

**DEVELOPMENT OF METHODS BASED
UPON MACHINE LEARNING, DEEP
LEARNING AND QUANTITATIVE MRI
FOR OBJECTIVE ASSESSMENT OF BRAIN
TUMORS**

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**CENTRE FOR BIOMEDICAL ENGINEERING
INDIAN INSTITUTE OF TECHNOLOGY DELHI**

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By

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CENTRE FOR BIOMEDICAL ENGINEERING

**Submitted in fulfillment of requirements of degree of Doctor of
Philosophy to the**



INDIAN INSTITUTE OF TECHNOLOGY DELHI

JUNE, 2025

Dedicated

to

My Parents & Family, Teachers

and

Almighty God

CERTIFICATE

This is to certify that the thesis entitled “**DEVELOPMENT OF METHODS BASED UPON MACHINE LEARNING, DEEP LEARNING, AND QUANTITATIVE MRI FOR OBJECTIVE ASSESSMENT OF BRAIN TUMORS,**” being submitted by Mr. **Virendra Kumar Yadav** to the Indian Institute of Technology Delhi for the award of ‘**Doctor of Philosophy**’, is a record of the bona fide research work carried out by him under our supervision and guidance. He has fulfilled the requirements for submission of this thesis, which, to the best of our knowledge, has reached the requisite standard. The material in the thesis has not been submitted, in part or whole, to any other university or institute for the award of any other degree or diploma.



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ABSTRACT

This thesis addresses some of the critical challenges in brain tumor diagnosis, classification, and post-surgical evaluations. By leveraging advanced quantitative imaging techniques, machine learning, and deep learning approaches, the studies aim to bridge some of the existing gaps in tumor segmentation, grading, and treatment planning, thereby improving diagnostic accuracy and optimizing therapeutic interventions.

This thesis consists of 5 chapters. Chapter 1 includes background about brain tumors, particularly Glioma. It also provides details on the role of MRI in its diagnosis, treatment planning, and monitoring. Some details on machine learning and deep learning are also included. A detailed literature review of the current research work in brain tumors is provided, followed by identifying research gaps. Finally, it presents the objectives of the current study, data information, and thesis outlines. Chapter 2 focuses on automated brain tumor segmentation. Accurate segmentation is vital for clinicians to make informed decisions regarding treatment strategies and monitor disease progression effectively. In this chapter, three sub-studies were conducted to develop frameworks using ML and DL models to segment gliomas and their subcomponents, such as enhancing tumors, non-enhancing tumors, and necrotic regions. The studies utilized multi-parametric MRI data from glioma patients. Optimization of the segmentation frameworks, including U-Net, MultiRes U-Net, and nnU-Net architectures, ensured robust and generalizable performance across multicenter datasets. Chapter 3 is on the grading and classification of gliomas, a critical aspect of brain tumor management that influences prognosis and therapeutic strategies. Conventional MR imaging often falls short of capturing the physiological

changes associated with tumor progression, necessitating advanced imaging methods. This chapter introduces two sub-studies for pre-operative glioma grading and subtype classification using quantitative DCE-MRI parameters and ML models. The first study focuses on distinguishing low-grade gliomas from high-grade gliomas based on quantitative perfusion parameters. The second study further classifies glioblastomas into IDH wild type and IDH mutant subtypes, which have distinct prognostic and therapeutic implications. A novel imaging biomarker, the "Fragmented Tumor Vasculature (FTV) sign," observed on susceptibility-weighted imaging, was proposed for differentiating IDH_{wt} glioblastomas from IDH_{mt} grade 4 astrocytomas.

Chapter 4 focuses on two critical challenges in the post-surgical evaluation of glioblastoma: distinguishing true progression from pseudoprogression and accurately segmenting post-surgical cavities. The first study integrates quantitative diffusion and perfusion MRI parameters with MGMT promoter methylation status to develop ML models for TP and PsP discrimination. On conventional neuroimaging, TP and PsP often present similar features, leading to diagnostic uncertainty for radiologists and oncologists. Misclassification can result in unnecessary repeat surgeries or the administration of expensive and potentially harmful therapies. By providing a precise distinction between TP and PsP, the proposed framework enables oncologists to adapt treatment plans promptly and reduce the psychological burden of "scanxiety" experienced by patients and their families.

The second study in Chapter 4 introduces a U-Net-based DL framework for segmenting post-surgical cavities in glioma patients. Accurate segmentation of resection cavities is essential for assessing the extent of tumor removal, planning

subsequent treatments like radiation therapy, and monitoring disease recurrence. Finally, Chapter 5 presents the conclusion and future directions.

Collectively, the studies presented in this thesis leverage quantitative multi-parametric MRI data and advanced ML/DL methodologies to address significant challenges in brain tumor management. By automating tumor segmentation, improving grading and classification accuracy, and enhancing post-surgical evaluation, these methods aim to optimize diagnostic workflows and support clinicians in making data-driven decisions.

Keywords: Tumor Segmentation, Dynamic Contrast-Enhanced MRI, Glioma Grading, Machine Learning, Deep Learning

सारांश

यह शोधपत्र मस्तिष्क ट्यूमर निदान, वर्गीकरण, और पोस्ट-सर्जिकल मूल्यांकन में कुछ महत्वपूर्ण चुनौतियों का समाधान करता है। उन्नत मात्रात्मक इमेजिंग तकनीकों, मशीन लर्निंग और डीप लर्निंग दृष्टिकोणों का उपयोग करके, यह अध्ययन ट्यूमर के खंडीयकरण, ग्रेडिंग और उपचार योजना में मौजूद कुछ महत्वपूर्ण अंतरालों को पाटने का प्रयास करता है, जिससे निदान की सटीकता में सुधार हो और चिकित्सीय हस्तक्षेपों का अनुकूलन किया जा सके। यह शोध कुल पाँच अध्यायों में विभाजित है। अध्याय 1 में मस्तिष्क ट्यूमर, विशेष रूप से ग्लियोमा की पृष्ठभूमि प्रस्तुत की गई है। इसमें इसके निदान, उपचार योजना और निगरानी में एमआरआई की भूमिका पर चर्चा की गई है। साथ ही, मशीन लर्निंग और डीप लर्निंग की संक्षिप्त जानकारी भी दी गई है। इस अध्याय में मस्तिष्क ट्यूमर से संबंधित वर्तमान शोध कार्यों की विस्तृत साहित्य समीक्षा प्रस्तुत की गई है, जिससे अनुसंधान में मौजूद प्रमुख अंतरालों की पहचान की गई। अंत में, इस अध्ययन के उद्देश्य, डेटा संबंधी जानकारी और शोध की रूपरेखा प्रदान की गई है।

अध्याय 2 मस्तिष्क ट्यूमर के स्वचालित खंडीयकरण पर केंद्रित है। सटीक खंडीयकरण चिकित्सकों को उपचार रणनीतियाँ निर्धारित करने और रोग की प्रगति की प्रभावी निगरानी में सहायता करता है। इस अध्याय में तीन उप-अध्ययन किए गए, जिनमें एमएल और डीएल मॉडलों का उपयोग करके ग्लियोमा और उसके उपघटकों, जैसे कि संवर्धित ट्यूमर, गैर-संवर्धित ट्यूमर और नेक्रोटिक क्षेत्रों के खंडीयकरण हेतु रूपरेखा विकसित की गई। इन अध्ययनों में ग्लियोमा रोगियों से प्राप्त मल्टी-पैरामीट्रिक एमआरआई डेटा का उपयोग किया गया। खंडीयकरण रूपरेखाओं का अनुकूलन, जिसमें यू-नेट, मल्टीरेस यू-नेट और एनएनयू-नेट आर्किटेक्चर

शामिल हैं, बहु-केंद्रित डेटासेट्स पर मजबूत और सामान्यीकृत प्रदर्शन सुनिश्चित करने के लिए किया गया।

अध्याय 3 ग्लियोमा के ग्रेडिंग और वर्गीकरण पर केंद्रित है, जो मस्तिष्क ट्यूमर प्रबंधन का एक महत्वपूर्ण पहलू है और रोग की भविष्यवाणी एवं उपचार रणनीतियों को प्रभावित करता है। पारंपरिक एमआर इमेजिंग अक्सर ट्यूमर प्रगति से संबंधित शारीरिक परिवर्तनों को सटीक रूप से पहचानने में असमर्थ होती है, जिससे उन्नत इमेजिंग विधियों की आवश्यकता होती है। इस अध्याय में पूर्व-ऑपरेटिव ग्लियोमा ग्रेडिंग और उपप्रकार वर्गीकरण के लिए दो उप-अध्ययन प्रस्तुत किए गए हैं, जिनमें मात्रात्मक डायनेमिक कंट्रास्ट-एन्हांसड मैग्नेटिक रेजोनेंस इमेजिंग पैरामीटर्स और एमएल मॉडल्स का उपयोग किया गया। पहला अध्ययन निम्न-ग्रेड ग्लियोमा और उच्च-ग्रेड ग्लियोमा को मात्रात्मक परफ्यूजन पैरामीटर्स के आधार पर विभेदित करने पर केंद्रित है। दूसरा अध्ययन ग्लियोब्लास्टोमा को आईडीएच वाइल्ड टाइप और आईडीएच म्यूटेंट उपप्रकारों में वर्गीकृत करता है, जो रोग की भविष्यवाणी और उपचार के दृष्टिकोण से महत्वपूर्ण हैं। इस अध्ययन में एक नवीन इमेजिंग बायोमार्कर "फ्रैगमेंटेड ट्यूमर वास्कुलचर संकेत", जिसे संवेदनशीलता भारित इमेजिंग पर देखा गया, प्रस्तावित किया गया है, जो आईडीएच वाइल्ड टाइप ग्लियोब्लास्टोमा को आईडीएच म्यूटेंट ग्रेड 4 एस्ट्रोसाइटोमा से भिन्न करने में सहायक है।

अध्याय 4 ग्लियोब्लास्टोमा के शल्य चिकित्सा के बाद के मूल्यांकन में दो प्रमुख चुनौतियों से संबंधित है: सत्य प्रगति और छद्म प्रगति के बीच अंतर करना और शल्य-चिकित्सा उपरांत गुहाओं का सटीक खंडीकरण। पहले अध्ययन में मात्रात्मक डिफ्यूजन और परफ्यूजन एमआरआई पैरामीटर्स को O-6-मेथिलगुआनिन-डीएनए मेथिलट्रांसफ़ेरेस प्रमोटर मिथाइलेशन स्टेटस के साथ एकीकृत कर एमएल मॉडल विकसित किए गए, जो सत्य प्रगति और छद्म प्रगति के बीच

भेद कर सकते हैं। पारंपरिक न्यूरोइमेजिंग में, सत्य प्रगति और छद्म प्रगति अक्सर समान विशेषताओं के साथ दिखाई देते हैं, जिससे रेडियोलॉजिस्ट और ऑन्कोलॉजिस्ट के लिए निदान में अनिश्चितता उत्पन्न होती है। गलत वर्गीकरण के कारण अनावश्यक शल्य क्रियाएँ या महंगे एवं संभावित रूप से हानिकारक उपचार किए जा सकते हैं। प्रस्तावित रूपरेखा, सत्य प्रगति और छद्म प्रगति के बीच सटीक अंतर प्रदान करके, ऑन्कोलॉजिस्ट को उपचार योजना को शीघ्रता से समायोजित करने और रोगियों तथा उनके परिवारों द्वारा अनुभव किए जाने वाले "स्कैनाइटी" के मानसिक तनाव को कम करने में सहायता करती है। अध्याय 4 का दूसरा अध्ययन ग्लियोमा रोगियों में शल्य उपरांत गुहाओं के खंडीयकरण के लिए एक यू-नेट आधारित डीप लर्निंग रूपरेखा प्रस्तुत करता है। पुनःकर्षण की निगरानी, विकिरण चिकित्सा जैसी उपचार रणनीतियाँ निर्धारित करने और ट्यूमर निष्कासन की सीमा का मूल्यांकन करने के लिए इन गुहाओं का सटीक खंडीयकरण आवश्यक है। अंत में, अध्याय 5 में अध्ययन के निष्कर्ष और भविष्य की दिशाएँ प्रस्तुत की गई हैं।

कुल मिलाकर, इस शोध में प्रस्तुत अध्ययनों ने मात्रात्मक मल्टी-पैरामीट्रिक एमआरआई डेटा और उन्नत मशीन लर्निंग एवं डीप लर्निंग पद्धतियों का उपयोग करके मस्तिष्क ट्यूमर प्रबंधन की प्रमुख चुनौतियों का समाधान करने का प्रयास किया है। स्वचालित ट्यूमर खंडीयकरण, ग्रेडिंग और वर्गीकरण की सटीकता में सुधार, तथा शल्य चिकित्सा के बाद के मूल्यांकन को सशक्त बनाने के माध्यम से, ये विधियाँ निदान प्रक्रियाओं को अनुकूलित करने और चिकित्सकों को डेटा-आधारित निर्णय लेने में सहयोग देने के उद्देश्य से विकसित की गई हैं।

किवर्ड्स: ट्यूमर खंडीयकरण, डायनेमिक कांट्रास्ट-एन्हांसड एमआरआई, ग्लियोमा ग्रेडिंग, मशीन लर्निंग, डीप लर्निंग

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Abbreviations

Biological and Clinical Terms

CNS	Central Nervous System
PNS	Peripheral Nervous System
WHO	World Health Organization
VEGF	Vascular Endothelial Growth Factor
IDH	Isocitrate Dehydrogenase
MGMT	O(6)-Methylguanine-DNA Methyltransferase
2-HG	2-Hydroxyglutaric Acid
HIF	Hypoxia-Inducible Factor
NADP+-	Nicotinamide Adenine Dinucleotide Phosphate
HIPAA	Health Insurance Portability and Accountability Act

Imaging Techniques

MRI	Magnetic Resonance Imaging
CT	Computed Tomography
PET	Positron Emission Tomography
DWI	Diffusion-Weighted Imaging
DTI	Diffusion Tensor Imaging
DCE-MRI	Dynamic Contrast-Enhanced MRI
DSC	Dynamic Susceptibility Contrast
MRS	Magnetic Resonance Spectroscopy
FLAIR	Fluid-Attenuated Inversion Recovery
PD	Proton Density
T₁-IR	Inversion Recovery

Tumor and Physiological Parameters

BBB	Blood Brain Barrier
EES	Extravascular Extracellular Space
AIF	Arterial Input Function
BAT	Bolus Arrival Time
CBV	Cerebral Blood Volume
CBF	Cerebral Blood Flow
MTT	Mean Transit time
VASARI	Visually Accessible Rembrandt Images
ITSS	Intra-Tumoral Susceptibility Signal
FTV	Fragmented Intra-Tumoral Thrombosed Microvasculature
ADC	Apparent Diffusion Coefficient
MD	Mean Diffusivity
FA	Fractional Anisotropy
CL	Linear Anisotropy
CP	Planar Anisotropy
CS	Spherical Anisotropy

Tumor Classification

LGG	Low Grade Glioma
HGG	High Grade Glioma
IDH_{wt}	IDH Wild Type
IDH_{mt}	IDH Mutant Type
GBM	Glioblastoma
TP	True Progression
PsP	Pseudoprogression
WT	Whole Tumor
ET	Enhancing Tumor
NCR	Necrotic Tumor

NET Non-Enhancing Tumor

Machine Learning & Deep Learning

AI Artificial Intelligence
ML Machine Learning
DL Deep Learning
SVM Support Vector Machines
RF Random Forests
LR Logistic Regression
KNN k-Nearest Neighbor
CNN Convolutional Neural Networks
ReLU Rectified Linear Unit
BCE Binary Cross Entropy
MSE Mean Squared Error
SMOTE Synthetic-Minority-Oversampling-technique
RBF Radial Basis Function
nnU-Net no-new-U-Net
MultiRes U-Net Multi-Resolution U-Net
V-Net Volumetric Network
ResNet Residual Network
FCN Fully Convolutional Network

Accuracy Metrics

TA Training Accuracy
VA Validation Accuracy
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Technical Terms

QP	Quantitative Parameters
FOV	Field of View
QPP	Quantitative Perfusion Parameters
SE	Spin Echo
FSE	Fast Spin Echo
RT	Relaxation Time
SPGR	Spoiled Gradient Recalled Echo
RF	Radio Frequency
LM	Levenberg-Marquardt
FT	Fourier Transform
TTFields	Tumor Treating Fields
SOC	Standard of Care
SPD	Sum of the Products of Diameters
GLCM	Grey-Level Co-occurrence Matrix
GLDM	Grey-Level Co-dependence Matrix
GLRLM	Grey-Level Run Length Matrix