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PRECISION-GUIDED MAXIMAL SAFE RESECTION OF DIFFUSE GLIOMAS IN THE MOLECULAR ERA: INTEGRATION OF FUNCTIONAL MAPPING, 5-ALA, INTRAOPERATIVE IMAGING, RAPID OPTICAL HISTOLOGY, AND ARTIFICIAL INTELLIGENCE

Abstract.

Background. Surgical management of diffuse gliomas is undergoing a transition from anatomically defined tumor removal toward biologically and functionally individualized resection. The conventional objective of gross-total resection based on contrast-enhanced or T2/FLAIR magnetic resonance imaging incompletely reflects the infiltrative architecture of gliomas and does not incorporate interindividual differences in molecular subtype, eloquent-network organization, or microscopic tumor burden. Recent advances in awake cortical–subcortical mapping, 5-aminolevulinic acid fluorescence, intraoperative ultrasound and magnetic resonance imaging, stimulated Raman histology, confocal laser endomicroscopy, nanopore-based molecular profiling, and artificial intelligence provide complementary sources of intraoperative information.

Materials and Methods. A structured narrative review of clinical trials, prospective multicenter studies, molecularly annotated surgical cohorts, and translational investigations published through August 2026 was performed. Evidence was synthesized around extent of resection, molecular subtype, functional preservation, intraoperative tumor detection, optical histology, and rapid molecular classification.

Results. Increasing extent of resection remains associated with improved oncological outcomes, but the magnitude and safe limit of cytoreduction vary according to patient age, tumor biology, residual contrast-enhancing and non-enhancing volume, and functional anatomy. Supramaximal resection has shown particularly favorable associations in IDH-mutant grade 2 gliomas when functionally feasible. 5-ALA improves detection of metabolically active high-grade tumor, while intraoperative ultrasound and MRI compensate for brain shift. FastGlioma, combining stimulated Raman histology with a foundation model, detected the degree of glioma infiltration with a mean AUROC of 92.1% in a prospective international cohort of 220 patients. DeepGlioma and rapid nanopore methylation classifiers demonstrate that molecular information can increasingly be generated within an intraoperative time frame.

Conclusion. The contemporary surgical endpoint should not be defined by radiographic completeness alone. A precision-guided resection strategy should integrate biological tumor probability, functional-network boundaries, updated intraoperative anatomy, molecular subtype, and anticipated postoperative neurological cost. The optimal boundary of resection is therefore patient-specific rather than purely MRI-defined.

Keywords: diffuse glioma; glioblastoma; maximal safe resection; supramaximal resection; awake mapping; 5-ALA; intraoperative ultrasound; stimulated Raman histology; artificial intelligence; molecular neurosurgery.

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ПРЕЦИЗИОННАЯ МАКСИМАЛЬНО БЕЗОПАСНАЯ РЕЗЕКЦИЯ ДИФФУЗНЫХ ГЛИОМ В МОЛЕКУЛЯРНУЮ ЭРУ: ИНТЕГРАЦИЯ ФУНКЦИОНАЛЬНОГО КАРТИРОВАНИЯ, 5-ALA, ИНТРАОПЕРАЦИОННОЙ ВИЗУАЛИЗАЦИИ, БЫСТРОЙ ОПТИЧЕСКОЙ ГИСТОЛОГИИ И ИСКУССТВЕННОГО ИНТЕЛЛЕКТА

Аннотация

Актуальность. Хирургия диффузных глиом переходит от анатомически ориентированного удаления опухоли к биологически и функционально персонализированной резекции. Традиционное понятие тотального удаления, определяемого по контрастному усилению или T2/FLAIR-сигналу на МРТ, не полностью отражает инфильтративный характер глиом и не учитывает различия молекулярного подтипа, индивидуальной организации функциональных нейрональных сетей и микроскопической опухолевой нагрузки. Современные методы функционального картирования в сознании, 5-ALA-флуоресценции, интраоперационного ультразвука и МРТ, стимулированной рамановской гистологии, конфокальной лазерной эндомикроскопии, быстрого молекулярного профилирования и искусственного интеллекта формируют новую концепцию прецизионной нейроонкологической хирургии.

Материалы и методы. Проведен структурированный нарративный обзор клинических исследований, проспективных многоцентровых работ, молекулярно аннотированных хирургических когорт и трансляционных исследований, опубликованных до августа 2026 года. Анализировались объем резекции, молекулярный подтип, сохранение функционально значимых зон, интраоперационная идентификация опухолевой ткани, оптическая гистология и ускоренная молекулярная классификация.

Результаты. Увеличение объема резекции сохраняет связь с улучшением онкологических исходов, однако оптимальный объем хирургического вмешательства определяется возрастом пациента, молекулярной биологией опухоли, остаточным контрастирующимся и неконтрастирующимся объемом и функциональной анатомией. Supramaximal-резекция демонстрирует особенно благоприятные результаты при IDH-мутантных глиомах 2-й степени при возможности функционально безопасного удаления. 5-ALA улучшает визуализацию биологически активной ткани, а интраоперационный ультразвук и МРТ компенсируют brain shift. FastGlioma продемонстрировала AUROC 92,1% при количественной оценке инфильтрации глиомы в международной проспективной когорте из 220 пациентов.

Заключение. Современная граница резекции должна определяться не только МРТ. Она должна формироваться на основании интеграции биологической вероятности опухоли, функциональных границ мозга, актуальной интраоперационной анатомии и молекулярного профиля заболевания.

Ключевые слова: диффузная глиома; глиобластома; максимальная безопасная резекция; supramaximal resection; awake mapping; 5-ALA; интраоперационный ультразвук; Raman-гистология; искусственный интеллект.

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MOLEKULYAR DAVRDA DIFFUZ GLIOMALARNI PRETSIZION MAKSIMAL XAVFSIZ REZEKSIYA QILISH: FUNKSIONAL XARITALASH, 5-ALA, INTRAOPERATSION VIZUALIZATSIYA, TEZKOR OPTIK GISTOLOGIYA VA SUN'IY INTELLEKT INTEGRATSIYASI

Annotatsiya

Dolzarblik. Diffuz gliomalar jarrohligi anatomik chegaralangan o‘smani olib tashlash konsepsiyasidan biologik va funksional jihatdan shaxsiylashtirilgan rezeksiya modeliga o‘tmoqda. Kontrastlangan yoki T2/FLAIR MRT chegaralariga asoslangan an'anaviy total rezeksiya gliomalarning infiltrativ xususiyatini to‘liq aks ettirmaydi hamda molekulyar subtip, individual funksional neyron tarmoqlar va mikroskopik o‘sma yuklamasini hisobga olmaydi. Awake mapping, 5-ALA fluorescensiya, intraoperatsion ultratovush va MRT, stimulated Raman histology, konfokal lazer endomikroskopiyasi, tezkor molekulyar profillash hamda sun'iy intellekt precision neyroonkologik jarrohlikning yangi imkoniyatlarini yaratmoqda.

Material va usullar. 2026-yil avgustigacha chop etilgan klinik tadqiqotlar, prospektiv ko‘p markazli ishlar, molekulyar tavsiflangan jarrohlik kohortalari va translatsion tadqiqotlar strukturaviy tahlil qilindi. Rezeksiya hajmi, molekulyar subtip, funksional xavfsizlik, intraoperatsion o‘sma identifikatsiyasi, optik gistologiya va tezkor molekulyar klassifikatsiya bo‘yicha ma'lumotlar tizimlashtirildi.

Natijalar. Kengroq rezeksiya yaxshiroq onkologik natijalar bilan bog‘liq bo‘lib qolmoqda, biroq optimal sitoreduksiya bemorning yoshi, o‘smaning biologik xususiyati, kontrastlanuvchi va kontrastlanmaydigan qoldiq hajm hamda funksional anatomiyaga bog‘liq. IDH-mutant 2-darajali gliomalarda funksional jihatdan xavfsiz supramaksimal rezeksiya ayniqsa istiqbolli natijalar ko‘rsatgan. FastGlioma 220 nafar bemorni qamrab olgan xalqaro prospektiv kohortada glioma infiltratsiyasini aniqlashda o‘rtacha 92,1% AUROC ko‘rsatgan.

Xulosa. Zamonaviy glioma jarrohligida rezeksiya chegarasi faqat MRTga asoslanmasligi kerak. O‘smaning biologik ehtimoli, funksional neyron tarmoqlar chegarasi, intraoperatsion anatomik ma'lumot va molekulyar subtip yagona qaror qabul qilish tizimiga integratsiya qilinishi lozim.

Kalit so‘zlar: diffuz glioma; glioblastoma; maksimal xavfsiz rezeksiya; supramaksimal rezeksiya; awake mapping; 5-ALA; intraoperatsion ultratovush; Raman gistologiyasi; sun'iy intellekt.

Introduction. Diffuse gliomas constitute a biologically heterogeneous group of infiltrating primary central nervous system tumors in which surgical cytoreduction remains a fundamental component of multimodal treatment. The modern molecular taxonomy has fundamentally changed the meaning of histological grade by integrating isocitrate dehydrogenase mutation, 1p/19q codeletion,

ATRX status, CDKN2A/B homozygous deletion, TERT promoter alterations, EGFR amplification, chromosome 7 gain/chromosome 10 loss, and other molecular characteristics into diagnostic and prognostic interpretation [1, 18, 33]. Consequently, the neurosurgeon no longer operates on a generic “low-grade” or “high-grade” glioma but on a disease whose expected biological behavior may vary profoundly despite superficially similar radiological appearance. At the same time, the fundamental surgical principle remains maximal safe resection. Multiple volumetric studies have demonstrated an association between increasing extent of resection and improved progression-free or overall survival in glioblastoma and lower-grade gliomas [3, 5, 7, 28]. In a landmark series of 500 patients with newly diagnosed glioblastoma, increasing volumetric extent of resection was associated with progressively improved survival even at high resection percentages [3]. Subsequent molecularly informed analyses demonstrated that residual contrast-enhancing and non-contrast-enhancing tumor volumes may carry different prognostic importance depending on age and tumor biology [5, 29].

The problem is that a diffuse glioma has no true macroscopic capsule. MRI defines a radiological phenotype rather than the absolute biological border of disease. Neoplastic glial cells may extend beyond contrast enhancement and beyond conventionally defined T2/FLAIR abnormality. Conversely, T2/FLAIR hyperintensity can contain variable proportions of infiltrating tumor, edema, gliosis, treatment-related tissue changes, and functionally indispensable white matter [5, 7, 15]. Therefore, radicality based exclusively on MRI is conceptually inadequate. A purely radiographic definition of completeness risks both under-treatment, when infiltrating tumor is left behind despite being functionally resectable, and over-treatment, when non-specific signal abnormality is pursued into eloquent networks. This conflict has become particularly relevant as the concept of supramaximal, supratotal, or supramarginal resection has gained momentum. Molecularly defined lower-grade glioma cohorts suggest that resection extending beyond the visible FLAIR-defined tumor may delay progression and malignant transformation in appropriately selected patients [7, 8]. The 2025 international RANO resect analysis of IDH-mutant grade 2 gliomas provided additional evidence that extent of resection categories carry molecularly dependent prognostic information, with resection beyond T2/FLAIR abnormalities showing particularly favorable long-term associations when neurologically feasible [8].

Yet “more resection” cannot be interpreted independently of neurological function. A new permanent language, motor, executive, visuospatial, or social-cognitive deficit can negate an oncological gain by reducing quality of life, functional independence, and the patient's ability to receive adjuvant therapy. The real surgical objective is consequently not maximal anatomical excision but optimization of the ratio between cytoreduction and neurological cost [6, 25, 27]. Modern glioma surgery is therefore becoming an information-integration problem. Functional mapping identifies tissue that cannot be removed without unacceptable functional consequences. 5-ALA provides metabolic fluorescence. Intraoperative ultrasound and intraoperative MRI compensate for spatial error generated by brain shift. Stimulated Raman histology and confocal laser endomicroscopy provide near-real-time microscopic tissue characterization. Artificial intelligence can quantify infiltration patterns that exceed unaided human visual discrimination, while nanopore sequencing increasingly allows molecular classification during the operative time window [12–20].

Materials and Methods. A structured narrative literature review was conducted with emphasis on adult diffuse glioma surgery. Evidence available through August 2026 was considered. Priority was assigned to randomized surgical trials, prospective multicenter studies, molecularly characterized surgical cohorts, externally validated classification systems, and translational studies with direct intraoperative applicability. The evidence was organized into six domains: extent of resection and molecular subtype; functional cortical and subcortical mapping; fluorescence-guided surgery; intraoperative anatomical updating; optical and AI-assisted tissue characterization; and rapid intraoperative molecular classification. Historical studies were included when they established major surgical concepts, including volumetric extent of resection, 5-ALA-guided surgery, and intraoperative MRI [3, 4, 9]. More recent evidence was emphasized for molecularly stratified resection, stimulated Raman histology, confocal laser endomicroscopy, artificial intelligence, and nanopore-based epigenomic classification [8, 14–21]. Because the included studies differed substantially in population, molecular taxonomy, imaging definitions, resection classifications, technologies, and outcome measures, no quantitative meta-analysis was attempted. The purpose was instead to construct a translational framework linking biological tumor detection with functional preservation. The principal conceptual endpoint of the review was defined as the precision surgical boundary, representing the maximal tissue volume with sufficient probability of clinically relevant tumor that can be removed without crossing an individualized functional-risk threshold.

Results. The historical association between cytoreduction and survival in glioblastoma remains robust across numerous observational studies. Sanai et al. demonstrated a continuous relationship between extent of resection and survival in 500 newly diagnosed glioblastomas, challenging the concept of a single binary threshold separating “subtotal” from “total” removal [3]. Subsequent systematic analyses strengthened the association between greater resection and survival [28]. More importantly, molecularly informed data suggest that the optimum surgical target may differ among biological subgroups. Molinaro et al. evaluated a development cohort of 761 patients with newly diagnosed glioblastoma and additional external validation cohorts. Maximal removal of contrast-enhancing tumor was associated with improved survival across subgroups, while additional reduction of non-contrast-enhancing tumor was associated with longer survival particularly in younger patients when safely achievable [5].

This observation challenges the conventional assumption that the enhancing boundary represents the biologically meaningful surgical endpoint. Glioblastoma infiltration extends beyond enhancement, and the non-enhancing compartment may contain substantial neoplastic burden [5, 22, 29]. Nevertheless, resection of FLAIR-abnormal tissue cannot be pursued indiscriminately because this compartment often intersects functionally integrated cortical and subcortical networks. The concept becomes even more important in IDH-mutant lower-grade gliomas. Rossi et al. analyzed molecularly defined lower-grade gliomas and found an association between supratotal resection and longer progression-free survival, lower malignant-transformation risk, and improved overall survival [7]. The cohort included 319 IDH-mutant tumors, making the findings more biologically interpretable than historical histology-only datasets. The 2025 RANO resect international multicenter study further standardized the interpretation of surgical radicality in IDH-mutant grade 2 gliomas. Resection beyond T2/FLAIR-defined tumor boundaries was associated with highly favorable long-term outcomes,

although the study remained retrospective and therefore does not establish a causal benefit of supramaximal resection [8]. The practical implication is that extent of resection cannot be represented by a universal numerical threshold. The meaningful target is determined by the interaction among molecular subtype, preoperative tumor volume, anatomical localization, functional organization, patient age, anticipated natural history, and adjuvant therapeutic options [5, 7, 8, 29].

Functional Anatomy Defines the Maximum Permissible Resection

Anatomical eloquence is an imperfect surrogate for functional eloquence. Language, executive control, praxis, visuospatial cognition, social cognition, and motor planning are distributed within individualized networks that may undergo substantial reorganization during the slow growth of diffuse gliomas [6, 25, 27]. Direct electrical stimulation remains one of the most powerful methods for identifying cortical and subcortical functional boundaries during glioma resection. Awake mapping is particularly valuable when tumors involve language, praxis, semantic, executive, or other higher-order networks. The central principle is not simply to identify a classical Broca or Wernicke region but to map the distributed network required for the patient's relevant functions [25, 27]. Subcortical mapping is especially important because white-matter tracts can represent the definitive stopping boundary. Cortical plasticity may permit removal of regions previously assumed to be indispensable, whereas injury to poorly compensable subcortical pathways can result in persistent deficits. Consequently, functional mapping transforms surgical strategy from lesion-centered resection toward network-preserving resection [6, 25]. This concept has acquired additional biological significance. Krishna et al. demonstrated that glioblastoma can functionally integrate with human neural circuits and that stronger functional connectivity between tumor-infiltrated regions and the surrounding brain was associated with worse survival and impaired language performance [22]. Thus, tumor–brain interaction is not simply a surgical obstacle. It may represent an active component of glioma biology. The future neurosurgical boundary may therefore need to account not only for the anatomical presence of tumor and the functional necessity of brain tissue, but also for the degree of pathological tumor–neural network integration [22, 30].

Fluorescence-Guided Surgery: Powerful but Biologically Incomplete

The randomized multicenter trial by Stummer et al. established 5-ALA fluorescence-guided surgery as a major advance in malignant glioma surgery. Fluorescence guidance substantially increased the frequency of complete removal of contrast-enhancing tumor and improved 6-month progression-free survival compared with white-light surgery [4]. 5-ALA is metabolized to fluorescent protoporphyrin IX, which accumulates preferentially in many high-grade glioma cells. Strong fluorescence is therefore useful for identifying biologically active tumor that may be difficult to distinguish under conventional white-light microscopy [4, 11]. However, fluorescence intensity is influenced by cellular density, metabolic state, tumor grade, molecular characteristics, optical conditions, prior treatment, and distance from the tumor core. Microscopically infiltrated tissue at the periphery may contain tumor below the threshold of visible fluorescence. Absence of macroscopic 5-ALA fluorescence consequently cannot be interpreted as histological absence of tumor [11, 15]. This limitation is particularly relevant during supramarginal resection. Fluorescence is highly useful as an intraoperative biomarker, but it does not provide a complete map of diffuse infiltration. The complementary nature of fluorescence and anatomical imaging is illustrated by recent work combining

5-ALA with intraoperative ultrasound. A 2025 study of high-grade glioma surgery reported complementary diagnostic performance between 5-ALA and ioUS, supporting the concept that biological fluorescence and updated anatomical imaging can compensate for different sources of error [10].

Intraoperative Imaging and the Brain-Shift Problem. Navigation based on preoperative MRI assumes that the brain remains geometrically stable. This assumption becomes progressively less valid after dural opening, cerebrospinal-fluid drainage, tumor debulking, osmotic therapy, and tissue deformation. Brain shift can make an anatomically accurate preoperative segmentation spatially inaccurate during later stages of resection. Intraoperative imaging addresses this problem by updating the surgical anatomy. In a randomized controlled trial, Senft et al. demonstrated that intraoperative MRI increased the probability of complete resection compared with conventional microsurgery in patients undergoing glioma surgery [9]. Intraoperative MRI provides high soft-tissue contrast but requires considerable infrastructure, operative time, specialized equipment, and workflow adaptation. Intraoperative ultrasound is more accessible, repeatable, comparatively inexpensive, and capable of real-time acquisition, although interpretation can be limited by acoustic artifacts, operator dependency, and reduced image quality after progressive resection [10, 31]. The future of ioUS is likely to involve AI-assisted interpretation. Rather than expecting every surgeon to acquire expert-level ultrasound pattern recognition, computer-vision algorithms may eventually provide real-time segmentation, confidence maps, and automatic registration with preoperative MRI. At present, however, prospective validation remains insufficient for autonomous clinical decision-making.

Table 1. Complementary intraoperative technologies in precision glioma surgery

Modality	Primary information provided	Major strength	Major limitation	Most appropriate role
Awake direct stimulation mapping	Functional necessity of cortex and white matter	Direct patient-specific functional testing	Requires cooperation and specialized team	Determining functional stopping boundary
5-ALA fluorescence	Metabolically active tumor	Immediate wide-field visual feedback	Reduced sensitivity in low-cellularity infiltration	High-grade tumor visualization
Intraoperative ultrasound	Updated anatomy	Real-time, repeatable, relatively accessible	Operator dependence and artifacts	Compensation for brain shift
Intraoperative MRI	Updated high-resolution anatomy	High soft-tissue contrast	Cost and workflow complexity	Residual tumor detection
Stimulated Raman histology	Label-free microscopic	Rapid tissue-level characterization	Requires tissue sampling and	Margin interrogation

	biochemical morphology		specialized optical system	
Confocal laser endomicroscopy	Cellular morphology	Near-real-time optical histology	Small field of view and variable image quality	Targeted optical biopsy
FastGlioma/AI-SRH	Probability and degree of tumor infiltration	Quantitative rapid inference	Clinical survival benefit not yet established	Margin classification
Nanopore methylation analysis	Molecular tumor identity	Rapid molecular classification	Sample quality and sequencing infrastructure	Intraoperative diagnostic refinement

Stimulated Raman Histology Changes the Meaning of an Intraoperative Margin. Conventional frozen-section pathology provides valuable intraoperative information but requires tissue transport, processing, freezing, sectioning, staining, and neuropathological interpretation. Sampling errors and freezing artifacts may reduce diagnostic confidence. Stimulated Raman scattering exploits molecular vibrational properties to generate label-free images of fresh tissue. The technique can produce virtual histological contrast reflecting lipids, proteins, cellularity, and tissue architecture without conventional fixation or staining [12, 13]. Orringer et al. demonstrated the feasibility of generating histology-like images of unprocessed neurosurgical tissue using stimulated Raman scattering microscopy [12]. Hollon et al. subsequently integrated stimulated Raman histology with deep neural networks and demonstrated near-real-time intraoperative brain-tumor diagnosis [13]. The major conceptual advance is that the surgeon can interrogate selected tissue at the resection interface rather than infer tumor probability exclusively from visual appearance or MRI signal. This is particularly relevant for diffuse gliomas because the clinically important question often is not whether the tumor core contains tumor, but whether a macroscopically normal-appearing marginal specimen contains a sufficiently high infiltrating-cell burden to justify further resection.

Artificial Intelligence and Quantification of Glioma Infiltration. DeepGlioma represented an early transition from AI-assisted histological diagnosis toward rapid molecular classification. Using stimulated Raman histology and deep learning, the system predicted key alterations defining adult diffuse glioma molecular categories. In a prospective international multicenter testing cohort of 153 patients, the reported mean molecular classification accuracy was approximately 93% [14]. FastGlioma moved the problem closer to the actual surgical margin. The visual foundation model was pretrained through large-scale self-supervised learning on approximately four million optical images and subsequently fine-tuned to quantify glioma infiltration in fresh, unprocessed surgical tissue [15]. In a prospective multicenter international cohort of 220 patients with diffuse glioma, FastGlioma achieved an average AUROC of 92.1 ± 0.9% for determining the degree of tumor infiltration. Performance remained high across centers, patient characteristics, and molecular subtypes, and the system outperformed conventional image-guided and fluorescence-guided adjuncts in a prospective head-to-head subgroup analysis [15]. Importantly, FastGlioma generates information in less than approximately 10 seconds after optical-image availability, making it conceptually compatible with operative decision cycles [15].

Nevertheless, diagnostic superiority must not be confused with demonstrated clinical superiority. FastGlioma has shown that microscopic infiltration can be classified rapidly and accurately. It has not yet demonstrated in a randomized trial that AI-guided extension of resection improves overall survival, neurocognitive outcome, or quality-adjusted survival. This distinction is essential. A perfect tumor detector cannot determine whether tumor-positive tissue should be removed if that tissue contains an indispensable language pathway. Therefore, AI should estimate tumor probability, whereas the neurosurgeon and functional-mapping system determine resectability.

Confocal Laser Endomicroscopy and Optical Biopsy. Confocal laser endomicroscopy offers a different route toward rapid intraoperative histology. Instead of removing tissue and generating a larger virtual slide, CLE can provide microscopic visualization of fluorescein-labeled tissue at cellular resolution. In a prospective multicenter assessor-blinded study involving 55 patients and 74 specimens, second-generation CLE achieved diagnostic accuracy of 89.2%, compared with 86.5% for frozen-section analysis. Sensitivity was 92.2% for both approaches, while the median diagnostic workflow was significantly faster with CLE [19]. A separate 2024 clinical trial reported an overall CLE diagnostic accuracy of 87% across intracranial lesions and approximately a tenfold reduction in processing time compared with frozen section [20]. AI-assisted CLE represents the next step. Deep-learning algorithms can filter non-diagnostic frames, identify tumor-associated morphology, and potentially provide near-real-time decision support [21]. However, CLE has an intrinsically restricted field of view, and tumor heterogeneity can create sampling bias. Accordingly, it is most appropriately conceptualized as targeted optical biopsy rather than a complete wide-field tumor-navigation system.

Rapid Molecular Classification During Surgery. Histological appearance alone is no longer sufficient for definitive classification of many CNS tumors. Molecular information can directly alter diagnosis, prognosis, expected natural history, and sometimes surgical strategy [1, 18, 33]. Rapid nanopore sequencing provides a potential solution because DNA molecules can be analyzed continuously during sequencing rather than after completion of a conventional sequencing run. Djirackor et al. demonstrated that intraoperative DNA methylation classification could influence neurosurgical strategy [18]. Vermeulen et al. subsequently developed Sturgeon, a deep-learning framework using sparse methylation information obtained through rapid nanopore sequencing for intraoperative CNS-tumor classification [16]. More recently, Brändl et al. introduced MethyLYZR for classification from sparse epigenomic data, further supporting the feasibility of live molecular diagnosis during neurosurgical workflows [17]. These approaches have important implications for surgery. The value is not limited to confirming that a lesion is a “glioma.” Rapid recognition of a specific molecular category may influence how aggressively an uncertain lesion should be approached, whether additional tissue should be sampled, how tissue should be allocated for downstream studies, and whether the intraoperative diagnosis is discordant with the preoperative assumption. The strongest future model will likely combine optical histology and molecular sequencing rather than regard them as competitors. SRH can provide rapid spatially resolved morphological information, whereas nanopore profiling provides molecular identity.

Table 2. Proposed molecular–functional surgical phenotypes

Surgical phenotype	Biological pattern	Functional context	Preferred surgical objective

IDH-mutant grade 2, non-eloquent	Long expected disease course, diffuse FLAIR infiltration	Low functional cost of extended resection	Consider functionally verified supramaximal resection
IDH-mutant grade 2, eloquent	Diffuse infiltration with favorable biology	High language/motor/cognitive network overlap	Mapping-defined maximal safe resection
IDH-wild-type glioblastoma, compact enhancing	Aggressive enhancing tumor	Functionally permissive location	Complete CE resection with evaluation of NCE compartment
IDH-wild-type glioblastoma, network-integrated	Aggressive biology with functional connectivity	Major eloquent overlap	Preserve network integrity despite residual microscopic disease
Radiologically ambiguous diffuse lesion	Molecular identity uncertain	Variable	Tissue diagnosis integrated with rapid molecular classification
Recurrent glioma	Therapy-related change mixed with viable tumor	Previously altered anatomy and networks	Target viable tumor using multimodal biological confirmation

Proposed Precision Surgical Boundary. The findings support a model in which the surgical boundary is not represented by a single line. Instead, three partially overlapping boundaries coexist. The first is the radiographic boundary, defined by contrast enhancement, FLAIR abnormality, diffusion, perfusion, metabolic imaging, and intraoperative anatomical updating. The second is the biological boundary, defined by fluorescence, SRH, CLE, molecular assays, and AI-derived probability of infiltrating tumor. The third is the functional boundary, defined by direct stimulation, neurophysiology, patient performance during awake surgery, white-matter architecture, and the anticipated neurological cost of additional resection. The precision surgical endpoint occurs where the expected oncological value of removing additional biologically abnormal tissue becomes lower than the expected functional cost. This can be conceptually expressed as a clinical decision function rather than a fixed anatomical margin: Continue resection when expected oncological benefit > expected permanent functional harm. The equation is not numerically validated, but it provides a useful framework. Both terms are patient-specific. A 32-year-old patient with an IDH-mutant grade 2 astrocytoma and a large functional reserve may rationally accept a different resection strategy from a 76-year-old patient with IDH-wild-type glioblastoma, limited performance status, and corticospinal tract invasion.

Proposed Prospective Study. A future trial should evaluate whether multimodal biological margin assessment actually improves meaningful patient outcomes rather than merely diagnostic

accuracy. A prospective multicenter study could include adults undergoing resection of newly diagnosed diffuse glioma. All patients would receive contemporary standard surgery including neuronavigation, intraoperative neurophysiology, and awake mapping when indicated.

The experimental group would additionally undergo systematic SRH/AI sampling of the intended final resection margin. Importantly, AI-positive tissue would not automatically be removed. Resection would continue only when functional mapping and anatomical assessment indicated acceptable neurological risk. The control group would undergo identical surgery without disclosure of AI-SRH infiltration scores. The primary endpoint should be a composite of residual biologically active tumor volume and absence of new permanent neurological deficit at 90 days. Secondary endpoints should include conventional MRI-defined extent of resection, postoperative neurocognition, return to work, quality of life, progression-free survival, overall survival, adjuvant-treatment completion, and cost-effectiveness. Such a design would answer a clinically relevant question: whether knowing more about microscopic tumor at the operative boundary actually allows surgeons to improve the balance between oncological control and function.

Table 3. Proposed prospective trial of precision-guided glioma resection

Study component	Proposed design
Population	Adults with newly diagnosed resectable diffuse glioma
Design	Prospective multicenter randomized or pragmatic controlled trial
Standard arm	Navigation + functional mapping ± 5-ALA ± ioUS/iMRI according to indication
Precision arm	Standard arm + systematic SRH/FastGlioma margin interrogation
Primary endpoint	Biologically adjusted residual tumor with no permanent neurological deterioration at 90 days
Secondary endpoints	MRI EOR, neurocognition, GOS/KPS, QoL, PFS, OS, return to work
Molecular stratification	IDH, 1p/19q, ATRX, CDKN2A/B, MGMT and other entity-specific markers
Safety rule	Functional mapping overrides AI-predicted tumor positivity
Follow-up	Early postoperative MRI, 3, 6, 12, and 24 months
Central hypothesis	Biological margin information improves oncological completeness only when integrated with functional-risk mapping

Discussion. The principal finding of this review is that the concept of maximal safe resection remains valid, but the definition of both “maximal” and “safe” has become substantially more sophisticated. Historically, maximum resection was determined visually. The introduction of MRI transformed this into radiographically defined resection. Fluorescence then added a biological signal. Intraoperative imaging corrected navigation drift. Awake mapping provided patient-specific functional boundaries. Optical histology and artificial intelligence now introduce microscopic infiltration probability into the same operative environment [4, 9, 13, 15]. The result is not simply a larger collection of surgical tools. It is a change in the epistemology of surgery: the neurosurgeon can increasingly ask different technologies different questions.

MRI asks where abnormal tissue is located anatomically.

5-ALA asks where metabolically fluorescent high-grade tumor is present.

ioUS asks where the lesion and resection cavity are after the brain has shifted.

Direct stimulation asks whether a structure is indispensable for function.

SRH and CLE ask what tissue is present at the microscopic level.

AI asks how likely that tissue is to represent tumor or a specific infiltration grade.

Nanopore sequencing asks what molecular entity is being treated.

None of these technologies provides the complete answer independently.

FastGlioma is particularly illustrative. Its prospective international validation represents a substantial methodological advance because the algorithm was not restricted to an internal retrospective image dataset. In 220 patients, the model maintained high performance across institutions and molecular glioma subtypes [15]. Yet the correct interpretation is not that AI should instruct the surgeon to continue cutting until all samples become negative. Diffuse gliomas can invade functionally indispensable brain. The histological presence of tumor is not equivalent to surgical expendability. This distinction becomes even more important in light of increasing evidence that glioma and neuronal networks interact biologically. High-grade glioma cells can integrate with neuronal activity, and functionally connected tumor regions may exhibit distinct biological behavior [22]. The surgical field is therefore simultaneously oncological and neurophysiological. Supramaximal resection must be interpreted in the same framework. The favorable associations reported in IDH-mutant lower-grade glioma should not be converted into a simplistic recommendation to remove a predetermined centimeter of tissue around every FLAIR lesion [7, 8]. “Supramaximal” should mean resection beyond conventional imaging boundaries when functional mapping demonstrates that such extension is neurologically acceptable. The 2025 RANO resect data provide a particularly important advance because they attempt to standardize the surgical vocabulary in molecularly defined IDH-mutant grade 2 disease rather than treating all lower-grade gliomas as biologically equivalent [8]. For glioblastoma, the problem differs. The infiltrative field is much broader and microscopic eradication by surgery is biologically unrealistic. Therefore, the operative objective is aggressive cytoreduction of safely accessible high-density tumor while preserving functional reserve for radiochemotherapy and subsequent treatment [2, 5, 28]. This distinction illustrates why a single universal metric such as “100% resection” is misleading. One hundred percent of contrast enhancement, one hundred percent of FLAIR abnormality, and one hundred percent of biologically infiltrated tissue represent entirely different surgical concepts. Another major finding is that intraoperative diagnosis is rapidly moving from morphology toward integrated molecular pathology. DeepGlioma, Sturgeon, MethyLYZR, and related methods demonstrate that clinically relevant molecular information can increasingly be generated within an operative time frame [14, 16–18]. This may be particularly valuable in diagnostically ambiguous lesions. If rapid molecular classification demonstrates that the preoperative assumption is incorrect, surgical strategy might be modified before closure rather than days after final pathology. However, the introduction of AI creates new methodological and ethical problems. Training data may not represent different populations, scanners, operative workflows, or uncommon molecular entities. Models may become overconfident under distribution shift. Accuracy measured at the image level may exaggerate patient-level performance. A system that performs well in a tertiary academic center may fail after transfer to a different tissue-preparation protocol. Consequently, future intraoperative AI

should display calibrated probabilities rather than categorical statements and should be able to abstain when confidence is insufficient. The most important future innovation may therefore not be another isolated device but a multimodal decision-support architecture. Such a platform could simultaneously display updated ioUS anatomy, cortical and subcortical stimulation sites, tract proximity, fluorescence intensity, SRH-derived tumor probability, and molecular information. The surgeon would remain responsible for the final decision, but the information burden would be transformed from fragmented screens into a unified patient-specific representation.

Limitations. The present review has several limitations. It is a structured narrative review rather than a formal systematic review or meta-analysis. Technologies were deliberately integrated across different levels of evidence, from randomized trials to proof-of-concept translational studies. The evidence supporting greater extent of resection is predominantly observational and therefore subject to selection bias. Patients whose tumors are more resectable often differ systematically from those with deeply infiltrative or functionally critical tumors. Similarly, associations between supramaximal resection and survival cannot prove that extending resection itself is entirely responsible for improved outcome. The strongest evidence for 5-ALA and intraoperative MRI comes from randomized studies [4, 9], whereas evidence for AI-SRH, CLE, and rapid nanopore classification is primarily diagnostic. These technologies should therefore not yet be assumed to improve survival merely because they improve tissue classification. Finally, molecular classifications and adjuvant therapeutic options continue to evolve. The clinical value of extensive resection may change as more effective targeted therapies become available for specific molecular glioma subgroups.

Conclusion. Diffuse glioma surgery is entering a precision era in which the surgical boundary can no longer be defined by preoperative MRI alone. Increasing extent of resection remains associated with improved oncological outcome, but the appropriate degree of cytoreduction differs according to molecular subtype, age, residual tumor compartment, functional anatomy, and expected natural history. In IDH-mutant grade 2 gliomas, functionally verified supramaximal resection appears increasingly relevant and has been associated with favorable long-term oncological outcomes [7, 8]. In glioblastoma, maximal resection of contrast-enhancing tumor remains a core objective, while removal of additional non-enhancing disease may provide benefit in selected patients when neurological safety permits. Awake cortical and subcortical mapping defines the functional limit of surgery. 5-ALA provides rapid metabolic visualization, while ioUS and iMRI compensate for intraoperative brain shift. Stimulated Raman histology and confocal laser endomicroscopy introduce microscopic tissue characterization into the operative workflow. FastGlioma represents a major advance by enabling rapid quantitative assessment of glioma infiltration with high diagnostic performance across a prospective multicenter cohort. DeepGlioma, Sturgeon, MethyLYZR, and nanopore sequencing further demonstrate that intraoperative decision-making can increasingly incorporate molecular identity rather than waiting for postoperative integrated pathology. The future surgical endpoint should therefore be conceptualized as a precision surgical boundary arising from the intersection of radiographic abnormality, biological tumor probability, and functional resectability. Artificial intelligence should not determine whether tissue is removed. Its role should be to reduce uncertainty about what the tissue represents. Functional mapping should remain capable of overriding biological positivity when removal carries an unacceptable neurological cost. The final objective of

modern glioma surgery is consequently not the largest possible resection. It is the largest biologically meaningful resection compatible with preservation of the patient's individualized neural networks and long-term functional independence.

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