Unmethylated	48 (22)	11.7	nd		1	ref
	Missing	2 (–)	–	–	–	–	–
First-line treatment[a]	Standard of care	146 (66)	11.8	nd	0.912	1	ref
	Temozolomide alone	7 (5)	9.4	5.4–13.5		1.40 (0.56–3.47)	0.470
	Temozolomide plus other	3 (2)	6.7	4.3–9.1		1.76 (0.43–7.21)	0.431
	Nitrosourea alone	3 (2)	11.4	5.0–17.8		1.07 (0.26–4.36)	0.930
	Nitrosourea plus other	5 (3)	8.9	6.8–11.1		1.18 (0.37–3.77)	0.776
	Other	10 (6)	7.9	4.5–11.4		1.33 (0.58–3.07)	0.503
	Missing	15 (–)	–	–	–	–	–
Number of recurrences	0	41 (6)	Not reached		< 0.0-01	0.14 (0.06–0.35)	0.000
	1	39 (16)	11.8	nd		0.44 (0.23–0.84)	0.013
	2	41 (20)	9.9	7.6–12.2		0.55 (0.30–1.02)	0.058
	3	25 (18)	7.5	7.0–8.0		1.15 (0.61–2.17)	0.661
	≥4	30 (21)	7.9	6.7–9.1		1	ref
	Missing	13 (–)	–	–	–	–	–
Recurrence	No recurrence	41 (6)	Not reached		< 0.0-01	0.21 (0.01–0.47)	< 0.001
	Any recurrence	135 (75)	8.9	7.9–9.9		1	ref
	Missing	13 (–)	–	–	–	–	–

N, number; CI, confidence interval; HR, hazard ratio; MGMT, O^6-methylguanine DNA methyltransferase; ref, reference; nd, not defined; KPS, Karnofsky performance status; eCRF, electronical case report form.
[a] Others include any systemic or local treatment coded by the investigator in addition to treatments specifically mentioned in the table.

received, for example, concurrent temozolomide with radiotherapy was not widely employed before 2005, and the method of IDH mutation detection.

Important strengths of the study are the large number of rare long-term survivor patients collected in a collaborative effort with central pathology review, the prospective collection of predefined data, and the inclusion of patients from different countries world-wide, minimising a potential selection bias.

In conclusion, the EORTC 1419 study represents the largest, centrally reviewed, rigorously compiled cohort of IDH wildtype glioblastoma patients with long-term survival in existence. There is a commitment to maintain and enlarge the database and to share data with qualified researchers proposing novel investigations. Upcoming analyses will address the identification of molecular markers associated with long-term survival in the subpopulation of patients with adequate tissue available, including DNA methylation profiling and gene panel sequencing. The focus will be on the patients without documented relapse and among these in particular the patients with tumours lacking *MGMT* promoter methylation. Further studies will report on poorly understood or incompletely investigated long-term cognitive, social, and quality of life outcomes in the EORTC 1419 ETERNITY patient cohort.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C.H. has received a research grant for protected time by the Filling the Gap foundation and honoraria for lecture from Vifor; E.L.R. has received honoraria for lectures or advisory board from Bayer, Janssen, Leo Pharma, Pierre Fabre, Seattle Genetics; J.C. has received research funding from Servier and Merck and consultant for Servier; R.S. reports consultation for Bayer, Astra Zeneca; W.W. reports consultation for Apogenix, Astra Zeneca, Bayer, Enterome, Medac, MSD and Roche/Genentech with honoraria paid to the Medical Faculty at the University of Heidelberg; F.D. has received honoraria for lectures or advisory board participation from Novocure; P.R. has received honoraria for lectures or advisory board participation from Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm, Merck Sharp and Dohme, Midatech, Novocure, QED, and Roche and research support from Merck Sharp and Dohme and Novocure; P.H. has received honoraria for lectures or advisory board participation or consulting from Bayer, Lilly, medac, Novartis, Novocure and Seagen; A.H. has received honoraria for lectures, consultation or advisory board participation from Novocure and Novartis; G.L. has received funding for a consulting or advisory role from Bayer, AbbVie, Orbus Therapeutics, BrainFarm, Health4U, Novartis, Braun and Janssen, and funding for travel from Roche, Bayer, and Ipsen; D.K. has received honoraria for lectures, consultation or advisory

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.05.002.

References

[1] Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021;18:170–86. https://doi.org/10.1038/s41571-020-00447-z.

[2] Wen PY, Weller M, Lee EQ, Alexander BA, Barnholtz-Sloan JS, Barthel FP, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol 2020;22(8):1073–113. https://doi.org/10.1093/neuonc/noaa106.

[3] Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. Neuro Oncol 2021;23:iii1–105. https://doi.org/10.1093/neuonc/noab200.

[4] Steinbach JP, Blaicher H-P, Herrlinger U, Wick W, Nägele T, Meyermann R, et al. Surviving glioblastoma for more than 5 years: the patient's perspective. Neurology 2006;66:239–42. https://doi.org/10.1212/01.wnl.0000194221.89948.a0.

[5] Burgenske DM, Yang J, Decker PA, Kollmeyer TM, Kosel ML, Mladek AC, et al. Molecular profiling of long-term IDH-wild-type glioblastoma survivors. Neuro Oncol 2019;21:1458–69. https://doi.org/10.1093/neuonc/noz129.

[6] Richardson TE, Kumar A, Xing C, Hatanpaa KJ, Walker JM. Overcoming the odds: toward a molecular profile of long-term survival in glioblastoma. J Neuropathol Exp Neurol 2020;79:1031–7. https://doi.org/10.1093/jnen/nlaa102.

[7] Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997–1003. https://doi.org/10.1056/NEJMoa043331.

[8] Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765–73. https://doi.org/10.1056/NEJMoa0808710.

[9] Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012;13:916–26. https://doi.org/10.1016/S1470-2045(12)70265-6.

[10] Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707–15. https://doi.org/10.1016/S1470-2045(12)70164-X.

[11] Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 2017;376:1027–37. https://doi.org/10.1056/NEJMoa1611977.

[12] Reifenberger G, Weber RG, Riehmer V, Kaulich K, Willscher E, Wirth H, et al. Molecular characterization of long-term survivors of glioblastoma using genome- and transcriptome-wide profiling. Int J Cancer 2014;135:1822–31. https://doi.org/10.1002/ijc.28836.

[13] Hartmann C, Hentschel B, Simon M, Westphal M, Schackert G, Tonn JC, et al. Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations. Clin Cancer Res 2013;19:5146–57. https://doi.org/10.1158/1078-0432.CCR-13-0017.

[14] Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 2009;27:4150–4. https://doi.org/10.1200/JCO.2009.21.9832.

[15] Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol 2009;27:5743–50. https://doi.org/10.1200/JCO.2009.23.0805.

[16] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 2021;23:1231–51. https://doi.org/10.1093/neuonc/noab106.

[17] Brat DJ, Aldape K, Colman H, Holland EC, Louis DN, Jenkins RB, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 2018;136:805–10. https://doi.org/10.1007/s00401-018-1913-0.

[18] Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, et al. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol 2020;139:603–8. https://doi.org/10.1007/s00401-020-02127-9.

[19] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20. https://doi.org/10.1007/s00401-016-1545-1.

[20] Gramatzki D, Dehler S, Rushing EJ, Zaugg K, Hofer S, Yonekawa Y, et al. Glioblastoma in the Canton of Zurich, Switzerland revisited: 2005 to 2009. Cancer 2016;122:2206–15. https://doi.org/10.1002/cncr.30023.

[21] Gramatzki D, Roth P, Rushing EJ, Weller J, Andratschke N, Hofer S, et al. Bevacizumab may improve quality of life, but not overall survival in glioblastoma: an epidemiological study. Ann Oncol 2018;29:1431–6. https://doi.org/10.1093/annonc/mdy106.

[22] Felsberg J, Wolter M, Seul H, Friedensdorf B, Göppert M, Sabel MC, et al. Rapid and sensitive assessment of the IDH1 and IDH2 mutation status in cerebral gliomas based on DNA pyrosequencing. Acta Neuropathol 2010;119:501–7. https://doi.org/10.1007/s00401-010-0647-4.

[23] Hartmann C, Meyer J, Balss J, Capper D, Mueller W, Christians A, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol 2009;118:469–74. https://doi.org/10.1007/s00401-009-0561-9.

[24] Felsberg J, Rapp M, Loeser S, Fimmers R, Stummer W, Goeppert M, et al. Prognostic significance of molecular markers and extent of resection in primary glioblastoma patients. Clin Cancer Res 2009;15:6683–93. https://doi.org/10.1158/1078-0432.CCR-08-2801.

[25] Tzaridis T, Schäfer N, Weller J, Steinbach J-P, Schlegel U, Seidel S, et al. MGMT promoter methylation analysis for allocating combined CCNU/TMZ chemotherapy: lessons learned from the CeTeG/NOA-09 trial. Int J Cancer 2021;148:1695–707. https://doi.org/10.1002/ijc.33363.

[26] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96. https://doi.org/10.1056/NEJMoa043330.

[27] Hottinger AF, Yoon H, DeAngelis LM, Abrey LE. Neurological outcome of long-term glioblastoma survivors. J Neurooncol 2009;95:301–5. https://doi.org/10.1007/s11060-009-9946-9.