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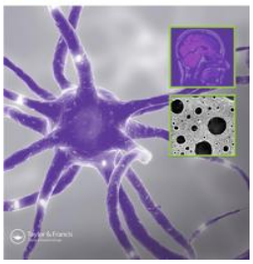

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PERSPECTIVE

Surgical decision making in the era of supramarginal glioma resections: a current perspective and narrative review

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ABSTRACT

Whether to surgically resect a margin of grossly normal appearing brain around anatomically amenable diffuse gliomas (i.e., perform a supratotal, supramarginal, or supramaximal resection) has been controversial. Over the past 5-10 years, however, evidence published by multiple independent groups has established a substantial survival benefit to this approach, moving the field towards a consensus that supramarginal resections should be offered when possible. However, many practitioners remain hesitant to offer supratotal resections due to concerns for variable neuropsychological outcomes and a mindset of "first, do no harm." Unfortunately, and perhaps counterintuitively, available data also suggest that opting for more conservative surgical approaches when more aggressive resections are possible may result in both suboptimal long-term functional and survival outcomes. To explore this complex and actively evolving issue, here I review evidence surrounding the multidimensional clinical impacts of supramarginal resections across all diffuse glioma subtypes. I then evaluate what is known about anatomical-functional relationships subserving cognition, behavior, and mood regulation, and I examine ethical considerations that arise when counseling patients at the difficult time of diagnosis. I then conclude with a set of case examples that demonstrate how the principles explored in this review can be applied in real-world situations to optimize, individualize, and humanize oncological and functional outcomes.

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1. Introduction

Adult diffuse gliomas (World Health Organization [WHO] grades 2–4) are incurable primary brain tumors that cause substantial morbidity [1,2]. Although we learn more about genetic and molecular markers of these tumors every day, current data strongly support the need for early, maximal safe surgical resections in virtually all glioma subtypes [3–7]. Amongst lesions that are anatomically amenable to complete radiographical resection, whether neurosurgeons should also resect a margin of otherwise radiographically and/or grossly normal appearing brain around the lesion (i.e., a supratotal, supramarginal, or supramaximal resection) historically has been controversial [8–12]. Over the past 5–10 years, however, iterative evidence published by multiple independent groups has consistently bolstered the case that supramarginal resections offer a substantial survival benefit for patients with both higher and lower grade lesions, moving the field toward a consensus that supramarginal resections should be the first-line surgical approach when possible [5,10,11,13–27]. However, many practitioners who treat glioma patients remain hesitant to offer supratotal resections and instead continue to opt for lesionectomies, or removal of the gross tumor only. The reluctance to perform a more aggressive surgery involving otherwise grossly normal-appearing brain is a multifaceted issue that can be rooted in (1) a desire to "do no harm;" (2) a concern for unpredictable cognitive, personality, and/or behavioral changes; and/or (3) a mistrust or misunderstanding of published data, among other factors. Unfortunately, and perhaps counterintuitively, available data also suggest that when more conservative surgical approaches are taken in tumors that are anatomically amenable to aggressive resections, both long-term functional and survival outcomes may be suboptimal [21,27,28]. To explore this complex and actively evolving issue, here I

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review published evidence surrounding the multidimensional clinical impacts of supramaximal resections, and I attempt to distill the plethora of information into tangible, applicable surgical principles to aid in *a priori* surgical decision making. In doing so, I evaluate what we know about anatomical-functional relationships subserving cognition and behavioral regulation, and I examine active ethical considerations that arise when counseling patients at the difficult time of diagnosis. I then present several real-world case examples to demonstrate how the principles explored above can be applied to individual cases, and I conclude with a brief look into some of the remaining unanswered questions and future directions in glioma surgery.

2. Oncological goals of glioma surgery

Diffuse gliomas are, by definition, non-curable diseases that require multidisciplinary treatment [29–33]. Years of cumulative data support beginning treatment with surgical resection, and a strong relationship has been established between expected survival and residual postoperative tumor volumes (i.e., extents of resection) for virtually all diffuse glioma subtypes [3,6,7,19,34–40]. Historically, oncological goals of glioma surgery have included: (1) procurement of tissue for pathological confirmation and molecular profiling, (2) cytoreduction (i.e., minimizing the number of cancer cells), and (3) reduction of lesional mass effect, all while preserving neurological function [41]. Newer insights into the nature of gliomas, however, have somewhat broadened these goals, as we now know diffuse gliomas behave less like local tumor masses (e.g., cerebral metastases, cavernomas, or grade 1 gliomas) and more like infiltrative diseases that (a) likely originate from subventricular zones, (b) spread either via radial, ontogenetic, or white matter tracts, and (c) disseminate well beyond gross lesional margins [12,42–47]. We also now know that glioma cells interact directly with neurons to form functional "cancer networks" whose edges, if left in place after surgery, can lead to more rapid local recurrence [44,48]. With these insights in mind, there has been a conceptual shift away from approaching glioma surgery as a "debulking" or "lesionectomy" procedure and more toward a "functional-anatomical amputation" of the affected brain region that additionally incorporates brain beyond the gross lesional boundaries when safe to do so (Figure 1) [8,10,28,44,49]. This idea is supported

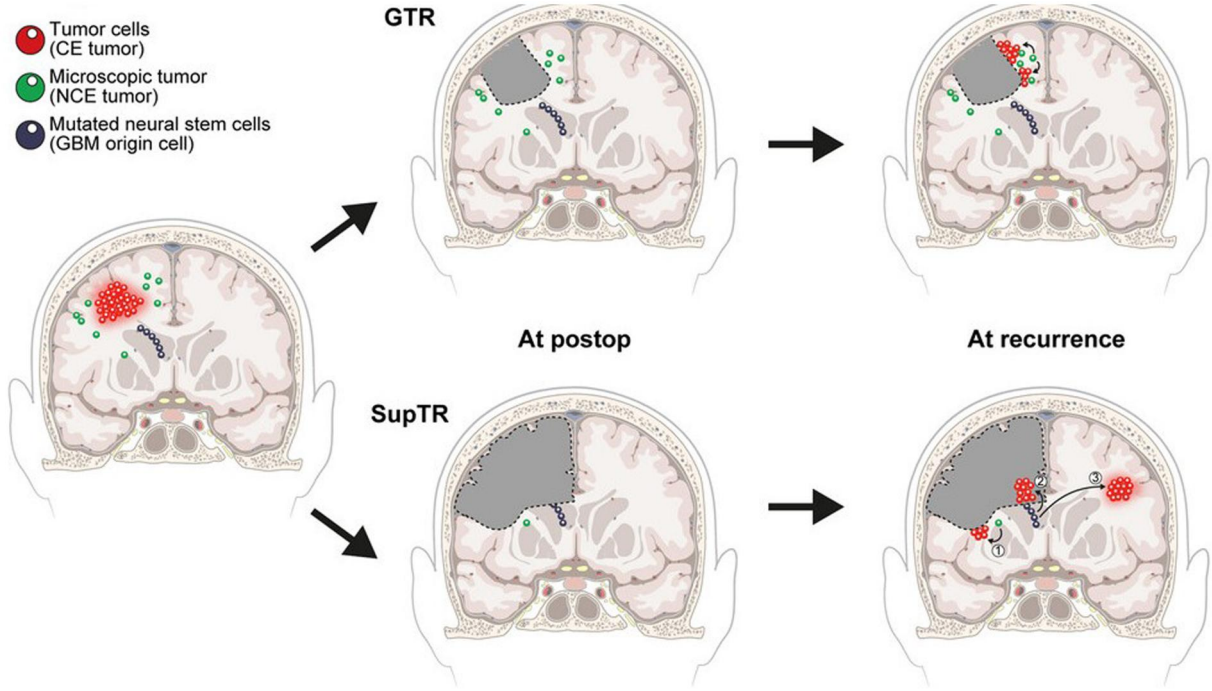


Figure 1. Illustration by *Yoo et al.* showing the conceptual difference between gross total and supratotal surgical approaches and their resultant recurrence patterns [18]. While gross total resection removes the tumor bulk, residual infiltrative cells lead to local recurrence more quickly than with supratotal resections. Recurrence in supratotal resections tend to happen later and more frequently at distant sites. Surgically, supratotal resections aim for functional-anatomical boundaries beyond gross tumor, ideally incorporating microscopic infiltrating tumor edges into the resection. This often delays recurrence until the mutated neural stem cells generate further tumor cells that spread via available white matter tracts or ontogenetic pathways. CE – contrast enhancing, NCE – non-contrast enhancing, GBM – glioblastoma, GTR – gross total resection, SupTR – supratotal resection. Reproduced with permission from *Yoo et al* [18].

by data that demonstrate recurrences after supratotal resections tend to happen later and more often at anatomically distant sites (i.e., >2cm from the resection cavity margin) when compared to gross or subtotal resections, which tend to recur sooner and more often perilesionally [18,50]. Practically speaking, treating unilobar lesions (especially within the frontal and non-dominant temporal lobes) with a functional-amputational approach often results in a complete or partial lobectomy (Figure 2) [14]. However, if a tumor infiltrates critical functional tissue, standard practice still dictates that the resection is stopped at a subtotal margin to prioritize maintenance of function over extent of resection [28,41,51]. This practice is consistent with data showing that new, permanent motor or language deficits acquired in surgery can negate the oncological survival benefit gained from the operation [27,52–54].

In sum, cumulative data from the past 10 years has augmented the oncological goals of glioma surgery toward amputating the "cancer network" by resecting as much of a margin beyond gross tumor as safely possible. Seeking functional margins of the brain as resection borders rather than gross tumor boundaries has repeatedly and reproducibly outperformed classical lesionectomies and debulking surgeries in virtually every oncological and functional domain for virtually every glioma subtype across time, institutions, and countries [8,10,16,22,25–27,41,55,56]. The consistency and breadth of this data has pushed the field toward recommending supramarginal resections as the first-line approach for all diffuse glioma subtypes when feasible at the time of diagnosis [8,27]. This goal subsequently implies all diffuse gliomas should be referred to high-volume brain tumor centers prior to their index operations, as supramarginal resections require subspecialized training and careful, longitudinal evaluations of neurological function [57,58]. In other words, there is no longer such an entity as a "simple" surgical glioma [57,58].

3. Radiographical evaluation of supramarginal extent of resection

Radiographically evaluating extent of supramarginal resections is an evolving field. Notably, the terms supramarginal, supramaximal, and supratotal are used interchangeably throughout the literature (and in this review) without widely agreed-upon definitions. Supramarginal resections tend to be quantified differently for contrast versus non-contrast enhancing lesions [26,34,59,60]. In lower and intermediate grade gliomas that are predominantly non-enhancing, T2 Fluid-Attenuated Inversion

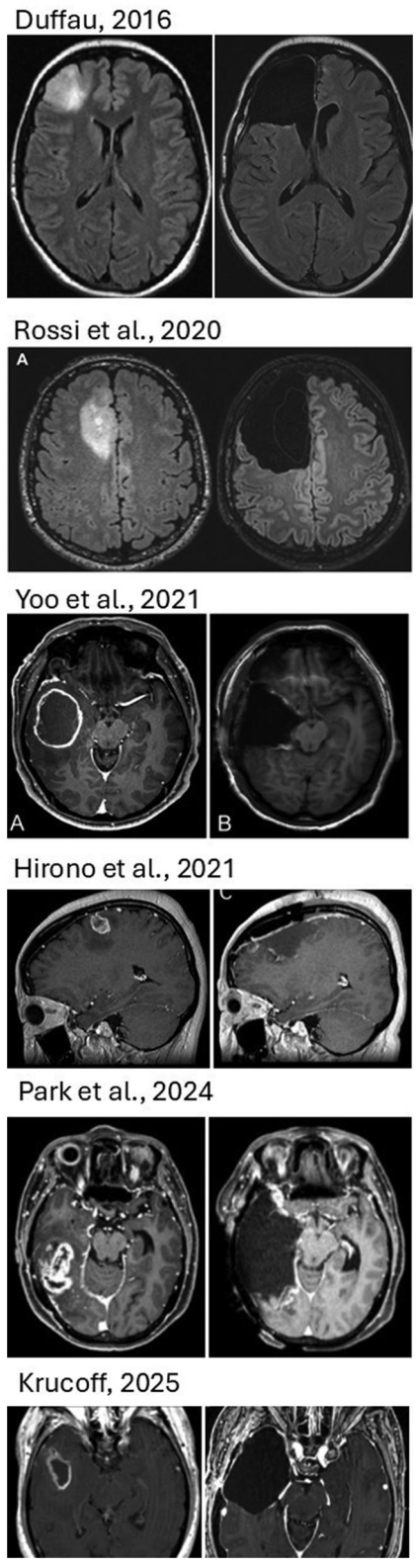


Figure 2. Examples of supratotal resections of diffuse gliomas published throughout literature. No consensus exists on how much of a margin needs to be resected beyond the lesion for maximum oncological benefit, but common practice includes taking resections to functional margins up to unilateral lobectomies when possible. Reproduced with permission from various sources [16,18,20,24,28].

Recovery (FLAIR) lesions, supramarginal resections have been defined by both (1) the absence of residual T2 FLAIR signal and (2) a larger postoperative resection cavity than preoperative lesional volume [20,25]. Ideally, extent of resection in non-enhancing lesions is evaluated either immediately postoperatively (preferably even with an intraoperative MRI) or 3-months postoperatively, as confounding FLAIR signal emerges and wanes between those timepoints due to evolving edema, retraction injury, and ischemia [34,61]. For contrast-enhancing masses, on the other hand, supramarginal resections tend to be defined by (1) a complete resection of the contrast-enhancing mass plus (2) a significant resection of the surrounding FLAIR [9,17,22,23,26,62–64]. Despite unresolved questions surrounding how much FLAIR needs to be resected for maximal oncological benefit, there does appear to be a clear trend toward more aggressive resections being associated with longer survival [23,26,27,64]. While there is minimal data expressly evaluating the effect of resection *beyond* FLAIR margins in contrast-enhancing lesions, partial or complete anatomical lobectomies to functional borders have been reported and seem to be associated with the best survival outcomes when possible (Figure 2) [14,16].

In 2022, the Response Assessment in Neuro-Oncology (RANO) resect group, an international, multidisciplinary group that aims to standardize radiographical glioma assessments, published and validated a new classification system for resections in WHO-grade 4 IDH-wt glioblastomas (Figure 3) [26]. In this schema, Class 1 resections represent supramarginal resections and are defined by (1) no residual contrast enhancing (CE) tumor and (2) $<5cm^3$ of residual non-contrast enhancing (nCE) tumor. Class 2 resections are subdivided into Class 2a, formerly gross total resections (i.e., no residual CE but $>5cm^3$ of residual nCE), and Class 2b, formerly near total resections (i.e., $<1cm^3$ of residual CE). Class 3 represents subtotal resections and are also stratified into 3a/3b based on residual CE tumor volume, whereas Class 4 cases are biopsy only. While this classification scheme is likely to become the new standard for evaluating contrast-enhancing glioma resections, no such consensus evaluation system currently exists for supramarginal resections in primarily FLAIR lesions, to my knowledge [65].

4. Survival outcomes

Evidence from around the globe, especially over the past 10 years, consistently and invariably supports a significant survival advantage in people with all types of diffuse gliomas who undergo supratotal resections [5,9,10,13–26,28,33,62–64,66]. This relationship holds up as a strong, independent, modifiable predictor of survival, even in the age of molecular and genetic diagnosis. For example, the RANO resect group validated their new classification system for extent of resection in 744 cases of WHO-grade 4 IDH-wt glioblastomas treated with surgical resection followed by radiation and temozolamide (TMZ) (i.e., standard Stupp protocol) [26]. They found statistically significant differences in overall survival based on extent of resection classification with median overall survivals of 24, 19, and 15 months for Class 1, 2, and 3 resections, respectively (Figure 4) [26]. This finding makes extent of resection the most impactful, modifiable risk factor for survival in IDH-wt glioblastoma, as it implies extending resections from Class 3 to Class 1 provides a shift of 9 months in the median survival curve. As a reference, the impact of TMZ plus Tumor-Treating Fields (i.e., alternating transcranial currents), which represents the current standard of care for adjuvant GBM treatment, has been shown to increase survival by about 8 months when added to radiation [29,30]. More recently, another group re-validated the prognostic impact of this classification scheme on 580 glioblastoma patients and found that patients who underwent RANO Class 1 resections had a median overall survivals of 35.6 months (95% CI: 30.9–40.4), whereas patients who underwent non-Class 1 resections survived only a median of 13.9 months (95% CI: 13.0–14.7; $p < 0.001$), suggesting an even larger potential influence on survival [22].

In IDH-mutant intermediate grade gliomas (WHO grades 2 and 3), *Rossi et al.* published a series of 319 such cases who had undergone craniotomies for surgical resection [25]. While controlling for molecular genotype, they noted profound progression-free, malignant progression-free, and overall survival advantages in patients who underwent supratotal resections versus gross total and subtotal resections (median overall survivals not-reached at 92 months versus 29 months and 27.5 months, respectively) (Figure 5) [25]. This relationship persisted when evaluating each molecular and histopathological subgroup of IDH-mut gliomas individually. These large case series represent a small fraction of the published data and are each bolstered by innumerable others that have replicated and/or produced similar findings, as well as multiple systematic reviews and meta-analyses that further establish extent of resection, up to and including supratotal resections, as the most impactful modifiable predictor of survival when combined with standard adjuvant treatment protocols.

Another underappreciated but critical modifiable predictor of survival is the postoperative volume of

RANO categories for extent of resection in glioblastoma					
Class 1: supramaximal CE resection	**Class 2: maximal CE resection**		**Class 3: submaximal CE resection**		**Class 4: biopsy**
	Class 2A: complete CE resection	*Class 2B: near total CE resection*	*Class 3A: subtotal CE resection*	*Class 3B: partial CE resection*	
0 cm^3 CE + ≤5 cm^3 nCE	0 cm^3 CE + >5 cm^3 nCE	≤1 cm^3 CE	≤5 cm^3 CE	>5 cm^3 CE	No reduction of tumor volume

Figure 3. New RANO Resect classification system for evaluating extent of resection in IDH-wt glioblastomas. In this system, supramaximal resections are Class 1, gross total resections are Class 2A, near total resections are Class 2B, subtotal resections are Class 3A, and debulking operations are Class 3B. CE – contrast enhancement, nCE – non-contrast enhancement. Reproduced with permission from *Karschnia et al* [26].

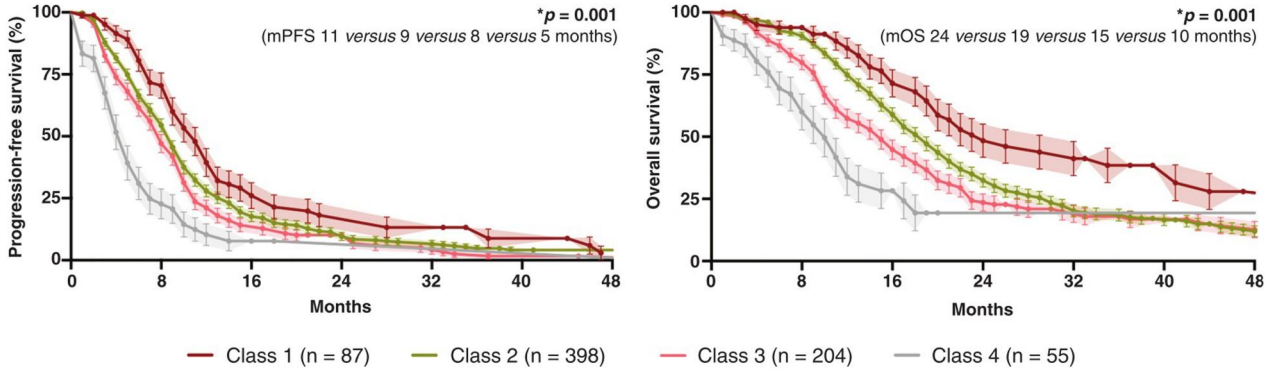


Figure 4. Progression-free and overall survival curves for grade 4 IDH-wt glioblastomas separated by new RANO Resect extent of resection classifications (see Figure 3). The difference in median overall survival of 9-months between Class 1 and Class 3 resections makes extent of resection the most impactful modifiable risk factor for this subgroup. mPFS - median progression-free survival, mOS - median overall survival. Reproduced with permission from by *Karschnia et al* [26].

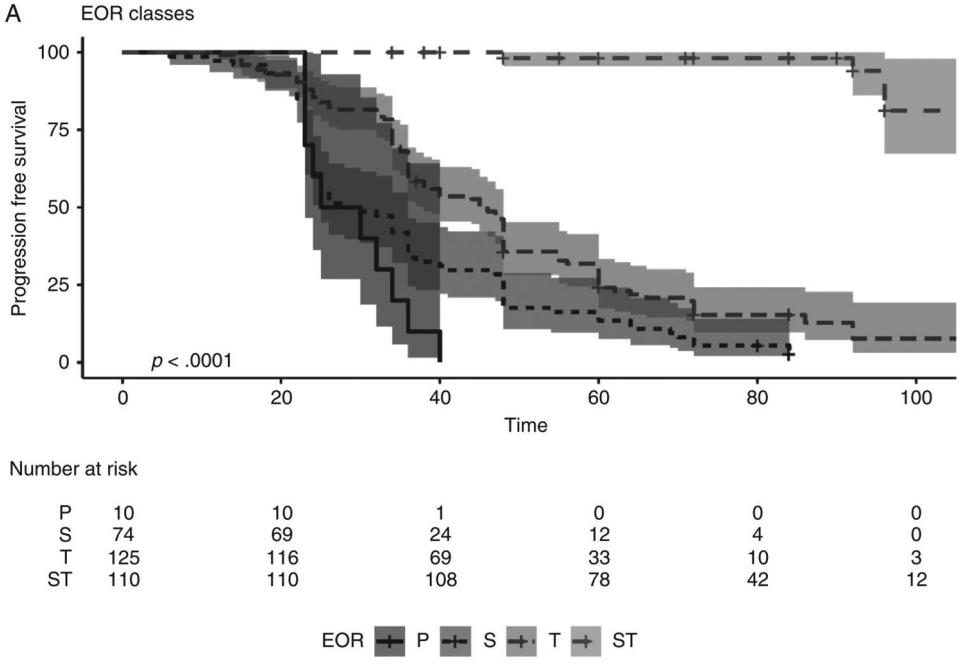


Figure 5. Progression-free survival curves for grade 2–3 IDH-mut diffuse gliomas separated by extent of resection. There is a profound progression-free survival advantage at 100 months postoperatively when a supratotal resection is achieved. EOR – Extent of Resection. P – partial, S – subtotal, T – gross total, ST – supratotal. Reproduced with permission from *Rossi et al* [25].

surgically-induced brain ischemia, as several groups have demonstrated that higher volumes of postoperative infarction predict worse survival even independently from other known risk factors, such as new neurological deficits (Figure 6) [67–70]. A leading hypothesis to explain this phenomenon is that postoperative infarction may become a nidus for hypoxia-induced tumor proliferation, as more aggressive patterns of recurrence, more diffuse disease burden, and shorter survivals have all been documented in cases with larger ischemic volumes [68–70]. The removal of otherwise residual ischemic brain in supratotal resections may also partially contribute to its known oncological benefit, but this has yet to be established.

5. Postoperative chemo-radiation depends on extent of resection

Standard of care for adult diffuse glioma treatment involves a multidisciplinary approach, which, in most cases, includes radiation and chemotherapy either immediately after the index surgery or upon recurrence [31,32,57]. Therefore, how radiation and chemotherapy factor into long-term oncological and functional outcomes needs to be incorporated into upfront surgical decision making. As explored above, when planning an operation, treating physicians need to account for both the potential downside of delaying radiation in higher grade lesions because of functional status decline from surgery, as well as the potential upside of negating the need for upfront radiation in cases of completely resected lower grade tumors [27,31,32,71]. Supporting this calculus is recent evidence suggesting that biopsying anatomically resectable high-grade gliomas prior to definitive surgery has a negative impact on survival, likely due to a delay in the initiation of chemoradiation from the time of diagnosis [58]. In lower-grade gliomas, current societal guidelines acknowledge the impact of extent of resection up to gross total resection on the need for chemo-radiation after the index surgery, suggesting that initial observation is reasonable for lower-grade lesions that are gross totally resected (Figure 7) [32,71]. Because early chemo-radiation may result in well-known, long-term side effects such as cognitive decline, severe fatigue, pancytopenia, and fertility complications, delaying its initiation represents potential long-term gains in quality of life, especially in younger individuals with longer natural life expectancies. In addition to quality-of-life benefits and complication avoidance, there is also some oncological benefit to delaying radiation, as lower grade gliomas that recur after chemo-radiation are known to have higher rates of genetic mutations that portend worse prognoses, such as CDKN2A homozygous deletions, than those that recur after surgery alone [72,73]. With this in mind, many high-volume centers focus on maximizing *overall* instead of *progression-free* survival,

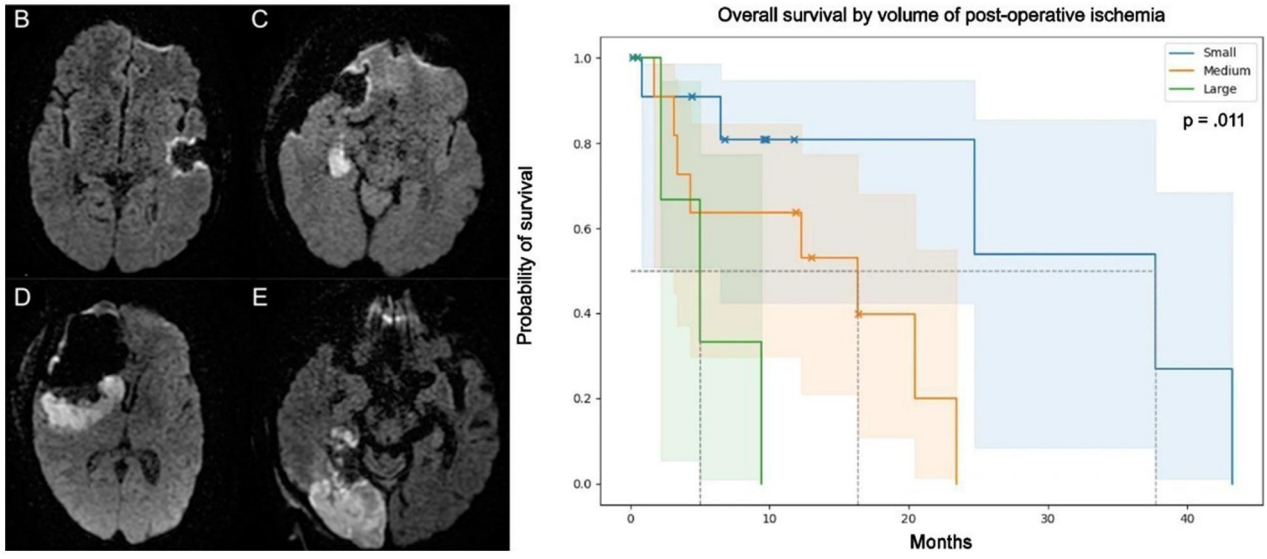


Figure 6. Overall survival curves for high-grade gliomas separated by volume of postoperative ischemic brain. The separation of these curves was found to be independent of new neurological deficit and other molecular markers, suggesting volume of infarction may be an independent risk factor for survival. Left image: Categories of sizes of postoperative ischemia, B – none/minimal, C – small, D – medium, E – large. Right image: Associated survival curves for each category. Reproduced with permission from *Aaronson et al* [67].

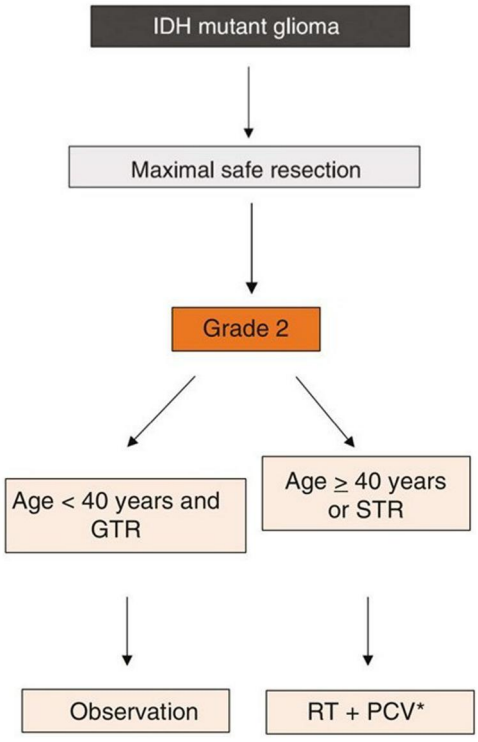


Figure 7. Current Society for Neuro-Oncology (SNO) guidelines for treatment after index surgery. For IDH-mut, WHO grade 2 gliomas, postoperative observation is recommended when at least a gross total resection (GTR) is achieved, whereas adjuvant chemo-radiation is recommended for subtotal resections (STR). Reproduced with permission from *Miller et al* [32].

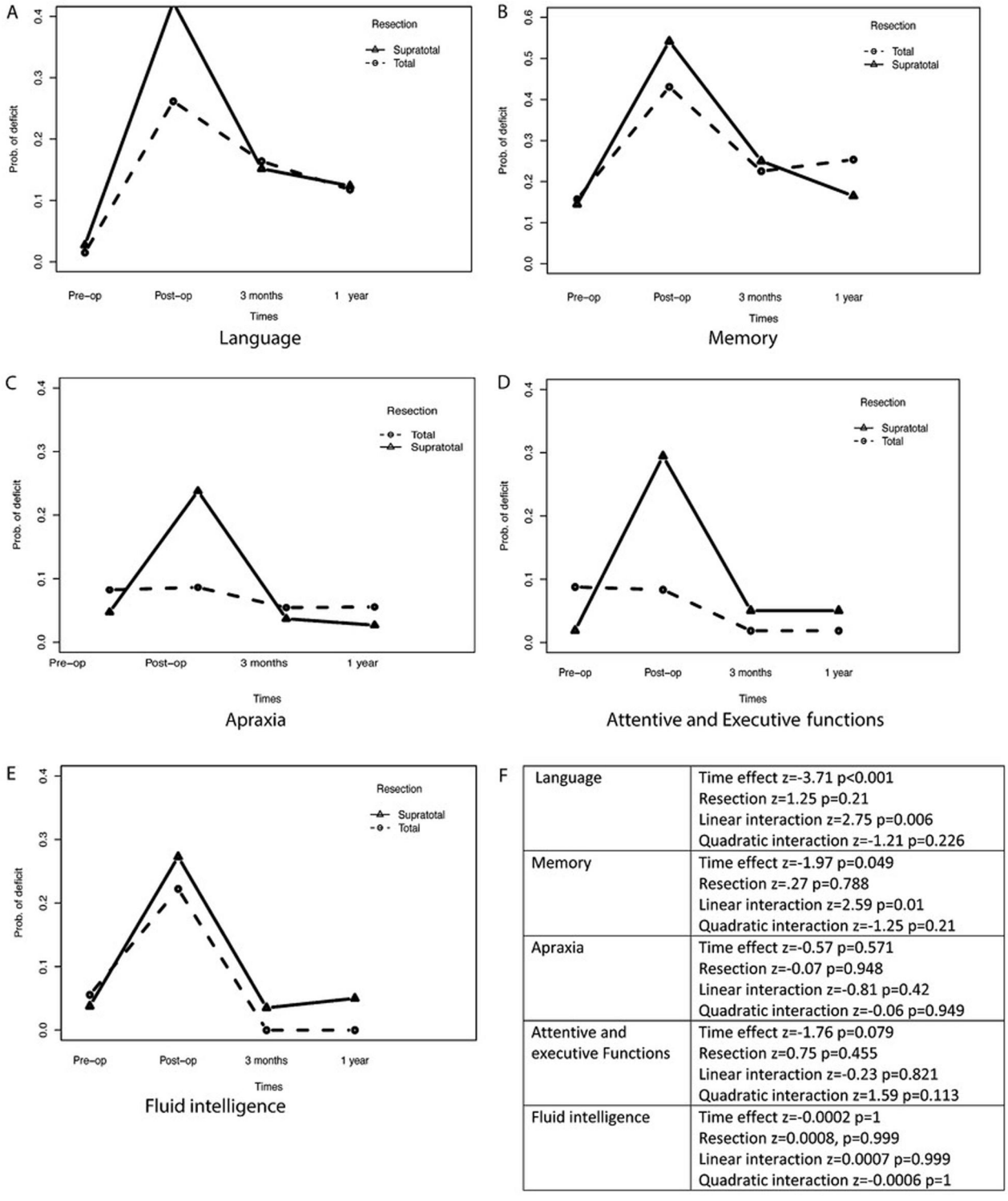
especially in younger patients with grade 2 tumors, by trying to delay the initiation of chemo-radiation in at-least gross totally resected tumors without evidence of early recurrence on surveillance MRIs. The differential impact of supra- versus gross total resections on adjuvant treatment planning, however, has not yet been incorporated into societal guidelines and awaits more long-term data, especially for grade 3 tumors. Furthermore, how supratotal resections impact postoperative radiation planning (i.e., dose lines) around variably sized resection cavities is a burgeoning topic of great debate.

6. Cognitive, mood, and behavioral outcomes

Given the emerging clarity of data supporting survival benefits in supratotal glioma resection, what might account for the slow adoption of this technique into real-world practice [8]? While the answer has many facets, a common theme is the physician's desire to "do no harm," along with the fear of inducing unpredictable changes in personality, cognition, or behavioral regulation, by resecting more brain than otherwise might be necessary. Supporting these fears is a renewed awareness of "silently eloquent" areas of the brain, or the idea that no part of the brain is truly non-functional [74]. This challenge requires us to address the following critical question: what do we know about anatomical-functional relationships subserving cognitive, mood, and behavioral domains?

While there is much yet to be learned about the structural and functional anatomical relationships that subserve cognition, mood, and behavioral regulation, there are general principles that have long guided surgical planning and patient counseling. Practically speaking, concerns about neuropsychological outcomes become most prevalent in frontal, temporal, and limbic-area tumors, where supramarginal resections are most frequently considered. It is critical to recognize that functional-anatomical relationships can have asymmetrical representations across the cerebral hemispheres, such as language, which can define which side we consider the "dominant" hemisphere [75–77]. Known anatomical-functional associations include frontal lobe injury and abulia (particularly when involving the anterior cingulate cortex and/or dominant caudate) [78–80], non-dominant temporal lobectomies and depressive symptoms (most well documented in the epilepsy literature) [81,82], non-dominant parietal lobe tumors with inattention and hemineglect [77,83,84], and limbic-area tumors with impaired mood regulation, attention, and verbal memory [77,85,86]. Recently, *Ng et al.* reported results from a detailed lesion-symptom mapping study that analyzed resected anatomy and non-recovered neuropsychological domains at 3-months in a cohort of 400 patients with diffuse low-grade gliomas who underwent awake surgery with cognitive mapping. They found a lack of recovery in picture naming linked to the left inferior temporal gyrus and inferior longitudinal fasciculus, semantic fluency linked to the left precuneus/posterior cingulate gyrus, phonological fluency linked to the left dorsomedial frontal cortex and frontal aslant tract, and spatial exploration linked to the right dorsomedial prefrontal cortex. Additionally, their data suggest that resections involving the left uncinate fasciculus, left corticostriatal tract, anterior corpus callosum, hippocampus, parahippocampus, and right frontal–mesial areas beyond the tumor margins were associated with a less pronounced recovery of each associated function [87]. On the other hand, *Rossi et al.* reported 1-year postoperative results in a similar cohort of 100 patients with low grade gliomas also underwent awake resections with cognitive mapping [28]. Of these cases, 60 underwent supratotal resections whereas 40 underwent gross total resections. Detailed neuropsychological evaluations displayed significant immediate postoperative cognitive

declines in both supra- and gross total resection groups that were more pronounced in the supratotal group in most domains; however, both groups significantly recovered their deficits by 3-months such that no significant difference was measurable between the groups at 3-months or 1-year (Figure 8). Other notable outcomes from the *Rossi et al.* series include better long-term seizure control in the supratotal resection group, and a higher deficit and complication rate in the subtotal resection group [28].



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Language	Time effect z=-3.71 p<0.001 Resection z=1.25 p=0.21 Linear interaction z=2.75 p=0.006 Quadratic interaction z=-1.21 p=0.226
Memory	Time effect z=-1.97 p=0.049 Resection z=.27 p=0.788 Linear interaction z=2.59 p=0.01 Quadratic interaction z=-1.25 p=0.21
Apraxia	Time effect z=-0.57 p=0.571 Resection z=-0.07 p=0.948 Linear interaction z=-0.81 p=0.42 Quadratic interaction z=-0.06 p=0.949
Attentive and executive Functions	Time effect z=-1.76 p=0.079 Resection z=0.75 p=0.455 Linear interaction z=-0.23 p=0.821 Quadratic interaction z=1.59 p=0.113
Fluid intelligence	Time effect z=-0.0002 p=1 Resection z=0.0008, p=0.999 Linear interaction z=0.0007 p=0.999 Quadratic interaction z=-0.0006 p=1

Figure 8. Neuropsychological outcomes after supratotal versus gross total resections of lower grade gliomas are roughly equivalent at 3-months and 1-year postoperatively. Higher scores indicate a higher probably of a deficit. Reproduced with permissiron from *Rossi et al* [28].

As contralesional homotopic brain regions are known to be critical for recovery, surgeons almost universally will not operate on truly bifrontal or biparietal lesions with symmetrical homotopic involvement. This means patients with so-called "butterfly" gliomas that cross the corpus collosum to involve symmetrical parenchyma of both hemispheres are typically not offered surgical resections [88]. However, as our knowledge of network-based neuroanatomy grows, several groups have challenged the dogma that all butterfly gliomas cannot be resected without poor neuropsychological outcomes [89–91]. For example, one group provided preliminary evidence that maintenance of the default mode network's integrity (i.e., through its connections to the anterior cingulate gyrus) may be the key differentiating factor in acceptable versus poor postoperative cognitive outcomes in these cases [92]. For a more detailed look into how network neuroscience is starting to be applied to glioma surgery, we refer the readers to our recent review [93].

While this summary of anatomical-functional associations is overly simplistic and notoriously heterogenous across individuals, it highlights the known stakes of intra-axial tumor resections, as some of the most feared outcomes involve permanent changes to cognition and personality [93,94]. Unfortunately, it is important to also note that, perhaps counterintuitively, data suggest that long term rates of neurological deficits are *higher* in cases of subtotal compared to supratotal resections, underscoring the relentless natural history of residual tumor that eventually leads to a deterioration of the neurological function the surgeon was hoping to preserve through a more limited resection [21,28]. For patients with diffuse gliomas, the difficult reality is that no matter the surgical approach, complete neuropsychological preservation may not be possible in every case.

7. Intraoperative functional brain mapping

Modern intraoperative brain mapping can provide highly predictable motor and language outcomes in the hands of specially trained neurosurgical oncologists [54–56,95–97]. For example, integrity of the primary motor system can be reliably monitored in real-time under total intravenous anesthesia (TIVA) using continuous motor evoke potentials (cMEP) and subcortical monopolar stimulation [97]. Clinical data suggests that cases with stable MEPs and a subcortical stimulation thresholds of at least 5 mA result in no permanent, surgically acquired motor deficits at 3-months postoperatively with near 100% accuracy (when excluding extraoperative causes) [95]. Alternatively, the gold standard for monitoring language, sensory, and higher-order mental processes is an awake craniotomy with real-time intraoperative testing [56]. During these procedures, bipolar stimulation is typically applied to the cortex or white matter while the patient performs a task, like picture naming, to test each brain site prior to and during its resection. While awake craniotomies used to be first line for motor mapping as well, there has been a general trend toward performing non-language, motor-only cases asleep to better differentiate potentially permanent deficits due to corticospinal tract injury from temporary deficits due to supplemental motor area (SMA) syndrome (a well-known, temporary hemiparesis that results from injury to the posterior superior frontal gyrus). In other words, while corticospinal tract injury versus SMA syndrome cannot be reliably differentiated based on awake clinical testing alone, they *can* be differentiated with asleep MEPs and monopolar white matter stimulation. Therefore, asleep motor mapping can permit more aggressive resections into the posterior superior frontal gyrus than awake craniotomies with a good assurance of recovery [97].

Whether cognitive and behavioral functions can be meaningfully and consistently mapped intraoperatively is controversial [98]. While some groups advocate for "a la carte" mapping of higher-order functions that are critical to an individual patient's *a priori* stated quality-of-life goals [99], this is not widely adopted due to (1) practical constraints of intraoperative time, exposure, and expertise; (2) concerns that many cognitive and behavioral functions are not focally localizable; (3) knowledge that these functions can be highly context specific, and (4) awareness that, like SMA syndrome, many surgically-induced cognitive deficits are temporary (Figure 8) [28]. A lot of work is being done to better predict long-term neuropsychological outcomes from different potential extents of resection, much of which is fueled by emerging knowledge generated by the human connectome project (HCP) on large-scale brain network function [93,100,101]. However, no consistent, usable, clinically validated data currently exists to guide treating physicians on individual-level cognitive or behavioral outcomes, to my knowledge.

Ultimately, outside of the general guiding principles and population-level data explored above, our collective ability to predict and map cognitive outcomes on an individual patient basis remains an area of needed innovation. However, it is widely accepted that the clinical experience of the treating team is critical to achieving the most personalized outcomes [8,55]. In this light, there has been a recent trend toward recommending that all glioma cases be referred to high volume tertiary care centers with

multidisciplinary neurosurgical oncology teams that can offer this expertise [8,55].

8. Integrating the oncological and functional impacts of surgery by WHO grade

Recently, the RANO resect group published a detailed review integrating both positive and negative oncological and functional effects from surgery into an overall impact timeline stratified by 2021 WHO tumor grade (Figure 9) [27]. In this rigorous work, the authors demonstrate that, in more aggressive tumors, such as grade 4 IDH-wt glioblastomas with median overall survivals of 12-17 months, the positive effects of more extensive resection become evident within weeks-to-months; however, the negative impacts of new neurological deficits that impair functional independence and prohibit initiation of chemo-radiation within 6-weeks postoperatively can be devastating and may shift the impact of surgery toward a net negative. In moderately aggressive tumors, such as grade 2 IDH-mut astrocytomas with median overall survivals ranging from 5-12 years, the oncological benefits of aggressive resection become most evident after years 3–7 and can result in a profound increase in median overall survival with a difference of up to 10 years [25,102,103]. Importantly, the authors note that tumor progression within the first decade following complete radiographical resection is rarely reported. In the grade 2 IDH-mut astrocytoma subgroup, moderate postoperative deficits that resolve with time likely have less of a negative impact on overall survival when compared to higher grade tumors. With increasing grades of IDH-mutant astrocytomas, new deficits that might delay adjuvant therapy seem to become more impactful. For the least aggressive diffuse gliomas, grade 2 IDH-mutant and 1p/19q-codeleted oligodendrogliomas, the impact of extent of resection on survival tends

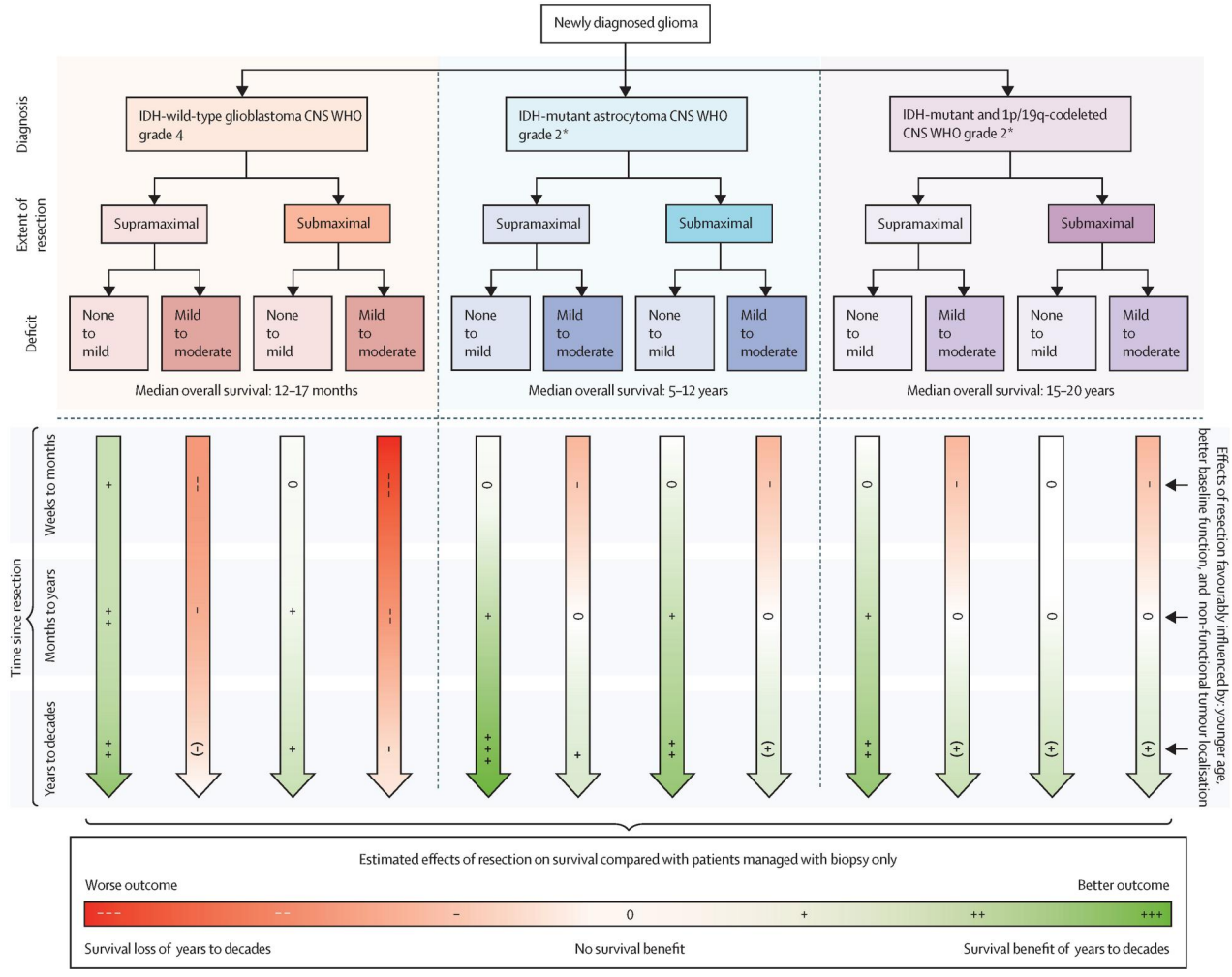

Figure 9. Integrated impact of extent of resection and new neurological deficits on overall survival by 2021 WHO tumor classification. The impact of both extent of resection (positive) and neurological deficits (negative) on overall survival are evident on shorter timescales in more aggressive tumors. The impact of supramarginal resection appears to be the greatest in moderately aggressive tumors, such as WHO grade 2 IDH-mut astrocytomas, and moderate neurological deficits that recover over time are also less impactful in this group. Reproduced with permission from *Karschnia et al* [27].

to emerge after greater than 6-years postoperatively. Because of the favorable natural history of oligodendrogliomas, the authors argue that the overall impact of extent of resection cannot yet be precisely quantified, including supramarginal resections. However, it is reasonable to hypothesize that the impact is likely similar to grade 2 astrocytomas, just on a longer timescale.

9. Ethical considerations and patient counseling

Trying to convey complex, nuanced themes about balancing survival with potential changes in cognition, personality, or behavior to a lay person who just received a devastating diagnosis of a brain tumor is incredibly difficult. Even with the best intentions of empowering individual choice through the informed consent process, *how* the presenting physician frames each option heavily impacts patient decisions, and often patients will defer to surgeon expertise. Therefore, the process of honing in on an appropriately tailored resection plan might be best be viewed as a team effort facilitated through a set of focused patient-physician interactions.

In cases where the anatomy of a glioma might be amenable to several surgical approaches with varying degrees of risk for temporary and/or permanent neurological changes counter-balanced by varying expected survival curves (Figure 10), often discussing the following items with patients can elucidate the optimized approach: (1) what a normal day entails; (2) what activities bring them joy; (3) what are they most looking forward to in the near future; (4) how risk-averse or proactive are they when dealing with their health; and (5) what scares them the most about their diagnosis and

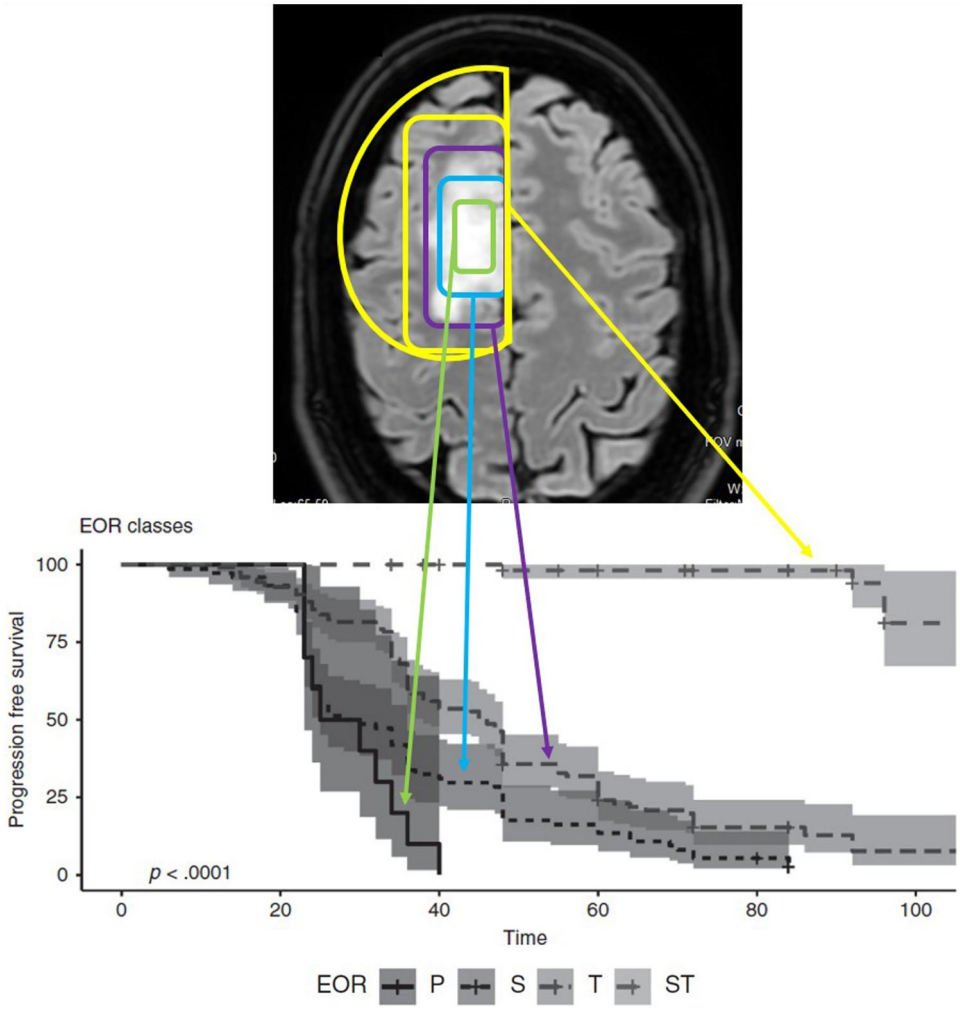

Figure 10. Potential resections for a 39-year-old female with a newly diagnosed right frontal FLAIR lesion (presumed to be an intermediate-grade diffuse glioma) projected onto the associated survival curves published by *Rossi et al* [25]. Green – central debulking (i.e., partial resection), Blue – subtotal resection, Purple – gross total resection (i.e., lesionectomy), Yellow – supratotal resections (rectangle – margin of normal tissue included in the resection, whereas the hemicircle represents a right frontal lobectomy). What remains unknown is the potential for permanent cognitive and/or behavioral consequences of each approach, as well as whether there would be any differential survival benefit between the two yellow resections.

undergoing surgery. Sometimes, just through this initial conversation, the answer to an otherwise murky and ethically complex issue becomes clear. In other words, by combining knowledge about the functional neuroanatomy of the tumor with the patient's personality, goals, hopes, and fears, an approach that has the best chance optimize their multi-dimensional outcome can be found. This means that the same tumor presenting to the same surgeon in two different individuals may be approached differently, which reflects an appropriate level of respect and deference to each individual's humanity.

It is critical to recognize that there is no scenario where a patient with a diffuse glioma can be treated without some form of intervention; and with or without treatment, their disease will eventually progress. Idealistic scenarios of perfect, long-lasting neurological preservation are not realistic in most instances, and attempts to apply the Hippocratic principle of "do no harm" to justify less aggressive approaches upfront, unfortunately, can paradoxically result in harm by under/inaction [21,104]. What has become clear to the community of physicians who subspecialize in and treat high volumes of gliomas is that patients tend to *do better all-around* when they have access to appropriately aggressive upfront treatments performed at specialized glioma centers with experienced multi-disciplinary care teams who navigate such scenarios frequently [8,21,55]. The counterintuitive finding that resecting *more* brain upfront can result *better* long-term combined outcomes is why specialized training in glioma surgery and brain mapping is so important, as it is it critical to (1) see patients do well from large surgeries to have the confidence to perform and guide patients and families through them, and (2) know the principles of anatomical boundaries, appropriate case selection, and critical mapping techniques necessary to perform aggressive surgeries without stepping over the edge of no return (i.e., non-recovery).

10. Case examples and decision making

Here I present four real-world cases that demonstrate how the principles gleaned from the data explored above can be used to inform surgical planning and patient counseling to design optimized, individualized resections aimed at balancing an individual's oncological and functional goals.

10.1. Case 1: Newly diagnosed left anterolateral temporal lobe FLAIR lesion in a 35-year-old

10.1.1. Case presentation

A 35-year-old right-handed female presented after a first-time seizure and was found to have an expansile FLAIR lesion in her left anterolateral temporal lobe with minimal contrast enhancement (Figure 11). Radiographically, this was most concerning for an intermediate-grade diffuse glioma. She was neurologically intact on exam, and a detailed neuropsychological assessment revealed a broadly normal cognitive profile. A task-based functional MRI confirmed strong left language dominance with functionally active speech/language areas at least 1 cm from the lesional borders. Discussion with the patient and her family revealed a strong desire to optimize longevity, as she had young children that she wanted to see grow. This represented both her greatest desire and biggest fear. She also worked as teacher's aide, and she wanted to be able to go back to work.

10.1.2. Surgery

The patient underwent an awake craniotomy with intraoperative language mapping and intraoperative

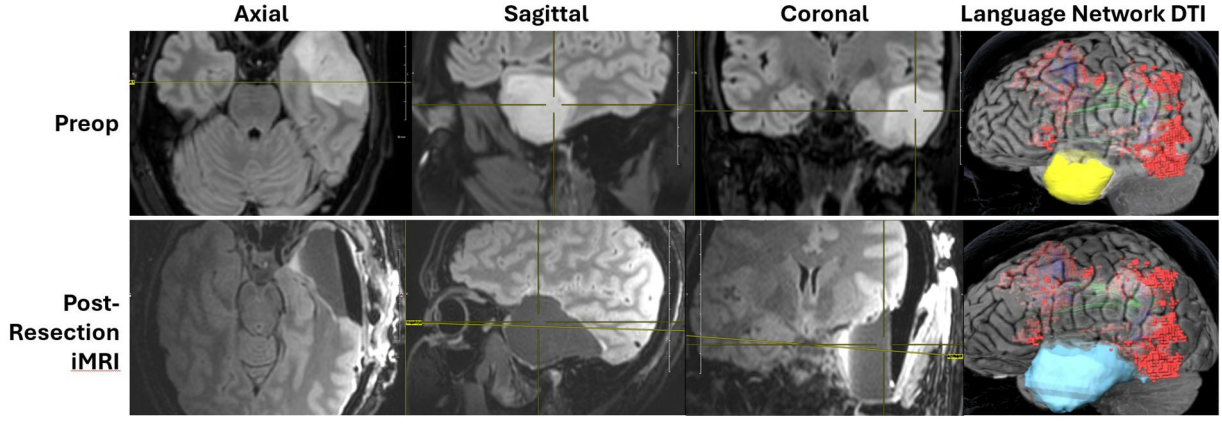

Figure 11. Pre- and postoperative FLAIR MRIs from a 35-year-old right-handed female who presented with a first-time seizure demonstrating a supramarginal resection of a grade 3 IDH-mut astrocytoma. Yellow – preoperative tumor volume. Blue – postoperative resection cavity.

MRI to attempt a supramaximal resection of the lesion to functional boundaries, which appeared anatomically feasible based on preoperative functional imaging. The resection was taken at least one gyrus beyond the gross lesional boundaries in all directions (~1cm posteriorly) (Figure 11). The hippocampus was left intact to minimize the impact of surgery on verbal memory, as the mesial temporal structures were not radiographically involved. Intraoperatively, she began having trouble naming during the inferior-posterior portion of the resection while traversing the fusiform gyrus and the inferior longitudinal fasciculus (ILF). Where she began to have difficulty was deemed the posterior margin of the resection.

10.1.3. Postoperative course

Immediately postoperatively, the patient had a moderate-to-severe predominantly semantic aphasia that was most pronounced on postoperative days 1 and 2. She began to significantly improve on postoperative day 3, and she was able to be discharged home with her family at that time. One month postoperatively, the patient showed significant improvement in her language function, but she still had difficulty with verbal memory (i.e., she was fluent in conversation and could name all presented visual objects but had difficulty explaining, for example, the subject of a podcast she had just listened to, per her family). Five months postoperatively, she and her family reported a full recovery of all language and cognitive symptoms, and repeat detailed neuropsychological testing revealed only mild persistent deficits in memory and semantic naming that could only be elicited with rigorous testing. She was able to return to her original work and caring for her children full-time. The patient has since opted out of further neuropsychological testing, as neither she nor her family notices any persistent deficits in her daily life. Her pathology revealed a WHO grade 3 astrocytoma (IDH-mut, MGMT unmethylated). Consistent with current guidelines for WHO grade 3 astrocytomas, she underwent subsequent radiotherapy with concurrent TMZ, followed by 6 cycles of adjuvant TMZ, and after which she declined further cycles. She is currently two-years out from diagnosis without evidence of progressive disease on her MRI.

10.1.4. Discussion & decision making

Data from *Rossi et al.* suggest that median progression free survivals for patients with grade 3 IDH-mut astrocytomas such as this who undergo subtotal resections is 24.5 months, gross total resections (i.e., lesionectomies) is 35 months, and supratotal resections is >48 months [25]. In this case, therefore, the fundamental questions were, (1) are the temporary and/or permanent deficits expected from each of the resection possibilities worth the increase in survival to this individual, and (2) how well can we manage the risks of worse-than-expected deficits? As the tumor was located in the anterolateral dominant temporal lobe and the patient described a desire to be aggressive, our discussion, therefore, revolved around preparing the patient and her family for an awake craniotomy with temporary aphasia and relatively minor long-term deficits in verbal memory that would be unlikely to impact her life goals. Risks of worse functional outcomes were minimized here by performing the procedure awake, minimizing intraoperative arterial sacrifice, and avoiding a dominant-sided hippocampectomy.

10.2. Case 2: Initial subtotal resection of a left frontal oligodendroglioma (WHO grade 3)

10.2.1. Case presentation

A 35-year-old right-handed female presented after a first-time seizure and was found to have an expansile, predominantly FLAIR lesion encompassing much of the left anteromedial frontal lobe with subtle patchy areas of intrinsic contrast enhancement (Figure 12). The patient underwent a craniotomy for debulking of the mass at an outside hospital, and the pathology revealed an oligodendroglioma, IDH-mut, 1p/19q co-deleted, with increased mitotic activity (WHO grade 3). She was subsequently referred to neuro-oncology and radiation oncology for adjuvant treatment, who then referred her to our institution for consideration of further upfront resection prior to chemoradiation. Her neurological examination was grossly intact, and detailed neuropsychological testing revealed only mild deficits in executive functioning. Discussions with the patient revealed a proactive mindset, as well as a strong desire for longevity, especially to see her young child grow, with her biggest fear being a permanent change in her personality and forgetting how to interact with her child. She did express a desire not to undergo awake surgery if possible. Functional imaging revealed left-dominant language with the expressive speech centers remote from margins of the FLAIR abnormality.

10.2.2. Surgery

The patient underwent a second craniotomy under general anesthesia for supramarginal resection of the residual tumor with intraoperative motor mapping and

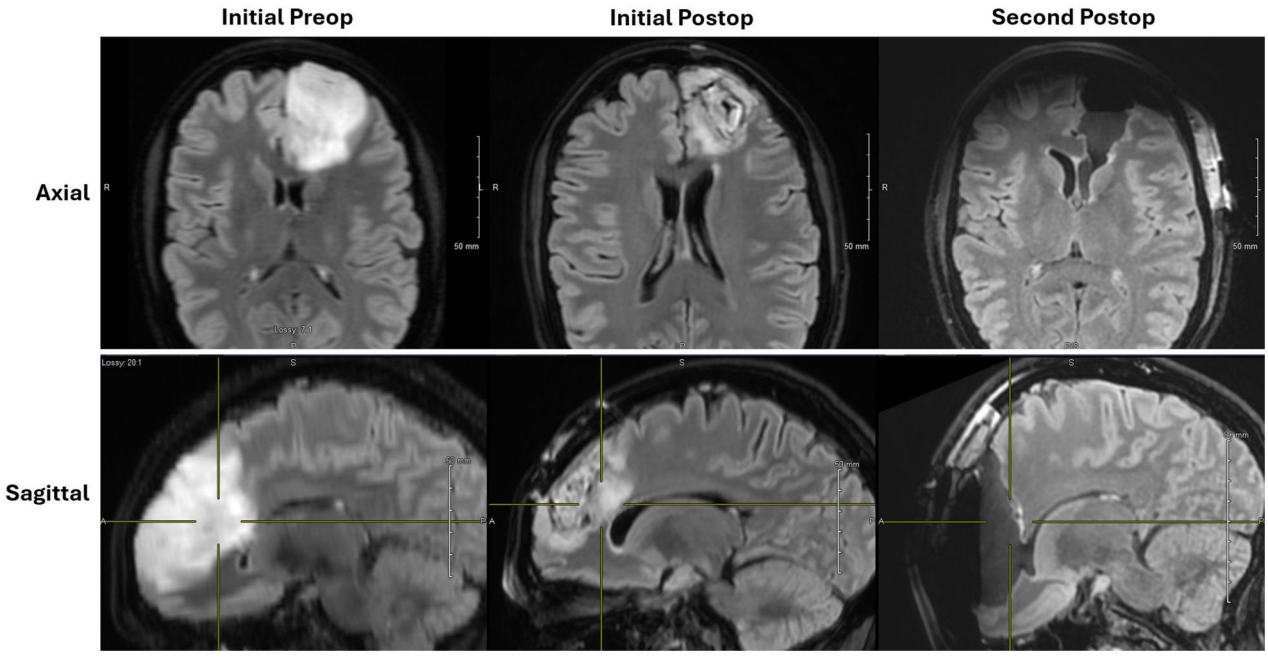

Figure 12. FLAIR MRIs from a 35-year-old right-handed female with a WHO grade 3 oligodendroglioma (IDH-mut, 1p/19q co-deleted) who underwent an initial craniotomy for debulking of the mass at an outside hospital and was subsequently referred for further surgical resection. According to data published by Rossi et al [25], extending her resection from subtotal (initial postop) to supramarginal (second postop) increased her median progression-free survival from 23 to >48 months.

intraoperative MRI. The surgery incorporated the dorsal portion of the frontal pole, amputated the anterior corpus callosum just beyond the lesion, and extended just beyond the visible FLAIR margin in all directions with the closest margin being on the posterolateral edge (toward the anteromedial curve of superior longitudinal fasciculus [speech fibers]) (Figure 12).

10.2.3. Postoperative course

Immediately postoperatively, the patient was grossly neurologically intact with a slightly more blunted affect. At her two-week follow up, she and her mother noted some increased social withdrawal that was concerning to them both. By her 5-month follow up, they both reported that this had fully resolved, and neither noted any residual deficits. Repeat neuropsychological testing at 5-months noted continued mild deficits in executive function with a slight decrease in performance in this domain after the second surgery, with stability in all other domains. The patient was able to go back to work full-time running her own crafting business, and she was able to resume caring for and interacting normally with her family. Consistent with current guidelines for grade 3 oligodendrogliomas, she subsequently underwent radiotherapy followed by PCV for 6 cycles. She is currently 8-months out from her second surgery without evidence of disease progression.

10.2.4. Discussion & decision-making

Data from *Rossi et al.* suggest that progression-free survivals in patients with grade 3 IDH-mut, 1p19q codeleted oligodendrogliomas such as this who undergo subtotal resections is 23 months, gross total resections is 36 months, and supratotal resections is >48 months [25]. Importantly, the radiation oncologist who received the patient after the initial surgery recognized that a maximal safe resection had not yet been achieved and referred the patient for a second surgical opinion. Given the dominant frontal lobe tumor location, the discussion with the patient revolved around expected temporary deficits from more extensive frontal lobe surgery, such as personality changes, abulia, and decrease executive functioning, and whether that merited the expected increase in longevity. To mitigate the possibility of these side effects becoming severe and permanent, the dominant caudate head (associated with abulia), inferior frontal gyri (associated with disinhibition), and lateral superior longitudinal fasciculus projections (associated with speech) were all protected. Notably, in this case, I felt it was surgically important to amputate the corpus callosum beyond the gross tumor margin to help prevent potential spread to the contralateral hemisphere (which would be functionally devastating), as anterior callosotomies are well-known to have minimal additional functional impacts. In a more ideal scenario, the patient would have been referred for specialized

care upfront (i.e., prior to the index operation) to avoid having to undergo two operations.

10.3. Case 3: Initial subtotal resection of a right temporal glioblastoma (IDH-wt, WHO grade 4) with early recurrence

10.3.1. Case presentation

A 60-year-old right-handed male presented with 3-4 months of increased fatigue, nausea, headache, and unintended weight loss. A brain MRI revealed a 4.2 cm ring-enhancing anterolateral right temporal lobe mass with extensive surrounding vasogenic edema most concerning for a high-grade glioma (Figure 13). He underwent a craniotomy for debulking of the mass at an outside hospital where he received a RANO Class 3 A resection [26]. Pathology revealed an IDH-wt, MGMT-unmethylated glioblastoma (WHO grade 4). This was followed by radiation with concurrent TMZ, and he elected not to use TTFields. On his 5-month surveillance MRI, substantial recurrence was noted, so he was referred to our center for consideration of further surgery. His neurological examination was grossly normal other than a partial left superior quadrantanopia. A detailed neuropsychological evaluation revealed a mild deficit in visual learning and memory with otherwise normal cognition. Discussions with the patient revealed a desire to be aggressive and to maximize longevity, and the patient confirmed that a denser left visual field cut would not impair his quality of life or work as a sales consultant.

10.3.2. Surgery

The patient underwent a second craniotomy for extension of the previous resection to include a full right temporal lobectomy (Figure 13). Pathology from the second operation confirmed tumor recurrence.

10.3.3. Postoperative course

Postoperatively, the patient was at his neurological baseline other than a denser left superior quadrantanopia. The patient was discharged from the hospital on postoperative day 1 and resumed work within 1 week of surgery. Due to a long travel burden and no noticeable neuropsychological deficits to the patient or his wife, he declined a five-month postoperative neuropsychological evaluation. He is now 5-months status post his second resection without evidence of a second recurrence despite electing to pursue only alternative treatment methods.

10.3.4. Discussion & decision-making

Data from Karschnia *et al.* suggest that the median overall survival in patients with grade 4 IDH-mut glioblastomas such as this who undergo RANO class 3 (subtotal) resections is 15 months, class 2 (gross or near total) resections is 19 months, and class 1 (supramarginal) resections is 24 months [26]. Fortunately, in the non-dominant temporal lobe, functional deficits are known to be relatively minor and can include visual field deficits and occasional temporarily increased depressive symptoms. Like Case 2, ideally this case should have been referred to a glioma center upfront, as evidence suggests that the delay in obtaining the

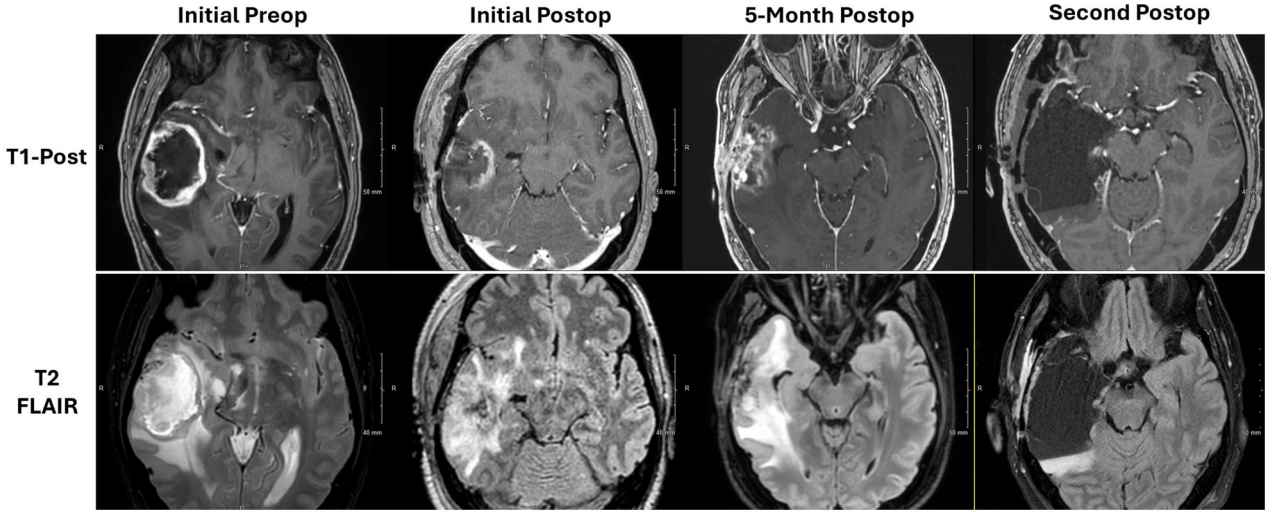

Figure 13. T1-post contrast and FLAIR MRIs from a 60-year-old male with a right temporal glioblastoma (IDH-wt, WHO grade 4) who underwent an initial RANO Class 3 A resection at an outside hospital and experienced early perilesional recurrence, then subsequently underwent a temporal lobectomy. According to data published by *Karschnia et al* [26], extending his resection from a Class 3 (subtotal) to Class 1 (supramarginal) at his index operation would have extended his median overall survival by 9 months (15 to 24 months) when combined with standard radiation and TMZ.

most aggressive, anatomically feasible resection likely affected his subsequent radiation plans and unnecessarily decreased his life expectancy [58].

10.4. Case 4: Newly diagnosed right frontoparietal FLAIR lesion in a 71-year-old

10.4.1. Case presentation

A 71-year-old right-handed female presented with 2 weeks of left hemibody and facial numbness, as well as left face and hand weakness. She was found to have an expansile predominantly FLAIR mass with patchy intrinsic contrast enhancement centered in the frontoparietal white matter and infiltrating the lateral pre- and postcentral gyri. Connectomic imaging revealed primary motor corticospinal/bulbar tracts running through the superior and medial margins of the tumor (Figure 14). Additionally, ventral attention network hubs were straddling the lesion anteriorly and posteriorly, and they were connected via white matter along the medial margin of the lesion. Neurological examination revealed decreased sensation in the left hemibody and face, as well as 4/5 left hand intrinsic muscle strength and a mild left facial droop. Preoperative neuropsychological evaluation revealed moderate deficits in visuospatial reasoning and hand orientation tasks. Preoperative conversations with the patient revealed that she would prefer to avoid any worsening of both temporary and permanent deficits as much as possible, but that she wanted treatment to prolong her life. She was retired and independent in her activities of daily living prior to developing these symptoms, and she hoped to return to independence for as long as possible.

10.4.2. Surgery

At the patient's request, she first underwent a stereotactic biopsy of the mass, which confirmed it to be a high-grade glioma. The patient then underwent an awake craniotomy with motor, sensory, and hemineglect monitoring, as well as intraoperative MRI. The resection was taken until the corticospinal tracts could be stimulated with bipolar stimulation at 2 mA (60 Hz, 1 ms) at the medial and superior resection cavity margins, suggesting immediate proximity [97]. Although the intraoperative MRI demonstrated residual FLAIR signal in these areas, further resection was not pursued (Figure 14).

10.4.3. Postoperative course

Pathology confirmed this to be a diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, MGMT-met, WHO grade 4. Functionally, the patient was stable postoperatively. She was discharged to inpatient rehabilitation for 10 days prior to returning home. She underwent radiation with concurrent TMZ, followed by adjuvant TMZ. Despite multiple medical comorbidities including morbid obesity, she survived for 18-months after her surgery.

10.4.4. Discussion & decision-making

While detailed survival data does not exist for this specific tumor type related to different extents of resection to my knowledge, the same principles of maximal safe resection apply. In this case, because the mass infiltrated the corticospinal tracts, the tumor was not anatomically amenable to a supramarginal, or even a gross total, resection. To minimize the chance of worsening neurological deficits from surgery, which would

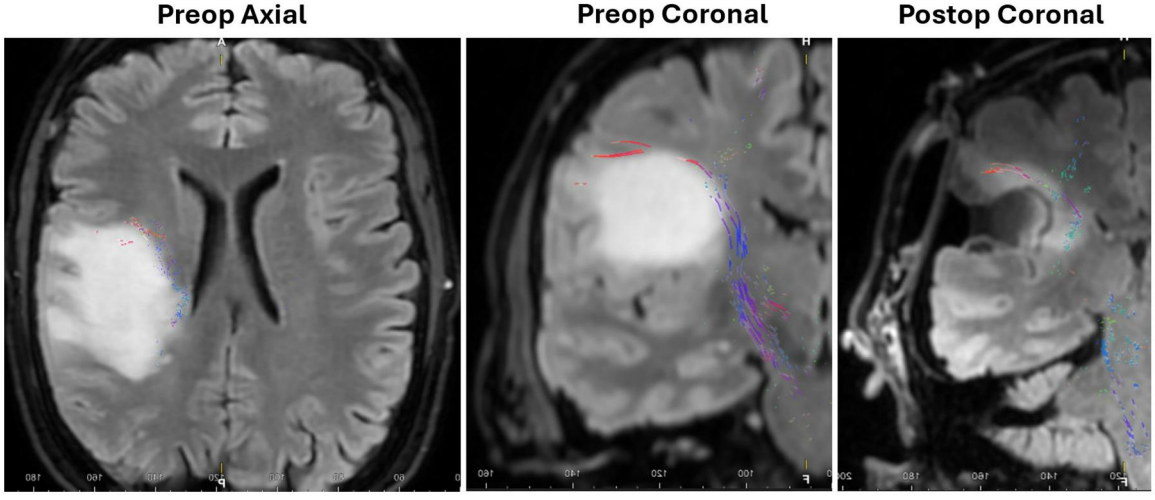

Figure 14. FLAIR MRIs from a 70-year-old female with a right frontoparietal diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, MGMT-met, WHO grade 4, who underwent a maximal safe resection of her lesion. The infiltration of the tumor into the corticospinal tracts (colorful lines) prevented a gross total resection in this case.

both negate any oncological benefits of cytoreduction and diminish her remaining quality of life, the surgery was performed awake to monitor for early signs of deficits known to be associated with the right inferior parietal lobe, such as hemineglect. Fortunately, this was not encountered, and about 80% of the tumor mass was able to be removed before reaching critical margins.

11. Remaining questions and future directions

Despite all we know about outcomes in supramarginal glioma surgery, there are many clinically important questions that remain unanswered. For example: (1) if one margin of the tumor abuts functional tissue, is there any benefit to supramarginal resections of the other margins?, and (2) how large does a supramarginal resection need to extend beyond the lesional borders to obtain maximum benefit, especially in low-grade glioma surgery? Toward answering these questions, several groups are currently examining advanced imaging techniques to predict areas of recurrence and differentiate edema from infiltrative tumor with promising but preliminary results [105–110]. In the functional and cognitive realms, while we know that many patients undergoing aggressive surgeries experience cognitive declines that significantly recover with time, predicting such outcomes on an individual basis is still a challenge. What remains undefined is a precise threshold of injury (i.e., percent of network resected) for which deficits in these domains might be permanent (short of bilateral involvement). The translation of newer insights from network neuroscience into clinical practice is providing hope for more precise surgical planning and preoperative counseling [93]. Along with these insights may also come the development of novel neuromodulation techniques that can (1) preoperatively induce neuroplasticity to remap critical functions away from invasive tumors to improve extent of resection while protecting function, and (2) enhance postoperative functional recovery for those who do not naturally recover on their own [111–113]. My lab is particularly interested in this area, as we are looking into whether long-term neuropsychological deficits may be associated with persistent abnormal functional connectivity of the remaining normal brain.

12. Limitations

The intent of this manuscript is to provide a useful distillation of the vast amount of recent surgical glioma evidence into guidance for treating physicians to use during the critical stage of preoperative surgical planning and patient counseling for patients with newly discovered diffuse gliomas. It is important to recognize that this is a perspective piece written by a single neurosurgeon who has trained and worked at only at academic tertiary care centers within the US, and, therefore, it does not encompass all perspectives. However, this analysis does incorporate data from around the world and a multitude of clinical care settings. These recommendations represent a good-faith assessment of currently available data, all of which can change in any moment with a single discovery. Additionally, this narrative review focuses on surgical factors for newly diagnosed tumors and does not delve deeply into non-surgical treatment modalities, management at the time of tumor recurrence, non-modifiable risk factors of disease, or advanced imaging techniques [114,115].

One of the challenges in making evidence-based recommendations for clinical applications in glioma surgery is that clinical problems present prospectively and individually, whereas most data guiding these decisions are retrospective and population-based. For example, in most of the studies reviewed above, differences in *a priori* surgical approaches are not assessed, as the surgeon(s) set out for a goal of maximal safe resection in each case. Therefore, caution needs to be exercised in extrapolating from their results to different *a priori* approaches (as I do in Figure 10). However, the validity of this extrapolation is supported by several high-quality studies that *did* analyze different *a priori* surgical approaches in similar patient populations across different hospital settings and produced consistent results [3,55]. Additionally, the uniformity of the results across the many large, retrospective case series that span multiple settings, countries, and treatment teams with a notable paucity of contradictory evidence further supports the appropriate extrapolation of these findings.

The lack of prospective studies in glioma surgery is a topic that is widely discussed and is due to many factors that are difficult to overcome, including: (1) heterogeneity of tumor characteristics, presentations, and demographics; (2) relative rarity of gliomas compared to other diseases; (3) difficulty in recruiting patients and treating physicians willing to randomize their surgical approaches; and (4) lack of equipoise in data supporting alternative approaches to upfront maximal safe resections. While an argument might be made that a lack of prospective data means there is not enough evidence to recommend one approach over another, the perspective outlined in this piece reflects the counterargument: that we do not have

prospective data because the data we do have is so strong and consistent with the experiences of high-volume centers that any prospective study randomizing an alternative approach would require an incredibly high bar to ethically justify. However, despite these limitations, there is one such study underway in glioblastomas that is designed to randomly and prospectively evaluate the effect of *a priori* attempts at supratotal versus gross total resections in anatomically feasible cases, which is a laudable undertaking [116].

13. Conclusions

While the mantra of "maximal safe resection" remains the standard surgical refrain in glioma surgery, in practice, this phrase is translated into one of three main conceptual approaches: (1) the most conservative approach of "debulking" the tumor, where the surgeon operates mainly within the grossly abnormal tumor margins to reduce its mass effect and the amount of viable tumor cells (i.e., cytoreduction) while minimizing the potential for injury to normal brain; (2) the very common approach of performing a "lesionectomy," or resecting the tumor to its radiographically and/or grossly abnormal margins, in an attempt to achieve a gross total resection while minimizing injury to potentially functional surrounding brain; and (3) the functional, or "supramarginal," approach, where brain is resected to functional borders irrespective of gross or radiographical tumor boundaries, which can lead to any extent of resection (up to lobectomies) based on functional anatomy. While all three approaches attempt to prioritize long-term functional preservation over aggressive resection, a plethora of recent data now strongly supports the functional approach as superior, moving the field toward a consensus that this should be the first-line approach when feasible. The counterintuitive finding that resecting more brain upfront can result in equivalent-or-better long-term oncological and functional outcomes in many cases underscores the ominous natural history of gliomas, and it suggests that the intent to "do no harm" with more conservate approaches may not always match the outcome. In fact, the most recent data suggests that extent of resection is the most impactful modifiable survival risk-factor in many diffuse glioma cases. As the field moves away from considering simple debulking of diffuse gliomas to be within standard of care, it follows that there are no longer "simple" surgical glioma cases. In this light, current data strongly support upfront referrals to specialized glioma centers for all diffuse gliomas to maximize patient outcomes. Choosing the appropriate surgical approach for any individual case should be informed through the patient-physician interaction and can be individualized for each patient based on their approach to their own healthcare, goals, hopes, and fears. Future directions for the field will be to develop techniques to more reliably predict long-term neuropsychological sequelae for different surgical boundaries on an individual basis, as well as to develop neuromodulation techniques to improve neurological recovery in cognitive and behavioral domains for those who may not recover on their own.

14. Article highlights

- Over the past 5-10 years, evidence has consistently and convincingly bolstered the case that supramarginal resections offer a substantial survival benefit for patients with both higher and lower grade diffuse gliomas, moving the field toward a consensus that supramarginal resections should be the first-line surgical approach when possible
- As the field moves away from considering simple debulking of diffuse gliomas to be within standard of care, it follows that there are no longer "simple" surgical glioma cases, and current data strongly support upfront referrals to specialized glioma centers for all diffuse gliomas prior to their index surgery to maximize patient outcomes
- Extent of resection is now recognized as the most impactful modifiable risk factor for survival (when combined with standard adjuvant treatment) in many diffuse glioma cases
- Choosing the appropriate surgical approach for each case should be informed through the patient-physician interaction. In ideal scenarios, surgeries can be individually tailored by applying relevant functional-anatomical principles to the patient's preferred healthcare approach, goals, hopes, and fears.
- Future directions for the field will be to develop techniques to more reliably predict long-term neuropsychological sequelae for different surgical boundaries on an individual basis, as well as to develop neuromodulation techniques to improve neurological recovery in cognitive and behavioral domains for those who do not recover on their own.

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