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Survival of diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria

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Abstract

Background. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) has recommended that isocitrate dehydrogenase 1 and 2 wildtype (*IDH1/2wt*) diffuse lower-grade gliomas (LGGs) World Health Organization (WHO) grade II or III that present with (i) a telomerase reverse transcriptase promoter mutation (*pTERTmt*), and/or (ii) gain of chromosome 7 combined with loss of chromosome 10, and/or (iii) epidermal growth factor receptor (*EGFR*) amplification should be reclassified as diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV (*IDH1/2wt* astrocytomas WHO IV). This paper describes the overall survival (OS) of *IDH1/2wt* astrocytoma WHO IV patients, and more in detail patients with tumors with *pTERTmt* only.

Methods. In this retrospective multicenter study, we compared the OS of 71 *IDH1/2wt* astrocytomas WHO IV patients, with radiological characteristics of LGGs, with the OS of 197 *IDH1/2wt* glioblastoma patients. Moreover, we compared the OS of 22 *pTERTmt* only astrocytoma patients with the OS of the *IDH1/2wt* glioblastoma patients.

Results. Median OS was similar for *IDH1/2wt* astrocytoma WHO IV patients (23.8 mo) and *IDH1/2wt* glioblastoma patients (19.2 mo) (Cox proportional hazards model: hazard ratio [HR] 1.27, 95% CI: 0.85–1.88, $P = 0.242$). OS was also similar in patients with *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only, and *IDH1/2wt* glioblastomas (HR 1.15, 95% CI: 0.64–2.10, $P = 0.641$).

Conclusions. The presented data confirm the cIMPACT-NOW recommendation and we propose that *IDH1/2wt* astrocytomas WHO IV in the absence of other qualifying mutations should be classified as *IDH1/2wt* glioblastomas.

Key Points

1. *IDH1/2wt* astrocytomas WHO IV have a similar OS as *IDH1/2wt* glioblastomas.
2. *pTERTmt* only astrocytomas also have a similar OS as *IDH1/2wt* glioblastomas.
3. *IDH1/2wt* astrocytomas WHO IV should be classified as *IDH1/2wt* glioblastomas.

Importance of the Study

The cIMPACT-NOW committee has recommended the classification of the new glioma subtype diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV. We show that these *IDH1/2wt* astrocytomas WHO IV, presenting with typical clinical, radiological, and histological characteristics of diffuse lower-grade gliomas, but that have either a *TERT* promoter mutation and/or *EGFR* amplification and/or gain of chromosome 7 and loss of chromosome 10 have a similar poor prognosis as glioblastomas. In the present report, all included cases had MRI scans that were fully consistent with a grade II or III tumor, and thus the histological findings do not simply represent a biopsy bias. Moreover, we identified a series of cases with only a *TERT* promoter mutation and confirmed their poor prognosis. Our data therefore support the reclassification of diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV as *IDH1/2wt* glioblastomas in a revised WHO classification.

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) aims to aid in the taxonomy of primary brain tumors in the period between official editions of the World Health Organization (WHO) classifications of brain tumors. In the third cIMPACT-NOW report, the committee recommended to reclassify isocitrate dehydrogenase 1 and 2 wildtype (*IDH1/2wt*) diffuse lower-grade gliomas (LGGs) of WHO grades II and III as diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV (*IDH1/2wt* astrocytomas WHO IV) if they present with (i) a telomerase reverse transcriptase promoter (*pTERT*) mutation (*mt*), and/or (ii) gain of chromosome 7 combined with loss of chromosome 10 (*7+/10–*), and/or (iii) epidermal growth factor receptor (*EGFR*) amplification (*amp*).[1–5] Although this classification defines the diagnostic molecular criteria for *IDH1/2wt* astrocytomas WHO IV, the data on the clinical characteristics and survival of these tumors are still very limited. Firstly, it is not clear whether the prognosis of patients presenting with *IDH1/2wt* astrocytomas WHO IV with classical radiological characteristics of LGGs (ie, absence of ring-like contrast enhancement with central necrosis) is similar to the prognosis of *IDH1/2wt* glioblastoma patients. Secondly, *pTERTmt IDH1/2wt* astrocytomas without *7+/10–* or *EGFRamp* (*pTERTmt* only) are now also assigned *IDH1/2wt* astrocytomas WHO IV, but it is unclear whether their prognosis is indeed similar to the other *IDH1/2wt* astrocytomas WHO IV. Rare cases have been described of more benign types of *IDH1/2wt* astrocytomas harboring a *pTERT* mutation.[4,6] The main objective of this retrospective study is to evaluate the clinical presentation and survival outcome of a cohort of diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma, WHO grade IV according to the cIMPACT-NOW criteria presenting with MRI characteristics of an LGG, and specifically the outcome of cases with *pTERT* mutations only.

Materials and Methods

Patient Population

In this retrospective multicenter cohort study, adult (≥18 y) patients with a newly diagnosed predominantly supratentorial *IDH1/2wt* LGG (WHO grade II or III) were identified from the Erasmus Medical Center Cancer Institute, the Haaglanden Medical Center, and the Leiden University Medical Center pathology databases as well as from the previously published dataset of Erasmus MC patients from Wijnenga et al.[7] Histopathological diagnoses were determined by local dedicated neuropathologists. Patients were included if (i) *IDH1/2* mutation status, the copy number status of chromosome 7 and chromosome 10, and the amplification status of *EGFR* had been assessed with a glioma tailored next-generation sequencing (NGS) panel, and (ii) MRI scans at the time of diagnostic surgery were available for review.[8] Patients with a histological diagnosis of an LGG but presenting with lesions suggestive of glioblastoma (ring-like contrast enhancement with evidence of central necrosis on the MRI at the time of histological diagnosis) were excluded (Fig. 1A). An historical cohort from the Erasmus MC of *IDH1/2wt* glioblastoma patients diagnosed with the NGS panel in a routine diagnostic setting between 2013 and 2019 was used to compare overall survival (OS).[8]The design of the study was approved by the institutional review boards of the participating centers and was conducted according to national and local regulations.

Baseline Tumor Characteristics and Additional Molecular Analysis

For glioma targeted NGS, patient tumor material was cut into 5 μm formalin-fixed paraffin-embedded slices and selected for regions with the highest tumor cell percentage as defined by the local neuropathologists. DNA was isolated using 5% Chelex 100 resin (Bio-Rad) and proteinase K digestion. NGS with a targeted neuro-oncology panel and single nucleotide polymorphism–based loss of heterozygosity analysis were performed as previously described.[9] If *pTERT* status was not covered by the NGS panel, a SNaPshot assay was performed for the 2 hotspot mutations in gliomas (C228T and C250T) as previously described.[10]

Clinical Characteristics

The collected baseline clinical characteristics included sex, age at diagnosis, Karnofsky performance status (KPS) before and 3 months after surgery, date and

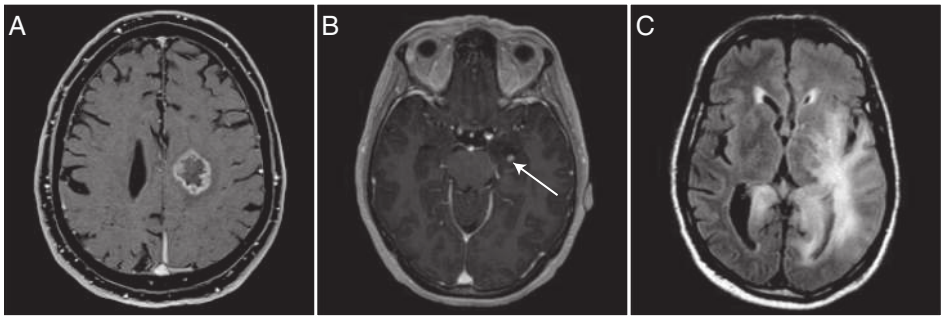

Fig. 1 MRIs made at the time of histological diagnosis of 3 different *IDH1/2wt* LGG patients. (A) Ring-like contrast enhancement on cT1w imaging, suggestive of glioblastoma; the patient was excluded from further analysis. (B) Minor contrast enhancement on cT1w imaging, not suggestive of glioblastoma; the patient was included for further analysis. (C) Typical gliomatosis cerebri on FLAIR imaging; a confluent hyperintense abnormality in at least 3 separate brain lobes.

symptom of onset, surgical procedure (biopsy or resection), histopathological diagnosis, and primary treatment after surgery. OS was measured from the date of the diagnostic MRI scan until death or was censored at the date of last follow-up.

Radiological Characteristics

Radiological data were taken from T2-weighted (T2w) images, T2-weighted fluid-attenuated inversion recovery (FLAIR) images, and T1-weighted images before and after intravenous contrast administration (cT1w). Baseline radiological characteristics were assessed using the MRI made before diagnostic surgery and included tumor location (hemisphere, lobe[s], basal ganglia, thalamus, brainstem, cerebellum), growth pattern (gliomatosis cerebri, multifocal), and presence and pattern of contrast enhancement (patchy, ring-like, nodular). The MRI scans were reviewed by the first author (C.M.S.T.), and scans with more than minor contrast enhancement (patchy, nodular) were also reviewed by the last author (M.J.v.d.B.). The radiological diagnosis gliomatosis cerebri was defined as a confluent hyperintense FLAIR or T2w abnormality in at least 3 separate brain lobes (Fig. 1C).

Statistical Analysis

OS was estimated using the Kaplan–Meier method and curves were compared using the log-rank test. Categorical variables were compared using Fisher's exact test. Continuous numeric variables were compared using the Mann–Whitney *U*-test and the Kruskal–Wallis test. The Cox proportional hazards model was used for univariable and multivariable analysis. All factors for univariable analysis were included in the multivariable analysis based on known prognostic effect from previous literature.[11–15] All *P*-values below 0.05 were considered to be statistically significant. Statistical analysis was performed using R (v3.6.0) and RStudio (v1.0.153).

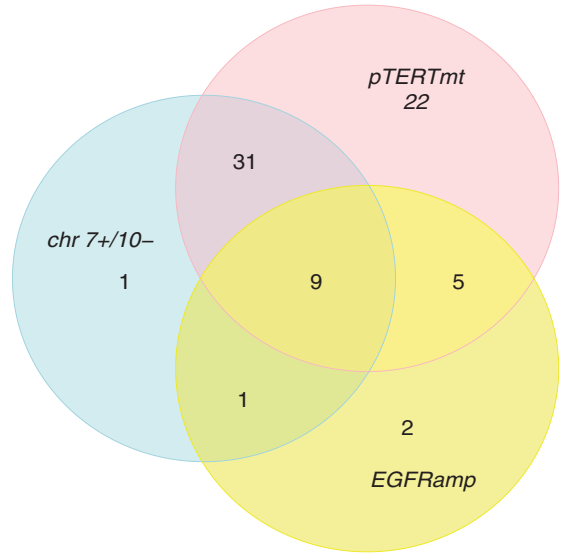

Fig. 2 A Venn diagram of the number of patients with *TERT* promoter mutations, *EGFR* amplification, and the signature of *7+/10–* within our cohort of *IDH1/2wt* LGGs.

Results

Cohort Distribution

A set of 126 *IDH1/2wt* LGG patients as confirmed by NGS analysis was identified from the 3 participating centers and assessed for eligibility. The patients were in part identified from a previous study on LGGs and in part during routine diagnostics.[5,7,8] Thirty-nine of these 126 patients were excluded: 3 patients with solely infratentorial lesions, 2 patients with insufficient NGS data, and 34 patients with ring-like contrast enhancement on MRI at the time of

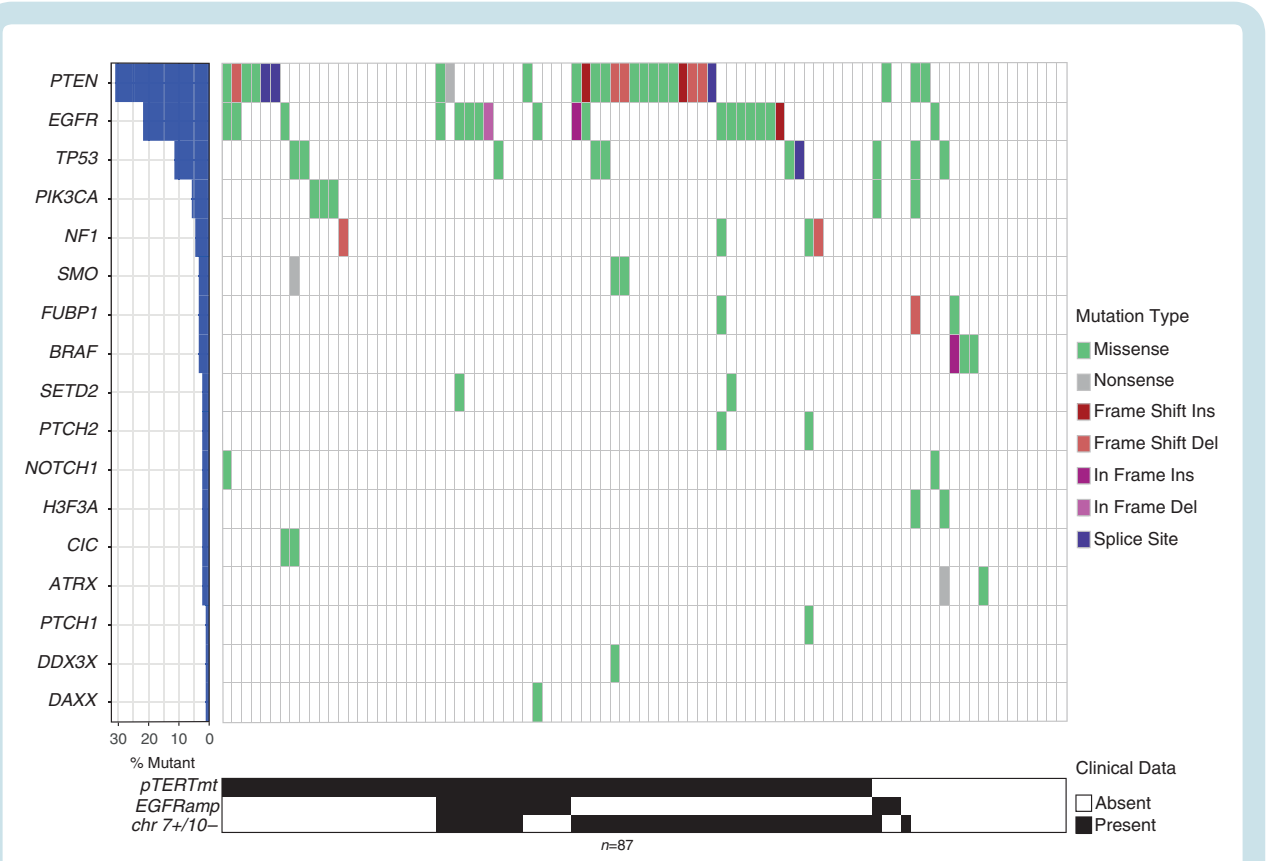

Fig. 3 A waterfall plot of the mutations as picked up by the glioma-specific NGS panel within the *IDH1/2wt* LGGs.

histological diagnosis. In 29 *IDH1/2wt* LGG patients, minor enhancement was present which was fully compatible with a grade II or III histology and these cases were included in this series.The included 87 patients were reclassified into 71 patients with molecular features of glioblastoma (*IDH1/2wt* astrocytomas WHO IV) and 16 patients without molecular features of glioblastoma (*IDH1/2wt* astrocytomas WHO II and III). Reclassification into *IDH1/2wt* astrocytomas WHO IV was based on the presence of a *pTERT* mutation in 67 patients, *EGFR* amplification in 17 patients, and the combined *7+/10–* signature in 42 patients (Fig. 2). In 22 of 67 *pTERTmt* patients the diagnosis of *IDH1/2wt* astrocytomas WHO IV was based solely on the *pTERT* mutation. A reference set containing 197 *IDH1/2wt* glioblastomas was identified from the Erasmus MC. All *IDH1/2wt* glioma patients were operated upon between October 2002 and May 2019.

The molecular features of our cohort were consistent with those frequently found in astrocytic tumors (Fig. 3). Mutations in *ATRX*, *BRAF*, and *H3F3A* were only observed in *IDH1/2wt* astrocytomas WHO II and III (12.5%, 18.8%, and 12.5%, respectively). Mutations in *EGFR* and *PTEN* were frequently observed in *IDH1/2wt* astrocytomas WHO IV (25.4% and 35.2%, respectively), but mutations in these genes were also sporadically seen in *IDH1/2wt* astrocytomas WHO II and III (6.3% and 12.5%, respectively). Three patients with a *BRAF* mutation were identified. Of the 2 patients with an *H3F3A* mutation, 1 had the *H3F3A K27M* mutation and 1 had the *H3F3A G34R* mutation.

Baseline Clinical and Radiological Characteristics

IDH1/2wt astrocytomas WHO IV patients had a higher age of onset than those with *IDH1/2wt* astrocytomas WHO II and III and *IDH1/2wt* glioblastomas (58 y vs 45 y and 55 y, respectively; $P = 0.006$). *IDH1/2wt* astrocytoma WHO IV patients presented more often with epilepsy than the *IDH1/2wt* glioblastoma patients (64.8% vs 27.4%, $P < 0.001$). *IDH1/2wt* glioblastoma patients were operated upon sooner after the presenting symptom than *IDH1/2wt* astrocytomas WHO IV patients (first symptom to first surgery: 1.1 mo vs 2.9 mo, $P < 0.001$; diagnostic scan to first surgery: 0.5 mo vs 1.3 mo, $P < 0.001$). A biopsy was performed more frequently in the *IDH1/2wt* astrocytomas WHO IV compared with the *IDH1/2wt* astrocytomas WHO II and II and the *IDH1/2wt* glioblastomas (83.1% vs 56.2% and 16.8%, respectively; $P < 0.001$). After the diagnostic surgery, *IDH1/2wt* glioblastomas were commonly treated with chemoradiation, while less than half of the *IDH1/2wt* astrocytomas WHO IV received both chemotherapy and radiotherapy (chemoradiation: 89.8% vs 42.3%, $P < 0.001$). Other clinical characteristics of the *IDH1/2wt* gliomas are summarized in Table 1.

Table 1 The clinical information of all *IDH1/2wt* gliomas as confirmed by a glioma specific NGS panel for diagnostic purposes*

Characteristics	*IDH1/2wt* Astrocytomas WHO IV	*IDH1/2wt* Astrocytomas WHO II and III	P^a	*IDH1/2wt* Glioblastomas	P^b	*IDH1/2wt* Astrocytomas WHO IV, *pTERTmt* only	P^c	All Patients	P^d
Patients, *n*	71	16		197		22		284	
Sex, *n* (%)			0.259		0.767		1.000		0.311
Female	24 (33.8)	8 (50)		62 (31.5)		7 (31.8)		94 (33.1)	
Male	47 (66.2)	8 (50)		135 (68.5)		15 (68.2)		190 (66.9)	
Age, y			0.012		0.010		0.394		0.006
Median	58	45		55		62		56	
Range	19–78	21–69		18–84		19–78		18–84	
Age groups, *n* (%)									
<40 y	6 (8.5)	5 (31.3)		19 (9.6)		2 (9.1)		30 (10.6)	
40–60 y	32 (45.1)	6 (37.5)		117 (59.4)		8 (36.4)		155 (54.6)	
>60 y	33 (46.5)	5 (31.3)		61 (31.0)		12 (54.5)		99 (34.9)	
Follow-up, y			0.185		0.857		0.252		0.331
Median	1.4	2.9		1.5		1.2		1.5	
Interquartile range (IQR)	0.8–2.5	0.8–4.1		1–2.2		0.7–2.3		0.9–2.4	
First symptom to surgery, mo			0.081		<0.001		0.476		<0.001
Median	2.9	8		1.1		2.2		1.5	
IQR	1.5–5.8	1.8–13.9		0.6–2.3		1.3–5.0		0.8–3.4	
First scan to surgery, mo			0.956		<0.001		0.582		<0.001
Median	1.3	1.3		0.5		1.1		0.6	
IQR	0.7–3.2	0.6–4.9		0.1–0.8		0.7–2.3		0.2–1.3	
Histopathology, *n* (%)			0.678		<0.001		1.000		<0.001
Glioma WHO II	45 (63.4)	9 (56.3)		0 (0)		15 (68.2)		54 (19.0)	
Glioma WHO III	14 (19.7)	3 (18.8)		0 (0)		2 (9.1)		17 (6.0)	
Glioblastoma	0 (0)	0 (0)		197 (100)		0 (0)		197 (69.4)	
Glioma NOS	12 (16.9)	4 (25)		0 (0)		5 (22.7)		16 (5.6)	
Symptom of onset, *n* (%)			0.102		<0.001		0.359		<0.001
Epilepsy	46 (64.8)	6 (37.5)		54 (27.4)		13 (59.1)		106 (37.3)	
Incidental finding	2 (2.8)	1 (6.3)		9 (4.6)		0 (0)		12 (4.2)	
Other	23 (32.4)	9 (56.3)		134 (68.0)		9 (40.9)		166 (58.5)	
Surgery modality, *n* (%)			0.039		<0.001		0.686		<0.001
Resection	12 (16.9)	7 (43.8)		164 (83.2)		2 (9.1)		183 (64.4)	
Biopsy	59 (83.1)	9 (56.3)		33 (16.8)		20 (90.9)		101 (35.6)	
Primary treatment, *n* (%)			0.094		<0.001		0.724		<0.001
No further treatment	9 (12.7)	6 (37.5)		9 (4.6)		4 (18.2)		24 (8.5)	

Table 1 Continued

Characteristics	*IDH1/2wt* Astrocytomas WHO IV	*IDH1/2wt* Astrocytomas WHO II and III	*P*[a]	*IDH1/2wt* Glioblastomas	*P*[b]	*IDH1/2wt* Astrocytomas WHO IV, *pTERTmt* only	*P*[c]	All Patients	*P*[d]
Chemotherapy	14 (19.7)	1 (6.3)		4 (2.0)		6 (27.3)		19 (6.7)	
Radiotherapy	18 (25.4)	2 (12.5)		7 (3.6)		6 (27.3)		27 (9.5)	
Chemoradiation	30 (42.3)	7 (43.8)		177 (89.8)		6 (27.3)		214 (75.4)	
Preoperative KPS			0.218		0.248		0.545		0.068
Median	90	100		90		90		90	
90–100, *n* (%)	50 (70.4)	14 (87.5)		122 (61.9)		14 (63.6)		186 (65.5)	
≤80, *n* (%)	21 (29.6)	2 (12.5)		75 (38.1)		8 (36.4)		98 (34.5)	
Postoperative KPS			0.259		0.889		0.400		0.286
Median	90	100		90		80		90	
90–100, *n* (%)	39 (55.7)	12 (75)		106 (53.8)		10 (47.6)		157 (55.5)	
≤80, *n* (%)	31 (44.3)	4 (25)		91 (46.2)		11 (52.4)		126 (44.5)	

*The indicated *P*-values compared a) *IDH1/2wt* astrocytomas WHO IV vs *IDH1/2wt* astrocytomas WHO II and III, b) *IDH1/2wt* astrocytomas WHO IV vs *IDH1/2wt* glioblastomas, c) *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only vs other *IDH1/2wt* astrocytomas WHO IV, and d) *IDH1/2wt* astrocytomas WHO IV vs *IDH1/2wt* astrocytomas WHO II and III vs *IDH1/2wt* glioblastomas.

The MRI characteristics at the time of histological diagnosis of 83 *IDH1/2wt* LGGs are shown in Table 2. Minor nodular or patchy contrast enhancement was present in 29 of the 83 *IDH1/2wt* LGGs (Fig. 1B). No occipital lesions were identified in *IDH1/2wt* astrocytomas WHO II and III. Slight infiltration into the brainstem was more frequently observed in *IDH1/2wt* astrocytomas WHO II and III compared with *IDH1/2wt* astrocytomas WHO IV (37.5% and 9%, respectively; $P = 0.009$). No other differences were observed between the *IDH1/2wt* astrocytomas WHO IV and the *IDH1/2wt* astrocytomas WHO II and III in location distribution, growth pattern (including gliomatosis cerebri), or presence of subtle contrast enhancement. In addition, no radiological differences were identified between *pTERTmt* only and other *IDH1/2wt* astrocytomas WHO IV. Gliomatosis cerebri was present in 35.8% of the *IDH1/2wt* astrocytomas WHO IV and 18.8% of the *IDH1/2wt* astrocytomas WHO II and III. The majority of the *IDH1/2wt* astrocytomas WHO IV were located in the temporal lobe, the insular region, and the parietal lobe. In *IDH1/2wt* astrocytoma WHO II and III patients more than half of the lesions were observed in the temporal lobe.

Survival Data of All IDH1/2wt Gliomas

At the time of analysis, 223 of 284 *IDH1/2wt* glioma patients were deceased: 53 *IDH1/2wt* astrocytoma WHO IV patients (74.6%), 165 *IDH1/2wt* glioblastoma patients (83.8%), and 5 *IDH1/2wt* astrocytoma WHO II and III patients (31.3%). Median follow-up of all *IDH1/2wt* glioma patients was 1.5 years (*IDH1/2wt* astrocytomas WHO IV: 1.4 y, *IDH1/2wt* glioblastomas: 1.5 y, *IDH1/2wt* astrocytomas WHO II and III: 2.9 y; Table 1). Median OS for the *IDH1/2wt* astrocytomas WHO IV and the *IDH1/2wt* glioblastomas was similar (23.8 mo vs 19.2 mo, log-rank test: $P = 0.25$), but the median OS of the *IDH1/2wt* astrocytomas WHO II and III was significantly longer compared with the other 2 glioma subtypes (median OS not reached, log-rank test: $P < 0.001$; Fig. 4).

Univariable analysis identified lower KPS before surgery as a significant unfavorable prognostic factor for survival (KPS ≤80 vs KPS 90–100: HR 1.54, 95% CI: 1.17–2.02, $P = 0.002$; Supplementary Table 1). Other prognostic factors from univariable analysis that showed a level of significance <0.10 included sex and age of onset, in which male patients were associated with a worse outcome (male vs female: HR 1.33, 95% CI: 1.00–1.76, $P = 0.05$) and younger patients were associated with a better prognosis (<40 y vs 40–60 y: HR 0.62, 95% CI: 0.39–0.97; >60 y vs 40–60 y: HR 1.02, 95% CI: 0.77–1.36; $P = 0.07$). Multivariable analysis taking into account age, sex, KPS before surgery, and the type of first surgery confirmed the similar survival of *IDH1/2wt* astrocytomas WHO IV and *IDH1/2wt* glioblastomas (HR 1.27, 95% CI: 0.85–1.88, $P = 0.242$) and the better survival in *IDH1/2wt* astrocytomas WHO II and III compared with *IDH1/2wt* astrocytomas WHO IV (HR 0.30, 95% CI: 0.12–0.78, $P = 0.013$; Supplementary Fig. 1). Adding primary treatment after surgery to the multivariable analysis led to similar results, although power of the analysis was reduced in comparison to the previously mentioned model (Supplementary Fig. 2).

Table 2 Radiological characteristics of *IDH1/2wt* LGGs as determined on MRI at the time of histological diagnosis*

Characteristics	*IDH1/2wt* Astrocytomas WHO IV	*IDH1/2wt* Astrocytomas WHO II and III	P^a	*IDH1/2wt* Astrocytomas WHO IV, *pTERTmt* only	P^b
Patients, *n*	67	16		21	
Hemisphere, *n* (%)			0.636		0.933
Right	23 (34.3)	7 (43.8)		8 (38.1)	
Left	30 (44.8)	5 (31.3)		8 (38.1)	
Bilateral	14 (20.9)	4 (25)		5 (23.8)	
Tumor location, *n* (%)					
Frontal lobe	33 (49.3)	6 (37.5)	0.421	11 (52.4)	0.391
Parietal lobe	34 (50.7)	5 (31.3)	0.178	13 (61.9)	0.569
Temporal lobe	50 (74.6)	10 (62.5)	0.360	18 (85.7)	1.000
Occipital lobe	17 (25.4)	0 (0)	0.034	8 (38.1)	0.763
Insula	39 (58.2)	6 (37.5)	0.168	15 (71.4)	0.376
Corpus callosum	23 (34.3)	3 (18.8)	0.368	10 (47.6)	0.568
Basal ganglia	32 (47.8)	6 (37.5)	0.580	12 (57.1)	0.567
Thalamus	25 (37.3)	7 (43.8)	0.776	10 (47.6)	0.775
Brainstem	6 (9)	6 (37.5)	0.009	4 (19.0)	0.223
Cerebellar	1 (1.5)	1 (6.3)	0.350	1 (4.8)	0.420
Growth pattern, *n* (%)					
Gliomatosis cerebri	24 (35.8)	3 (18.8)	0.241	11 (52.4)	0.394
Multifocal	6 (9.0)	1 (6.3)	1.000	1 (4.8)	0.636
Minor contrast enhancement, *n* (%)					
Present	21 (31.3)	8 (50)	0.146	5 (23.8)	1.000

*Only patients with available cT1w imaging and either FLAIR or T2w imaging were incorporated in this table. The indicated *P*-values compared a) *IDH1/2wt* astrocytomas WHO IV vs *IDH1/2wt* astrocytomas WHO II and III, and b) *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only vs other *IDH1/2wt* astrocytomas WHO IV.

The survival of the *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only was similar to the survival of the *IDH1/2wt* glioblastomas (median OS: 14.4 mo vs 19.2 mo, log-rank test: $P = 0.89$; Supplementary Fig. 3). At the time of analysis, 18 *pTERTmt* only patients (81.8%) were deceased, and median follow-up of the *pTERTmt* only patients was 1.2 years. Univariable analysis identified both sex and KPS before surgery as significant prognostic factors, in which male patients and patients with a KPS below 80 had a shorter OS (male vs female: HR 1.40, 95% CI: 1.02–1.92, $P = 0.04$; KPS ≤80 vs KPS 90–100: HR 1.40, 95% CI: 1.04–1.89, $P = 0.03$; Supplementary Table 2). The similar survival in *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only and *IDH1/2wt* glioblastomas remained after correction for confounding factors in multivariable analysis (*IDH1/2wt* glioblastomas vs *IDH1/2wt* astrocytomas WHO IV, *pTERTmt* only: HR 1.15, 95% CI: 0.64–2.10, $P = 0.641$; Supplementary Fig. 4).

In 3 *pTERTmt* only patients *EGFR* mutations were identified (*A289D*, *A289V*, and *P596L*). It could be argued that these 3 tumors should not be classified as *pTERTmt* only *IDH1/2wt* astrocytomas WHO IV. However, even without these 3 samples, survival of *pTERTmt* only patients was similar to *IDH1/2wt* glioblastomas (median OS: 14.4 mo vs 19.2 mo, log-rank test: $P = 0.94$; Supplementary Fig. 5).

Discussion

Diffuse astrocytic glioma, *IDH1/2* wildtype, with molecular features of glioblastoma WHO grade IV represent a new glioma subtype proposed by the cIMPACT-NOW committee. The diagnostic criteria require testing for *pTERT* mutation status, for chromosome copy alterations of chromosome 7 and 10, and for *EGFR* amplification, all of which can be routinely performed. This study's confirmation of poor survival in *IDH1/2wt* LGG patients (with clinical, radiological, and histological characteristics meeting the classical criteria for grade II or III glioma) in the presence of these molecular markers supports a reclassification in the next official WHO classification of *IDH1/2wt* astrocytomas WHO IV to *IDH1/2wt* glioblastomas. Moreover, patients with *IDH1/2wt* astrocytomas with only *pTERT* mutations had a similar poor outcome.

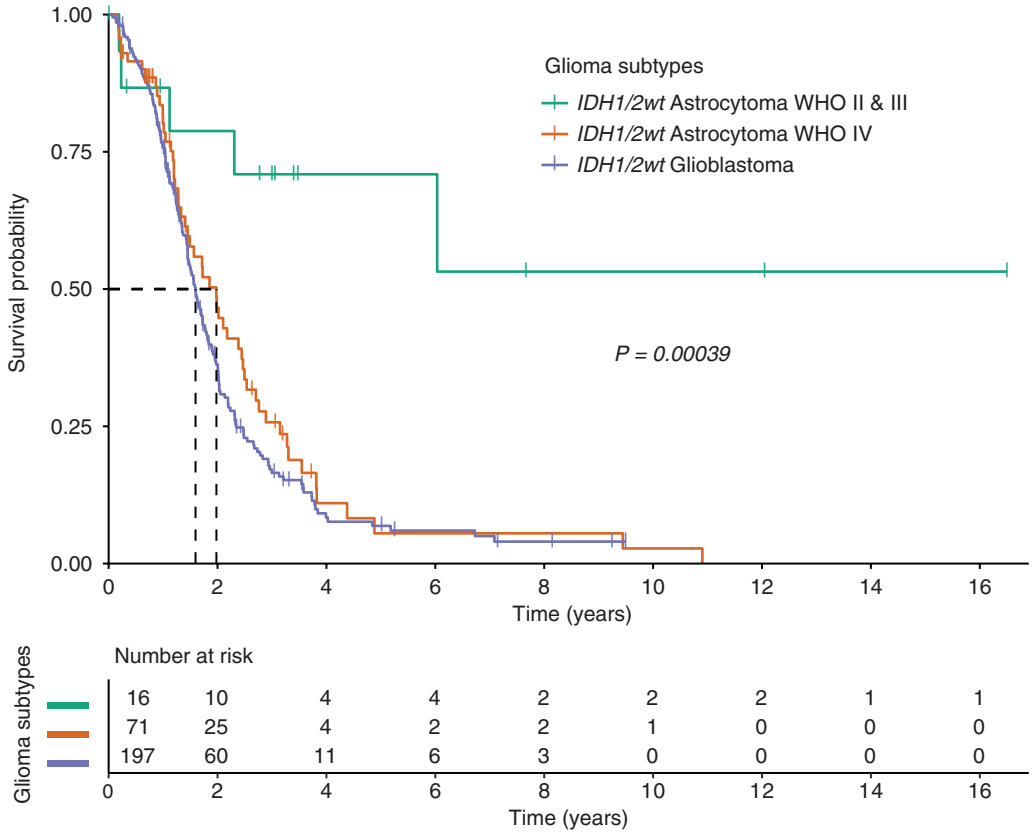

Fig. 4 Kaplan–Meier curves of the OS of the *IDH1/2wt* astrocytomas WHO II and III, the *IDH1/2wt* astrocytomas WHO IV, and the *IDH1/2wt* glioblastomas. The dashed line represents the median OS.

In this cohort, we did not find a *BRAF* mutation in the *IDH1/2wt* astrocytomas WHO IV group and therefore also no *BRAF* mutations in the *pTERTmt* only group. This is important because *BRAF* mutations are also found in pleomorphic xanthoastrocytomas and these tumors may have *pTERT* mutations and a markedly improved survival compared with other glioma subtypes.[4,6]

Of note, the OS of *IDH1/2wt* glioblastoma patients in our dataset may appear markedly longer than historical cohorts (19.2 mo vs 14–16 mo in large studies).[13,16-18] However, the longer survival is largely explained by the measurement of OS from first diagnostic scan until death, whereas most cohorts measure from date of randomization, which typically adds 2–3 months. In addition, our dataset contained a relatively young population of *IDH1/2wt* glioblastoma patients and age is a well-known prognostic factor for poor survival in gliomas.[11–15] Until recently routine NGS was only performed in younger glioblastoma patients. However, after correction for age in the multivariable analysis the OS of the *IDH1/2wt* astrocytomas WHO IV and the *IDH1/2wt* glioblastomas remained similar.

The most important limitation of our study is its retrospective design. This design made it impossible to control for the treatment regimens after surgery, which may have impacted on survival. Due to the non-glioblastoma radiological and histological diagnosis, most *IDH1/2wt* astrocytomas WHO IV were treated less intensively and this may have adversely affected outcome. Moreover, our study was restricted to patients in whom *IDH1/2* status was assessed with a glioma dedicated NGS panel. This was reflected in a younger *IDH1/2wt* glioblastoma cohort as mentioned earlier. Finally, we used the original clinical diagnosis without review, as this was the way the patients were initially diagnosed.

In conclusion, this study has shown similar survival of patients with *IDH1/2wt* astrocytomas WHO IV and *IDH1/2wt* glioblastomas. Furthermore, this similar survival is also present in *IDH1/2wt* astrocytoma patients with *pTERTmt* only. Our data therefore support the classification of *IDH1/2wt* astrocytomas WHO IV with the *IDH1/2wt* glioblastomas, without further distinctions. Further prospective studies should try to understand why these tumors do not show the classical radiological and histopathological characteristics of glioblastoma.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

astrocytoma | glioblastoma | cIMPACT-NOW | *IDH* | *TERT*

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