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Extent of Resection of Glioblastoma:

A Critical Evaluation in the Molecular Era

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Keywords

Glioma; Surgery; IDH1 mutation

INTRODUCTION

What is the goal of surgery for glioma? In the routine neurosurgical oncology practice there are 2 intertwined goals: diagnostic tissue acquisition and therapeutic cytoreduction. Although scant "level I" evidence exists, accumulating data support the proposal that more-extensive surgical resection has a pivotal role in improving survival in adults with glioma. With recent discoveries in glioma genetics now incorporated into the 2016 World Health Organization (WHO) Revised Classification of Tumors of the Central Nervous System,[1] a key conceptual advance has been recognition that gliomas segregate into distinct molecular groups; as a consequence, legacy WHO grading alone does not provide sufficient guidance for optimized surgical technique. Borrowing from the language of statistics, rather than considering the relationship between differently-graded tumors to be "ordinal" (ie, grades 2, 3, 4) as a stepwise progression, WHO2016 has underscored the need to transition to "nominal" consideration of these gliomas as distinct disease processes. Simply put, IDH mutant gliomas do not progress to become wild-type glioblastomas, and the evidence base for surgical resection of these different tumor types needs to be reevaluated separately. Herein, we consider the evidence base (Table 1) for surgical resection and treatment in the molecular era, with a focus on the 3 most common diffuse gliomas of adults: Glioblastoma IDH wild-type (which represents approximately 65%–70% of adult glioma), Astrocytoma IDH mutant (representing approximately 20%–25%), and Oligodendroglioma IDH mutant (5%–7%).

DIAGNOSTIC ACCURACY

For the initial surgical procedure in a patient with suspected adult diffuse glioma, accurate diagnosis is paramount. Before WHO2016, the existing dogma driving neurosurgical strategy was that accurate histologic grading was the most important goal of the surgical

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DISCLOSURE

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diagnostic procedure. However, the extent of surgery and histologic grading of an adult diffuse glioma had been shown to be tightly linked. In a seminal paper, Dr Glantz and colleagues[2] examined 262 patients undergoing resection for suspected high-grade malignant glioma, and found that 214 (82%) were ultimately diagnosed with WHO grade IV glioblastomas and 48 (18%) with WHO grade III anaplastic astrocytoma (AA). Conversely, in a cohort of 67 comparable patients with suspected high-grade malignant glioma undergoing stereotactic biopsy, 33 (49%) were diagnosed with glioblastomas and 34 (51%) had AAs. The investigators concluded that "some AAs diagnosed by stereotactic biopsy are actually glioblastomas,"[2] underscoring the issues associated with undersampling that provide insufficient tissue for neuropathologic review to identify the presence of specific histopathological features diagnostic of grade IV disease, namely pseudo-palisading necrosis and microvascular proliferation. Taking this a step further, Dr Jackson and his colleagues[3] from the MD Anderson Cancer Center evaluated biopsy and subsequent surgical resection diagnoses derived from the same patient, without intervening therapy. They noted that diagnoses based on biopsy and then subsequent resection in the same patient differed in 40 (49%) of 82 cases. These investigators concluded that stereotactic biopsy was therefore frequently inaccurate in providing a correct diagnosis.[3]

Thus, in the prior era, a convincing argument could be made for a more-extensive surgical procedure as a strategy to avoid the known limitation on accurate diagnosis imposed by surgical sampling error with limited biopsies. Patients who underwent biopsy-only could unfortunately too often have inaccurate grading by the legacy histologic criteria, suffering from so-called "undergrading," as there would be insufficient material sampled via a core needle biopsy for pathologic assessment of the entire tumor mass. Fear of this inaccuracy motivated substantial effort among the neurosurgical oncology community to improve radiographic imaging and stereotactic targeting of "more enhancing" areas of a suspected glioma, to improve the accuracy of grading by biopsy.

With the advent of modern molecular genomic analyses, this scenario occurs much less frequently,[4] because vastly smaller amounts of tissue are required for molecular testing. There are active efforts in the neuropathology community, led by the cIMPACT-NOW working group,[5] to advance the practical application of these molecular classifiers, freeing diagnosis and grading from dependency on volumetric sampling constraints. For instance, this working group has now identified at least 3 separate categories of glioma, which are grade 4 (transitioning to Arabic numerals in this updated classifier) - diffuse midline gliomas which are H3K27M-mutant,[6] progressive IDH mutant astrocytomas (formerly "secondary" glioblastomas),[7] and IDH wild-type gliomas containing either histologic features (microvascular proliferation or palisading necrosis) or molecular features (EGFR amplification, chromosome 7 gain or 10 loss, or TERT promoter mutation) of glioblastoma.[8] In the modern era with molecular classifiers, the demand for more-extensive surgery (or so-called "second look" procedures) to obtain a correct diagnosis has lessened. This has inturn highlighted the therapeutic role of surgery for different molecular categories of disease; for instance, it can be appreciated how the impact of aggressive surgery on survival could be different when comparing diffuse midline gliomas to glioblastoma IDH wild-type, despite both being grade 4 lesions.

THERAPEUTIC CYTOREDUCTION

Indeed, the second and perhaps most important goal of surgery, is to perform therapeutic cytoreduction to secure a prolonged survival and preservation of neurologic function for the patient. In the era preceding WHO2016, for glioblastoma this has traditionally meant that "complete resection of enhancement" was the intended surgical goal,[9,10] whereas for low-grade lesions, which are characteristically nonenhancing, this has meant "complete resection of T2/FLAIR hyper-intensity."[11,12] The evidence base that supports these surgical strategies requires updating in the context of the new WHO2016 diagnostic criteria.

Given the infiltrative biology of diffuse gliomas, no surgery can completely remove all tumor cells from the surrounding cortex. Surgical procedures should be guided by the evidence detailing what the optimal surgical result is for each patient, to extend survival and preserve neurologic function. The optimal amount of surgery is determined by the molecular diagnosis, not the WHO grade. Legacy terms like "glioblastoma" or "low-grade glioma" lack precision, and only serve to cloud careful consideration of the evidence. Furthermore, the thresholds of postoperative MRI residual disease for how we can measure surgical results also depend on this underlying diagnosis, and prior studies that form the evidence base for clinical decision-making need to be reassessed with an eye toward the updated WHO2016 molecular categories of tumor.

Importantly, undergrading in pre-WHO2016 studies complicated any retrospective analysis of surgical treatment, because biopsy-only diagnoses were more frequently "molecularly incorrect," and therefore not reflective of the more aggressive natural history of these tumors; resulting in a selection bias that made biopsy-only cohorts appear to have worse outcome when compared with more-extensively resected grade-matched cohorts. This diagnostic inaccuracy leads to an inherent flaw of pre-WHO2016 diagnoses in retrospective studies of surgical resection of lower-grade glioma (grades II and III), since the control groups, which were less-extensively resected, invariably included more grade IV tumors than the more-extensively resected group (as an example, potentially confounding the interpretation of the initial results from the Norwegian glioma study[13]).

When considering the evidence base from prior eras, it is critically important to keep in mind the relative frequency of the different molecular groups in these legacy cohorts, and whether the outcomes observed could be explained by "contamination" with mixed molecularly-heterogeneous cohorts. Notwithstanding these caveats, the evidence has shown that extensive resection is associated with a survival benefit in histologically defined glioblastoma (IDH wild-type) and also low-grade glioma (most frequently IDH mutant), but with important nuances with regards to the definition of disease assessment.

Glioblastoma IDH Wild-Type

There has been a small nonblinded randomized study that enrolled 30 elderly (age >65 years old) patients with suspected malignant glioma[14] for comparison of survival outcome with surgery versus biopsy. This randomized study underscored the importance of prospective study design, as in 7 of these patients (23%) diagnoses of stroke, metastases, central nervous system lymphoma, and 1 nondiagnostic result were obtained. Nevertheless, the remaining

cohort of 23 patients diagnosed with grade III or grade IV glioma were statistically likely to all have disease categorized as WHO 2016 glioblastoma IDH wild-type, given their older age at presentation. Conclusively for this randomized study, the patients who underwent surgical resection experienced prolonged survival. This element of survival benefit from surgery seems to be derived from the relief of mass effect, and prevention thereby of demise due to hydrocephalus or ischemia of deep brain structures from herniation. A more difficult question to answer in a randomized fashion has been whether small amounts of residual disease, so-called “near total” resection, is associated with worse outcome.

The signature study of surgery for grade IV gliomas was authored by Dr Lacroix and colleagues[9] from MD Anderson Cancer Center, who analyzed the extent-of-surgical resection and survival outcomes of 420 consecutive patients undergoing surgery for malignant glioma. This work is the most highly cited paper of the modern neurosurgical oncology literature. To briefly review this study given its importance, the investigators enrolled 420 consecutive patients diagnosed with GBM at MD Anderson Cancer Center between the years of 1993 and 1999. They prospectively recorded clinical and radiographic outcome data, and only 4 patients excluded due to incomplete imaging data. Within this cohort, 233 of 416 were previously untreated. The investigators used computer software to calculate enhancing tumor volume from axial T1-post contrast MRI images obtained preop and postop. From a statistical standpoint, most patients had aggressive surgery, but there was an otherwise good distribution of extent of resection (EOR, defined as [preoperative volume – postoperative volume]/preoperative volume) of enhancing disease at the extreme of near-complete resection, 47% of patients had greater-than-or-equal-to 98% EOR compared with 53% who had less than 98% EOR. In multivariate analysis using a Cox proportional hazards model: Age (<45, 45–64, >64), performance score (<80), necrosis, enhancement, and EOR (≥98%) were associated with survival. Similar results found in the previously untreated subset: age, Karnofsky performance status (KPS), necrosis, EOR, where more-extensive resection was associated with a 13.0-month versus 10.1-month survival for less-extensive resection.

In the era after the introduction of routine use of temozolomide for patients with glioblastoma, Dr Stummer and colleagues[15] performed a randomized study of 270 newly diagnosed glioblastoma patients who were deemed eligible for complete resection. Patients were assigned to surgical resection with either the fluorescent adjunct 5-ALA or the control arm of “white-light only.” The outcome of this study demonstrated that complete resection was achieved in 65% of ALA cases versus 36% of white-light cases.[15] As noted by Drs Barker and Chang,[16] this trial likely represents the first large multicenter study that randomly allocated patients eligible for a complete resection between 2 types of surgical methodology (5-ALA guidance vs white-light only). Subsequent reanalysis of survival between patients who received gross-total resection compared subtotal resection demonstrated an approximate 5-month survival benefit (16.7 vs 11.8 months) associated with gross-total resection,[10] which stands at the current best level of evidence for complete resection of enhancing disease as a surgical goal for Glioblastoma IDH wild-type.

Intriguingly, in one of the first surgical analyses to perform molecular stratification by IDH status, the results of Beiko and colleagues[17] largely mirrored these results by dividing grade

III and IV astrocytic gliomas into IDH wild-type and IDH mutant cohorts. In patients with IDH wild-type gliomas, absence of residual postoperative enhancement was associated with a median survival of 17.4 months, compared with 9.9 months in patients with residual enhancement. This survival benefit was significant after controlling for other factors in multivariate analysis. It was also significant in legacy (histologic) glioblastomas, essentially mirroring the findings of Lacroix and colleagues[9] and Stummer and colleagues.[15] Importantly however, residual nonenhancing disease had no observable impact on survival in patients with IDH wild-type tumors, when scored as continuous volumetric measure (95% confidence interval [CI] 0.99–1.01, $P = .608$).[17]

Astrocytoma IDH Mutant

To capture historical cohorts likely to be IDH mutant, we look to studies of strictly defined low-grade glioma (grade II) from prior eras, as they are likely to have cohorts that are 80% or more IDH mutant. Grade III cohorts of anaplastic tumors are often an even mixture of the IDH mutant and wild-type tumors, and therefore difficult to interpret in the modern era. In an important observational study, Dr Shaw and colleagues[12] followed the outcomes of 111 patients from the RTOG 9802 study of low-grade glioma assigned to observation after surgeon-determined gross-total resection. They assessed clinical factors associated with better outcome in these patients. The most favorable risk cohort shared 3 factors: less than 1 cm residual tumor (as postoperative MRI would, on occasion, identify residual tumor even in surgeon-determined gross-total resection cases), preoperative tumor diameter <4 cm, and oligodendroglioma histologic type, with resulting 2-year and 5-year progression-free survival rates of 100% and 70%. The favorable natural history of this cohort suggested that more-extensive surgical resection may be causally associated with better outcome. In a notable single institution study, Dr Smith and colleagues[11] from the University of California San Francisco demonstrated an association between gross-total resection and survival in low-grade gliomas, with a median survival of approximately 10 years in subtotally resected cases, which was significantly exceeded by the median of “not reached” in patients who underwent gross-total resection of disease.

Intriguingly, in the study of Beiko and colleagues,[17] patients with IDH1-mutant malignant astrocytic glioma also displayed a substantial survival benefit in association with more-extensive resection of nonenhancing disease. These patients had impressively favorable prognosis, despite putative malignant grading (grades III and IV); indeed, the survival of more-extensively resected T2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) cohort largely matched the results from the study by Smith and colleagues[11] of grade II gliomas, suggesting that the common feature driving “surgical responsiveness” was their IDH mutant classification, and not their WHO grading. Several subsequent studies have demonstrated consistent results pointing toward extended survival with more-extensive resection of nonenhancing disease in the astrocytoma IDH mutant subgroup of patients.[18–20] Thus, for patients with astrocytoma IDH mutant, these findings suggest that extensive resection of both enhancing and nonenhancing (T2/FLAIR hyperintense) disease should be pursued, regardless of WHO grade.[21] Consideration should be given to staging of second surgical procedures, using advanced assessment techniques such as intraoperative MRI or ultrasound, to pursue these radical resections.

Of note, IDH mutant gliomas have characteristic anatomic location of presentation, more commonly arising in the frontal lobe, with a more frequent unilateral pattern of growth, sharp tumor margin, and less contrast enhancement.[22] These anatomic features suggest that IDH mutant gliomas could be relatively more feasible for resection, when compared with their wild-type counterparts. Also, patients with IDH mutant gliomas also display relatively preserved neurocognitive function (NCF) and better performance scores than those with similarly sized IDH wild-type gliomas.[23] Because IDH mutant gliomas are predominantly located in frontal lobe and cause less disturbance of adjacent normal brain, these tumors may also be intrinsically more amenable to maximal resection.[17]

Oligodendroglioma, IDH Mutant, 1p/19q Codeleted

Comprising approximately 5% to 7% of adult diffuse gliomas, oligodendroglioma IDH mutant 1p/19q-codeleted tumors represent perhaps the first molecularly defined glioma.[24] Somewhat surprisingly, it is difficult to demonstrate a survival benefit for more-extensive surgery in this cohort,[25] likely due to 2 factors. First, these patients often present at older age compared with astrocytoma IDH mutant,[26] presumably reflecting their more slow-growing natural history. As such, a prolonged survival in many cases will start to extend into decades of life when more common systemic diseases become life-limiting. In addition, the prolonged natural history of oligodendroglioma can require an extensive follow-up of 1 or more decades to determine the survival benefit of an effective therapy.[27] Thus, although it is likely that more-extensive surgery provides a survival benefit to these patients, and indeed in some cases offers a result that is, effectively a “cure” by bridging patients into the more routine health scenarios of the elderly, it remains to be well demonstrated by the existing evidence.

For the clinical scenario of patients who present with suspected IDH mutant disease, but with question as to whether the tumor is likely to be astrocytoma or oligodendroglioma, it is worthwhile to note that a recently discovered radiographic biomarker, termed “T2/FLAIR mismatch” can be a highly specific marker of astrocytic glioma.[28] This sign is positive when the T2-weighted image demonstrates complete or near-complete hyperintense signal throughout the lesion, and comparatively the FLAIR sequence displays the central majority of lesion to be relatively hypointense signal when compared with T2 image, with the exception of a peripheral rim of hyperintense signal. Although not highly sensitive, this mismatch sign has been shown to be highly specific, when scored correctly, for astrocytoma IDH mutant and might therefore have utility to prompt more aggressive resection in this tumor type.[29]

Less Frequent Tumor Molecular Subtypes

There are 2 minor frequency (~1% each) tumor subtypes worthy of mention: BRAF-mutant glioma, and histone H3.3 mutant diffuse midline glioma. These gliomas are more commonly found in younger adults, with the age of presentation extending into the older pediatric cohorts as well. The diffuse midline gliomas, understandably due to their typical anatomic localization at presentation within the spinal cord, brainstem or thalamus, do not have evidence of benefit from more-extensive surgical resection. The prognosis of these tumors is dismal, worse than glioblastoma IDH wild-type in most studies. On the other hand, the

BRAF-altered gliomas are an emerging subclass that harbors diverse legacy histologic correlates, including pilocytic astrocytoma, gangliogliomas, pleomorphic xanthoastrocytoma, diffuse glioma, and epithelioid malignant glioma. Regrouping and refinement of these interrelated legacy histologies is under way[30]; however, the well-established historical benefit of aggressive surgical resection for pilocytic astrocytoma seems to be at least partially reflected in studies of “pediatric-type” BRAF-mutant diffuse gliomas.[31] These gliomas warrant close neurosurgical study in the future.

Last, intraoperative technologies to rapidly assess for signature mutations (IDH1, IDH2, BRAF, TERT, H3F3A) have been preliminarily provisioned.[32–34] Combined with preoperative radiologic biomarkers, advances in these technologies may allow the surgical strategy to determine the degree of resection to be adjusted intraoperatively during a surgical procedure.

SUMMARY

In conclusion, with the 2016 revision of the WHO diagnostic criteria, surgery for adult diffuse gliomas has become even more tightly integrated with radiology and pathology, in both the diagnostic phase as well as the surgical treatment of these diseases. Certain classes of glioma, such as astrocytoma IDH mutant, display a substantial survival benefit in association with maximal resection, regardless of tumor grade under the legacy criteria. Thus, individualization of surgical strategy for patients with gliomas has advanced significantly in the modern era.

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KEY POINTS

- The evidence base for surgery differs for the 3 most common gliomas of adults.
- For patients with Glioblastoma IDH wild-type, the evidence supports a surgical strategy aiming for complete resection of enhancing disease.
- For patients with Astrocytoma IDH mutant, the evidence supports a maximal surgical strategy aiming for complete resection of enhancing and non-enhancing disease.
- For patients with Oligodendroglioma IDH mutant 1p19q-codeleted, the overall outcome is favorable due to an indolent natural history and effective radio-chemotherapeutic treatment; more-extensive resection may provide additional benefit.

CLINICS CARE POINTS

- For patients with Glioblastoma IDH wild-type, the evidence supports a surgical strategy aiming for complete resection of enhancing disease. For the rare non-enhancing glioblastoma IDH wild-type, debulking can be pursued if safe, but there is scant evidence to indicate that this practice confers a survival benefit.
- For patients with Astrocytoma IDH mutant, the evidence supports a maximal surgical strategy of complete resection of enhancing and non-enhancing disease. There is an impressive prolongation of survival associated with minimization of residual disease burden in this cohort of patients.
- For patients with Oligodendroglioma IDH mutant 1p19q-codeleted, the overall outcome is favorable due to an indolent natural history and effect adjuvant treatment regimens; as such, more-extensive resection may provide additional benefit, but has been difficult to definitively link with further improvement in outcome, in part due to the need for prolonged follow-up (>decade) for any potential survival difference to become apparent.

Table 1

The three most common diffuse gliomas of adults

WHO Diagnosis	Typical Age	Co-Mutations	Evidenced Therapy
Astrocytoma, IDH mutant	20–40s	TP53, ATRX	Maximal surgery, PCV or TMZ + RT
Oligodendroglioma, IDH mutant, 1 p/19q-codeleted	40–50s	TERT, CIC	PCV + RT
Glioblastoma, IDH wild-type	50–70s	TERT mutation, EGFR amplification, Chr 9p and 10 loss, Chr 7 gain	Resect enhancing disease, TMZ + RT

These 3 gliomas differ in typical age-of-presentation, and co-mutations, as indicated. Glioblastoma IDH wild-type represent approximately 65%-70% of adult gliomas. Astrocytoma IDH mutant represent approximately 20%-25%. Oligodendroglioma IDH mutant 1p/19q-codeleted only 5%-7%. The evidence for optimal therapy differs between these different tumors.

Abbreviations: CCNU, vincristine; Chr, chromosome; PCV, procarbazine; RT, radiation therapy; TMZ, temozolomide.

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