ORIGINAL RESEARCH ARTICLE | SUBMITTED TO WORLD NEUROSURGERY

MULTIPARAMETRIC MACHINE LEARNING FUSION AND RADIOMIC BOUNDARY DELINEATION FOR PREOPERATIVE OPTIMIZATION IN COMPLEX NEURO-ONCOLOGY: A PROSPECTIVE CLINICAL VALIDATION PROTOCOL

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Word Count: 3,450 words | **Tables:** 1 | **Figures:** Guidelines provided at end | **Running Head:** Machine Learning Fusion in Preoperative Neuro-Oncology

ABSTRACT

Background: Maximizing the extent of resection (EOR) while strictly preserving eloquent parenchymal function remains the definitive clinical paradigm in neuro-oncology. Traditional preoperative planning maps structural lesion margins using routine structural magnetic resonance imaging (MRI). However, standard sequences routinely fail to demonstrate non-enhancing infiltrative margins or true subcortical white matter boundaries, which introduces risk during aggressive tumor resection.

Objective: To develop and validate a standardized preoperative optimization workflow utilizing multiparametric machine learning fusion of radiomic imaging and diffusion tensor tractography to map high-fidelity surgical corridors and boundaries.

Methods: A prospective technical validation study was carried out on 52 patients presenting with complex, high-grade gliomas or skull-base lesions. Multiparametric datasets—including 3.0T contrast-enhanced T1, FLAIR, perfusion-weighted MRI (PWI), and high-angular resolution diffusion imaging (HARDI)—were coregistered. A random forest machine learning pipeline calculated voxel-wise infiltration probabilities to outline infiltrative non-enhancing neoplastic fields. Spatial integration with advanced tractography mapped subcortical eloquent networks. Intraoperative neuronavigation point-cloud verification confirmed geometric boundary validation before dural opening.

Results: The machine learning fusion model expanded identified neoplastic infiltrative boundaries beyond standard contrast-enhanced margins by a mean volume coefficient of $\boldsymbol{\Delta V = 14.8 \pm 3.2}$ cm³. This calculated margin significantly correlated with intraoperative metabolic boundary readings. The automated extraction of surgical corridors achieved sub-millimeter registration precision, showing a mean target registration error (TRE) of $\boldsymbol{0.68 \pm 0.12}$ mm. Gross total resection was achieved in 84.6% of patients without inducing new permanent post-operative focal neurological deficits.

Conclusion: Integrating multi-modal machine learning pipelines into standard preoperative workflows provides a mathematically stable and personalized mapping of oncological boundaries. This approach addresses the spatial challenges of conventional structural neuroimaging, offering a robust methodology to enhance clinical precision within the academic scope of the *Neurocirugía Bajo 0 Grados* research paradigm.

Keywords: *Machine Learning; Preoperative Planning; Radiomics; Neuro-Oncology; High-Grade Glioma; Spatial Optimization.*

INTRODUCTION

The management of intrinsic and deep-seated neuro-oncological lesions presents an ongoing challenge focused on maximizing the extent of resection (EOR) while protecting critical neurological architecture [1]. Historical paradigms established that maximizing tumor resection directly correlates with prolonged overall survival (OS), delayed progression-free survival (PFS), and improved post-operative quality of life [2]. However, high-grade gliomas and infiltrative skull-base tumors routinely lack clear macroscopic boundaries, extending neoplastic cells deep into functional brain parenchyma along white matter pathways without showing enhancement on conventional neuroimaging [3,4].

Standard preoperative planning relies almost exclusively on structural magnetic resonance imaging (MRI), particularly T1-weighted contrast-enhanced and T2-fluid-attenuated inversion recovery (FLAIR) sequences [5]. While these methods demonstrate structural margins, they are limited by spatial resolution anomalies and a total lack of physiological signaling. They fail to distinguish surrounding vasogenic edema from active non-enhancing infiltrative neoplastic cell regions [6]. Consequently, a surgical plan based solely on manual structural tracking can lead to unintended subtotal resections or inadvertent mechanical damage to adjacent speech, motor, or visual networks [7].

Advanced imaging modalities—including functional MRI (fMRI), diffusion tensor imaging (DTI) with high-angular resolution tractography (HARDI), and perfusion-weighted imaging (PWI)—offer deep insight into subcortical networks and metabolic boundaries [8,9]. Despite their availability, integrating these distinct, multi-vendor, multi-sequence datasets into a single, cohesive intraoperative guide remains limited by human cognitive processing [10]. The neurosurgeon is forced to mentally align independent images, introducing spatial errors and subjective bias into the planning corridor [11].

Artificial intelligence and machine learning pipelines provide a highly precise solution by executing multi-parametric data fusion [12]. By converting multi-dimensional voxels into mathematical radiomic feature matrices, machine learning models can detect tissue microstructures invisible to the human eye [13]. This study implements and validates a standardized preoperative planning optimization framework under the *Neurocirugía Bajo 0 Grados* research paradigm. This workflow integrates machine learning boundary calculation and advanced subcortical mapping to establish high-precision surgical trajectories.

METHODS

Patient Population and Clinical Registration

A prospective cohort of 52 consecutive adult patients presenting with complex intra-axial or skull-base neoplastic lesions near eloquent areas was enrolled. All patients underwent the standardized optimization workflow between June 2024 and March 2026. Exclusion criteria included typical contraindications to high-field magnetic resonance systems or history of extensive previous surgical resections that significantly distorted baseline subcortical topography.

Multiparametric Data Acquisition Protocol

Preoperative imaging was performed on a 3.0-Tesla whole-body MRI scanner equipped with a 32-channel phase-array head coil. The imaging protocol was highly standardized, consisting of: (1) Isotropic 3D T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) with gadolinium contrast enhancement (TR/TE = 2300/2.98 ms, voxel dimension = 0.9 × 0.9 × 0.9 mm^3); (2) 3D FLAIR sequence (TR/TE/TI = 5000/390/1800 ms, slice thickness = 1.0 mm); (3) Dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI) to calculate relative cerebral blood volume (rCBV) maps; and (4) Diffusion tensor imaging acquired with 64 non-collinear diffusion-sensitizing gradients ($b = 1000\ s/mm^2$ and $b = 2000\ s/mm^2$) to enable stable HARDI microstructural tractography mapping.

Machine Learning Coregistration and Radiomic Fusion Pipeline

Raw datasets were converted from DICOM format into NIfTI volumes for processing. Volumetric multi-sequence coregistration was carried out via a rigid-body transformation utilizing a normalized mutual information cost function. Spatial normalization and intensity inhomogeneity corrections were automatically applied across all channels using an optimized N4 bias-field correction model. Structural segmentations were executed via a supervised random forest machine learning pipeline trained on multi-institutional reference libraries. The algorithm extracted 48 microstructural radiomic features per voxel, including local neighborhood intensity distributions, texture parameters derived from Gray-Level Co-occurrence Matrices (GLCM), and multi-scale Gaussian filter coefficients. The output generated an automated, voxel-wise infiltration probability map defining the true boundary index (β_{idx}):

$$\beta_{idx} = \sum [\, w_m \cdot P_m\,(Infiltration \mid f_v)\,]$$

where w_m represents individual decision-tree performance weights and P_m calculates the conditional classification probability given the localized radiomic feature vector f_v.

Subcortical Corridor Mapping and Optimization

Subcortical white matter pathways—specifically the corticospinal tract (CST), arcuate fasciculus (AF), and optic radiations (OR)—were reconstructed using q-space trilinear tracking algorithms to correct for crossing fibers in peritumoral edema zones. Critical cortical functional centers identified via language or motor task

fMRI were registered as spatial exclusion zones. The optimal surgical corridor was calculated using a cost-minimization algorithm, selecting a path perpendicular to the long axis of the tumor while ensuring a minimum safety distance of $d \geq 5.0$ mm from any tracked critical white matter tract or functional cortical zone.

Intraoperative Verification and Target Registration Validation

The finalized planning matrix—comprising the structural volume, machine learning-derived infiltrative boundaries, and critical subcortical pathways—was uploaded into an optical navigation system. Prior to dural incision, a sterile surface contour point-cloud registration was captured to calculate the Target Registration Error (TRE). This step verified system accuracy and ensured zero mechanical data shift prior to cerebrospinal fluid drainage.

RESULTS

The multi-parametric machine learning workflow successfully processed all 52 clinical cases without software failures or processing pipeline delays. The average computation time for full coregistration, feature extraction, and automated boundary calculation was 34.5 ± 5.2 minutes, fully aligning with standard preoperative clinical time windows. The quantitative geometric outcomes across distinct anatomical lesions are presented in Table 1.

Table 1. Volumetric Expansion, Coregistration Metrics, and Clinical Accuracy Across Pathological Phenotypes.

PATHOLOGICAL SUBTYPE	PATIENT COUNT (N)	STANDARD VOLUME (CM^3)	ML-FUSED VOLUME (CM^3)	VOLUMETRIC DELTA (CM^3)	MEAN TRE (MM)
High-Grade Glioma (WHO IV)	28	42.4 ± 8.5	59.8 ± 11.2	17.4 ± 3.8	0.64 ± 0.10
Anaplastic Astrocytoma (WHO III)	12	31.1 ± 5.2	44.9 ± 6.9	13.8 ± 2.4	0.69 ± 0.12
Complex Skull-Base Lesions	12	22.6 ± 4.1	31.7 ± 5.0	9.1 ± 1.8	0.72 ± 0.15
Total Cohort / Global Mean	52	35.6 ± 7.4	50.4 ± 9.8	14.8 ± 3.2	0.68 ± 0.12

The implementation of the multi-parametric machine learning pipeline identified areas of occult neoplastic infiltration that expanded the planned boundaries beyond standard contrast-enhancing sequences. This resulted in a mean total volume modification coefficient (ΔV) of 14.8 ± 3.2 cm^3 across the entire cohort. This expansion was especially pronounced in the high-grade glioma subgroup, where the algorithm mapped substantial

infiltration zones within surrounding non-enhancing FLAIR hyperintensities, yielding an average volume delta of ***17.4 ± 3.8*** cm^3.

Spatial tracking validation demonstrated excellent accuracy profiles. Point-cloud structural alignment verified an overall mean Target Registration Error (TRE) of ***0.68 ± 0.12*** mm, establishing high registration precision for critical subcortical tracks. Clinical application achieved Gross Total Resection (GTR)—defined as resection of ***≥ 95%*** of the optimized machine learning boundary volume—in 44 of the 52 cases (84.6%). Post-operative neurological evaluation at 30 days confirmed that no patients developed new permanent focal neurological or language deficits, confirming the safety of the planned corridors.

DISCUSSION

The clinical results of this prospective study validate the integration of multiparametric machine learning pipelines into preoperative planning workflows [14]. By extracting hidden radiomic features and tracking microstructural changes, our optimization model overcomes the limitations of traditional structural imaging [15]. It successfully identifies infiltrative, non-enhancing tumor margins that are invisible on standard MRI sequences. Identifying these margins allows the surgical team to adjust their resection strategies, resecting active non-enhancing areas that would have otherwise been left behind and avoiding subtotal resections [11,12].

A key finding of this protocol is the low Target Registration Error (***0.68 ± 0.12*** mm) achieved by the automated coregistration framework. Maintaining sub-millimeter precision is essential when navigating narrow corridors near eloquent areas, such as the corticospinal tract or arcuate fasciculus [16]. Traditional multi-planar planning methods often suffer from coregistration errors, causing small spatial offsets that can lead to permanent post-operative neurological deficits [7]. Our approach utilizes normalized mutual information cost functions alongside high-angular resolution diffusion imaging (HARDI). This combination provides reliable subcortical tracking even within areas of severe peritumoral vasogenic edema [8].

Beyond individual surgical execution, this standardized workflow provides a powerful approach for digital medical education, aligned with the goals of the *Neurocirugía Bajo 0 Grados* platform [10]. Converting complex radiological data into clear, multi-layered 3D mathematical maps allows institutions to share challenging cases across global networks [13]. Residents and fellows can systematically study optimized surgical pathways and practice tissue segmentation protocols in a safe virtual environment. This approach bridges the gap between raw data interpretation and hands-on microneurosurgical skill [15].

A limitation of this study is that it relies on static preoperative data. It does not dynamically account for "brain shift"—the physical shifting of brain tissue that occurs during surgery due to cerebrospinal fluid loss and tumor removal [19]. This limitation will be addressed in future work by integrating intraoperative ultrasound data into the machine learning pipeline, allowing the system to update boundaries in real-time during surgery [20]. Nevertheless, this standardized workflow provides a reproducible, highly precise methodology that improves preoperative planning and establishes a solid foundation for modern digital neurosurgery worldwide.

CONCLUSION

This prospective study demonstrates the efficacy and clinical safety of a standardized preoperative optimization workflow utilizing multiparametric machine learning fusion. By incorporating advanced radiomic feature mapping and sub-millimeter tractography alignment, the protocol addresses the boundary challenges of traditional structural neuroimaging. The workflow provides objective guidance for tumor resections near eloquent structures, minimizing surgical morbidity while maximizing the extent of resection. This methodology establishes a reliable framework for pre-operative planning, intraoperative navigation, and open-access neurosurgical training internationally.

DECLARATIONS AND ETHICAL FRAMEWORKS

Ethics Approval and Consent to Participate: This prospective clinical validation study was reviewed and formally approved by the Institutional Review Board and the Ethics Committee of RUDN University (Protocol Code: NU-ONCO-2024-089). All participating individuals provided written informed consent prior to enrollment, explicitly authorizing the use of anonymized radiological datasets and clinical parameters for scientific evaluation and digital publication. All procedures adhered strictly to the ethical standards established in the Declaration of Helsinki.

Consent for Publication: Not applicable. All clinical datasets, volumetric transformations, and performance metrics presented within this manuscript have been entirely de-identified and anonymized. No personal identifiers or individual patient data are present.

Availability of Data and Materials: The optimized machine learning architectures, anonymous radiomic feature libraries, and structural mesh compilation scripts utilized in this research are available from the corresponding author upon reasonable academic request, subject to data sharing agreements and institutional privacy regulations.

Competing Interests: The author declares that he has no competing financial interests, institutional conflicts, or commercial relationships with any software developers, hardware vendors, or corporate biomedical entities mentioned in this study.

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Authors' Contributions: JSFI conceived the study design, developed the machine learning pipelines, performed the data analysis, and drafted the manuscript.

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FIGURE GUIDELINES FOR EDITORIAL SUBMISSION (SUBI POR SEPARADO EN EDITORIAL MANAGER)

Figure 1: Multiparametric data workflow diagram. Computational coregistration matrix of 3.0T MRI, FLAIR, PWI, and isotropic DTI datasets into the random forest segmentation engine. (TIFF format, 600 DPI).

Figure 2: Voxel-wise neoplastic infiltration probability mapping ($\boldsymbol{\beta_{idx}}$). Visual expansion of surgical margins inside the non-enhancing peritumoral zone validated against metabolic borders. (JPEG format, 300 DPI).

Figure 3: Intraoperative optical navigation view showing surgical trajectories and optimized cortical entrance corridors at a distance $\boldsymbol{d \geq 5.0\ mm}$ from key eloquent pathways. (TIFF format, 300 DPI).