Invited Commentary

A Common Rule for Resection of Glioblastoma in the Molecular Era

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In this issue of *JAMA Oncology*, Molinaro et al[1] retrospectively assess the value of aggressive resection of glioblastoma (GBM) across molecular subtypes in a timely analysis. Both the large number of participants and the use of a significant development cohort and a multicenter validation cohort add strength to the findings.

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Glioblastoma is the most common type of primary brain tumor and is also the most difficult to treat. Despite modern multimodal therapy including resection, radiotherapy, chemotherapy, and alternating electric fields, GBM remains one of the most aggressive and lethal cancers, with 5-year survival rates of less than 10%.[2]

Surgery is the oldest form of treatment for GBM; it is necessary in order to establish a histological diagnosis and may also be used to relieve symptoms of mass effect by mechanical cytoreduction. However, the amount of tumor that should be removed during surgery (ie, extent of resection [EOR]) and its subsequent effect on outcome has sparked longstanding controversy among neurosurgeons and neuro-oncologists. Unfortunately, there is, and perhaps always will be, a dearth of randomized studies designed to adequately address this question. Moreover, reviewing the bulk of retrospective—albeit high-quality—literature on this subject is confounded by the fact that, until recently, GBM was thought to be a single histopathological entity instead of a group of molecularly heterogenous tumors with distinct biological characteristics and natural histories.

In 2016, the World Health Organization introduced a role for molecular classification in the diagnosis and prognostication of gliomas. One genetic marker that has become of paramount importance consists of alterations in the isocitrate dehydrogenase (*IDH*) gene. Whether a tumor harbors a mutation in *IDH* is now the first and most critical piece of data when discussing a new diagnosis of glioma. Essentially, modern definitions dictate that not all GBMs are created equal; indeed, patients with mutated *IDH* GBM have been shown to have median survival that is more than twice as long as that of patients with wild-type *IDH*.[3]

In this study, Molinaro and colleagues[1] provide a framework for conceptualizing the potential benefits of EOR in the setting of molecular groups for GBM. Unlike the growing body of literature focused on the differentiating characteristics between wild-type and mutant *IDH* GBM, Molinaro et al[1] instead seek to establish a common ground. When it comes to surgery, they propose a general rule: maximal resection should be considered for all patients with GBM, even in the molecular era. In fact, for patients 65 years or younger, surgical removal of even the infiltrative non–contrast-enhancing disease augmented the survival benefit. This conclusion is strengthened considerably by the finding that EOR was not simply a surrogate marker for *IDH*-mutant disease, which frequently develops in the frontal lobe and is theoretically more amenable to aggressive resection.[4]

A number of questions as well as opportunities for future investigation remain. The present study is consistent with a mounting trend in the field toward the prognostic importance of non–contrast-enhancing tumor in GBM. However, in practice, the imaging features that distinguish non–contrast-enhancing tumor and other common processes such as vasogenic edema are often difficult to define. This is a crucial detail, especially in the brain, where EOR must always be balanced against the risk of damage to surrounding eloquent tissue. Although maximal surgery was found to prolong survival despite *IDH* mutation status, other molecular characteristics or combinations thereof may ultimately demonstrate the capacity to identify tumors that would specifically benefit from greater EOR. If so, information obtained through emerging imaging modalities,[5] liquid biopsy,[6] or rapid intraoperative diagnosis[7] could be exploited to help guide clinical decision-making in real time. Last, additional work will be needed to better understand how molecular diagnoses and EOR might intersect to potentially influence the role of adjuvant therapies for glioma, especially in younger patient cohorts.

In all, despite the added complexity associated with the molecular era, the role of surgery for GBM certainly deserves continued consideration. Greater EOR of contrast-enhanced disease improves survival despite age and molecular classification. In younger patients (ie, <65 years), aggressive resection that includes non–contrast-enhanced disease also provides benefit. For now, the best available evidence supports maximal, but safe, tumor resection for GBM.

ARTICLE INFORMATION

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Published Online: February 6, 2020. doi:10.1001/jamaoncol.2019.6384

Conflict of Interest Disclosures: None reported.

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