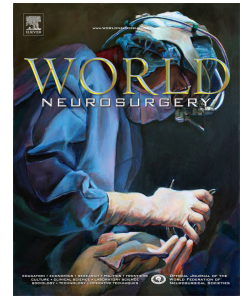


Journal Pre-proof

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PII: S1878-8750(25)00876-9

DOI: <https://doi.org/10.1016/j.wneu.2025.124518>

Reference: WNEU 124518

To appear in: *World Neurosurgery*

Received Date: 1 August 2025

Revised Date: 22 September 2025

Accepted Date: 23 September 2025

Please cite this article as: MORETTI ME, BROGGI M, SCHIARITI M, RESTELLI F, BARBIERI EM, FONTANELLA MM, MALTONI D, FIORAVANTI A, ZOIA C, MONTALBETTI A, LEONARDI M, CAMARDA G, SOLDINI E, MARESCA L, MATTIOLI L, CIOCCA R, BOCCARDI E, DIMECO F, FERROLI P, Evaluation Of Presurgical Outcome Predictors In Oncological Neurosurgery, *World Neurosurgery* (2025), doi: <https://doi.org/10.1016/j.wneu.2025.124518>.

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Evaluation Of Presurgical Outcome Predictors In Oncological Neurosurgery

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Keywords: Outcome Prediction, Brain Tumor, Surgical Complexity, Prognostic Modelling, Meningioma, Glioma, Neurosurgical Oncology

Running title: Outcome Prediction in Brain Tumors

Evaluation Of Presurgical Outcome Predictors In Oncological Neurosurgery

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ABSTRACT

Background: Brain tumor (BT) resection carries a significant risk of postoperative functional impairment. Existing surgical complexity scales (e.g., Milan Complexity Scale) do not account for factors such as preoperative tumoral edema or deep tumor location (DTL), which may influence outcome. This study evaluates whether these variables improve prediction of six-month postoperative functional outcomes.

Methods: We conducted a prospective multicenter cohort study including 231 patients undergoing BT resection. Preoperative variables (tumor size, eloquence, deep location, vascular/cranial nerve manipulation, posterior fossa location, edema) were collected. Functional status was assessed preoperatively and six months postoperatively using the Karnofsky Performance Scale (KPS) and modified Rankin Scale (mRS). Patients were grouped based on whether their six-month KPS/mRS scores worsened versus remained stable/improved. Correlations and multivariate logistic regression identified predictors of functional decline. Hierarchical clustering explored risk combinations.

Results: Among 231 patients, 59% had tumors located in eloquent areas, 18% in DTL and 39% presented with edema. Both preoperative edema and DTL were significantly associated with functional deterioration at six months. Multivariate analysis identified edema ($p=0.011$), eloquent region involvement ($p=0.037$), vascular manipulation ($p=0.040$), tumor size >4 cm ($p=0.041$) and DTL ($p=0.046$) as independent predictors of decline. Cluster analysis showed that combinations of adverse factors—particularly edema, large size, deep or posterior fossa location, and neurovascular manipulation—were associated with the highest risk of poor outcomes.

Conclusions: Preoperative tumoral edema and DTL are underrecognized predictors of functional deterioration after BT surgery. Their inclusion in preoperative risk models could enhance prognostic accuracy and guide surgical decision-making in neuro-oncology.

Keywords: Outcome prediction, Surgical complexity, Prognostic modelling, Meningioma, Glioma, Neurosurgical oncology

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MANUSCRIPT:

Introduction

Neurosurgical resection remains the cornerstone of brain tumor (BT) treatment, yet it carries substantial perioperative risks.¹ Despite significant technological advancements, these procedures continue to pose considerable challenges due to the imperative of achieving maximal safe tumor removal while preserving neurological function.² Surgical outcomes are further modulated by tumor heterogeneity, anatomical location, and patient-specific variables.³

Traditional hospital metrics—such as mortality rates, length of hospital stay, and reoperation frequency—offer a limited perspective, as they fail to fully capture surgical complexity or individualized risk profiles.⁴⁻⁶ Several grading systems have been developed to stratify surgical risk: the Milan Biometric- Surgical Score, for example, enhances risk prediction by integrating biometric and surgical parameters.⁷ The Milan Complexity Scale (MCS) classifies procedures based on anatomical, technical, and patient-related factors, identifying key predictors of postoperative functional decline: tumor size, cranial nerve involvement, vascular manipulation, posterior fossa location, and resection within eloquent brain areas.^{8,9}

A persistent challenge in evaluating neurosurgical outcomes lies in the variability of data collection and follow-up protocols across institutions, which complicates standardized benchmarking.^{10,11} This issue is particularly salient in neuro-oncology, and the use of large-scale clinical registries facilitates the tracking of outcomes, supports multicenter research, and contributes to the optimization of patient care.^{4,12-14}

To address these challenges, the Neurosurgical Outcome Network (NEON) was established as a collaborative initiative among a number of Italian neurosurgical centres. NEON aims at improving the monitoring of patient outcomes and at identifying predictors of surgical success, by introducing a standardized classification framework that quantifies postoperative neurological status using validated performance scales.¹³ This structured methodology enables the application of machine learning (ML) models to refine risk stratification and support personalized surgical planning.¹⁵

Since the development of MCS, two additional variables — peritumoral edema and deep cerebral tumor location (DTL)- have been identified as potential predictors of both postoperative neurological decline and surgical complexity.¹⁶⁻¹⁸ Their inclusion within the MCS is expected to enhance the precision and granularity of preoperative risk assessment, particularly in neuro-oncological populations where conventional anatomical predictors may be insufficient.

This study aims at evaluating the prognostic value of peritumoral edema and deep brain location as candidate variables for inclusion in the MCS, focusing on their ability to predict postoperative complications. To this end, we analyze their association with neurological outcomes at six months post-surgery. Furthermore, we explore their interaction with established predictors in shaping recovery trajectories and identify high-risk patient clusters.

This preliminary analysis provides a foundation for refining predictive models and advancing risk stratification in neuro-oncological surgery.

Materials and methods

Participants

The research protocol was approved by the ethical committee of the Fondazione IRCCS Istituto Neurologico Carlo Besta (FINCB) and all patients signed a dedicated informed consent form. The study population comprised patients affected by BT and scheduled for surgical tumor resection from May 2023 to May 2024 at the following four centers: FINCB, Ospedale Moriggia Pelascini Gravedona, ASST Cremona and Spedali Civili di Brescia. Data were gathered from prospectively collected institutional databases across all participating centers.

Patient records were reviewed for individuals of all ages who received a diagnosis of a possible BT of any type and underwent surgery aimed at achieving a maximal safe tumor resection (e.g., craniotomy for tumor removal or endoscopic endonasal resection). Patients were excluded if they had incomplete follow-up data, underwent non-oncological neurosurgical procedures, or if only biopsy or pre-planned partial resections were performed.

Data Collection and Statistical Analysis

Data were prospectively collected, encompassing patient demographics, clinical characteristics, and surgical details. The Karnofsky Performance Scale (KPS) and the modified Rankin Scale (mRS) were used to evaluate the patients' general health status before surgery and at 6 months after surgery.^{19,20} These scale were chosen because they have the strongest support in the literature for estimating surgery-related outcomes, and they have been also effective in predicting early morbidity in patients with intracranial tumors.²¹ Candidate predictive factors of postoperative worsening were defined as follows: tumor size (diameter ≥ 4), surgery in an eloquent area (yes, no), major brain vessel manipulation (yes, no), cranial nerve manipulation (yes, no), surgery in the posterior fossa (yes, no) and presence of edema (yes, no). Furthermore, the presence of diffuse and perilesional edema has been observed. Specifically, surgery in an eloquent area was considered if it was performed within motor, sensory, language or visual cortex. Surgery in deep brain location (yes, no) was considered if it was performed in the hypothalamus, thalamus, adjacent to the internal capsule, in the brainstem or in the pineal region.⁸ The presence of edema was classified as either diffuse or perilesional. Information regarding the type of surgery and extent of tumor resection was recorded. All evaluated demographic, clinical, and surgical factors were summarized using descriptive statistics. Continuous variables are reported as means $\pm$ standard deviations and ranges, while categorical variables are expressed as frequencies (percentages). Correlation analyses were performed to examine the relationships between several outcome predictors and improvements in KPS and mRS at discharge. Spearman's correlation was applied for categorical variables. In addition to these analyses, a multivariate cluster analysis was conducted with the goal of revealing the combined efficacy of clusters of outcome predictors that may not be readily apparent in univariate analysis. Second, a logistic regression model was built to investigate the strength of the relationship between the change in the patient's general health status at 6 months after surgery. The outcome was defined as the difference between the KPS and mRS score before surgery and that at 6 months, and all cases were categorized as either improved/unchanged or worsened. Odds ratios (OR) were used to evaluate the predictive power of the logistic regression model. In fact, OR measures how much the odds of the outcome change for a one-unit increase in the predictor variable.

Clusters of primary outcome predictors were identified by hierarchical clustering. These clusters were cross-referenced with a correlation matrix obtained by evaluating the statistical significance of correlations between each primary outcome predictor and others, using the Squared Euclidean Distance as a measurement. Subsequently, through interpretation of dendrograms and the agglomeration schedule, we identified several clusters that were then combined in six subsequent stages of hierarchical clustering. Logistic regression analyses were applied to these clusters to evaluate their predictive power on postoperative outcomes, particularly focusing on the likelihood of KPS and mRS deterioration.

Results

Descriptive Analysis

The study enrolled a total of 231 patients, with 55.4% being male. The average age was 54.41 years, with a range spanning from 10 to 85 years. Regarding comorbidities, 9.96% of patients had cardiopathy, 6.1% had diabetes, and 1.3% had chronic bronchopulmonary disease, while 31.6% had arterial hypertension; 15.2% of patients were identified as habitual smokers and 6.9% were diagnosed with psychiatric disorders. The mean body mass index (BMI) was 25.1.

Radiological analysis revealed that 59% of tumors were located in eloquent brain areas, while 18.18% were situated in deep central regions (see above). Peritumoral edema was present in 39.3% of cases, and vessel manipulation occurred in 41% of surgeries, with cranial nerve manipulation in 37.9% of cases. The most common tumor types were gliomas (41.4%) and meningiomas (37%), and most frequent tumor locations were frontal (22.1%), temporal (19.9%) and in the cerebellopontine angle (12.1%).

Lesion lateralization was distributed as follows: 37% were right-sided, 49.6% left-sided, 10.4% were midline, and 3% were bilateral. Complete tumor resection was achieved in 60.6% of cases, with subtotal resections in 35.3% and partial resections in 4.1% (For detailed data, refer to the Supplementary Table 1).

Correlation Analysis

On the basis of the relative KPS and mRS improvements calculated as shown above (Table 1), we explored the strength and direction of the relationships between primary outcome predictors and relative improvements at follow-up. This allowed us to assess how different predictors are associated with performance scales at various time points throughout the disease course.

All outcome predictors were correlated, to varying degrees, with a deterioration in both KPS and mRS at 6 months. Strong negative correlation was observed between manipulation of eloquent areas and KPS improvement ($r = -0.535$, $p = 0.016$), indicating that surgeries involving these critical regions are associated with significantly lower autonomy scores. This aligns with the known risk of disrupting vital functions such as language, motor skills, or sensory processing in these areas.²² While the correlation with mRS was weaker ($r = -0.302$, $p = 0.06$), the trend suggests a potential impact on global functional outcomes. Manipulations in the posterior fossa show weak correlations with both KPS ($r = -0.059$) and mRS ($r = -0.088$), with no significant p-values. This suggests that, in this cohort, posterior fossa surgeries may not be a predominant factor influencing postoperative functional recovery. However, given the potential severity of deficits in this region, further investigation with larger sample sizes may clarify this relationship. Cranial nerve manipulation shows a moderate negative correlation with both KPS ($r = -0.204$, $p = 0.071$) and mRS ($r = -0.189$, $p = 0.035$). Although the correlation is stronger for mRS, the data suggest that cranial nerve involvement during surgery poses a risk for postoperative functional impairments, likely related to motor and sensory deficits affecting everyday activities.

The analysis shows that a tumor size greater than 4 cm is significantly associated with worse functional outcomes at 6 months, both on the KPS scale ($r = -0.152$, $p = 0.001$) and the mRS scale ($r = -0.137$, $p = 0.010$). Although the strength of the correlation is modest, the statistical significance indicates that the effect is consistent across the analysed cohort.

Vessel manipulation negatively correlates with both KPS ($r = -0.153$, $p = 0.072$) and mRS ($r = -0.151$, $p = 0.044$). A significant negative correlation is observed between deep cerebral location surgeries and both KPS ($r = -0.41$, $p = 0.047$) and mRS ($r = -0.3$, $p = 0.037$). These findings reflect the high risk associated with operating in deep-seated brain regions, where manipulation can disrupt vital pathways and lead to lasting deficits in patient autonomy. Edema presents a moderate negative correlation with both KPS ($r = -0.492$, $p = 0.074$) and

mRS ($r = -0.676$, $p = 0.08$). Although these correlations do not reach strict statistical significance, they suggest that edema can substantially impair recovery, particularly on the mRS scale. This emphasizes the role of managing secondary complications such as brain swelling to improve long-term autonomy.

Results of Deterioration Analysis – Logistic Regression

KPS Deterioration

The logistic regression analysis for the deterioration of the KPS at the 6-month follow-up revealed several significant predictors.

The presence of edema significantly increases the odds of KPS deterioration ($OR = 1.52$, $p = 0.011$). Lesions located in eloquent areas of the brain almost double the likelihood of KPS deterioration ($OR = 1.82$, $p = 0.037$). This confirms the predictive power of lesion location in eloquent areas, as previously evidenced in correlation analyses. Vessel Manipulation also shows a significant impact on KPS deterioration ($OR = 1.298$, $p = 0.04$). Lesions larger than 4 cm significantly increase the odds of KPS deterioration ($OR = 1.419$, $p = 0.041$) too. Non-significant predictors include deep location and cranial nerve manipulation, although they still show relatively high odds ratios. Central deep location increases the likelihood of KPS deterioration by 35% ($OR = 1.357$, $p = 0.046$), suggesting its potential impact in later stages of post-surgical evolution (Table 2).

mRS Deterioration

The logistic regression analysis for the deterioration of the mRS at the 6-month follow-up identified several significant predictors of postoperative outcomes. These predictors provide valuable insights into the factors most likely to contribute to neurological decline in the medium-to-long term. Edema significantly increases the odds of mRS deterioration ($OR = 1.243$, $p = 0.04$). Additionally, lesions located in eloquent areas of the brain increase the odds of mRS deterioration by 61.2% ($OR = 1.612$, $p = 0.047$). Vessel manipulation was also found to significantly affect mRS deterioration ($OR = 1.783$, $p = 0.003$). Tumor size, specifically lesions larger than 4 cm, was another important factor, significantly increasing the odds of mRS deterioration ($OR = 1.409$, $p = 0.049$). However, non-significant predictors, such as posterior fossa involvement, deep location, and cranial nerve

manipulation, were also noted, though their statistical significance was not confirmed. The small sample size may have impacted these results. Overall, the logistic regression analysis underscores the importance of edema, lesion location, vessel manipulation, and tumor size as key predictors of postoperative functional decline (Table 3).

Multivariate Analysis – Clustering

We identified clusters by analysing the correlation matrix in Table 4, confirming existing groupings and identifying additional ones. Cluster membership variables were then created and incorporated into the regression analysis to assess their predictive value. More specifically, the correlation matrix confirms the strength of correlations (0.584, p -value <0.001) between size and increasing severity of edema (increscent from perilesional to diffuse). It also finds a positive correlation between the lesion being in the posterior fossa and presence of ordinally increscent edema (from lack thereof to perilesional and diffuse) with a moderate strength of correlation of 0.237 and a p -value <0.001 . There is also a statistically significant correlation between the lesion being in the posterior fossa and both intraoperative vessel manipulation, (0.217, $p=0.007$), and intraoperative cranial nerve manipulation (correlation coefficient: 0.272, $p= <0.001$), maybe due to the specific anatomical structures present in the posterior fossa and their accessibility. Furthermore, deep location and location in the posterior fossa are significantly correlated (correlation coefficient: 0.148, $p=0.048$), confirming the results from the analysis. Not too surprisingly, eloquent area is not directly correlated with statistical significance with $p<0.05$ to any of the other outcome predictors and thus sits in a cluster of its own.

Hence, in addition to the 3 aforementioned clusters, we included a few more inclusive ones, with more than two variables:

- Cluster 4: Posterior Fossa, Deep Central Location, Vessel Manipulation and Cranial Nerve manipulation
- Cluster 5: Size > 4 cm, Edema, Posterior Fossa, DTL, Vessel Manipulation and Cranial Nerve manipulation.

Clusters 4 and 5 gradually include all primary outcome predictors with the exclusion of eloquent area, which has no direct correlation with any of the other outcome predictors. We

included each of the Clusters as covariates in a binary logistic regression, with KPS at 6 months and mRS at 6 months as dependent variables, to assess the predictive value of each of the clusters of outcomes. Cluster 1 (edema and size) barely reaches statistical significance with regards to KPS, with odds of deterioration being 31% higher in patients with both edema and size superior to 4 cm (CI=1.02-2.15 p=0.04).

Cluster 2 (vessel manipulation and cranial nerve manipulation) grazes statistical significance (p=0.045) and reaches statistical significance (p=0.019) respectively in KPS and mRS. Patients with both vessel manipulation and cranial nerve manipulation are 21% more likely to deteriorate as measured by the modified Rankin Scale.

Cluster 3 (which coincides with patients who have both location in the posterior fossa and deep central location) doesn't reach statistical significance in either of the outcome measures, however we suspect this may be at least in part due to the small number of patients intersected with posterior fossa localization of the lesion.

The clusters with the highest odd ratios and statistical significance are by far Cluster 4 (Posterior Fossa, DTL, Vessel Manipulation and Cranial Nerve manipulation) and Cluster 5 (Cluster 4 with the addition of size and edema, namely all the outcome predictors except for eloquent area).

Discussion

In this study, preoperative peritumoral edema and deep-seated tumor location emerged as key predictors of postoperative neurological decline, complementing the “Big Five” factors of the Milan Complexity Scale.⁸ Our findings indicate that patients with significant edema or tumors in deep structures (e.g., thalamus, basal ganglia, brainstem) had worse functional outcomes at discharge and at six months post-surgery.^{23,24} This is in line with previous literature. For example, Schoenegger et al. found that preoperative edema in glioblastoma patients was associated with higher rates of neurological deficits and complications.²⁵ Similarly, Ohmura et al. reviewed the mechanisms by which vasogenic edema – often driven by VEGF-mediated permeability – distorts anatomy, increases intracranial pressure, and exacerbates surgical risk.²⁶ Although edema did not always reach statistical significance in early postoperative outcomes, it showed robust associations with long-term deterioration in both KPS and mRS in our cohort. These results suggest that edema may either directly

impair brain recovery or reflect more biologically aggressive tumors.^{26,27} However, other studies such as the one from Yang et al. have noted that edema alone may not independently predict survival in glioblastoma, highlighting a potential interplay with tumor grade and location.¹⁷

Deep tumor location also proved to be a critical predictor. These tumors locations pose a high risk due to their proximity to eloquent tracts and deep vascular structures.^{28,29} Our findings corroborate those of Grossman and Ram, who reported worse functional outcomes for posterior fossa and centrally located tumors.³⁰ Similarly, Gritsch et al. confirmed that deep-seated gliomas were associated with decreased survival rates and increased surgical complexity.¹⁶ These tumors are often less accessible, and their resection may risk damaging neural hubs essential for cognition and motor function.

Intraoperative vessel manipulation also emerged as a strong predictor of functional deterioration, consistent with reports by Alotaibi and Lanzino, who described how vascular injury can cause ischemic events or vasospasm following tumor resection.³¹ Our data reinforce the need for microsurgical precision and the use of real-time monitoring to mitigate these risks. Cranial nerve manipulation, although showing weaker correlations, was still associated with moderate declines in mRS, aligning with the findings of Staartjes et al., who emphasized the clinical relevance of intraoperative anatomical interactions.^{4,19} In contrast, posterior fossa tumors did not reach statistical significance in our dataset, likely due to a small sample size. However, the high odds ratios observed align with literature describing the surgical challenges and high morbidity rates associated with this region.³⁰ Further studies with larger cohorts are needed to confirm these trends.

To better understand the interplay of risk factors, we conducted a cluster analysis, which revealed that combinations of predictors -such as edema, DTL, and vessel manipulation- had greater prognostic value than individual variables alone. Cluster 5, which included all primary variables except eloquent area involvement, was a statistically significant predictor of six-month outcome. These findings are supported by the growing body of research on ML models in neuro-oncology, which integrate multivariate data to predict outcomes. For instance, Senders et al. demonstrated that ML algorithms can surpass traditional logistic regression in predicting survival in glioblastoma by incorporating imaging, molecular, and clinical features.¹⁵

The NEON protocol enabled this type of multidimensional analysis by standardizing data collection across centers.¹³ By integrating these findings into a future NEON-based predictive scale, incorporating both classical and novel variables (such as edema and deep location), we aim to improve surgical planning and patient counselling. Such tools are increasingly necessary given the complexity of modern neuro-oncological care. Nevertheless, this study has several limitations. The main one is intrinsic in its multicentric nature, with heterogeneous included tumor types and locations and different surgeons involved. Besides, the relatively small number of patients with posterior fossa tumors or cranial nerve manipulation limited statistical power concerning these two variables. Additionally, non-neurological comorbidities and molecular tumor subtypes were not included, which could influence recovery trajectories. An inherent limitation of the present investigation, in divergence from the original Milan Complexity Scale study, resides in the absence of a formally specified multivariate predictive model for postoperative functional trajectories. A comprehensive evaluation of model generalizability on independent, unseen datasets demands a markedly enlarged patient cohort; to this end, we are currently curating and statistically interrogating an extended dataset under a dedicated research protocol, the outcomes of which will be detailed in a subsequent publication.

Conclusions

In conclusion, our study suggests that edema and deep tumor location are relevant and under-recognized predictors of functional outcome following BT surgery. Integrating these variables into preoperative risk models could refine prognostic stratification and aid in surgical decision-making. Supported by recent literature, this expanded model can serve as the basis for future AI-enhanced tools aimed at improving patient care in neuro-oncology.^{15,16,25}

Acknowledgments

Nothing to disclose.

Bibliography

1. Nguyen TTT, Greene LA, Mnatsakanyan H, Badr CE. Revolutionizing Brain Tumor Care: Emerging Technologies and Strategies. *Biomedicines*. 2024;12(6):1376. doi:10.3390/biomedicines12061376
2. Hervey-Jumper SL, Berger MS. Role of Surgical Resection in Low- and High-Grade Gliomas. *Curr Treat Options Neurol*. 2014;16(4):284. doi:10.1007/s11940-014-0284-7
3. Chang EF, Clark A, Smith JS, et al. Functional mapping-guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. *J Neurosurg*. 2011;114(3):566-573. doi:10.3171/2010.6.JNS091246
4. Staartjes VE, Stumpo V, Kernbach JM, et al. Machine learning in neurosurgery: a global survey. *Acta Neurochir (Wien)*. 2020;162(12):3081-3091. doi:10.1007/s00701-020-04532-1
5. Stumpo V, Kernbach JM, van Niftrik CHB, et al. Machine Learning Algorithms in Neuroimaging: An Overview. In: ; 2022:125-138. doi:10.1007/978-3-030-85292-4_17
6. Trinh VT, Davies JM, Berger MS. Surgery for primary supratentorial brain tumors in the United States, 2000–2009: effect of provider and hospital caseload on complication rates. *J Neurosurg*. 2015;122(2):280-296. doi:10.3171/2014.9.JNS131648
7. Tariciotti L, Fiore G, Carapella S, et al. A Frailty-Adjusted Stratification Score to Predict Surgical Risk, Post-Operative, Long-Term Functional Outcome, and Quality of Life after Surgery in Intracranial Meningiomas. *Cancers (Basel)*. 2022;14(13):3065. doi:10.3390/cancers14133065
8. Ferroli P, Broggi M, Schiavolin S, et al. Predicting functional impairment in brain tumor surgery: the Big Five and the Milan Complexity Scale. *Neurosurg Focus*. 2015;39(6):E14. doi:10.3171/2015.9.FOCUS15339
9. Staartjes VE, Broggi M, Zattra CM, et al. Development and external validation of a clinical prediction model for functional impairment after intracranial tumor surgery. *J Neurosurg*. 2021;134(6):1743-1750. doi:10.3171/2020.4.JNS20643
10. Theodosopoulos P V., Ringer AJ, McPherson CM, et al. Measuring surgical outcomes in neurosurgery: implementation, analysis, and auditing a prospective series of more than 5000 procedures. *J Neurosurg*. 2012;117(5):947-954. doi:10.3171/2012.7.JNS111622
11. Karhade A V, Larsen AMG, Cote DJ, Dubois HM, Smith TR. National Databases for Neurosurgical Outcomes Research: Options, Strengths, and Limitations. *Neurosurgery*. 2018;83(3):333-344. doi:10.1093/neuros/nyx408
12. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. 2021;18(3):170-186. doi:10.1038/s41571-020-00447-z
13. Ferroli P, Schiavolin S, Mariniello A, et al. Towards a common language in neurosurgical outcome evaluation: the NEON (NEurosurgical Outcome Network) proposal. *J Neurosurg Sci*. 2023;67(3). doi:10.23736/S0390-5616.23.05968-4
14. Asher AL, McCormick PC, Selden NR, Ghogawala Z, McGirt MJ. The National Neurosurgery Quality and Outcomes Database and NeuroPoint Alliance: rationale, development, and implementation. *Neurosurg Focus*. 2013;34(1):E2. doi:10.3171/2012.10.FOCUS12311

15. Senders JT, Staples P, Mehrtash A, et al. An Online Calculator for the Prediction of Survival in Glioblastoma Patients Using Classical Statistics and Machine Learning. *Neurosurgery*. 2020;86(2):E184-E192. doi:10.1093/neuros/nyz403
16. Gritsch S, Batchelor TT, Gonzalez Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. *Cancer*. 2022;128(1):47-58. doi:10.1002/cncr.33918
17. Yang H, Bai G, Zhang Y, et al. The concept of “Four Walls, Two Poles” in the lesions of the thalamus and ganglion regions: case report and literature review. *BMC Surg*. 2021;21(1):55. doi:10.1186/s12893-021-01059-9
18. Berhouma M, Jacquesson T, Jouanneau E, Cotton F. Pathogenesis of peri-tumoral edema in intracranial meningiomas. *Neurosurg Rev*. 2019;42(1):59-71. doi:10.1007/s10143-017-0897-x
19. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale: An examination of its reliability and validity in a research setting. *Cancer*. 1984;53(9):2002-2007. doi:10.1002/1097-0142(19840501)53:9<2002::AID-CNCR2820530933>3.0.CO;2-W
20. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607. doi:10.1161/01.STR.19.5.604
21. Reponen E, Tuominen H, Korja M. Evidence for the Use of Preoperative Risk Assessment Scores in Elective Cranial Neurosurgery. *Anesth Analg*. 2014;119(2):420-432. doi:10.1213/ANE.0000000000000234
22. D’Amico RS, Englander ZK, Canoll P, Bruce JN. Extent of Resection in Glioma—A Review of the Cutting Edge. *World Neurosurg*. 2017;103:538-549. doi:10.1016/j.wneu.2017.04.041
23. Ho ML, Rojas R, Eisenberg RL. Cerebral Edema. *American Journal of Roentgenology*. 2012;199(3):W258-W273. doi:10.2214/AJR.11.8081
24. Liu Z, Liu J, Dai K, et al. Clinical outcomes of the neuroendoscopic far lateral supracerebellar infratentorial approach for resection of deep brain lesions. *Sci Rep*. 2025;15(1):11169. doi:10.1038/s41598-025-96162-9
25. Schoenegger K, Oberndorfer S, Wuschitz B, et al. Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma? *Eur J Neurol*. 2009;16(7):874-878. doi:10.1111/j.1468-1331.2009.02613.x
26. Ohmura K, Tomita H, Hara A. Peritumoral Edema in Gliomas: A Review of Mechanisms and Management. *Biomedicines*. 2023;11(10):2731. doi:10.3390/biomedicines11102731
27. Ying YZ, Li HY, Dong GH, et al. Postoperative peritumoral edema is correlated with the prognosis in intracranial meningioma with preoperative peritumoral edema. *Neurosurg Rev*. 2024;47(1):872. doi:10.1007/s10143-024-03116-2
28. Hasegawa H, Vakharia K, Carlstrom LP, et al. Long-term surgical outcomes of intracranial epidermoid tumors: impact of extent of resection on recurrence and functional outcomes in 63 patients. *J Neurosurg*. 2022;136(6):1592-1600. doi:10.3171/2021.5.JNS21650
29. Lee SH, Park KJ, Kang SH, Jung YG, Park JY, Park DH. Prognostic Factors of Clinical Outcomes in Patients with Spontaneous Thalamic Hemorrhage. *Medical Science Monitor*. 2015;21:2638-2646. doi:10.12659/MSM.894132
30. Grossman R, Ram Z. Posterior Fossa Intra-Axial Tumors in Adults. *World Neurosurg*. 2016;88:140-145. doi:10.1016/j.wneu.2015.12.066

31. Alotaibi NM, Lanzino G. Cerebral vasospasm following tumor resection. *J Neurointerv Surg.* 2013;5(5):413-418. doi:10.1136/neurintsurg-2012-010477

TABLES

Table 1 - *Spearman's Rho Correlations of Outcome Predictors with KPS and mRS improvements at 6-month follow-up*

Variable	KPS 6 months	mRS 6 months
<i>Eloquent Area</i>		
Correlation Coefficient	-0.535	-0.302
Sig. (2-tailed)	0.016*	0.060
N	110	124
<i>Edema</i>		
Correlation Coefficient	-0.492	-0.676
Sig. (2-tailed)	0.074	0.08
N	110	124
<i>Posterior Fossa</i>		
Correlation Coefficient	-0.059	-0.088
Sig. (2-tailed)	0.059	0.13
N	83	94
<i>Vessel Manipulation</i>		
Correlation Coefficient	-0.153	-0.151
Sig. (2-tailed)	0.072	0.044*
N	104	117
<i>Deep central location</i>		
Correlation Coefficient	-0.41	-0.3

Sig. (2-tailed)	0.047*	0.037*
N	108	122
<i>Cranial nerve manipulation</i>		
Correlation Coefficient	-0.204	-0.189
Sig. (2-tailed)	0.071	0.035*
N	111	125
<i>Size > 4cm</i>		
Correlation Coefficient	-0.152	-0.137
Sig. (2-tailed)	0.001*	0.010*
N	142	154

* $p < 0.05$

Table 2 - Logistic Regression Results for KPS Deterioration

Predictor	B (Coefficient)	Standard Error	Wald	df	p-value	Exp(B) Odds Ratio
Edema	0.377	0.110	14.76	1	0.011*	1.520
Eloquent Area	0.175	0.019	17.5	1	0.037*	1.820
Posterior Fossa	0.584	0.398	12.4	1	0.070	1.794
Vessel Manipulation	0.226	0.203	20.1	1	0.040*	1.298
Central Deep Location	0.305	0.106	18.7	1	0.046*	1.357
Cranial Nerve Manipulation	1.201	0.581	21.5	1	0.064	1.530
Size > 4cm	0.92	0.25	9.135	1	0.041*	1.419
Constant	-1.913	0.329	21.06	1	0.047*	

Abbreviations: df=degrees of freedom

* $p < 0.05$

Table 3 - Logistic Regression Results for mRS Deterioration

Predictor	B (Coefficient)	Standard Error	Wald	df	p-value	Exp(B) (Odds Ratio)
Edema	1.133	0.325	16.8	1	0.04*	1.243
Eloquent Area	0.477	0.335	12	1	0.047*	1.612
Posterior Fossa	0.454	0.275	14.6	1	0.070	1.575
Vessel Manipulation	1.017	0.221	19.2	1	0.003*	1.783
Central Deep Location	0.305	0.272	5.6	1	0.069	1.737
Cranial Nerve Manipulation	1.083	0.392	21.5	1	0.090	1.42
Size > 4cm	1.437	0.34	11	1	0.049*	1.409
Constant	-1.277	0.655	21.06	1	0.051	

Abbreviations: df=degrees of freedom

* $p < 0.05$

Table 4 – Results of a logistic regression evaluating the predictive value of each cluster on the degradation of the KPS at 6 months.

Predictor	B (Coefficient)	Standard Error	p-value	Exp(B)(Odds Ratio)	95% CI for Exp(B)
<i>Cluster 1</i>	0.162	0.281	0.049*	1.318	1.02 – 2.15
<i>Edema and Tumor Size</i>					
<i>Cluster 2</i>	0.697	0.449	0.045*	1.419	0.99 – 2.78
<i>Vessel Manipulation and Cranial Nerve Manipulation</i>					
<i>Cluster 3</i>	0.832	0.392	0.13	1.192	0.29 – 4.2
<i>Deep Central Location and Posterior Fossa</i>					
<i>Cluster 4</i>	1.591	0.218	0.001*	1.912	1.19 – 3.52
<i>Posterior Fossa, Deep Central Location, Vessel Manipulation, and Cranial Nerve Manipulation</i>					
<i>Cluster 5</i>	1.29	0.315	0.003*	1.64	1.21 – 3.76
<i>Posterior Fossa, Deep Central Location, Vessel Manipulation, and Cranial Nerve Manipulation, Tumor size, edema</i>					
<i>Constant</i>	-1.312	0.436	0.051		

Abbreviations: CI=Confidence Interval

* $p < 0.05$

Evaluation Of Presurgical Outcome Predictors In Oncological Neurosurgery

Abbreviations List:

AI: Artificial Intelligence

BMI: Body Mass Index

BT: Brain Tumor

CI: Confidence Interval

DTL: Deep Tumor Location

DF: Degrees of Freedom

KPS: Karnofsky Performance Scale

MBSS: Milan Biometric-Surgical Score

MCS: Milan Complexity Scale

ML: Machine Learning

mRS: modified Rankin Scale

NEON: Neurosurgical Outcome Network

OR: Odds Ratio

VEGF: Vascular Endothelial Growth Factor

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be constructed as a potential conflict of interest.

Funding: This work was partially supported by the Italian Ministry of Health (RRC).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta (protocol code NEON, nr.9; date of approval: 9 November 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients or from the minors' legal guardian/next of kin to publish this paper.

Data Availability Statement: The data presented in this study are available in the present article. Further data on review search or data regarding clinical cases are available upon request to the corresponding author (M.B.).

Authors' contribution: Michela Moretti, Morgan Broggi, and Paolo Ferroli made substantial contributions to the conception and design of the manuscript. Marco Schiariti, Francesco Restelli, Edoardo Barbieri, Marco Fontanella, Antonio Fioravanti, Cesare Zoia, Andrea Montalbetti, Matilde Leonardi, Giorgia Camarda, Elisabetta Soldini, Leonardo Maresca, Luca Mattioli, Riccardo Ciocca, Erica Boccardi, and Francesco Di Meco contributed to data acquisition. Davide Maltoni provided support for the analysis and interpretation of the data. All authors participated in drafting the manuscript, with Morgan Broggi and Michela Moretti critically revising it. All authors read and approved the final version of the manuscript and contributed equally to the work.