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Neurocognitive Outcomes Following Surgical Intervention for Frontal Lobe Tumors: A Longitudinal Study

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Abstract: Background: Executive function, attention, memory, and language networks are at risk of disruption due to frontal lobe tumor and surgery. Objective: To describe the neurocognitive profiles at 24 months after surgical resection of tumors of the frontal lobe and to determine clinical, tumor-related, and surgical predictors for the trajectory of cognitive outcomes. The methods used in this illustrative longitudinal cohort design involved a neuropsychological battery that was administered at four time points: preoperatively and at 1, 6, 12, and 24 months after resection of a frontal lobe tumor were modeled (N = 129 patients). Mixed-effects regression and multivariate regression were used to assess associations with tumor, surgical, and demographic variables and cognitive trajectories. The results for the current simulated dataset showed that overall composites of cognitive performance showed transient decline in the immediate postoperative period followed by gradual recovery; however, the pattern of change over time varied from one domain to another across executive functions, memory, attention, processing speed, and language. The key factors for the long-term cognitive trajectory were modeled as extent of resection, tumor laterality, involvement of the dorsolateral prefrontal cortex, and postoperative complications. Conclusions: The modeled results reflect the typical pattern of findings from the literature on frontal lobe tumors, that of a cognitive dip in the early postoperative phase followed by some recovery, but with specificity of the vulnerable domains and a substantial number of patients with persistent deficits. This could facilitate multidisciplinary surveillance and individualized rehabilitation planning but needs to be validated with data collected in the real world.

Keywords: Neurocognitive, Surgical, Intervention, Function, Tumor Neurocognitive.

INTRODUCTION

The frontal lobes are involved in executive control, working memory, attention regulation, language production, and social cognition (Morita, M. *et al*., 2021). Tumors in or invading the structures of the frontal lobe (gliomas, meningiomas, and metastatic lesions) can cause measurable cognitive change due to both the disruption of tissue and the surgical intervention needed for resection (Dwan, T. M. *et al*., 2015; Mekler, S. *et al*., 2025). Previous studies have reported on a variety of cognitive outcomes following frontal lobe tumor surgery, from transient postoperative cognitive deficits with significant recovery to ongoing, domain-specific deficits, especially in executive functioning and processing speed (Noll, K. *et al*., 2022).

Patients with primary brain tumors are at high risk for postoperative cognitive change, but there is little evidence to guide clinicians in identifying patients at greatest risk for cognitive decline (Habets, E. J. *et al*., 2014). This is the paper to specifically investigate presurgical predictors of postoperative cognitive outcomes following brain tumor resection using studies with multivariate analysis (Gilbert, S. J., & Burgess, P. W. 2008). In a highly diverse literature base, baseline cognitive performance proved to be the most consistent predictor of postoperative cognitive outcomes, better than other factors that are typically considered, such as sociodemographic and tumor-related factors (Liouta, E. *et al*., 2016). The results highlight the clinical relevance of routine preoperative cognitive assessment as a component of routine care in neuro-oncology, for risk stratification, patient counselling, and perioperative monitoring (Paulsen, J. S. 2009). The paper also identifies a significant gap in the literature on modifiable presurgical factors, suggesting future research in the field of cognitive prehabilitation and targeted interventions to enhance cognitive and quality of life outcomes. Primary brain tumors (PBT) are a diverse group of tumors that develop in or around the brain (Paulsen, J. S. 2009). Although PBTs make up a relatively small percentage of adult cancers, they are increasing in incidence worldwide (1) and have a significant impact on patients and caregivers. Traditionally, clinical research and therapy has been directed toward improving survival (Dubois, B. *et al*., 2000).

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Surgical resection to maximize removal of the tumor while preserving neurological status and cognitive function is often the first line of treatment for a PBT (Kemali, D. *et al*., 1985). The effect of surgery on cognition is complex and variable, however. Some studies report improvement in cognition, whilst others demonstrate mixed findings; deterioration in the immediate postoperative period, followed by partial or full recovery to baseline status. Other studies report no effect of surgery, with cognition remaining stable.

METHODS AND MATERIALS

Grasping How To Design And Set Up A Study.
The design was a single-center prospective longitudinal cohort that tracked patients up to 24 months after surgery. Data collection points were established at baseline (within 7 days preoperatively), as well as 1, 6, 12, and 24 months postoperatively.

Participants
A total of 129 adult patients with age ≥ 18 years with a radiologically or histologically confirmed tumor in the frontal lobe scheduled for an elective craniotomy were modeled. Patients with primary or secondary tumors with a predominant frontal lobe location, who were to undergo surgical resection (cases with biopsy only excluded), with adequate baseline language skills for neuropsychological evaluation, and without pre-existing major neurocognitive disorder not directly caused by the tumor were included. The following exclusion criteria were used: Patients with a history of cranial surgery, primary brain tumor in the frontal lobe other than meningioma, and severe preoperative impairment that prevented completion of baseline assessment.

Handle Results and Data from Surgery and Clinic. Manage Surgery and Clinical Data.
The following data were abstracted from the medical record: surgical approach (awake craniotomy versus craniotomy under general anesthesia), intraoperative mapping, extent of resection (gross total resection, near-total resection, subtotal resection, or partial resection, defined as the tumor area remaining according to the post-operative MR that occurred within 72 hours of surgery), tumor laterality, histological grade, and postsurgical complications (including seizure, infection, hydrocephalus).

Neurocognitive Assessment
Five cognitive domains, namely: executive function (Trail Making Test B, Wisconsin Card Sorting Test), memory (Hopkins Verbal Learning Test-Revised), attention (Digit Span, Trail Making Test A), processing speed (Symbol Digit Modalities Test), and language (Boston Naming Test, verbal fluency), were assessed using a standardized battery. Domain scores were then z-scored for age and education, and a cognitive composite score was computed as the average of the domain z-scores.

Statistical Analysis
Demographic, tumor, and surgical data were summarized using descriptive statistics. Linear mixed-effects models with random intercept per patient and fixed effects for time, extent of resection, tumor laterality, and the interactions were used to model the change in cognitive scores over time at the composite and domain-specific levels. Multivariate linear regression was used to determine the independent associations with 24-month composite cognitive z-score, adjusting for age, baseline cognitive status, tumor grade, extent of resection, and post-operative complications. Throughout the analysis, an alpha value of 0.05 was used.

As mentioned above, all values presented in Section 3 are hypothetical values designed to show a possible table layout and reporting format and should not be interpreted as values obtained from a real patient population.

RESULTS

Table 1: Assessment Baseline demographic and clinical characteristics of the cohort (N = 129).

Characteristic	n (%) or mean ± SD	Range
Age, years	52.4 ± 13.7	19–78
Sex, female	58 (45.0%)	—
Education, years	14.1 ± 3.2	6–20
Karnofsky Performance Status (baseline)	84.6 ± 9.8	60–100
Baseline seizures (any)	47 (36.4%)	—
Baseline composite cognitive z-score	-0.42 ± 0.81	-2.35 to 1.20
Handedness, right	117 (90.7%)	—

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Table 2: Findings of Tumor characteristics by location, laterality, and histology.

Characteristic	**n (%)**	**Mean size, cm ± SD**
Laterality — Left	64 (49.6%)	3.8 ± 1.5
Laterality — Right	58 (45.0%)	3.6 ± 1.4
Laterality — Bilateral	7 (5.4%)	4.9 ± 1.8
Subregion — Dorsolateral prefrontal cortex	41 (31.8%)	—
Subregion — Orbitofrontal/medial	29 (22.5%)	—
Subregion — Premotor / precentral	35 (27.1%)	—
Subregion — Diffuse / multi-subregion	24 (18.6%)	—
Histology — Low-grade glioma (WHO I–II)	46 (35.7%)	—
Histology — High-grade glioma (WHO III–IV)	38 (29.5%)	—
Histology — Meningioma	31 (24.0%)	—
Histology — Metastasis	14 (10.9%)	—

Table 3: Surgical outcomes approach and extent of resection.

Variable	**n (%)**	
Awake craniotomy	37 (28.7%)	
Craniotomy under general anesthesia	92 (71.3%)	
Intraoperative mapping used	58 (45.0%)	
Gross total resection (≥ 98%)	61 (47.3%)	
Near-total resection (90–97%)	34 (26.4%)	
Subtotal resection (70–89%)	22 (17.1%)	
Partial resection (< 70%)	12 (9.3%)	
Median operative time, min (IQR)	218 (176–265)	

Table 4: Composite cognitive z-score across follow-up time points (mixed-effects model estimates).

Time point	**Estimated mean z-score (95% CI)**	**Change from baseline**	**p-value**
Baseline	-0.42 (-0.56, -0.28)	—	—
1 month	-0.79 (-0.95, -0.63)	-0.37	< 0.001
6 months	-0.51 (-0.66, -0.36)	-0.09	0.041
12 months	-0.33 (-0.48, -0.18)	+0.09	0.038
24 months	-0.24 (-0.40, -0.08)	+0.18	0.006

Table 5: Domain-specific outcomes cognitive z-scores at baseline with 1 month, and 24 months.

Domain	**Baseline**	**1 month**	**24 months**
Executive function	-0.55	-1.02	-0.31
Memory	-0.38	-0.61	-0.20
Attention	-0.40	-0.74	-0.18
Processing speed	-0.44	-0.88	-0.27
Language	-0.32	-0.53	-0.22

Table 6: Postoperative complications and association with 12-month cognitive decline (composite z-score decrease ≥ 0.5 from baseline).

Complication	**n (%) of cohort**	**% with cognitive decline**	**p-value**
Postoperative seizure	19 (14.7%)	47.4%	0.012
Surgical site infection	6 (4.7%)	33.3%	0.291
Symptomatic hydrocephalus	4 (3.1%)	50.0%	0.184
New motor/speech deficit (transient)	23 (17.8%)	52.2%	0.003
None of the above	83 (64.3%)	21.7%	Reference

Table 7: Multivariate linear regression: predictors of 24-month composite cognitive z-score.

Predictor	**β (SE)**	**95% CI**	**p-value**
Age (per 10 years)	-0.09 (0.03)	-0.15, -0.03	0.004
Baseline composite z-score	0.46 (0.07)	0.32, 0.60	< 0.001
Gross/near-total vs. subtotal/partial resection	0.28 (0.09)	0.10, 0.46	0.002

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High-grade vs. low-grade histology	-0.31 (0.10)	-0.51, -0.11	0.003
Dorsolateral prefrontal involvement	-0.24 (0.09)	-0.42, -0.06	0.009
Any postoperative complication	-0.22 (0.08)	-0.38, -0.06	0.008
Awake craniotomy vs. general anesthesia	0.11 (0.09)	-0.07, 0.29	0.221

DISCUSSION

This longitudinal presentation shows a typical tumor frontal lobe literature trend of a decrease in composite cognitive function in early post-surgery, most notably at 1 month, which then improved gradually and partially over the next 2 years, and did not reach preoperative baseline across the cohort (Helmstaedter, C. A. *et al*., 2001). The curve here is similar to that described following craniotomy for both low-grade and high-grade lesions and has several interlocking clinical implications: a steep decline in the recovery curve followed by a flatter recovery curve that does not reach the pre-craniotomy level (Andrewes, H. E. *et al*., 2013). First, the severity of the immediate postoperative cognitive impairment implies that the early postoperative period, when family members and treatment teams are most likely to be focused on wound healing, seizure prophylaxis, and oncologic next steps, is also the most vulnerable period in terms of cognitive function, making brief cognitive screening a part of routine postoperative care more likely to be effective than waiting until outpatient follow-up to perform formal neuropsychological testing. Second, the continued recovery past twenty-four months, instead of levelling off at six months, suggests that a patient's eventual functional level would be systematically underestimated by the early neuropsychological evaluation, and that the planning and decision of whether to return to work or driving should be reconsidered multiple times, not just once at six months (Duffner, P. K. 2010).

This dissociation is also generally consistent with the anatomic rationale for frontal lobe surgery, which relies heavily on the distributed frontal-subcortical and frontal-parietal circuits that are susceptible to both primary resection as well as the diffuse effects of retraction, edema and disruption of white matter tracts including the superior longitudinal fasciculus and anterior thalamic radiations, This relative sparing need not be seen as a reflection of the unimportance of language risk in frontal lobe surgery, but rather may reflect successful implementation of existing surgical protections (awake mapping, cortical and subcortical stimulation, and functional localization prior to surgery) specifically designed to protect language networks, while similar protections during surgery for executive function and processing speed are less standardized and less routinely used(Marne, Z. *et al*., 2020; Arain, M. *et al*., 2013; Pletschko, T. *et al*., 2018).

The multivariate results provide some insight into who is likely to be more or less likely to deviate from the typical course. Long-term composite cognitive outcome was associated with greater extent of resection, though this may seem counterintuitive to those who believe that greater extent of surgery equates with greater cognitive injury (Traunwieser, T. *et al*., 2020). This, however, is in keeping with the large number of neuro-oncological studies that indicate that continued progression of the tumour burden, especially for infiltrative gliomas, is associated with continued cognitive decline due to continued mass effect, peritumoral edema, seizure activity, and, in the case of higher-grade lesions, faster regrowth requiring earlier reoperation and/or salvage therapy. That is, the average cognitive burden of leaving tumour behind could, on average, be greater than the average cognitive burden of a more aggressive resection, so long as resection is carried out with modern and sophisticated adjuncts like neuron avigation and intraoperative mapping that limit the risk of harm to functional tissue. This has a direct clinical implication: cognitive outcome should not be used as a reason to perform less radical resection, as under-resection will have its own trajectory of decline to which, as with most single-cohort studies, this model is only partially able to account in 24 months (Armstrong, C. L. *et al*., 2002). A clinically meaningful cognitive decline at 12 months was also significantly more common when patients had postoperative complications, especially seizures or new motor or speech deficits. This has been an important finding because the final cognitive outcome of tumor surgery of the frontal lobe is not solely a function of the surgical procedure, as unplanned events occurring during the procedure also contribute to the overall cognitive insult to the patient, and may prompt closer neuropsychological monitoring of these patients, and earlier referral to cognitive rehabilitation, even if imaging and neurological examination seem reassuring at hospital discharge

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(González, I. J. A. *et al*., 2008; Bunevicius, A. *et al*., 2014; Correa, D. D. *et al*., 2008).

One interpretation to be taken seriously is the lack of independent association between awake craniotomy and long-term cognitive outcome in the modeled multivariate analysis. A disproportionately large group of patients have tumors in areas where the baseline risk of cognitive and functional impairment is high: awake craniotomy with intraoperative mapping is reserved for these patients (Dhandapani, M. *et al*., 2015; Dhandapani, S. *et al*., 2013). This is a textbook case of 'confounding by indication': In a simple observational comparison, the patients who most likely underwent awake mapping are also the patients who had the highest a priori risk, leading to an apparent benefit that might be a downside. While an analysis of 10 or more years of similar cases might statistically account for the cognitive benefit, this would be ethically and practically challenging in this population or require more sophisticated observational methods like propensity score matching, instrumental variable analysis, or comparison with a historical cohort operated on prior to the routine use of mapping at a given center. In any real-life extrapolation of this framework, it is important to consider the surgical approach variable carefully and for minimum, the indication for awake mapping should always be reported along with the outcome, to allow readers to make their own judgements regarding the degree of confounding (Mattei, T. A. *et al*., 2005).

These patterns, actual or, as in this case, representative, have some bounds in which they can be generalized (Delgado-López, P. D. *et al*., 2020). The limited number of patients in a single-center cohort, despite having good follow-up retention, results in weak statistical power of the analyses for modest effect size or for fine-grained sub-group analyses such as outcomes by specific tumor subregion by histological grade. Another issue is attrition, the number of patients lost to follow-up in the case of a disease that worsens with age: patients with the worst underlying disease courses tend to be the ones who don't come back for further treatment, and so the reported recovery curve for a cohort of patients with even modest attrition is almost certainly an overestimate of what the recovery curve would look like for a cohort of patients followed to the end of the disease (Somers, D. C., & Sheremata, S. L. 2013). Another structural limitation is the lack of a non-surgical control group; the absence of any group of patients undergoing biopsy alone or radiation or watchful waiting means that it is impossible to fully separate the effects of the tumor itself on cognitive functioning from the effects of the surgical procedure, and any conclusions about the direct causal role of resection on early cognitive decline should be treated as provisional. Lastly, a single standardized battery, no matter how well validated, cannot capture the range of cognitive and psychosocial changes that patients (and their family members) often report after surgery on the frontal lobes, changes that are not well measured by standard tests of memory, attention, and executive function, and may be more relevant to a patient's return to work, relationships, and independent living than the composite z score (Nagahama, Y. *et al*., 2001).

These factors, compounded, indicate some avenues for future research on this type of framework. Statistically powerful generalizations, especially on the basis of which specific combinations of tumor site, tumor type, and surgery technique are most likely to lead to continued deterioration, would be greatly enhanced by multicenter collaboration (Rushworth, M. F. S. *et al*., 2002). Advanced structural and functional MRI could provide insight into the field by providing anatomical and functional data, such as by the means of diffusion tensor tractography of frontal white matter pathways and resting state connectivity, for direct patient-specific prediction of cognitive risk (Petruo, V. A. *et al*., 2018). Further follow-up is needed to determine whether the rate of recovery modeled here continues or levels off or worsens in some patients due to the progression of the disease, delayed radiation effects, or cognitive changes associated with aging. Lastly, incorporating structured, validated measures of social cognition and measures of functional tasks, in addition to the standard neuropsychological batteries, would guarantee the outcomes measured are relevant to what is most important to patients and families in the years following frontal lobe tumor surgery.

CONCLUSION

The main factors that predicted long-term outcome were extent of resection, tumor grade, dorsolateral prefrontal involvement, and postoperative complications. The patterns, if confirmed in real prospectively collected data, would help support the routine longitudinal neuropsychological surveillance and early targeted cognitive rehabilitation for patients with these risk features after frontal lobe tumor surgery.

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