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Point/counterpoint: The role of re-resection in recurrent glioblastoma

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Background

For patients with glioblastoma, microsurgical resection followed by concomitant radiochemotherapy and maintenance TMZ chemotherapy represents the standard of care.[1,2] Numerous contemporary studies showed a substantial association between postoperative tumor volume and overall survival,[3,4] and recent studies even suggested that supramaximal resection beyond the contrast-enhancing borders may translate into an additional survival benefit.[5] This evidence ushered us into the era where neurosurgeons aim to complete maximal safe resections whenever possible.[6] Despite surgical efforts and intensive multimodal therapies, these tumors inevitably progress after a median of 8–9 months and recurrent glioblastoma is characterized by a poor prognosis.[7] Therapeutic management at the time of recurrence is ill-defined as no therapeutic approach has convincingly shown an effect for prolonging post-recurrence survival in a controlled, randomized trial.

The utility of surgical re-resection remains debated, with some studies failing to demonstrate favorable effects of surgical re-resection at tumor progression,[8,9] while others have associated re-resection with improved outcomes.[7,10–12] Comparison between different studies or post-hoc analyses from prospective cohorts are substantially hampered given that historical protocols did not adequately control for extent of re-resection,[13] but rather dichotomized patients according to whether individuals underwent re-resection. Also, the evaluation for an oncological role of re-resection in historical protocols is further complicated by the introduction of the WHO 2021, which necessitates molecular testing in the diagnosis of glioblastoma[14]; thereby eliminating the previously included entity of "IDH-mutant glioblastomas." Randomized controlled trials on re-resection appear difficult to conduct, as physicians and patients are both hesitant to exclude potentially resectable tumors from re-resection. As such, the ReSurge trial (NCT02394626) is the only currently active trial for such a patient population: 120 patients with first recurrence of a glioblastoma and in which complete re-resection of the contrast enhancement is judged feasible are randomized to undergo re-resection or non-surgical treatment per physician's preference, with the primary endpoint being overall survival from the date of inclusion. Results are eagerly awaited since recruitment has been ongoing since 2015. Until those data are available, evidence for the use of re-resection in glioblastoma patients rests largely upon retrospective cohorts. Here, we delineate the arguments for and against re-resection (**Table 1**) and contextualize the pertinent clinical literature into the framework for managing patients with recurrent glioblastoma.

Point: The Case in Favor of Re-resection

The goal of surgical resection for recurrent glioblastoma is typically to remove as much of the contrast-enhancing tumor as judged feasible, and several retrospective studies have suggested that re-resection may represent a powerful therapeutic modality in appropriately selected patients.[7] Median post-progression survival times of 9–12 months have been reported,[7,15] and different studies on patients with IDH-wildtype glioblastoma meeting the diagnostic criteria of the WHO 2021 classification reported an association between the use of re-resection and more favorable outcome.[7,10]

In this context, one needs to acknowledge selection bias as only patients with more circumscribed disease, good performance status, and tumors located in areas with a low risk for serious neurological deficits are most often considered candidates for surgery; however, two distinct studies have a provided evidence for a link between the extent of surgery and disease response. First, Suchorska and colleagues conducted a post-hoc analysis of the DIRECTOR trial.[11] This randomized multi-center trial compared two different regimens of dose-intensified temozolomide for first glioblastoma recurrence following combined radiochemotherapy

Table 1. Clinical Factors for Consideration in Favor of and Against Re-resection for Recurrent Glioblastoma.Arguments for and against re-resection for patients with first recurrence of a glioblastoma and individual patient factors to consider.

In favor of re-resection	Against re-resection
decision-making when considering re-resection	
focal recurrence	disseminated recurrence
lesion in less-functional brain areas	deep-seated or eloquent lesions
good clinical functioning	poor clinical functioning
overall arguments on re-resection	
potential oncological benefits from cytoreduction	risk of neurological deficit
reduction in mass effect	potentially delayed initiation of adjuvant treatment
decreased cerebral edema	potential wound healing complications
re-characterization of molecular tumor profile	hospitalization necessary

per EORTC-26981/22981.[16] As the study failed to meet its primary endpoint defined as superiority of one regimen over the other, this allowed the pooling of the two treatment arms to assess the effects of re-resection among this otherwise homogenously treated cohort of 93 patients. Here, patients in whom complete re-resection of the contrast-enhancing tumor was achieved had a prolonged post-recurrence survival of 12.9 months (95%-CI: 11.5–18.2 months) (and better quality of life) compared to 6.5 months (95%-CI: 3.6–9.9 months) among patients with incomplete re-resection and 9.8 months (95%-CI: 6.6–15.1 months) among patients who did not undergo re-resection. Notably, there were no outcome differences between the latter two groups; suggesting that only complete re-resection of the contrast-enhancing tumor translates into a survival benefit. While the DIRECTOR trial used a glioblastoma definition from the pre-molecular era of the WHO 2007 classification (thereby potentially also including IDH-mutant tumors),[17] the key findings of the post-hoc analysis were recently corroborated by the RANO *resect* group on a clinically well-annotated cohort retrospective cohort of 681 patients with first recurrence of an IDH-wildtype glioblastoma.[7,18] A decrease in the hazard risk for death was observed with each cm^3 less residual contrast-enhancing tumor, and 1 cm^3 contrast-enhancement on postoperative MRI was the cut-off which needed to be achieved in order for patients who underwent re-resection to identify with better post-recurrence survival compared to patients handled without surgery. Importantly, the findings from the DIRECTOR trial as well as from the RANO *resect* group on a prognostic value of higher extents of re-resection held true on multivariable analyses controlling for potential clinical or demographic findings (including MGMT promotor methylation status).

With such encouraging contemporary studies on the prognostic value of re-resection, how can we make sense of older studies which failed to demonstrate an association between re-resection and surgery?[8,9,12] Readily available surgical adjuncts including intraoperative 5-ALA fluorescence to identify tumor remnants,[19] intraoperative MRI to anatomically guide resection,[20] Raman spectroscopy to tailor the re-resection according to tumor cell density within the infiltration zone,[21] neurophysiological monitoring to respect critical structures,[22] and amino acid PET to display the metabolically active tumor[23] have dramatically improved the perception of which tumor is considered "resectable" and minimized the risk for inadvertent tumor remnants (**Figure 1A–C**). This is exemplified by the study of the RANO *resect* group in which 217 of 307 patients (70.7%), who underwent re-resection had less than 1 cm^3 residual contrast-enhancing tumor. With a median volume of about 3 cm^3 and complete re-resection rates of about 50% in older studies on cohorts operated between 2001 and 2011 (ie, prior to the widespread application of the above mentioned surgical adjuncts),[10,24] it is tempting to speculate that maximal re-resection can now be more frequently achieved in patients considered to be surgical candidates while the findings from older studies on re-resection were shifted toward negative results due to a higher numbers of incomplete resections.

In addition to establishing an effect of more extensive re-resection with longer survival, re-resection per se and the combination with systemic therapies or reirradiation has been described as safe in several studies. The rate of new post-operative deficits of any grade is estimated to be in the range of 20%,[7,25] which appears comparable to the up to 25% radionecrosis rate following reirradiation.[26] Moreover, up to 30% of hematological toxicities are expected following CCNU (which is considered the preferred chemotherapeutic treatment of choice as control arm in randomized clinical trials such as GBM Agile)[16]; however, those tend to be transient while deficits from local therapies are usually permanent in nature. Also a combined multimodal approach utilizing re-resection followed by reirradiation with or without CCNU is perceived as safe, and the ongoing European-union funded LEGATO project (EORTC NCT05904119) therefore allows re-resection prior to randomization to show superiority of combining a second course of radiation with CCNU over CCNU alone.[27]

Besides cytoreduction and a reduction in mass effect, the benefits of surgery also include tissue acquisition to allow the differentiation between viable recurrent tumor and treatment related changes. This comes with profound clinical implications, as patients in which exclusively radionecrosis is found might be spared from adjuvant second-line therapies which might be used by

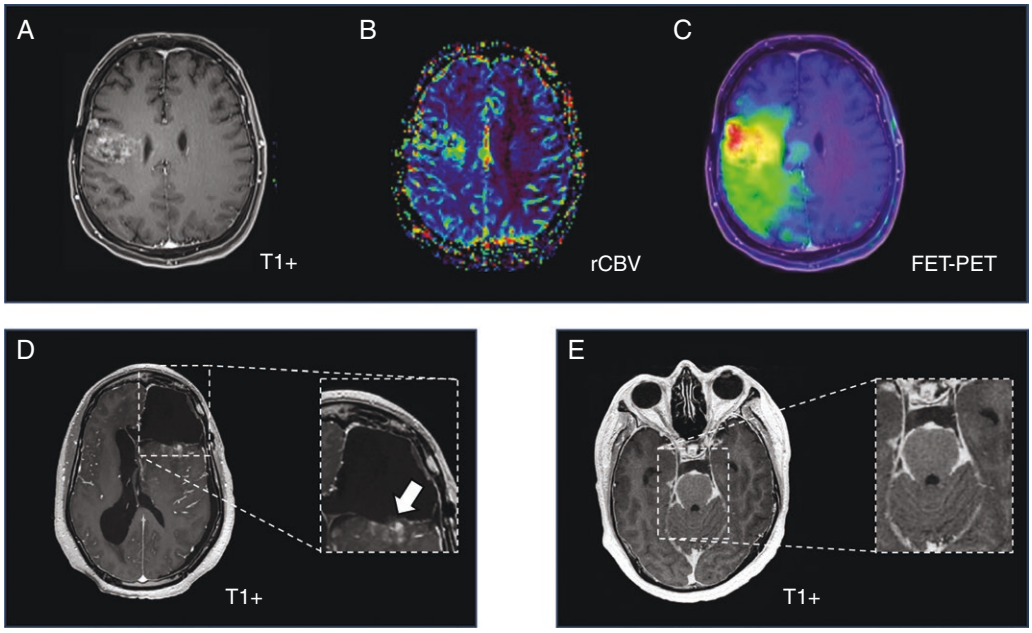

Figure 1. Imaging performed in patients with glioblastoma and suspected tumor progression. A–C: area of progressive ill-defined enhancement at the posterior aspect of the right frontal lobe (A; T1+) associated with elevated relative cerebral blood volume (B; rCBV) and prominent FET uptake (C; FET-PET), supporting true tumor progression. D: focal area of contrast enhancement bordering the resection cavity in a less functional brain area (arrow; T1+), supporting decision-making for re-resection. E: diffuse leptomeningeal enhancement (T1+) around the brain stem, supporting decision-making against re-resection.

centers to consolidate the surgical success. As patients in whom no highly proliferative tumor was found to have a better post-recurrence survival,[28] the neuropathological findings after re-resection therefore allow for prognostication and patient guidance. In turn, the detection of potential molecular targets may inform targeted therapies: this is illustrated by the open-label, single-arm ROAR trial (NCT02034110), which has demonstrated meaningful response rates of up to 30% of recurrent high-grade glioma patients with $BRAF^{V600E}$-mutant tumors following treatment with dabrafenib plus trametinib.[29] Further molecular targets, including *FGFR*-alterations, *NTRK*-fusions or high tumor mutational burden, which may emerge upon recurrence, are currently being investigated.[30] Similarly, window-of-opportunity/phase 0-trials necessitate sampling following the neoadjuvant administration of experimental drugs, which eventually allows for pharmacodynamic as well as pharmacokinetic analyses; and thus inform whether the patient should continue the therapeutic agent in case of sufficient intra-tumoral penetrance and target modulation.[31] Besides the implications for the individual patient, a breakthrough in the treatment of glioblastoma will only be possible once the longitudinal (epi-)genomic tumor and the critical factors for tumor progression can be understood in more detail. Repetitive tissue sampling is assigned a crucial role in enhancing our understanding of resistance mechanisms and vulnerabilities in glioblastoma therapy;[31] and re-resection may thus contribute to new translational findings.

Counterpoint: The Case Against Re-resection

Autopsy specimens from patients who succumbed to glioblastoma demonstrate diffuse brainstem infiltration at the time of death, highlighting the challenge that any local treatment approach faces when trying to halt disease progression beyond the first-line therapy.[32] In the absence of mature data from a controlled randomized trial, any findings on an association between re-resection and outcome could theoretically be explained by inherent selection bias and a variable duration between completion of adjuvant first-line therapy and recurrence. However, an alternative hypothesis is that lower extent of re-resection represents a surrogate marker for glioblastoma recurrences with close proximity to critical brain regions and an inherently worse prognosis. In line with this assumption, re-resection might only be considered rather early in the disease course prior to extensive tumor growth into eloquent structures which naturally selects for patients who experience longer post-recurrence survival. As such, patients with a slower growing disease are more likely to be suitable for a greater number of re-resections; which is one limitation of retrospective studies postulating an association between the number of re-resections and outcome.[33] It should be noted that the publications from Suchorska and colleagues as well as from the RANO *resect* group found a marginal difference of about one month in time to first progression

between patients with or without re-resection.[7,11] A recent Cochrane study on therapies for progressive glioblastoma did not find a single study on re-resection which was deemed suitable for a network meta-analyses, highlighting the rather low level of evidence associated with studying re-resection in this patient population.[34]

Even when a survival benefit from cytoreduction by re-resection might exist, it is unclear whether this is true for the majority of patients or only for a selected subgroup of individuals: it has been estimated that only one in four patients facing first progression might be considered as candidates for re-resection.[35] Extrapolating that complete re-resection of the enhancing tumor component might be possible in 50–70% of surgical candidates, only a small number of patients may eventually derive a meaningful clinical benefit from re-resection. The findings from the ongoing ReSurge trial will therefore need to be discussed with caution, as generalizability to a larger patient cohort might potentially be hampered considering that a final sample size 120 patients has been postulated but recruitment is ongoing since 2015 in more than 25 centers. Also, there is so far no evidence that re-identification of molecular targets in recurrent glioblastoma or the introduction of "molecular" tumor boards has translated into a widespread improvement of survival[36]; with $BRAF^{V600E}$-targeting drugs being the only exception which may indeed prolong survival.[29] However, only about 1–2% of glioblastomas exhibit a $BRAF^{V600E}$-mutation and that mutation is typically conserved across progression, which offers the chance to test the tissue from the first resection at initial diagnosis and confirm at recurrence using liquid biopsy.[37,38]

While re-resection has been shown to be safe in high volume centers, even with the low rate of new postoperative neurological deficits following re-resection, the median postoperative KPS for these patients is lower than after resection in the upfront setting.[25] One reason outcomes following re-resection for recurrent glioblastoma have yielded such heterogeneous results among different reports is the surgical "goal" is less well established and hence varies substantially between studies. Accurately delineating the planned re-resection volume is also more challenging. In contrast to the setting of a newly diagnosed tumour, areas of enhancement can often be treatment related changes and it is not always possible to reliably distinguish between active tumor and post-treatment effects (including pseudo-progression and radiation necrosis). While demonstration of predominantly post-treatment effects at re-resection is a good prognostic feature, as noted above, one could argue that it would be preferable to avoid re-resection in such patients, as it conveys a risk of additional deficits without a decrease in tumor burden. Imaging advances (eg, MR perfusion, spectroscopy, and amino acid PET) may help determine the extent or localization of viable enhancing tumor and therefore the surgical target.[39] These techniques are also helpful for characterizing the non-enhancing tumor component, though there is no consensus regarding what extent of re-resection beyond contrast enhancing tumor should be targeted in patients with recurrence glioblastoma.[40,41] While a prognostic benefit of extending to the non-enhancing tumor component has been shown for initial resection,[5] this has not yet been demonstrated for re-resection.[7] Additionally, the significance of the extent of non-enhancing tumor in the setting of recurrence and how it might affect suitability for re-resection are currently not clear and warrant further investigation.

Given that the current reports are rife with the inherent limitations of retrospective analyses, the lack of data on neurocognition and patient-reported outcomes represents another limitation in the evidence on re-resection. Extrapolating from the newly diagnosed setting, any neurological deficit at the time of recurrence is likely to result in a worsened overall survival and a poorer quality of life for patients.[42,43] While smaller institutional studies and the post-hoc analyses from the DIRECTOR trial suggest that quality of life might be retained following re-resection,[11,44] the effects of surgery on these parameters are insufficiently characterized. Considering glioblastoma progression constitutes the advanced stage of a disease which cannot be cured by current means, the number of months with a high quality of life matters tremendously for patients. Here, the burdens of surgery extend beyond the mere measurements of neurological function: multiple outpatient visits, the risk for infections which delays the initiation of further adjuvant therapies, and the associated costs for hospitalization may also affect the patient's well-being. The ongoing ReSurge trial includes secondary endpoints on health-related quality of life and total numbers of days spent at home (or at care facilities) will provide insights on these outcome parameters. As of now, there are also alternative treatment approaches that may provide local control and are generally associated with shorter hospital stays than open re-resection: smaller case series suggest laser ablation may be non-inferior to surgical re-resection for accessible recurrences,[45] while other groups have explored stereotactic radiosurgery for recurrent glioblastoma and suggested similar outcomes when compared to other salvage therapy strategies.[46] With no prospective head-to-head study between local treatment modalities on the horizon, a critical discussion of all available therapeutic options considering the patterns of recurrence, the center's expertise, and the patient's preference is critical.

Outlook

When contextualizing the role of re-resection in the treatment of patients with recurrent glioblastoma, it is to be acknowledged that neither the Society for Neuro-Oncology (SNO) nor the European Association of Neuro-Oncology (EANO) recognized superiority of a single second-line treatment regimen over another.[1,2] Until well-designed clinical trials provide strong evidence for any treatment strategy for recurrent glioblastoma, re-resection remains a viable option for patients considered eligible for surgery. In addition to improvements in progression-free and overall survival, future trials should explore the impact of re-resection on patients' quality of life, particularly in comparison to alternative approaches, such as re-irradiation, chemotherapy, or best supportive care. For individuals considered eligible for re-resection, the ReSurge trial is expected to provide high-quality evidence on whether surgery represents a viable option in prolonging post-recurrence survival. In addition to clinical trials, the creation of comprehensive, prospective registries that follow all patients with newly diagnosed glioblastoma is critically

important to address the selection bias that exists in retrospective studies of patients undergoing re-resection, and to explore which anatomic (eg, location), tumor (eg, size), and patient (ie, performance status) factors that may independently influence outcome. Selection of candidates for surgery should rest upon the tumor localization, presumed postoperative tumor volume, and clinical functioning of the patient, and proper patient selection might be interpreted as key for surgical success (**Figure 1D, E**).[7] In this context, it is important to note that functional mapping of the surgical boundaries might be more accurate in delineating functional areas than the mere anatomical tumor localization, and re-organization may occur over the disease course. Neurosurgeons and neuro-oncologists should also be open to embedding re-resection into study protocols of more innovatively designed, early-staged window-of-opportunity/phase 0-trials.[31] Such studies allow for pharmacodynamic/pharmacokinetic insights for preoperatively administered drugs, and surgery serves as a cornerstone to investigate drug delivery, vaccine development, and biomarker discovery[47,48]; expanding the potential therapeutic benefit beyond traditional cytoreduction. Moreover, re-resection provides tissue sampled according to a pre-defined and standardized tissue acquisition protocol. By using that tissue, more research into biomarkers of response could help identify patients from whom re-resection may be more efficacious based on their initial tumor profile. Notably, biomarkers to inform surgeons about the potential benefits of re-resection will need to be available in almost real-time to be pragmatic at time of surgery.[21]Collectively, the possible benefits of surgery reach beyond cytoreduction, and re-resection remains an integral part of therapeutic approaches for selected patients with low risk for the introduction of new deficits and well-accessible lesions. While re-resection cannot offer cure to affected patients, it should be recognized as a potential second-line therapeutic approach in properly selected patients. Inclusion of patients into a clinical trial seems most appropriate whenever feasible and enrollment might be considered "standard-of-care" at first recurrence of a glioblastoma, where re-resection can be incorporated into trial protocols.

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Study concept and design: J.S.Y., P.K. Data collection: J.S.Y., P.K. Data analysis and interpretation: J.S.Y., M.S.B., A.L., A.K.S., M.N., S.M.C., O.S., P.K. Manuscript drafting: J.S.Y., P.K. Manuscript revising: J.S.Y., M.S.B., A.L., A.K.S., M.N., S.M.C., O.S., P.K.

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