The Rise and Fall of "Biopsy and Radiate": A History of Surgical Nihilism in Glioma Treatment

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• Surgery • Glioma • Resection

COMMONLY HELD VIEWS ABOUT GLIOMA TREATMENT

Infiltrating gliomas, defined as World Health Organization grade II through IV astrocytic or oligodendoglial neoplasms, are known to all with even casual exposure to their clinical history as invariably multiply recurrent and eventually fatal, albeit at grade-specific rates, despite lesionectomy, adjuvant radiotherapy, and chemotherapy.[1–3] Despite generations of effort, the outcome for these lesions has improved only marginally, and the cure rate remains dismally low.[3] The future of glioma therapy is in the laboratory, and eventually some molecular-based therapy will be developed that will be the ultimate solution for this terrible disease, because surgery clearly is not.[4] In many cases, aggressive surgery is ill-advised, pointless, and harmful. In these cases, biopsy and radiation alone serves as an acceptable alternative to surgery, despite the dismal prognosis with this approach.

The paragraph above summarizes how many surgeons and oncologists view treatment of gliomas. Many of these views are handed down between clincians, yet given that there are not definitive class 1 studies demonstrating most of these statements, we feel these views are worth a critical reassessment. This article summarizes much of what been taught regarding glioma treatment and, more specifically, glioma surgery. Unquestionably, a great deal of published data support this ideology, not the least of which are from the collective experience of many who have treated patients using this paradigm. The purpose of the article is not to entirely discount these ideas, but rather to critically address the scientific and clinical foundations on which these approaches are based. A review of the scientific studies supporting the commonly held beliefs about gliomas shows that these nihilistic ideas regarding gliomas are based on overgeneralizations of older historical studies that have been applied to the greater concept of what gliomas are, how they behave, and what should be done to treat them.

NIHILISM IN GLIOMA SURGERY

High-grade gliomas, notably glioblastoma, behave extremely aggressively. Regardless of grade, they have a high rate of recurrence and progression to higher grades, such as glioblastoma, and are ultimately fatal in most patients.[5] These tumors notoriously infiltrate normal brain, meaning that surgical resection generally involves removal of functional

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tissue. Hence, these tumors are difficult to remove completely, especially when neoplastic cells spread widely throughout the brain.[6] Given these challenges, many neurosurgeons still (despite evidence to the contrary) choose to avoid this risk by instead biopsying these tumors and then radiating them.

IS NIHILISM JUSTIFIED?

The Hemispherectomy Experience

A common belief is that, regardless of radiographic appearance, gliomas disseminate widely and have often microscopically infiltrated even across to the contralateral hemisphere at initial presentation. Thus, many claim that gliomas are incurable.[4,7] As support, many authors refer back to early studies attempting to cure glioblastoma with hemispherectomy. The recurrence rates despite this approach are cited as the ultimate proof that surgery cannot definitively treat these tumors.

The most prominent report by Dandy[8] in *JAMA* in 1928 described the approach in five patients. Two of these patients died of early postsurgical complications and one was still alive at last follow-up. The remaining two patients died of recurrent tumors 3 months and 3.5 years after surgery, respectively. The patient who died at 3 months was noted to have disease extending into the basal ganglia that was intentionally not resected.[8] The patient who lived 3.5 years was in a coma at presentation and lived well beyond the present mean life expectancy despite no adjuvant therapy, which was not available in 1928.

The only other notable report, which was published in 1949, is of five patients who underwent surgery at the Cleveland Clinic.[9] One of these patients died from early postoperative complications; two died of a recurrent tumor 15 months and 3 years after surgery; one died 4 years after surgery from a traumatic brain injury; and one lived at least 10 years after surgery. After this article was published, reports about hemispherectomy in glioma become fewer, and the latest report identified was in 1975, in which the patient died from a contralateral meningioma.[10]

Given this paucity of evidence, particularly the lack of any current evidence, one cannot say what hemispherectomy would do for patients with glioma, and what it would accomplish if tried today when applied in the context of existing management paradigms. Given that most of these reports are 60 years to 80 years old and predate MRI and CT, many important facts about these patients are unknown, most notably whether these tumors were bilaterally disseminated at diagnosis, making hemispherectomy a suboptimal option. Information regarding radiographic extent of resection is also not available for these patients. 5-Aminolevulinic acid (5-ALA) certainly was not used, because operating microscopes with or without fluorescent filters were not available to visualize it. None of these patients received radiotherapy or chemotherapy. No repeat surgeries were performed for recurrence, because there was no way to detect it until the patient was near death. Many of these patients could have died of the siderosis that occurred frequently with old techniques of hemispherectomy, because no insight into this problem was available at the time, and detailed postmortems looking for this problem were not performed on many of these patients. Furthermore, the histopathologic diagnostic criteria of gliomas have changed several times since these reports. No control cohort is available with any meaningful relevance to contemporary therapy, and therefore perhaps all of these patients experience recurrence, but after many more years.

Thus, one of the key pieces of evidence dismissing glioma surgery as futile is from from decades-old case series of five or fewer patients who were managed using outdated surgical techniques, outdated diagnostic techniques, and outdated adjuvant treatment paradigms. In addition, these patients were diagnosed using outdated criteria, and had inadequate follow-up according to today's standards of evidence in surgical studies. This fact is stunning when considering the large number of patients who are denied full aggressive surgical treatment for gliomas based partly on these outdated studies.

The Tumor Cell Dissemination Story

Grade II through IV astrocytomas and oligodendrogliomas are known as infiltrating gliomas based on their long observed tendency to spread widely throughout the brain far beyond the primary site of disease. This finding was first documented by Bailey and Cushing,[11] 1926, and was most fastidiously documented by Scherer[12] in a report in 1940. In this frequently cited autopsy study of 120 patients with gliomas, Scherer concludes that, except for ependymomas, "infiltrative growth must be regarded as characteristic of the enormous majority of gliomatous tumors." He then concludes that "complete extirpation is not possible." He notes that, even in this study of postmortem gliomas, bilateral involvement with tumor was observable in only 30% of these cases.

Certainly, several autopsy studies subsequent to Scherer have shown that these tumors can spread widely, to the point that this propensity of gliomas to migrate throughout the brain in some cases is

beyond debate.[13–15] The autopsy-based literature has failed, however, in a fallacy of extension. More specifically, many clinicians have concluded that because evidence shows that many gliomas demonstrate widespread microcellular dissemination at the end stage (ie, the subjects in most postmortem studies), this implies that all gliomas are widely disseminated at diagnosis, including lower-grade astrocytomas. Furthermore, it implies that these distant microcellular satellite cells are the source of the tumor that ultimately kills the patient. In this belief system, leaving the tumor behind seems perfectly reasonable, because aggressive treatment would be futile if more tumor is always extending beyond the margins of the resection.

The most prescient argument against this belief system is an observation practitioners are all familiar with, namely that most glioma recurrences, especially with low grades, occur near or within the previous resection cavity.[16,17] Studies have shown that approximately 76% of glioblastoma recurrences occur within 2 cm of the surgical resection margin.[17] This finding argues strongly that the problem with the current surgical paradigm is inadequate control of tumor at the margins, rather than the presence of distant disease, in most patients treated. Thus, the issue for most failures is inherently inadequate margins of resection, not far-flung satellite cells. This theory is further strengthened by studies showing that radiotherapy margins could be successfully reduced from whole-brain fields to fields extending just 2 cm beyond the resection bed,[5] suggesting that infiltration is largely by cells just beyond the edge of MRI-guided tumor resection cavity that cause recurrence. The radiation oncology world figured out many years ago that the problem is usually at the margins and not the whole brain.

To further show that the issue for most of these tumors, at least initially, is local treatment failure, the authors refer to four well-executed, influential, and frequently cited studies from the CT/MRI era showing the existence of infiltrating tumor cells beyond the area of radiographic tumor involvement. Although frequently cited as evidence of the futility of aggressive glioma surgery by those who have not read them closely with a critical eye, these studies in fact show that the problem is probably one of inadequate resection margins in many cases.

Salazar and Rubin, 1976

Salazar and Rubin[14] reported an autopsy study of 42 patients with glioblastoma who died shortly after diagnosis (meaning not altered by treatment), including 35 supratentorial tumors, 6 intratentorial tumors, and 2 spinal tumors. They concluded that 29 of 35 patients had tumor that extended outside the clinically expected boundary of the tumor. Of these 35 tumors, 9 had spread to the contralateral hemisphere, only 4 had spread to infratentorial structures, and 4 had spread from peripheral brain to deep structures not anticipated clinically. Of the 29 peripherally located glioblastomas, 6 crossed to the other hemisphere, 4 invaded the deep structures, and 2 invaded the infratentorial brain. Although they do not publish whether any of these patients were duplicated in these classes, the findings imply that, at worst, 48% of these patients with rapidly fatal glioblastomas had anatomic characteristics that would make aggressive surgical resection undesirable. The findings also fail to account for the fact that the study was performed on patients diagnosed in the 1950s and 1960s, when these tumors were generally caught much closer to end stage than is likely common in contemporary practice. Thus, even in the worst case scenario, many of these tumors are still not as widely disseminated as seems to be suggested in the nihilistic view.

Burger and colleagues, 1983

In perhaps one of the most interesting studies of this group, Burger and colleagues[15] focused on analyses of surgical specimens and autopsies in 20 patients with untreated high-grade gliomas (5 cases), lesions in patients experiencing remission who died of other diseases (3 cases), and recurrent tumors (12 cases), correlating pathologic findings with imaging characteristics.[15] They found that in untreated glioblastoma, although cells were present outside the area of imaging abnormality, no evidence of tumor cells could be found beyond 3 cm outside of tumor center, nor any tumor cells in the contralateral hemisphere. Similarly, lesions in remission did not show any evidence of widespread dissemination. Only at recurrence did the investigators note tumor cells spread far beyond the primary tumor site, but they also noted that the greatest concentration of tumor cells was seen locally. Together with the previous study, this suggests again that widespread dissemination is an end-stage, not primary, trait of glioblastomas in most cases.

Kelly and colleagues, 1987

By far the most influential study on this topic (cited more than 400 times) was that of Kelly and his team[18] at New York University. In this landmark study, they performed serial stereotactic biopsies both inside and outside of the tumor volume, thus obtaining 195 biopsy specimens in 40 patients, including 8 grade IV tumors, 7 grade III tumors, 17 low-grade astrocytomas, and 8 low-grade oligodendrogliomas. By doing so, they

were able to correlate MRI and CT findings with histologic specimens, and this study is widely cited as providing proof that MRI and CT underestimate the true extent of tumor involvement. More importantly, it showed that T2 changes, previously thought to be edema from the tumor, were often also tumor tissue.

This important study is frequently cited, but how many people have critically reviewed the numbers in this study is unclear, because these numbers show that regardless of grade, MRI does not miss many tumor cells. For example, of the 117 biopsies containing infiltrating tumor cells, only 18 (15%) were found in regions with a normal T1 signal. Higher sensitivity was found for T2 images, with 5 of 128 (4%) specimens with infiltrating tumor cells found in regions with a normal T2 signal. Thus, although tumor infiltration outside the area of tumor tissue does occur, critical analysis of this important data set shows that regardless of tumor grade, if the areas of abnormal T2 signal are resected, most of the infiltrating cells are removed in most patients. Furthermore, taking a slight margin is likely removing an even higher number of cells. Thus, in defining this report in a binary fashion, instead of a probabilistic one, many practitioners justified discontinuing glioma surgery.

Pallud and colleagues, 2010

Similar to the study by Kelly and colleagues,[18] Pallud and colleagues[19] reported on 16 patients with low-grade oligodendrogliomas studied with serial stereotactic biopsies performed using a rigorous paradigm. They increased their histologic yield through using mindbomb homolog 1 (MIB-1) labeling to identify mitotic cells that may have been missed by simple histology. The investigators show that although tumor cells are frequently found outside the MRI region, they are seldom found far from it in these low-grade tumors. More specifically, they did not find evidence that MIB-1–positive cells are located outside of a 2-cm perimeter around the tumor at a higher rate than in normal brain. Thus, the investigators concluded that low-grade oligodendrogliomas are locally infiltrative to approximately 2 cm but are probably not widely disseminated at initial diagnosis. This idea of the local 2- to 3-cm margin of tumor infiltration is similar to the observation of Burger and colleagues,[15] who found that these tumors are frequently locally infiltrative at diagnosis.

IS AN AGGRESSIVE SURGICAL PHILOSOPHY WARRANTED?

Based on the earlier discussion, the authors suggest that one can safely conclude that, although many gliomas are widely disseminated at end stage, sparse evidence suggests that they are always widely disseminated far beyond the imaging-defined tumor borders at initial diagnosis. At the very least, one can reasonably hypothesize that some patients present with localized lesions at diagnosis. Beyond just a simple lack of evidence, reason exists to also disbelieve that these gliomas are widely disseminated in initial stages. First, recurrent disease is classically seen as local recurrence at the margins, with multifocal disease and cerebrospinal fluid dissemination much less common. More importantly, cells distant from the primary tumor at diagnosis would lie outside of conventional radiotherapy fields, and thus distant foci would be expected to grow faster than more proximally located cells. The fact that, despite this, most recurrences occur in the margins of the lesionectomy cavity suggests that the wide-flung cells are not what kills patients with glioma, but rather the inadequately treated margins.

Furthermore, associating widespread invasion and dissemination with early-stage tumors is simply incompatible with current understanding of cancer biology, because these tumors usually need to acquire several mutations to gain those abilities, which takes time and possibly exposure to DNA-altering therapies, such as radiation and alkylating chemotherapy.[20] Regardless, with any tumor, one can logically hypothesize that outward radial spread from the primary tumor mass should lead to a decreasing probability of finding a cancer cell with increasing distance from the primary site. In other words, even if the tumor had invasive properties uniformly at initial presentation, it takes time for tumor cells to reach distant sites, and thus the probability of finding a cancer cell infiltrating seemingly normal brain is likely not equal for distant sites and the margins.

In addition, a growing body of evidence shows that aggressive lesionectomy is superior to subtotal lesionectomy and biopsy. Class 1 evidence includes the randomized experience with 5-ALA–guided resections, which showed that gross total resection conferred improved survival compared with less-aggressive lesionectomy.[21] Additionally, the landmark trial by Stupp and colleagues[3] reporting a survival benefit with temozolomide and radiotherapy over radiotherapy alone showed a 6-month survival benefit with surgery over biopsy alone in both arms of the trial, although the study did not aim to address this comparison. Meta-analyses of class 2 and 3 data have suggested that aggressive surgery confers a survival benefit regardless of grade.[2] Similarly, two recent well-executed retrospective volumetric studies have shown a survival benefit for patients with glioblastoma receiving

aggressive complete or near-complete resections compared with less-aggressive resections.[22,23] A large study of low-grade astrocytomas similarly showed a stepwise improvement in 8-year survival for patients with greater than 90% resection compared with those with lesser resections (91% vs 60%).[24] In addition to extending survival, complete removal has been shown to improve seizure control in both retrospective studies and meta-analyses.[25,26] Thus, although not a cure, aggressive lesionectomy improves survival and renders biopsy and radiation alone an archaic strategy for treating most of these patients.

IS THE RISK WORTH IT?

The predominant reason surgeons provide for not aggressively attacking these tumors, and instead promoting the option of biopsy and radiation, is that they wish to avoid hurting the patient with surgery, especially because glioma is thought to be incurable. Although no studies have directly compared the quality of life between the two treatment paradigms, what follows are a list of reasons why aggressive surgery, even in many high-risk brain areas, is worth the risk in most cases.

- Most importantly, patients have the right to be offered the option of living longer (even if only slightly longer) with a deficit versus dying earlier with longer retention of function (of course with the possibility that the tumor will cause a deficit). By not even offering patients the option of aggressive resection, practitioners are making the decision for them.
- Many of the deficits surgeons are afraid to cause will happen eventually if the tumor is allowed to grow. These patients eventually stop coming to the clinic and die at home, reinforcing the idea that conservative treatment helped the patient.
- Many deficits caused by surgery improve or resolve with time and rehabilitation. Deficits caused by tumors generally get worse over time.
- Functional deficits can often be avoided with intraoperative mapping and other functional mapping.
- Often areas that practitioners are sure will cause a deficit if removed do not cause this deficit. The brain has the ability to reorganize its cortical regions over time, and sometimes this is to the patient's advantage.
- No adjuvant therapy is more likely to work on a huge tumor burden than on a small one. Thus, although not a cure, removing more cells likely improves the efficacy of these adjuvant treatments.
- Function is routinely sacrificed without a great deal of debate in several life-threatening conditions to prolong life, making aggressive glioma surgery not without precedent, such as
  - Limb amputation for gangrene, cancer,
  - Liver transplant requiring immunosuppression for liver cancer,
  - Total proctocolectomy with ostomy in patients with familial adenomatous polyposis,
  - Esophagectomy for esophageal cancer,
  - Pneumonectomy for lung cancer,
  - Large disfiguring skin resection for aggressive skin cancers,
  - Conditions such as orbital exenteration and mandibulectomy for aggressive nasopharyngeal and skull base malignancies, and
  - Sacrectomy for chordoma.
- Functional loss is considered an acceptable risk by some in the pursuit of gross total resection for several benign intracranial tumors. These losses include
  - Facial nerve palsy in vestibular schwannoma,[27–43]
  - Cranial neuropathy in skull base meningiomas,[44]
  - Carotid sacrifice and bypass for cavernous sinus meningiomas,[45,46] and
  - Sagittal sinus sacrifice and bypass for parasagittal meningiomas.[45,47]

MARGINS IN GLIOMA SURGERY

The idea of treating the margins in these tumors has been around in radiation oncology for some time, yet has never entered the neurosurgical stream of consciousness. Part of this is nihilism; people simply do not wish to push the resection beyond the imaging boundaries of the tumor for something they view is a pointless effort, especially in light of the widely held belief that even hemispherectomy has failed. Additionally, there is likely inadequate awareness that most of the tumor cells are located within 2- to 3- cm margins of the tumor. Thus, few attempts have been made to see what surgically removing gliomas with a wide margin, followed by adjuvant therapy, could accomplish, especially if that margin takes the surgeon near or into the speech or motor areas. Certainly, some cases exist in which a 3-cm margin is not worth the risk; however, the appropriate boundaries for aggressive surgery have not been studied in any significant detail, because most practitioners think that

tumor cells are present all over the brain in these cases and therefore it does not make a difference.

The authors could identify two studies in which the idea of aggressively removing brain in excess of the MRI-defined lesion barrier was formally addressed. One was the 1984 study by Laws and colleagues,[48] which showed a survival benefit for patients with gliomas treated with a lobectomy over lesionectomy. Unfortunately, this interesting finding was not further fleshed out in an analysis segregating these patients by grade, so whether this is a true finding is unclear. A more recent and more convincing effort was published last year by Yordanova and colleagues,[4] who showed that using intraoperative mapping techniques to push the resection margin up to eloquent brain regions obtained a supramaximal resection with margins. Although the follow-up is modest, they reported that all patients achieved their normal preoperative neurologic function and that none experienced malignant transformation with a median follow-up of approximately 3 years (range, 1–10 years). This finding provides preliminary support for the thesis that, given that most of the infiltrating tumor cells are within 2 to 3 cm of the tumor, aggressive local therapy is the most effective approach to at least significantly reducing the number of cells an adjuvant therapy must kill.

Thus, although whether excising the primary mass with a margin will help is unclear, one can reasonably assume that in many cases it will help, or at least be better than what is currently done, which fails in nearly every case. In this paradigm, the newly diagnosed glioma is viewed as a probability function, wherein the probability of cell infiltration decreases as a function of distance from the visible tumor tissue. Certainly, this approach is consistent with the existing histologic data for many patients.

FUNDAMENTAL PROBLEMS WITH NIHILISM FOR PATIENTS WITH GLIOMA

Regardless of the uniqueness of gliomas, they still are a solid tumor, and the basic tenets of oncology still apply. Most notably, because a neoplasm is a heterogenous collection of different cell populations, an inherent percentage of cells in any given tumor are resistant, or less sensitive, to any adjuvant therapy, including radiotherapy, conventional chemotherapy, and targeted molecular therapy.[49] Despite a heterogeneous population of cells, no cell population in gliomas is resistant to surgical removal. Thus, surgical cytoreduction is the cornerstone of most successful therapies for any cancer; it dramatically reduces the number of cells that need to be destroyed by adjuvant therapy, and thus reduces the chance of encountering a resistant cell population. Few success stories in solid tumor oncology do not begin with gross total resection of the primary lesion as a starting point. Breast, colon, lung, pancreas, stomach, ovary, and nasopharyngeal cancers and melanoma represent a few examples in which the critical role of cytoreductive surgery has been vividly shown.

Why does nihilism hurt us as tumor surgeons and researchers? Why does it hurt patients? Quite simply, it causes otherwise intelligent clinicians to follow a nonsensical treatment paradigm, thinking they are doing the patient a favor by leaving a highly malignant tumor growing in their brain, and to just treat it with a therapy that is known to have only marginal benefit in most cases.[50] It stops oncologists as a group from trying to improve techniques for removing these tumors from difficult areas, such as the thalamus, insula, and caudate,[51] because it makes it alright to quit on these patients as a specialty; “The cure will come from the laboratory.[7]”

Perhaps the cure will come from the laboratory in this lifetime; however, in the meantime, the authors argue that nihilism hurts practitioners’ progress as scientists and surgeons. It has cast a cloud of doubt on every negative glioma therapy study to date, because it has forced many therapies targeting a single pathway, yielding partial benefits in simple animal studies, to take on the millions of cells in visible tumor masses, instead of the much smaller number of cells left behind by an aggressive resection with wide margins (again, the foundation of an oncologic resection). Undoubtedly, many otherwise promising drugs have been relegated to the dustbin of history after being tested on inadequately resected tumors. Secondly, nihilism has collectively allowed suboptimal glioma surgeries. With the view that glioma resection is marginally pointless, practitioners as a group reconcile with mediocrity in glioma surgery. Any tumor specialist knows exactly to what this statement refers. Practitioners have all seen cases in which 20% resection has been performed for a right frontal glioma, or tumors that have been biopsied and radiated at another center that is entirely outside eloquent tissue. Many practitioners operating on gliomas do not use microscopic visualization for these cases, even when working on tumors around delicate structures such as the middle cerebral artery, simply because they do not plan on going near these structures. Glioma surgery for many is macrosurgery, because in their eyes total removal is not a goal. Large residual tumors are common. None of these acts of sloppy thinking or sloppy surgery would be well regarded with surgery for vestibular schwannoma, yet this attitude is

tolerated with glioma surgery, because many think glioma surgery does not make a difference.

CONCLUSION: THE FUTURE OF GLIOMA SURGERY

The common belief is that the cure for gliomas will come from the laboratory. Intuition suggests that these therapies are unlikely to work in a paradigm in which surgeons leave behind large amounts of tumor, hoping that the adjuvant therapy will take care of the remainder. As the neurosurgical community gradually arises out of the nihilistic sleep of the "biopsy and radiate" years and realizes that, barring a miracle cure, the only hope for gliomas therapy lies in treating small residual tumors, it will be increasingly important to approach this new era with an open mind. The authors encourage surgeons to take glioma surgery more seriously than in the past, and believe that the next natural, yet critical, step is to define the boundaries of an acceptable risk/benefit ratio in well-controlled cohorts on whom surgery is performed using modern techniques and who are treated using modern adjuvant paradigms. Surgical techniques for difficult gliomas must be refined in much the same methodical, anatomic way that meningioma surgery and vestibular schwannoma surgery have been. In short, glioma is a devastating disease, and little can be accomplished by giving up on it.

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