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CLINICAL ARTICLE

Huge heterogeneity in survival in a subset of adult patients with resected, wild-type isocitrate dehydrogenase status, WHO grade II astrocytomas

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OBJECTIVE World Health Organization grade II gliomas are infiltrating tumors that inexorably progress to a higher grade of malignancy. However, the time to malignant transformation is quite unpredictable at the individual patient level. A wild-type isocitrate dehydrogenase (IDH-wt) molecular profile has been reported as a poor prognostic factor, with more rapid progression and a shorter survival compared with IDH-mutant tumors. Here, the oncological outcomes of a series of adult patients with IDH-wt, diffuse, WHO grade II astrocytomas (AII) who underwent resection without early adjuvant therapy were investigated.

METHODS A retrospective review of patients extracted from a prospective database who underwent resection between 2007 and 2013 for histopathologically confirmed, IDH-wt, non–1p19q codeleted AII was performed. All patients had a minimum follow-up period of 2 years. Information regarding clinical, radiographic, and surgical results and survival were collected and analyzed.

RESULTS Thirty-one consecutive patients (18 men and 13 women, median age 39.6 years) were included in this study. The preoperative median tumor volume was 54 cm^3 (range 3.5–180 cm^3). The median growth rate, measured as the velocity of diametric expansion, was 2.45 mm/year. The median residual volume after surgery was 4.2 cm^3 (range 0–30 cm^3) with a median volumetric extent of resection of 93.97% (8 patients had a total or supratotal resection). No patient experienced permanent neurological deficits after surgery, and all patients resumed a normal life. No immediate postoperative chemotherapy or radiation therapy was given. The median clinical follow-up duration from diagnosis was 74 months (range 27–157 months). In this follow-up period, 18 patients received delayed chemotherapy and/or radiotherapy for tumor progression. Five patients (16%) died at a median time from radiological diagnosis of 3.5 years (range 2.6–4.5 years). Survival from diagnosis was 77.27% at 5 years. None of the 21 patients with a long-term follow-up greater than 5 years have died. There were no significant differences between the clinical, radiological, or molecular characteristics of the survivors relative to the patients who died.

CONCLUSIONS Huge heterogeneity in the survival data for a subset of 31 patients with resected IDH-wt AII tumors was observed. These findings suggest that IDH mutation status alone is not sufficient to predict risk of malignant transformation and survival at the individual level. Therefore, the therapeutic management of AII tumors, in particular the decision to administer early adjuvant chemotherapy and/or radiation therapy following surgery, should not solely rely on routine molecular markers.

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KEYWORDS diffuse WHO grade II astrocytoma; molecular biology; IDH status; surgery; survival; oncology

ABBREVIATIONS AII = grade II astrocytoma; GBM = glioblastoma; IDH = isocitrate dehydrogenase; IDH-wt = wild-type IDH; NADPH = nicotinamide adenine dinucleotide phosphate; OS = overall survival; PA = pilocytic astrocytoma; PCR = polymerase chain reaction; TERTp = *TERT* gene promoter; VDE = velocity of diametric expansion.

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World Health Organization grade II gliomas in adults are infiltrating tumors that inexorably grow, migrate along the white matter tracts, and progress to a higher grade of malignancy. However, the timing of their malignant transformation is quite unpredictable at the individual level.[12] The classification and grading of diffuse gliomas has traditionally been based primarily on histopathological features. However, the more recent 2016 WHO classification for gliomas emphasizes molecular data and ushers in a new era in neuropathology in which genotype is incorporated into an integrated diagnosis.[25] Indeed, molecular biomarkers have now become an established component of the neuropathological diagnosis because these biomolecular parameters provide additional value in prognostication. For diffuse gliomas, isocitrate dehydrogenase (IDH) status is central to the molecular diagnosis. More than 80% of WHO grade II and III astrocytomas are IDH mutated, while, by definition, all oligodendrogliomas are IDH mutated with 1p and 19q codeletion.[37]

Since its discovery in 2008,[31] the prognostic value of IDH mutations has been extensively investigated. Several pioneer studies reported decreased survival for patients with wild-type IDH (IDH-wt) WHO grade II and III gliomas.[11,24,35,38] Using next-generation sequencing technologies, more recent studies have considerably expanded the knowledge of the molecular profile of gliomas, and these data confirmed the less-favorable outcomes of IDH-wt gliomas in a series of grade II and III mixed tumors.[5,7,18,21,36] For example, in a Cancer Genome Atlas Research Network study, lower-grade IDH-wt gliomas exhibited a median overall survival (OS) of 1.7 years.[5] Nevertheless, in 2 studies in which the proportion of IDH-wt WHO grade II tumors was larger (36 tumors in the study by Suzuki et al.[36] and 19 tumors in the study by Ceccarelli et al.[7]), OS data were more heterogeneous: analysis of data for a patient subgroup enriched with patients with grade II tumors showed increased survival.

Although IDH-wt grade II gliomas lack necrosis and microvascular proliferation and therefore do not fulfill the histological definition of glioblastoma (GBM), their molecular profile is strikingly similar to that of primary IDH-wt GBMs. Indeed, they have been predominantly reported as displaying a GBM-like genetic, transcriptomic, and epigenetic profile.[5,21,36] However, for the subgroup of patients with extended OS, tumors had a mutational and epigenetic landscape suggestive of the grade I pilocytic astrocytoma (PA) with more frequent mutations in the *BRAF*, *FGFR1*, and *NF1* genes.[7]

Therefore, due to the discrepancy regarding the prognostic value of IDH status in the current literature, which is a crucial parameter in defining optimal management at the individual level in patients with grade II gliomas, we studied a consecutive and homogeneous cohort of 31 adults who underwent resection of IDH-wt, diffuse, WHO grade II astrocytoma (AII). Our goal was to analyze oncological outcomes in patients following surgery who did not receive early adjuvant therapy by integrating various clinical and radiological characteristics in this defined subpopulation with an unfavorable biomolecular pattern according to the revised WHO classification. We extended the molecular characterization of these tumors to include mutations in the *TERT* gene promoter (TERTp), as well the *BRAF* and *FGFR1* genes that are commonly seen in grade I astrocytomas. Of note, although we also investigated ATRX status, we did not analyze the status of CIC and FUBP1 because these mutations in gliomas are associated with oligodendroglial differentiation, IDH mutation, and 1p19q loss of heterozygosity,[3,9] which is a profile that does not correspond to the AII cohort in this study.

Methods

Selection of Patients and Evaluation Methods

We performed a retrospective review of adult patients extracted from our prospective database who were surgically treated between 2007 and 2013 for histopathologically confirmed supratentorial, IDH-wt, non–1p19q-codeleted AII. All patients had a minimum follow-up of 2 years.

Clinical characteristics (age, sex, neurological status), radiological features (topography, tumor volume, velocity of diameter expansion), surgical results (extent of resection, delay before administering adjuvant oncological therapy), and survival were collected and analyzed.

Radiological Examination

The topography of each tumor was accurately analyzed using preoperative 3D MR images (T1-weighted and spoiled gradient-echo images obtained with and without gadolinium, T2-weighted images, and FLAIR images). In the first period of this series, preoperative tumor volume was calculated using the 3 largest diameters (D1, D2, and D3) of FLAIR hyperintensity in 3 orthogonal planes (axial, sagittal, and coronal). An estimation of tumor volume was calculated using the ellipsoid approximation ([D1 × D2 × D3]/2), as previously reported.[30] The volume of the residual tumor (if present) was calculated at 3 months postoperatively using the same method for the FLAIR MR images used to determine the preoperative volume. In the second period of the series, both pre- and postoperative glioma volumes were calculated using dedicated software (Myrian, Intrasense). Of note, it has been shown that volumes calculated with the 3-diameter technique closely approximate those derived using the segmented method.[26] The tumor growth rate (i.e., the velocity of diametric expansion [VDE]) was derived from serial MR image sets obtained prior to surgery using a previously described method.[30] Mean tumor diameter was calculated from the tumor volume using the following formula: mean tumor diameter = $(2 \times \text{volume})^{1/3}$. VDE (the slope of the mean tumor diameter growth rate) was plotted as a function of the mean tumor diameter over time. Finally, scans obtained during the postoperative follow-up period were examined for the presence of enhancement.

Surgical Procedure

All surgical procedures were performed using the asleep-awake-asleep technique with intraoperative direct electrical stimulation that allowed for mapping of the cortical and subcortical eloquent structures. In all cases,

resection was continued until critical neural networks were identified by positive mapping to optimize the extent of resection while preserving quality of life. Technical details of our functional mapping–guided surgical procedure have been extensively described in previous reports.[4,14–16]

Histological Analysis

All tumor samples were examined twice by a neuropathologist: the first time at diagnosis and a second time during a reevaluation of every slide for the present study.

Molecular Analysis

Tumor and blood samples were collected from each patient at surgery after obtaining his or her informed consent. Tumor DNA was isolated from frozen tumor samples using the QIAamp DNA mini-kit (Qiagen, GmbH). For 1p19q status determination, reference DNA was extracted from the patient's EDTA-treated peripheral blood sample using the MagNA Pure Compact automatic extractor (Roche).

Determination of IDH Mutational Status

IDH1 status was at first determined by polymerase chain reaction (PCR) amplification of exon 4 with the following primers: IDH1F, 5′-TGTAAAACGACGGCCAGTACCAAATGGCACCATACGA-3′; and IDH1R, 5′-CAGGAAACAGCTATGACCTTCATACCTTGCTTAATGGGTGT-3′.

The forward and reverse chains were analyzed on an ABI Prism 3130XL genetic analyzer (Applied Biosystems, Thermo Fisher Scientific). If no mutation was detected, PCR amplification and double-strand Sanger direct sequencing of exon 4 of the *IDH2* gene was performed with the following primers for PCR amplification: IDH2F, 5′-TGTAAAACGACGGCCAGTCAAGCTGAAGAAGATGTGGAA-3′; and IDH2F, 5′-CAGGAAACAGCTATGACCAGAGACAAGAGGATGGCTA-3′.

Determination of 1p19q Loss of Heterozygosity

All WHO grade II gliomas were systematically tested for 1p19q codeletion during the study period at our institution. The 1p19q status was determined by microsatellite analysis for loss of heterozygosity using highly polymorphic markers: 8 markers were used to screen the entire 1p chromosome arm (from the 1p36.32 to 1p 21.2 bands) and 4 markers were used to screen the 19q chromosome arm (from the 19 q12 to 19 q13.41 bands).

Determination of the Mutational Status of TERTp

TERTp was amplified using the TERT-F (5′-TGTAAAACGACGGCCAGTACCCGTCCTGCCCCTTCACCTTC-3′) and *TERT* primers (5′-CAGGAAACAGCTATGACCGACGCAGCGCTGCCTGAAACTC-3′) followed by Sanger sequencing using the ABI Prism 3130XL genetic analyzer.

Determination of Mutational Status in the Hotspot Regions of the *BRAF* and *FGFR1* Genes

Exon 15 of *BRAF* and exons 12 and 14 of *FGFR1* were amplified by PCR using the following primers: BRAFexon15F, 5′-TGTAAAACGACGGCCAGTCTGTTTTCCTTTACTTACTACACCTC-3′; BRAFexon15R, 5′-CAGGAAACAGCTATGACCAATCAGTGGAAAAATAGCCTCAATTC-3′; FGFR1exon12F, 5′-TGTAAAACGACGGCCAGTCCCAAGTAAATGAGTCTCAACGTG-3′; FGFR1exon12R, 5′-CAGGAAACAGCTATGACCACTGATACCCCAGCTCAGATCTTC-3′; FGFR1exon14F, 5′-TGTAAAACGACGGCCAGTACCTCCCCGCCTCCCGCTCTCCCTT-3′; and FGFR1exon14R, 5′-CAGGAAACAGCTATGACCGTTCTCGCCCACCCCACTCCTTGC-3′.

Statistical Analysis

OS was defined as the time from histopathological diagnosis to death. Survival curves were calculated using the Kaplan-Meier method with SPSS software (version 22, IBM Corp.). In addition, we compared 2 subgroups: the first group consisted of patients who were deceased at the last follow-up, and the second group consisted of patients who were alive at the last follow-up. Sex, age at diagnosis, duration of follow-up, delay before adjuvant therapy, and survival were analyzed in both groups, and these characteristics were compared using SPSS with univariate analysis via the Student t-test.

Results

Clinical Characteristics

Thirty-one consecutive patients who underwent awake resection according to the functional boundaries of the diffuse AII with no IDH1/IDH2 mutation and no 1p19q codeletion fulfilled the eligibility criteria. The characteristics of this population are summarized in Table 1.

There were 18 men and 13 women (sex ratio 1.38) with a median age at diagnosis of 39.6 years (range 17–63 years). The most common presenting symptom was epilepsy, with partial seizures in 13 patients (41.9%) and generalized seizures in 14 patients (45.2%). For 3 other patients (9.7%), the discovery of the glioma was incidental (MRI performed for unrelated reasons). For the remaining patient, an MRI was ordered because of diplopia (Table 1).

Preoperative neurological examination and neuropsychological assessment revealed normal neurocognitive results in 10 patients (32.3%), attention or memory disorders in 7 patients (22.6%), language disturbances (semantic paraphasia) in 8 patients (25.8%), decreased executive functioning in 2 patients (6.5%), and psychomotor slowness in 1 patient (3.2%). Of note, 10 patients (32.2%) had medically refractory seizures prior to surgery (Table 1).

Radiographic Characteristics

Glioma Location

Tumor locations are summarized in Table 2. Fifteen tumors (48.39%) involved the temporal lobe (9 left- and 6 right-sided tumors); 8 tumors (25.81%) had insular involvement (4 left- and 4 right-sided paralimbic gliomas); 5 tumors (16.13%) were located in the frontal lobe (2 on the left and 3 on the right side); 2 (6.45%) were localized to the left parietal lobe; and 1 tumor (3.23%) infiltrated the occipital lobe (left temporooccipital tumor).

TABLE 1. Summary of the clinical data

Variable	Value
Sex	
Men	18
Women	13
Median age at diagnosis (range), yrs	39.64 (17–63)
Median follow-up, mos	74.03
1st symptom	
Generalized seizures	14 (45.16)
Partial seizures	13 (41.93)
Incidental discovery	3 (9.68)
Diplopia	1 (3.23)
Preop neurological status	
Asymptomatic	10 (32.26)
Intractable epilepsy	10 (32.26)
Speech disorders	8 (25.81)
Attention or memory disorders	7 (22.58)
Dysexecutive disorders	2 (6.45)
Psychomotor slowness	1 (3.23)

Values are shown as the number of patients (%) unless otherwise indicated.

Preoperative Tumor Volume, VDE, and Extent of Resection

The median initial tumor volume was 54.15 cm^3 (range 3.5–180 cm^3). Of note, only 5 of 31 patients were evaluated using the 3-diameter technique. Thus, the more accurate segmented method of volumetric assessment was used in the vast majority of cases (26 patients; 84%).

Median growth rate (VDE) was 2.45 mm/year (range 0.4–5 mm/year) (Table 3). In this population, VDE was not calculated for 8 patients for the following reasons: either a significant mass effect required urgent surgery, and thus only 1 MRI evaluation was obtained preoperatively, or only 2 preoperative MRI evaluations were obtained that were too close in time to permit accurate extrapolation. In addition, 1 patient had preoperative chemotherapy. Among the other 23 patients, 3 (13%) had VDE less than 1 mm/year, 9 patients (39.1%) had VDE between 1 and 2 mm/year, 5 patients (21.74%) had VDE between 2 and 3 mm/year, 4 patients (17.4%) had VDE between 3 and 4 mm/year, and only 2 patients (8.7%) had a VDE greater than 4 mm/year (Fig. 1).

The median residual volume after surgery was 4.29 cm^3 (range 0–30 cm^3). The median volumetric extent of resection was 93.97% (Table 3), including 4 gross-total resections (2 right temporal tumors, 1 left temporal tumor, and 1 glioma in the right supramarginal gyrus) and 4 supratotal resections (2 right temporal tumors, 1 left precentral tumor, and 1 glioma in the left angular gyrus).

TABLE 2. Tumor locations

Location	Lt Hemisphere	Rt Hemisphere	Total
Frontal lobe	2 (6.45)	3 (9.68)	5 (16.13)
Parietal lobe	2 (6.45)	0 (0)	2 (6.45)
Temporal lobe	9 (29.04)	6 (19.35)	15 (48.39)
Temporo-occipital lobe	1 (3.23)	0 (0)	1 (3.23)
Paralimbic system	4 (12.9)	4 (12.9)	8 (25.81)

All values are shown as the number (%) of tumors.

TABLE 3. Pre- and postoperative tumor volumes

Volume	Value
Median preop volume, cm^3	54.15
Median postop volume, cm^3	4.29
Median extent of resection, %	93.97
Median preop growth rate, mm/yr	2.45

Histological Analysis

The neuropathological diagnosis of WHO grade AII was confirmed on re-review of imaging for all 31 patients in the current study.

Molecular Characteristics

By definition, all tumors in the current study were IDH-wt and lacked 1p19q codeletion. In addition, only 1 tumor had a TERTp C228T mutation. No tumors had mutations in *BRAF* exon 15 or exons 12 and 14 of *FGFR1* (the so-called PA-like mutations). Among the 31 gliomas, 5 tumors had a total loss of ATRX expression.

Postoperative Course

No patient experienced postoperative permanent neurological deficits, and all patients resumed a normal life.

Due to the high extent of resection (94% on average) and because these grade II astrocytoma patients were managed prior to the new 2016 WHO classification,[25] no immediate postoperative adjuvant treatment was given. The median follow-up was 74 months (range 24–157 months), including 2–4 years in 7 patients (22.6%), 5–7 years in 16 patients (51.6%), and > 7 years in 8 patients (25.8%). Two patients (6.45%) had follow-up of more than 10 years (Fig. 2).

In the follow-up period, 18 patients received delayed adjuvant treatment. Adjuvant therapy was started for the following reasons in the case of postoperative residual tumor: 1) occurrence of enhancement; 2) acceleration of growth rate (VDE > 8 mm/year); 3) tumor volume of 10–15 cm^3 reached due to FLAIR progression; and/or 4) occurrence of new clinical symptoms (e.g., seizures).[17] Chemotherapy with temozolomide was the first therapeutic option. However, if new contrast enhancement was observed and/or VDE accelerated beyond 8 mm/year then radiotherapy was initiated. In practice, 16 patients (51.6%) received chemotherapy (temozolomide) with a median delay of 35.6 months and 11 patients (35.5%) underwent radiation therapy with a median delay of 31.9 months (Table 4). Of note, 9 patients received both treatments. In 7 patients (22.58%), new contrast enhancement was seen on postoperative surveillance MRI, with a median delay between diagnosis and onset of enhancement of 32 months (range 24–43 months). Five of these patients died during the follow-up period. In the 13 other patients (41.9%), no adjuvant treatment was

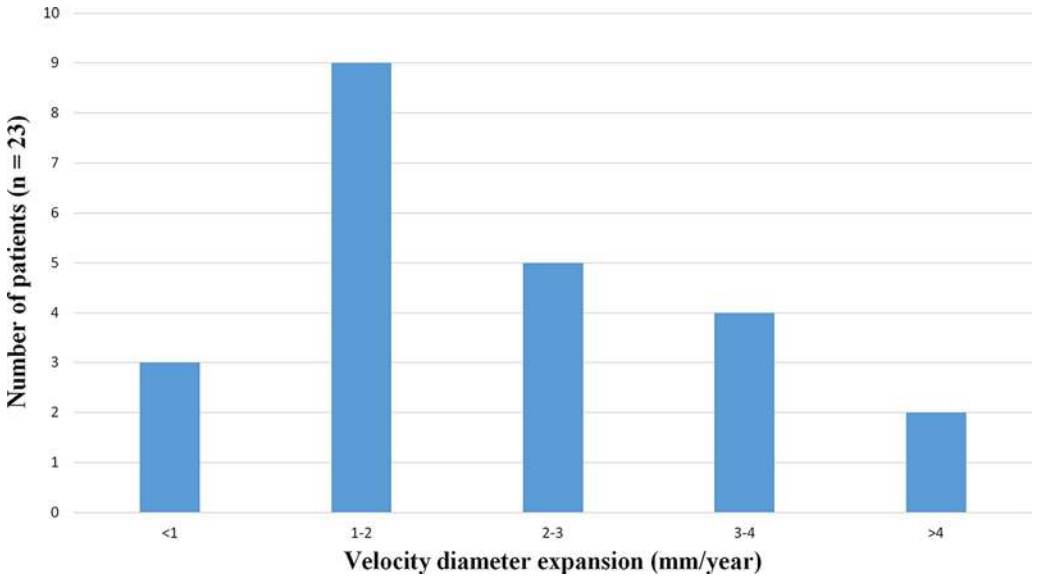

FIG. 1. Distribution of VDE. Figure is available in color online only.

administered, with a median follow-up of 79 months in this subgroup (range 33–157 months).

Survival Analysis

Survival from diagnosis was 77.27% at 5 years for the entire study cohort. Five of 31 patients died during the follow-up period at a median time from radiological diagnosis of 3.5 years (range 2.6–4.5 years) (Fig. 3). None of the 21 patients with long-term follow-up (> 5 years) had died at study closure.

There were no significant differences in the clinical and radiological characteristics between the survivors and the patients who died with regard to the median age at diagnosis (45.2 years for the population of patients who died vs 38.6 years for survivors; p = 0.29), initial tumor volume (median 61.2 cm^3 for the population of patients who died vs 5.9 cm^3 for survivors; p = 0.71), extent of resection (median 91.6% of the subgroup of patients who died vs 94.5% of survivors; p = 0.11), or residual volume (median 4.7 cm^3 for the subgroup of patients who died vs 4.2 cm^3 for survivors; p = 0.81). In particular, there were no differences between the rates of gross-total and supratotal resections (none of these patients died within 76–78 months of follow-up). In addition, there were no correlations between growth rate and survival: median VDE prior to surgery in the population of patients who died early was 3.14 mm/year (range 1.6–4.8 mm/year) vs 2.26 mm/year (range 0.4–5 mm/year) in the population of long-term survivors (p = 0.88). No association was found between ATRX status and outcome. There was a similar distribution of tumor locations between the subgroup of patients who died (1 left fronto-insular, 1 left temporo-occipital, 1 left temporal, 1 right fronto-temporo-insular, and 1 right temporal tumor) and the subgroup of survivors (p = 0.22) (Table 5). Finally, by applying the clinical risk classification described by Pignatti et al.[32] to our cohort, we did

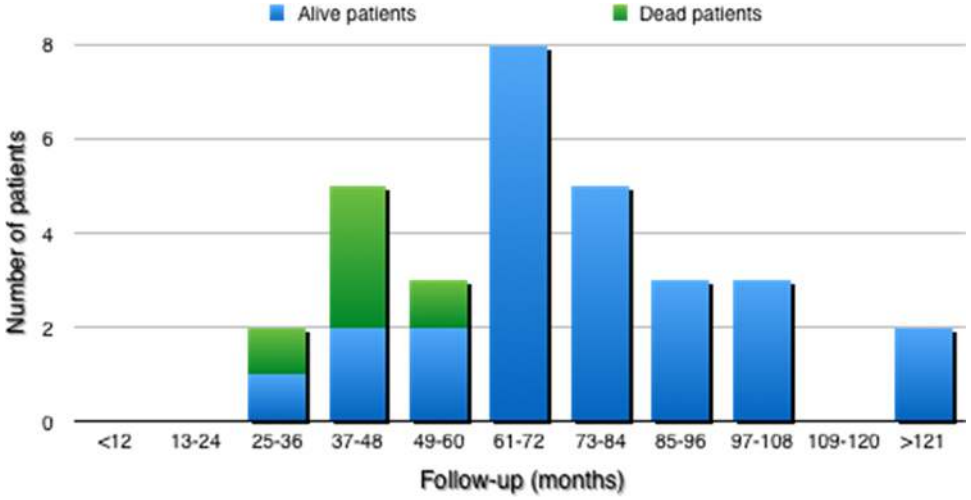

FIG. 2. Heterogeneous relationship between follow-up and survival. Figure is available in color online only.

TABLE 4. Adjuvant therapy

Therapy	Value
Chemotherapy, n (%)	16 (51.61)
Radiotherapy, n (%)	11 (35.48)
No adjuvant therapy, n (%)	13 (41.94)
Median delay from diagnosis to chemotherapy, mos	35.62
Median delay from diagnosis to radiotherapy, mos	31.89

not find any significant impact on survival associated with age > 40 years (2 of 5 patients who died were < 40 years), presence of neurological deficits before surgery, largest tumor diameter (3 of 5 patients who died had tumors with a diameter < 6 cm), or tumor crossing the midline (only 1 patient had contralateral infiltration through the corpus callosum and he was still alive at the time of this report).

Two Cases of Left Temporoinsular Low-Grade AII With Different Evolutions

There were 2 patients who had similarly appearing left temporoinsular diffuse AII (Figs. 4 and 5). VDE was 4 mm/year for the first patient and 5 mm/year for the second. Both patients benefited from subtotal resection: namely, 95% extent of resection for the first patient and 90% for the second patient. The histopathological and molecular results were similar. However, the first patient died only 27 months after diagnosis despite receiving chemotherapy and radiotherapy, while the second patient is still alive after a follow-up of 60 months. The second patient did receive 18 months of adjuvant temozolomide and is currently undergoing routine surveillance with no recent significant growth noted on MRI. In both cases, resection was stopped because semantic paraphasia was elicited with stimulation of the inferior frontooccipital fascicle (within the temporal stem) at the depth of the resection cavity. These 2 examples illustrate the heterogeneity in oncological outcomes despite identical biomolecular patterns.

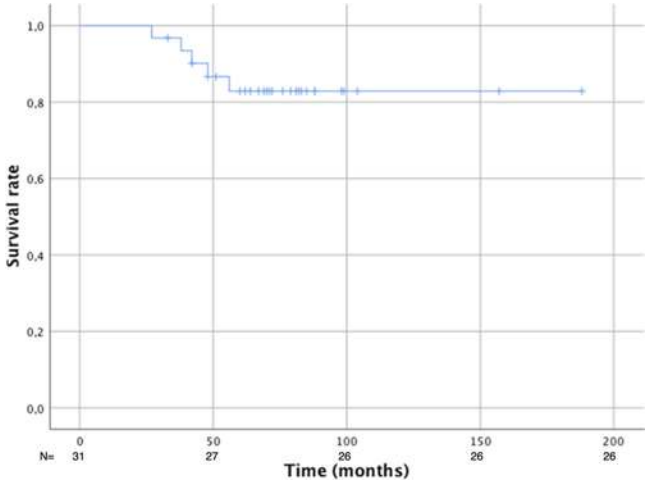

FIG. 3. Kaplan-Meier estimate of survival from diagnosis. Figure is available in color online only.

TABLE 5. Characteristics of the alive and deceased patients at the last follow-up

Characteristic	Alive	Dead	p Value*
No. of patients	26	5	
Median age at diagnosis, yrs	38.57	45.2	0.29
Median preop tumor volume, cm^3	52.29	61.2	0.71
Median postop residual volume, cm^3	4.2	4.7	0.81
Median extent of resection, %	94.46	91.6	0.11

* All values are nonsignificant.

Discussion

The current WHO classification is based on combined phenotypic (histological) and genotypic parameters, thereby yielding integrated diagnoses.[25] Indeed, substantial progress has been made with respect to the molecular pathogenesis of gliomas, especially the role of IDH mutations (IDH1 and IDH2) in predicting the clinical behavior and prognosis of grade II gliomas.[5,7,11,24,35,36,38] IDH mutations are frequent in diffuse astrocytomas (88%) and oligodendrogliomas (79%), as well as in secondary GBM.[37] Thus, IDH mutations are considered to be among the earliest genetic alterations in WHO grade II gliomas. Consistent with this notion, Watanabe et al.[37] demonstrated that IDH1 mutations were early events in gliomagenesis in 51 patients who provided sequential biopsies, with no cases of IDH1 mutation occurring after the acquisition of *TP53* mutation or loss of 1p/19q. In a confirmation of this first result, Suzuki et al. demonstrated, at the whole-exome scale, that *IDH* gene mutations presented the largest variant allele frequency compared with other co-occurring gene mutations, thereby making them a founder event in tumors harboring these mutations.[36]

The *IDH1* gene (2q33) and *IDH2* gene (15q26) encode the enzyme IDH1 of the cytosolic citric and acid cycle. IDH1/2 is a homodimeric enzyme that catalyzes the conversion of isocitrate to α-ketoglutarate and produces nicotinamide adenine dinucleotide phosphate (NADPH). IDH1 mutation occurs at arginine 132, while IDH2 mutation occurs at arginine 172 or arginine 140. Although both IDH1 and IDH2 mutations occur in diffuse low-grade gliomas, IDH2 mutations are much less common than IDH1 mutations.[1] Gliomas with IDH1/2 mutations result in a gain of function of metabolic enzymes IDH1 and 2. The mutant protein loses normal enzymatic activity, resulting in the production of an oncometabolite (R-2-hydroxyglutarate) that consumes NADPH. Elevated levels of 2-hydroxyglutarate inhibit enzymes that regulate cellular epigenetic status, including α-ketoglutarate–dependent histone demethylases, the TET family of 5-methylcytosine hydroxylases, and DNA demethylases, thereby resulting in genome-wide epigenetic alterations. Mutant IDH changes the inherent redox environment by altering the ratio of NADPH to NADP, with NAD depletion conferring a metabolic susceptibility characteristic of IDH1 mutant tumors.[2]

Currently, on the basis of IDH mutation status, WHO grade II and III gliomas can be primarily classified as IDH-mutated "true" lower-grade gliomas and IDH-wt gliomas. IDH-wt gliomas typically exhibit molecular pro-

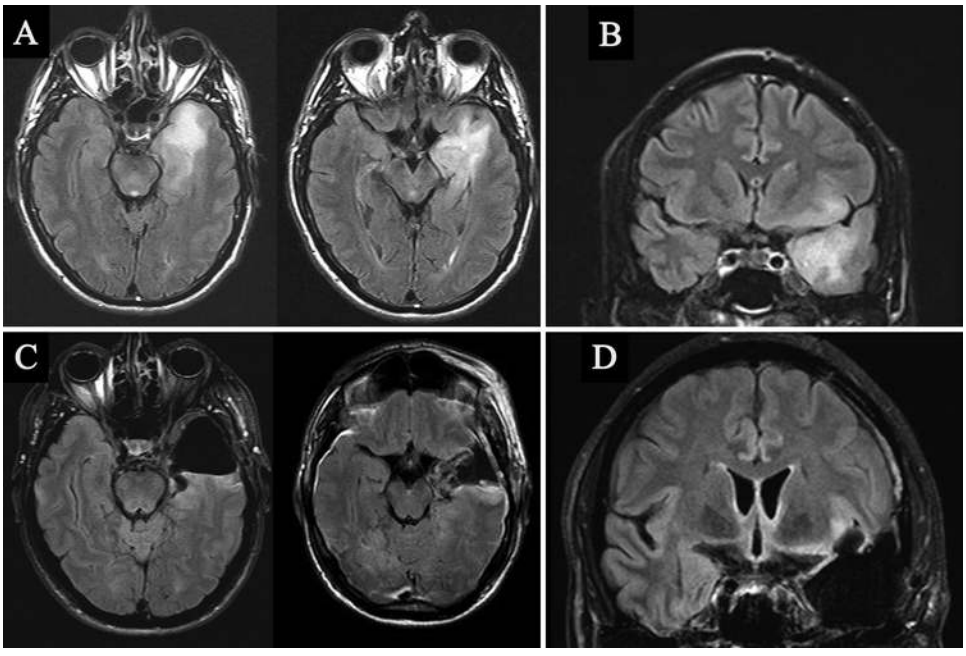

FIG. 4. Preoperative axial (**A**) and coronal (**B**) and postoperative axial (**C**) and coronal (**D**) FLAIR images obtained in a patient who died 27 months after the diagnosis of a left temporoinsular IDH-wt AII that was subtotally resected.

files similar to GBM, although they have a slightly better prognosis than de novo GBM. The molecular characteristics that are more often associated with IDH-wt lower-grade gliomas are indistinguishable from those of WHO grade IV gliomas, including genetic lesions affecting cell cycle regulation (CDKN2A/B, CDK4, and RB1), tyrosine kinase receptors (EGFR, PDGFRA), major cell signaling pathways (PI3K-AKT-mTOR and MAP-kinases), and the TP53-related pathway.[5,36] In other words, according to the histomorphological criteria for grading infiltrating gliomas, while IDH-wt grade II and III gliomas lack necrosis and microvascular proliferation (and thus fall short of the

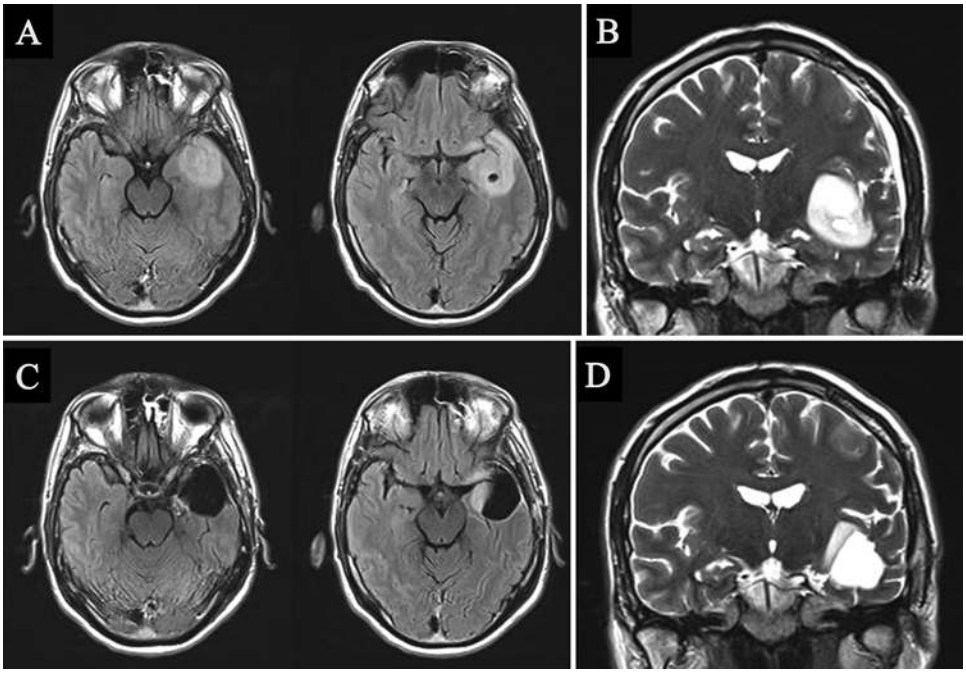

FIG. 5. Preoperative axial (**A**) and coronal (**B**), and postoperative axial (**C**), and coronal (**D**) FLAIR images obtained in a patient who is still alive and undergoing simple surveillance at 60 months after the diagnosis of a left temporoinsular IDH-wt AII that was subtotally resected.

histological definition of GBM), their molecular profiles are similar to IDH-wt WHO grade IV gliomas and they also display a more aggressive clinical behavior.[5,7,18,21,36]

However, in cohorts with a better-balanced grade II/III glioma ratio, the grade itself became a factor of stratification when OS curves were considered: the differences between IDH-mutated tumors (type I and II) and IDH-wt tumors (type III) were much more significant for grade III than grade II tumors in the Suzuki et al. study.[36] On the basis of the DNA methylation results, Ceccarelli et al.[7] distinguished a cluster of IDH-wt tumors enriched in lower-grade tumors, which itself was subdivided into 2 groups with very different OS profiles. The group with the best survival was called "PA-like" and included mostly lower-grade gliomas.[7]

In our experience, we observed a huge heterogeneity in survival data in a subset of 31 consecutive IDH-wt AIIs that were resected. We identified 1 subgroup of 5 patients who underwent subtotal resection and died rapidly—that is, at a median time from radiological diagnosis of 3.5 years—while OS in patients with WHO grade II gliomas who benefited from early (sub)total resection was 14–15 years in recent surgical series.[6,22,29,34] However, in a second subgroup, none of the 21 patients with a long-term follow-up over 5 years died (including 2 patients who underwent surgery more than 10 years ago). Thus, the 5-year survival rate is 77.27%. Furthermore, no adjuvant treatment was administered to 13 patients (41.9%), and the median follow-up was 79 months (range 33–157 months) in this subgroup.

Our findings challenge the data reported in the recent literature with respect to IDH-wt AII. First, we demonstrated that long survival is possible even in the absence of IDH mutation and 1p19q codeletion. These findings mean that even though the IDH pattern is a crucial parameter in patients with AII, this criterion in isolation is not reliable enough to predict survival at the individual level, and IDH-wt status does not confer an equal prognosis as in GBM. It is worth noting that median VDE was 2.45 mm/year (range 0.4–5 mm/year) in this series, which is in agreement with the known natural history of WHO grade II gliomas.[27] We have already reported that VDE is a strong prognostic factor for survival that is independent of IDH status.[19] Our present results confirm that a slow growth rate correlates with improved survival even in patients with IDH-wt grade II glioma. Second, we have demonstrated that postoperative adjuvant chemotherapy and/or radiotherapy is not mandatory for all patients with IDH-wt AII, in particular following radical resection. Indeed, we recommend simple observation following surgery in patients with supratotal, total, and even subtotal resection that results in less than 10–15 cm^3 of residual tumor on the condition that VDE is < 8 mm/year. We recommend early postoperative adjuvant therapy for patients with partial resection (residue > 15 cm^3) and/or residual tumor growth rate > 8 mm/year. To this end, we also recommend close radiological monitoring with MRI every 3 months. In other words, the decision to initiate early adjuvant chemotherapy or radiotherapy should not be decided from the IDH and 1p19q codeletion profile of the tumor in isolation. Indeed, it has been previously demonstrated that extent of resection was not significantly correlated to the molecular profile of WHO grade II glioma. In particular, extent of resection was found to be independent of IDH status, and thus the impact of tumor removal on survival was due to surgery per se.[10,22] As a consequence, the long-term survival in our experience in comparison with the literature could be due, at least in part, to the maximal safe surgical approach advocated by our group.[6,13,39] Third, we observed an important heterogeneity in tumor behavior in this homogeneous subset of IDH-wt AIIs, with patients who died within 3–4 years after diagnosis (in agreement with the results of previous studies on IDH-wt AII[5]) but also in patients with extended survival. Of note, we failed to identify prognostic factors by comparing these 2 subgroups because there were no significant differences between the clinical and radiological characteristics in both subpopulations with respect to median age at diagnosis, initial volume, tumor location (mainly in the temporal lobe and paralimbic system, which is in line with our previous report that more frequently showed an unfavorable molecular pattern in temporo-insular low-grade glioma[20]), extent of resection, or residual volume. Of note, these results are in contrast with those of Metellus et al.,[28] who reported a particular radiological profile and a systematic unfavorable prognosis in a small group of 7 IDH-wt gliomas. However, their series included a mix of grade II and III gliomas.[28] The lack of identification of prognostic factors between patients with a short OS versus those who were still alive after a long-term follow-up may be explained by the small sample of patients due to the fact that this IDH-wt molecular profile is rare in grade II gliomas. Thus, further studies with more cases of IDH-wt AII are needed to differentiate the distinct clinico-radiological and molecular subgroups in this nonhomogeneous entity. Indeed, with the lack of common, canonical mutations, IDH-wt grade II gliomas are more difficult to classify than IDH-mutated grade II gliomas.[5,36] In other words, IDH-wt AII might be considered a provisional entity for further classification into new prognostic subgroups using additional genetic analyses.

To this end, The Cancer Genome Atlas and other groups using next-generation sequencing facilities have discerned a large number of additional alterations that are acquired in low-grade gliomas.[5] More recently, TERTp mutations that correspond to the activation of the telomere length maintenance process have been found to be the most prevalent in gliomas of all grades. In lower-grade IDH-wt gliomas, TERTp mutations are associated with a worse prognosis.[8,23] Indeed, in a recent series of 160 adult IDH-wt gliomas, which consisted of 120 anaplastic astrocytomas (WHO grade III) and 40 diffuse astrocytomas (WHO grade II), Reuss et al.[33] observed that TERTp mutations were exclusively restricted to molecular glioblastoma and correlated with worse clinical outcomes. Interestingly, only 1 of our patients had a TERTp mutation. Although this finding in our cohort could support the better prognosis observed in the subgroup of patients who were still alive with a long-term follow-up greater than 5 years, the subgroup of patients with rapid death within 3–4 years following diagnosis also lacked TERTp mutation. Similarly, while BRAF mutation is associated with a better prognosis in IDH-wt gliomas,[7] it is worth noting that no tumors had

mutations in BRAF exon 15 in our series, including the subgroup with prolonged survival. The genetic alterations in IDH-wt gliomas are therefore more diverse and occur at a lower frequency than seen in IDH-mutated tumors. This presupposes a more complex partition of IDH-wt tumors into smaller groups in accordance with the large heterogeneity in outcomes we observed in the present series.

There are 2 main limitations in our study. First, the number of patients is small. However, it is worth noting that IDH-wt AII is a rare entity. Further series with a larger number of cases are needed to confirm our preliminary results. In addition, the molecular investigation was not exhaustive. We focused our analyses on the main biomolecular markers that are used in clinical practice, but other mutations might be implicated. Whole-exome techniques could be used to identify more homogeneous subgroups in terms of clinical evolution.

Conclusions

Because the partitioning pattern regarding the combination of genetic events remains to be elucidated in lower-grade IDH-wt glioma, it is currently not possible to predict prognosis at the individual level with a high degree of reliability solely based on molecular considerations. Indeed, we observed substantial heterogeneity in survival data in a subset of 31 resected IDH-wt AII. Therefore, the therapeutic management—in particular the decision to administer early adjuvant chemotherapy or radiotherapy following maximal safe resection—should not be decided based on routine molecular markers only, including IDH status, but rather in conjunction with patient-specific clinical and radiographic factors.

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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.

Author Contributions

Conception and design: Duffau. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Study supervision: Duffau.

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