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Association of *MGMT* Promoter Methylation Status With Survival Outcomes in Patients With High-Risk Glioma Treated With Radiotherapy and Temozolomide

An Analysis From the NRG Oncology/RTOG 0424 Trial

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IMPORTANCE The initial report of NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0424 demonstrated a 3-year overall survival benefit with the addition of temozolomide to radiotherapy compared with a historical control. However, an important end point of the trial—evaluation of the association between O^6-methylgaunine-DNA-methyltransferase (*MGMT*) promoter methylation and survival outcomes—was not previously reported.

OBJECTIVE To examine the proportion of patients in NRG Oncology/RTOG 0424 with *MGMT* promoter methylation and its association with survival outcomes.

DESIGN, SETTING, AND PARTICIPANTS Specimens collected were analyzed after trial completion to determine *MGMT* promoter methylation and *IDH1/2* status and the association between *MGMT* status and survival outcomes. A model derived from logistic regression (MGMT-STP27) was used to calculate *MGMT* promoter methylation status. Univariate and multivariable analyses were performed using the Cox proportional hazards regression model to determine the association of *MGMT* status with survival outcomes. Patient pretreatment characteristics were included as covariates in multivariable analyses.

MAIN OUTCOMES AND MEASURES Progression-free survival (PFS) and overall survival (OS).

RESULTS Of all 129 eligible patients in NRG Oncology/RTOG 0424, 75 (58.1%) had *MGMT* status available (median age, 48 years; age range, 20-76 years; 42 [56.0%] male): 57 (76.0%) methylated and 18 (24.0%) unmethylated. A total of 13 unmethylated patients (72.2%) had astrocytoma as opposed to oligoastrocytoma or oligodendroglioma, whereas 23 methylated patients (40.4%) had astrocytoma. On univariate analyses, an unmethylated *MGMT* promoter was significantly associated with worse OS (hazard ratio [HR], 3.52; 95% CI, 1.64-7.56; $P < .001$) and PFS (HR, 3.06; 95% CI, 1.55-6.04; $P < .001$). The statistical significances were maintained in multimarker multivariable analyses, including *IDH1/2* status for both OS (HR, 2.70; 95% CI, 1.02-7.14; $P = .045$) and PFS (HR, 2.74; 95% CI, 1.19-6.33; $P = .02$).

CONCLUSIONS AND RELEVANCE In this study, *MGMT* promoter methylation was an independent prognostic biomarker of high-risk, low-grade glioma treated with temozolomide and radiotherapy. This is the first study, to our knowledge, to validate the prognostic importance of *MGMT* promoter methylation in patients with grade II glioma treated with combined radiotherapy and temozolomide and highlights its potential prognostic value beyond *IDH1/2* mutation status.

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Supplemental content

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Low-grade gliomas (LGGs; World Health Organization [WHO] grade II) display significant variability in clinical behavior. Median survival time ranges from a few to more than 10 years.[1] Accordingly, optimal management remains controversial. The role of chemotherapy had not been established until the recent results of NRG Oncology/Radiation Therapy Oncology Group (RTOG) 9802, which revealed improved overall survival (OS) among patients with high-risk LGG treated with radiotherapy and a procarbazine, lomustine, and vincristine (PCV) regimen compared with radiotherapy alone.[2] However, significant adverse effect profiles of PCV often prevent patients from completing planned therapy. Therefore, use of temozolomide, a more tolerable alkylating agent, instead of PCV in LGG is currently under active investigation.

NRG Oncology/RTOG 0424 was a single-arm, phase 2 study of high-risk LGG treated with radiotherapy and temozolomide and represents the only completed trial of radiotherapy plus temozolomide in LGGs.[3] High risk was defined as having at least 3 of 5 risk factors as defined by Pignatti et al[4]: age older than 40 years, largest preoperative tumor diameter of 6 cm or more, tumor invading the corpus callosum, astrocytoma histologic features, and preoperative neurologic deficits. The initial report of this study showed a 3-year OS rate of 73.1% among those treated with temozolomide-based chemoradiotherapy, which was significantly higher than the rate in a historical control group of 54% for treatment with radiotherapy alone.[3,4] However, the analyses of O^6-methylgaunine-DNA-methyltransferase (*MGMT*) (OMIM 156569) methylation were not available in the initial report.[3] The protocol was amended during accrual to mandate tissue sample submission for retrospective analysis of *MGMT* status because the importance of *MGMT* was not known at the time of trial design. Promoter methylation of *MGMT* results in epigenetic silencing of the *MGMT* gene and associated loss of protein expression,[5] leading to accumulation of DNA damage and increased sensitivity to temozolomide.[6,7] Previous clinical studies[8,9] have found a prognostic effect of *MGMT* promoter methylation in patients with glioblastoma treated with temozolomide-based chemoradiotherapy. Thus, analysis of *MGMT* promoter methylation is essential to further evaluate the added benefit of temozolomide to radiotherapy in patients with LGG.

Correlative data from LGG phase 3 trials are limited because of tumor rarity and related tissue collection and follow-up requirements. Only a recent phase 3 study (European Organisation for Research and Treatment of Cancer trial 22033-2603) of grade II gliomas, which randomized patients to receive radiotherapy or temozolomide, has analyzed *MGMT* status in prospectively treated patients with grade II gliomas. *MGMT* status was found to be methylated in 135 of the 150 tumors tested (90.0%).[10] To date, no significant progression-free survival (PFS) difference has been detected in patients treated with radiotherapy or temozolomide in this study; OS analyses and full evaluation of the predictive potential of molecular subtypes have not yet been completed.[10]

Of importance, NRG Oncology/RTOG 0424 is the only LGG trial using a temozolomide-based chemoradiotherapy regimen, providing a unique opportunity to evaluate molecular markers. This follow-up study to the initial report[3] sought to evaluate *MGMT* methylation status and its association with survival outcomes in conjunction with isocitrate dehydrogenase 1 (*IDH1*) (OMIM 147700) or isocitrate dehydrogenase 2 (*IDH2*) (OMIM 147650) mutational status because of their known association with the hypermethylation (glioma-CpG island methylator phenotype) phenotype.[11] We report, for the first time to our knowledge, the proportion of *MGMT* methylation and its prognostic significance (a study end point) in a prospective study of radiotherapy and temozolomide in high-risk LGG (NRG Oncology/RTOG 0424).

Key Points

Question Is *MGMT* promoter methylation a significant prognostic biomarker in patients with World Health Organization grade II glioma treated with radiotherapy and temozolomide?

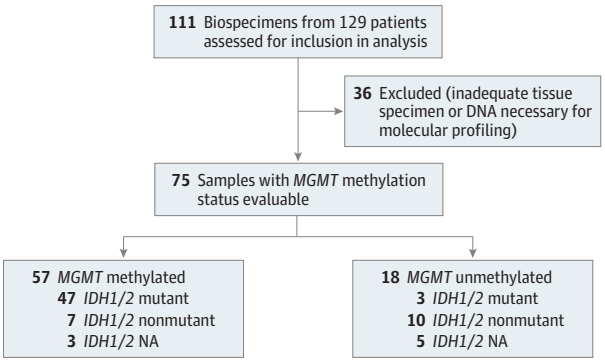
Findings In this correlative analysis of the NRG Oncology/RTOG 0424 trial, the proportion of patients with *MGMT* promoter methylation was 57 of 75 (76%) vs 18 of 75 (24%) unmethylated. *MGMT* promoter methylation was significantly correlated with progression-free and overall survival on univariate and multivariate analyses with and without adjusting for *IDH1/2* status (wild type vs mutant).

Meaning The results of this study suggest that *MGMT* promoter methylation can be used as an independent prognostic biomarker in World Health Organization grade II gliomas, and its incorporation into future clinical trial designs may be warranted.

Methods

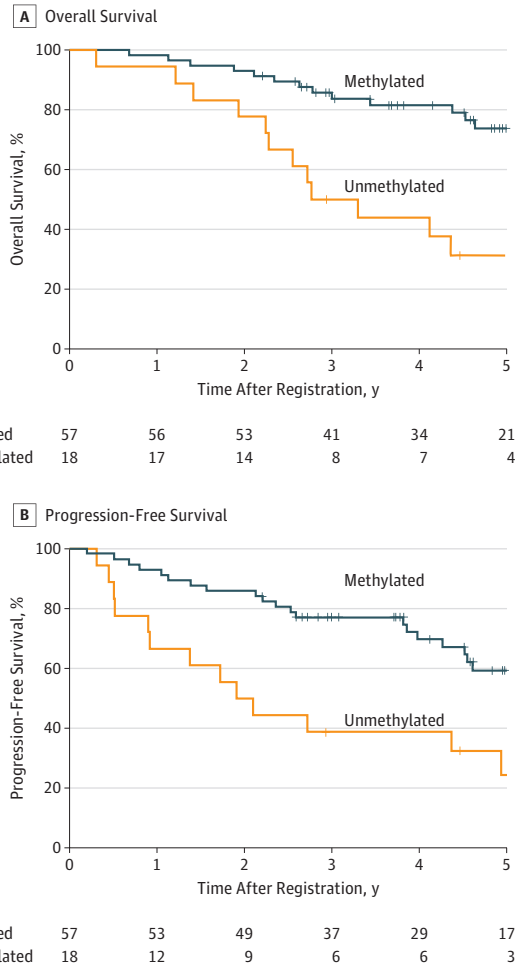
Collected specimens were analyzed to determine *MGMT* promoter methylation (a prespecified secondary end point of the study) and *IDH1/2* status (a post hoc analysis) and correlation between *MGMT* status and survival outcomes. A model derived from logistic regression (MGMT-STP27) was used to calculate *MGMT* promoter methylation status from Illumina HumanMethylation450 BeadChip data.[12] *IDH1/2* mutation status was determined by next-generation sequencing with a customized IonTorrent panel. The OS was defined as time from registration to death or the last follow-up date on which patients were reported to be alive. The PFS was defined as time from registration to progression or death, whichever came first, or the last follow-up date on which patients were reported to be alive without disease progression. The OS and PFS rates were estimated using the Kaplan-Meier method.[13] Hazard ratios (HRs) were calculated using the Cox proportional hazards regression model[14] and tested using the log-rank test. Multivariable analyses were performed, including age, sex, histologic features, neurologic function, Zubrod performance score, and tumor crossing midline as covariates. Patients participating in NRG Oncology/RTOG 0424 provided informed consent based on an institutional review board–approved protocol at the enrollment site. The correlative analysis was conducted with an institutional review board–approved waiver of consent from The Ohio State University because of the retrospective and deidentified nature of the study.

Figure 1. Flow Diagram



MGMT promoter methylation and *IDH1/2* mutation analysis for NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0424. Tissue sample collection was not mandatory for this trial. NA indicates not available.

Figure 2. *MGMT* Promoter Methylation and Survival in NRG Oncology/Radiation Therapy Oncology Group 0424



MGMT methylation was significantly associated with overall survival (hazard ratio, 3.52; 95% CI, 1.64-7.56; $P < .001$) (A) and progression-free survival (hazard ratio, 3.06; 95% CI, 1.55-6.04; $P < .001$) (B).

Results

Of all 129 eligible patients, 75 (58.1%) had *MGMT* status available (median age, 48 years; age range, 20-76 years; 42 [56.0%] male) (**Figure 1**). Most of the patient pretreatment characteristics were comparable between patients with and without *MGMT* status (eTable 1 and eTable 2 in the Supplement). Because of limited biopsy tissue, it is understandable that most patients with *MGMT* status underwent partial or total resection (eTable 1 and eTable 2 in the Supplement). As expected, most unmethylated patients (13 [72.2%]) had astrocytoma as opposed to oligodendroglioma or mixed tumors, whereas 23 methylated patients (40.4%) had astrocytoma (eTable 1 in the Supplement). Of the 75 patients, 57 (76.0%) were *MGMT* methylated and 18 (24.0%) were unmethylated (Figure 1). No patients were lost to follow-up. On univariate analyses, an unmethylated *MGMT* promoter was significantly associated with worse OS (hazard ratio [HR], 3.52; 95% CI, 1.64-7.56; $P < .001$) and PFS (HR, 3.06; 95% CI, 1.55-6.04; $P < .001$) (**Figure 2**). The median OS and PFS times were not reached for the methylated group but were 3.0 years for OS (95% CI, 2.3 to not reached) and 2.0 years (95% CI, 0.9-4.9 years) for PFS for the unmethylated group (Figure 2). On multivariable analyses, without including *IDH1/2* mutation status, statistical significances were maintained, with an HR of 2.89 (95% CI, 1.31-6.38; $P = .009$) for OS and an HR of 2.97 (95% CI, 1.48-5.96; $P = .002$) for PFS (**Table**). Because of the association between *MGMT* promoter methylation and *IDH1/2* mutation status, multimarker multivariable analyses were also performed (Table), and statistical significances for the effects of *MGMT* promoter methylation were maintained for both OS (HR, 2.70; 95% CI, 1.02-7.14; $P = .045$) and PFS (HR, 2.74; 95% CI 1.19-6.33; $P = .02$).

Discussion

Although the results from the primary analyses of NRG Oncology/RTOG 0424 demonstrated a benefit with the addition of temozolomide to radiotherapy compared with the historical control, there are multiple limitations to consider. The molecular landscape of the patients in this study and in the historical control data was unknown. Consequently, the current study regarding *MGMT* methylation status is critical because the trial could potentially be unrepresentative of the whole patient population with respect to *MGMT* methylation or the newly defined WHO molecular subgroups.[15]

Of importance, the current study on a subset of patients found that most patients were *MGMT* methylated. For the first time to our knowledge, this study showed in prospectively collected grade II tumors treated with radiotherapy plus temozolomide that *MGMT* promoter methylation was significantly associated with PFS and OS, in consideration of other important clinical variables and *IDH1/2* mutations. The results are critical, demonstrating that *MGMT* methylation may be a prognostic biomarker and may represent a class of patients who have better prognoses.

Table. Cox Proportional Hazards Regression Model for Overall and Progression-Free Survival[a]

Survival	Hazard Ratio (95% CI)	*P* Value
Overall survival		
Unimarker analysis		
MGMT status (unmethylated vs methylated)	2.89 (1.31-6.38)	.009
Age (continuous)	1.06 (1.02-1.10)	.007
Multimarker analysis[b]		
MGMT status (unmethylated vs methylated)	2.70 (1.02-7.14)	.045
IDH1/2 status (mutant vs nonmutant)	0.42 (0.16-1.12	.08
Age (continuous)	1.05 (1.00-1.10)	.04
Progression-free survival		
Unimarker analysis		
MGMT status (unmethylated vs methylated)	2.97 (1.48-5.96)	.002
Sex (male vs female)	2.91 (1.35-6.29)	.007
Multimarker analysis[b]		
MGMT status (unmethylated vs methylated)	2.74 (1.19-6.33)	.02
IDH1/2 status (mutant vs nonmutant)	0.51 (0.22-1.15)	.10
Sex (female vs male)	0.32 (0.14-0.72)	.006

[a] All models derived from stepwise selection with a significant level of .10 for entering into the model. Variables considered in all models were as follows: *MGMT* promoter methylation status, age, sex, histologic features, neurologic function, Zubrod score, and tumor crossing the midline. Most patients had partial or total resection; therefore, the extent of surgery (biopsy vs resection) was not included as a covariate in this analysis. Most patients had the largest preoperative tumor diameter of 5 cm or greater; therefore, tumor size (<5 vs ≥5 cm) was not included as a covariate in this analysis.

[b] Multimarker analysis was performed using 67 patients for which both *IDH* mutation status and *MGMT* methylation status were available.

Limitations

Because of the limitations of the small sample size of the entire study and specifically the *IDH* nonmutant population, it will be important to delineate in the future whether *MGMT* promoter methylation adds prognostic value only to the *IDH* nonmutant subgroup (eFigure 1 and eFigure 2 in the Supplement). Another limitation of this study is that molecular data were not available from historical controls. Therefore, we could not fully determine from the current data which molecular subtypes of LGGs benefit from the addition of temozolomide to radiotherapy. Thus, it is imperative that future clinical trials include molecular markers as stratification or eligibility criteria. Future analyses will include examining the prognostic significance of *MGMT* methylation with other known prognostic markers, such as the newly defined WHO subgroups (including 1p/19q codeletion status) with long-term follow-up data.

Conclusions

This study demonstrated that *MGMT* methylation may be an independent prognostic biomarker of high-risk LGGs treated with temozolomide and radiotherapy in NRG Oncology/RTOG 0424. Which LGG molecular subtypes receive benefit from the addition of temozolomide to radiotherapy remains elusive. Of note, this is the first study, to our knowledge, to validate the prognostic importance of *MGMT* promoter methylation in patients with LGGs treated with temozolomide and radiotherapy by using multivariable analyses with prospectively collected clinical data.

ARTICLE INFORMATION

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