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Review

Contemporary surgical strategies for resection of intracranial gliomas

Jan Kueckelhaus [a,1], Sebastian Jeising [a,1], Jacob S. Young [b], Arthur Wagner [c], Jasper K.W. Gerritsen [d], Chiara Negwer [c], Bernhard Meyer [c], Oliver Schnell [a], Jörg-Christian Tonn [e], Philipp Karschnia [a,c,*]

[a] Department of Neurosurgery, Uniklinikum Erlangen, Friedrich-Alexander Universität-Erlangen-Nuremberg, Erlangen, Germany
[b] Department of Neurological Surgery, University of California, San Francisco, USA
[c] Department of Neurosurgery, Technical University of Munich, Munich, Germany
[d] Department of Neurosurgery, Erasmus MC Cancer Institute, Rotterdam, Netherlands
[e] Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany

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ABSTRACT

Diffuse gliomas are the most common primary brain tumors in adults. Maximal safe resection represents the recommended initial management step for affected patients, and accumulating evidence emphasizes the favorable effects of more extensive resection on survival. The oncological role of surgery seems to be most pronounced in tumors with an aggressive natural history, and the concept of supramaximal resection is currently emerging, particularly in IDH-wildtype glioblastoma and IDH-mutant astrocytoma. Interactive effects between more extensive resection and other clinical prognostic markers on outcome have recently been described, and a more profound understanding of these interactions can help in identifying patients most likely to benefit from aggressive surgery. Advanced pre-operative imaging, intraoperative diagnostics of the molecular tumor properties, fluorescence-guided approaches, and real-time feedback on the tumor cell content at the margins of the resection cavity allow neurosurgeons to tailor the extent of resection according to the presumed biological tumor boundaries. Advances in functional mapping techniques have been established to push the resection boundaries while avoiding jeopardizing outcome by preserving neurological functioning. In the current review, we discuss the evidence for resection across different glioma subtypes. We then outline contemporary resection strategies to achieve maximal resection, elaborate on technical adjuncts to minimize the risk of clinical deterioration even when resecting tumors located in eloquent brain areas, and finally elaborate on emerging intraoperative diagnostics, which may affect surgical strategies. As such, this review aims to provide neurosurgeons with the information needed to navigate judicious surgical decision-making in an era of precision neurosurgical care.

Introduction

Diffuse gliomas represent the most prevalent primary brain tumors in adult patients in Europe and the United States [1]. Maximal safe resection is recommended as the first therapeutic step in the newly diagnosed setting [2], and cytoreductive surgery has been demonstrated to improve survival for patients with tumors historically designated as low- or high-grade gliomas [3,4]. The assumption for an oncological role of resection is supported by favorable associations between smaller tumor residual volumes and prolonged survival in glioma patients [5,6], regardless of whether the residual tumor was left behind inadvertently or due to proximity to critical brain regions [7]. As any oncological benefit derived from more extensive resection is negated when a severe new neurological deficit is induced [6,8–10], nuanced weighting of the potential oncological effects of resection against the risk for clinical deterioration is paramount for judicious surgical decision-making. To not jeopardize good clinical functioning through surgery and thereby retain reasonable quality of life is of particular importance, as gliomas virtually always recur even when an aggressive multi-modal treatment is provided, and gliomas cannot be cured by current surgical (or medical) means given the infiltrative nature of the disease.

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* Corresponding author.
E-mail address: p.karschnia@neurooncg.org (P. Karschnia).

[1] Co-first authors.

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In order to equip neurosurgeons with tools to maximize resection while minimizing the risk for clinical deterioration, a broad range of technical adjuncts has been established that shape contemporary surgical approaches, ranging from techniques for accurate mapping of eloquent regions to advanced imaging or fluorescence techniques for delineation of tumor borders beyond what is visualized on conventional MRI [11]. Also, a more profound understanding of the biological properties paired with diagnostic advances to make the molecular tumor signature available to the neurosurgeon as early as possible during the operation is emerging to guide which patient is more likely to benefit from more extensive resection [12]. While we are therefore ushered into an era of precision neuro-oncology also from a surgical perspective, resective strategies are becoming increasingly complex to navigate for neurosurgeons. In this review, we summarize the evidence for a role of resection across different glioma subtypes, discuss contemporary strategies to optimize surgical decision-making, technical adjuncts utilized during surgery, and highlight ongoing challenges and future directions to inform and guide further research.

Data driven decision-making: the role of resection across different glioma entities

IDH-wildtype glioblastoma grade 4

With an incidence of 60% among all adult-type gliomas, IDH-wildtype glioblastoma constitutes the most frequently encountered glioma entity and is identified with a poor prognosis of a median overall survival between 12 and 17 months [1,13]. In a disease typically characterized by substantial contrast enhancement on T1-weighted MR imaging, maximal resection of the contrast-enhancing tumor portion has traditionally been the primary goal for surgery. Observations from post-hoc analyses from prospective datasets and multi-center retrospective studies support the assumption that more extensive resection of the contrast enhancement translates into more favorable disease control, independent of the adjuvant treatment scheduled [14–16]. Highly emphasized over the last decade was the finding that resection beyond the enhancing tumor borders into the surrounding non-enhancing tumor portion might provide an additional survival benefit [29].

Recent efforts of the RANO *resect* group resulted in a four-tier classification system to standardize terminology for the extent of resection based on the residual enhancing as well as non-enhancing tumor volume that has been proven to be prognostic in multiple cohorts [5,17,18]. This RANO framework shifts the focus from relative tumor reduction towards the absolute residual volume as the clinically meaningful surgical metric from an oncological standpoint. Within this classification system, survival follows a graded pattern, with complete resection of the contrast enhancement (i.e., 0 cm^3 tumor remnant) associated with a median overall survival of approximately 19 months. Further reduction of residual non-enhancing tumor to <5 cm^3 remnant, defined as 'supramaximal' resection, is associated with a more favorable survival profile as reflected by a median overall survival of about 24 months. The least favorable outcome can be observed for patients undergoing biopsy only; however, some potential for confounding needs to be acknowledged, given that individuals triaged to undergo biopsy often identify with clinical characteristics inherent to worse outcomes such as severe baseline deficits or a high level of frailty [5].

IDH-mutant astrocytomas and oligodendrogliomas grade 2-3

Compared to the poor survival of patients with IDH-wildtype glioblastomas, individuals affected by IDH-mutant gliomas of WHO grade 2-3 frequently experience substantially longer disease courses, regularly exceeding seven to ten years for astrocytomas and ten to fifteen years for oligodendrogliomas [13]. For these IDH-mutant tumors, the beneficial effects of early maximal safe surgery compared to biopsy were first demonstrated in the pre-molecular era: Jakola and colleagues reported on patients presenting to one of two Norwegian neuro-oncological centers, where region A preferentially administered a biopsy-only approach and region B more frequently scheduled a resective strategy for newly diagnosed 'low-grade' gliomas at a time of uncertainty which strategy to pursue [3,19]. With cohorts presenting to either center being balanced with respect to demographical or clinical confounders, this quasi-randomized, retrospective comparison reported longer overall survival for patients being more frequently treated with a resective strategy due to presentation to center B. Importantly, those findings held true when the tumors were retrospectively re-assigned as astrocytomas or oligodendrogliomas according to the current WHO 2021 classification [20].

In patients with IDH-mutant tumors, which characteristically present with none or only faint enhancement, the surgical target is typically the T2/FLAIR-hyperintense tumor portion. Again, the RANO *resect* group established a classification distinguishing four resection classes for postoperative patient stratification based on absolute residual T2/FLAIR tumor volume in a large, multicenter, IDH-stratified cohort with external validation [21]. Notably, any residual enhancing tumor portion (if present at initial pre-operative imaging) translates into a less favorable outcome comparable to large non-enhancing tumor portions [22,23]. In turn, supramaximal strategies are associated with a favorable survival profile in both astrocytomas and oligodendrogliomas of WHO grade 2 [21]. Importantly, the oncological effects of resection in IDH-mutant tumors depend on the presence on a 1p19q-codeletion: in astrocytoma, lower residual non-enhancing volumes result in an earlier and more consistent divergence of survival curves after about three to five years; whereas in 1p19q-codeleted oligodendroglioma, curve separation occurs only after five to seven years and is less pronounced than in astrocytomas. Such observations corroborate earlier single-institutional studies on a disease-specific benefit from the extent of resection in IDH-mutant gliomas [24]. However, no prospective randomized trial exists, and given the weight of current observational evidence favoring extensive resection, such a trial would now be ethically difficult to justify. A salient point of discussion remains on how the oncological effects of resection are to be contextualized in light of the increasing application of pharmacological IDH-inhibition for the adjuvant treatment of IDH-mutant tumors [25].

Other gliomas of WHO grade 4

For IDH-mutant astrocytomas of WHO grade 4, only limited case series exist on an association between resection and outcome given that the WHO classification has only recently introduced the diagnosis of 'IDH-mutant astrocytoma grade 4' by replacing the prior diagnosis of 'IDH-mutant glioblastoma' [26]. Single-institutional retrospective cohorts support the notion that patients benefit prognostically from minimizing the contrast-enhancing tumor portion, which speaks in favor of maximal safe reduction [27–30]. Whether additional supramaximal resection of the non-enhancing tumor might come with an additional survival benefit remains to be elucidated. In adult diffuse midline glioma, surgery is predominantly diagnostic and has no established survival benefit since the location in deep-seated midline structures renders meaningful resection impossible in most cases [31–33]. Surgical contribution usually consists of stereotactic biopsy or partial resection to alleviate mass-induced symptoms and provide molecular information to guide adjuvant therapy.

Patient-specific surgical decision-making

Beyond defining the optimal extent of resection once a resective strategy has been chosen, an equally important aspect of surgical decision-making is the upfront triage between biopsy and resection itself. In the primary setting, biopsy may be preferred over upfront resection when preoperative imaging is inconclusive, necessitating histo-molecular clarification prior to defining a resection target, or when

the lesion's location precludes safe resection [34]. In the recurrent setting, biopsy can serve to differentiate true tumor progression from treatment-related changes (e.g., pseudoprogression or radiation necrosis) and to capture molecular evolution under treatment pressure, informing the choice of neoadjuvant or targeted adjuvant regimens, including enrollment into window-of-opportunity trials [35]. Ultimately, the decision between biopsy and resection – and, if resection is pursued, its intended extent – must be individualized for each patient in a multidisciplinary setting, integrating multimodal imaging, resectability, molecular profile, clinical trajectory, and patient preference [36].

Various clinical predictors of outcome are known to interact with the oncological benefits of resection. A major predictor of whether cytoreductive surgery in glioma translates into improved survival is the postoperative functional status [37,38]. Multiple scoring systems are used, including global performance measures such as the Karnofsky Performance Status (KPS) and the ECOG Performance Status, neurological deficit scales such as the National Institutes of Health Stroke Scale (NIHSS), and patient-centered instruments such as Patient-Reported Outcome Measures (PROM). However, these tools assess different domains, are difficult to compare across studies, and there is no standardized definition of an exact cut-off being associated with less favorable outcomes. Traditionally, many clinical trials have used a Karnofsky Performance Status (KPS) of $\geq$70% as the eligibility threshold for patients to receive adjuvant therapy following surgery. Any severe postoperative deficit prohibiting the patient from undergoing medical treatment reliably negates the benefits of resection [9,39]. Due to increased time of recovery and options to safely postpone adjuvant treatment in IDH-mutant grade 2 (-3) glioma, the effect of some small level of postoperative deterioration may be prognostically less detrimental compared to grade 4 glioma [18]. Still, surgical decision-making centers on preserving functional integrity which remains a major challenge in clinical practice given the substantial heterogeneity in perceived resectability across experts [40–42]. To some extent, baseline frailty individualizes preoperative risk assessment by capturing physiological reserve and thereby predicting the likelihood of maintaining a postoperative functional status that enables adjuvant therapy [43,44].

Whether higher age is an independent risk factor for less favorable outcomes or rather a surrogate for a higher level of frailty remains unclear. Traditional cutoffs to divide the population in younger and elderly patients resolve around 65–70 years in glioblastoma patients. While the beneficial effects of larger extents of resection in glioblastoma certainly apply to younger patients, evidence is mixed in the elderly population: Teske et al. reported a survival benefit for maximal contrast-enhancing resection in elderly patients over the age of 65 years, whereas no benefit for supramaximal resection could be shown [45]. In contrast, the randomized multi-center ANOCEF trial did not show any survival benefits in patients older than 70 years when comparing resection against biopsy only [46]. However, as the trial took eleven years to include a total of 109 individuals (in France where there are more than 2.000 newly diagnosed glioblastoma cases per year) [47], the findings from ANOCEF need to be interpreted with caution given the risk for selection bias. In case of "low-grade" glioma, long-held assumptions regarding the role of age on the outcome (with an age over 40 years being considered as high-risk for less favorable outcomes) [48] are challenged by new molecular findings indicating that age in those historic studies might simply be a surrogate for IDH-wildtype status [49].

Effects of resection may also vary in the recurrent setting, with no evidence for a benefit of supramaximal resection strategies being reported so far [50]. Furthermore, the association between contrast-enhancing resection and outcome appears more consistently reported in MGMT-unmethylated tumors [16], whereas findings are conflicting in methylated tumors; suggesting that the impact of resection may be more pronounced in unmethylated tumors. Beyond MGMT status, epigenetic profiling may further refine this relationship by distinguishing high-neural and low-neural glioblastoma subgroups based on their resemblance to neural transcriptional programs: high-neural tumors, which are reflective of neuronal cell states, show a significant survival benefit from complete resection of the enhancing disease while less extensive resection seems to be needed in order to translate into a survival benefit for patients with low-neural tumors [12,51]. Together, these findings support the concept that epigenetic tumor characteristics could modulate the oncological benefit of resection and argue for a more molecularly informed surgical strategy.

Strategies to preserve neurological function: the 'safe' in maximal safe resection

Over the past two decades, there have been various technical developments that allow pre- and intraoperative mapping to preserve brain function during surgery. Preoperative mapping of eloquent brain regions relies on visualization via advanced imaging modalities such as functional MRI (fMRI), magnetoencephalography (MEG), diffusion tract imaging (DTI), or by transcranial magnetic stimulation paired with a neuronavigation system (navigated transcranial magnetic stimulation; nTMS).

fMRI measures task- or resting-state-related changes in blood oxygen level-dependent sequences as a surrogate of neuronal activity to localize eloquent cortex. Yet, specificity of detecting eloquent areas is complicated if a high level of neoangiogenesis within the tumor may impact the measured blood oxygen levels in adjacent brain areas [52,53]. In contrast, magnetoencephalography (MEG) measures magnetic fields generated by synchronized neuronal activity, enabling noninvasive localization of eloquent cortical areas, overcoming vascular interference. Thus, fMRI and MEG provide insights into the functional network organization of language [54]. However, clinical utility remains largely confined to cortical mapping with limited ability to delineate subcortical pathways and is further constrained by technical demands.

DTI reliably identifies the corticospinal tract, arcuate fasciculus, and optic radiation as well as their displacement by tumor mass or edema by exploiting direction-dependent diffusion of water molecules in the white matter tracts visualized on diffusion-weighted images. One key limitation is the "crossing fiber problem", whereby the model assumes a single dominant diffusion direction per voxel and therefore fails to resolve intersecting fibers [55]. This results in an unreliable depiction of the intersecting superior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and frontal aslant tract, which are critically involved in language processing, including semantic, phonological, and executive language functions. Consequently, DTI may underestimate critical language networks [56,57].

nTMS creates an electrical cortical field by transcranial magnetic pulses to induce or inhibit cortical functions. This can be utilized to map the motor cortex and motor language cortex (Fig. 1). Thereby, nTMS data may inform the surgical strategy in experienced centers with respect to the size of the craniotomy, the corticotomy, the surgical corridor, and therewith also patient communication in terms of risk assessment [58]. By disproving suspected primary motor cortex involvement preoperatively, it furthermore may facilitate a more extensive resection strategy and therefore enhance the extent of resection without increasing neurological deficits [59].

Each preoperative brain mapping technique is constrained by possibly unreliable spatial congruence intraoperatively due to brain shift. Sensitivity and specificity of DTI for subcortical pyramidal tract mapping is estimated at >90% compared with direct subcortical electrical stimulation as the ground truth [56]. nTMS has an accuracy of <10 mm for the identification of cortical motor areas. Sensitivity and specificity range from approximately 10–100% for language mapping with nTMS, but negative predictive values are comparably high (57–100%) and can therefore guide surgical strategy [60]. In selected cases, where awake surgery is contraindicated, combining DTI and nTMS may ultimately serve as a rescue strategy for language-eloquent lesions [61].

Fig. 1. nTMS for preoperative brain-mapping. MRI shows a left frontal glioblastoma with ring-enhancing contrast-enhancement (A, T1-weighted sequence) without significant edema (B, T2-weighted sequence). nTMS is used to visualize the corticospinal tract (orange; C) and a dedicated language testing allows visualization of the fasciculus longitudinalis superior (red; D).

Intraoperative neurophysiological monitoring of the white matter tracts together with cortical and subcortical mapping using direct electrical stimulation to identify critical motor pathways and language function is the gold standard for preservation of neurological function [62]. Classical cortical stimulation is based on the Penfield paradigm, i.e., low-frequency direct cortical stimulation of the exposed cortex to evoke transient functional responses and delineate eloquent areas, whereas modern subcortical mapping increasingly relies on focal train stimulation to define white-matter tract boundaries. Motor-evoked potentials can be evoked using transcranial or direct cortical stimulation and recorded via needle electrodes in the respective muscle groups. For cortical motor mapping, monopolar high-frequency stimulation is nowadays applied as a train of pulses in awake patients and is particularly suitable for subcortical mapping as it allows a threshold-based estimation of corticospinal tract proximity [63]. Awake mapping was originally developed mainly for epilepsy surgery, eventually adopted for low-grade gliomas and is now increasingly applied in selected high-grade glioma cases [39]; it is performed with direct cortical or subcortical bipolar stimulation during continuous motor and language testing, using a relatively focal current spread with brief repeated pulses or short trains at intensities adjusted individually, often beginning in the low milliampere range and titrated upward until a motor dysfunction or language arrest, paraphasia, or anomia is elicited [64]. Subcortical mapping during awake resection can then be continued with repeated stimulation at the same focal settings [65].

Thus, intraoperative brain mapping (including awake resections) significantly enhances the extent of resection and reduces the risk of late severe neurological deficits in tumors with proximity to language- or motor-associated regions [66], potentially leading to longer overall and progression-free survival [67,68]. Persistent language deficits can be reduced down to a rate of 1.6–2.3% at 6-month follow-up in both low- and high grade gliomas when awake mapping is used for language-associated tumors [69,70]. Important limitations of awake brain mapping are fixed neurological deficits prior to surgery, anesthesiologic contraindications (e.g., airway surveillance), patient exhaustion, or refractive seizures during surgery. Considering incremental improvements in survival for glioblastoma patients and survival of patients with IDH-mutant tumors in the range of decades, neurocognitive assessment is gaining importance [71]. Higher-order cognitive functions (e.g., semantic cognition, inhibition, set shifting, social cognition, and multitasking) can also be tested by intraoperative awake brain mapping and preserved depending on patient consultation [72, 73]. Finally, patients with eloquently located low-grade gliomas may show frequent (up to 80%) neurological worsening after aggressive resection under intraoperative awake mapping but almost all patients recover their preoperative status within three months and some even improve [74]. A landmark study on intraoperative language and motor mapping in 250 patients with both low- and high-grade gliomas showed rates of 8.4% worsening in language and 6.4% in motor functions. However, 3–6 months after surgery, only 1.6% continued to have a language and 0.8% a motor deficit, thus highlighting the significance of direct electrical stimulation and awake mapping for the intraoperative disease specific decision-making on the onco-functional balance [69].

Strategies to delineate the tumor borders: the ‘maximal’ in maximal safe resection

Given the diffuse infiltrating nature of gliomas, a salient point of discussion remains what the exact goal of resection should be. As detailed for the respective entities above, the term ‘supramaximal resection’ is defined by evaluating not only the contrast-enhancing tumor but also the remaining non-contrast enhancing tumor on T2/FLAIR-weighted images and has been applied to at least three conceptually distinct strategies: purely anatomical resections following fixed neuroanatomical boundaries (e.g., temporal lobectomy), radiologically defined approaches extending the resection target by a standardized imaging margin or threshold (e.g., a fixed 1 cm margin beyond contrast enhancement), and an emerging, still largely experimental approach in which the resection margin is tailored to direct spectroscopic or molecular markers of tumor infiltration.

The distinction between a clearly demarcated hyperintense abnormality consistent with infiltrative neoplastic tissue from pure vasogenic edema can be challenging, yet non-contrast-enhancing tumor differs in the involvement of gray matter, a more focal expansion in the parenchyma, an eccentric distribution from the lesion, and relatively mild hyperintensity compared to edema [75]. For non-contrast enhancing IDH-mutant glioma, the target of supramaximal resection is complete resection of the T2/FLAIR-tumor and even beyond in the initially non-infiltrated parenchyma, also resulting in significant survival advantage [21]. If maximal resection in glioblastoma refers to the enhancing tumor portion and to the T2/FLAIR-hyperintense tumor portion in IDH-mutant gliomas, then the emerging concept of ‘supramaximal’ resection will need to be realigned with imaging findings reliably representing expansile tumor.

The combined use of conventional MRI with positron emission tomography (PET) using radiolabeled amino acids may further improve the identification of infiltrative glioblastoma tissue beyond the MR-visible margins [76]. It can be used not only in an attempt to distinguish progression from treatment-induced changes but also for pre-operative surgical planning. While a number of different tracers are available [77], (18F)-fluoro-ethyl-L-tyrosine (FET) PET is most commonly used, and the observed PET volume exceeds the contrast-enhancing volume on MRI by 86% of newly diagnosed glioblastoma patients, while in 10% of the patients FET uptake can even be detected outside FLAIR hyperintensity [78]. A prospective, multicenter, randomized trial (NOA 10/ARO 2013-1, GLIAA) therefore assessed the outcome for patients with recurrent glioblastoma undergoing re-irradiation by employing a radiotherapy target volume based on 18F-FET PET and found no survival advantage compared to MR-based target volume delineation. However, single-institution retrospective studies have established a prognostic significance of lower postoperative FET PET volume after resection [79] and showed that even in patients with complete resection of the MR contrast enhancement, postoperative FET PET tumor volume <1 cm^3 translated into a substantially longer survival in glioblastoma patients [80]. It is therefore tempting to speculate that the GLIAA study has failed not because of the use of PET but because radiotherapy *per se* might not be as effective as desired in the recurrent setting; and instead its value might lie in the intraoperative neuronavigation-assisted identification of PET tumor volume to guide a metabolically informed maximized tumor resection.

Chemical exchange saturation transfer (CEST) MRI indirectly detects low-concentration metabolites by saturating exchangeable protons and measuring the resulting reduction in the water signal using specific sequences. Several studies have assessed the potential of CEST MRI for glioma grading, predicting the molecular subtype, differentiating recurrence from treatment-related changes and prognosis prediction [81]. For instance, amide proton transfer-CEST several weeks after radiotherapy provides an indirect measure of protein concentration and is associated with survival in both IDH-wildtype and -mutant glioma [82]. Amine chemical exchange saturation transfer echo planar imaging further identifies non-contrast enhancing tumor portions by detecting pH changes in the tumor microenvironment and correlates with histological proliferation markers and recurrence patterns in glioblastoma [83]. Together, CEST MRI holds a potential for imaging of the molecular (residual) tumor extent, yet its implications for neurooncological neurosurgery remain to be determined within prospective high-quality trials.

Intraoperative visualization of residual tumor during resection is feasible through intraoperative MRI (ioMRI), fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) or fluorescein, and intraoperative ultrasound (ioUS). In a prospective, single-center, randomized trial, ioMRI enhanced the rate of complete tumor resection (96%) without worsening neurological status compared to conventional white-light microneurosurgery (68%) by detecting residual resectable tumor in a third of patients and resulting in continuation of resection [84]. 5-ALA accumulates as fluorescent protoporphyrin IX in glioblastoma cells, and after oral administration intraoperative blue-light-induced pink fluorescence in the tumor area increases the rate of complete resection of the contrast-enhancing component compared with conventional white-light surgery, resulting in significantly longer 6-month progression-free survival [4]. Interestingly, the use of fluorescence-guided surgery increases the risk of temporary impairment of neurological function. Yet, the overall benefit of extended resections with associated longer PFS and fewer repeat resections may outbalance these deficits as they are mostly transient in nature [85]. Another fluorescent dye, fluorescein, visualizes areas of disturbed blood-brain-barrier under a dedicated light filter in green to yellow. The sensitivity of fluorescein for high-grade glioma to detect histological tumor is about 85% [86]. Median residual contrast-enhancing tumor volume after fluorescein guided surgery in high-grade glioma compared to white light resection in a retrospective, single-institution analysis including 347 patients was 0 cm^3 vs. 3.6 cm^3 with significantly longer PFS and OS [87]. A retrospective analysis of 209 patients showed that the use of 5-ALA vs. fluorescein had similar extents of resection as well as OS [88]. 5-ALA fluorescence had been thought to be tumor cell specific; on the cellular level however, histological and molecular data showed that reactive astrocytes and myeloid cells significantly accumulate and metabolize protoporphyrin IX questioning 5-ALA-specific fluorescence in glioma cells [89,90]. Further prospective studies are therefore warranted to investigate the differences in impact on the extent of resection, survival benefit, and costs for these fluorescence agents in high-grade glioma [91]. Comparing ioMRI and 5-ALA fluorescence guided surgery in a prospective, controlled, multicenter, parallel-group trial including 314 patients showed similar rates of complete resections, postoperative residual tumor volume, and survival [16]. Yet, the prospective combined application of 5-ALA and ioMRI showed improved survival compared to a retrospective ioMRI alone cohort in a single-institution investigation [92]. Thus, prospective studies might focus on investigating combined approaches.

Real-time, cost-effective brain tumor imaging is feasible through ioUS, capable of visualizing both contrast and non-contrast enhancing lesions. In a meta-analysis including both high- and low-grade gliomas, pooled sensitivity in detecting residual tumor tissue was 72.2% with 93.5% specificity [93]. Additionally, ioUS can be used to correct for brain shift and improve the accuracy of preoperatively registered neuronavigation [94]. 5-ALA and ioUS are often considered complementary technologies, and as such, ioUS was used in about half of the patients of the 5-ALA cohort whereas only in about a third of patients in the ioMRI cohort in the prospective trial comparing ioMRI vs. 5-ALA fluorescence guidance [16]. Yet, high-quality data on the specific comparison of ioUS and ioMRI are missing, with only small series with inconsistent findings [95,96].

Histological examination of intraoperative fresh frozen sections has been considered the gold standard in the assessment of suspected tumor histology. It is, however, limited by intraoperative turn-around time, the presence of a trained and experienced neuropathologist, as well as heterogenous tissue composition in recurrent disease, and therefore not suitable to assess tumor margins. By detecting differences in the composition of molecules, stimulated Raman histology (SRH) provides high-resolution virtual H&E images of fresh surgical specimens label-free in the operating room within minutes (Fig. 2) [97]. In a simulation, a large-scale self-supervision trained visual foundation model based on SRH outperformed ioMRI and 5-ALA for detecting residual tumor. Even in FLAIR-positive regions, SRH reliably differentiated edema from tumor infiltration. Together, the risk for safely resectable dense tumor remnants might be higher using ioMRI or 5-ALA compared to SRH [98]. Yet, an effect of SRH-based complete cellular resection on survival or recurrent patterns remains to be determined in a prospective clinical trial.

Emerging concepts and future directions

While a 'supramaximal' resection strategy is emerging in patients with IDH-wildtype and -mutant tumors, the oncological value of such ever-increasing extents of resection likely reaches a limit when surgery results in diminished functional outcome. To therefore assess the concept of supramaximal resection in a prospective manner, two randomized controlled, multicenter trials from Europe and North America (BOLD: NCT04243005, planned enrollment $n = 90$; and G-SUMIT: NCT04737577, planned enrollment $n = 72$) were recruiting patients to undergo either complete resection of the contrast-enhancement or supramaximal resection (defined per trial protocol as 1 cm beyond the enhancing margins); however, both trials were stopped prematurely, and the pooled results from those trials are now eagerly awaited. Two more trials are currently still enrolling patients: first, the FLAMINGO trial (Japan Registry of Clinical Trials study number: 1031230245) aims to evaluate the resection of FLAIR hyperintense regions ("FLAIR-

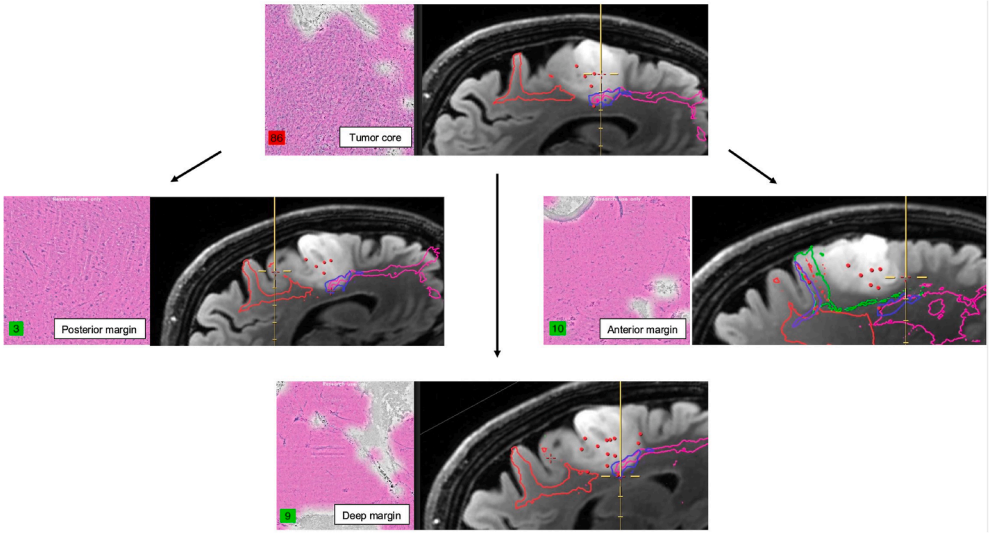

Fig. 2. Use of intraoperative Raman spectroscopy to identify tumor margins. Example of Raman spectroscopy images from the tumor core (top) and tumor margins. Scores represent *GliomaReveal* values and demonstrate a decrease as the resection moves beyond the region of dense tumor infiltration. The yellow crosshairs indicate the position of the neuronavigated pointer referenced to the preoperative MRI [98,106,107].

ectomy", defined as complete contrast-enhanced resection and at least 20% of the surrounding FLAIR hyperintense lesion) in 130 Japanese patients. Second, the ATLAS/NOA-29 trial (German Clinical Trials Register number: 00035314) evaluates anterior temporal lobectomy in 178 patients compared to resection of the enhancing lesion only in newly diagnosed temporal glioblastoma.

Today, epigenetic information becomes available already during tumor surgery, using nanopore sequencing. It allows for intraoperative molecular classification of tumors through methylation analysis within up to 90 min when sampled from appropriate tumor regions [99]. As epigenetic profiling may predict the benefit from the extent of resection [12,51], this technology could be combined with Raman spectroscopy to plan and execute the extent of resection intraoperatively.

As the surgical field is moving towards the glioma infiltration zone akin to the concept of "minimal residual disease", rapid genotyping of tumor-specific variants could guide detection of molecular tumor margins in such cases (Fig. 3). Advances in PCR technology have recently enabled the detection of clonal *IDH1* R132H (present in 95% of IDH-mutant glioma) as well as *TERT* C228T/C250T (present in 80% of GBM and 97% of oligodendroglioma) and *BRAF* V600E variants (present in pleomorphic xanthoastrocytoma or ganglioglioma) within 15–25 min after biopsy as surrogates for molecular tumor burden [100,101]. Thus, a single-center study with a prospective cohort of 44 adult glioblastoma patients combined volumetric MRI-based extent-of-resection analysis with rapid PCR-based detection of TERT promoter mutation at the surgical margin and found that achieving an undetectable molecular margin was associated with significantly prolonged PFS and a favorable trend for OS [102].

Focusing on the infiltrative glioma margins also resonates with a growing body of literature derived from the emerging field of 'cancer

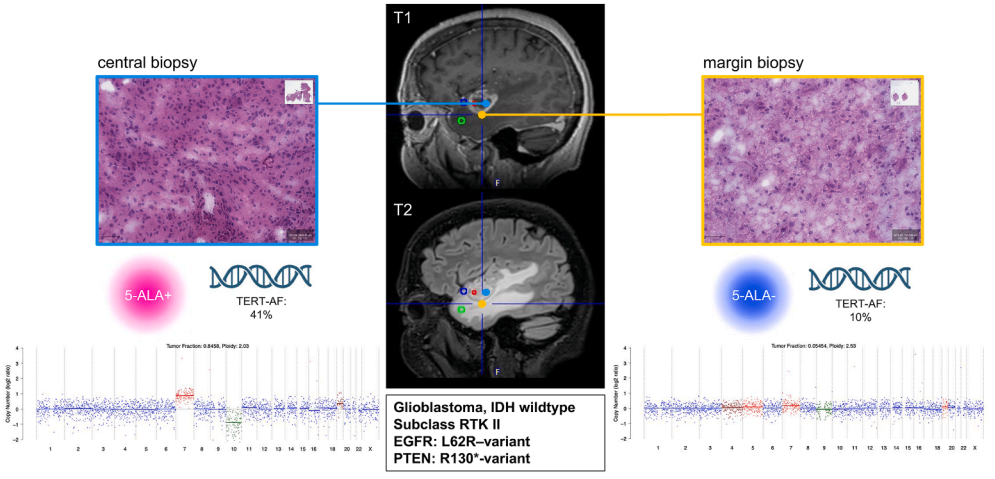

Fig. 3. A spatial multiomic visualization of molecular tumor margins. Navigated biopsies were sampled and processed for comprehensive histo-molecular workup: A fresh frozen section of a central biopsy (cyan) from a 5-ALA-induced fluorescent area of this temporal lesion revealed a highly cellular, pleomorphic glial neoplasm with marked nuclear atypia, microvascular proliferation, and necrosis, consistent with glioblastoma. PCR for TERT-promotor mutation (as a surrogate for molecular tumor burden) showed a mutant allele frequency of 41%. Nanopore-based copy number analysis revealed a characteristic gain of chromosome 7 and loss of chromosome 10, consistent with a glioblastoma-associated genomic signature. Fresh frozen section from the non-fluorescent tumor margin (yellow) still revealed molecular tumor burden (mutant TERT-promotor AF: 10%) with diffusely infiltrating atypical glial cells with increased cellularity, lacking necrosis or microvascular proliferation, consistent with peripheral tumor infiltration. Nanopore sequencing did not reach a diagnostic score in this sample. Parts of this illustration were created using BioRender.com.

neuroscience' [103]: first, gliomas induce neuronal alteration of their peritumoral neural environment, which can even be recorded intraoperatively. Second, fMRI or MEG visualize this synchronous neural activity between spatially separated brain regions and can identify regions of high and low connectedness. Molecular analyses from such highly connected areas show increased synapse formation as well as high-neural epigenetic signatures. Clinically, a high functional connectedness of the tumor is correlated with impaired cognition. Ultimately, patients with high intra- and peritumoral connectedness show significantly shorter survival. From a surgical perspective, tumor removal significantly decreases peritumoral connectedness and therefore might improve outcome. This spatial intra- and peritumoral connectedness could inform surgical strategy i) in cases where extent of resection must be spatially tailored due to functional borders or ii) so that supramaximal resection could be pronounced in highly connected peritumoral areas. These findings also make it possible to consider spatially targeted pharmacological or neuromodulatory surgical treatment approaches to disconnect the tumor from its integration into neuronal networks [104,105].

Current trials such as BOLD, G-SUMIT, FLAMINGO, and ATLAS/NOA-29 not only refine the definition of optimal resection volume but also highlight the need to balance aggressive cytoreduction with functional preservation. Advances in epigenetic profiling as well as real-time detection of clonal *IDH*, *TERT*, and *BRAF* variants, combined with functional network imaging, could soon transform intraoperative decision-making into a biologically and functionally guided strategy, and it is likely that we will be witnessing a future of precision neuro-oncology also from a surgical perspective.

Author contributions

Study concept & design: BM, OS, JCT, PK.
Data collection: JK, SJ, JSY, JKWG, AW, CN, PK.
Data analysis & interpretation: JK, SJ, JSY, JKWG, AW, CN, PK.
Manuscript drafting: JK, SJ, PK.
Manuscript revising: JSY, JKWG, AW, CN, BM, OS, JCT, PK.

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Declaration of competing interest

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