# Challenges Associated with Reoperation in Patients with Glioma

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**KEYWORDS**

• Reoperation • Recurrence • Redo surgery • Progression • Glioblastoma • Glioma

**KEY POINTS**

- Indications for reoperation in patients with glioma are numerous.
- Inherent risks at each stage of the surgery should be anticipated.
- For glioma resection, consider the approach for a recurrent operation when planning the incision aat the first surgery.

## BACKGROUND

Glioma is a disease with an increasing variety of treatment modalities and combinations, but surgical resection, when feasible, remains the first intervention, with a well-established evidence base. Repeat tumor resection, or rather reoperation for glioma, was first reported more than 30 years ago[1] but with increased survival and advances in surgical technology it is arguably more common in clinical practice now than at any other time.[2–4] The critical appraisal of reoperation for glioma in the neurosurgical literature is mixed. Although individual surgeons may recall patients with exceptionally good outcomes from reoperation and individual centers may report favorable results, all these accounts are tainted by selection bias in so far as surgeons tend to select younger, better performance status patients with focal disease where further adjuvant oncologic treatments are known to be available.[5,6] These are, more than likely, the patients who would have better survival regardless of intervention. Furthermore, the variation in treatments for recurrent or progressive glioma (including chemotherapy, cavity chemotherapy, brachytherapy, immunotherapy, vascular endothelial growth factor inhibitors, tumor treating fields, laser ablation, repeat external beam radiation, radiosurgery, and various trial agents) is greater than at first surgery because of lack of a standard of care, leading to more heterogeneous populations and less clear statistical comparisons.[7] This article offers a concise overview of the real world indications for reoperation, aids to patient selection offered by the evidence available, and the practical issues facing the surgeon at reoperation relating to surgical technique and technologies.

## INDICATIONS FOR REOPERATION AND SURGICAL GOALS

Of primary import, is to have a clear outline of what the rationale for offering reoperation is, rather than simply determining whether it is surgically feasible.

Cytoreduction remains the principle reason for reoperation and national guidelines, albeit several years old, reflect this in recommending "repeat cytoreductive surgery… in symptomatic patients with locally recurrent or progressive malignant glioma."[8] Attempts to quantify the degree of cytoreduction needed for survival benefit have suggested 80% of the contrast-enhancing mass is the optimum threshold,[9] but a more recent meta-analysis identified radiographic gross total resection is most strongly associated with overall

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survival advantage.[10] Biopsy and/or cytoreduction may be indicated for multiple reasons: inadequate initial surgery, regrowth at the operated site, regrowth at a separate site, or new radiographic change in an old lesion necessitating pathologic confirmation.

Excising residual disease after a first inadequate surgery is justified because increased extent of resection correlates with extended overall survival in the newly diagnosed population[11] including lower grades,[12] and conversely residual disease after first surgery is associated with worse cognitive function and poorer patient-reported outcomes.[13] Larger series in the literature support this idea that reoperation salvages the effect of incomplete first resection, with overall survival and time to progression from the date of first surgery being extended in reoperated cases but not interval time from reoperation to death.[14,15]

There are additional benefits to obtaining more tissue, however, because diagnosis may also be improved or reclassified because of additional tissue acquired during reoperation. In patients where the diagnosis has been established at the first surgery by biopsy, it has been shown that the diagnosis is changed in 38% of cases because of availability of a greater volume of tissue for the neuropathologist to analyze.[16] Limited tissue volume for analysis, such as after biopsy or subtotal resection, leads to a higher chance of a sampling error. It has been shown for glioblastoma, for example, that the diagnosis is two-fold greater for individual surgical specimens greater than 10 mL than those of lower volume.[17] Furthermore, so-called "adaptive brain tumor studies," such as GBM-AGILE[18] in North American and BRAIN-MATRIX[19] in the United Kingdom, are heavily leveraged on tissue and so ongoing changes in tumor biomarkers and genetics obtained at reoperation are likely to be increasingly important if not essential for pivoting the patient into new and different clinical trial arms.

Beyond just upgrading or augmenting the original diagnosis, reoperation may help resolve diagnostic uncertainty in progressive tumor versus radionecrosis or pseudoprogression. Despite studies evaluating the utility of sophisticated imaging techniques, tissue remains the gold standard for diagnosis. This diagnostic uncertainty preoperatively should not prevent intervention in the symptomatic patient, because resection of radionecrosis as a treatment goal in and of itself seems to reduce edema and improves symptoms.[20]

Improving symptoms is a key feature of reoperation in general and caution should be exercised with the asymptomatic patient[21] who has only radiologic progression because the evidence of morbidity from reoperation is not insignificant (18% neurologically worse compared with 8% after first craniotomy).[22] Exceptions may include patients requiring high doses of steroids where reoperation may reduce their steroid dependence[23] or the need for bevacizumab.[6] Finally, seizures are a major symptom contributing to morbidity and reduced quality of life in patients with glioma and reoperation may have a role in reducing seizure frequency in this population.[24]

With regards to patient selection, systemic reviews suggest younger age and better performance status as patient factors predicting a better prognosis[25] but tumor factors, such as location adjacent to eloquent areas and volume, should also be considered.[8] An important tumor factor in the modern World Health Organization classification era is genetic markers and molecular classification. It has been shown that IDH1 mutant malignant astrocytomas may do better with aggressive resection and performing additional surgery after incomplete resection may be beneficial compared with patients with wild-type tumors.[26] Also, older patients with O-6-Methylguanine-DNA Methyltransferase (MGMT)-unmethylated tumors may actually have more to gain by reoperation despite the additional morbidity risk because there are limited second-line chemotherapy options for them.[27,28] Scoring systems have been devised for determining the benefit of reoperation[29] and in one pediatric study blinded external review of imaging helped provide an objective opinion on "resectability" for reoperation without the bias of the original surgeon.[30]

Lastly, from a practical perspective, reoperation allows unparalleled access to the brain-tumor interface and remaining infiltrated brain. Until drug delivery to this brain improves either via improved pharmacology (allowing the drug to reach the tumor cells in adequate concentration), via blood-brain barrier opening,[31] convection-enhanced delivery mechanisms,[32] or future unrealized methods, surgery offers the only possibility to place chemotherapy (as biodegradable polymers or wafers[33]) or brachytherapy[34] agents that treat the infiltrative region around the resection margin.

## PRACTICAL CHALLENGES DURING REOPERATION

Repeat resection is complicated because of several factors, which are discussed in the order they are encountered from skin to tumor cavity.

Regarding the skin incision, there is undoubtedly a modern trend for smaller, straight incisions at first surgery, dividing skin, galea, muscle, and

periosteum in the same cut. This may have immediate benefits for the patient in terms of minimal hair shave, a faster opening, less blood loss, faster closure in as few as two layers, reduced postoperative pain and swelling compared with raising a larger scalp flap, and potentially faster wound healing and suture removal. Although these gains are palpable for diseases where a single surgery over the life of the patient is expected (eg, small vertex meningioma), these benefits may be less beneficial for patients with glioma who may need repeat surgeries and for recurrent disease, which may be under, nearby, or at a considerable distance from the first craniotomy. In addition, radiation therapy is invariably required after tumor resection, and as illustrated in **Fig. 1**, may directly traverse the scar when the incision is fashioned directly over the tumor. Furthermore, nearly all patients with glioma are treated with dexamethasone, which is known to increase the incidence of wound breakdown and infection frequently resulting in reoperation.[35] Scars invariably contract and once radiation therapy and steroids have been administered, tissue tension is likely to be significantly increased by the time of reoperation. When positioning for reoperation, an assistant can be asked to advance the scalp on either side of the scar toward the incision before pinning to ensure there is not further tension placed during clamp application. Some creativity with the scar, such as curving or bending previous incisions and/or undermining the galea from the pericranium, also helps to relieve direct tension on the wound and aid healing. In extremis, plastic surgery colleagues should be consulted for assistance with wound closure. Several studies suggest it may be possible to predict where glioblastoma recurrence will occur[36] from the preoperative scans even before the first surgery. This information should be strongly considered when planning the first incision, taking into account how it can accommodate surgery for a future recurrence in the predicted location. Consideration of how recurrent tumor may be approached at a future surgery and planning of the incision and opening for reoperation at first surgery is the recommended practice. Scalp closure is typically performed using suture. If the galea is incompetent, one can consider using nylon suture using full-thickness, interrupted, vertical mattress technique. Lastly, sutures should be removed cautiously, and wounds reviewed early, especially if any patient-reported concerns.

Moving deeper, it is advisable to try and separate and retain periosteum as a vascularized flap to "underlie" the skin and galeal closure. When placing bioplates and burrhole covers in particular, consideration should be given to where

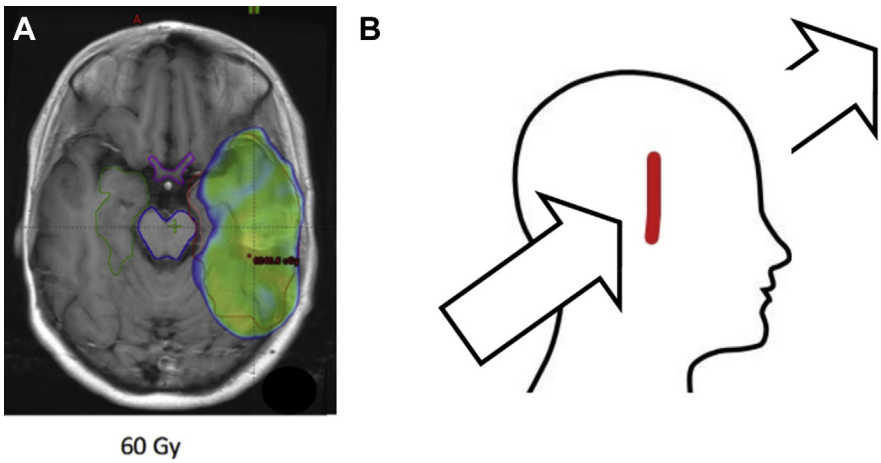


**Fig. 1.** A "simple" temporal high-grade glioma that lies superficially may be amenable to a small, straight preauricular incision (*B*) that is quick to open and close, heals nicely, and is covered by hair. Consider, however, the typical radiation field (*A*) that is needed to treat such a tumor and how this interacts with the incision. At a potential reoperation this small, straight incision is wholly inadequate and may need to be curved forward or backward to obtain enough exposure to access recurrent/progressive tumor and any adjacent cortical areas that may need to be mapped. In regards to the skin, the irradiated scar is devascularized, contracted orthogonal to the cut, thinned because of steroids, and exacerbated further by bioplates or burrhole covers directly underlying the incision. It is better to take the time to raise a larger flap initially that serves for future operations and keeps the scalp and bone over the tumor well covered and vascularized. (*Adapted from* Gzell C, Back M, Wheeler H, et al. Radiotherapy in glioblastoma: the past, the present and the future. Clin Oncol (R Coll Radiol). 2017;29(1):18; with permission.)

these will lie in relation to the skin incision. Without periosteum or muscle (eg, temporalis) atop a plate, the risk of hardware exposure and biofilm adherence to it by bacteria is more likely in the event of a superficial wound breakdown (Fig. 2). It is advised that these prostheses be placed away from the suture line under the scalp or at least covered with vascularized periosteum (Fig. 3). At reoperation, one can always relocate the plates away from the incision line, discarding the existing covers or plates. One might consider removing the fibrous plug in a prior burrhole because it represents an avascular nidus for future infection.

The bony opening should be considered at the first surgery with the temptation to perform a limited craniotomy to access the tumor balanced against the thought of where recurrence might occur and what further exposure might be needed in future. Frequently, the flap is anticipated to be adherent to the dura. One should tailor the craniotomy flap as need for the recurrence, to be the same, outside and encompassing the prior flap, or even inside a previous larger flap to help minimize interaction with scar at the prior defect between flap and surrounding skull or to give better exposure with which to dissect and preserve dura rather than injuring during flap elevation. One should be prepared and anticipate that the dura may be missing or dehisced creating a potential interaction between the pia and inner craniotomy surface.

Beneath the bone the dura is often adherent and scarred because of radiation, peritumoral inflammation, tumor growth, scar from prior surgery, and necrosis. It is advisable to circumferentially free the cortex from the underlying dura around the dural opening and classic sharp dissection with attention to microsurgical technique should be applied especially when the pia and cortical vessels are adherent. Preserving the pia is of critical importance to preserving the integrity and function of the underlying brain. Adherence of the pia to the dura at the margins, in addition to scar adhering veins to the dura, may prevent passing subdural electrodes for monitoring. During closure, a lip of free dura needs to be dissected to accept suture. If the dura seems inadequate for coverage of the defect then duroplasty may be considered; because cerebrospinal fluid leak is problematic for these patients (and a particular problem with intracavity chemotherapy[37]),

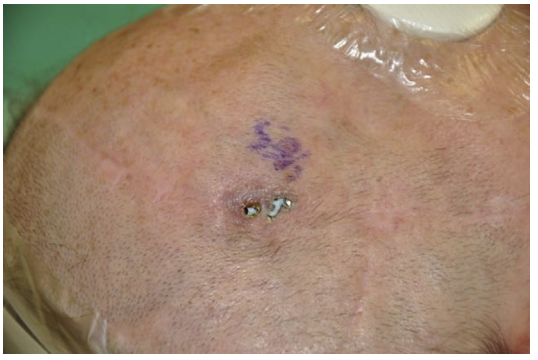

**Fig. 2.** The result of operation, adjuvant chemoradiotherapy, reoperation, and wound failure in a patient with glioblastoma. Multiple incisions, hardware (eg, bioplates and burrhole covers directly under the incision), the scalp in the direct line of radiation beam, and prolonged steroid therapy may lead to wound failure with exposure of hardware and ultimately delays in therapy and reduced quality of life. Careful planning of the incision at the first surgery may prevent wound-related issues, but judicious closure, reduced skin tension, thoughtful siting of plates, and plastic surgery involvement should be used.

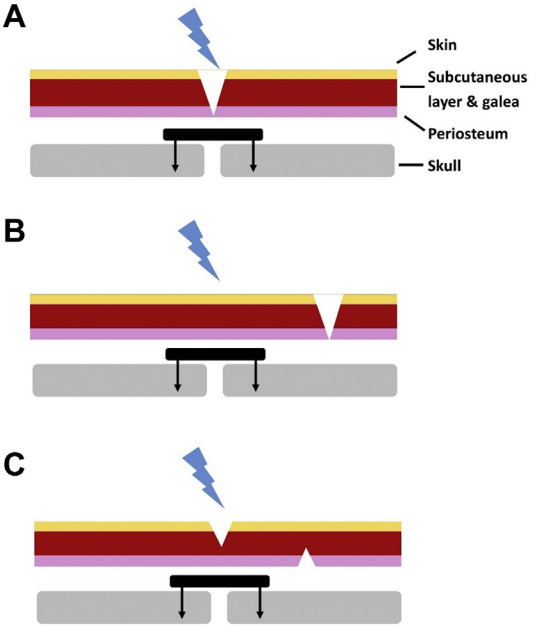


**Fig. 3.** Consideration of placement of the incision, plates, and craniotomy should prevent the situation in *A* where the radiotherapy beam directly crosses the scar and the burrhole cover or dog boneplate is beneath the incision. Ideally the scar should be offset from the line of radiation therapy as in *B* with the burrhole cover or plate protected by full thickness scalp. As a compromise, the situation in *C* is preferable to *A*. The scar overlies the edge of the craniotomy but an underlay of periosteum provides some coverage and reduces the possibility of hardware exposure should the superficial wound fail.

watertight closure and reinforcement with an onlay graft and synthetic "glue" as needed may be used.

Many of the conventional tools for identifying tumor boundaries preoperatively and intraoperatively[38] are rendered less useful at reoperation. With respect to neuronavigation, the T2 and FLAIR signal are altered following irradiation and the volume of FLAIR hyperintensity, for example, no longer seems to be prognostic[39] making it more challenging to plan the limits of resection preoperatively. Fluid or cyst cavities are often drained early but conversely this may lead to brain shift inaccuracy with image guidance. Functional MRI activation areas have also been shown to alter with radiotherapy[40] and plasticity may have led to reorganization of cortical functions. Therefore, previously noneloquent areas should not be assumed to be safe for resection. Intraoperative ultrasound is a tremendously useful tool in intrinsic brain tumor resection but in a systematic review, performance has been shown to be worsened during reoperation.[41] Borders are less well defined and the radiation-induced hyperintensity seen on FLAIR and T2 MRI sequences blurs the acoustic interface, typically well-defined during a first surgery. 5-Aminolevulinic acid (5-ALA) is an increasingly available adjunct in glioma surgery in North America and has been proposed to be standard of care for reoperation.[42] This is despite reports from Europe, which suggest caution when trying to use fluorescence to discriminate tumor from treatment change.[43] As with primary surgeries, use of 5-ALA must be accompanied by thoughtful preoperative planning and judicious intraoperative monitoring to prevent increased resection at the expense of function. Overall, more careful preoperative planning for the intracranial phase of the surgery is needed for reoperation with a clear plan for the intended margin, perhaps giving greater credibility to more immutable landmarks, such as sulci, ventricles, or dural boundaries and en bloc or circumferential resection rather than internal debulking.

## SUMMARY

Reoperation carries many potential benefits in terms of cytoreduction, diagnostic yield, symptom relief, reduction of steroids, increased effectiveness of adjuvant therapies, delivery of adjuvant therapies, and ultimately survival. One should select patients logically and with a clear surgical goal, taking account of the previous operations, diagnosis (including prior pathology, grade, and genetics), age, tumor location and volume, performance status, and adjuvant options. Once the decision to reoperate has been made, functional and advanced imaging should be updated as necessary with a clear plan for surgery created with regards planned extent of resection and approach. Careful attention to detail in the operating room includes wound preparation; extending or reopening the incision to allow the necessary bony exposure; and maneuvers to reduce tension, such as advancing the scalp during pinning. Insight and humility are required if wounds look likely to fail because of atrophic scalp necessitating assistant from a plastic surgeon. Careful intraoperative progress should address adhesions of dura to cortex and fluid in the previous cavity. Surgical neuronavigation, ultrasound, and 5-ALA may all be used but with the knowledge that the utility of all these modalities are altered by previous surgery, chemotherapy, and radiotherapy. Closure must be meticulous and the dura watertight. Careful consideration of these principles results in fewer complications and improved patient outcome.

## CLINICS CARE POINTS

- Consider the indications for reoperation: cytoreduction because of inadequate first surgery or tumor regrowth, obtain further diagnostic tissue to confirm diagnosis, for trials or to guide adjuvant therapy, symptom control (including seizures), steroid reduction, possible radionecrosis with diagnostic uncertainty, place chemotherapy or radiotherapy delivering implant in cavity.
- Consider patient factors: age, performance status, symptoms, ability to tolerate future therapy.
- Consider the tumor factors: location, volume, isocitrate dehydrogenase (IDH), and MGMT status.
- Wound issues: plot target with image guidance and consider incision location and scalp integrity.
- Be prepared for pia adherence to the dura using sharp dissection to preserve pia. Be wary of ultrasound and MRI as sole guide to distinguishing tumor from invaded brain. Consider adjuncts, such as 5-ALA.
- Ensure watertight dural closure, use fresh bioplates, attempt underlay skin with vascularized periosteum, wean steroids as soon as possible, and review wound early especially if any patient-reported concerns.

## DISCLOSURE

The authors have nothing to disclose.

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