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Case study

The utilization of MGMT promoter methylation testing in United States hospitals for glioblastoma and its impact on prognosis

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ABSTRACT

Multiple studies have identified O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status to be an important prognostic factor in glioblastoma (GBM). We used the National Cancer Data Base (NCDB) to analyze completeness of coding for MGMT as well as to compare outcomes of GBM patients treated with adjuvant chemoradiation based on MGMT promoter methylation status (positive, negative, unknown).

Patients diagnosed with GBM from 2010 to 2012 who received adjuvant chemoradiation were identified. MGMT promoter methylation status was obtained. The Kaplan-Meier method was used to assess overall survival (OS) by coding status of MGMT promoter methylation (positive, negative, unknown) and Cox regression analysis was used to assess impact of covariables on OS.

There were 12,725 patients who met the study criteria, of which 626 (4.9%) were MGMT+, 1,037 (8.1%) were MGMT− and 11.062 (86.9%) were coded as unknown/not coded. Treatment at academic centers was strongly associated with MGMT promoter status testing (OR 2.23, $p < 0.001$), as well as hospital facility within the Northeast (OR 1.55, $p < 0.001$). The median and 2-year OS was 20 months and 40.2% for MGMT+ compared to 15 months and 24.1% for MGMT−, respectively ($p < 0.001$). For those coded as MGMT unknown, median and 2-year OS was 14.6 months and 27.5%, which was significantly worse compared to MGMT+ ($p < 0.001$) but not compared to MGMT− ($p = 0.78$). On multivariable analysis, MGMT+ was strongly associated with improved OS (HR 0.74, $p < 0.001$).

Despite convincing evidence that MGMT promoter methylation status has a strong influence on prognosis; it appears to be a highly underutilized test in United States hospitals.

1. Introduction

The standard of care for glioblastoma (GBM) is surgical resection followed by adjuvant chemoradiation (CRT) with the alkylating agent, temozolomide. This was supported by the seminal study by Stupp et al. in which there was significant benefit for those who received CRT over radiation alone [1]. Since then, numerous studies have shown that tumors with promoter methylated O^6-methylguanine-methyltransferase (MGMT), a DNA repair enzyme, have improved response to temozolomide.

Despite the introduction of MGMT promoter methylation status as both a prognostic and predictive biomarker, there appears to be a lack of concurrence regarding the most sensitive technique for methylation status determination, indications for routine testing, and established alternative treatment options [2,3]. The utility of routine MGMT testing in patients with GBM may be of important relevance once distinct and personalized treatment strategies for methylated and unmethylated patients are available. Until then, temozolomide chemotherapy is given to patients regardless of methylation status.

We sought to study practice patterns of MGMT promoter methylation testing using the National Cancer Data Base (NCDB) to analyze completeness of coding for MGMT as well as to compare outcomes of patients with GBM treated with adjuvant chemoradiation based on MGMT promoter methylation status (positive, negative, unknown).

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2. Methods

The NCDB is a hospital-based registry that is the joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is estimated that 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. Exemption was obtained from the New York Harbor Veterans Affairs Committee for Research and Development prior to the initiation of this study.

Starting in 2010, the National Cancer Database started collecting data on the status of the methylguanine methyl transferase (MGMT) promoter. Therefore, we identified all patients diagnosed with glioblastoma (histologic code 9440) between 2010 and 2012. Treatment with chemoradiation is not directly coded within the NCDB. Patients were identified as receiving chemoradiation if both treatments started within 14 days of each other. Those who had biopsy only were considered to have no surgery. Patients who survived 3 months or less from diagnosis were excluded from this analysis in order to account for immortal time bias [4].

Clinical, pathologic, and demographic details were collected and compared between those who were MGMT+ and MGMT− using Chi Square analysis, Fisher's Exact test and Mann-Whitney where appropriate. Overall survival was analyzed via the Kaplan-Meier method and compared via the log-rank test. Univariable and multivariable logistic regression analysis was used to assess for predictors for MGMT coding. The variables analyzed included age (≤60, >60), year of diagnosis (2010, 2011, 2012), gender (male, female), facility type (non-academic, academic), race (White, Black, Other), tumor size (<3 cm, 3–5 cm, >5 cm, unknown), surgery (unknown, none, subtotal resection, gross total resection), facility location (Northeast, South, Midwest, West). Variables with a p-value < 0.1 on univariable analysis were included in the multivariable model. The p-value of the Hosmer and Lemeshow test was >0.05.

Univariable and multivariable Cox regression was performed to assess for predictors for improved survival in those with MGMT promoter methylated status. The variables included were age (continuous), gender (male, female), race (White, Black, Other), facility type (academic, non-academic), tumor size (≤3 cm, 3–5 cm, >5 cm, unknown), surgery (unknown, none, subtotal resection, gross total resection), and MGMT promoter methylation status (MGMT+, MGMT−). The proportional hazards assumption was tested for all factors and the assumption of linearity was verified for the age variable. All analyses were conducted using SPSS V 23.0 (IBM Inc, Armonk NY, USA). All tests were two sided with a p value < 0.05 the threshold for significance.

3. Results

3.1. Patient characteristics

There were 12,725 patients who met the study criteria. Of these, 626 (4.9%) were coded as MGMT positive, 1037 (8.1%) were coded as MGMT negative, and 11,062 (86.9%) were coded as unknown/not coded in medical record. There were 9808 deaths (77.1%) and the median follow up for living patients was 23.8 months (interquartile range 16.4–32.6 months). The median age at diagnosis was 61 years (interquartile range 53–69 years) and the median tumor size was 4.8 cm (interquartile range 3.4–6.5 cm). With regard to radiation therapy, the median dose was 6000 cGy (interquartile range 5940–6000 cGy). In terms of surgical extent, 1645 (12.9%) did not undergo surgical resection, 5.562 (43.7%) underwent a subtotal resection, 4333 (34.1%) underwent a gross total resection, and 1185 (9.3%) were unknown regarding whether or not surgery was performed. Surgery, when performed, took place a median of 1 day from diagnosis (interquartile range 0–6 days). Chemotherapy was initiated a median of 32 days from diagnosis (interquartile range 24–42 days) and radiation therapy was initiated a median of 33 days from diagnosis (interquartile range 25–42 days). Further details regarding patient characteristics are available in Table 1 and a comparison between those who were MGMT+, MGMT− are available in Table 2.

3.2. Logistic regression

On multivariable logistic regression, hospital location in the Northeast (OR 1.62, 95% CI 1.37–1.93, p < 0.001) and the South (OR 1.20, 95% CI 1.01–1.42, p = 0.04) were associated with an increased likelihood of MGMT testing. Treatment at academic centers were strongly associated with MGMT testing (OR 1.97, 95% CI 1.76–2.21, p < 0.001). Increasing age, no surgical resection or subtotal resection were associated with a decreased likelihood of MGMT testing. In order to account for those who were treated in multiple centers, a sensitivity analysis was performed repeating the univariable and multivariable logistic regression studies only including patients treated in a single center (n = 10,164) and there were no significant changes to the results. Further details regarding the

Table 1
Patient characteristics by MGMT methylation status.

	MGMT+ (n = 626)	MGMT− (n = 1037)	Unknown (n = 11,062)
Age (y, median)	61 (IQR 53–69)	60 (IQR 52.5–67)	62 (IQR 65–69)
Year of diagnosis			
2010	153 (24.4%)	307 (29.6%)	3615 (32.7%)
2011	194 (31.0%)	284 (27.4%)	3744 (33.8%)
2012	279 (44.6%)	446 (43.0%)	3703 (33.5%)
Tumor size			
≤3 cm	117 (18.7%)	214 (20.6%)	2260 (20.4%)
3–5 cm	231 (36.9%)	390 (37.6%)	4033 (36.5%)
>5 cm	170 (27.2%)	274 (26.4%)	2846 (25.7%)
Unknown	108 (17.3%)	159 (15.3%)	1923 (17.4%)
Gender			
Male	326 (52.1%)	647 (62.4%)	6575 (59.4%)
Female	300 (47.9%)	390 (37.6%)	4487 (40.6%)
Race			
White	581 (92.8%)	957 (92.3%)	10,143 (91.7%)
Black	29 (4.6%)	42 (4.1%)	561 (5.1%)
Other	16 (2.6%)	38 (3.7%)	358 (3.2%)
Surgery			
Unknown	87 (13.9%)	131 (12.6%)	967 (8.7%)
None	49 (7.8%)	76 (7.3%)	1520 (13.7%)
STR	256 (40.9%)	443 (42.7%)	4863 (44.0%)
GTR	234 (37.4%)	387 (37.3%)	3712 (33.6%)
Facility type			
Non-academic	253 (40.4%)	384 (37.0%)	6245 (56.5%)
Academic	373 (59.6%)	653 (63.0%)	4817 (43.5%)
Facility location			
Northeast	173 (29.1%)	310 (31.6%)	2025 (19.3%)
South	160 (26.9%)	319 (32.5%)	3006 (28.6%)
Midwest	153 (25.7%)	222 (22.6%)	3537 (33.7%)
West	109 (18.3%)	130 (13.3%)	1933 (18.4%)
Tumor focality			
Unifocal	443 (70.8%)	736 (71.0%)	7968 (72.0%)
Multifocal	82 (13.1%)	125 (12.1%)	1650 (14.9%)
Unknown	101 (16.2%)	176 (17.0%)	1444 (13.0%)

IQR = interquartile range, MGMT+ = methyl guanine methyl transferase promoter methylated, MGMT− = methyl guanine methyl transferase promoter unmethylated, STR = subtotal resection, GTR = gross total resection.

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