Editorial

The success of NRG-GBM-RPA: biomarker-based classification, where to next?

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Glioblastoma (GBM) is an aggressive primary brain tumor in which outcomes are poor (1). Treatment for GBM had been limited until 2005 with the seminal study by Stupp and colleagues in which the addition of concurrent and adjuvant temozolomide (TMZ) to adjuvant radiotherapy improved median overall survival (mOS) by approximately 2.5 months (2). Since then, radiation therapy with TMZ has been the backbone for management of GBM in the postoperative setting. Initially developed in 1993, the recursive partitioning analysis (RPA) was created to prognosticate patients with high-grade gliomas (including anaplastic astrocytoma and GBM) (3). This classification was further modified and verified in GBM patients treated with radiation and TMZ (1,4). The original RPA classification and the subsequent simplification RPA for GBM included non-molecular-based factors including age, functional status (Karnofsky Performance Status), surgery *vs*. biopsy, mental status, neurological function, and radiation dose. A subsequent nomogram that was developed to analyze GBM patients treated with modern therapy also assessed similar factors including treatment assignment, age, extent of surgery, mental status score, and steroid use (5). These factors are largely clinical and do not include biomarkers.

More recently, with our improved understanding of molecular pathways associated with specific cancers and a move towards personalized medicine, there has been a significant shift toward prognosticating patients based on biomarkers in both primary and metastatic brain tumor settings (6-10). Furthermore, this has led to the development of the new WHO grading classification for glioma (11). For GBM, O^6-methylguanine-DNA methyltransferase (*MGMT*) gene silencing through MGMT promoter methylation has been shown to be favorably prognostic in patients with GBM (12). Similarly, isocitrate dehydrogenase 1 (IDH1) mutation is associated with improved survival (13). Large efforts to further understand the genomic landscape of GBM were conducted by The Cancer Genome Atlas Research Network (14,15). A recent nomogram proposed for estimating survival among newly diagnosed GBM patients included MGMT methylation status (16); however, little is known about additional biomarkers in the clinical setting of GBM.

In the article titled "Molecular-Based Recursive Partitioning Analysis Model for Glioblastoma in the Temozolomide Era" by Bell and colleagues, the authors established a new NRG-GBM-RPA model for prognosticating patient outcomes using a cohort of GBM patients treated with chemoradiation with TMZ. A total of 452 patient tissue specimens from NRG Oncology RTOG 0525 were obtained and quantitative fluorescence immunohistochemistry was performed on tissue microarrays. The NRG Oncology RTOG 0525 trial is a randomized phase III trial comparing standard adjuvant TMZ with a dose-dense schedule. All patients received concurrent chemoradiation (17).

Twelve protein biomarkers were analyzed including epidermal growth factor receptor (EGFR), NFKBp65, pNFKBp65, pAKT, pERK, pmTOR, IGF1R, MGMT, phosphatase and tensin homolog (PTEN), survivin, Ki-67, and Src. Two hundred ninety-four patients had remaining tissue for additional stains for VEGFR1, VEGFR2,

pSRCY419, pSRCY529, CD24, CD44, p16, p53, PARP-1, and c-Met. Quantitative immunofluorescence was performed and prognostic significance was analyzed using Cox regression. Using the outcomes of the biomarker stains, patients were stratified into three NRG-GBM-RPA classes: NRG-GBM-RPA class I (patients with MGMT level less than median or patients with MGMT levels greater than or equal to median but less than 50 years old), NRG-GBM-RPA class II (MGMT levels greater than or equal to median and greater than or equal to 50 years old with c-MET levels less than top quartile) and NRG-GBM-RPA class III (MGMT levels greater than or equal to median and greater than or equal to 50 years old with c-MET levels greater than or equal to top quartile). The proposed NRG-GBM-RPA classification was validated using 176 samples from patients treated at the University of Utrecht assessed via semiquantitative immunohistochemical validation. Results from the study showed that the NRG-GBM-RPA model improved stratification of patient outcomes as compared to the RTOG RPA model. Furthermore, the authors validated these findings in an independent data set using semiquantitative immunohistochemistry to stain for MGMT and c-MET.

Patients with GBM have poor outcomes despite standard-of-care therapy, but a small subset of patients experience longer survival. The goal is to identify different subsets of patients in which we can further tailor clinical trials and therapies to improve outcomes. The authors should be congratulated for their efforts toward incorporating molecular markers into their prognostication model by assessing molecular pathways associated with GBM. The mOS for the three classes was 21.0, 16.6, and 9.4 months for classes I, II, and III, respectively. Compared to the current RPA classification, the NRG-GBM-RPA improved patient stratification and has the potential to influence future clinical trials and decision making. The question at this time is how to implement this classification at a global level.

Currently, MGMT status is analyzed in a binary fashion: MGMT promoter methylated or unmethylated. In contrast, MGMT and c-MET protein status in the NRG-GBM-RPA are assessed based on the degree of expression (greater than or equal to median MGMT expression *vs.* MGMT expression less than median or cytoplasmic c-MET greater than or equal to top quartile less than top quartile). Challenges with using protein expression on a global scale are currently seen in the use of PD-L1 expression in the setting of immunotherapy and non-small cell lung cancer in which the degree of expression impacts prognostic and predictive power (18). These include tissue heterogeneity, tissue processing, antibody selection, staining platform, and interpretation. With respect to implementing NRG-GBM-RPA, tissue arrays were used for both the initial RTOG 0525 tissue samples as well as the subsequent validation study with quantitative immunofluorescence and semiquantitative immunohistochemistry assays, respectively. The use of tissue arrays for staining limits many of the previously mentioned variables. Whether this can be applied in a setting in which tissue samples from newly diagnosed patients with GBM are assessed individually is unclear at this time. Additionally, the usage of median and quartile limits as cut-offs for protein expression may be challenging for institutes that do not have a sufficient GBM tissue bank to establish a full standard range of c-MET or MGMT protein expression. Further clarification is needed to apply this on a larger scale. Lastly, a few additional questions exist regarding how to incorporate additional clinical data not assessed in the patient cohort selected from RTOG 0525. This includes IDH1 mutational status as well as patients that are receiving tumor-treating fields (19).

NRG-GBM-RPA shows significant promise toward achieving personalized prognostication of patients with GBM. Should this classification be implemented in future clinical trials, further questions need to be considered.

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Footnote

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