Molecular, Histological, and Clinical Characteristics of Oligodendrogliomas: A Multi-Institutional Retrospective Study

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BACKGROUND: Reports suggest that phosphatidylinositol 3-kinase pathway alterations confer increased risk of progression and poor prognosis in oligodendroglioma, IDH-mutant, and 1p/19q-codeleted molecular oligodendrogliomas (mODG). However, factors that affect prognosis in mODG have not been thoroughly studied. In addition, the benefits of adjuvant radiation and temozolomide (TMZ) in mODGs remain to be determined.

OBJECTIVE: To evaluate the role of *PIK3CA* mutations in mODGs.

METHODS: One hundred seven mODGs (2008-2019) diagnosed at 2 institutions were included. A retrospective review of clinical characteristics, molecular alterations, treatments, and outcomes was performed.

RESULTS: The median age was 37 years, and 61 patients (57%) were male. There were 64 (60%) World Health Organization (WHO) grade 2 and 43 (40%) WHO grade 3 tumors. Eighty-two patients (77%) were stratified as high risk (age 40 years or older and/or subtotal resection per Radiation Treatment Oncology Group-9802). Gross-total resection was achieved in 47 patients (45%). Treatment strategies included observation (n = 15), TMZ (n = 11), radiation (n = 13), radiation/TMZ (n = 62), and others (n = 6). Our results show a benefit of TMZ vs observation in progression-free survival (PFS). No difference in PFS or overall survival (OS) was observed between radiation and radiation/TMZ. *PIK3CA* mutations were detected in 15 (14%) mODG, and shorter OS was observed in *PIK3CA*-mutant compared with *PIK3CA* wild-type mODGs (10.7 years vs 15.1 years, *P* = .009). WHO grade 3 tumors showed a shorter PFS, but no significant difference in OS was observed between WHO grades.

CONCLUSION: Our findings suggest that mODGs harboring *PIK3CA* mutations have worse OS. Except for an advantage in PFS with TMZ treatment, adjuvant TMZ, radiation, or a combination of the two showed no significant improvement in OS.

KEY WORDS: Oligodendroglioma *IDH1/IDH2*-mutant, 1p/19q-codeleted, *IDH1*, *IDH2*, *PIK3CA*, Temozolomide, Oligodendroglioma treatment, Molecular oligodendroglioma

Oligodendrogliomas comprise 5.3% of gliomas.[1,2] Based on the 2016 World Health Organization (WHO) fourth

revised edition, the diagnosis of oligodendroglioma requires *IDH1/IDH2* mutation and 1p/19q-codeletion.[3] Recent studies have shown that genetic alterations can correlate with outcomes in molecularly defined gliomas (eg, *CDKN2A/B* loss in isocitrate dehydrogenase [IDH]-mutant astrocytomas and *EGFR* amplification or *TERT* promoter mutation in IDH wild-type astrocytomas).[4,5] However, studies analyzing mutations that correlate with survival in molecular oligodendrogliomas (mODG) are limited.[6,7]

The phosphatidylinositol 3-kinase (PI3K) is an important regulator of cellular growth, transformation, adhesion, apoptosis, survival, and motility. PI3K activation drives various downstream pathways that regulate several cellular functions including those involved in tumor development

and progression.[8] Overexpression of the p110α catalytic subunit of PI3K (PIK3CA) leads to cellular transformation with concomitant phosphorylation of proteins in the AKT pathway.[8] PIK3CA mutations are present in 15% to 20% of mODG.[9-12] Recent studies have demonstrated that PI3K/AKT/mTOR pathway activation drives xenograft model formation, progression of disease, and poor outcomes in mODG.[13,14] This pathway has also been associated with shorter survival in IDH-mutant astrocytomas.[15] However, PIK3CA mutations were not an independent prognostic marker in multivariable analysis (MVA) of IDH-mutant astrocytomas despite showing a trend toward shorter overall survival (OS).[5,15] Although studies suggest the possible relevance of PIK3CA mutations, the association between PIK3CA mutations and outcome in mODGs needs further evaluation.

Clinical trials have demonstrated the efficacy of procarbazine, lomustine, and vincristine (PCV) therapy in patients with mODG.[16-19] In current clinical practice, patients with mODGs are frequently treated with temozolomide (TMZ), instead of PCV, based on its efficacy in high-grade astrocytomas, easiness of use, and favorable side effects profile.[20] However, there is a lack of randomized clinical trials (RCTs) supporting the benefit of TMZ in mODG.

In this study, we assessed the prognostic value of PIK3CA mutations in 107 patients with mODG. Moreover, we evaluated the effects of TMZ, radiotherapy (RT), and the combination of both in the survival of patients with mODG.

METHODS

Patients and Tumor Samples

We retrospectively reviewed electronic medical records of patients with mODG diagnosed at 2 institutions between 2008 and 2019. Inclusion criteria were (1) diagnosis of oligodendroglioma with confirmed IDH1/IDH2 mutation and 1p/19q-codeletion and (2) PIK3CA mutation evaluated by sequencing (**Supplementary Digital Content 1**, http://links.lww.com/NEU/B511).

Age, sex, race, tumor diameter, histological diagnosis, extent of resection (EOR), risk stratification, treatment, recurrence, salvage therapy, and survival were collected using REDCap electronic data capture tools.[21] Tumors were classified following the 2016 WHO Classification of Tumors of the Central Nervous System[3] (**Supplementary Digital Content 2**, http://links.lww.com/NEU/B512). Radiographical EOR was classified as gross total resection (GTR), subtotal resection, or biopsy, as previously described.[22] Risk stratification was performed according to the Radiation Treatment Oncology Group (RTOG 9802) criteria: age 40 years or older and/or subtotal resection.[23,24]

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Recurrences and therapeutic interventions were determined by individual assessment of cases by an institutional multidisciplinary tumor board (**Supplementary Digital Content 2**, http://links.lww.com/NEU/B512). The primary end points were progression-free survival (PFS) and OS. This study was approved by both institutional review boards and adheres to the Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Waiver of informed consent was granted because of the retrospective nature of this study.

Molecular Evaluation

IDH1 p.R132H status was evaluated using immunohistochemistry in some cases. IDH1/IDH2 and/or PIK3CA mutations were evaluated by sequencing (**Supplementary Digital Content 2**, http://links.lww.com/NEU/B512).[25,26] 1p/19q status was assessed by fluorescence in situ hybridization using a locus-specific identifier (LSI) 1p36 and LSI 19q13 dual-color probes from Abbott Molecular Inc, as previously described[27] and obtained from electronic medical records.

Statistical Analysis

Descriptive statistics were evaluated by using the Fisher exact test/Mann–Whitney U-test. The Kaplan–Meier method was used to plot survival curves and examined by using a 2-sided log-rank test. The MVA was built using stepwise selection by combing forward and backward selection techniques to select the variables. The Akaike information criterion was used to compare the quality of the set of statistical models. The MVAs include the treatment center as a strata variable and have been corrected by the stratified Cox model. After the model selection, the final variables were used for further analysis. Age was classified using the Pignatti and RTOG 9802 cutoff criteria.[23,24,28] P-values were 2-sided, and a $P \leq .05$ was considered statistically significant. Statistical analyses were performed in R (v.3.5.2), EZR (1.40),[29] and Prism v.8.4.2 (GraphPad). The oncoplot figure was generated using cBioPortal available tools (https://www.cbioportal.org/)[9,10] (**Supplementary Digital Content 2**, http://links.lww.com/NEU/B512).

RESULTS

Patient Characteristics

We identified 107 mODG. The median age at diagnosis was 37 years (interquartile 30.5-47 years), 61 patients (57%) were male, and most (78%) were non-Hispanic White patients. Tumor diameter was ≥5 cm in approximately half of the patients, and 47 (45%) underwent GTR. Sixty-four (60%) and 43 cases (40%) were classified as WHO grade 2 and 3, respectively. Ninety-five tumors (88.8%) were IDH1-mutant, and 12 (11.2%) were IDH2-mutant. Forty-seven of 64 (73%) WHO grade 2 mODGs were considered high risk according to the RTOG 9802 criteria.

First-line therapies included observation (n = 15, 14%), TMZ alone (n = 11, 10.3%), RT alone (n = 13, 12.1%), RT/TMZ (n = 62, 58%), and others (n = 6, 5.6%). Adjuvant RT was performed in 81 (76%) patients. Forty-seven patients (44%) received ≥12 cycles of chemotherapy (CT). PIK3CA mutations were present in 15 cases (14%) (Figure 1). There were no significant differences in clinical characteristics between institutions (Table 1), except for race, in which institution 2 had a higher percentage of non-Hispanic White patients (84% vs 67%, P = .017).

OS and PFS in mODG

The median follow-up (n = 107) was 80.9 months (6.7 years). At the time of this report, 61 patients (57%) showed evidence of progression with a median PFS of 79.5 months. Patients with mODG WHO grade 3 had significantly worse PFS compared with WHO grade 2 in univariable (71 vs 83 months, *P* = .044, log-rank test) and MVA (hazard ratios 1.91 [1.07-3.42], *P* = .029; Table 2). Other demographic and clinical characteristics were not associated with PFS.

At the time of this report, 25 patients (23%) were deceased with a median OS of 165.4 months (13.8 years). *PIK3CA*-mutant mODG demonstrated worse OS in both univariable (128.5 vs 180.8 months, *P* = .009, log-rank test; Figure 2) and MVA (hazard ratios 3.59 [1.19-10.84], *P* = .023). Other factors, such as WHO grade, age, tumor diameter, EOR, and adjuvant therapies, did not demonstrate a statistically significant association with OS (Table 3).

PIK3CA Mutation in mODG

Evaluation of *PIK3CA* mutations and their biological effect showed that 15 patients (14%) harbored 19 missense mutations and 1 truncating mutation (Figure 1). Eighteen of these 20 mutations are considered "oncogenic," and 2 are "likely oncogenic" according to Catalogue Of Somatic Mutations In Cancer (COSMIC) and OncoKB databases. In addition, 13 mutations are known to cause gain of function, and 3 are likely to cause gain of function of *PIK3CA*[30,31] (**Table S1, Supplementary Digital Content 3**, http://links.lww.com/NEU/B513). There were no significant differences in clinical characteristics between *PIK3CA*-mutant and wild-type patients (**Table S2, Supplementary Digital Content 4**, http://links.lww.com/NEU/B514).

Adjuvant Treatment Strategies in mODG

Subanalysis (excluding 6 patients treated with PCV or procarbazine/lomustine) showed that patients with mODG treated with TMZ (n = 73) were more often older (*P* = .008), WHO grade 3 (*P* = .044), and more frequently received RT (*P* = .0002) than patients not treated with TMZ (n = 28) (**Table S3, Supplementary Digital Content 5**, http://links.lww.com/NEU/B515). However, subanalysis of grade 2 high-risk mODGs (n = 42, PFS *P* = .412, and OS *P* = .322) and WHO grade 2, regardless of the risk criteria (n = 59, PFS *P* = .513, and OS *P* = .171), failed to demonstrate benefit in OS or PFS after treatment with TMZ (**Figure S1, Supplementary Digital Content 6**, http://links.lww.com/NEU/B516).

Patients (n = 75) who received RT (excluding 6 patients treated with PCV or procarbazine/lomustine) were more likely WHO grade 3 (*P* = .010) and more frequently received TMZ (*P* = .0002) than patients not treated with RT (n = 26) (**Table S4, Supplementary Digital Content 7**, http://links.lww.com/NEU/B519). However, there was no survival benefit from RT (PFS *P* = .299, OS *P* = .389). Subanalyses by WHO grade or RTOG risk criteria were not performed given the relatively small sample size and events.

Additional analysis, regardless of grade or risk category, demonstrated that RT + TMZ was not superior to RT only in both OS and PFS (**Figure S2, Supplementary Digital Content 8**, http://links.lww.com/NEU/B521).

DISCUSSION

Key Results

We retrospectively evaluated a multi-institutional database of mODG to identify the role of *PIK3CA* mutation status as a

FIGURE 1. *Oncoplot of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted patients. IDH, isocitrate dehydrogenase; OS, overall survival; PFS, progression-free survival; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; TMZ, temozolomide.*
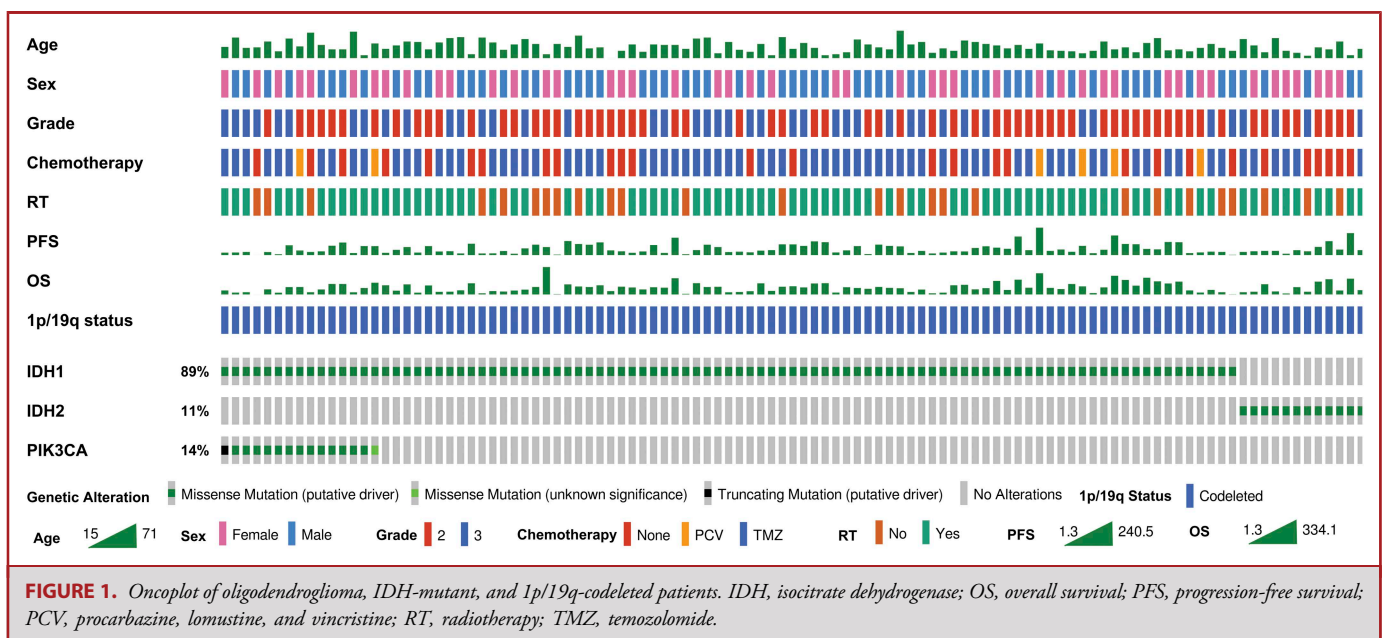
TABLE 1. Demographics and Clinical Characteristics of Oligodendroglioma, IDH-Mutant, and 1p/19q-Codeleted

Characteristic	Oligodendrogliomas (n = 107)	Institution 1 (n = 39)	Institution 2 (n = 68)	P value
Age at diagnosis, median (IQR)	37 (30.5-47)	41 (32.5-48.5)	36 (30.0-45.0)	.244
Male, N (%)	61 (57)	20 (51)	41 (60)	.420
Race, N (%)				**.017**
Non-Hispanic White	83 (78)	26 (67)	57 (84)	
African American	7 (7)	6 (15)	1 (1)	
Hispanic	9 (8)	5 (13)	4 (6)	
Asian	2 (1)	1 (3)	1 (1)	
Others	6 (6)	1 (3)	5 (7)	
Tumor maximum diameter ≥5 cm[a]	46 (50)	14 (44)	32 (53)	.512
WHO grade 2	64 (60)	23 (59)	41 (60)	1.000
Grade 2 high risk (RTOG 9802), N (%)[b]	47 (73)	16 (70)	31 (76)	.769
First-line CT, N (%)				.183
No CT	28 (26)	11 (28)	17 (25)	
Temozolomide	73 (68)	28 (72)	45 (66)	
Other CT[c]	6 (6)	0 (0)	6 (9)	
First-line radiotherapy	81 (76)	27 (69)	54 (79)	.251
CT No. of cycles, N (%)				.971
0 cycles	33 (31)	13 (33)	20 (29)	
1-5 cycles	13 (12)	4 (10)	9 (13)	
6-11 cycles	14 (13)	5 (13)	9 (13)	
≥12 cycles	47 (44)	17 (44)	30 (44)	
Extent of resection, N (%)[d]				.147
Gross total resection	47 (45)	12 (38)	33 (49)	
Subtotal resection	50 (48)	22 (59)	28 (41)	
Biopsy	8 (7)	1 (3)	7 (10)	
PIK3CA-mutant	15 (14)	6 (15)	9 (13)	.778

CT, chemotherapy; IDH, isocitrate dehydrogenase; IQR, interquartile range; RTOG, Radiation Treatment Oncology Group; WHO, World Health Organization.
[a]Tumor diameter was not available for 15 patients.
[b]RTOG 9802 criteria was calculated only from grade 2 molecular oligodendrogliomas (n = 64).
[c]Other chemotherapy included 3 patients treated with lomustine/procarbazine/vincristine and 3 patients treated with lomustine/procarbazine.
[d]Extent of resection was not available for 4 patients.
The Stupp protocol was consistent with radiotherapy and concomitant temozolomide according to the treatment protocol previously described.
P ≤ .05 was considered as statistically significant and denoted in bold.

prognostic marker. Our results support a deleterious effect of *PIK3CA* activating mutations in the survival of patients with mODGs. This finding is consistent with previous studies using the The Cancer Genome Atlas (TCGA) database and a xenograft oligodendroglial model.[13,14] In agreement with the CODEL initial trial results, our study shows that TMZ does not seem to provide a significant benefit to patients with mODG.[32] By contrast, evidence from multiple studies supports a benefit of PCV in combination with RT for mODGs.[16-19]

TABLE 2. Multivariable Cox Proportional Hazard Regression Models of Progression-Free Survival in Oligodendroglioma, IDH-Mutant, and 1p/19q-Codeleted (n = 107)
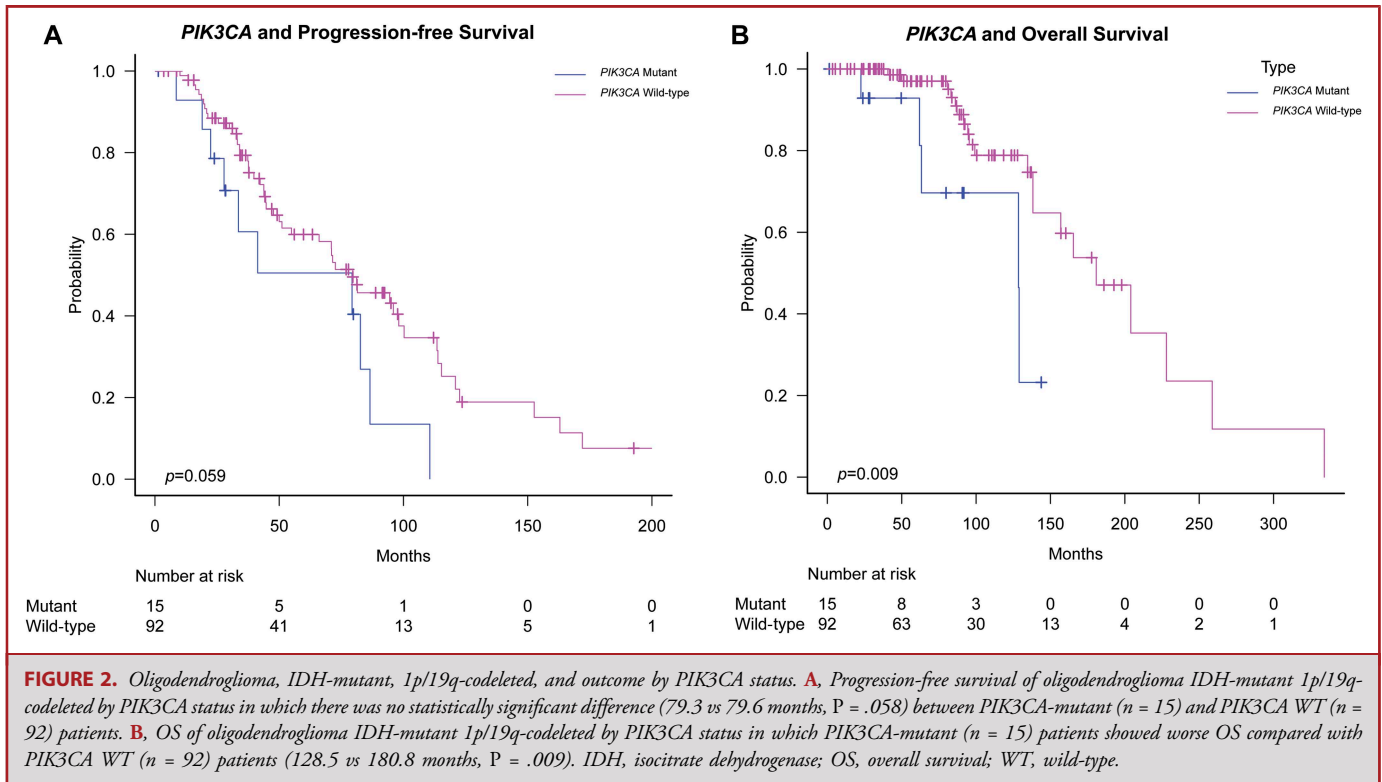
Variable	HR (95% CI)	P value
WHO (grade III vs II)	1.91 (1.07-3.42)	**.029**
PIK3CA (mutant vs wild-type)	1.74 (0.86-3.52)	.124

HR, hazard ratios; IDH, isocitrate dehydrogenase; WHO, World Health Organization.
P ≤ .05 was considered as statistically significant and denoted in bold.

Interpretation and Generalization
PIK3CA Mutation in mODG

Our results show that *PIK3CA*-mutant mODGs have significantly worse survival than *PIK3CA* wild-type mODGs (Figure 2B and Table 3). PI3K/AKT/mTOR pathway alterations and *PIK3CA* mutations have been shown to promote malignant progression in oligodendroglioma xenograft models.[13,33] A recent study using multifaceted computational assessment of risk in mODG observed that PI3K pathway activation (*PIK3CA* activating mutations and *PIK3R1* inactivating mutations) are strongly associated with imaging and histological findings of advanced disease and correlated with poor clinical outcomes.[14] However, other studies have not identified this association. For example, Tateishi et al[13] did not observe a correlation between *PIK3CA* mutation and mODG. However, this cohort was smaller (45 patients), and only 4 patients were *PIK3CA*-mutant. Aoki et al[15] evaluated genetic alterations and survival in 141 mODGs, but *PIK3CA* was only assessed as part of the RTK-PI3K-mTOR pathway, in which they included 24 other genes. Other studies

FIGURE 2. *Oligodendroglioma, IDH-mutant, 1p/19q-codeleted, and outcome by PIK3CA status.* **A,** *Progression-free survival of oligodendroglioma IDH-mutant 1p/19q-codeleted by PIK3CA status in which there was no statistically significant difference (79.3 vs 79.6 months, P = .058) between PIK3CA-mutant (n = 15) and PIK3CA WT (n = 92) patients.* **B,** *OS of oligodendroglioma IDH-mutant 1p/19q-codeleted by PIK3CA status in which PIK3CA-mutant (n = 15) patients showed worse OS compared with PIK3CA WT (n = 92) patients (128.5 vs 180.8 months, P = .009). IDH, isocitrate dehydrogenase; OS, overall survival; WT, wild-type.*

evaluating survival and genetic alterations in mODG had a low incidence of *PIK3CA* mutations (2.1%-4.1%) and did not report an association between *PIK3CA* and survival.[34,35] However, the study by Wijnenga et al[35] only included WHO grade 2 tumors. Although previous studies have associated *PIK3CA* mutations with WHO grade 3 oligodendrogliomas, this was performed before the molecular definition of oligodendrogliomas.[36] In our study, there was no significant association between WHO grade and *PIK3CA* status (**Supplementary Digital Content 4**, http://links.lww.com/NEU/B514). We observed that all *PIK3CA*-mutant patients were *IDH1*-mutant (Figure 1).

It has been demonstrated that pathway inhibitors (PI3K, AKT, and mTOR inhibitors) induce cytotoxic effects in *PIK3CA*-mutant but not in *PIK3CA* wild-type oligodendroglioma cells,

suggesting that activating mutations in the PIK3/AKT/mTOR pathway may predict response to targeted therapies.[13] Additional studies evaluating the role of *PIK3CA*-activating mutations in mODG are needed to validate our results.

Treatment Strategies in mODG

We did not observe therapeutic benefits of RT alone, although our sample size was small. RCTs evaluating RT against observation (delayed RT) have shown benefit in PFS but not in OS in low-grade glioma (LGG).[37] Whether this is true for mODG remains to be answered, especially considering the effects of RT on quality of life (eg, detrimental effects on cognition).[38,39]

To date, no RCT comparing observation with CT or RT + CT for LGG or mODG has been performed. Long-term follow-up RCTs have demonstrated the substantial benefit of sequential RT and PCV compared with RT alone for anaplastic oligodendroglioma.[16,17] In high-risk LGG, Buckner et al[40] demonstrated that RT + PCV is superior to RT alone. This survival benefit was consistent in post hoc analysis of mODG.[19] Importantly, most of the patients treated with PCV in the RCT tolerated 3 treatment cycles (6 cycles goal) because of hematological side effects. However, the benefits of PCV were evident despite shorter therapy.[17,18,40] The NOA-04 RCT subanalysis demonstrated superiority of PCV compared with TMZ in anaplastic oligodendroglioma with an improved PFS (PCV 9.4 vs 4.46 years) and a trend toward improved OS (PCV not reached vs 8.09 years).[41] No difference has been observed between RT and TMZ

TABLE 3. Multivariable Cox Proportional Hazard Regression Models of OS in Oligodendroglioma, IDH-Mutant, and 1p/19q-Codeleted (n = 107)

Variable	HR (95% CI)	P value
WHO (grade III vs II)	2.02 (0.69-5.96)	.104
RTOG 9802 (high vs low risk)	0.47 (0.19-1.17)	.104
PIK3CA (mutant vs wild-type)	3.59 (1.19-10.84)	**.023**

HR, hazard ratios; IDH, isocitrate dehydrogenase; OS, overall survival; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.
P ≤ .05 was considered as statistically significant and denoted in bold.

monotherapy in WHO grade 2, high-risk oligodendroglioma.[42] Although a single-arm trial of RT + TMZ reported increased survival in LGG when compared with historical reports of RT alone,[43] this benefit is not observed when the 5-year OS is compared with more recent studies with a similar population treated with RT alone. Moreover, it seems that the 5-year OS is lower than patients treated with RT + PCV.[40] The CODEL RCT initial analysis showed that TMZ-treated patients had shorter PFS and a nonsignificant lower 3-year and 5-year OS compared with RT-treated patients.[32] These RCT study arms were modified because of the benefit of RT + PCV. Currently, the phase III CODEL study (NCT00887146) is recruiting patients in 2 arms (RT + TMZ and RT + PCV). This trial will be crucial to evaluating the role of RT + TMZ in mODG.

In our study, there was no benefit of RT, TMZ, or the combination of both in OS. Despite our small sample size, the results are concordant with a recent retrospective study which showed no benefit from TMZ, RT, or their combination in WHO grade 2 mODG.[20] Importantly, recent studies have demonstrated that TMZ is an independent risk factor for malignant transformation and mismatch repair pathway defects, which in turn could lead to worse survival.[44,45]

EOR and Outcome in mODG

Surgical resection serves multiple objectives including cytoreduction, tissue for diagnosis and molecular characterization, and symptomatic control (neurological deficit and seizure control).[46] There are no RCTs evaluating the role of surgical resection in mODG. These studies are unlikely to be performed because of evidence showing survival benefits of higher resection rates and decreased residual volume in mODG.[47-49] The absence of outcome benefit in mODG with GTR in our study could be explained due to the small number of patients who underwent biopsy, as our practice is to perform maximal safe resection. Other factors historically associated with outcomes, such as tumor diameter and age older than 40 years, were not associated with PFS or OS in mODG.

WHO Grade and Survival in mODG

The prognostic value of histological grading of mODG based on the WHO criteria is unclear.[46] In our study, WHO grade 3 correlated with shorter PFS. However, no statistically significant association was observed between WHO grade and OS. WHO grade 3 patients were treated more frequently with adjuvant therapies, which might obscure possible differences in OS between grade 2 and 3 mODG. The lack of a significant association between WHO histological grade and the survival of patients with mODG is in agreement with the findings of recent studies.[15,50] However, the lack of prognostic value of WHO histological grade in mODG needs to be confirmed by additional studies including a large number of patients with a long-term follow-up.

Limitations

The limitations of our study include its retrospective design, potential selection bias (only 41.8% of all patients with mODG underwent analysis for *PIK3CA* mutations; **Supplementary Digital Content 1**, http://links.lww.com/NEU/B511), and differences in treatment patterns among institutions. Some subgroups were small and not adequately powered to detect differences in response to therapies; therefore, statistical analysis was not performed in such subgroups. Karnofsky performance status was not available for several patients, precluding its inclusion in the statistical analysis. Our analysis failed to reveal an association between WHO histological grade, race, age, and use of TMZ and RT with OS. While a limited sample size contributes to a higher type 2 error probability and negative results should be interpreted with caution in the setting of limited statistical power, other studies have also shown similar lack of association between histological grade, TMZ and RT, and OS in mODG.[15,20,32,50]

CONCLUSION

Our results demonstrate that *PIK3CA*-mutant mODGs have worse OS. This result is in agreement with other studies (using the TCGA database and xenograft models) that have associated activation of the PI3K pathway with more aggressive growth of oligodendrogliomas. In agreement with the CODEL initial study, our results show that TMZ did not seem to improve outcomes in patients with mODG.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplementary Digital Content 1. Study patient selection flowchart.

Supplementary Digital Content 2. Methodology.

Supplementary Digital Content 3. Table S1. PIK3CA mutations in mODG and their functional consequence. Oligodendroglioma, IDH-mutant, 1p/19q-codeleted PIK3CA mutations, and biological function.

Supplementary Digital Content 4. Table S2. Demographics and clinical characteristics of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted by PIK3CA status (n = 107).

Supplementary Digital Content 5. Table S3. Demographics and clinical characteristics of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted by temozolomide treatment (n = 101).

Supplementary Digital Content 7. Table S4. Demographics and clinical characteristics of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted by radiotherapy treatment (n = 101).

Supplementary Digital Content 6. Figure S1. Subanalysis of oligodendroglioma, IDH-mutant, 1p/19q-codeleted, and outcome by temozolomide therapy. **A** and **B**, PFS and OS of grade 2 high-risk mODG by TMZ, in which there was no statistical significance difference between TMZ-treated (n = 29) and TMZ-untreated (n = 13) patients in both PFS (54.9 vs 66.0 months, *P* = .412) and OS

(138.2 months vs undefined, *P* = .322). **C** and **D**, PFS and OS of mODG WHO grade 2 regardless of the risk criteria by TMZ, in which there was no statistically significant difference between TMZ-treated (n = 38) and TMZ-untreated (n = 21) patients in both PFS (113.5 vs 72.6 months, *P* = .513) and OS (138.2 vs 334.1 months, *P* = .171). The high and low risks were determined according to the Radiation Oncology Treatment Group criteria. Patients with other treatments (n = 6) were excluded from this subanalysis. PFS, progression-free survival; OS, overall survival; mODG, molecular oligodendroglioma; TMZ, temozolomide.

Supplementary Digital Content 8. Figure S2. Radiotherapy vs radiotherapy and temozolomide in oligodendroglioma, IDH-mutant, and 1p/19q-codeleted. **A** and **B**, PFS and OS of mODG treated with RT + TMZ (n = 62) vs RT-treated (n = 13) patients, in which there was no statistically significant difference between treatments in both PFS (79.6 months vs 71 months, *P* = .767) and OS (165.4 months vs 138.2 months, *P* = .348). Patients with other treatments (n = 6) were excluded from this subanalysis. PFS, progression-free survival; OS, overall survival; mODG, molecular oligodendroglioma; RT, radiotherapy; TMZ, temozolomide.