Preoperative and intraoperative neuromonitoring and mapping techniques impact oncological and functional outcomes in supratentorial function-eloquent brain tumours: a systematic review and meta-analysis

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Summary

Background Supratentorial function-eloquent brain tumour surgeries challenge the balance between maximal tumour resection and preservation of neurological function. This study aims to evaluate the efficacy of preoperative and intraoperative mapping techniques on resection outcomes and post-operative deficits.

Methods This systematic review and meta-analysis examined literature up to March 2023, sourced from PubMed, Embase, and Medline. Criteria for inclusion were studies on patients undergoing surgery for supratentorial brain tumours, comparing preoperative mapping only (POM), intraoperative neuromonitoring and mapping (IONM), and combined techniques (POM&IONM), excluding non-randomized controlled trials. Data extraction focused on rates of gross total resection (GTR) and focal neurological deficits (FNDs). The main outcomes, assessed through a random-effects model and Cochran's Q-test for subgroup analysis. The study protocol is published on PROSPERO CRD42024512306.

Findings 19 studies involving 992 patients were included. Systematic review with meta-analysis revealed a non-significantly higher average GTR rates for POM&IONM (49.13%) and POM (50.79%) compared to IONM alone (41.23%). Highest rates of GTR were achieved with tractography-guided resection in POM group (66.59% versus fMRI–20.00%, $p = 0.0004$), multimodal stimulation in IONM group (54.16% versus low frequency stimulation (LFS)–13.29%, $p < 0.0001$) and in POM&IONM group (65.88% versus LFS–37.77%, $p = 0.0036$). Within the same tumour histology–metastasis, high grade and low grade glioma–there are no differences in the GTR rates achieved in the different groups ($p > 0.05$). In language-eloquent tumours and in awake craniotomy techniques regardless of tumour functional eloquence, POM&IONM group had higher GTR when compared to IONM groups (language eloquent tumours–POM&IONM 43.31% versus IONM–15.09%, $p = 0.022$; awake craniotomy technique–POM&IONM–41.22% versus IONM–12.08%, $p = 0.0006$). Permanent FNDs were higher in the IONM group (IONM-73.0%; POM-29.6%; POM&IONM-33.7% of immediate postoperative deficits, $p = 0.0010$).

Interpretation A combined POM&IONM approach is responsible for higher rates of GTR in patients with language eloquent tumours and in both awake and asleep craniotomy techniques regardless of the tumour functional eloquence. The tumour histology is not relevant for differences in GTR rates among different mapping and monitoring strategies. Permanent postoperative FNDs are more likely with standalone utilization of IONM.

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Abbreviations: GTR, Gross total resection; POM, Preoperative mapping; IONM, Intraoperative neuromonitoring; POM&IONM, Preoperative mapping and intraoperative neuromonitoring; HFS, High-frequency stimulation; LFS, Low- frequency stimulation; nTMS, Navigated transcranial magnetic stimulation; fMRI, Functional magnetic resonance imaging; EoR, Extent of resection; FND, Focal neurological deficit

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Keywords: Intraoperative neuromonitoring; High-frequency stimulation; Low- frequency stimulation; Navigated transcranial magnetic stimulation; Functional magnetic resonance imaging; Tractography; Extent of resection; Focal neurological deficit

Research in context

Evidence before this study

Preoperative mapping (POM) and intraoperative neuromonitoring (IONM) techniques are increasingly utilized to enhance the extent of resection (EoR) in supratentorial brain tumors while minimizing neurological deficits. Existing literature highlights the efficacy of individual modalities like tractography and direct cortical stimulation (DCS) but lacks comprehensive comparative data on their combined use. Meta-analyses to date have focused on isolated outcomes, without integrating the implications for functionally eloquent areas.

Added value of this study

This systematic review and meta-analysis synthesized data from 19 studies comprising 992 patients to compare POM, IONM, and their combination (POM&IONM). The findings demonstrate that combined techniques improve gross total resection rates and reduce permanent neurological deficits, particularly in language-eloquent tumors and awake craniotomies. Specific modality combinations, such as nTMS with tractography and DCS, showed superior outcomes, offering actionable insights for clinical practice.

Implications of all the available evidence

The integration of POM and IONM optimizes onco-functional balance by maximizing resection while preserving neurological function, particularly in eloquent brain areas. Combined approaches enable better preoperative planning and real-time intraoperative decision-making. These findings advocate for adopting multimodal techniques, tailored to individual patient and resource contexts, to improve surgical outcomes in neuro-oncology.

Introduction

More than 12,000 individuals in the UK and around 350, 000 individuals worldwide are diagnosed with brain tumours annually,[1,2] most commonly supratentorial intracranial tumours in the parietal, frontal and temporal lobes.[3] Despite advancements, prognosis and overall survival remain poor. Treatment often involves surgical resection in conjunction with adjuvant oncology treatment. Maximising the extent of resection (EoR) whilst preserving eloquent areas have demonstrably improved life expectancies and overall survival rates in glioblastomas (GBM),[4] low grade gliomas (LGG)[5,6] and metastases.[7] Therefore, preoperative mapping (POM) and intraoperative neuromonitoring and mapping (IONM) techniques have become paramount in brain tumour surgery, aiding in the identification of eloquent areas, image-based grading and histological phenotyping.[8]

Among POM techniques, functional magnetic resonance imaging (fMRI) is popular cortical mapping technique as it significantly reduces permanent postoperative neurological deficits, mortality and morbidity.[9,10] However, fMRI has reduced specificity compared to intraoperative techniques such as direct cortical stimulation (DCS).[11] Preoperative navigated transcranial magnetic stimulation (nTMS) demonstrates similar accuracy compared to DCS particular in the cortical localization of the functional upper limb area, potentially increasing the extent of resection (EoR) in motor-eloquent brain tumours whilst reducing deficits.[12,13] Nevertheless, this technique fails to achieve similar results when the functional areas of the leg and language are considered.[14] Preoperative tractography is the only available technique that allows for *in vivo* subcortical dissection, increasing the safety of surgical resection in eloquent tumours.[15] Nevertheless, it is limited by artefacts that are minimized by multiple algorithms and its intraoperative accuracy is hampered by brain shift and deformation.[16]

IONM techniques are increasingly adopted in eloquent brain tumour surgery. DCS and subcortical stimulation are the gold-standard methods[13,17,18] with the potential to maximise EoR whilst minimizing functional deficits, providing real-time information about functional boundaries. Intraoperative tractography can provide real time information about the integrity and distance to eloquent subcortical matter,[16] accounting for brain shift and deformation unlike preoperative tractography but it is restricted by limited intraoperative MRI availability, increased operative time and costs.[19–22]

A personalized onco-functional balance is crucial to maximise EoR whilst preserving quality of life[23] as post-surgical complications are strongly associated with longer length of stay, increased hospital costs and greater risk of other comorbidities and mortality.[24] Also, they have a negative impact in the adjuvant oncological treatment and therefore in the overall outcome of the oncological disease.[25] However, controversy exists between the best way to achieve this delicate balance. POM, IONM or a combination of both

techniques are appealing approaches with different additional benefits but with limitations in their real-world application due to availability, cost and expertise.[26–28] Therefore, the aim of this systematic review and meta-analysis is to understand the implications of the different mapping and monitoring techniques in the extent of resection and postoperative neurological deficits.

Methods

Registration and reporting standards

We performed this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1: Prisma). The study protocol is published on PROSPERO CRD42024512306.

Search strategy

A comprehensive literature search was performed using Pubmed, OVID, Medline and EMBASE from database inception to 13th March 2023. Our search returned 3894 records, of which 19 articles including 22 cohorts of 992 patients met our inclusion criteria.

Eligibility criteria

We sought patient cohort data based on case series, published in English in peer-reviewed journals reporting adult (age>18 years old) patients presenting with supratentorial tumours managed with surgical intervention and the use of POM, intra-operative neuromonitoring and mapping (IONM) or a combination of both (POM&IONM). Biopsies, posterior fossa tumours and paediatric cases were excluded. We reviewed the bibliographies of included studies for further patient cohort data meeting our eligibility criteria. The outcome measures were EoR and new postoperative focal neurological deficit (FND).

Study selection

Three investigators (N.R, E.M, A.A) independently screened all titles and abstracts for eligibility. The full text of eligible studies was reviewed for inclusion. A.V acted as a mediator in cases of disagreement.

Data extraction

Data extraction was performed independently by two authors (AO and EM) from each unique study cohort to ensure consistent extraction of patient, tumour and

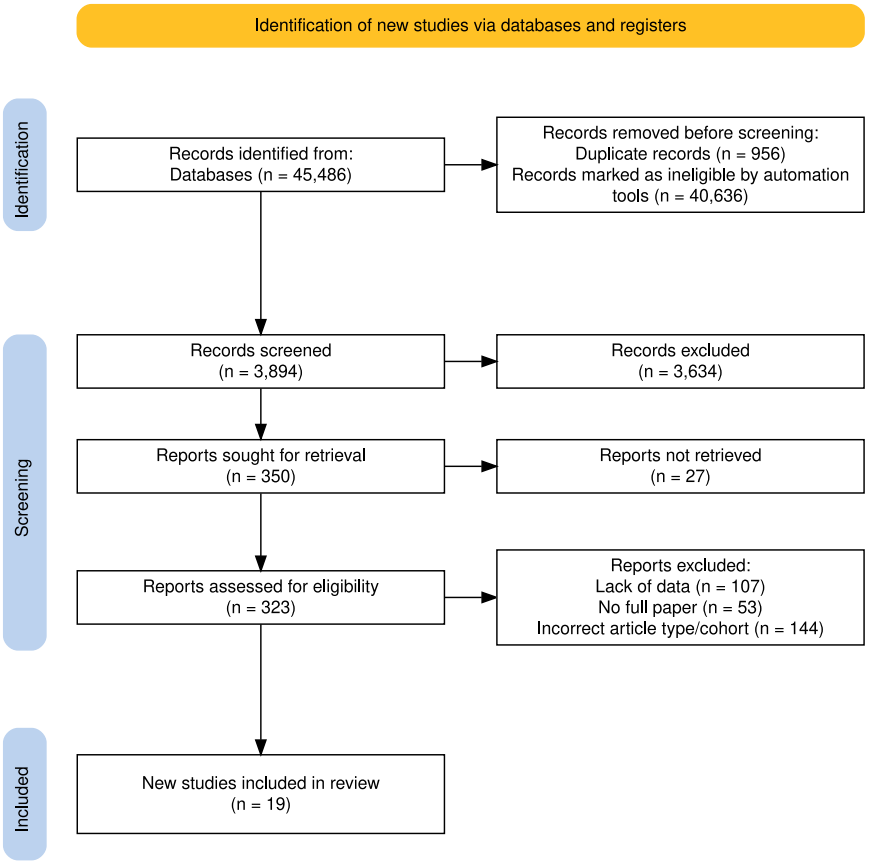

Fig. 1: PRISMA Flow chart.

treatment characteristics. The data points extracted are displayed in (Table 1).

Risk of bias

We used the NHLBI Study Quality Assessment Tools[29] to assess for low validity of results or any subsequent bias. If there was a high risk of bias, they were excluded after an independent review A.V. and A.B.M).

Statistical analysis

Data collection was performed in Microsoft Excel (Version 16.76) with data manipulation and statistical analysis performed in RStudio using the meta, dmetar and metafor libraries (Version: 4.2.3). Articles selected for pooled quantitative analysis were those which met inclusion criteria and detailed EoR. GTR was defined as those articles which explicitly categorised resection as GTR or if a value of 100% EOR was given. Outcome data was dichotomised into GTR or Non-GTR and mean percentage rate of GTRs for each article as well as pooled estimates were calculated. Meta-analyses were reported against the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Significant Heterogeneity was determined via the I^2 test as a measure of between-study effect size variability, τ^2 as a measure of between-study variance and Cochran's Q statistic as a measure of differences in calculated effect sizes compared to fixed model estimates (p-value <0.05). When significant heterogeneity was present, the random-effects model was used for meta-analysis through the inverse variance, restricted maximum-likelihood estimator approach using the DerSimonian-Laird (DSL) method.

Article characteristics	Patient cohort characteristics	Tumour characteristics
No. of Individual Articles = 19	Total Number (n = 22) = 992	Tumour Laterality (n = 12) • Left Sided = 54.6%
No. of Patient Cohorts Investigated = 22	Sex (n = 18) = 55.8% Male Mean age (n = 17) = 49.2 (±SD 8.43)	WHO Grade (n = 667) • 3 & 4 = 62.2% • 1 & 2 = 37.8%
Publication Location (n = 19) • Europe = 11 • North America = 6 • Asia = 2	Pre-Operative Deficit at Presentation (n = 13) • Any Deficit (n = 13) = 39.2% • Motor Deficit (n = 11) = 35.6% • Language Deficit (n = 10) = 15.0% • Visual Deficit (n = 8) = 6.0% • Seizures (n = 8) = 36.2%	Tumour Type (n = 464) • GBM = 39.2% • Metastasis = 29.7% • Oligodendroglioma = 9.1% • Astrocytoma = 19.2% • Other = 2.8%
Year of Publication (n = 19) • 2014–Present = 8 • 2004–2014 = 9 • Prior to 2004 = 2	Left Sided Dominance (n = 3) = 100%	Tumour Location (n = 696) • Frontal = 41.7% • Insular Centred = 28.7% • Parietal = 18.7% • Temporal = 8.2% • Other = 4.4%

SD = Standard Deviation, WHO = World Health Organisation, GBM = Glioblastoma Multiforme.

Table 1: **Characteristics of included articles, patients and tumour types.**

In situations where subgroup analyses featured <10 studies, the Hartung-Knapp-Sidik-Jonkman (mHKSJ) method was utilised, adjusting τ^2 estimates for small sample bias with the Sidik-Jonkman Estimator and adjusting confidence intervals with a t-distribution to minimise Type I errors. Cochran's Q statistic was deemed significant when p-value <0.10 in such scenarios to avoid Type II errors. % Mean GTRs extracted from each study were transformed using the Arcsine Square Root technique to account for extremes and stabilise variances calculated, with estimates back-transformed for interpretability. Shapiro Wilk testing was performed post-hoc to confirm normality of study estimates.

Publication bias was assessed using contour-enhanced funnel plots comparing the log odds of changes in % GTR against study size, with Egger's test used to confirm findings. Sensitivity analysis involved: Influence Analysis, Leave-out Meta Analysis and Graphical display Of Study Heterogeneity (GOSH). Grouped effect sizes were compared to each other via Cochran's Q-test between groups and within groups via subgroup meta-analysis.

Data on Focal Neurological Deficits (FND) was also extracted, including a compilation of all motor, visual and language deficits recorded in patients post-operatively. This did not include any neuro-cognitive deficits due to the lack of data to enable for comparisons to be made. Due to the substantial heterogeneity in the reporting of FNDs across studies, a meta-analysis could not be performed. Instead, this was analysed holistically with a combination of Pearson's Chi-Square (X^2) and Fisher's exact tests (if expected values < 5), identifying independence between categorical variables with odds ratios (OR) with 95% confidence intervals (CI) were calculated. Values were considered significant if $p < 0.05$ and Pearson's residuals were explored to determine cause of significance across multiple groups.

Role of the funding source

No funding was received for the production of this manuscript.

Results

A total of 992 patients were identified from 22 patient cohorts across 19 research articles. A summary of article, patient and tumour characteristics can be found in Table 1.

All 22 cohorts documented IONM, POM or POM&IONM with a total of 505 GTRs achieved across 992 patients included (50.91%). Overall heterogeneity was significant (I^2 = 91.7% [95% CI: 88.8%–93.9%], τ^2 = 0.042 [95% CI: 0.021–0.089], Q(21) = 252.90, p-value <0.0001). Overall, no publication bias was detected in primary analysis (b = 0.5532, [95% CI: 0.3370–0.7696], z = –0.7086, p = 0.48) (Supplementary Figure S1).

Following Arcsine Square Root Transformation, all proportions reported followed a normal distribution (Supplementary Table S1). Sensitivity Analyses revealed no studies were significant outliers and did not heavily influence between-study heterogeneity observed on their own (Supplementary Figures S2–S5, Table 2). Following random-effects meta-analysis, average GTR rate was calculated as 49.13% [95% CI: 37.78%–60.53%] in POM&IONM, 50.79% [95% CI: 20.76%–80.51%] in POM and 41.23% [95% CI: 19.51%–64.92%] in IONM overall across studies. However, no significant difference in GTR likelihood amongst POM, IONM and POM&IONM was found following adjustments for study-level and subgroup-level heterogeneity (Q(2) = 0.38, *p*-value = 0.83) (Fig. 2).

Preoperative and intraoperative mapping and monitoring techniques

The studies were analysed according to the specific submodality.

In POM group, tractography resulted in a GTR rate of 66.59% [95% CI: 50.84%–80.64%], significantly higher than fMRI with 20.00% likelihood [95% CI: 5.86%–39.81%] (Q(1) = 12.54, *p*-value = 0.0004) (Fig. 3a).

In the *IONM* and POM&IONM *groups*, the techniques were divided according to the IONM paradigm of stimulation used in:

1. Low-Frequency Stimulation mapping (LFS, Penfield Technique)
2. High-Frequency Stimulation (HFS, Taniguchi Technique)
3. Multimodal (more than one IONM technique, including HFS)

IONM stimulation technique significantly impacts GTR likelihood in IONM (Q(2) = 30.78, $p \leq 0.0001$) and POM&IONM (Q(2) = 11.27, $p = 0.0036$) groups. In both cases, Multimodal approaches produced the highest GTR likelihood (IONM only: 54.16% [95% CI: 4.46%–98.34%]; POM&IONM: 65.88% [95% CI: 40.44%–87.19%]) whilst LFS had the lowest likelihood of achieving GTR [IONM only: 13.29% [95% CI: 8.24%–19.32%]; POM&IONM: 37.77% [95% CI: 26.00%–50.31%]) (Fig. 3b).

Specific combinations of POM and IONM were analysed amongst the *POM&IONM group* according to their report in the literature.

1. fMRI and DCS (fMRI + DCS)
2. Pre and Intraoperative tractography (Tract + ITract)
3. fMRI + tractography and DCS (fMRI + Tract + DCS)
4. Tractography and DCS (Tract + DCS)
5. nTMS and DCS (nTMS + DCS)
6. fMRI + nTMS + Intraoperative Tractography + DCS (fMRI + nTMS + ITract + DCS)

Following meta-analysis, fMRI + nTMS + ITract + DCS achieved the highest GTR rate of 63.64% [95% CI: 34.52%–88.13%], significantly greater than all other combinations (Q(5) = 18.83, *p*-value = 0.0021) (Fig. 3c).

Histology

Tumour histology had no significant impact on GTR likelihood among the groups. For metastasis, GTR was achieved in 93.50% of patients with POM&IONM [95% CI: 66.34%–100.00%], similar to IONM–84.78% [95% CI: 2.88%–100.00%], (Q(1) = 0.88, *p*-value = 0.35) (Supplementary Material S7A). No differences were observed between groups neither in high grade glioma (Q(2) = 0.55, *p*-value = 0.76)–POM&IONM—GTR in 43.97% [95% CI: 29.21%–59.31%] versus POM—GTR in 52.24% [95% CI: 34.20%–69.98%] and IONM—GTR in 49.71% [95% CI: 40.18%–59.26%] (Supplementary Material S7B)—nor in low grade glioma (Q(2) = 2.45, *p*-value = 0.29)–POM&IONM—GTR in 47.08% [95% CI: 8.40%–88.09%] versus IONM–GTR in 14.29% [95% CI: 8.84%–19.87%] and POM—GTR in 14.29% [95% CI: 1.57%–36.58%])—trend towards a higher rate in POM&IONM but no statistical significance is reached (Supplementary Material S7C).

Motor versus language eloquent tumours

In motor-eloquent tumours, POM&IONM achieved a slightly higher but non-significant GTR rate of 47.46% [95% CI: 30.68%–64.54%] when compared with IONM [GTR—37.71%, 95% CI: 16.89%–61.25%], (Q(1) = 0.43, *p*-value = 0.51) (Fig. 4a). In language-eloquent tumours, POM&IONM achieved significantly higher GTR likelihood of 43.31% [95% CI: 8.27%–82.94%], than IONM

Monitoring modality	n	New deficit	No deficit	% deficit		n	Transient	Permanent	% permanent		n	Motor	Language
POM (n = 2)	143	27	116	18.9	POM (n = 2)	27	19	8	29.6	POM (n = 1)	4	4	0
IONM (n = 4)	194	37	157	19.07	IOM (n = 4)	37	10	27	73.0	IOM (n = 2)	8	5	3
P&IOM (n = 10)	375	88	287	23.5	P&IOM (n = 6)	83	55	28	33.7	P&IOM (n = 4)	35	24	11
X^2 = 2.1192, df = 4, p-value = 0.71					X^2 = 18.452, df = 4 p-value = 0.0010					*p-value = 0.83*^{F}			

POM = Preoperative Monitoring, IOM = Intraoperative monitoring, P&IOM = Pre- & Intraoperative monitoring, X^2 = Chi Square test, ^{F} = Fisher's exact test, OR = Odds Ratio.

Table 2: **Overall monitoring modality and postoperative deficit rate, time course & type.**

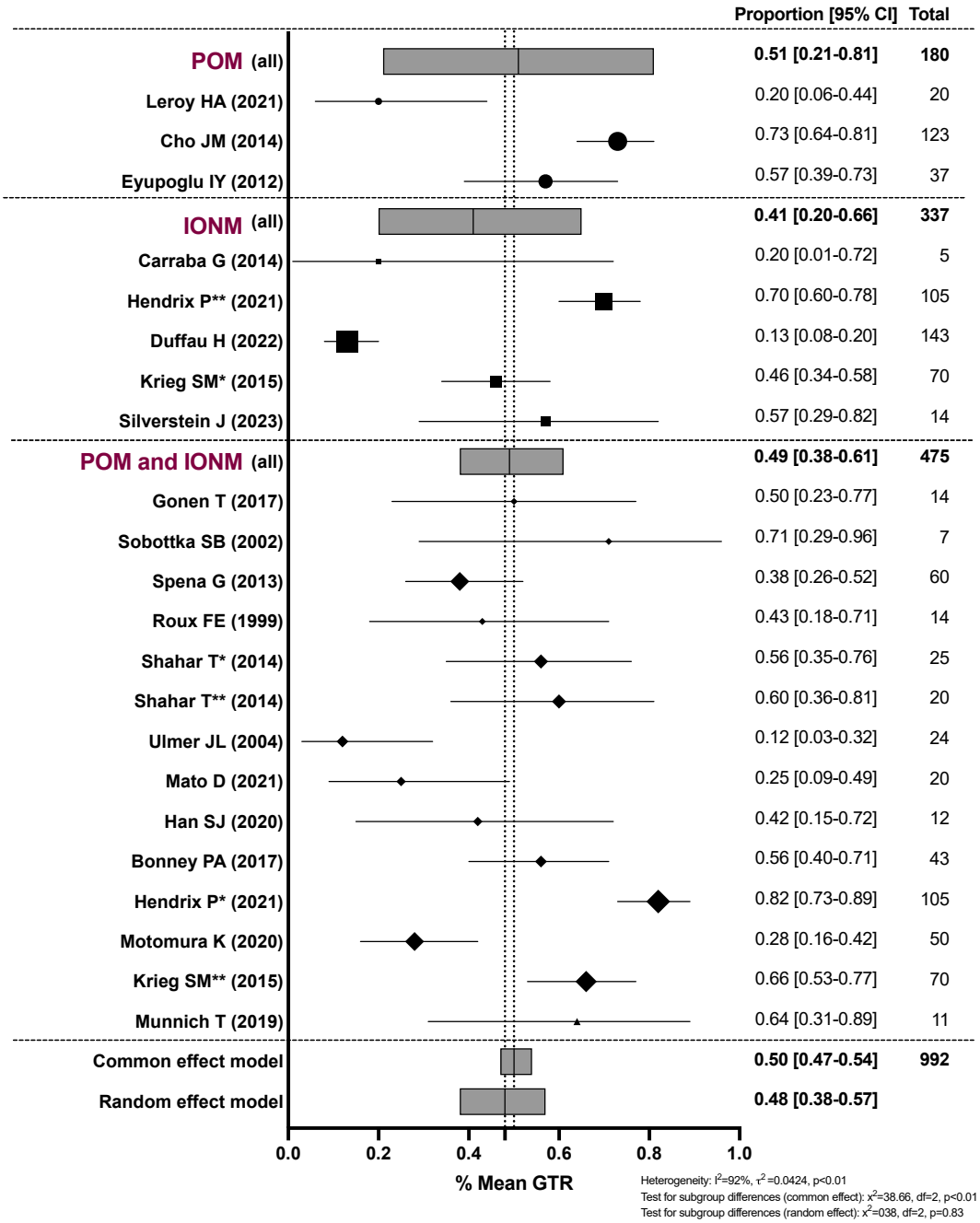

Fig. 2: Multimodal imaging and monitoring for glioma surgery with intraoperative neuronavigation and IONM. Forest plot summarizing the gross total resection (GTR) rates based on the use of intraoperative neuromonitoring (IONM) alone, POM (preoperative mapping) combined with IONM, and POM alone. Proportions and confidence intervals (CI) are shown for individual studies and pooled estimates.

[GTR—15.09%, 95% CI: 5.15%–29.04%], Q(1) = 5.22, *p*-value = 0.022] (Fig. 4b).

Asleep versus awake surgery

Performing surgical procedures awake significantly affected choice of neuromonitoring irrespectively of the functional eloquence at risk. When awake, POM&IONM performed significantly better at achieving GTR of 41.22% [95% CI: 31.70%–51.07%] compared to IONM only at 12.08% [95% CI: 0.00%–99.92%], (Q(1) = 11.70, *p*-value = 0.0006). With asleep surgery, POM&IONM achieved the highest GTR rate of 36.82% [95% CI:

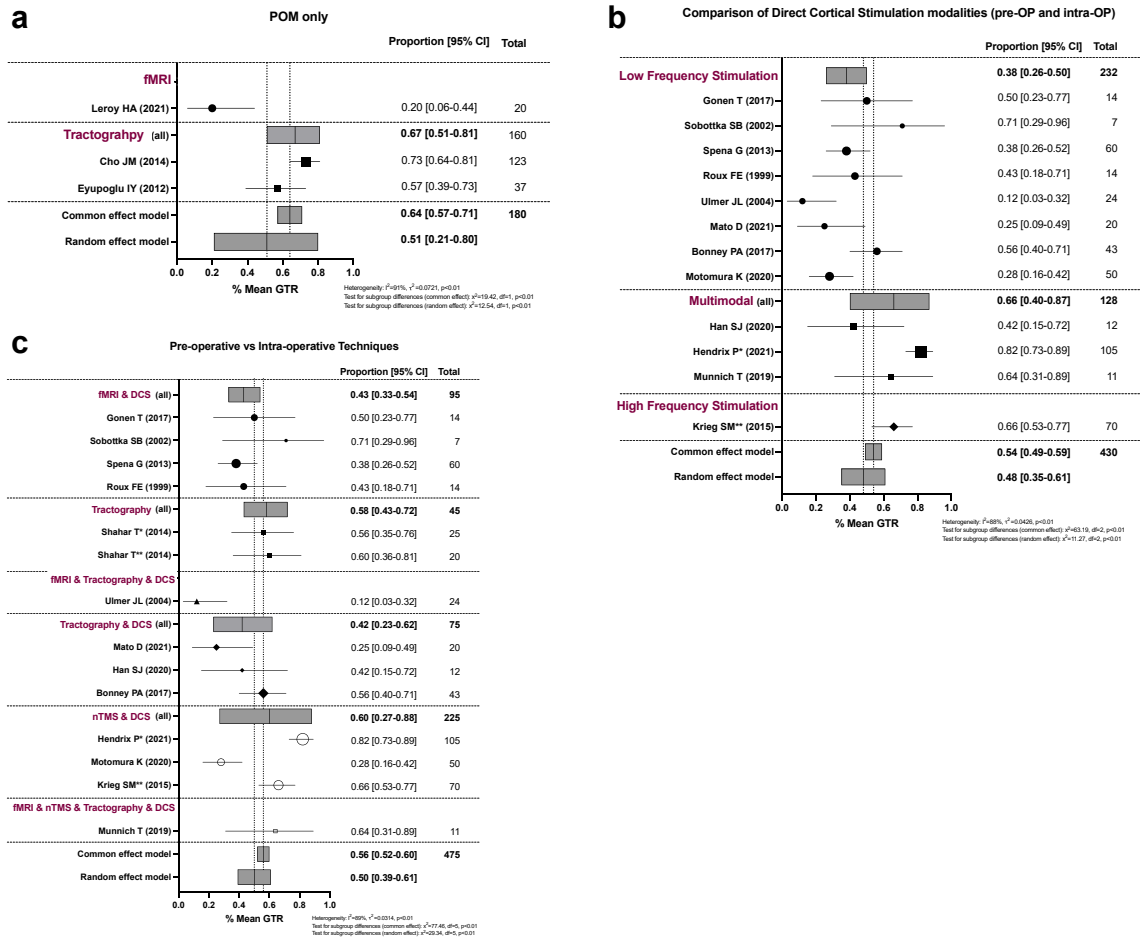

Fig. 3: (a) Forest plots showing GTR rates in patients undergoing surgery with different POM only approaches. (b) Forest plots showing GTR rates amongst different IONM stimulation types within the POM&IONM and IONM only subgroups. (c) Forest plot showing GTR rates amongst different combinations of POM&IONM used.

7.17%–73.76%], compared to IONM [GTR—29.15%, 95% CI: 0.00%–89.82%] and POM [GTR—38.21%, 95% CI: 0.00%–100%], however this was not found to be significantly different (Q(2) = 0.20, *p*-value = 0.90) (Fig. 4c).

Mixed-effects, identity-linked meta-regression was performed on the previously arcsine transformed primary meta-analysis to explore potential sources of heterogeneity, using the Random Effects Maximum Likelihood (REML) estimator of τ^2, with overall modality choice, type of POM and IONM as predictors of GTR likelihood as the outcome. Variable selection was dependent on data availability from all studies. The assumption of normality was verified using Shapiro–Wilk Tests, Q–Q plots of random effects terms and multicollinearity was checked for using Variance Inflation Factors (VIFs). Residuals of the models were plotted to visually assess for homoscedascity (Supplementary Data, Tables S3A and 3B).

Univariate meta-regression illustrated overall modality choice (POM versus IONM versus POM&IONM) was a poor moderator accounting for between-study heterogeneity within the primary meta-analysis (QM(2) = 0.4760, *p*-value = 0.79, QE(19) = 214.2488, *p*-value <0.0001) (Supplementary Data, Table S3A). When stratifying further by modality type, this explained over half of residual heterogeneity (R2 = 59.34%), illustrating that Preoperative Functional Imaging and DCS (b = 0.3190, 95% CI: 0.0467–0.5913, *p*-value = 0.022) was associated with a significant increase in GTR likelihood, with Preoperative nTMS and DCS (b = 0.2129, 95% CI: –0.0042—0.4301, *p*-value = 0.05) showing a borderline positive association and LFS (b = –0.2984, 95% CI: –0.5697 to –0.0270 *p*-value = 0.031) demonstrating a significant association with reduction in GTR likelihood.

In both models, normality was assumed in the distribution of random effects with a mean of 0 and estimated variance of τ^2 = 0.046 (SE = 0.0184) and τ^2 = 0.017

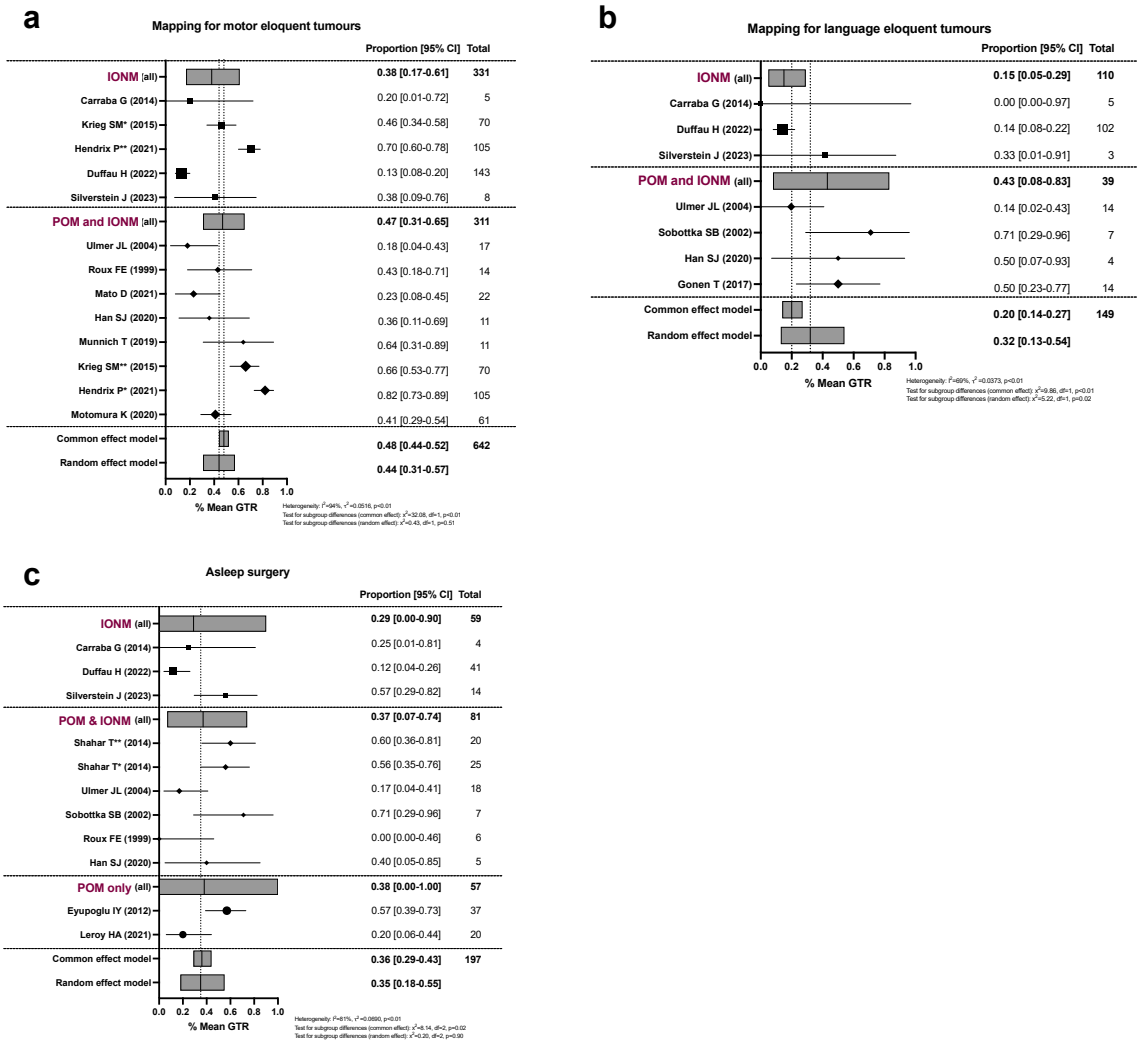

Fig. 4: (a)Forest plot demonstrating GTR rates amongst POM&IONM versus IONM only approaches in motor-eloquent tumours. (b) Forest plot demonstrating GTR rates within language-eloquent tumours comparing POM&IONM versus IONM approaches. (c) Forest plot demonstrating GTR rates of patients undergoing awake or asleep surgery comparing POM&IONM versus POM and IONM only approaches.

(SE = 0.0115) respectively. Moderator Coefficients were found to be significant (QM(10) = 29.0311, *p*-value = 0.0012), however overall moderator significance was not maintained following Permutation Testing (*p*-value = 0.062), with LFS only becoming borderline significant (*p*-value = 0.055). As expected due to data availability issues, significant unexplained residual heterogeneity was still present between studies (I2unaccounted = 70.16%, H2 = 3.35, QE(11) = 31.9671, *p*-value = 0.0008), following a normal distribution (Supplementary Data, Table S3B).

Post-operative focal neurological deficit (FND)

The rates of FND were: POM–18.9% versus IONM—19.07% versus POM&IONM–23.47%. The differences showed no statistically significant difference (X2 = 2.1192, *p*-value = 0.71) (Fig. 5A). The rate of permanent FND however was found to be significantly higher in the IONM group (IONM–73.0%; POM–29.6%; POM&IONM–33.7%, X2 = 18.452, df = 2 *p*-value = 0.0010) (Fig. 5B and Table 2).

When comparing differing neuromonitoring modalities and postoperative FND, data was available for 143 patients in the POM group (n = 2), 194 patients in the IOM group (n = 4) and 375 patients in the POM&IOM group (n = 10). Data on the time course of FND was available for 27 in the POM group (n = 2), 37 in the IOM group (n = 4) and 83 in the P&IOM group (n = 6).

When comparing differing sub modalities within monitoring groups and postoperative FND, within the POM group a new FND was found in 20.0% of the fMRI

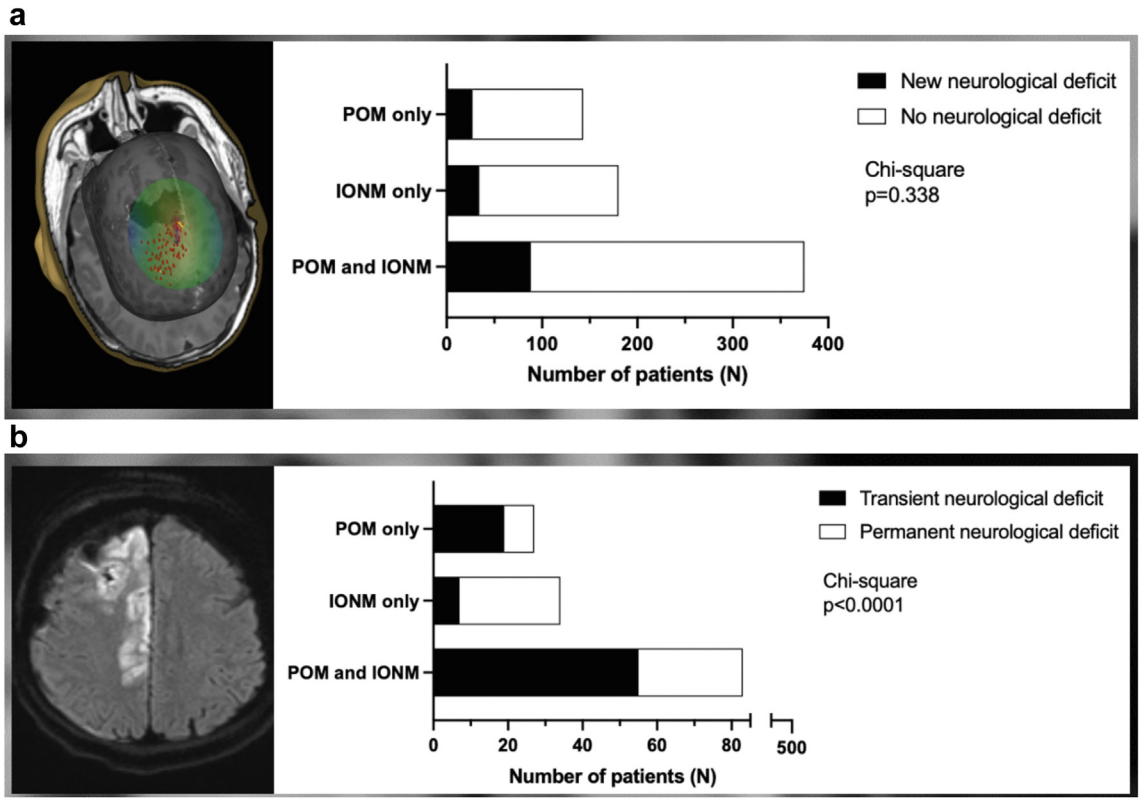

Fig. 5: Effectiveness of combined multimodal mapping and monitoring techniques in glioma resection. (a) Bar chart comparing the incidence of new neurological deficits in patients who underwent surgery with POM only, IONM only, or both modalities combined. (b) Bar chart illustrating the occurrence of transient versus permanent neurological deficits in the same patient groups. The statistical significance of the differences is indicated by chi-square tests, with *p*-values provided. The analysis reflects the impact of combining POM and IONM on preserving neurological function.

group compared to 18.7% in the tractography group which was not significantly different (OR = 1.09, 95% CI 0.24–3.82, *p*-value = 1.0). There were also similar rates of permanent deficits between these groups (fMRI–25.0% *versus* Tractography–30.4%, OR = 1.30 (0.085–78.58) *p*-value = 1.0).

Within the POM&IOM group, a new FND was significantly less likely within the fMRI + Tract + DCS (4.2%) compared to 9.1% with fMRI + nTMS + ITract + DCS, 10.0% with Tract + DCS, 22.2% with nTMS + DCS and 35.8% with the worst performing fMRI + DCS (X2 = 16.489, df = 4, *p*-value = 0.0024). However, among all patients with temporary deficits, the fMRI + DCS group had significantly lower rates of permanent deficits (18.8%) compared to the other sub modalities with time course data–42% with nTMS + DCS and 100% in fMRI + nTMS + ITract + DCS (X2 = 6.7066, df = 2, *p*-value = 0.035) (Table 3).

On analysis within the IOM group, a new FND was significantly more likely within the HFS group (30.0%) compared to 11.8% in the multimodal group (X^2 = 8.0815, df = 1, *p*-value = 0.0044). However, no significant differences were observed were observed between the groups when permanent deficits only were considered (HFS–85.7% *versus* multimodal 69.2%, OR = 0.3867 (0.0461–2.830) *p*-value = 0.39). Within the POM&IONM group, higher FND rate was associated with LFS (32.8%) compared to 21.4% in HFS and 9.5% in multimodal groups (X^2 = 21.968, df = 2, *p*-value = <0.0001). These were however significantly less likely to be permanent deficits in the LFS group (17.5%) compared to HFS (60%) and multimodal groups (81.8%, X^2 = 22.69, df = 2, *p*-value = <0.0001) (Table 4).

Discussion

Monitoring and mapping techniques impact the oncological and functional outcomes of supratentorial functional eloquent brain tumour surgery. Overall, POM–stand-alone or in addition–to IONM techniques increase the odds of gross total resection despite thisstatistical significance was not achieved. Preoperative tractography in POM group, multimodal stimulation techniques in IONM and POM&IONM groups and nTMS-DCS/fMRI-nTMS-ITract-DCS combinations in POM&IONM group are the submodalities within each group that achieved

Monitoring modality	n	New deficit	No deficit	% deficit		n	Transient	Permanent	% permanent		n	Motor	Language
POM submodality													
Functional (n = 1)	20	4	16	20.0	Functional (n = 1)	4	3	1	25.0	Functional (n = 1)	4	0	0
Tractography (n = 1)	123	23	100	18.7	Tractography (n = 1)	23	16	7	30.4	Tractography (n = 0)	–	–	–
OR = 1.09 (0.24–3.82) p-value = 1^{F}					*OR = 1.30 (0.085–78.58) p-value = 1*^{F}					*n/a*			
IONM submodality													
DCS Only (n = 4)	194	37	157	19.07	DCS Only (n = 4)	37	10	27	73.0	DCS Only (n = 2)	8	5	3
X^2 = n/a, df = n/a, p-value = n/a					*n/a*					*n/a*			
P&IOM submodality													
PF + ID (n = 4)	95	34	61	35.8	PF + ID (n = 2)	32	26	6	18.8	PF + ID (n = 1)	27	18	9
PFT + ID (n = 1)	24	1	23	4.2	PFT + ID (n = 0)	–	–	–	–	PFT + ID (n = 1)	2	1	1
PT + ID (n = 1)	20	2	18	10.0	PT + ID (n = 0)	–	–	–	–	PT + ID (n = 2)	6	5	1
PN + ID (n = 3)	225	50	175	22.2	PN + ID (n = 3)	50	29	21	42.0	–	–	–	–
PFN + ITD (n = 1)	11	1	10	9.1	PFN + ITD (n = 1)	1	0	1	100.0	–	–	–	–
X^2 = 16.49, df = 4, p-value = 0.0024					***X^2 = 6.71, df = 2, p-value = 0.035***					*p value = 0.67* ^{F}			

POM = Preoperative Monitoring, IOM = Intraoperative monitoring, P&IOM = Pre- & Intraoperative monitoring, fMRI and DCS = PF + ID), Pre and Intraoperative tractography (P&IT), fMRI + tractography and DCS = PFT + ID, Tractography and DCS = PT + ID, nTMS and DCS = PN + ID, fMRI + nTMS, Intraoperative Tractography + DCS = PFN + ITD, X^2 = . Chisquare test,^{F} = Fishers exact test, OR = Odds Ratio.

Table 3: **Submodality monitoring modality and postoperative deficit rate, time course & type.**

higher odds of GTR. There are no differences in the GTR rates among the different groups within the same considered histology—metastasis, low grade and high grade gliomas. The impact of POM&IONM technique is particularly significant in language-eloquent lesions. A new permanent postoperative FND is more likely in the IONM group and a permanent postoperative FND is less likely with the fMRI + DCS submodality combination or when using LFS in the POM&IONM group (Fig. 5).

Preoperative mapping emerges as a significant factor to achieve GTR. This is reflected in the overall higher GTR rates achieved in the POM and POM&IONM groups, despite the lack of statistical significance, and the significantly better results achieved in language-eloquent tumours. Multiple factors are potentially responsible for this finding. POM assists the individual functional relation between the tumour and the cortical and subcortical surroundings. This is crucial for appropriate patient selection,[30] may change the surgical approach,[31] and is a valuable tool in predicting the extent of resection (tumour infiltration versus displacement of eloquent areas)[32,33] Combined together, this empowers surgical teams with a better functional-anatomy surgical planning which paves the way to more aggressive surgical resections.[34] Different motor[35–37] and language[33,38] stratification risk scores have been proposed in the literature that provide a better counselling and informed consent before proceeding to surgery. Therefore, it is likely that groups where POM techniques are used have a more streamlined pathway for surgical resection selection and a potential bias towards surgery for patients where GTR is more likely without a significant neurological morbidity due to exclusion of *false-eloquent lesion*

Monitoring modality	n	New deficit	No deficit	% deficit		n	Transient	Permanent	% permanent		n	Motor	Language
IOM stimulation technique													
Penfield only (n = 0)	–	–	–	–	Penfield Only (n = 0)	–	–	–	–	Penfield Only (n = 0)	–	–	–
Unimodal (n = 1)	70	21	49	30.0	Unimodal (n = 1)	21	3	18	85.7	Unimodal (n = 0)	–	–	–
Multimodal (n = 2)	110	13	97	11.8	Multimodal (n = 2)	13	4	9	69.2	Multimodal (n = 1)	5	2	3
X^2 = 8.0815, df = 1, p-value = 0.0045					*OR = 0.3867 (0.0461–2.830) p-value = 0.39F*					*n/a*			
P&IOM stimulation technique													
Penfield Only (n = 7)	189	62	127	32.8	Penfield Only (n = 3)	57	47	10	17.5	Penfield Only (n = 4)	35	24	11
Unimodal (n = 1)	70	15	55	21.4	Unimodal (n = 1)	15	6	9	60	Unimodal (n = 1)	–	–	–
Multimodal (n = 2)	116	11	105	9.5	Multimodal (n = 2)	11	2	9	81.8	Multimodal (n = 3)	–	–	–
X^2 = 21.968, df = 2, p-value = <0.0001					*X^2 = 22.69, df = 2, p-value = <0.0001*					*n/a*			

POM = Preoperative Monitoring, P&IOM = Pre- & Intraoperative monitoring X^2 = . Chisquare test,^{F} = Fishers exact test, OR = Odds Ratio. When comparing differing paradigms of stimulation and new FND, data was available in the IOM group for 70 patients with HFS (n = 1) and 110 patients with multimodal stimulation (n = 2). In the POM&IONM group, data was available for 189 patients with LFS (n = 7), 70 patients with HFS (n = 1) and 116 patients with multimodal stimulation techniques (n = 2). This reduced to 57 (n = 3), 15 (n = 1) and 11(n = 2) respectively when detailing the time course of new FND.

Table 4: **Fidelity monitoring modality and postoperative deficit rate, time course & type.**

patients.[32] Nevertheless, the high results in the POM group match the ones in the POM&IONM group which supports previous literature where functional mapping—regardless if preoperative or intraoperative—is associated with larger extent of resection (EoR).[34,39,40]

Among the POM techniques, tractography proved to be superior to fMRI in achieving GTR. Several publications focused on either lesion-to-tract approaches[33,35,41–43] or DTI-metric approaches[44–47] (surrogate marker of structural integrity) to select patients with supratentorial motor and language eloquent brain tumours and they validate their findings in large cohort of patients even though extensive external validation is lacking. The integration of preoperative tractography in surgical planning helps to guide the intraoperative mapping and therefore understanding the intraoperative mapping information. fMRI in brain tumour surgery has important challenges particularly related with the potential impact of brain-related vascularization, infiltration, intratumoural haemorrhage and oedema in the brain oxygen level-dependant (BOLD) signal.[48] This may produce significant artifacts, a non-linear neurovascular response modelling and abnormal deoxyhaemoglobin level in the tumour hemisphere contributing to a mixture of false positive and negatives in this population.[49,50] However, the main difference in the surgical outcomes is probably related with the anatomical level of the information provided: cortical *versus* subcortical. Cortical mapping impacts only on entry zones in the cortex whilst subcortical mapping are relevant throughout the surgical resection and therefore more likely to influence the overall EoR. Cortical functional information as a seed for tractography dissection may improve the impact of this cortical mapping techniques in surgical outcomes as this cortical-subcortical integration has the potential to reduce the false positive rates of cortical mapping approaches.[51,52]

Multimodal stimulation are related with higher likelihood of GTR when compared with LFS. In particular, LFS can locate functional subcortical matter in the vicinity of the resection boundaries but cannot give information about the estimate distance to this subcortical matter from the resection boundaries, which is the main advantage of HFS-based mapping and monitoring protocols, particularly if associated with EEG and other techniques in multimodal paradigms.[53,54] This difference could allow for a more aggressive resection and hence, higher likelihood of GTR. Multimodal IONM not only also involves HFS motor mapping, with this added benefit, but also, other neurophysiological techniques with real-time monitoring of other functional areas during resection (somatosensory and visual among others), which may be at risk during surgery. Having this real time information about the function of these areas could again, promote higher rates of GTR.[55]

Combined cortical-subcortical information with DCS showed conflicting results in terms of probability of GTR when nTMS and fMRI were compared in the POM&IONM group. The better results held by nTMS-Tractography-DCS subgroup when compared to the fMRI-Tractography-DCS probably stem from the differences in the way the signals provided by both techniques are generated. Taking motor function as an example, TMS generates electrophysiological signals related to the location of motoneurons whilst fMRI interprets differences in blood oxygenation during a certain motor task to identify the motor cortex.[56] nTMS generated maps have a better spatial overlap with DCS when compared with fMRI and DCS.[57] Congruent information promotes the higher impact of these techniques combined together. Despite high reliability in the mapping of core muscles for both techniques, fMRI shows more accurate face-generated motor mappings whilst nTMS had better performance in hand and foot.[57] As resection of tumours in face-eloquent area is usually not associated with permanent motor deficits,[58] this can further explain the decrease impact of fMRI in the preoperative mapping phase. fMRI + nTMS + ITract + DCS was overall the best combination which highlights the complementary role played by both techniques in the preoperative evaluation of M1.[56] Nevertheless, the lack of widespread availability of intraoperative tractography and the costs involved when multiple mapping and monitoring techniques are used translate in a limitation factor to the generalization of this combined approach.

POM&IONM approach proved to be particularly successful in language-eloquent tumours and in awake craniotomy techniques when compared with IONM group. We decided to present the data for both language-eloquent and awake craniotomy independently because some of the series included report awake surgery for motor-eloquent lesions and therefore there is not a duplication of the results obtained. The benefits of a combined approach are well illustrated at subcortical level. Despite the well-recognized impact of tractography in surgical planning and intraoperative guidance,[59,60] the limitations imposed by brain shift and deformation as well as neuroplasticity[61] renders IONM paramount to assess this language and motor functions. In asleep surgery, a similar effect is observed. We hypothesize these results are related with a pre-surgical informed location of eloquent areas that may improve intraoperative interpretation of IONM signals (particularly when motor function is considered). Also, in patients with language-eloquent tumours not eligible for an awake procedure, preoperative mapping information may contribute to increase the EoR as no other intraoperative reliable mapping technique is available (only preliminary data is available about cortical–cortical evoked potentials in neuro-oncology).[62]

Permanent postoperative FNDs are more likely in the IONM group. Some reasons can explain this findings: IONM may encourage the surgical team to push the resection boundaries as long as the neurophysiological signals are stable.[63] Instability of a neurophysiological

signal in turn may prompt a warning call from the neurophysiology team. At this point, only reversibility of a signal change (favoured by a corrective action by the surgical team, such as a surgical break or halt) could result in a non-permanent FND.[64,65] Unfortunately, irreversible signal changes often result in permanent FNDs and reversibility of a signal change is not always guaranteed by corrective surgical action as much as this is encouraged.[63] The addition of POM to IONM assists in the interpretation of the intraoperative information.[28] This may offer a better overall understanding of the tumour-functional anatomy correlation. If the surgical team is more aware of these boundaries, they may take corrective action sooner to reverse IONM signal changes, increasing the chance that the FND is only transitory.

fMRI + DCS combined submodality and LFS paradigms of stimulation are associated with decrease likelihood of permanent postoperative FNDs in POM&IONM group. The literature supports that the majority of the neurological deficits arise from subcortical injury[66] given the larger cortical areas of disconnection that arise from subcortical tract damage.[67] We hypothesize that techniques focused on less specific cortical mapping techniques (such as fMRI) are related with less extensive resections (as discussed above) that are interrupted at a larger distance from the core functional areas and therefore responsible for decreased rates of permanent postoperative FNDs.[68] Also, postoperative deficits arising from changes in multimodal techniques where electrophysiological measures at cortical and subcortical level that provide information about integrity of functional pathways and distance-to-tract are obtained are more likely to be permanent. LFS-only paradigm provides a less comprehensive functional information and therefore, the changes observed are more likely to be reversible.

Our critical appraisal found the following limitations in this study. Due to a lack of volumetric data, a detailed assessment of EoR according to the most updated definitions could not be done. Significant heterogeneity was found in the definitions of "Subtotal", "Partial" and "Near Total Resection" amongst the included papers. Hence, only GTR was considered in the analysis as the definition is more consensual and avoids introducing significant biases from considering other forms of resection. In addition to this, restricting papers to those published in English may have introduced selection bias, as certain protocols and equipment may be favoured in English-speaking countries making our results more difficult to generalise to the rest of the world. With regards to subgroup analysis, publication bias was found during the analysis as studies did not have similar sample sizes. Due to the lack of individual patient data matched to outcomes, this meant raw proportions (i.e. % GTR, % PND) had to be utilised instead of more controlled estimates that would allow for direct, consistent comparisons such as Odds Ratios.[64–66,69] Three papers[67,68,70] documented use of POM-only and 4[71–74] IONM-only methods, resulting in unbalanced comparisons that reduce the confidence of our results. Whilst alternative estimators of heterogeneity had been used in subgroup analyses <10 studies, inaccurate estimation of between-study heterogeneity in this situation is another significant limitation. In addition to this, not all possible techniques were included (e.g. EEG, MEG) as data was insufficient. During the subgroup analysis of tumour histology, we have considered that in within each of the 3 main types of histologies analysed—metastasis, low grade and high grade gliomas—there was no difference in the GTR rates among the groups. We are aware that within the low grade glioma analysis, there was a trend towards higher rates in the POM&IONM compared with the others (POM&IONM—47.08 versus POM—14.29% and IONM—14.29%). Despite the potential clinical relevance of this data, we have decided not to focus on this difference given the heterogeneity in the POM&IONM group results that precluded the statistical significance and for the purpose of data analysis consistency throughout this work. There were 15 papers[34,68,70,72–83] reporting postoperative deficits as our inclusion criteria only featured EoR, with limited data on the duration of detected postoperative deficits restricting our conclusions. A complete meta-regression was not possible due to the heterogeneity in patient populations not enabling for effective pooling at the study level and a lack of individual patient data matched from outcomes (e.g. GTR incidence) to important covariates such as anatomical location, proximity to eloquent structures, WHO Histology Grading, Awake/Asleep Surgery, Tumour type among others. Ultimately, the choice of POM and IONM techniques should be made on an individual basis with regards to the above covariates to maximise onco-functional balance, hence we highly encourage future studies to publish individual case-by-case data to allow for more granular analysis.

To date, this is the first paper known to examine the impact of POM, IONM and POM&IONM techniques in surgical and functional outcomes to empower oncology units to make the most informed decisions for a patient-centred approach adapted to their particular reality in terms of resource availability. Given the stark differences of countries and health systems involved, it was also not feasible to perform a cost-analysis. However, the data analysed with regards to EoR and FND will help guide local decision makers in prioritising more cost-effective treatment.

Preoperative and intraoperative mapping and monitoring strategies that involve subcortical structural, functional and distance-to-tract information—tractography and multimodal stimulation—are related with larger GTR. Different functional eloquence and surgical techniques (but not tumour histology) have impact in the GTR rates among the groups–higher for POM&IONM in language-eloquent tumours awake

surgery. Permanent FNDs are related with the mapping and monitoring techniques used for surgical planning and resection–higher in the IONM-only group.

Contributors

Each authors contribution.

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Data sharing statement

Data available at request.

Declaration of interests

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Appendix A. Supplementary data

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References

1 UK CR. Brain, other CNS and intracranial tumours incidence statistics [Internet]. Cancer Res UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/incidence; 2023.

2 Ilic I, Ilic M. International patterns and trends in the brain cancer incidence and mortality: an observational study based on the global burden of disease. *Heliyon*. 2023;9. https://doi.org/10.1016/j.heliyon.2023.e18222.

3 McKinney PA. Brain tumours: incidence, survival, and aetiology. *J Neurol Neurosurg Psychiatry*. 2004;2.

4 Brown TJ, Brennan MC, Li M. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2:1460–1469. https://doi.org/10.1001/jamaoncol.2016.1373.

5 Albuquerque LAF, Almeida JP, Macêdo Filho LJM, Joaquim AF, Duffau H. Extent of resection in diffuse low-grade gliomas and the role of tumor molecular signature—a systematic review of the literature. *Neurosurg Rev*. 2021;44:1371–1389. https://doi.org/10.1007/s10143-020-01362-8.

6 Elsheikh M, Bridgman E, Lavrador JP, Lammy S, Poon MTC. Association of extent of resection and functional outcomes in diffuse low-grade glioma: systematic review & meta-analysis. *J Neuro Oncol*. 2022;160:717–724. https://doi.org/10.1007/s11060-022-04192-4.

7 Winther RR, Hjermstad MJ, Skovlund E. Surgery for brain metastases—impact of the extent of resection. *Acta Neurochir*. 2022;164:2773–2780. https://doi.org/10.1007/s00701-021-05104-7.

8 Fen Yang T. SY5.2. Intraoperative monitoring and mapping during brain tumor surgery. *Clin Neurophysiol*. 2021;132. https://doi.org/10.1016/j.clinph.2021.02.044.

9 Kiesel B, Thomé CM, Weiss T. Perioperative imaging in patients treated with resection of brain metastases: a survey by the European Association of Neuro-Oncology (Eano) Youngsters committee. *BMC Cancer*. 2020;20. https://doi.org/10.1186/s12885-020-06897-z.

10 Vysotski S, Madura C, Swan B. Preoperative fmri associated with decreased mortality and morbidity in brain tumor patients. *Interdiscip Neurosurg*. 2018;13:40–45. https://doi.org/10.1016/j.inat.2018.02.001.

11 Asadifar A, Khazaei R, Mokarian P, Kaviani MA. Assess the overall postoperative morbidity among patients with brain tumors by using preoperative functional magnetic resonance imaging: a systematic review and meta-analysis. *Int J Health Sci Public Online*. 2022:6156–6165. https://doi.org/10.53730/ijhs.v6nS8.13746.

12 Yan PF, Yan L, Zhang Z. Accuracy of conventional MRI for preoperative diagnosis of intracranial tumors: a retrospective cohort study of 762 cases. *Int J Surg*. 2016;36:109–117. https://doi.org/10.1016/j.ijsu.2016.10.023.

13 Jeltema HR, Ohlerth AK, Wit A. Comparing navigated transcranial magnetic stimulation mapping and "gold standard" direct cortical stimulation mapping in neurosurgery: a systematic review. *Neurosurg Rev*. 2021;44:1903–1920. https://doi.org/10.1007/s10143-020-01397-x.

14 Eibl T, Schrey M, Weigel J. Assessing the feasibility of mapping the tibialis anterior muscle with navigated transcranial magnetic

stimulation in neuro-oncologic patients. *Sci Rep*. 2022;12. https://doi.org/10.1038/s41598-022-23444-x.
15 Ordonez-Rubiano EG, Johnson JM, Abdalá-Vargas N. Preoperative tractography algorithm for safe resection of tumors located in the descending motor pathways zone. *Surg Neurol Int*. 2023;14. https://doi.org/10.25259/SNI_230_2023.
16 Manan AA, Yahya N, Idris Z, Manan HA. The utilization of diffusion tensor imaging as an image-guided tool in brain tumor resection surgery: a systematic review. *Cancers Basel*. 2022;14. https://doi.org/10.3390/cancers14102466.
17 Takahashi S, Vajkoczy P, Picht T. Navigated transcranial magnetic stimulation for mapping the motor cortex in patients with rolandic brain tumors. *Neurosurg Focus*. 2013;34:E3. https://doi.org/10.3171/2013.1.FOCUS133.
18 G R, A S, A C, et al. The role of navigated transcranial magnetic stimulation for surgery of motor-eloquent brain tumors: a systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2019;180. https://doi.org/10.1016/j.clineuro.2019.03.003.
19 Foroglou N, Zamani A, Black P. Intra-operative MRI (Iop-mr) for brain tumour surgery. *Br J Neurosurg*. 2009;23:14–22. https://doi.org/10.1080/02688690802610587.
20 Matsumae M, Nishiyama J, Kuroda K. Intraoperative MR imaging during glioma resection. *Magn Reson Med Sci*. 2021;21:148–167. https://doi.org/10.2463/mrms.rev.2021-0116.
21 Schulder M, Carmel PW. Intraoperative magnetic resonance imaging: impact on brain tumor surgery. *Cancer Control*. 2003;10:115–124. https://doi.org/10.1177/107327480301000203.
22 Abraham P, Sarkar R, Brandel MG. Cost-effectiveness of intraoperative MRI for treatment of high-grade gliomas. *Radiology*. 2019;291:689–697. https://doi.org/10.1148/radiol.2019182095.
23 Ng JCH, See AAQ, Ang TY, Tan LYR, Ang BT, King NKK. Effects of surgery on neurocognitive function in patients with glioma: a meta-analysis of immediate post-operative and long-term follow-up neurocognitive outcomes. *J Neuro Oncol*. 2019;141:167–182. https://doi.org/10.1007/s11060-018-03023-9.
24 Zetterling M, Elf K, Semnic R, Latini F, Engström ER. Time course of neurological deficits after surgery for primary brain tumours. *Acta Neurochir*. 2020;162:3005–3018. https://doi.org/10.1007/s00701-020-04425-3.
25 De la Garza-Ramos R, Kerezoudis P, Tamargo RJ, Brem H, Huang J, Bydon M. Surgical complications following malignant brain tumor surgery: an analysis of 2002–2011 data. *Clin Neurol Neurosurg*. 2016;140:6–10. https://doi.org/10.1016/j.clineuro.2015.11.005.
26 Jenkinson MD, Barone DG, Bryant A. Intraoperative imaging technology to maximise extent of resection for glioma. *Cochrane Database Syst Rev*. 2018;1. https://doi.org/10.1002/14651858.CD012788.pub2.
27 5-aminolevulinic acid hydrochloride (5-ala). –guided surgical resection of high-grade gliomas: a health technology assessment. *Ont Health Technol Assess Ser*. 2020;20:1–92.
28 Butenschön VM, Ille S, Sollmann N, Meyer B, Krieg SM. Cost-effectiveness of preoperative motor mapping with navigated transcranial magnetic brain stimulation in patients with high-grade glioma. *Neurosurg Focus*. 2018;44. https://doi.org/10.3171/2018.3.FOCUS1830.
29 Background. Development and use of study quality assessment tools | NHLBI, NIH n.d.. https://www.nhlbi.nih.gov/node/80102. Accessed March 22, 2024.
30 Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T. Functional magnetic resonance imaging and diffusion tensor tractography incorporated into an intraoperative 3-dimensional ultrasound-based neuronavigation system: impact on therapeutic strategies, extent of resection, and clinical outcome. *Neurosurgery*. 2010;67(10):1227. https://doi.org/10.1227/01.NEU.0000371731.20246.AC.
31 Zakaria H, Haider S, Lee I. Automated whole brain tractography affects preoperative surgical decision making. *Cureus*. 2017;6(9):e1656. https://doi.org/10.7759/cureus.1656.
32 Raffa G, Marzano G, Curcio A, Espahbodinea S, Germanò A, Angileri FF. Personalized surgery of brain tumors in language areas: the role of preoperative brain mapping in patients not eligible for awake surgery. *Neurosurg Focus*. 2022;53:3.
33 Sollmann N, Fratini A, Zhang H, Zimmer C, Meyer B, Krieg SM. Associations between clinical outcome and tractography based on navigated transcranial magnetic stimulation in patients with language-eloquent brain lesions. *J Neurosurg*. 2019;132(4):1033–1042. https://doi.org/10.3171/2018.12.JNS182988.
34 Krieg SM, Sollmann N, Obermueller T. Changing the clinical course of glioma patients by preoperative motor mapping with navigated transcranial magnetic brain stimulation. *BMC Cancer*. 2015;15. https://doi.org/10.1186/s12885-015-1258-1.
35 Rosenstock T, Grittner U, Acker G, et al. Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. *J Neurosurg*. 2017;126(4):1227–1237. https://doi.org/10.3171/2016.4.JNS152896.
36 Rosenstock C, Häni L, Grittner U, et al. Bicentric validation of the navigated transcranial magnetic stimulation motor risk stratification model. *J Neurosurg*. 2021;136(4):1194–1206. https://doi.org/10.3171/2021.3.JNS2138.
37 Duy Hung N E, N DL, N HV, et al. Predictive value of preoperative diffusion tensor imaging for evaluating postoperative outcomes of supratentorial glioma in the motor function area. *Ther Clin Risk Manag*. 2023;19:269–278. https://doi.org/10.2147/TCRM.S402622.
38 Sollmann D, Zhang H, Fratini A, et al. Risk assessment by presurgical tractography using navigated TMS maps in patients with highly motor- or language-eloquent brain tumors. *Cancers Basel*. 2020;12(5):1264. https://doi.org/10.3390/cancers12051264.
39 Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Effenterre R. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry*. 2005;76:845–851.
40 Witt Hamer PC, Sg R, Ah Z, H D, Ms B. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. *J Clin Oncol*. 2012;30:2559–2565.
41 Sollmann N, Kelm A, Ille S, et al. Setup presentation and clinical outcome analysis of treating highly language-eloquent gliomas via preoperative navigated transcranial magnetic stimulation and tractography. *Neurosurg Focus*. 2018;44(6):E2. https://doi.org/10.3171/2018.3.FOCUS1838.
42 Caverzasi E, Hervey-Jumper SL, Jordan KM, et al. Identifying preoperative language tracts and predicting postoperative functional recovery using HARDI q-ball fiber tractography in patients with gliomas. *J Neurosurg*. 2016;125(1):33–45. https://doi.org/10.3171/2015.6.JNS142203.
43 Tuncer MS, Salvati LF, Grittner U, et al. Towards a tractography-based risk stratification model for language area associated gliomas. *Neuroimage Clin*. 2020. https://doi.org/10.1016/j.nicl.2020.102541.
44 Hayashi Y, Kinoshita M, Nakada M, Hamada J. Correlation between language function and the left arcuate fasciculus detected by diffusion tensor imaging tractography after brain tumor surgery. *J Neurosurg*. 2012. https://doi.org/10.3171/2012.8.JNS12348.
45 Kinoshita M, Nakada M, Okita H, Hamada JI, Hayashi Y. Predictive value of fractional anisotropy of the arcuate fasciculus for the functional recovery of language after brain tumor resection: a preliminary study. *Clin Neurol Neurosurg*. 2014. https://doi.org/10.1016/j.clineuro.2013.12.002.
46 Morita N, Wang S, Kadakia P, Chawla S, Poptani H, Melhem ER. Diffusion tensor imaging of the corticospinal tract in patients with brain neoplasms. *Magn Reson Med Sci*. 2011;10:239–243. https://doi.org/10.2463/mrms.10.239.
47 Li J, Chen X, Zhang J, et al. Intraoperative diffusion tensor imaging predicts the recovery of motor dysfunction after insular lesions. *Neural Regen Res*. 2013;8:1400.
48 Lakhani DA, Sabsevitz DS, Chaichana KL, Quiñones-Hinojosa A, Middlebrooks EH. Current state of functional MRI in the presurgical planning of brain tumors. *Radiol Imaging Cancer*. 2023. https://doi.org/10.1148/rycan.230078.
49 Hou BL, M B, Kk P, Nm P, Ph G, Ai H. Effect of brain tumor neovasculature defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. *Neuroimage*. 2006;32:489–497.
50 N F, K S, Y K. Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. *Neuroimage*. 2004;21:1464–1471.
51 Jarret J, Boré A, Bedetti C, Descoteaux M, Brambati SM. A methodological scoping review of the integration of fMRI to guide dMRI tractography. What has been done and what can be improved: a 20-year perspective. *J Neurosci Methods*. 2022. https://doi.org/10.1016/j.jneumeth.2021.109435.
52 Belotti F, Tuncer MS, Rosenstock T, Ivren M, Vajkoczy P, Picht T. Predicting the extent of resection of motor-eloquent gliomas based on TMS-guided fiber tracking. *Brain Sci*. 2021;11(11):1517. https://doi.org/10.3390/brainsci11111517.
53 Nossek E, Korn A, Shahar T, et al. Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological

assessment and 3-dimensional ultrasonography-based navigation. *Clin Artic J Neurosurg*. 2011;114(3):738–746. https://doi.org/10.3171/2010.8.JNS10639.
54 Szelényi A, Senft C, Jardan M, et al. Intra-operative subcortical electrical stimulation: a comparison of two methods. *Clin Neurophysiol*. 2011;122(7):1470–1475. https://doi.org/10.1016/j.clinph.2010.12.055.
55 Brandmeier S, Taskiran E, Bolukbasi FH, Sari R, Elmaci I. Multimodal intraoperative neurophysiological monitoring in neurosurgical oncology. *Turk Neurosurg*. 2018;28:204–210. https://doi.org/10.5137/1019-5149.JTN.19177-16.1.
56 Krings T, Buchbinder BR, Butler WE, et al. Functional magnetic resonance imaging and transcranial magnetic stimulation: complementary approaches in the evaluation of cortical motor function. *Neurology*. 1997;48(5):1406–1416. https://doi.org/10.1212/wnl.48.5.1406.
57 Weiss C, Nettekoven C, Rehme AK, et al. Mapping the hand, foot and face representations in the primary motor cortex–retest reliability of neuronavigated TMS versus functional MRI. *Neuroimage*. 2013. https://doi.org/10.1016/j.neuroimage.2012.10.046.
58 Lutz K, Häni L, Kissling C, Raabe A, Schucht P, Seidel K. Resection of low-grade gliomas in the face area of the primary motor cortex and neurological outcome. *Cancers Basel*. 2023. https://doi.org/10.3390/cancers15030781.
59 Bello L, Castellano A, Fava E, et al. Intraoperative use of diffusion tensor imaging fiber tractography and subcortical mapping for resection of gliomas: technical considerations. *Neurosurg Focus*. 2010;28(2):E6. https://doi.org/10.3171/2009.12.FOCUS09240.
60 Aibar-Durán JÁ, Quintana-Schmidt C, Álvarez Holzpafel MJ, et al. Intraoperative use and benefits of tractography in awake surgery patients. *World Neurosurg*. 2020. https://doi.org/10.1016/j.wneu.2020.01.210.
61 Voets NL, Pretorius P, Birch MD, Apostolopoulos V, Stacey R, Plaha P. Diffusion tractography for awake craniotomy: accuracy and factors affecting specificity. *J Neuro Oncol*. 2021;153(3):547–557. https://doi.org/10.1007/s11060-021-03795-7.
62 Seidel K, Wermelinger J, Alvarez-Abut P, et al. Cortico-cortical evoked potentials of language tracts in minimally invasive glioma surgery guided by Penfield stimulation. *Clin Neurophysiol*. 2024;161:256–267. https://doi.org/10.1016/j.clinph.2023.12.136.
63 Holdefer RN, Skinner SA. Motor evoked potential recovery with surgeon interventions and neurologic outcomes: a meta-analysis and structural causal model for spine deformity surgeries. *Clin Neurophysiol*. 2020;131(7):1556–1566. https://doi.org/10.1016/j.clinph.2020.03.024.
64 Sun X, Ioannidis JPA, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. *JAMA*. 2014;311:405–411. https://doi.org/10.1001/jama.2013.285063.
65 Schmid CH, Lau J, McIntosh MW, Cappelleri JC. An empirical study of the effect of the control rate as a predictor of treatment efficacy in meta-analysis of clinical trials. *Stat Med*. 1998;17:1923–1942. https://doi.org/10.1002/(SICI)1097-0258(19980915)17:17<1923::AID-SIM874>3.0.CO;2-6.
66 Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med*. 2002;21:1575–1600. https://doi.org/10.1002/sim.1188.
67 Eyüpoglu IY, Hore N, Savaskan NE. Improving the extent of malignant glioma resection by dual intraoperative visualization approach. *PLoS One*. 2012;7. https://doi.org/10.1371/journal.pone.0044885.
68 Cho JM, Kim EH, Kim J. Clinical use of diffusion tensor image-merged functional neuronavigation for brain tumor surgeries: review of preoperative, intraoperative, and postoperative data for 123 cases. *Yonsei Med J*. 2014;55:1303–1309. https://doi.org/10.3349/ymj.2014.55.5.1303.
69 Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An empirical study of summary effect measures in meta-analyses. *Int J Epidemiol*. 2002;31:72–76. https://doi.org/10.1093/ije/31.1.72.
70 Leroy HA, Strachowksi O, Tuleasca C. Microsurgical resection of fronto-temporo-insular gliomas in the non-dominant hemisphere, under general anesthesia using adjunct intraoperative MRI and no cortical and subcortical mapping: a series of 20 consecutive patients. *Sci Rep*. 2021;11. https://doi.org/10.1038/s41598-021-86165-7.
71 Duffau H. Awake mapping with transopercular approach in right insular-centered low-grade gliomas improves neurological outcomes and return to work. *Neurosurgery*. 2022;91:182–190. https://doi.org/10.1227/neu.0000000000001966.
72 Carrabba G, Bertani G, Cogiamanian F, et al. Role of intraoperative neurophysiologic monitoring in the resection of thalamic astrocytomas. *World Neurosurg*. 2016;94:50–56. https://doi.org/10.1016/j.wneu.2016.06.049.
73 Hendrix P, Dzierma Y, Burkhardt BW. Preoperative navigated transcranial magnetic stimulation improves gross total resection rates in patients with motor-eloquent high-grade gliomas: a matched cohort study. *Neurosurg*. 2021;88:627–636. https://doi.org/10.1093/neuros/nyaa486.
74 Silverstein JW, Shah HA, Greisman JD, et al. Adjustable, dynamic subcortical stimulation technique for brain tumor resection: a case-series. *Oper Neurosurg Hagerstown Md*. 2023;25:161–167. https://doi.org/10.1227/ons.0000000000000724.
75 Spena G, D'Agata F, Panciani PP, Buglione di Monale M, Fontanella MM. Supratentorial gliomas in eloquent areas: which parameters can predict functional outcome and extent of resection? *PLoS One*. 2013;8:e80916. https://doi.org/10.1371/journal.pone.0080916.
76 Motomura K, Takeuchi H, Nojima I, et al. Navigated repetitive transcranial magnetic stimulation as preoperative assessment in patients with brain tumors. *Sci Rep*. 2020;10(1):9044. https://doi.org/10.1038/s41598-020-65944-8.
77 Bonney PA, Conner AK, Boettcher LB. A simplified method of accurate postprocessing of diffusion tensor imaging for use in brain tumor resection. *Oper Surg*. 2017;13:47–59. https://doi.org/10.1227/NEU.0000000000001181.
78 Mato D, Velasquez C, Gómez E, Lucas E, Martino J. Predicting the extent of resection in low-grade glioma by using intratumoral tractography to detect eloquent fascicles within the tumor. *Neurosurg*. 2021;88. https://doi.org/10.1093/neuros/nyaa463.
79 Roux FE, Boulanouar K, Ranjeva JP. Usefulness of motor functional MRI correlated to cortical mapping in Rolandic low-grade astrocytomas. *Acta Neurochir Wien*. 1999;141:71–79. https://doi.org/10.1007/s007010050268.
80 Ulmer JL, Salvan CV, Mueller WM. The role of diffusion tensor imaging in establishing the proximity of tumor borders to functional brain systems: implications for preoperative risk assessments and postoperative outcomes. *Technol Cancer Res Treat*. 2004;3:567–576. https://doi.org/10.1177/153303460400300606.
81 Sobottka SB, Bredow J, Beuthien-Baumann B, Reiss G, Schackert G, Steinmeier R. Comparison of functional brain PET images and intraoperative brain-mapping data using image-guided surgery. *Comput Aided Surg Off J Int Soc Comput Aided Surg*. 2002;7:317–325. https://doi.org/10.1002/igs.10060.
82 Han SJ, Teton Z, Gupta K, Kawamoto A, Raslan AM. Novel use of stimulating fence-post technique for functional mapping of subcortical white matter during tumor resection: a technical case series. *Oper Surg*. 2020;19:264–270. https://doi.org/10.1093/ons/opaa027.
83 Gonen T, Gazit T, Korn A. Intra-operative multi-site stimulation: expanding methodology for cortical brain mapping of language functions. *PLoS One*. 2017;12. https://doi.org/10.1371/journal.pone.0180740.