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A new prognostic classification may help clinical decision-making in glioblastoma

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New research shows that taking molecular variables into account will improve the prognostic classification of the lethal brain cancer called glioblastoma (GBM).

The study was led by researchers at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James).

Published in the journal *JAMA Oncology*, the study found that adding significant molecular biomarkers to the existing GBM classification system improves the prognostic classification of GBM patients who have been treated with radiation and the drug temozolomide.

The current model has been used internationally for nearly two decades and is based on clinical variables alone. It was created before the introduction of temozolomide, which, along with radiation, is the current standard of care for GBM.

The new, refined classification was derived using samples from 452 GBM patients treated with radiation and temozolomide. It includes such key molecular markers as MGMT- and c-MET-protein expression, along with clinical variables including age, performance status, extent of resection and neurological function.

The researchers validated the model in an independent group of 196 patients.

"Our study has established and independently validated a novel molecular classification of glioblastoma, perhaps the most aggressive of all human malignancies," says principal investigator Arnab Chakravarti, MD, chair and professor of Radiation Oncology and co-director of the Brain Tumor Program.

"The revised model offers a more accurate assessment of prognostic groups in GBM patients who have been treated with radiation and temozolomide.

"We believe that incorporating c-MET and MGMT protein expression enhances the prognostic classification of glioblastoma patients over and above the traditional clinical variables, and that it will improve clinical decision making," says Chakravarti, who is also the Max Morehouse Chair in Cancer Research at Ohio State. "Furthermore, the inclusion of MGMT protein provides insight into the potential for resistance to radiation and temozolomide."

More than 11,880 new cases of GBM were estimated to occur in 2015, with overall survival averaging 12 to 15 months.

The five-year survival rate for GBM is 5 percent in the United States. However, a small subset of patients experiences longer survival, which suggests the presence of underlying tumor differences and the need for a better prognostic classification model.

For this study, Chakravarti and his colleagues used tissue samples obtained from the clinical trial RTOG 0525 (Clinicaltrials.gov identifier NCT00304031), a phase III trial that compared standard adjuvant temozolomide with a dose-dense schedule in patients with newly diagnosed GBM.

The researchers analyzed expression levels of 22 proteins for prognostic

significance of overall survival.

Key technical findings include:

- Higher MGMT protein level was significantly associated with decreased MGMT promoter methylation and vice-versa;
- MGMT protein expression had greater prognostic value for overall survival compared with MGMT promoter methylation;
- The new model significantly improves outcome stratification over both the current model and over MGMT promoter methylation.

"There is a critical need for a more refined, molecularly based classification of glioblastoma in this era of temozolomide therapy," Chakravarti says. "Our model can be used to stratify GBM patients for future clinical studies on the global level."

More information: Erica Hlavin Bell et al, Molecular-Based Recursive Partitioning Analysis Model for Glioblastoma in the Temozolomide Era, *JAMA Oncology* (2017). DOI: 10.1001/jamaoncol.2016.6020

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