

**RADIOMICS ANALYSIS OF MAGNETIC RESONANCE
IMAGING FOR RADIOSURGERY PLAN QUALITY
ASSESSMENT AND GENETIC MUTATION DETECTION
IN BRAIN TUMORS**

by

Esra Sümer Arpak

B.S., in Biomedical Engineering, Erciyes University, 2015

M.S., in Electrical and Computer Engineering, Abdullah Gül University, 2018

Submitted to the Institute of Biomedical Engineering
in partial fulfillment of the requirements
for the degree of
Doctor
of
Philosophy

Boğaziçi University

2025

**RADIOMICS ANALYSIS OF MAGNETIC RESONANCE
IMAGING FOR RADIOSURGERY PLAN QUALITY
ASSESSMENT AND GENETIC MUTATION DETECTION
IN BRAIN TUMORS**

APPROVED BY:

Prof. Dr. Esin Öztürk Işık
(Thesis Advisor)

Prof. Dr. Ahmet Ademoğlu

Assoc. Prof. Dr. Ayça Erşen Danyeli

Asst. Prof. Dr. Ali Bayram

Asst. Prof. Dr. Pınar S. Özbay

DATE OF APPROVAL: 16 January 2025

ACKNOWLEDGMENTS

I'm truly fortunate to have Prof. Dr. Esin Ozturk-Isik as my mentor, role model, and thesis advisor. Her expertise, patience, dedication in excellence, and teaching me about being a good researcher have shaped not just this thesis but my growth as a researcher. Beyond academic guidance, I thank her for all the support and encouragement in my personal life.

I thank my thesis committee members Prof. Dr. Ahmet Ademoğlu and Asst. Prof. Dr. Ali Bayram for their invaluable comments throughout my Ph.D. work. I also thank Prof. Dr. Alp Dincer and Assoc. Prof. Dr. Ayça Erşen Danyeli for their help with clinical questions and providing clinical data for my thesis work. I also wish to thank the members of the Computational Imaging Laboratory, my great friends, and future colleagues Gökçe Hale Hatay, Asım Samlı, Gülce Turhan, Buse Buz Yaluğ, Tuğay İlyasoğlu Güven, and Ayşe İrem Çetin for their endless help, all invaluable scientific discussions, and making the work environment peaceful and fun. I also thank all my schoolmates and dormmates, Morteza Teymoori, Samet Şahin, and İlayda Duru for making Boğaziçi University a memorable experience. I wish to thank Meryem Şahin Erdoğan and Sefa Erdoğan for their great friendship, like a family, and for sharing the countless moments of laughter and experiences we had over the years. I would also like to thank Bengisu and Çağatay Koçer for being there from the beginning as precious companions in my life.

I wish to thank my parents, Selma and Nusret Sümer, and my sisters, Fatma and Serap, for their unconditional love and support in my life. I thank my brothers-in-law, Emir Oker, and Harun Varinli, for their encouragement and support. I feel deeply happy to belong to such a loving and supportive family. Lastly, I want to thank my husband, Arda Arpak, who is my constant source of motivation and strength. His endless love, patience, and unwavering support have been the key during the most challenging moments. I am also grateful to his family, Leman, Mahir, and Aslı Arpak

for their encouragement and support during this Ph.D. journey.

This thesis was supported by Technological Research Council of Turkey (TUBITAK) 2211A National Ph.D. Fellowship Programme, TUBITAK 1003 grant (#216S432), TUBITAK 1001 grant (#119S520), and Boğaziçi University Scientific Research Fund (#19482P). Additionally, I would like to acknowledge The Council of Higher Education 100/2000 Ph.D. scholarship program, allowing me to focus on my thesis work.



ACADEMIC ETHICS AND INTEGRITY STATEMENT

I, Esra Sümer Arpak, hereby certify that I am aware of the Academic Ethics and Integrity Policy issued by the Council of Higher Education (YÖK) and I fully acknowledge all the consequences due to its violation by plagiarism or any other way.

Name :

Signature:

Date:

ABSTRACT

RADIOMICS ANALYSIS OF MAGNETIC RESONANCE IMAGING FOR RADIOSURGERY PLAN QUALITY ASSESSMENT AND GENETIC MUTATION DETECTION IN BRAIN TUMORS

Magnetic resonance imaging (MRI) is essential in clinical practice for understanding brain tumor biology, optimizing treatment strategies, and predicting prognosis. Recent advancements in computation and artificial intelligence have integrated MRI into big data for precision medicine. Radiomics, a noninvasive and quantitative technique, converts imaging data into high-dimensional datasets, revealing encrypted information linking to the tumor pathophysiology to improve the precision of diagnosis, prognosis, and treatment planning. This thesis focused on specific brain tumors—vestibular schwannomas, gliomas, and meningiomas—and included clinical, anatomical imaging, and pathological data. We aimed to develop radiomics-based pipelines to: i) evaluate Gamma Knife dose planning quality and treatment outcomes, ii) predict isocitrate dehydrogenase (IDH) mutation status and prognosis in glioma patients with validation on an external dataset, and iii) assess alterations in neurofibromatosis type 2 (NF2) gene and predict recurrence-free survival (RFS) in meningiomas. The key findings of the dissertation included: tumor shape irregularity affected Gamma Knife dose planning quality without having an influence on treatment outcomes for vestibular schwannomas; the degree of sphericity and intensity patterns of gliomas on MRI were important predictors of IDH mutation status and prognosis; and structural MRI radiomics were strongly correlated with NF2 loss and RFS in meningiomas. These results highlighted the potential of radiomics in the decision-making framework, providing new insights into neurooncology.

Keywords: Magnetic Resonance Imaging, Brain Tumors, Radiomics, Machine Learning, Survival.

ÖZET

BEYİN TÜMÖRLERİNDE RADYOCERRAHİ PLANI KALİTESİNİN DEĞERLENDİRİLMESİ VE GENETİK MUTASYON TESPİTİ İÇİN MANYETİK REZONANS GÖRÜNTÜLEME'NİN RADYOMİK ANALİZİ

Manyetik rezonans görüntüleme (MRG), beyin tümörü biyolojisinin anlaşılması, tedavi stratejilerinin optimize edilmesi ve prognozun öngörülmesi açısından klinik pratikte temel bir araçtır. Hesaplama ve yapay zeka alanındaki son gelişmeler, MRG'yi hassas tıp için büyük veri analizine entegre etmiştir. Radyomikler, invaziv olmayan ve nicel bir teknik olarak, görüntüleme verilerini yüksek boyutlu veri setlerine dönüştürerek, tümör fizyopatolojisiyle bağlantılı şifreli bilgileri ortaya çıkarır ve tanı, prognoz ve tedavi planlamasının hassasiyetini artırır. Bu tez, vestibüler schwannomlar, gliomalar ve meningiomlar gibi belirli beyin tümörlerine odaklanmış ve klinik, anatomik görüntüleme ve patolojik verileri içermektedir. Tezin amacı, radyomik tabanlı iş akışları geliştirerek: i) Gamma Knife doz planlama kalitesini ve tedavi sonuçlarını değerlendirmek, ii) glioma hastalarında izositrat dehidrojenaz (IDH) mutasyon durumunu ve prognozu öngörmek (harici bir veri setiyle doğrulama ile), iii) nörofibromatozis tip 2 (NF2) genindeki değişiklikleri değerlendirmek ve meningiomalarda nüksüz sağkalımı (recurrence free survival-RFS) tahmin etmektir. Tezin temel bulguları şunları içermektedir: Tümör şekilsizliği, vestibüler schwannomlar için Gamma Knife doz planlama kalitesini etkilerken, tedavi sonuçlarını etkilememiştir; gliomaların MRG'deki küresellik derecesi ve yoğunluk desenleri, IDH mutasyon durumu ve prognozun önemli öngörücüleri; yapısal MRI radyomikleri, NF2 kaybı ve meningiomalarda RFS ile güçlü bir şekilde ilişkililiydi. Bu sonuçlar, radyomiklerin karar verme süreçlerindeki potansiyelini vurgulamakta ve nöroonkolojiye yeni bakış açıları sunmaktadır.

Anahtar Sözcükler: Manyetik Rezonans Görüntüleme, Beyin Tümörleri, Radyomikler, Makine Öğrenmesi, Sağkalım.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	iii
ACADEMIC ETHICS AND INTEGRITY STATEMENT	v
ABSTRACT	vi
ÖZET	vii
LIST OF FIGURES	xi
LIST OF TABLES	xv
LIST OF SYMBOLS	xvi
LIST OF ABBREVIATIONS	xvii
1. BACKGROUND	1
1.1 Primary Brain Tumors	1
1.1.1 Vestibular Schwannoma	2
1.1.2 Glioma	3
1.1.3 Meningioma	5
1.2 Gamma Knife Stereotactic Radiosurgery	6
1.3 Magnetic Resonance Imaging of Brain Tumors	10
1.4 Radiomics as Image-based Biomarkers for Precise Medicine	14
1.4.1 Radiomics Applied on Brain Tumors	19
1.5 Aim and Outline of the Thesis	20
2. THE EFFECT OF TUMOR SHAPE IRREGULARITY ON GAMMA KNIFE TREATMENT PLAN QUALITY AND TREATMENT OUTCOME: AN ANAL- YSIS OF 234 VESTIBULAR SCHWANNOMAS	21
2.1 Introduction	21
2.2 Materials and Methods	23
2.2.1 Subjects	23
2.2.2 Magnetic Resonance Imaging	23
2.2.3 GK Treatment and Dose Plan Indices	23
2.2.4 Feature Extraction	24
2.2.5 Statistical Analysis	25
2.2.6 Machine Learning for Prediction of Dose Plan Quality	27

2.2.7	Treatment Outcome Analysis	28
2.3	Results	29
2.3.1	Patient Population, Dose Plan Indices, and Shape Irregularity Features	29
2.3.2	Correlations Between Dose Plan Indices and Shape Irregularity Features	29
2.3.3	Correlations Between Dose Plan Indices and Shape Irregularity Features in Patient Subgroups Stratified by Tumor Volume . . .	34
2.3.4	Associations of Shape Irregularity Features and Dose Planning Indices	35
2.3.5	Feature Selection and Machine Learning Models	35
2.3.6	The Effects of VioS and Dose Plan Indices on Treatment Outcome	39
2.4	Discussion	39
2.5	Conclusion	46
3.	T2W MRI RADIOMICS MODELS TO PREDICT IDH MUTATION STATUS AND SURVIVAL IN GLIOMAS: A MULTICENTER STUDY	47
3.1	Introduction	47
3.2	Methods	49
3.2.1	Patients, Imaging Protocol, and Tumor Segmentation	49
3.2.2	Pathological and Genetic Evaluation	50
3.2.3	Pre-processing of Data	50
3.2.4	Feature Extraction, Model Construction, and External Validation	50
3.2.5	Statistical Analysis	52
3.2.6	Radiomic Risk Score Computation	53
3.2.7	Survival Analysis	53
3.3	Results	54
3.3.1	Patient Characteristics and Harmonization of Two Cohorts . . .	54
3.3.2	Identifying Radiomic Features Associated with IDH Mutation .	55
3.3.3	Performances of Radiomics Classifiers in Identifying IDH Mutation	56
3.3.4	Performance of the Survival Prediction Models	59
3.4	Discussion	64
3.5	Conclusion	67

4. RADIOMICS TO PREDICT NF2-LOSS AND RECURRENCE IN MENINGIOMAS	68
4.1 Introduction	68
4.2 Methods	69
4.2.1 Patient Characteristics for Predicting NF2 Loss	69
4.2.2 Radiomics Analysis	69
4.2.3 Recurrence Prediction	70
4.3 Results	71
4.3.1 NF2-Loss Prediction	71
4.3.2 Recurrence Prediction	72
4.4 Discussion	74
4.4.1 Prediction of NF2-Loss	74
4.4.2 Prediction of Recurrence	76
4.5 Conclusion	76
5. CONCLUSION	78
REFERENCES	80

LIST OF FIGURES

Figure 1.1	Anatomical presentation of VS. Illustration of anatomical sites of vestibular and cochlear nerves [1].	3
Figure 1.2	Flowchart showing the diagnostic steps in adult type diffuse gliomas, based on the most relevant molecular markers [2].	5
Figure 1.3	The brain structures that meningiomas originate. Meningiomas may progress to invade dura mater with several high-risk alterations [3].	6
Figure 1.4	Graphic representation of a single dose plan. The red area in DVH is for the target, and the green DVH is for a larger area that includes the target and doses above 9 Gy. The blue area represents regions where the dose is below 50% of the prescribed dose threshold (<9 Gy) [4].	7
Figure 1.5	Series images of a patient with right-sided VS: (a) CE-T1w, (b) T2w, (c) CE-T1w with tumor segmentation [5].	11
Figure 1.6	The MRI images of patients with WHO grade 2 astrocytoma (top row) and WHO grade 4 glioblastoma (bottom row). From left to right: CE-T1w, FLAIR, T2w, and pre-contrast T1w MRI sequences are shown. [6].	12
Figure 1.7	MRI scans of WHO grade 2 astrocytoma before first surgery in A) a T2-weighted sequence and B) a FLAIR sequence. A follow-up examination 11 years after surgery showed C) an enlargement of the remaining lesion on T1w and D) DSC showed high rCBV, indicating WHO grade 4 astrocytoma [7].	13
Figure 1.8	Axial MRI images of malignant meningioma: A) T1w, B) CE-T1w axial presenting a heterogeneously enhancing mass with dural tail. C) Axial T2w image displaying surrounding edema. D) A DWI image showing heterogeneous areas of restricted diffusion. [8].	15

Figure 1.9	The general workflow of radiomics includes image acquisition, image pre-processing, tumor segmentation, feature extraction, feature selection, and analysis.	16
Figure 1.10	Calculation of example radiomics features: GLCM and GLRLM at $\theta = 0$ (adapted from [9]).	18
Figure 2.1	A perfect sphere ($a = b = c$) was given in A. The brain tumors are not perfect spheres, and they have different axis lengths as depicted in B ($a \neq b \neq c$) (adapted from Saad et al. [10]).	25
Figure 2.2	Workflow of the shape feature extraction. (I) MRI images of two representative vestibular schwannomas. (II) The tumor ROIs (red) were defined by an experienced neurosurgeon. (III) 3D tumor models constructed using tumor outlining. (IV) Tree different shape features for tumor A and B. The differences in shape irregularity in the two tumors can be identified by investigating their fatness, elongation, and VioS. Tumor A was flat and irregular, tumor B was more spherical.	26
Figure 2.3	The violin plots outline the median value (white dot) and interquartile range (thick gray bar) of the shape irregularity features: (A) sphericity, (B) elongation, (C) compactness, (D) flatness, (E) spherical disproportion, (F) SVR_N , and (G) VioS for different TV subgroups. The P-values were Bonferroni adjusted and obtained using a Kruskal-Wallis test followed by Dunn's post-hoc test.	31
Figure 2.4	The univariate linear regression analysis results for the correlation of VioS with SI, GI, EI, and PCI.	36
Figure 2.5	Comparisons of patient characteristics and dose plan indices with/without hearing preservation (A) and tumor growth control (B).	42
Figure 3.1	Workflow for image preprocessing and radiomics feature extraction.	51
Figure 3.2	Workflow for model training and external validation regarding the application of ComBat harmonization to radiomics features. The models were trained and externally validated using both features with and without ComBat harmonization.	51

Figure 3.3	The overall pipeline of radiomics models using the discovery dataset is shown, with the models being externally validated using the validation cohort.	53
Figure 3.4	The impact of image intensity normalization applied to T2w MR images: (A) before intensity normalization and (B) after intensity normalization. Each line represents a patient's image intensity histogram [11].	55
Figure 3.5	Violin plots show the distributions of twelve selected features in the IDH-wt and IDH-mut subgroups of Cohort 1. For each pair of distributions, P-values were computed from the Mann-Whitney U test with Bonferroni correction ($P < 0.0042$).	57
Figure 3.6	Top-selected radiomics features identified using discovery cohort were also tested using validation cohort along with Mann-Whitney U test with Bonferroni correction ($P < 0.0042$) for discriminating IDH-wt and IDH-mut tumors.	58
Figure 3.7	The impacts of the RS, sex, age, and tumor grade on OS in multivariable Cox analysis: (A) overall discovery cohort, (B) overall external validation cohort, (C) IDH-wt patients of discovery cohort, and (D) IDH-wt patients of validation cohort (red: $P < 0.0125$).	61
Figure 3.8	The Kaplan-Meier survival curves of patients in Cohort 1 (A), Cohort 2 (B), and IDH-wt subgroups of Cohort 1 (C) and Cohort 2 (D) are displayed as low-risk (blue) and high-risk (red) groups. The differences of OS between the low- and high-risk groups were assessed by Log-rank tests.	63
Figure 4.1	The workflow of the study for prediction of NF2 status in meningioma patients.	70
Figure 4.2	The workflow of the study for prediction of NF2 status in meningioma patients.	71
Figure 4.3	The most informative features (Lasso selection frequency $> 80\%$) for differentiating NF2-NL and NF2-L meningiomas (* P : 0.008).	73

Figure 4.4	The distributions of selected radiomics and clinical features in the recurrent and non-recurrent PFM (*P:0.05).	74
Figure 4.5	The impact of the selected radiomics and clinical features on RFS in multivariable Cox analysis (red: $P < 0.05$).	75



LIST OF TABLES

Table 2.1	Description of five radiomic features extracted from tumor models.	27
Table 2.2	Patient characteristics and summary of dose planning indices of this study (*: $P < 0.05$ and **: $P < 0.001$).	30
Table 2.3	Spearman correlation analysis of all tumor models (overall) and subgroups (Group 1/2/3) for evaluating the relationship of each shape feature with dose planning indices (* $P < 0.00125$).	33
Table 2.4	Univariate linear regression analysis results using VioS.	35
Table 2.5	Best classification results for each dose plan indices using either the features selected by RFE-SVM or VioS in the training and test datasets.	38
Table 2.6	Summary demographic, clinical, and plan indices of patients included in the outcome analysis.	40
Table 2.7	The results of univariable and multivariable analyses for examining Gardner-Robertson serviceable hearing preservation after GK radiosurgery.	41
Table 2.8	The results of univariable and multivariable analyses examining tumor growth control after GK radiosurgery.	41
Table 3.1	Clinical and molecular-pathologic variables in the two multicenter datasets.	56
Table 3.2	Classification performance of radiomics-based model on Cohort 1 and validation cohort (Cohort 2).	60
Table 3.3	Univariable and multivariable Cox proportional hazards regression for overall survival in discovery cohort (Cohort 1) and validation of survival model on Cohort 2 (* $P: 0.0125$).	62
Table 4.1	The selected features with frequencies of above 20% using Lasso feature selection process.	72
Table 4.2	Univariable and multivariable Cox proportional hazards regression for RFS following GK treatment in PFM (* $P: 0.05$).	75

LIST OF SYMBOLS

T	Tesla
χ^2	chi-square



LIST OF ABBREVIATIONS

2HG	2-hydroxyglutarate
ADC	Apperant diffusion coefficient
AUC	Area under curve
AVM	Arteriovenous malformations
BBB	Blood-brain barrier
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CDI	Conformity distance index
CE-T1w	Contrast enhanced T1w
CI	Conformity index
CNS	Central Nervous System
CT	Computed tomography
DCE	Dynamic contrast enhanced
DSC	Dynamic susceptibility contrast
DVH	Dose volume histograms
DWI	Diffusion weighted imaging
EGFR	Epidermal growth factor receptor
EI	Efficiency index
FLAIR	Fluid attenuated inversion recovery
GB	Gradient boost
GI	Gradient index
GK	Gamma Knife
GLCM	Gray level co-occurrence matrix
GLDM	Gray level dependence matrix
GLRLM	Gray level run length matrix
GLSZM	Gray Level Size Zone Matrix
HR	Hazard ratio
IDH-mut	IDH-mutant

IDH-wt	IDH-wildtype
IDH	Isocitrate dehydrogenase
kNN	k nearest neighbor
Lasso	Least absolute shrinkage and selection operator
ML	Machine learning
MRS	Magnetic resonance spectroscopy
NF2	Neurofibromatosis Type 2
NGTDM	Neighborhood Gray Tone Difference Matrix
PCA	Principle component analysis
PCI	Paddick's Conformity index
RF	Random forest
ROC	Receiver operating characteristic
ROI	Region of interest
RS	Risk score
RTOG	Radiation Therapy Oncology Group
SRS	Stereotactic radiosurgery
SVM	Support vector machine
SVR	Surface-to-Volume Ratio
SVR _N	Normalized Surface-to-Volume Ratio
T1w	T1-weighted
T2w	T2-weighted
TERT	Telomerase promoter
TSI	Tumor shape irregularity
TV	Target volume
VioS	Volumetric index of Sphericity
VOI	Volume of interest
VS	Vestibular Schwannomas
WHO	World Health Organization
XGBoost	Extreme gradient boost

1. BACKGROUND

1.1 Primary Brain Tumors

Primary brain tumors are uncontrolled growing cells originating from brain parenchyma and its adjacent structures. These tumors consist of a diverse range of both benign and malignant types and form 1.3% of all new cancer cases [12]. World-wide, brain tumors are a significant public health issue due to a low 5-year survival rate (33.4%) [12] and profoundly impacting patients' quality of life [13]. The cause of primary brain tumors remains poorly understood; but cancer-causing mutations play a central role. The main symptoms of brain tumors differ depending on the tumor's location, size, and aggressiveness. The most common symptoms are headaches, seizures, cognitive impairment, aphasia, depression, and motor deficits through the disease course [14]. There are four common approaches for treating brain tumors: surgery, chemotherapy, radiation therapy, and radiosurgery. Despite advances in treatment strategies, primary brain tumor survival rates have remained poor in recent years [15]. After complete resection along with chemotherapy, recovery from low-grade tumors with no or minimal deficits can be expected. However, high-grade gliomas are often not curable [16].

Formerly, the tumor classification was based on histological findings, such as ancillary immunohistochemical and ultrastructural examinations [17]. More recently, advancements in molecular examinations have led to dramatic changes in tumor classification systems, increasingly becoming based on molecular alterations, which carry great diagnostic and prognostic importance. The most recent World Health Organization classification of central nervous system tumors (WHO CNS5) classified more than 100 types of brain tumors, many with distinct types and variants, each with its spectrum of biological characteristics, treatments, and prognosis according to their molecular and histological features, highlighting the importance of precise diagnosis [17]. The WHO tumor grading system has long been used and is based on histological

markers such as proliferation, necrosis, nuclear atypia, and mitosis [18]. WHO tumor grading system aims to provide information on tumor aggressiveness and patient prognosis. Although subjective examination leads to inter-observer variations in tumor grading system based on histology [19], the grading system remained used in neurooncology. With the new WHO CNS classification, integrating histopathological findings with molecular features has enhanced the classification of brain tumors compared to relying solely on histopathological assessment.

1.1.1 Vestibular Schwannoma

Vestibular schwannomas (VS), also known as acoustic neuromas, are Schwann-originating cells of the vestibulocochlear nerve, accounting for 8% of all intracranial neoplasms (Figure 1.1) [20]. Although VS are usually benign, they have a significant risk of hydrocephalus and brainstem compression due to the enlarged mass effect. The patients with VS commonly present hearing loss, tinnitus, and vertigo [21]. The majority of VS are unilateral and sporadic (nonhereditary mutations), which can occur at any age. However, VS associated with Neurofibromatosis Type 2 (NF2) mutations (about 5%) leads to hereditary disease mostly at younger ages (ages of 20-40). When mutations affect the tumor suppressor gene NF2 on chromosome 22, it leads to the deregulation of signaling pathways responsible for the production of Schwann cells [22].

Management strategies vary for patients with VS, including observation, surgical resection, and radiotherapy, depending on tumor volume, aggressiveness, and patient status. Observe, watch, and rescan approach is an accepted option for the small growing VS, asymptomatic tumors, with regular MRI follow-ups to monitor growth [23]. Interventional treatment is preferred for removing the larger or symptomatic mass [24]. Stereotactic radiosurgery (SRS) is an important alternative to conventional surgery, particularly for medium-sized tumors or patients who are not surgical candidates. SRS proposes a minimally invasive and effective procedure for Koos grade I-III (scaling I-IV representing tumor growth characteristics) with high tumor control rates [25]. There

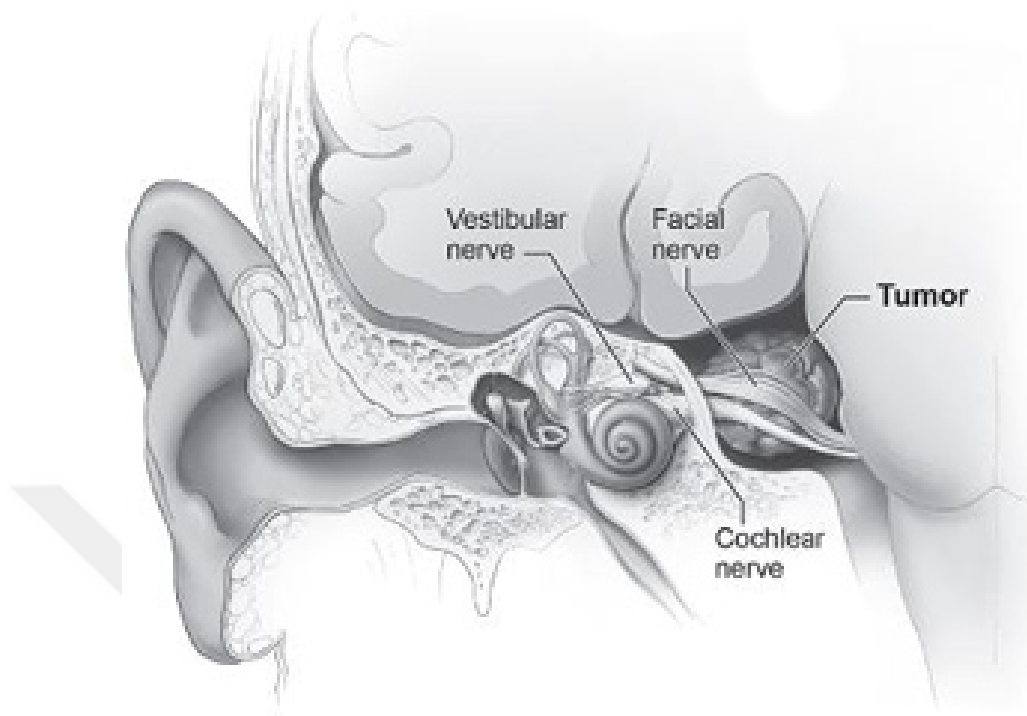


Figure 1.1 Anatomical presentation of VS. Illustration of anatomical sites of vestibular and cochlear nerves [1].

are various SRS treatment methods, including Gamma Knife (GK) [26], CyberKnife, and dedicated linear accelerator (LINAC) [27].

1.1.2 Glioma

Gliomas are infiltrative primary intracranial tumors accounting for about 24.5% of all primary brain and CNS tumors and 80.9% of malignant tumors [28]. These tumors arise from glial cells and rapidly infiltrate surrounding healthy tissues, leading to blood-brain barrier (BBB) disruptions, making them one of the most aggressive malignant brain tumors. New emerging knowledge of genetic alterations has improved glioma variants' characterization and definition. Each genetic biomarker is associated with a glioma variant with distinct histologic features and WHO grade of malignancy.

Isocitrate dehydrogenase (IDH1 or IDH2, IDH) has been the hallmark genetic alteration among these markers. IDH mutation (IDH-mut) catalyzes the formation of 2-hydroxyglutarate (2HG), leading to epigenetic changes in gene expression [29]. While these changes promote tumorigenesis, the resulting tumors often have a slower growth rate and less aggressive behavior compared to IDH-wildtype (IDH-wt) gliomas [30]. 1p/19q codeletion accompanying IDH mutation is used to define IDH-1p19q-codel and IDH-1p19q-non-codel glioma subtypes. IDH-1p19q-codel gliomas are oligodendrogliomas (WHO grade 2 and 3) usually co-occur with telomerase promoter (TERT) and capicua (CIC) mutations [17]. On the other hand, IDH-1p19q-non-codel gliomas (astrocytomas) typically co-express with alpha-thalassemia mental retardation X-linked (ATRX) and tumor protein p53 (TP53) mutations [17, 31] with WHO grade ranging in 2-4 [17]. Although two subtypes of gliomas—oligodendrogliomas and astrocytomas—have the common IDH-mut, their survival rates and treatment strategies still significantly differ [32]. This highlights the importance of combining multiple molecular features to classify into distinct entities, which is summarized in a flowchart with the most relevant genetic markers (Figure 1.2).

IDH-wt glioblastomas are usually rapid-growing, high grade (WHO grade 4), and present very poor prognosis [28]. TERT mutation, epidermal growth factor receptor (EGFR) amplification, and combined gain of chromosome 7/loss of chromosome 10 (+7/ − 10) play a significant role in prognosis and treatment outcome in glioblastomas. Although O6-methylguanine-DNA methyltransferase (MGMT) methylation was not included in CNS5 guidelines, it is a key prognostic biomarker in glioblastoma [33]. TERT mutation is thought to promote tumor growth in glioblastomas and TERT mutant (TERT-mut) IDH-wt patients have been reported to have the worst overall survival [34, 32].

Most patients with gliomas present symptoms of epilepsy, headache, neurocognitive impairment, and signals related to increased intracranial pressure [35]. The treatment strategy for gliomas consists of surgical resection, radiation therapy, and temozolomide chemotherapy depending on various factors, including genetic alterations, tumor location, tumor size, patient status, etc. [35]. The considerable heterogeneity

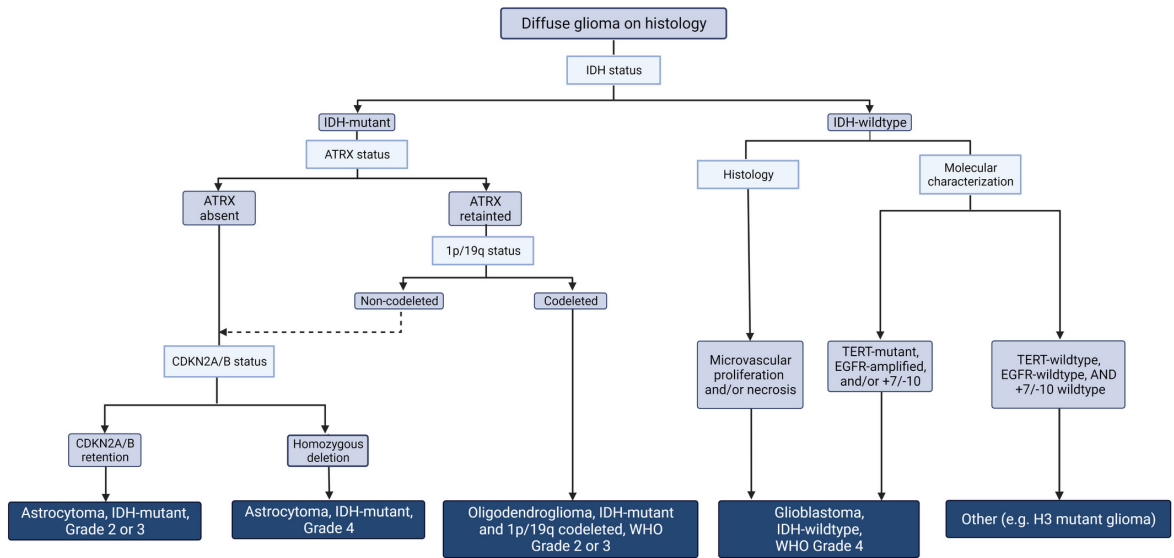


Figure 1.2 Flowchart showing the diagnostic steps in adult type diffuse gliomas, based on the most relevant molecular markers [2].

on both spatial and molecular levels highlights the inherent limitations of treatment options in gliomas.

1.1.3 Meningioma

Meningiomas are the most frequent primary intracranial tumors, accounting for approximately one-third of all primary CNS tumors [36]. These tumors arise usually from dura, and frequently observed at the skull base, and locations of dural reflections as shown in Figure 1.3 [37]. Although most meningiomas are slow growing, some variants could be more aggressive (WHO grades 2 and 3) and have severe risks for recurrence, brain invasion, and progression to higher grade [38]. Some symptoms, including fatigue, neurological deficits, headaches, and seizures, could be observed in patients with meningiomas.

Discoveries on genetic alterations in meningiomas led to more detailed subtype classification (currently 15 entities), directly improving the estimation of recurrence and prognosis. Alterations in NF2 seen in 60% of all meningiomas are the most fre-

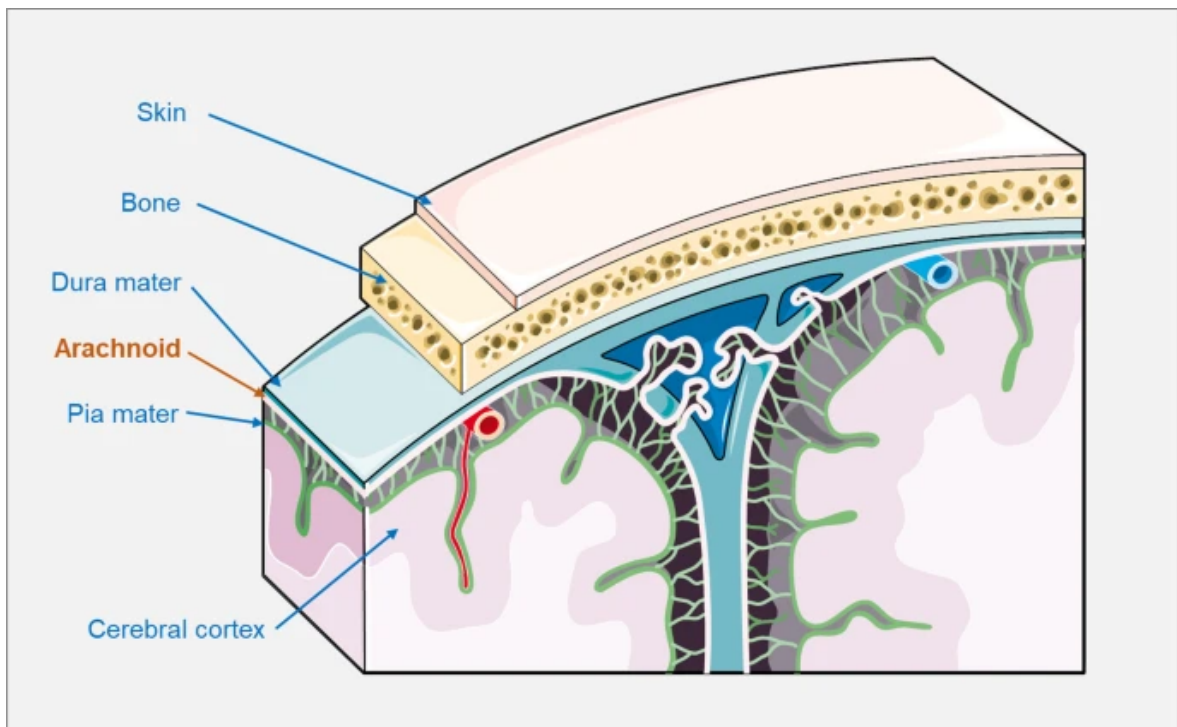


Figure 1.3 The brain structures that meningiomas originate. Meningiomas may progress to invade dura mater with several high-risk alterations [3].

quent [39] and are known as the initial alteration for aggressive type meningiomas [40]. Additionally, TERT-mut meningiomas tend to recur with poor treatment outcomes [41]. Most meningiomas are primarily treated with conventional surgery based on tumor size, location, genetic subtype, and patient symptoms. However, for patients who are not eligible for conventional surgery, either SRS or chemotherapy has been used as a first-line treatment [42].

1.2 Gamma Knife Stereotactic Radiosurgery

GK delivers a combination of small radiation beams to the targets, including benign and malignant tumors, functional disorders, and vascular malfunctions [43]. The high radiation beams intersect at an isocenter and construct nearly a spherical dose distribution inside the target, whereas the intensity of dose should decrease at a short distance from the isocenter to avoid delivering ablative radiation to the surrounding

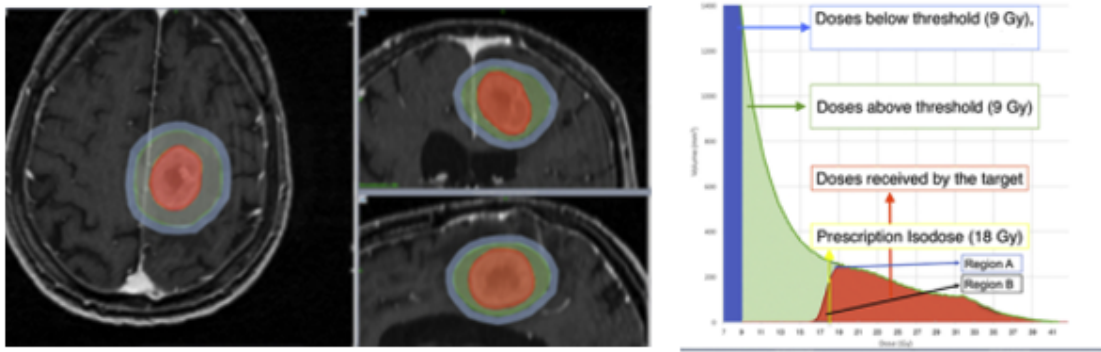


Figure 1.4 Graphic representation of a single dose plan. The red area in DVH is for the target, and the green DVH is for a larger area that includes the target and doses above 9 Gy. The blue area represents regions where the dose is below 50% of the prescribed dose threshold (<9 Gy) [4].

normal brain [44]. The GK treatment planning procedure begins with brain imaging using MRI or computed tomography (CT). Additionally, planar angiography can be an option for arteriovenous malformations (AVMs) [45]. After imaging, patients' images are transferred to the treatment planning system to map data into stereotactic space. Contouring is necessary to delineate the target and critical structures. The dose planning of GK is based on packing spherical doses into the target. GK planner tries to find the optimum locations and weights of isocenters iteratively.

The evaluation of dose distribution is essential to quantify the conformity and steepness of the dose gradient and compare multiple plans. The dose distribution of plans can be visualized and analyzed using isodose curves and dose volume histograms (DVH) (Figure 1.4). Isodose curves provide the level of radiation and allow to visualize whether radiation leaks out or if any part of the target is not irradiated with the prescribed dose [46]. DVH provide the uniformity of dose in the structure and offer insight into patient dosimetry [47]. The main shortcoming of DVHs is the absence of spatial information where the hot and cold spots are [44].

Moreover, comparing different treatment plans based on DVHs can lead to a complicated analysis of treatment plans, since it contains a large number of curves and lines for comparative plans [48]. To determine the quality of the treatment plan based

on a score, several dose plan indexes have been proposed over the years. The most frequently cited parameters for the scoring of radiosurgery treatment plan quality are coverage, homogeneity, and conformity, defined in the Radiation Therapy Oncology Group (RTOG) guideline [48]. These dose planning indices are important when deciding which plan is clinically more appropriate to deliver. The most commonly employed metrics for evaluating the GK treatment planning are:

1. Target Volume (TV): Target volume is defined as the volume contoured during treatment planning by the medical physicist [49].

2. Coverage: Coverage is defined for radiosurgery quality assessment corresponding to a fraction of the prescription isodose. Coverage is the ratio of minimum dose in the target and prescription dose [50]. Here a value of 1.0 means the prescribed dose completely encloses the target volume, 0.8-0.9 represents a minor deviation, and lower than 0.8 indicates a major deviation from the ideal planning.

3. Conformity Index (CI): Conformity index (CI) also defines how the targeted volume is enclosed by the treatment. CI can be computed by dividing the volume of the prescription isodose surface by the target volume [48].

4. Selectivity Index (SI): SI is an indicator of the extent to which surrounding healthy tissue is preserved from irradiation [49]. An ideal value is >0.9 . The SI formulation is as follows, where PIV represents peripheral isodose volume:

$$SI = \frac{TV_{PIV}}{PIV}. \quad (1.1)$$

5. Paddick's Conformity Index (PCI): PCI is an alternate conformity measure that considers the irradiated proportion of normal tissue [51]. PCI is the multiplication of coverage and SI as,

$$PCI = \frac{TV_{PIV}^2}{TV \times PIV}. \quad (1.2)$$

6. Gradient Index (GI): GI has been proposed as a supplemental approach that investigates the steepness of dose falloff outside the target [52]. The plans with similar conformity measures could be differentiated using GI. An ideal value of GI could be <3.0 for a treatment plan [49], and calculated as,

$$GI = \frac{PIV_{50\%}}{PIV}. \quad (1.3)$$

7. Homogeneity Index (HI): HI indicates the uniformity of dose within the target volume and could be less than 2.0 for the ideal case [48]. The score is calculated with the following formula [49] as,

$$HI = \frac{\text{Maximum dose}}{\text{Prescription dose}}. \quad (1.4)$$

Different dose indices have been compared in the literature. Coverage and conformity indices have been evaluated by Lomax et al. [12]. The study indicated that conformity measures changed according to the type and location of tumor. For a tumor that is smaller than 1 cm^3 , the conformity indices did not seem as a very useful indicator of the quality of the plan [53]. Additionally, the conformity and gradient indices showed dependency on the tumor size. Because of the limitations of current dose planning indices, researchers have been working on new treatment metrics in order to quantify treatment quality more accurately. Wu et al. proposed a new metric called conformity distance index (CDI), which is based on distance and independent of the tumor volume [54]. CDI indicates how well the prescription isodose conforms to the target boundaries by analyzing the distance between two 3D meshes. Thomas et al. proposed a new approach, which is the area under the curve (AUC) of DVHs metric, for comparing different plan qualities (VMAT and Gamma Knife) in radiosurgery treatment [55]. More recently, the efficiency index (EI) has been defined as the ratio of the energy delivered to the target over total energy [4]. This index integrates the conformity, gradient, and mean dose to the target measurements into a single metric, which varies from 0 to 1 (a value of 1 indicates a perfect plan). Another study published in 2019 investigated whether the surface area of target volume could be used as

a metric for predicting how much surrounding tissue is affected by irradiation. The results show that the target surface area could be used for normal brain toxicity risk analysis in radiosurgery [56].

In GK, the TV is covered by spheres since the procedure of treatment planning is based on the sphere packing algorithm. This algorithm tries to find the best sphere combinations in terms of location, size, and weight to reach optimum dose distribution in an iterative manner. Although the approach is well-suited for spherical targets, a major part of intracranial lesions is not spherical except for brain metastasis [57]. For this reason, irregularly shaped targets present special challenges in radiosurgery treatment planning. In order to conform to irregular/complex targets without destroying the healthy brain, multiple shots with different isocenters have been applied [58, 59, 60]. However, it is important to note that the increased number of isocenters in the target volume improves conformity but may result in increased toxicity and dose heterogeneity [61]. So, there is a trade-off between conformity and toxicity to peripheral structures. In the same study, more dose heterogeneity was associated with increased toxicity. Moreover, studies have shown that irregularly shaped tumors lead to more complex and time-consuming treatment plans [62, 63, 64]. Thus, an effort was made to determine whether target shape, volume, and distance to critical structures (brain stem, cranial nerves, and pituitary glands) affect the treatment efficiency [65]. In that study, skull base tumors were categorized according to complexities in terms of shape irregularities, tumor volumes, and distance to critical structures. The study indicated that the radiosurgery system could generate conformal treatment plans even for complex structures. However, the researchers suggested a longer follow-up to determine the efficiency of treatment plans.

1.3 Magnetic Resonance Imaging of Brain Tumors

MRI plays an essential role in understanding brain tumor biology, optimizing treatment strategies, and predicting prognosis. Conventional MRI, including contrast-enhanced MRI, is the first-line imaging technique on suspicion of brain tumors, ideally

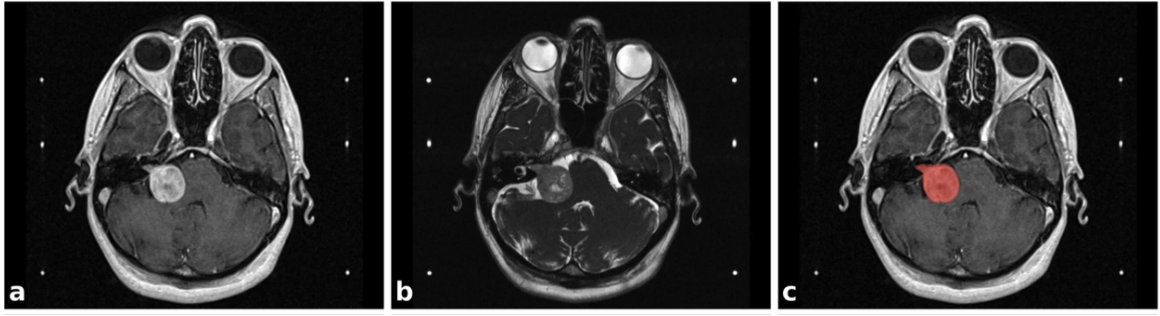


Figure 1.5 Series images of a patient with right-sided VS: (a) CE-T1w, (b) T2w, (c) CE-T1w with tumor segmentation [5].

performed with a standardized brain tumor MR imaging protocol [66]. The main idea of using structural MRI is to localize the brain tumor, assess its relationship with the brain structures, and guide possible biopsies. Beyond structural information, advanced MRI sequences provide detailed information about tumor characterization, improving diagnostic accuracy, treatment planning, and monitoring [67]. Therefore, there is a significant overlap between MRI findings and tumor subtypes.

With regard to VS, T1-weighted (T1w) MRI acquired before and after contrast injection is the gold standard for initial assessment (Figure 1.5) [68]. For differential diagnosis of VS from other brain pathologies such as cysts, glioma, and multiple sclerosis (MS), T2-weighted (T2w) MRI with diffusion-weighted imaging (DWI) should be included in the imaging protocol [69]. The vestibulocochlear nerve and its branches are evaluated with submillimetric T2w sequence [70]. While VS usually appear isointense on T1w MRI, they show strong contrast enhancement on contrast-enhanced T1w (CE-T1w) MRI. On T2w MRI, the lesion appears heterogeneously hyperintense, and larger lesions may potentially display cystic degeneration and hemorrhage [69].

Gliomas are intra-axial tumors that have widely varied appearances on MRI, which are often difficult to distinguish from treatment-related changes and other intracranial lesions. Key MRI findings of gliomas include hypo- or iso-intense signal on T1w MRI, hyperintense signal on T2w MRI and fluid-attenuated inversion recovery (FLAIR) with possible cerebral edema, as can be seen in Figure 1.6. Contrast

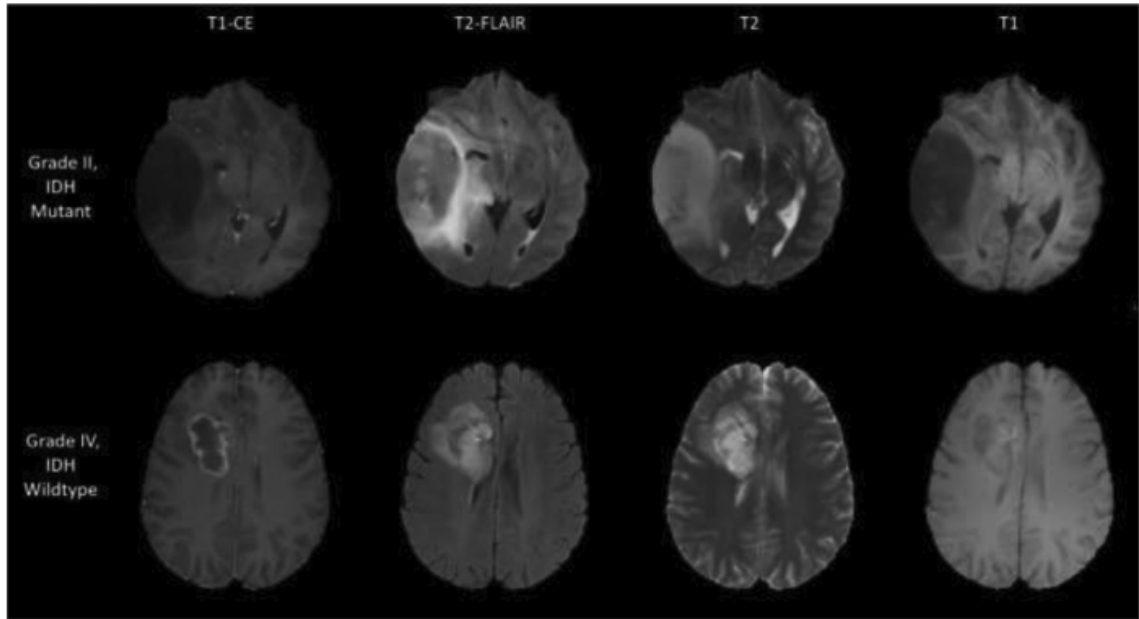


Figure 1.6 The MRI images of patients with WHO grade 2 astrocytoma (top row) and WHO grade 4 glioblastoma (bottom row). From left to right: CE-T1w, FLAIR, T2w, and pre-contrast T1w MRI sequences are shown. [6].

enhancement, necrosis, and ill-defined infiltration to surrounding brain tissues are distinguishable using CE-T1w MRI. Although contrast enhancement with central necrosis is the hallmark of high-grade gliomas (HGG), other pathologies (abscess and MS) could present with similar imaging features [71]. Additionally, one-third of malignant gliomas are non-enhancing [72]. Therefore, contrast enhancement is a non-specific imaging characteristic of HGG. On the other hand, the presence of homogeneous hyperintense T2 signal and hyperintense FLAIR region with a peripheral rim has been called 'T2-FLAIR mismatch'; a sign specific to astrocytomas [73]. On conventional MRI, oligodendrogliomas appear quite similar to astrocytomas but with pronounced calcifications [7].

Beyond structural MRI techniques, advanced MRI sequences offer the ability to interrogate pathophysiological differences between glioma subtypes in terms of vasculature, perfusion, and chemical changes. Commonly employed advanced MRI techniques are perfusion-weighted imaging (PWI), MR spectroscopy (MRS), and DWI [71]. Various studies with different MRI modalities can be used in a multivariate framework to

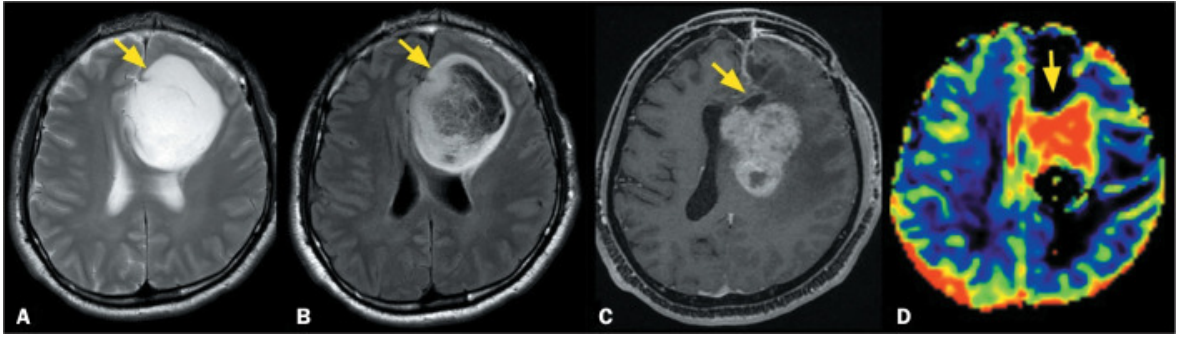


Figure 1.7 MRI scans of WHO grade 2 astrocytoma before first surgery in A) a T2-weighted sequence and B) a FLAIR sequence. A follow-up examination 11 years after surgery showed C) an enlargement of the remaining lesion on T1w and D) DSC showed high rCBV, indicating WHO grade 4 astrocytoma [7].

provide markers associated with the underlying complex biology of gliomas. Dynamic contrast-enhanced (DCE) and dynamic susceptibility-weighted contrast-enhanced (DSC) MRI are used to assess tumor angiogenesis. While DSC provides cerebral blood flow (CBF) and cerebral blood volume (CBV) maps evaluating the size and density of normal vessels supplying neoplasms, DCE estimates vascular permeability by measuring contrast leakage through blood brain barrier (BBB) [74]. It has been shown that increased relative CBV (rCBV) is associated with active angiogenesis and aggressive tumor biology (Figure 1.7) [75]. Histogram-based analysis on CBV has been applied to assess the tumor heterogeneity [76], tumor grading, and outcome prediction in gliomas [77]. Additionally, IDH-wt gliomas possessed higher rCBV compared to IDH-mut counterparts [78]. Proton-MRS also non-invasively detects 2-hydroxyglutarate (2HG) in gliomas for identifying IDH-mut status [79]. Another significant clinical application of MRS is its role in image-guided biopsy procedures locating high proliferative regions for eliminating biopsy sampling errors [80]. Glioma-related diffusion changes in the brain have been investigated with DWI, which are found useful in grading [81] and differential diagnosis of gliomas [82].

Meningiomas are usually seen as well-defined masses with strong enhancement on CE-T1w MRI. They often display dural attachments and appear as iso/hyperintense on T2w and FLAIR images. Associated peritumoral edema and calcification may be observed around the meningioma [83], particularly when the tumor exhibits larger

volumes. A representative case is given in Figure 1.8. As advanced MRI methods have become more commonly utilized in meningioma imaging, these techniques offer additional insights into meningioma grade and aggressiveness, improve the diagnosis of meningiomas, and aid in preoperative planning. It has been reported that meningiomas are hypervascular; therefore, their rCBV is higher than those of gliomas and metastases [84]. It has also been reported that the metabolites detectable by proton MRS reliably predict the grading of intracranial meningiomas [85]. Previous studies have shown that malignant meningiomas exhibit lower apparent diffusion coefficient (ADC) values compared to benign meningiomas [86]. Despite total tumor resection, meningiomas recur in 24-32% of the cases within 15 years. Additionally, 95% recurrent meningiomas grow from the same region again [87]. MRI findings are found to be useful in identifying this aggressive tumor behavior preoperatively, which would improve the therapeutic strategy (more aggressive surgical resection or adjuvant radiotherapy) and postoperative surveillance of patients. Preoperative MRI features such as tumor size on MRI, irregular shape, presence of edema, and extent of resection are the risk factors for recurrence of meningiomas [88, 89, 90].

1.4 Radiomics as Image-based Biomarkers for Precise Medicine

Brain tumors present a heterogeneous and complex nature, which makes the treatment and clinical decision-making difficult. Additionally, the imaging of such heterogeneous tumors limits the predictive power of current MRI techniques. The advancements in the computational power of image analysis techniques have led to converting medical images into quantifiable representations, which is called "radiomics" [91]. Although radiomics grew out of oncology research, it can be readily adapted to all other diseases [92]. A subgroup of radiomics, radiogenomics, investigates the association between imaging findings and gene expression patterns and mutations of diseases and has great attention in the research community.

The application process of radiomics includes six main steps: (A) image acquisition, (B) delineating volume of interest (VOI), (C) image pre-processing, (D) feature

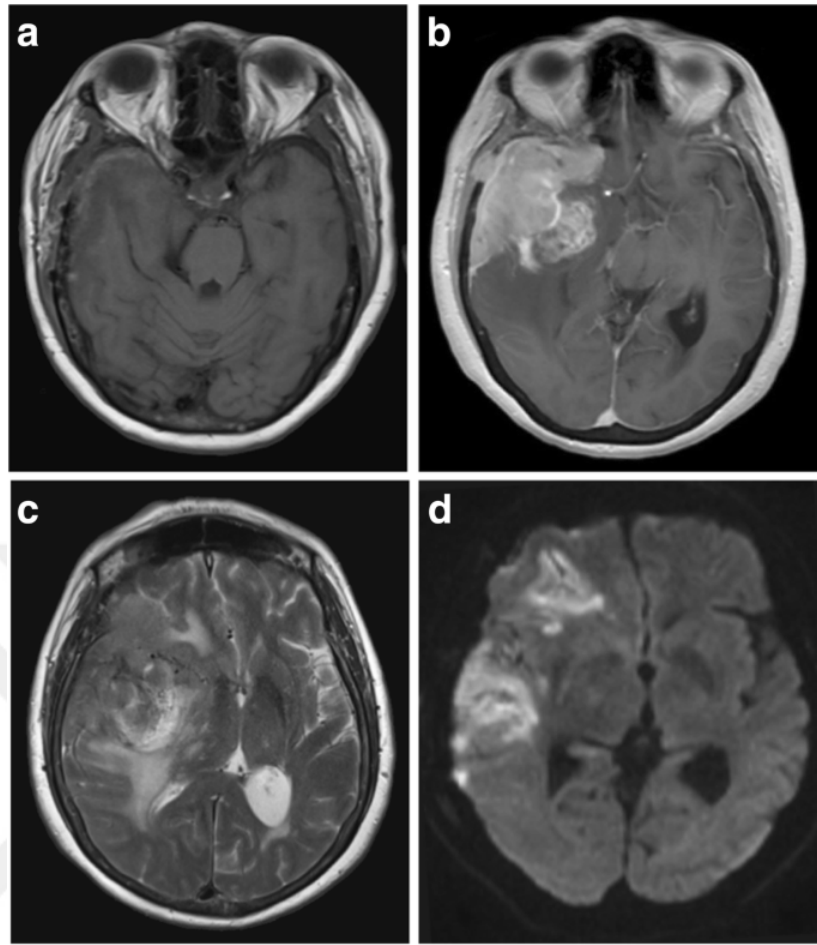


Figure 1.8 Axial MRI images of malignant meningioma: A) T1w, B) CE-T1w axial presenting a heterogeneously enhancing mass with dural tail. C) Axial T2w image displaying surrounding edema. D) A DWI image showing heterogeneous areas of restricted diffusion. [8].

extraction, (E) feature selection, (F) model generation and analysis. A common workflow of radiomics is given in Figure 1.9.

- **Data acquisition:** The first step of radiomics analysis is to acquisition of imaging data (MRI, CT, positron emission tomography (PET)/CT, etc.). Variations in imaging protocols, reconstruction methods, and different vendors are likely to affect the power of radiomics. Therefore, it is essential to present quantitative imaging with error bars or to standardize the original image data to enhance consistency [92].
- **Image preprocessing:** To increase the reproducibility and generalizability of radiomics, several preprocessing steps, including spatial resampling, intensity nor-

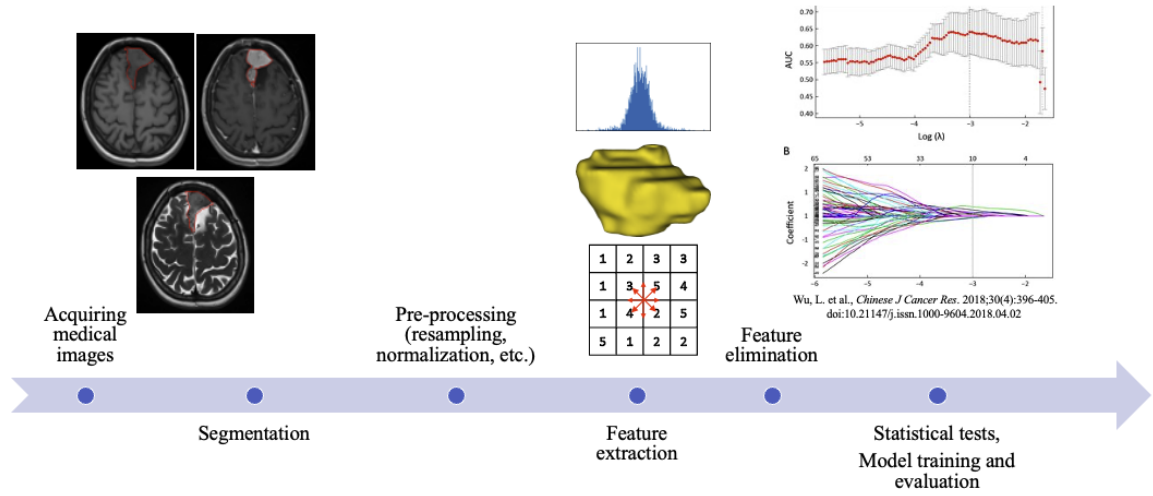


Figure 1.9 The general workflow of radiomics includes image acquisition, image pre-processing, tumor segmentation, feature extraction, feature selection, and analysis.

malization, noise suppression, bias correction, and registration are used. Intensity normalization is usually applied to images with relative intensity values; however, it should not be preferred on quantitative intensity values such as ADC maps.

- Segmentation:** Delineating region of interest (ROI) is the most critical component since the data is generated from these regions [92]. Segmentation could be employed with manual, semi-automatic, and automatic methods. Manual segmentation is time-consuming since brain tumors may have indistinctive tumor borders like gliomas, which makes the process vulnerable to inter- and intra-observer variances. Several machine learning (ML) approaches have been developed and evaluated for automatic lesion segmentation to overcome variation challenges [93, 94]. Although there is no universal segmentation method that works for all cases, it has been suggested that semi-automatic methods such as region growing or active contours and automatic methods followed by manual curation might produce optimum segmentation results [95].
- Feature extraction:** The radiomics features are grouped into three, namely: (i) shape-based features for quantifying the geometric shape of a tumor, (ii) first-order features describe intensity distribution represented by histograms without

using their neighboring information, (iii) and texture features to assess statistical neighboring relationships between pixels/voxels or groups [91]. The descriptive matrices encode the specific spatial relations between pixels/voxels and texture features are computed from these matrices. Texture features include Gray Level Co-occurrence Matrix (GLCM) [96], Gray Level Run Length Matrix (GLRLM) [97], Gray Level Size Zone Matrix (GLSZM) [98], Neighborhood Gray Tone Difference Matrix (NGTDM) [99], and Gray Level Dependence Matrix (GLDM) [100]. Features can be computed from the original image or from filtered images. These filters are applied to enhance details, identify recurrent patterns, eliminate noise, and enhance edges. The applied mathematical transformations include the Laplacian of Gaussian (LoG), wavelet, square root, and logarithm filters. Shape-based features measure the geometric properties of a defined area. For example, total volume, surface-to-volume ratio, compactness, and sphericity in both two-dimensional (2D) and three-dimensional (3D) surfaces can be calculated [101]. First-order intensity features use common histogram descriptors such as mean, median, skewness, and kurtosis to characterize the distribution of intensity values in the ROI [101]. However, these features do not capture the spatial relationships between intensities, which are crucial for describing the texture of an image. In contrast, second-order statistics are designed to quantify texture by analyzing the spatial relationships within the ROI. GLCM (Figure 1.10) captures neighboring information of pixel pairs in the defined ROI along different directions (horizontal, vertical, or diagonal for a 2D analysis or 13 directions for a 3D analysis). Subsequently, from these matrices, statistical features can be computed, such as autocorrelation, correlation, cluster shade, variance, entropy, etc. GLRLM computes the number of consecutive pixels with the same intensity value (Figure 1.10). The features that define run percentage, run length non-uniformity, short and long run emphasis, etc. could be extracted. Similarly, GLSZM computes the number of pixel zones with the same intensity level. Then, the fractions of size zones, and large and small zone emphasis could be calculated. NGTDM quantifies the difference between a gray value and the mean gray value of its neighbors within a specified distance. The main features are busyness, complexity, and contrast, which are high when rapid changes occur in the image. Similar to

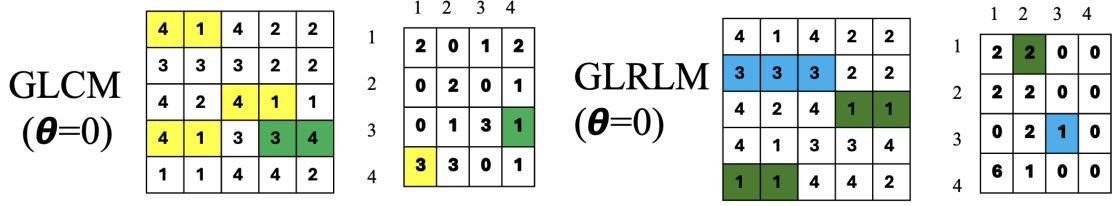


Figure 1.10 Calculation of example radiomics features: GLCM and GLRLM at $\theta = 0$ (adapted from [9]).

NGTDM, GLDM measures gray level diversity by using the relationship between a central voxel and its neighbors by a defined distance. Features like small dependence emphasis, large dependence emphasis, and dependence non-uniformity are common GLDM features [102].

- **Feature selection and dimensionality reduction:** Radiomics can generate a large number of features, some of which will be redundant. Feature selection is the way of selecting the most predictive features while eliminating redundant features [101]. Feature selection is important to make models easy to interpret, to remove multicollinearities, and to reduce overfitting risk [103]. Several feature selection algorithms, which can be classified as supervised and unsupervised methods, have been applied to radiomics. Unsupervised techniques, e.g., clustering, do not consider the class labels. By contrast, supervised techniques take the class label into account while finding the optimal feature subset based on feature contributions to the prediction. Commonly used methods are filter-based methods such as variation threshold, Mann-Whitney U test, Chi-squared score, and inter-class correlation coefficient analysis. Although wrapper methods, such as recursive feature elimination or sequential feature selection (forward-backward), are more efficient in finding the best feature subset by evaluating their performances in models, they are computationally intensive. On the other hand, embedded methods (ridge and least absolute shrinkage and selection operator (LASSO)) select the optimal feature subset in model training with consideration of inter-feature interactions. Embedded methods are more efficient and powerful than wrapper and filter-based methods. Dimensionality reduction can also be accom-

plished by converting the features like using principal component analysis (PCA); however, this leads to loss of feature trace. Multilevel feature selection methods can identify key features by leveraging the complementarity of various feature selection algorithms [104].

- **Model generation and analysis:** Depending on the analysis’s objective, various machine learning (ML) techniques can be used to create predictive models. ML algorithms can analyze complex patterns in radiomic data that are not discernible by human observers. When analyzing survival data, popular algorithms include the Cox proportional hazards model, neural networks, support vector machines (SVM), decision trees (such as random forests), linear regression, and logistic regression, particularly incorporated in radiomics analysis.

1.4.1 Radiomics Applied on Brain Tumors

Radiomics has been increasingly applied in brain tumors to improve the predictive accuracy of diagnosis [105], prognosis [106], and treatment outcome [107] in neurooncology studies. For gliomas, radiomics has shown significant promise in several areas. Glioma subtypes across different WHO grades present considerable heterogeneity in their imaging characteristics. Radiomics has the potential to capture this heterogeneity by analyzing features such as texture, shape, and intensity from MRI scans. These features can be correlated with histopathological and molecular characteristics of the tumors. Since grading is mandatory for risk stratification in gliomas, differentiation of tumor grades were conducted using radiomics [108, 109] and showed that intensity-based parameters show good discriminative ability with the area under curves (AUC) >0.85 . Several studies have correlated multimodal MRI radiomics with molecular information of gliomas, such as isocitrate dehydrogenase (IDH) mutation status and 1p19q codeletion, which are critical for prognosis and treatment planning [110, 111, 112]. In the clinical course of glioma, it is important to predict patient prognosis and likelihood of treatment response. Textural features from multimodal conventional MRI have shown predictive power for prediction of overall survival (OS)

and progression-free survival (PFS) [113, 114]. Advanced MRI techniques, including DWI, PWI, and MRS, have been integrated into radiomic analyses to enhance the characterization of gliomas. Combining these modalities with radiomics has improved the accuracy of glioma grading and the prediction of treatment outcomes [115, 116].

In the context of meningiomas, radiomics has been primarily utilized to predict the pathological grade of meningiomas. In grading, textural and shape features were found to be significantly correlated with tumor grades [117, 118]. Combined radiomics have successfully distinguished meningioma subtypes with high validation accuracy (0.94) [119]. These features can also help in assessing the extent of tumor invasion into surrounding tissues, which is crucial for surgical planning [120]. Another study showed that the radiomics approach was able to predict recurrence in skull base meningioma patients [121]. They included preoperative T2w, DWI, and CE-T1w MRI, to obtain an accuracy of 0.90.

1.5 Aim and Outline of the Thesis

The overall aim of this thesis is to use radiomics to assist in clinical decision-making regarding GK treatment planning, genetic alterations, survival, and recurrence analysis in patients with gliomas or meningiomas. Following this background, this thesis presents an approach that introduces a radiomics method for assessing GK treatment quality and treatment outcome (Chapter 2). Next, the predictive power of radiomics for IDH-mut detection and survival estimation is evaluated on retrospective and external datasets (Chapter 3). Chapter 4 presents radiomics-based models to predict NF2-loss and recurrence free survival (RFS) in meningiomas. Finally, the main objectives and results of the present thesis are summarized along with the prospects of radiomics in the field of neurooncology (Chapter 5).

2. THE EFFECT OF TUMOR SHAPE IRREGULARITY ON GAMMA KNIFE TREATMENT PLAN QUALITY AND TREATMENT OUTCOME: AN ANALYSIS OF 234 VESTIBULAR SCHWANNOMAS

2.1 Introduction

GK [122] is a neurosurgical tool that has been used to treat a wide range of intracranial tumors, including vestibular schwannomas [123, 124] meningiomas [125], gliomas [126], and brain metastases [127], via delivering a precise and high-dose radiation to a target area. Intracranial tumors that are treated using GK radiosurgery exhibit wide variations in volume and shape, and conforming to these variations is a fundamental characteristic of GK dose plans. Over the years, the absolute focus of minimizing radiation exposure to the surrounding brain tissue has led to a dose planning approach in GK that is significantly different from standard radiotherapy planning [49]. An intentional, uneven dose distribution with peak doses within the intracranial target and a steep dose fall-off outside are characteristics of GK dose plans [62, 128]. Such conformal plans are achieved with the use of a sphere packing algorithm. Although this algorithm provides great conformality, any irregularity of tumor shape secondarily results in dose heterogeneity within and outside the target. Measuring the effects of tumor shape irregularity (TSI) on dose plan metrics can be useful in clinical decision-making and GK planning, but has not been studied in detail before.

In current GK dose planning practices the primary aim is to conform the radiation dose to the TV as efficiently as possible. It is widely accepted that the dose delivered to the margin of the TV is the most important variable affecting the clinical outcome and there is wide agreement on the prescription doses to treat each pathology [129]. On the contrary, the guidelines on dose distribution within and outside the target are far less standardized. Conforming the dose to the previously contoured TV is

performed manually or supervised by the operator. The planning process is informed by several well-established treatment quality metrics that have been thoroughly investigated over the years [4]. Among these, SI [49], GI [52], PCI [51], and EI [4] offer valuable approximations on how the distribution of radiation dose is delivered to TV and how sharply it decreases through surrounding tissue. Nevertheless, the influence of TSI on plan quality, measured by current metrics, and its effect on dose heterogeneity and the ultimate clinical outcome, has yet to be extensively studied. Previous attempts have quantified TSI using radiomics, which transforms medical images into quantitative feature spaces [130, 131, 92]. Limkin et al. [132] reported strong correlations between radiomic shape features and TSI. In addition to the radiomic features, Saad et al. [10] proposed two- and three-dimensional (2D/3D) shape-based imaging biomarkers and a new metric called ‘volumetric index of sphericity’ (VioS) to represent tumor morphology, and reported VioS as a significant predictor of survival in lung cancer. On the other hand, only a few studies have investigated the effect of shape irregularity and TV on dose plan indices [133, 134]. Wu et al. examined the effects of TV and shape complexity on simulated targets, and reported that the ratio of prescription isodose volume to the TV (PITV) and PCI values were higher than the conformity measures for smaller and more irregular targets [133]. More recently, Saraiva et al. suggested that the sphericity degree of a target volume can be used to evaluate the dose distribution in GK treatment planning [134]. However, the effects of TV and TSI on GK treatment planning quality and clinical outcome have not been fully investigated.

Vestibular schwannoma is a non-cancerous and slow-growing intracranial tumor. When vestibular schwannoma enlarges, the hearing and balance nerves are affected and usually leads to one-sided asymmetric hearing loss and balance [1]. In this study, vestibular schwannomas were used as the tumor model since they have sharp tumor margins on magnetic resonance imaging (MRI) and don’t invade to surrounding tissues.

The aims of this study were threefold: (i) quantifying TSI using radiomic shape features as well as sphericity and VioS, (ii) analyzing the relationships between TSI and core GK dose plan indices (SI, GI, PCI, and EI) and (iii) investigating the impact of TSI on treatment outcomes in vestibular schwannomas.

2.2 Metarials and Methods

2.2.1 Subjects

In this retrospective study, 234 vestibular schwannoma patients treated with GK at Acibadem Mehmet Ali Aydınlar University Altunizade Hospital were included. Thirty-one of these patients underwent previous surgery. The study protocol was approved by the local ethics committee (Applications to Acibadem University and Acibadem Healthcare Institutions Medical Research Ethics Committee (ATADEK-2020/19)). Written informed consent was obtained from all patients. All methods were performed in accordance with the relevant guidelines and regulations of the approved ATADEK.

2.2.2 Magnetic Resonance Imaging

The patients were scanned on a 1.5T or a 3T clinical MR scanner (Siemens Prisma Fit, Erlangen, Germany). The brain tumor MRI protocol included post-contrast (Gadolinium-DTPA) T1-weighted (T1w-Gd) TurboFLASH volumetric imaging (repetition time [TR]=2080 ms, echo time [TE]=2.67 ms at 3T; TR=2240 ms, TE=3.04 ms at 1.5T) and 3D fluid-constructive interference of steady-state (TR=5.72 ms, TE=2.55 ms at 3T; TR=5.76 ms, TE=2.58 ms at 1.5T). Each target volume was manually delineated by a neurosurgeon (K.Ö.) with 17 years of experience using Gamma Plan Software (Elekta-Sweden) on T1w-Gd. Three-dimensional models of each tumor were created from the region of interests (ROIs) using 3D Slicer software [135].

2.2.3 GK Treatment and Dose Plan Indices

The GK dose plans were prepared using a Leksell Gamma Plan 10.0 system (Elekta Instrument AB, Stockholm, Sweden) and the treatments were delivered using the Gamma Knife Perfexion or ICON platforms, which are identical in their radiation

delivery equipment. GK dose planning is operator-dependent, and all planning for this study was performed by a single neurosurgical team. Four dose plan indices including PCI [51], GI [52], SI [49] and EI [4] were used to evaluate the dose plan quality.

Active cochlear protection was performed in all patients using “dynamic shaping” function of Leksell Gamma Plan 10.0 software and/or margin dose reduction. Maximum cochlear dose was 5.60 [1.50, 16.10] Gy (median [min,max]). The possible complications were monitored for the patients with a follow-up period of two years (n=148). Some complications were observed in a total of nine patients, and included temporary increased gait imbalance (n=4, 2.70%), dizziness (n=4, 2.70%), and facial hypoesthesia (n=3, 2.02%). PCI, GI, SI, and EI dose plan metrics were computed in the routine GK treatment planning.

2.2.4 Feature Extraction

SVR, flatness, elongation, spherical disproportion, and compactness were derived to quantify TSI using the Radiomics extension of 3D Slicer software. SVR was normalized SVR_N by multiplying it by the average of the three principal semi-axes of the tumor model (Figure 2.1), since SVR is proportional to $1/r$. Sphericity [134] and VioS [10] were computed to show how much a tumor model approached a sphere. A detailed information about shape irregularity features is provided in Table 2.1. Figure 2.2 shows two examples of tumor models and their corresponding shape metrics. Model (A) had an irregular shape (flatness=0.25, elongation=0.31, and VioS=0.38); while model (B) was more spherical (flatness=0.83, elongation=0.92, and VioS=0.55). The sphericity degree is calculated as,

$$Sphericity = TV/V_{CS} = \sqrt[3]{\frac{d_{SV}}{d_{CS}}}, \quad (2.1)$$

where V_{CS} is the volume of the smallest circumscribed sphere that would fit into

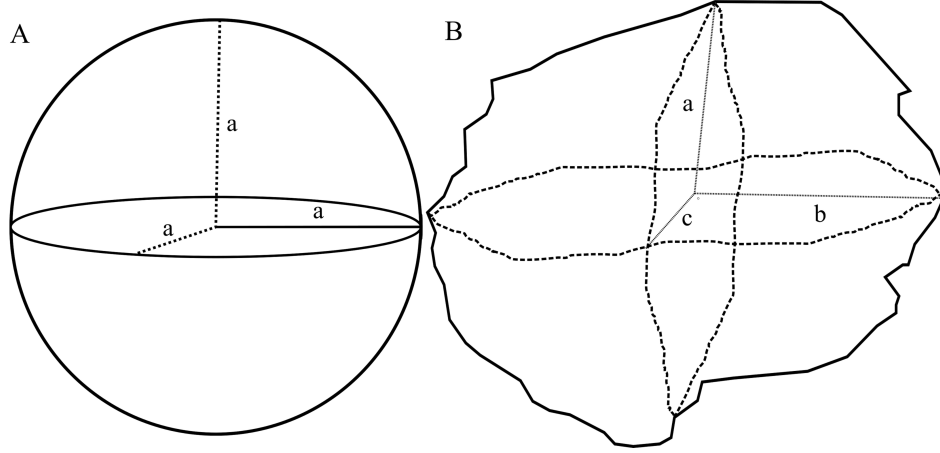


Figure 2.1 A perfect sphere ($a = b = c$) was given in A. The brain tumors are not perfect spheres, and they have different axis lengths as depicted in B ($a \neq b \neq c$) (adapted from Saad et al. [10]).

the tumor, and d_{SV} and d_{CS} are the diameters of spheres that would have the same volume as the target and the circumscribing sphere, respectively [134].

Finally, VioS [10] measures the tumor shape divergence from a perfect sphere, computed as:

$$VioS = \frac{I_{AS}}{I_{IS}} \quad (2.2)$$

where I_{IS} is the SVR of a sphere that would have the same volume as the tumor, and I_{AS} is the SVR of the actual shape computed as $(4\pi r^2)/(\frac{4}{3}\pi r^3)$. The r value was estimated as the average of the three principal semi-axes (Figure 2.1).

2.2.5 Statistical Analysis

The cohort was divided into three TV subgroups (group 1: $TV < 1 \text{ cm}^3$; group 2: $1 < TV < 5 \text{ cm}^3$; group 3: $TV > 5 \text{ cm}^3$) to evaluate the effect of TV on the TSI and dose plan indices. A χ^2 test was performed to compare the sex distributions between

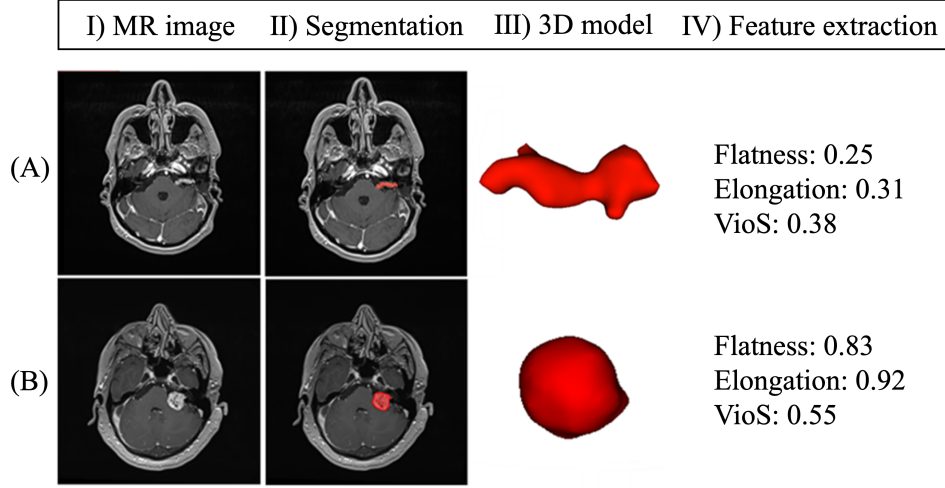


Figure 2.2 Workflow of the shape feature extraction. (I) MRI images of two representative vestibular schwannomas. (II) The tumor ROIs (red) were defined by an experienced neurosurgeon. (III) 3D tumor models constructed using tumor outlining. (IV) Tree different shape features for tumor A and B. The differences in shape irregularity in the two tumors can be identified by investigating their flatness, elongation, and VioS. Tumor A was flat and irregular, tumor B was more spherical.

subgroups. The Kruskal-Wallis test, followed by Dunn's post-hoc test, was applied to compare age, dose plan indices, and TSI features across subgroups. P-values lower than 0.0041 were considered statistically significant for the Kruskal-Wallis test. For Dunn's test, a P-value of <0.05 was considered statistically significant. All statistical tests were performed using stats model [136] and scikit-posthocs toolboxes [137] in Python 3.7.6.

The associations between the TSI and dose plan indices were investigated using a Spearman rank correlation test (r) after multivariate outlier elimination and P-values <0.00125 were considered statistically significant after Bonferroni multiple comparison correction. Feature selection was run for each dose planning index separately using Lasso [138]. Before Lasso feature selection, multicollinear shape features ($r \geq \pm 0.9$) were removed. Then, the entire dataset was divided into training (80%) and test (20%) datasets, and the optimal Lasso regularization parameter (λ) was selected by applying 3-fold cross-validation to the training dataset for each dose planning index. The experiment was run 100 times, and the feature with the overall highest coefficient was selected as the top discriminative feature for each dose planning index. Finally, a univariate linear regression analysis was employed to define the relationship between

Table 2.1
Description of five radiomic features extracted from tumor models.

Radiomic Feature	Description	Formulation
Surface to Volume Ratio	The ratio of surface area (A) to volume of the model (V). A lower value indicates a sphere-like shape.	$\frac{A}{V}$
Compactness	Quantifies how compact tumor shape is relative to a sphere that gives a value of 1.	$36\pi \frac{V^2}{A^3}$
Flatness	Shows the ratio of lengths of the largest and smallest principal axes. (1 for non-flat object/sphere and 0 for flat object/single slice segmented region)	$\sqrt{\frac{\lambda_{least}}{\lambda_{major}}}$
Elongation	The ratio of major (λ_{major}) and minor (λ_{minor}) axes of segmented volume. A value of 1 indicates not elongated (circle like) and 0 reflects maximally elongated object.	$\sqrt{\frac{\lambda_{minor}}{\lambda_{major}}}$
Spherical Disproportion	The ratio of the surface area of the tumor region to the surface area of a sphere which has the same volume of the tumor. The value of 1 reflects a perfect sphere (R is the radius of sphere).	$\frac{A}{4 \times \pi \times R^2}$

the selected feature and the dose planning index of interest. Then, a univariate linear regression analysis was used to define the relationship between the selected feature and the dose planning index of interest.

2.2.6 Machine Learning for Prediction of Dose Plan Quality

ML algorithms were used to predict high dose plan indices based on the shape features. The expected values of the dose plan indices were set as the median values for the entire patient cohort. Seven shape irregularity features (standardized to zero mean and unit variance) were used as predictor variables, and each dose plan index was used as an independent response variable. RFE with a linear kernel SVM was used to

identify the optimal shape features to predict each dose plan index independently [139]. Subsequently, logistic regression (LR), linear discriminant analysis (LDA), GB, SVM, and RF algorithms were used for supervised machine learning. After determining the optimal feature subsets and hyperparameters using training data (80% of the entire data), the model performances were assessed on the independent test set (20% of the entire data). Accuracy, sensitivity, and specificity were calculated for the prediction of each response variable. All machine learning implementations were run in Python using the Scikit-learn library.

2.2.7 Treatment Outcome Analysis

“Tumor growth control” (no persistent volumetric tumor growth at 2 years after treatment; data available for 148 primary vestibular schwannomas out of 234 patients) and “serviceable hearing preservation” (defined as maintenance of Gardner-Robertson class I or II hearing function at 2 years; data available for 83 patients with primary tumors) were used as outcome measures. The sex distribution differences between patients with persistent tumor growth or no growth, and patients with serviceable hearing preservation or loss were compared using a χ^2 test. Univariable and multivariable Cox proportional hazards models were also used to evaluate the influence of TSI on tumor control and serviceable hearing preservation. For tumor control, the model included following variables: age, sex, TV, Koos grade, margin dose, coverage index (CI), SI, GI, EI and VioS. For serviceable hearing preservation, maximum cochlear dose, cochlea-target distance and radiation dose to tumor margin were added to the above variables. Additionally, the respective variables were compared between the subgroups of tumor growth and serviceable hearing using a Mann-Whitney U test.

2.3 Results

2.3.1 Patient Population, Dose Plan Indices, and Shape Irregularity Features

Table 2.2 shows the demographics and the median [range] dose planning indices of the vestibular schwannoma cohort of this study. The TV values ranged from 0.01 cm³ to 20.01 cm³, which were divided into low (group 1, TV < 1 cm³, 83 patients), medium (group 2, 1-5 cm³, 89 patients), and high (group 3, >5 cm³, 62 patients) TV groups. The sex and age distributions were similar in all subgroups (P=0.897 and P=0.767, respectively). Group 1 had a statistically significantly lower SI (P<0.001), lower PCI (P<0.001) and EI (P<0.001), and higher GI (P<0.001) than groups 2 and 3. Similarly, group 2 patients had lower SI (P=0.0003), PCI (P=0.0005), and EI (P=0.0024), and higher GI (P=0.007) than group 3. Therefore, SI, PCI, and EI were higher and GI was lower in large TVs.

Figure 2.3 shows the distributions of the shape features in the TV subgroups. Compactness (P=0.106) and spherical disproportion (P=0.105) were not significantly different between subgroups. Group 3 had the highest sphericity, elongation, flatness, and VioS and the lowest normalized surface-to-volume ratio (SVR_N). Additionally, Group 1 had lower sphericity, elongation, flatness, and VioS than groups 2 and 3 (P<0.001 for all) and higher SVR_N than group 3 (P<0.001). In contrast, group 2 had significantly higher sphericity, elongation, flatness, and VioS than group 1 (P<0.001 for all) and lower sphericity and VioS than group 3 (P<0.001 for both).

2.3.2 Correlations Between Dose Plan Indices and Shape Irregularity Features

The Spearman correlation coefficients (r) of the association between the TSI metrics and GK planning indices are provided in Table 2.3. In the overall patient cohort, all shape features had statistically significant correlations with the dose plan

Table 2.2

Patient characteristics and summary of dose planning indices of this study (*: $P < 0.05$ and **: $P < 0.001$).

	TV<1 cm³ (Group 1)	1 cm³<TV<5 cm³ (Group 2)	TV>5 cm³ (Group 3)	P-value	Overall
Number of patients (M, F)	83 (38,45)	89 (39,50)	62 (26,36)	0.897	234 (103,131)
Age Median [Range]	52 [21,78]	50 [18,87]	47 [18,89]	0.767	50 [18,89]
SI Median [Range]	0.74 [0.2, 0.96]	0.86 [0.57,0.96]	0.91 [0.75,0.99]	2.4E-19 1 vs 2**, 1 vs 3**, 2 vs 3**	0.80 [0.20, 0.99]
PCI Median [Range]	0.70 [0.20, 0.83]	0.83 [0.57,0.96]	0.89 [0.62,0.94]	1.5E-24 1 vs 2**, 1 vs 3**, 2 vs 3**	0.80 [0.20,0.96]
GI Median [Range]	2.83 [2.5, 4.00]	2.68 [2.40, 3.39]	2.54 [2.41,2.99]	8.4E-17 1 vs 2**, 1 vs 3**, 2 vs 3*	2.70 [2.40, 4.00]
EI Median [Range]	0.41 [0.12, 0.63]	0.49 [0.30, 0.58]	0.52 [0.02, 0.59]	1.5E-18 1 vs 2**, 1 vs 3**, 2 vs 3*	0.48 [0.02,0.63]

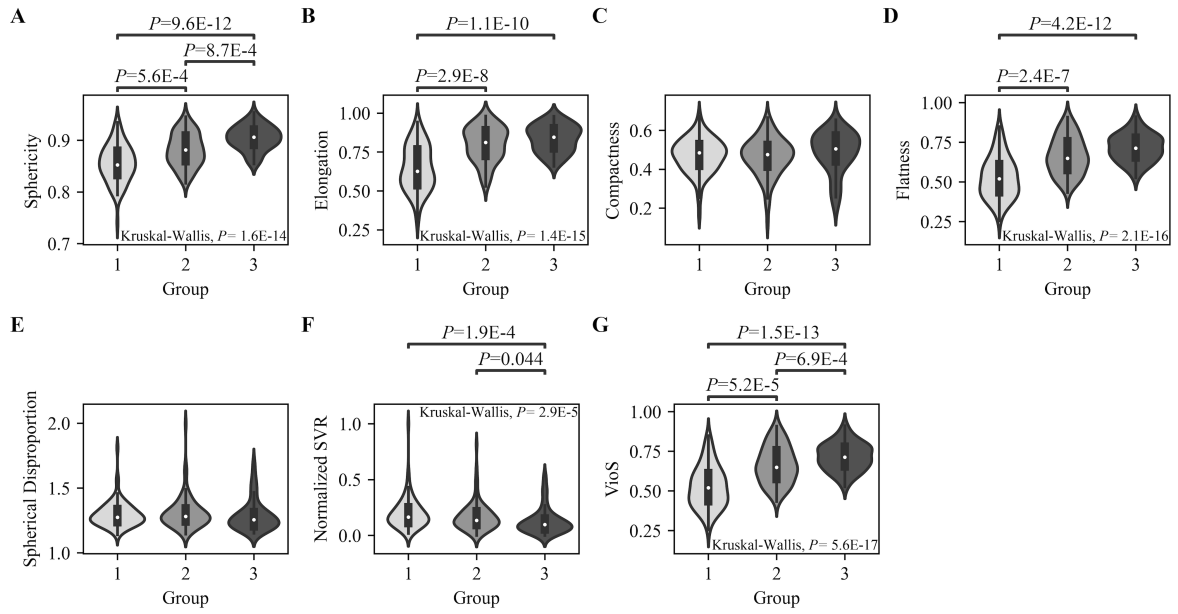


Figure 2.3 The violin plots outline the median value (white dot) and interquartile range (thick gray bar) of the shape irregularity features: (A) sphericity, (B) elongation, (C) compactness, (D) flatness, (E) spherical disproportion, (F) SVR_N , and (G) VioS for different TV subgroups. The P-values were Bonferroni adjusted and obtained using a Kruskal-Wallis test followed by Dunn's post-hoc test.

indices ($P < 0.001$). Surface to volume ratio (SVR) had the highest correlation with all the plan indices; the corresponding correlation values were $r = -0.74$, $r = 0.62$, $r = -0.72$, and $r = -0.79$ for SI, GI, EI, and PCI, respectively ($P < 0.00125$ for all). Although the correlations decreased after normalization, SVR_N still showed significant correlations with SI, GI, EI, and PCI ($r = -0.53$, $r = 0.4$, $r = -0.49$, $r = -0.59$, respectively; $P < 0.001$). Flatness had a direct relationship with SI, EI and PCI ($r = 0.55$, $r = 0.53$, $r = 0.61$, respectively; $P < 0.001$) and an inverse relationship with GI ($r = -0.48$, $P < 0.001$). The results showed that elongation had a direct relationship with SI ($r = 0.46$, $P < 0.001$), EI ($r = 0.49$, $P < 0.001$), and PCI ($r = 0.53$, $P < 0.001$), and an inverse relationship with GI ($r = -0.37$, $P < 0.001$). Spherical disproportion was consistently associated with SI ($r = -0.44$), GI ($r = 0.23$), EI ($r = -0.39$), and PCI ($r = -0.46$; $P < 0.001$ for all). Similarly, compactness was significantly related to the dose plan indices ($r = 0.42$, $r = -0.27$, $r = 0.43$, and $r = 0.5$ for SI, GI, EI, and PCI, respectively; $P < 0.001$). GI and sphericity were negatively correlated ($r = -0.52$, $P < 0.001$), whereas SI, EI, and PCI were positively correlated ($r = 0.55$, $r = 0.57$, $r = 0.63$, respectively; $P < 0.001$). A scale-independent shape feature, VioS, had correlations higher than 0.6 with SI, EI, and PCI ($r = 0.63$, $r = 0.69$,

$r=0.68$, respectively; $P<0.001$ for all), and a negative correlation with GI ($r=-0.58$, $P<0.001$). The last column of Table 2.3 shows the correlations between shape features and TV. TV was strongly correlated with SVR ($r=-0.98$, $P<0.001$) and moderately to SVR_N ($r=-0.36$). TV was significantly related to elongation, flatness, sphericity, and VioS ($r=0.52$, $r=0.59$, $r=0.53$, and $r=0.6$) but not to spherical disproportion and compactness ($r=-0.13$, $P=0.06$ and $r=0.17$, $P=0.02$, respectively). The results suggested that SI, EI, and PCI increased while GI decreased as the tumor shape became more spherical. Additionally, larger vestibular schwannomas presented more regular shapes.



Table 2.3
Spearman correlation analysis of all tumor models (overall) and subgroups (Group 1/2/3) for evaluating the relationship of each shape feature with dose planning indices (*P<0.00125).

Shape features	Treatment Parameters				
	SI	GI	EI	PCI	TV
SVR	Overall	-0.74*	0.62*	-0.72*	-0.79*
	Group 1/2/3	-0.44*/-0.5*/-0.41	0.55*/0.33/0.23	-0.64*/-0.57*/-0.42	-0.54*/-0.54*/-0.53*
	Overall	-0.53*	0.4*	-0.49*	-0.36*
SVR_N	Group 1/2/3	-0.28/-0.47*/-0.41	0.16/0.2/0.39	-0.27/-0.53*/-0.62*	-0.33/-0.48*/-0.59*
	Overall	0.55*	-0.48*	0.53*	0.61*
	Group 1/2/3	0.21/0.34/0.27	-0.38*/-0.11/-0.41	0.33/0.42*/0.44	0.31/0.38*/0.41
Flatness	Overall	0.46*	-0.37*	0.49*	0.53*
	Group 1/2/3	0.15/0.23/0.06	-0.32/-0.15/-0.24	0.17/0.36*/0.2	0.25/0.32/0.2
	Overall	-0.44*	0.23*	-0.39*	-0.46*
Spherical	Group 1/2/3	-0.24/-0.47*/-0.42	0.05/0.16/0.4	-0.22/-0.47*/-0.65*	-0.28/-0.57*/-0.62*
	Overall	0.42*	-0.27*	0.43*	0.5*
	Group 1/2/3	0.21/0.49*/0.46	-0.03/-0.16/-0.4	0.22/0.49*/0.72*	0.28/0.57*/0.62*
Compactness	Overall	0.55*	-0.52*	0.57*	0.63*
	Group 1/2/3	0.23/0.28/0.42	-0.24/-0.36*/-0.43	0.3/0.46*/0.54*	0.3/0.37*/0.52*
	Overall	0.63*	-0.58*	0.69*	0.68*
VioS	Group 1/2/3	0.25/0.37*/0.38	-0.26/-0.34/-0.41	0.27/0.54*/0.55*	0.33/0.38*/0.55*
	Overall				
	Group 1/2/3				

2.3.3 Correlations Between Dose Plan Indices and Shape Irregularity Features in Patient Subgroups Stratified by Tumor Volume

The results of the correlation analyses in the TV subgroups are provided in Table 2.3. Group 1 showed significant correlations only between SVR and the plan indices ($r=-0.44$, $r=0.55$, $r=-0.64$, $r=-0.54$ for SI, GI, EI, and PCI, respectively; $P<0.001$). In group 2, SVR_N consistently had significant associations with the dose plan indices ($r=-0.47$, $r=-0.53$, $r=-0.48$ for SI, EI, and PCI, respectively; $P<0.001$), except GI ($r=0.2$, $P=0.07$). Flatness was negatively associated with GI ($r=-0.38$, $P=0.0006$) in group 1 and positively correlated with EI ($r=0.42$, $P<0.001$) and PCI ($r=0.38$, $P=0.0004$) in group 2. Only EI was significantly associated with elongation in group 2 ($r=0.36$, $P=0.001$). EI and PCI were negatively correlated with spherical disproportion in groups 2 and 3 with lower than -0.47 correlation coefficients ($P<0.001$ for both). Compactness, sphericity, and VioS had positive correlations with EI and PCI in groups 2 and 3, with correlation coefficients ranging from 0.37 to 0.72 ($P<0.001$). Despite the significant correlations between the shape irregularity features and TV in the overall patient cohort, TV was not significantly correlated to the shape irregularity features in most subgroups. Only SVR had consistent correlations with TV in the subgroups. Additionally, the increments in sphericity and VioS were correlated with TV increments only in group 2 ($r=0.41$, $P=0.0001$, and $r=0.35$, $P=0.001$, respectively). Meanwhile, the results suggested that the correlation coefficients between the shape irregularity features, excluding SVR, and the dose plan indices increased as the tumors got larger. SVR_N and compactness had stronger correlations with GI, EI, and PCI. Additionally, flatness and spherical disproportion showed stronger correlations with dose plan indices in higher volume subgroups. The correlation coefficients of sphericity and VioS shape features with all the dose plan indices also increased consistently from group 1 to group 3.

Table 2.4
Univariate linear regression analysis results using VioS.

Response	Predictor	Estimate $\pm$ std	P-value	95% CI	Adj. R^2
SI	Intercept	0.6649 $\pm$ 0.020	3.05E-87	(0.626,0.704)	0.272
	Slope	0.2485 $\pm$ 0.028	1.21E-16	(0.194, 0.303)	
GI	Intercept	2.9312 $\pm$ 0.031	1.47E-174	(2.870,2.992)	0.242
	Slope	-0.3593 $\pm$ 0.043	1.27E-14	(-0.445,-0.274)	
EI	Intercept	0.3419 $\pm$ 0.013	1.23E-70	(0.317,0.367)	0.377
	Slope	0.1995 $\pm$ 0.018	1.67E-23	(0.165,0.234)	
PCI	Intercept	0.6175 $\pm$ 0.018	1.71E-88	(0.582,0.653)	0.331
	Slope	0.2636 $\pm$ 0.025	1.03E-20	(0.214,0.314)	

2.3.4 Associations of Shape Irregularity Features and Dose Planning Indices

The least absolute shrinkage and selection operator (Lasso) feature selection identified VioS as the most associated feature with all the dose plan indices. Table 2.4 shows the univariate multiple linear regression analysis results for predicting dose indices based on VioS. VioS had statistically significant linear relationships with SI, GI, EI, and PCI with adjusted R^2 values of 0.27, 0.24, 0.38, and 0.33, respectively ($P < 0.001$ for all models). The scatter plots of VioS and dose plan indices with fitted regression lines and 95% confidence intervals are shown in Figure 2.4.

2.3.5 Feature Selection and Machine Learning Models

Table 2.5 shows the best classification results for each dose plan index using either VioS or the features selected by combination of recursive feature elimination and support vector machine (RFE-SVM). While RFE-SVM selected only VioS as the best predictive feature for SI, the effective features for predicting GI were VioS, elongation, flatness, compactness, and sphericity. Similarly, VioS and compactness were

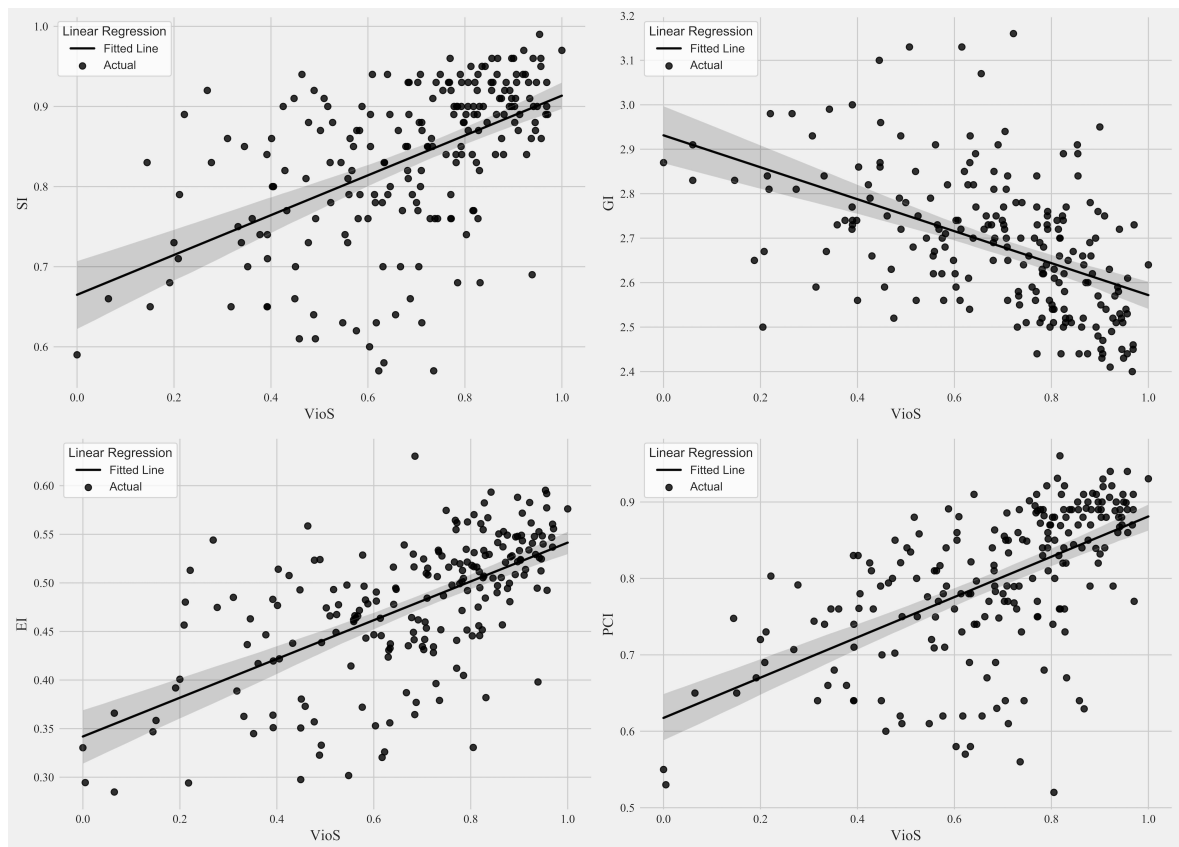


Figure 2.4 The univariate linear regression analysis results for the correlation of VioS with SI, GI, EI, and PCI.

predictive features for EI. On the other hand, the predictive feature subset of PCI consisted of VioS, sphericity, flatness, compactness, and SVR_N . The highest training accuracy for predicting EI and PCI was 90.37% using a random forest (RF). The highest classification accuracy of 74.47% (sensitivity=64%, specificity=86.36%) was obtained for predicting SI using the selected features of VioS with gradient boosting (GB) on the test dataset. On the other hand, an accuracy of 74.47% (sensitivity=72%, specificity=77.27%) was obtained for predicting GI. The highest classification accuracy for predicting EI was 82.98% (sensitivity=84%, specificity=81.82%). The highest accuracy of 85.11% was achieved with an RF classifier (sensitivity=79.17%, specificity=91.30%) for predicting PCI.

Table 2.5

Best classification results for each dose plan indices using either the features selected by RFE-SVM or VioS in the training and test datasets.

Selected Features		Class. Method	n	Acc/Sens/Spec (%)
SI	VioS	GB	Training	73.8/73.20/74.44
			n0=90, n1=97	
			Testing	74.47/64/86.36
			n0=22, n1=25	
GI	VioS, elongation, flatness, compactness, sphericity	RF	Training	80.21/80.81/79.55
			n0=88, n1=99	
			Testing	74.47/72/77.27
			n0=22, n1=25	
EI	VioS, compactness	RF	Training	90.37/88.66/92.22
			n0=90, n1=97	
			Testing	82.98/84/81.82
			n0=23, n1=24	
PCI	VioS, sphericity, flatness, compactness, SVR_N	RF	Training	90.37/91.75/88.89
			n0=90, n1=97	
			Testing	85.11/79.17/91.30
			n0=23, n1=24	
SI	VioS	GB	Training	73.8/73.20/74.44
			n0=90, n1=97	
			Testing	74.47/64/86.36
			n0=22, n1=25	
GI	VioS	RF	Training	78.61/77.78/79.55
			n0=88, n1=99	
			Testing	72.34/68/77.27
			n0=22, n1=25	
EI	VioS	GB	Training	77.54/73.20/82.22
			n0=90, n1=97	
			Testing	80.85/76/86.36
			n0=23, n1=24	
PCI	VioS	GB	Training	74.33/68.04/81.11
			n0=90, n1=97	
			Testing	89.36/79.17/100
			n0=23, n1=24	

VioS was selected as a predictive feature for all dose plan indices. Therefore, the machine learning models were further trained with only VioS, and their performances were evaluated on the test set. With VioS, we observed slightly decreased accuracies for the predictions of GI and EI. In contrast, the accuracy for predicting PCI increased to 89.36% (sensitivity=79.17%, specificity=100%) using VioS as the only feature with GB.

2.3.6 The Effects of VioS and Dose Plan Indices on Treatment Outcome

Table 2.6 shows the summary of clinical and treatment parameters of the vestibular schwannoma patients with 2-years follow-up. Sex and age distributions did not significantly differ between patients with serviceable hearing preservation or loss ($P=0.64$ and $P=0.38$, respectively). Clinical and treatment variables also were similar, as shown in Figure 2.5(A). Following GK treatment, the serviceable hearing preservation rate at 2 years was approximately 75.9%. Univariable and multivariable Cox regression analyses showed that none of the covariates had an effect on hearing preservation ($P>0.05$ for all), as presented in Table 2.7. Similarly, sex and age distributions didn't significantly differ between patients with or without tumor growth control ($P=0.41$ and $P=0.38$, respectively). Additionally, Figure 2.5(B) shows clinical and treatment parameters of patients with or without tumor growth control were similar. Two years after GK treatment, the tumor growth control rate was about 85.1%. Multivariable Cox analysis confirmed that margin dose was associated with increased tumor growth control at two years (Table 2.8).

2.4 Discussion

GK radiosurgery is an established technology for delivering radiation selectively to intracranial targets. The primary aim of GK dose planning is to conform to any irregularities of the target shape. GK dose planning protocols are best suited for spherical targets, but most intracranial pathologies have irregular shapes [140]. Additionally, GK

Table 2.6

Summary demographic, clinical, and plan indices of patients included in the outcome analysis.

Patient characteristics	
Number of patients (M, F)	148 (69, 79)
Age Median [Range]	50 [87, 18]
TV (cm³) Median [Range]	1.41 [0.015, 14.86]
Koos grade value (%)	
I	21(14.2%)
II	59 (39.9%)
III	49 (33.1%)
IV	19 (12.8%)
Gardner-Robertson Class	
I	31 (21%)
II	52 (35.1%)
III, IV, and V	65 (43.9%)
GK Treatment Parameters	Median [Range]
SI	0.85 [0.20, 0.97]
CI	0.97 [0.74, 1.00]
GI	2.70 [2.40, 4.00]
EI	0.48 [0.13, 0.63]
PCI	0.79 [0.20, 0.96]
Central dose (Gy)	24.00 [20.00, 30.00]
Margin dose (Gy)	12.00 [10.50, 12.00]
Cochlea- target distance (mm)	1.80 [0.00, 10.00]
Maximum cochlear dose (Gy)	5.60 [1.50, 16.10]
Observation period (months)	24 [24, 52]

Table 2.7

The results of univariable and multivariable analyses for examining Gardner-Robertson serviceable hearing preservation after GK radiosurgery.

Covariate	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age	1.01 (0.97, 1.04)	0.70	1.00 (0.97, 1.04)	0.94
Sex	0.72 (0.30, 1.77)	0.48	0.72 (0.28,1.86)	0.50
Koos	1.28 (0.80, 2.04)	0.30	1.36 (0.58, 3.15)	0.48
TV	1.08 (0.72, 1.61)	0.72	0.63 (0.26, 1.54)	0.31
Margin dose	1.00(0.64,1.56)	1.00	0.98 (0.61, 1.56)	0.93
Cochlea-target distance	1.05 (0.67,1.66)	0.82	1.16 (0.62, 2.17)	0.64
CI	1.09 (0.68, 1.73)	0.73	1.76 (0.70, 4.43)	0.23
SI	1.32 (0.76, 2.29)	0.32	0.53 (0.04, 7.20)	0.64
GI	0.82 (0.48, 1.40)	0.48	1.65 (0.40, 6.88)	0.49
EI	1.34 (0.81, 2.21)	0.26	4.29 (0.18, 100.28)	0.37
Maximum cochlear dose	1.01(0.65,1.56)	0.98	1.27 (0.62, 2.63)	0.51
VioS	1.36 (0.81, 2.28)	0.24	1.17 (0.58, 2.39)	0.66

Table 2.8

The results of univariable and multivariable analyses examining tumor growth control after GK radiosurgery.

Covariate	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age	1.00 (0.97, 1.03)	0.88	0.98 (0.95, 1.01)	0.28
Sex	0.63 (0.27, 1.51)	0.30	0.55 (0.23, 1.33)	0.18
Koos	0.84 (0.52, 1.35)	0.47	0.58 (0.26, 1.26)	0.17
TV	1.01 (0.67, 1.53)	0.96	0.91 (0.46, 1.82)	0.79
Margin dose	0.71(0.51, 1.00)	0.05	0.60 (0.41, 0.89)	0.01
CI	0.81 (0.58, 1.13)	0.21	1.04 (0.47, 2.31)	0.92
SI	1.57 (0.89, 2.79)	0.12	2.08 (0.26, 16.53)	0.49
GI	1.15 (0.79, 1.68)	0.46	1.13 (0.35, 3.66)	0.84
EI	1.32 (0.82, 2.12)	0.25	1.08 (0.06, 17.96)	0.96
VioS	1.16 (0.75, 1.80)	0.51	1.07 (0.57, 2.03)	0.82

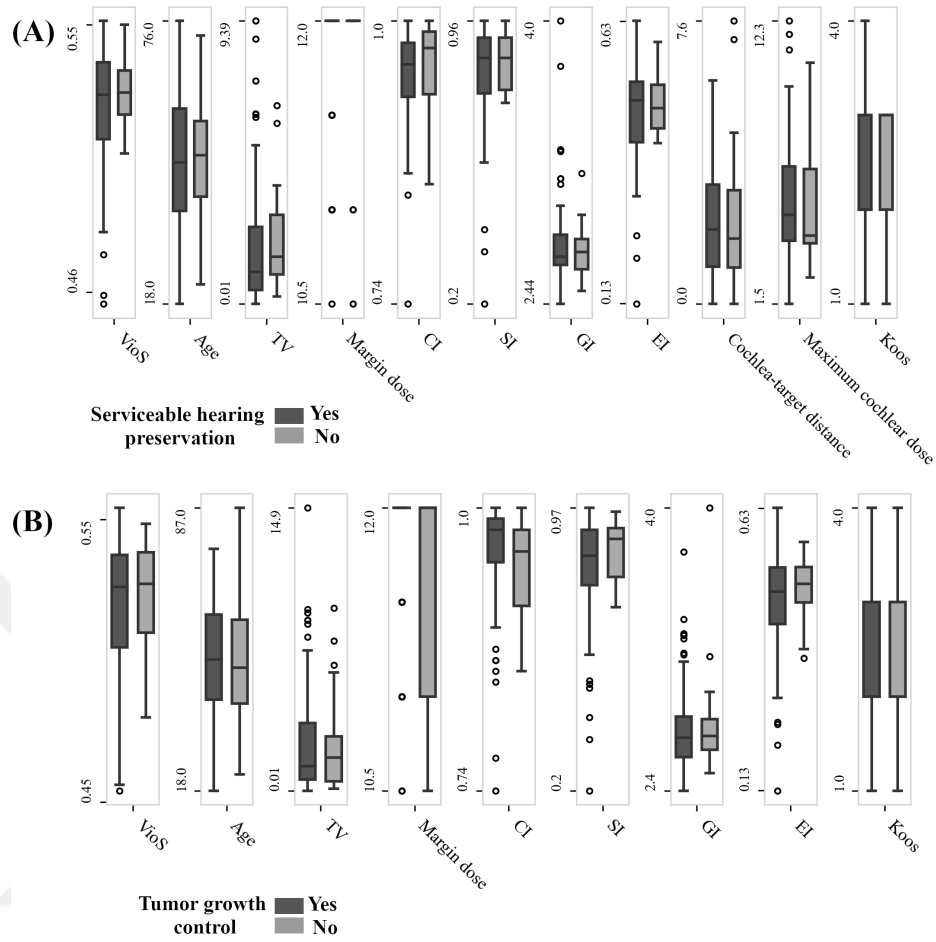


Figure 2.5 Comparisons of patient characteristics and dose plan indices with/without hearing preservation (A) and tumor growth control (B).

dose planning becomes more complex with increasing irregularity, resulting in a heterogeneous dose distribution within the target and in surrounding areas [140, 58, 60, 57]. In this study, we examined the impact of tumor shape irregularity on dose plan quality and identified key parameters influencing treatment outcomes in vestibular schwannomas. To quantify tumor shape irregularity, we employed seven distinct metrics, including traditional methods like surface-to-volume ratio, flatness, elongation, spherical disproportion, compactness, and sphericity, as well as a more advanced approach using VioS. Our results indicated that the radiomics-based shape irregularity features and treatment plan quality were significantly correlated. Additionally, irregularly shaped and smaller tumors had lower SI, EI, PCI, and higher GI, indicating worse plan quality. Although the TSI didn't have a significant effect on treatment outcomes, the margin dose was defined as a significant factor affecting tumor growth control at two years.

Moreover, machine learning algorithms successfully predicted higher dose plan indices based on tumor shape features. While it is widely recognized that the shape and size of the target influence dose distribution, only a limited number of studies have explored the impact of Tumor Shape Irregularity (TSI) on radiosurgery dose plan indices [133, 134]. Wu et al. [133] created mathematical simulations of targets with different degrees of irregularity and concluded that the TSI was inversely correlated with PCI. Additionally, Chagas-Saraiva et al. [134] reported that tumor sphericity degree facilitated the assessment of the dose distribution within the target. Similarly, our results indicated that irregular tumors had less conformal dose distribution.

Radiomics is a relatively new field that has been scarcely applied to vestibular schwannomas. Previous studies have mainly focused on predicting the vestibular schwannoma growth rate [141], transient enlargement [142], prognosis [143], and treatment response [144] using radiomics features. According to our results, the TSI features were not only correlated with dose plan indices, but also had the potential to predict the treatment plan quality in vestibular schwannomas. Especially, VioS was identified as a strong predictor of plan quality using machine learning algorithms. Predicting the highest possible dose plan quality for a given tumor shape may be relevant in the clinical practice as GK treatment planning is still a manual process.

Previous studies regarding the effect of target volume (TV) on dose plan indices across different pathologies have reported conflicting results [145, 146]. For instance, Menon et al. [143] found that PCI was not influenced by changes in TV of 60 AVMs [145]. In contrast, Stanley et al. suggested that PCI depends on TV [146]. Furthermore, we found that dose plan indices were strongly influenced by tumor volume (TV). Larger tumors exhibited higher SI, EI, and PCI values, while GI was lower. These variations can be attributed to differences in lesion characteristics and distinct planning strategies [53]. Unlike malignant tumors or AVMs, vestibular schwannomas are benign and primarily expand rather than invade surrounding tissues, resulting in a more spherical shape as TV increases. This was an important confounding factor in our study, because a more spherical tumor shape resulted in improved plan quality metrics for larger tumors. The SVR estimation not only depended on but had strong

correlations with TV. To overcome this limitation, we normalized TV-dependent shape features before the analysis. Nevertheless, the shape features, except the compactness and spherical disproportion, were still significantly correlated with TV, indicating that larger vestibular schwannomas had a more spherical or less irregular shape.

There is considerable variability in the size of vestibular schwannomas at the time of GK treatment, and the dose plan indices are significantly influenced by the TV. Two main effects are observed: Firstly, treatment quality metrics are not suitable in very small tumors [146, 147]. In a similar vein, Lomax et al. [53], observed that the conformity index decreased as TV in smaller than 1 cm^3 . Additionally, tumors with a TV of smaller than 0.2 cm^3 were not included in the analysis [52]. In addition, Wu et al. [133] examined the impact of TV on PITV and PCI resulting that conformity decreases in targets with smaller volumes. On the other hand, dose plan indices are better in larger tumors, even though they result in a higher dose to adjacent tissues [52, 148]. This leads to increased complication rates, despite improved quality metrics. To overcome these paradoxical effects, we systematically analyzed the relationships between TV and dose plan indices by further subdividing our cohort into small-, medium- and large-volume subgroups. In line with the previous studies' findings, we noticed that tumors with smaller TVs had worse plan quality indices than larger tumors.

Tumor growth control was chosen to assess the efficiency of the treatment and serviceable hearing preservation was chosen as a measure of safety of the treatment. GK treatment rates were comparable to the values reported in the current literature [149]. We also tested the effect of TSI on the treatment outcome. A previous large cohort study reported that serviceable hearing preservation, clinical tumor control, and radiographic tumor control were not affected by any factors including patient age and sex, laterality, tumor grade, prescription isodose, mean, maximum, and minimum target doses, RTOG conformity and homogeneity indices, energy index, SI, and PCI [150]. Additionally, they reported that lower GK dose rates ($<2.67 \text{ Gy/min}$) were associated with improved outcome on progressive symptomatic hearing loss and functional nerve dysfunction. In contrast, Brown et al. reported that coverage and age had adverse effects on hearing loss [151]. According to our results, TSI did not have a

significant impact on tumor growth control or serviceable hearing preservation at two years after GK. It seems that low TSI of a benign and non-infiltrative tumor would not significantly impact the ability of GK technology. Previously, it was shown that GK significantly reduced the dose to critical structures by using its dynamic shaping feature while delivering treatment [152]. Recently, Paddick et al. compared GK with different SRS platforms and revealed that the extracranial dose was the lowest for GK [153]. Thus, GK delivers the necessary dose to the TV while limits to radiate peripheral inner ear structures. Another reason might be that the operator could manually compensate for the dose heterogeneity caused by TSI by manipulating the treatment plan. Even if a minor effect on treatment outcome arised from TSI, one should keep in mind that our sample size might be limited to show such an effect. On the other hand, we identified higher margin dose as a significant factor affecting tumor growth control which had already been proven in other studies [129].

This study had also some limitations. There is no ideal machine learning method that provides the best solution to every problem [154]. For this study, we investigated five different state-of-the-art classifiers with a feature selection process, RFE-SVM [155], which is one of the most popular algorithms for selecting the best feature subset. However, we did not observe higher accuracies for all the response variables after feature elimination due to the limited number of shape irregularity features. Other feature selection and machine learning algorithms may be tested on a larger feature set for improved prediction accuracy. Moreover, the quantification of shape irregularity is a fundamental problem in mathematics, and there is no single perfect measure. Therefore, we chose a comprehensive approach and analyzed seven different shape metrics in a large and homogenous patient cohort. Furthermore, although the treatment quality indices used in this study are widely accepted, they are mere mathematical models and do not necessarily reflect the biological reality.

2.5 Conclusion

In conclusion, TSI was identified as a significant factor affecting GK dose plan quality but not the treatment outcomes in vestibular schwannomas. With increasing size, tumors become more spherical resulting in higher plan quality. Among several shape irregularity metrics, VioS was the strongest predictor of GK plan quality in vestibular schwannomas. Consequently, quantifying tumor shape irregularity and predicting dose plan indices beforehand could provide the clinician with an initial estimation of achievable plan quality during manual dose planning. Further analyses using different pathologies, different operators, and prospective study designs may facilitate a better understanding of the effect of TSI on GK dose planning.

3. T2W MRI RADIOMICS MODELS TO PREDICT IDH MUTATION STATUS AND SURVIVAL IN GLIOMAS: A MULTICENTER STUDY

3.1 Introduction

Gliomas are infiltrative primary intracranial tumors accounting for about 24.5% of all CNS neoplasms, and 80.9% of malignant brain tumors [28]. The five-year survival rate of gliomas ranges from 5% to 95%, depending on tumor subtype, molecular features, grade, and other factors [156]. It has been reported that IDH mutation is a significant prognostic factor for gliomas and has been associated with better treatment response and overall survival [30, 32, 34]. Although the IDH mutation has been detected by immunochemistry and genomic sequence analyses, intra-tumoral heterogeneity of gliomas might lead to incorrect results [157, 158]. Additionally, serial biopsies are required through disease course and therapies [159].

MRI is essential in understanding glioma biology, guiding the treatment plan, and predicting prognosis. There has been significant interest in identifying the relationship between MRI findings, IDH mutation status [160] and OS [161]. It has been shown that the tumor location [162, 163] contrast enhancement characteristics [164], edema [165, 166], and necrosis [167] were associated with the IDH mutation status and prognosis. In addition to conventional MRI, multiple advanced MRI techniques can provide comprehensive pathophysiological features of the whole tumor and improve diagnostic and prognostic specificity [168]. The studies showed that IDH-mutational status [169] and survival [170] could be estimated through blood perfusion characteristics measured with relative cerebral blood volume (rCBV) maps. Diffusion tensor imaging (DTI) metrics have also been correlated with IDH mutation status [171] and survival [172] of gliomas and enable better imaging of tumor margins, which shows tumor invasion. Metabolic profiles of gliomas have been correlated with IDH mutation [173] and patient survival [174] using proton MRS. Identifying imaging markers that

provide noninvasive information regarding IDH mutation status and survival is important, enabling appropriate treatment administration and prognosis estimation for gliomas.

The advancements in MR image analysis have enabled the transformation of the images into quantifiable representations. Radiomics extracts a large number of quantitative and mineable features from standard imaging modalities [91]. The subgroup of radiomics, radiogenomics, investigates the association between imaging findings and gene expression patterns and mutations of diseases. Fully automated extraction of radiomics features from tumor segmentation results in three major feature categories: first-order intensity, shape, and texture features [91]. Many publications have demonstrated that radiomics have the ability to detect the IDH mutation status [175, 176, 177, 178, 179, 180] and estimate the survival [181, 182] of gliomas from various MRI modalities. However, it is of utmost importance to externally validate the radiomics-based models to show the generalizability of the predictive power. Radiomics-based models often lack high predictive performance on unseen external data caused by differences in MRI protocol, MRI vendors, and feature extraction parameters [183]. Recent works have shown improved generalizability of radiomics-based models by applying intensity normalization to MR images [184, 180] and batch-effect correction techniques [185].

We hypothesized that quantitative radiomic parameters derived from MRI could represent underlying biological information of gliomas related to IDH mutational status and prognosis. Therefore, this study aimed to construct and validate radiomics-based models using T2w MRI. The study evaluated the predictive power of radiomics for the noninvasive preoperative estimation of IDH mutation status and prognosis in gliomas. We used a dataset from a local institution for model development, training, and internal testing for our analyses. Moreover, we performed external testing using the publicly available University of California San Francisco Preoperative Diffuse Glioma MRI (UCSF-PDGM) dataset.

3.2 Methods

3.2.1 Patients, Imaging Protocol, and Tumor Segmentation

In this retrospective study, two independent cohorts of 638 primary glioma patients with T2w MRI data were included. Patients were excluded based on the following criteria: (i) prior surgery or biopsy before imaging, (ii) absence of a histopathological diagnosis of primary glioma, and (iii) presence of multifocal or multicentric brain tumors.

The pre-operative imaging data of the discovery cohort (Cohort 1) were retrospectively collected from Acibadem University Altunizade Hospital after approval of the local ethics committee (Acibadem Healthcare Institutions Medical Research Ethics Committee (ATADEK-2016-9/10)). Cohort 1 consisted of 213 patients (IDH-mut/IDH-wt: 106/107, f/m: 89/124, (mean $\pm$ std) age: 45.52 $\pm$ 14.46 years), who were scanned with the preoperative brain tumor MRI protocol, including T2w MRI (TR/TE: 3470/107 ms, image size= 728 $\times$ 896 $\times$ 20 mm, and pixel dimensions= 0.26 $\times$ 0.26 $\times$ 6.5 mm) at a 3 T clinical MR scanner (Skyra, Siemens, Germany). Tumor segmentations were performed manually based on the hyperintense regions on T2w MRI using 3D Slicer software and validated by a junior radiologist (S.A.). [135].

The validation cohort (Cohort 2) was the publicly available UCSF-PDGM dataset from The Cancer Imaging Archive (TCIA). Cohort 2 consisted of 425 gliomas (IDH-mut/IDH-wt: 90/335, f/m:168/257, (mean $\pm$ std) age: 57.28 $\pm$ 14.89 years) [186]. A pre-operative brain tumor MRI protocol, including T2w MRI (image size= 240 $\times$ 240 $\times$ 155mm and pixel dimensions= 1 $\times$ 1 $\times$ 1mm) was performed on a 3 T scanner (Discovery 750, GE Healthcare, Waukesha, Wisconsin, USA). Multicompartment tumor segmentation of study data was performed as a part of the 2021 BraTS challenge [187]. We merged the multicompartment tumor segmentations into a single hyperintense tumor region on T2-weighted MRI for radiomics calculations.

3.2.2 Pathological and Genetic Evaluation

The histopathological examinations of local cohort (Cohort 1) were conducted on the surgical resected tissue to determine the tumor grade based on 2021 WHO CNS5. Resected tissue samples were also investigated for IDH1/IDH2 mutations using minisequencing or Sanger sequencing methods [34]. The IDH mutation status of the external dataset (UCSF-PDGM) was obtained from TCIA, with details of the genetic tests described in the related paper [186].

3.2.3 Pre-processing of Data

To minimize the effect of any inhomogeneity arising from different scanners and inter-subject variations, the images were preprocessed prior to feature extraction (Figure 3.1). For Cohort 1, T2w images and corresponding tumor masks were resampled to isotropic voxel dimensions of $1 \times 1 \times 1 \text{ mm}^3$. N4 bias correction was applied to correct spatial intensity heterogeneity on T2w images [188] followed by skull-stripping [189]. Cohort 2 images had an isotropic voxel dimension of $1 \times 1 \times 1 \text{ mm}^3$ and underwent N4 bias correction and skull stripping. For the harmonization of two independent datasets, a piecewise linear histogram matching technique was applied to the preprocessed images [11].

3.2.4 Feature Extraction, Model Construction, and External Validation

Feature extraction was performed using the PyRadiomics tool for Cohort 1 and Cohort 2, considering the same set of 1,820 features [130], which included intensity, shape, and texture features. The textural parameters were computed from the GLCM, GLRLM, GLSZM, NGTDM, and GLDM. Cohort 1 was used to perform feature selection as the discovery cohort. Additionally, to harmonize radiomic features between Cohort 1 and Cohort 2, the ComBat algorithm was applied [190]. This process generated a second set of radiomic features for each cohort. The entire feature extraction

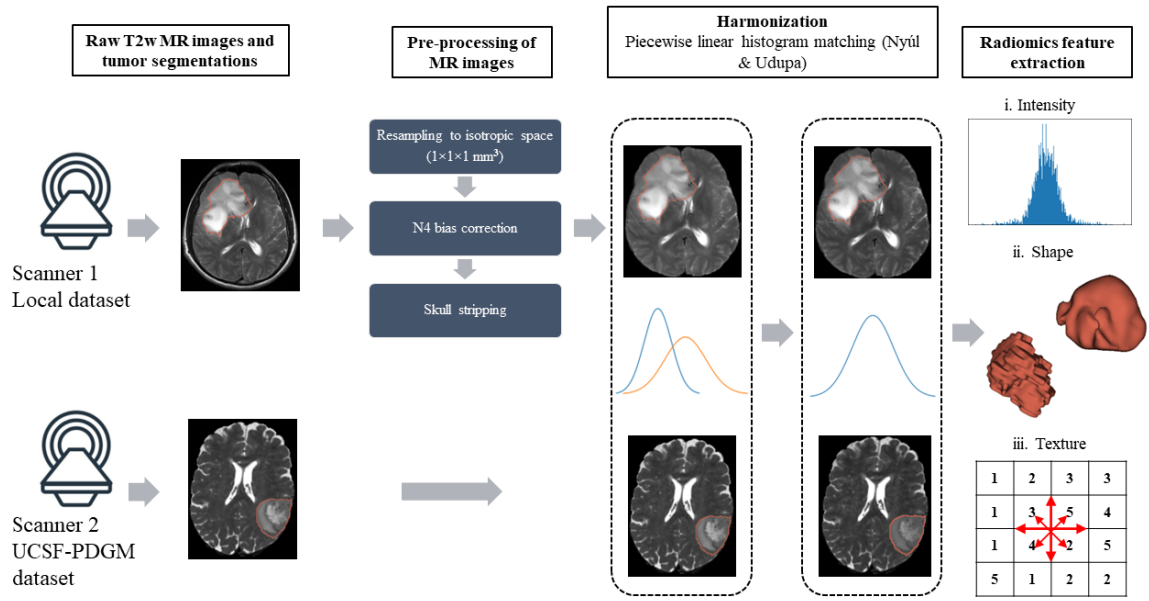


Figure 3.1 Workflow for image preprocessing and radiomics feature extraction.

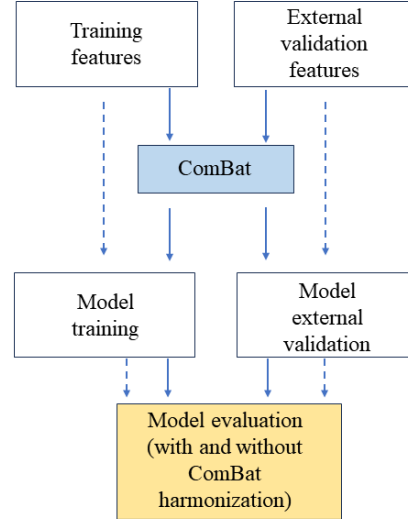


Figure 3.2 Workflow for model training and external validation regarding the application of ComBat harmonization to radiomics features. The models were trained and externally validated using both features with and without ComBat harmonization.

and model construction were then repeated using the ComBat-harmonized features, as shown in Figure 3.2.

The overall machine-learning workflow is given in Figure 3.3. Cohort 1 was used to construct different radiomics models and optimize models' hyperparameters. The models' predictive performances were determined using Cohort 1 and independent validation data (Cohort 2). More specifically, in the 10-fold cross-validation scheme, we first performed a feature selection procedure employing both unsupervised/supervised approaches on the training data of Cohort 1. The final feature subset was determined with a selection frequency $\geq 70\%$ to avoid overfitting [191]. The feature subset was then used as input for selecting the best hyperparameters of machine learning classifiers (k-nearest neighbor (kNN), logistic regression, support vector machines (SVM), linear discriminant analysis, decision trees, random forest, and extreme gradient boost (XGBoost)). The hyperparameters were chosen through a 5-fold cross-validated grid search according to the selection frequency. The IDH mutation status of Cohort 1 was then classified using the most selected hyperparameters and characteristics with a repeated 50×10 -fold cross-validation. In Cohort 2, we randomly removed 245 samples from the majority class to achieve a better balance in class distributions within the external validation dataset, aligning it with the distribution in the discovery cohort. The undersampling was repeated with 50 iterations with different seed values to enhance the generalizability of the results. In the last step, we trained the tuned models with a complete set of samples of Cohort 1 and validated on undersampled Cohort 2. The accuracy, recall, precision, and receiver operating characteristic area under the curve (ROC AUC) were used to quantify the prediction performances of the radiomics-based models.

3.2.5 Statistical Analysis

The statistical analysis was performed using Python 3.8.16. The selected radiomics features and age were compared between IDH-mut and IDH-wt gliomas using a Mann-Whitney U test with Bonferroni correction ($P < 0.0042$). The sex distributions of the patients were compared between the IDH subgroups using a χ^2 test.

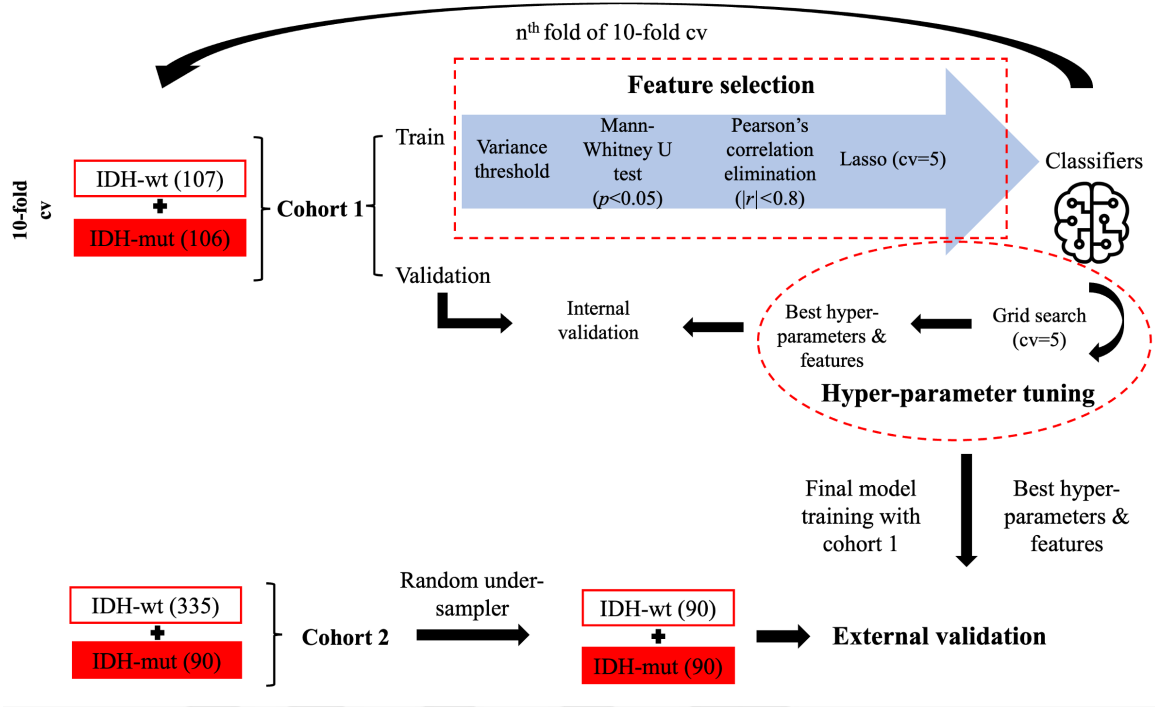


Figure 3.3 The overall pipeline of radiomics models using the discovery dataset is shown, with the models being externally validated using the validation cohort.

3.2.6 Radiomic Risk Score Computation

For the construction of a radiomics based risk score (RS), Lasso feature selection was applied to identify the most relevant features. The discovery dataset was split into training (80%) and test (20%) sets to determine the optimal subset of radiomics features. This process was repeated 100 times with different seed values, and the final feature subset was composed of features selected with a frequency greater than 70%. The RS was then calculated for both cohorts using the selected features and their corresponding Lasso coefficients ($RS = \sum \text{selected feature values} \times \text{Lasso coefficient of the features}$).

3.2.7 Survival Analysis

The survival analyses were performed for (i) IDH-wt patients (Cohort 1: alive ($n = 53$) and dead ($n = 48$), Cohort 2: alive ($n = 133$) and dead ($n = 201$)) and

(ii) all patients (Cohort 1: alive ($n = 138$) and dead ($n = 53$), Cohort 2: alive ($n = 213$) and dead ($n = 211$)). Since the data for the IDH-mut group in Cohort 1 was not mature (with only five deceased patients compared to 85 survivors), we did not perform survival analysis for this subgroup.

Univariable and multivariable Cox regression analyses were used to evaluate the effects of RS and clinical features- age, sex, and WHO tumor grade- on OS ($P < 0.0125$). Patients in the discovery cohort with an RS greater than the median value were classified as high-risk, while those with an RS lower than the median were classified as low-risk. For the external validation of the prognostic value of RS, Cohort 2 was divided into low- and high-risk clusters using the same RS threshold. The Kaplan-Meier survival curves of these groups were then compared using a log-rank test ($P < 0.05$).

3.3 Results

3.3.1 Patient Characteristics and Harmonization of Two Cohorts

Table 3.1 shows the summary of patients' clinical and molecular-pathologic characteristics. The median age of Cohort 1 was 45 years (range: 20–77), while for Cohort 2, it was 60 years (range: 19–94). While sex distributions were similar ($P = 0.60$) in Cohort 1 and 2, patient ages were significantly higher in Cohort 2 and ($P = 5.67E-18$). In Cohort 1, 107 patients (50%) were IDH-mut, while in Cohort 2, 90 patients (21%) had IDH mutations. The sex distributions did not differ significantly between the IDH-mut and IDH-wt subgroups in Cohort 1 and Cohort 2 ($P = 0.42$ and $P = 0.65$, respectively). Patients in the IDH-wt subgroups were significantly older than those in the IDH-mut subgroups in both Cohort 1 and Cohort 2 ($P = 5.21E-17$ and $1.63E-33$, respectively). Figure 3.4 shows histograms of T2w MR images before and after applying the image intensity normalization, which improved the consistency of intensity distributions among patients as well as across two different datasets.

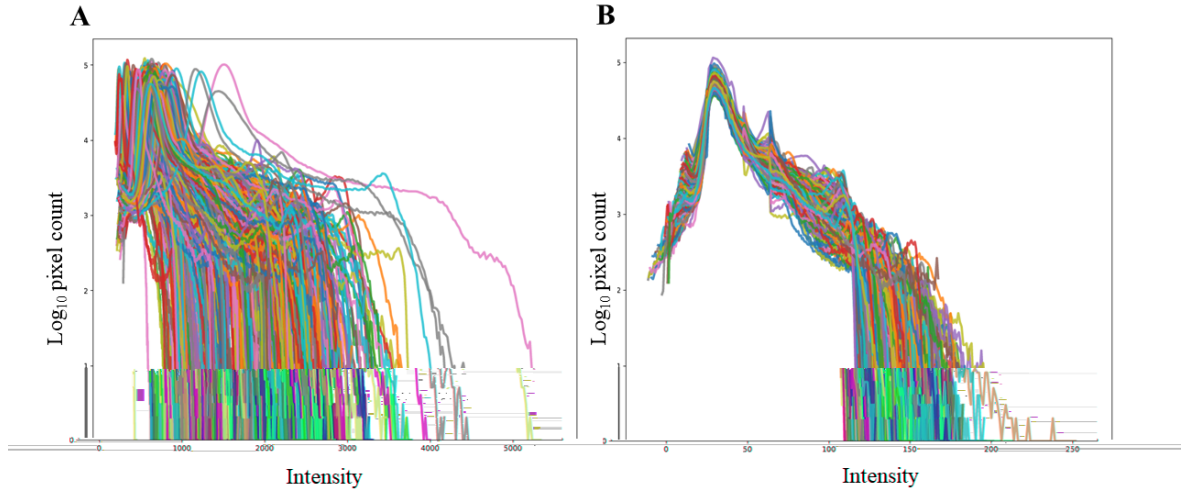


Figure 3.4 The impact of image intensity normalization applied to T2w MR images: (A) before intensity normalization and (B) after intensity normalization. Each line represents a patient's image intensity histogram [11].

3.3.2 Identifying Radiomic Features Associated with IDH Mutation

After the feature selection procedure, 12 radiomic features were retained with greater predictive value. The distributions of these 12 top-selected features in IDH-wt and IDH-mut gliomas of Cohort 1 are given in Figure 3.5. Seven radiomics features significantly differed between IDH-wt and IDH-mut gliomas in Cohort 1 ($P < 0.0042$). IDH-wt tumors had significantly higher GLRLM short-run low gray-level emphasis (with square filtering), skewness (3D local binary pattern (LBP)), GLCM cluster shade (with square filtering), and GLCM Imc1 ($P < 0.002$, for all). On the other hand, IDH-mut tumors had significantly higher sphericity, GLSZM small area emphasis (with Laplacian of Gaussian filter (LoG)), and GLDM dependence variance (with wavelet high-low-low (HLL) filtering).

The same radiomics feature subset was used to identify differences between the IDH-mutational subgroups in Cohort 2, and their distributions are shown in Figure 3.6. Four of the selected radiomic features were significantly different between the

Table 3.1
Clinical and molecular-pathologic variables in the two multicenter datasets.

	Cohort 1 (number of patients (percentage))	Cohort 2 (number of patients (percentage))
Total	213	425
Age(range)	45(20,77) years	60(19,94) years
Sex (female)	81 (42%)	167 (39%)
IDH-wt	107 (50%)	335 (79%)
IDH-mut	106 (50%)	90 (21%)
WHO Grade 2	66 (31%)	52 (12%)
WHO Grade 3	64 (30%)	38 (9%)
WHO Grade 4	83 (39%)	335 (79%)
Oligodendroglioma (IDH-mut, 1p19q codeleted)	39 (18%)	13 (3%)
Astrocytoma (IDH-mut, 1p19q non-codeleted)	67 (32%)	77 (18%)
Glioblastoma (IDH-wt)	107 (50%)	335 (79%)

IDH-wt and IDH-mut subgroups of Cohort 2 ($P < 0.0042$). While IDH-mut tumors had significantly higher sphericity, GLDM dependence variance (wavelet HLL filtering), and GLSZM small area emphasis (with LoG filtering), IDH-wt tumors showed significantly higher GLRLM short-run low gray-level emphasis (with square filtering) ($P < 0.001$, for all).

3.3.3 Performances of Radiomics Classifiers in Identifying IDH Mutation

The predictive performances of the top three machine learning models for IDH mutation using radiomics features are presented in Table 3.2. In Cohort 1, the top performances were achieved with logistic regression (accuracy= 0.80, recall= 0.78, precision= 0.83, ROC AUC of 0.90), followed by SVC (accuracy= 0.80, recall= 0.79, precision= 0.81, and ROC AUC 0.90) and linear discriminant analysis (accuracy= 0.80,

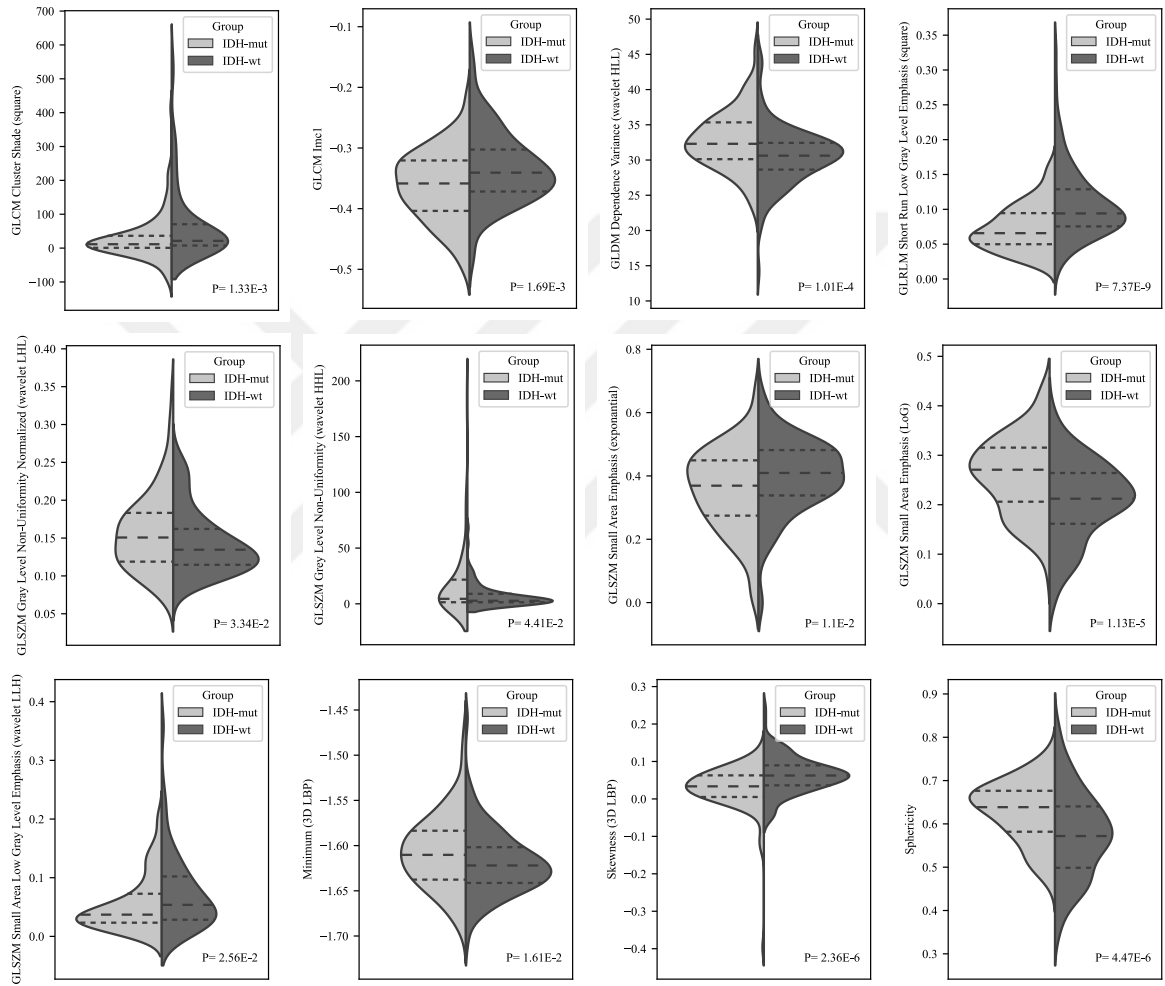


Figure 3.5 Violin plots show the distributions of twelve selected features in the IDH-wt and IDH-mut subgroups of Cohort 1. For each pair of distributions, P-values were computed from the Mann-Whitney U test with Bonferroni correction ($P < 0.0042$).

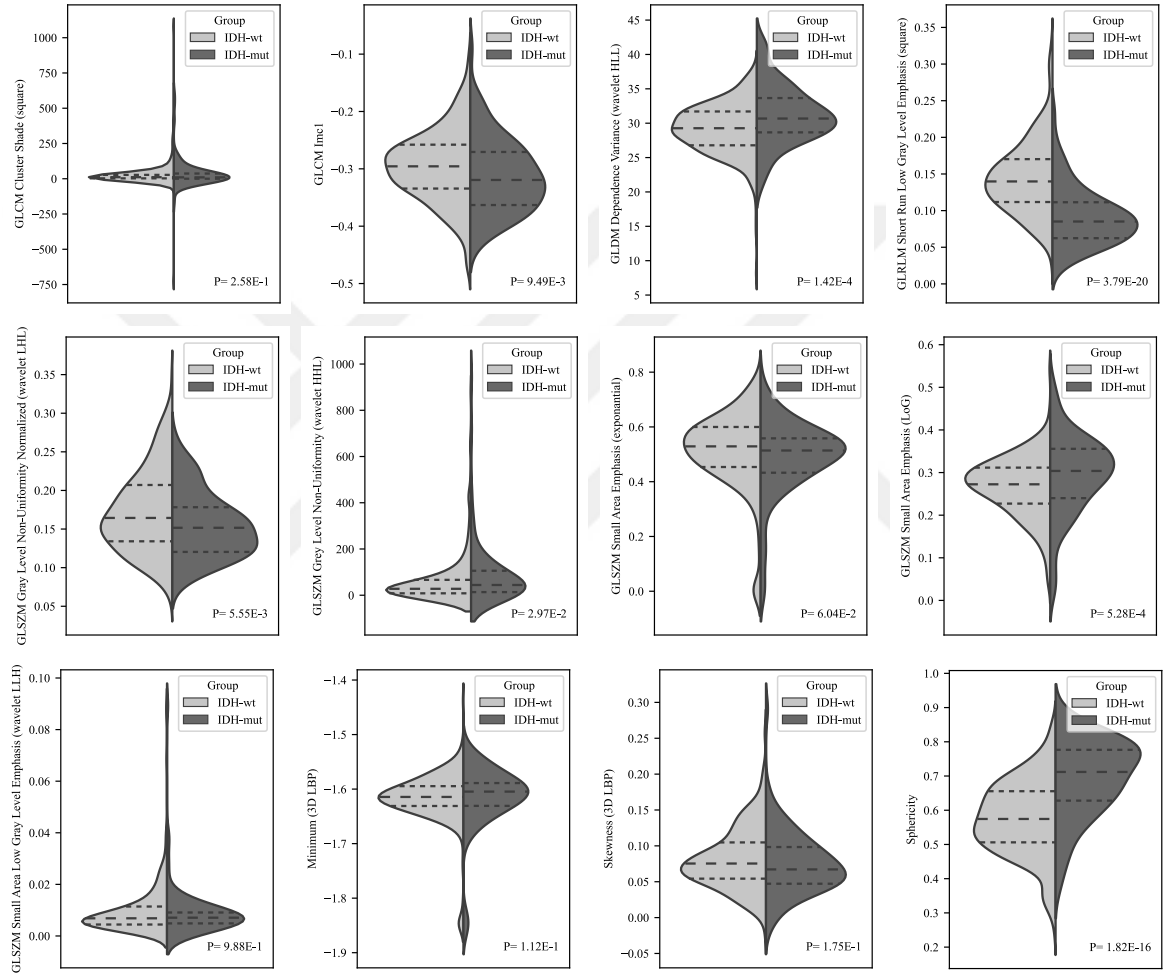


Figure 3.6 Top-selected radiomics features identified using discovery cohort were also tested using validation cohort along with Mann-Whitney U test with Bonferroni correction ($P < 0.0042$) for discriminating IDH-wt and IDH-mut tumors.

recall= 0.76, precision= 0.83, and ROC AUC= 0.89) without ComBat harmonization. By applying ComBat harmonization to radiomics features, we achieved an ROC AUC of 0.92 for all three classifiers (accuracy $\geq$ 0.83, recall $\geq$ 0.82, and precision $\geq$ 0.84).

In the validation cohort, IDH mutation was detected most effectively with logistic regression (accuracy = 0.69, recall = 0.83, precision = 0.64, and ROC AUC = 0.69) and random forest (accuracy = 0.69, recall = 0.72, precision = 0.68, ROC AUC = 0.69) classifiers using the features obtained without harmonization (Table 3.2). On the other hand, a decision tree classifier resulted in a predictive accuracy of 0.68 (recall= 0.85, precision= 0.65, and ROC AUC= 0.68). Using a random forest classifier, ComBat harmonized features achieved a slightly lower accuracy of 0.61 (recall= 0.41, precision= 0.68, and ROC AUC= 0.61).

3.3.4 Performance of the Survival Prediction Models

The RS values were computed based on six radiomics features (sphericity, maximum (with wavelet-LLH filtering), GLCM cluster prominence (with wavelet-HLH filtering), GLSZM zone variance (with wavelet-LLL filtering), skewness (3D LBP filtering), and GLZM small area low gray level emphasis (with square filtering)) for all patients in Cohort 1. For the IDH-wt subgroup of Cohort 1, five features (GLSZM small area high gray level emphasis (with 3D LBP), maximum (with wavelet LHL filtering), maximum (with wavelet LLH filtering), skewness (3D LBP), and GLSZM small area emphasis (with LoG filtering)) were used for RS calculation. The median RS values (-0.0094 for all patients and -0.0077 for the IDH-wt subgroup of Cohort 1) were used for risk stratification. These same thresholds were subsequently applied to Cohort 2.

Median follow-up was median [range]=24 [0,134] months in Cohort 1 and median [range]=13 [0,89] months in Cohort 2. While the age distribution significantly differed between the low- and high-risk patient subgroups in Cohort 1 ($P=1.14E-8$), the sex distribution was similar ($P = 0.06$). Similarly, in Cohort 2, the sex distribution did not significantly differ between the low- and high-risk subgroups ($P = 0.29$), while age

Table 3.2
Classification performance of radiomics-based model on Cohort 1 and validation cohort (Cohort 2).

Cross-validation (50×10-fold cross-validation) on ACU dataset (IDH-mut: 106 and IDH-wt: 107)									
Classifiers	Without ComBat harmonization				With ComBat harmonization				
	Acc	Recall	Prec	ROC-AUC	Classifiers	Acc	Recall	Prec	ROC-AUC
Logistic regression	0.80±0.01	0.78±0.01	0.83±0.01	0.90±0.01	Logistic regression	0.83±0.01	0.82±0.01	0.85±0.01	0.92±0.01
SVC	0.80±0.01	0.79±0.01	0.81±0.01	0.90±0.01	Random forest classifier	0.84±0.01	0.83±0.02	0.84±0.01	0.92±0.01
Linear discriminant analysis	0.80±0.01	0.76±0.01	0.83±0.01	0.89±0.01	XGBoost	0.84±0.01	0.85±0.01	0.84±0.01	0.92±0.01
External validation on UCSF PDGM dataset (IDH-mut: 90, IDH-wt:90)									
Classifiers	Without ComBat harmonization				With ComBat harmonization				
	Acc	Recall	Prec	ROC-AUC	Classifiers	Acc	Recall	Prec	ROC-AUC
Logistic regression	0.69±0.02	0.83±0.00	0.64±0.02	0.69±0.02	Random forest classifier	0.61±0.02	0.41±0.00	0.68±0.04	0.61±0.02
Random forest classifier	0.69±0.02	0.72±0.00	0.68±0.02	0.69±0.02	XGBoost	0.60±0.02	0.31±0.00	0.67±0.05	0.58±0.02
Decision tree classifier	0.68±0.02	0.85±0.00	0.65±0.02	0.68±0.02	kNN	0.54±0.03	0.54±0.00	0.55±0.03	0.55±0.03

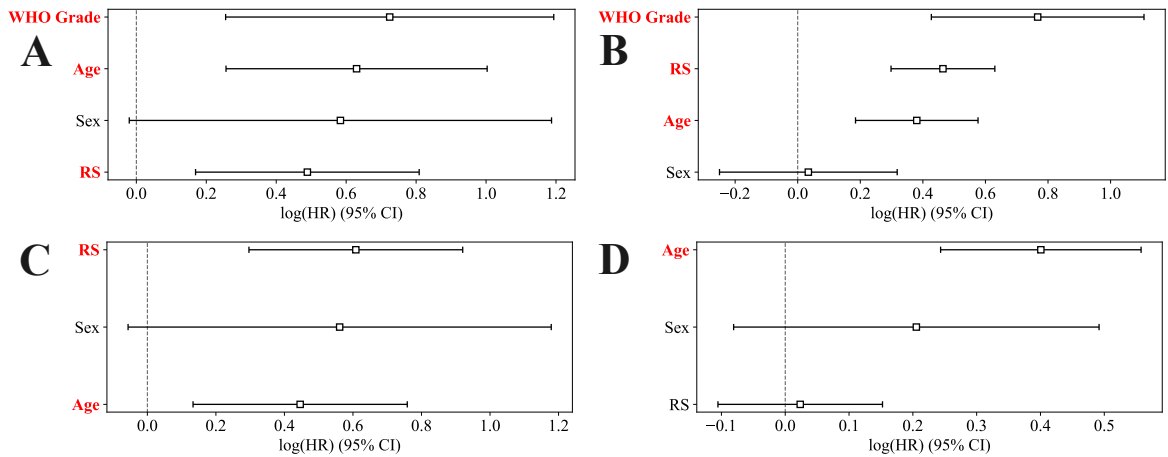


Figure 3.7 The impacts of the RS, sex, age, and tumor grade on OS in multivariable Cox analysis: (A) overall discovery cohort, (B) overall external validation cohort, (C) IDH-wt patients of discovery cohort, and (D) IDH-wt patients of validation cohort (red: $P < 0.0125$).

significantly differed between the two subgroups ($P = 1.63E-17$).

The results of the univariable and multivariable Cox proportional hazards models (hazard ratio (HR) and P values) are summarized in Table 3.3. Additionally, Figure 3.7 shows the impacts of clinical features- age, sex, WHO grade- and RS on OS in multivariable Cox regression analysis. Univariable and multivariable Cox regression analysis of clinical features and RS revealed that age, RS, and WHO grade were significantly associated with OS in cohorts 1 and 2 ($P < 0.005$, for all). Moreover, age and RS were identified as independent prognostic factors for the IDH-wt subgroup of Cohort 1 ($P \leq 0.01$ for age and $P < 0.005$ for RS); while only age was associated with OS in the IDH-wt subgroup of Cohort 2 ($P < 0.005$ for both univariable and multivariable Cox analysis).

According to the results of the Kaplan-Meier analysis, high-risk patients had significantly shorter OS compared to low-risk patients in both Cohorts 1 and 2 ($P = 1.48E-8$ and $P = 1.84E-15$, respectively, Figure 3.8 A and B). RS stratified patients in the IDH-wt subgroup of Cohort 1 with significantly shorter OS in the high-risk cluster ($P = 3.05E-4$, Figure 3.8 C). However, RS was not identified as a prognostic factor for OS in the IDH-wt subgroup of Cohort 2 ($P = 9.99E-1$, Figure 3.8 D).

Table 3.3

Univariable and multivariable Cox proportional hazards regression for overall survival in discovery cohort (Cohort 1) and validation of survival model on Cohort 2 (*P:0.0125).

Discovery cohort				Validation cohort			
Univariable		Multivariable		Univariable		Multivariable	
Covariate	HR(95%CI)	P	HR(95% CI)	P	HR(95% CI)	HR(95% CI)	P
Age	2.95(2.18,3.99)	<0.005*	1.88(1.29, 2.73)	<0.005*	2.18(1.85, 2.57)	1.46(1.20,1.78)	<0.005*
Sex	1.79(1.00,3.18)	0.05	1.79(0.98,3.28)	0.06	1.12(0.85,1.48)	1.03(0.78,1.37)	0.81
RS	2.80(2.17,3.62)	<0.005*	1.63(1.18, 2.25)	<0.005*	2.01(1.77,2.29)	1.59(1.35,1.88)	<0.005*
WHO Grade	3.95(2.52,6.22)	<0.005*	2.06(1.29,3.30)	<0.005*	3.02(2.16,4.21)	2.15(1.53,3.02)	<0.005*
IDH-wt discovery cohort				IDH-wt validation cohort			
Univariable		Multivariable		Univariable		Multivariable	
Covariate	HR(95%CI)	P	HR(95% CI)	P	HR(95% CI)	HR(95% CI)	P
Age	1.65(1.20,2.27)	<0.005*	1.56(1.14, 2.14)	0.01*	1.48(1.26,1.73)	1.49(1.28,1.75)	<0.005*
Sex	1.38(0.76,2.49)	0.29	1.75(0.95,3.25)	0.07	1.16(0.87,1.54)	1.23(0.92,1.64)	0.16
RS	1.96(1.46,2.62)	<0.005*	1.84(1.35, 2.51)	<0.005*	0.99(0.87,1.13)	1.02(0.90,1.16)	0.72

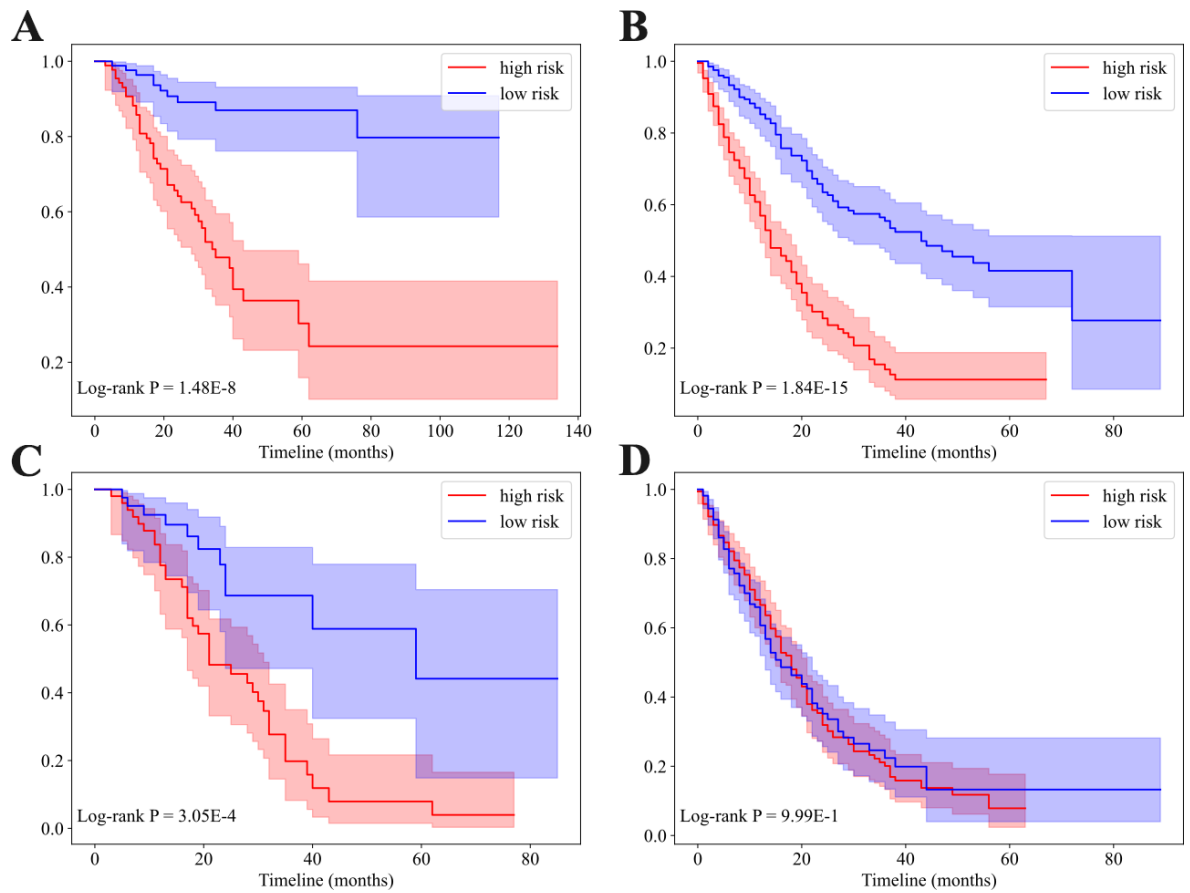


Figure 3.8 The Kaplan-Meier survival curves of patients in Cohort 1 (A), Cohort 2 (B), and IDH-wt subgroups of Cohort 1 (C) and Cohort 2 (D) are displayed as low-risk (blue) and high-risk (red) groups. The differences of OS between the low- and high-risk groups were assessed by Log-rank tests.

3.4 Discussion

MRI is an essential imaging modality for the diagnosis and management of gliomas. In routine clinical settings, molecular subtyping and the assessment of patient prognosis are typically based on histopathology, which can be difficult to determine from preoperative conventional MRI [192]. With the continuous development of radiomics-based models, researchers have increasingly utilized radiomics analysis for precision medicine in gliomas. Previously, radiomics has been used for diagnosis [193], as well as to predict tumor grade [194], molecular subtypes [195], recurrence [196], and survival [197] of gliomas. However, the stability and generalizability of radiomics-based models are still bottlenecks of their clinical translation. Thus, we developed radiomics models based on preoperative T2w MRI images after applying a piecewise linear histogram matching technique to predict the IDH mutation status and to develop a risk stratification model for glioma patients. Importantly, the prediction models were tested on an independent external dataset. In addition, we investigated the potential of a radiomic-based risk score (radiomics score-RS) for the stratification of risk in patients with glioma. The effect of RS and clinical features- age, sex, and WHO tumor grade- on patients' OS were also evaluated. Radiomics-based models have shown the ability to predict IDH mutation status and prognosis with strong performance.

In the current study, we employed T2w MR images, as this sequence is well-accepted and widely available in routine clinical settings. Moreover, Yogananda et al. stated that conventional T2w MRI has the potential to predict IDH mutation status in gliomas as effectively as multi-contrast MRI [198]. Another study suggested that T2w MR image features were more predictive for identifying IDH mutation status than features extracted from T1-weighted (T1w) and fluid-attenuated inversion recovery (FLAIR) MRI [175].

Various radiomics features, such as intensity, shape, and texture, have been analyzed for predicting IDH mutational status in gliomas. Among these, texture features demonstrated significant discriminative power compared to the other features, accounting for nine of the twelve selected features in this study. Additionally, of the twelve

selected features, seven features significantly differed between the IDH mutational subgroups in Cohort 1, while four features showed significant differences in Cohort 2. IDH-wt tumors had significantly lower sphericity values, indicating that aggressive tumors tended to have more irregular boundaries compared to IDH-mut tumors [199]. Beyond the tumor shape regularity, intratumoral heterogeneity is another hallmark of glioma, especially in IDH-wt tumors (glioblastoma), and has been associated with poor prognosis [200]. Another study has shown that texture features correlate with intratumoral heterogeneity, which may not be readily apparent to the naked eye [103]. One of the GLRLM features, short run low gray level emphasis, captures the prevalence of small low intensity clusters indicating necrotic and heterogeneous areas in IDH-wt tumors. While GLSZM small area emphasis (sigma= 4mm) suggested uniform textures in IDH-wt tumors, this could be due to over-suppression of finer details with Gaussian filtering. In IDH-mut cases, GLCM Imc1 feature was close to -1, suggesting homogeneous structures in the tumor compared to IDH-wt cases with greater texture complexity. Similarly, higher GLCM cluster shade in IDH-wt tumors implies higher asymmetry in neighboring pixels and presence of nonuniform textures in the tumor. Similarly, GLDM dependence variance measures diversity in patterns with higher values indicating more heterogeneous structures. IDH-mut tumors showed higher GLDM dependence variance, which could indicate their heterogeneous structure due to pronounced edema within tumor region, leading to increased variability in the texture of T2w MRI. Higher skewness in IDH-wt tumor regions indicated asymmetry in intensity distributions. These findings were partly consistent with the literature and demonstrated the benefits of incorporating texture analysis for identifying IDH mutational status, in addition to intensity and shape-based radiomics features [201, 202, 203, 204].

Previous studies have shown that IDH mutation could be determined using radiomics extracted from MRI with ROC AUC ranging from 0.73 to 0.97 [175, 178, 201, 202, 203, 205, 204, 206, 207, 208, 209], which were similar to or better than the performance of the radiomics models used in the present study. Most studies have mainly used local institutional [178, 201, 203, 205, 206, 207, 209] or publicly available datasets [175, 204]; nonetheless, our study featured a local cohort in addition to an independent validation cohort. Moreover, ComBat harmonization was utilized to deter-

mine whether or not radiomics-powered decisions could be improved by removing non-biological batch-related effects between different datasets originating from differences in scanners, imaging protocols, and other non-biological effects. ComBat-harmonized and non-harmonized features demonstrated good accuracy in cross-validated IDH mutation detection in Cohort 1, achieving ROC AUCs of 0.91 and 0.92, respectively. On the external validation cohort (Cohort 2), the predictive performance of radiomics models were reduced with ROC AUCs of 0.69 and 0.61 for non-harmonized and harmonized radiomics models, respectively. ComBat harmonization did not yield performance improvements for the radiomics-based machine learning models. The lack of enhancement in classification on the external dataset could be due to ComBat disrupting meaningful feature distributions leading to worse performance [210]. This highlights the need for radiomics-specific harmonization techniques. Another reason might be that the size of the discovery cohort was insufficient to accurately estimate batch effects, leading to poor harmonization [211].

Many radiomics based prediction models have been developed for survival prediction in gliomas [212, 110, 213, 214, 181]. A consensus from previous studies has shown that prediction models based on radiomics are prognostic factors independent of traditional factors (such as sex, age, WHO tumor grade, molecular features, and others). These models could be combined with traditional risk factors to predict the prognosis of glioma patients more accurately. In the current study, we identified a significant relationship between radiomics-based RS and OS in gliomas. Patients with RS values higher than the median had a relatively worse prognosis compared to those with lower RS values. Our results indicated that radiomics-assisted models might provide a preoperative, non-invasive, and low-cost tool for individualized survival stratification in gliomas.

This study had some limitations. The tumor segmentations were performed by a researcher under the supervision of a junior radiologist. Therefore, inter-observer variability assessment was not applied. Additionally, analysis using multi-compartment segmentations, such as enhancing and necrotic regions, was not employed to extract comprehensive information from the whole tumor region on T2w MRI. Another limi-

tation was that IDH-mut cases were fewer than IDH-wt cases in Cohort 2, so random undersampling was employed to achieve a more balanced distribution, similar to the discovery cohort. Moreover, the discovery cohort data was obtained from a single institution in this retrospective study, which was used to build the models for differentiating IDH mutational status and estimating prognosis. Although the models were validated on an external independent cohort, it is necessary to test them on larger patient cohorts from multiple institutions. Another limitation was that our follow-up period was insufficient to track all the patients to their endpoints, which may limit the effectiveness of our survival models. Future work will continue to track all currently censored patients. Additionally, there is an undeniable need to design a prospective validation cohort for future directions.

3.5 Conclusion

In conclusion, this study extends the use of radiomics in glioma research by investigating the detection of IDH mutations and survival analysis. In addition, RS is an independent biomarker for OS estimation and could be combined with traditional prognostic factors for better and individualized risk stratification in patients with gliomas. The sphericity and texture patterns of the tumor region defined on preoperative T2w MRI were identified as important factors for IDH mutational status and OS in gliomas.

4. RADIOMICS TO PREDICT NF2-LOSS AND RECURRENCE IN MENINGIOMAS

4.1 Introduction

Meningiomas cover one-third of primary brain tumors and they are heterogeneous in their age of presentation, anatomical location as well as molecular genetic alterations [215]. The majority of meningiomas are classified as benign (grade I) according to the WHO 2016 grading system, while atypical (WHO grade II) or anaplastic (WHO grade III) meningiomas have shown significantly worse prognosis [216]. In recent years, genetic biomarkers have contributed to the understanding of biological behavior, treatment response, and consequently prognosis of brain tumors [217]. Loss of NF2 function (NF2-L) is observed in 2/3 of all meningiomas [218]. This most commonly presents as the loss of an allele of the gene (copy number loss). Additional alterations such as mutations are generally seen in addition to the copy number loss. Tumors carrying NF2 alterations have been associated with a more aggressive biology (being more invasive, prone to present in and progress to higher histological grades due to genomic instability) and poor prognosis [219, 220]. Thus, identifying the molecular subset with NF2 loss at the time of diagnosis may support treatment decision-making.

About 25% of all meningiomas are located along the parasagittal and falx regions [215]. Parasagittal and falx meningiomas (PFM) are located around vital venous structures, which precludes a complete surgical resection. Therefore, residual tumors after surgery, regrowth, or recurrences are more common in PFM than in other anatomical localizations [221]. GK radiosurgery is a valid and effective treatment modality in these situations [222].

In this study, we aim to predict the NF2-L and recurrence free survival (RFS) in meningioma patients by using quantitative radiomic features obtained from preoperative anatomical MRI.

4.2 Methods

4.2.1 Patient Characteristics for Predicting NF2 Loss

MRI data of 85 patients diagnosed with meningioma were included in this study after written informed consent (mean age= 53.11 ± 13.54 years, median age of 54 [range 26-86] years, female/male ratio:1.83). Forty patients were grade I, 42 patients were grade II, and three patients were grade III. The patients were scanned at pre-surgery time point on a 3T clinical MR scanner (Siemens Healthcare, Erlangen, Germany) using a brain tumor imaging protocol that included post-contrast (gadolinium (Gd)) T1w SE MRI (TR/TE= 415/10 ms). Based on the assessment of surgical specimen, 38 of the tumors were NF2-L and 47 of them had no copy number loss (NF2-NL), as determined by digital droplet PCR using pre-validated TaqMan probes.

4.2.2 Radiomics Analysis

The radiomics workflow of the study is given in Figure 4.1. First, the CE tumor volumes were manually segmented using 3D Slicer software [223]. Then, a 100 gray-level normalization scale was applied to MR images. To minimize the effect of inhomogeneity between acquisitions, images were z-score normalized and resampled to the same resolution ($1 \times 1 \times 1$ mm³). A total of 1132 radiomic features were computed using PyRadiomics [130]. For feature selection, collinear features were eliminated using pairwise Spearman's correlation filter ($r > \pm 0.7$) and then the features with low variance were removed from the feature set. Then, the Lasso feature selection method was applied to the training set to search for the optimal predictive features. This process was repeated 100 times with different seed values and the final feature subset was determined with features with a frequency of above 80%. The differences of selected radiomics features between NF2-L and NF2-NL meningiomas were assessed by a Mann-Whitney U test. $P < 0.0083$ was determined as the significance level after a Bonferroni correction. Finally, NF2-L and NF2-NL meningiomas were classified using a logistic regression classifier with 10-fold cross-validation and 100 repetitions with different seed

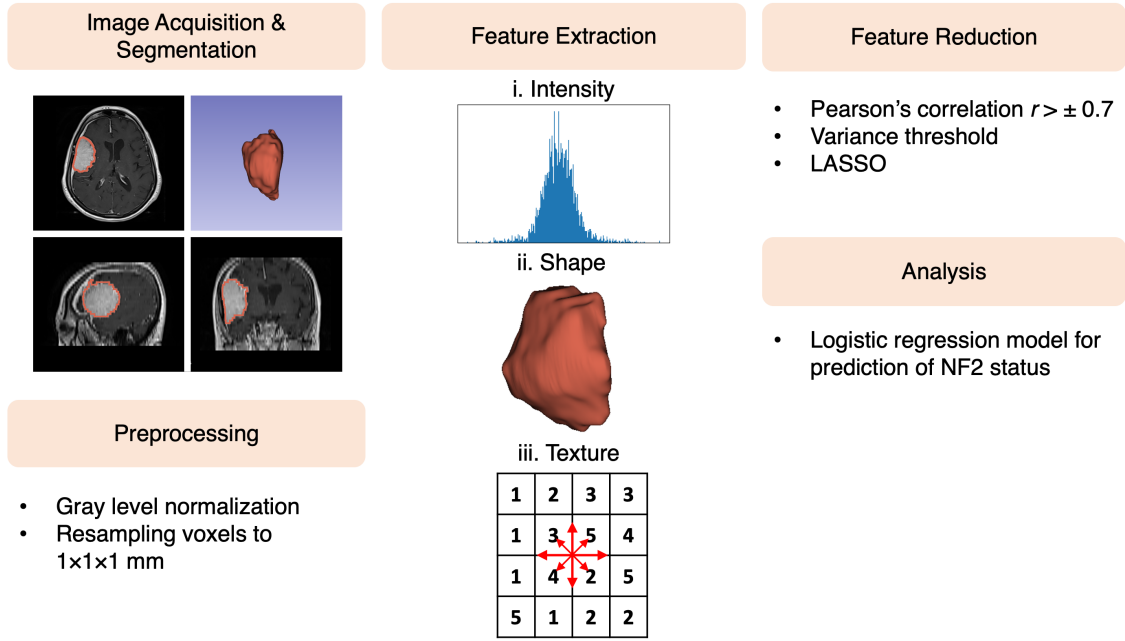


Figure 4.1 The workflow of the study for prediction of NF2 status in meningioma patients.

values.

4.2.3 Recurrence Prediction

For estimating recurrence after GK, we retrospectively collected data from 105 patients with PFM (m/f: 0.48, age: 54 ± 12 years, nine local recurrences). Pre-GK brain protocol, including pre- and post-contrast T1-weighted MRI (T1w, TR/TE= 2080/2.67ms) and T2-weighted MRI (T2w, TR/TE= 7640/107ms), were acquired using a 3T clinical MRI scanner (Siemens Healthcare, Erlangen, Germany). The radiomics workflow of this part of the study is given in Figure 4.2. First, the contrast-enhancing (T1) and T2 hyperintense (T2) tumor volumes were manually segmented by a neurosurgeon. Then, a 100-gray-level normalization scale was applied to MR images. To minimize the effect of inhomogeneity between acquisitions, images were z-score normalized and resampled to the same resolution ($1 \times 1 \times 1$ mm³). From each modality, 1132 radiomics features were extracted, including first-order statistics, shape, and texture using PyRadiomics [130]. A pairwise Spearman's correlation filter ($r > \pm 0.7$), low

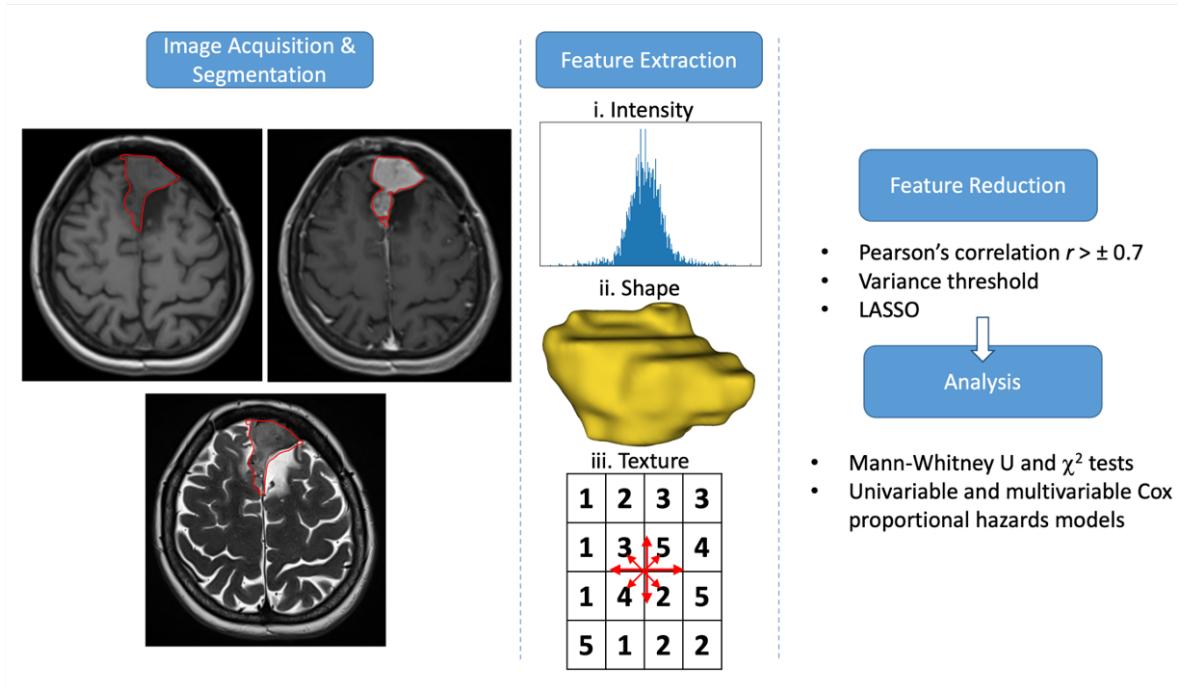


Figure 4.2 The workflow of the study for prediction of NF2 status in meningioma patients.

variance threshold, and Lasso were consecutively applied to identify the features most predictive of RFS. The differences between recurrent and non-recurrent meningiomas in terms of selected radiomics, age, pre-op tumor volume (TV), coverage, and selectivity were assessed by Mann-Whitney U tests, while Chi-square tests were used to assess the differences of sex and the multiplicity of tumors. Univariable and multivariable Cox proportional hazards models were applied to identify the significant factors related to recurrence.

4.3 Results

4.3.1 NF2-Loss Prediction

The pairwise Spearman's correlation and variance thresholding retained 24 predictor features, while Lasso resulted in six features with selection frequency above 80% for the prediction of NF2-L (Table 4.1). Among selected radiomics features, NF2-L

Table 4.1

The selected features with frequencies of above 20% using Lasso feature selection process.

Radiomic Feature	Frequency
GLCM Cluster Shade with wavelet (HHL)	100
Minimum	99
90Percentile	93
90Percentile (LoG filtered)	90
Skewness with wavelet (LLH)	85
Maximum with wavelet (HLH)	83
Least Axis Length	24
GLRM Long Run Low Grey Level Emphasis with wavelet (LLH)	22

tumors showed significantly lower grey level co-occurrence matrix cluster shade with wavelet high-high-low pass filtering, original image first order 90th percentile, and higher first order skewness with wavelet low-low-high pass filtering compared to NF2-NL tumors ($P < 0.0083$) (Figure 4.3). The best performance for prediction of NF2 status was obtained with a logistic regression classifier that resulted in an accuracy of 0.80 ± 0.03 (0.85 ± 0.04 precision and 0.73 ± 0.05 recall).

4.3.2 Recurrence Prediction

Sex distributions and multiplicity of tumors didn't significantly differ between the recurrent and non-recurrent PFM patients ($P=0.6$ and $P=0.54$, respectively). Recurrent patients presented at a significantly higher age and higher pre-op TV and lower coverage compared to non-recurrent patients ($P < 0.05$, Figure 4.4). Five radiomics features significantly differed in recurrent and non-recurrent groups ($P < 0.05$, Figure 4.4). While recurrent patients presented significantly higher T2 skewness (Laplacian of Gaussian (LoG) filtered), T2 maximum, T1 maximum, and T1 skewness, they had lower T2 skewness (wavelet filtered) compared to non-recurrent patients.

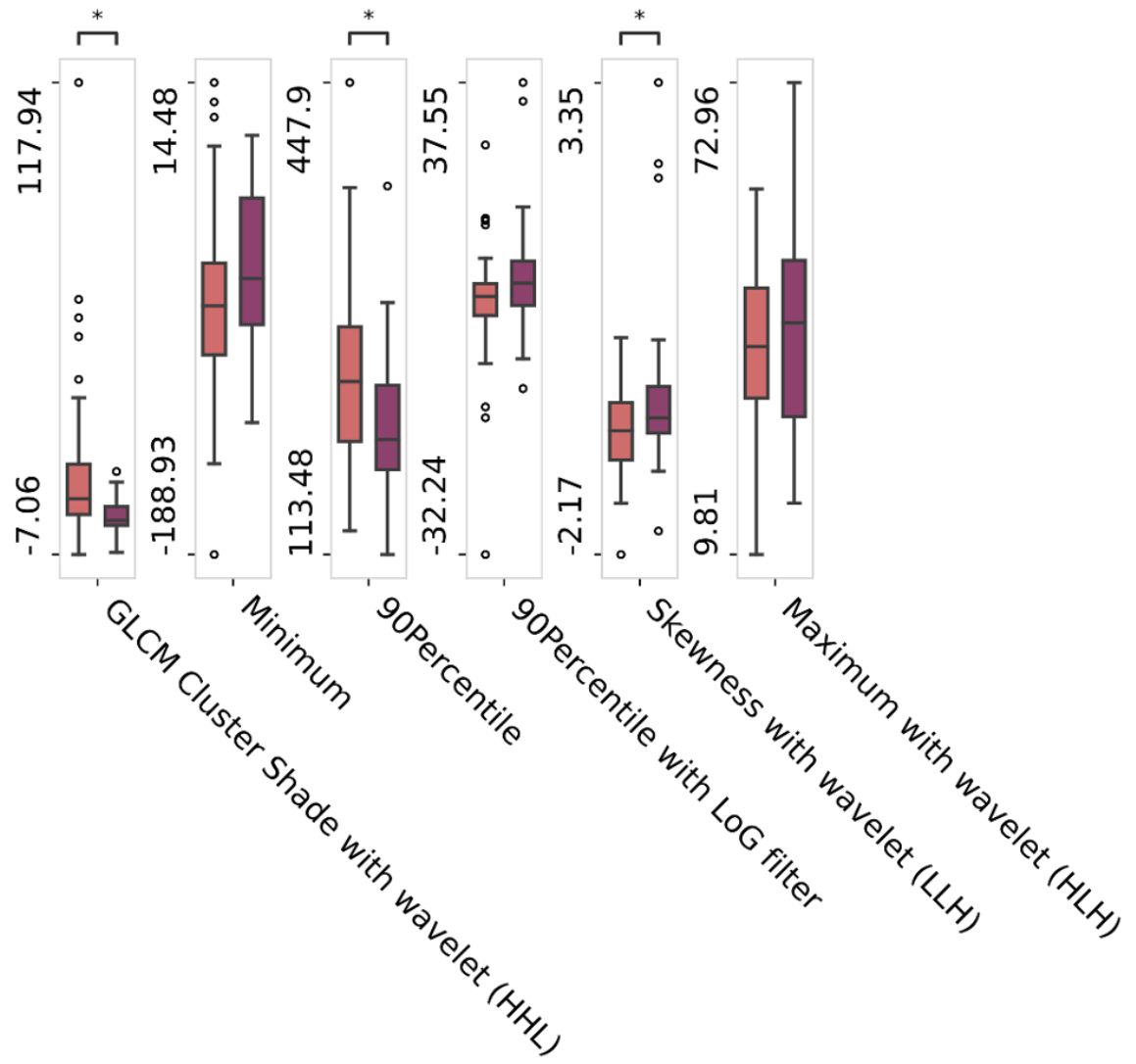


Figure 4.3 The most informative features (Lasso selection frequency >80%) for differentiating NF2-NL and NF2-L meningiomas (*P: 0.008).

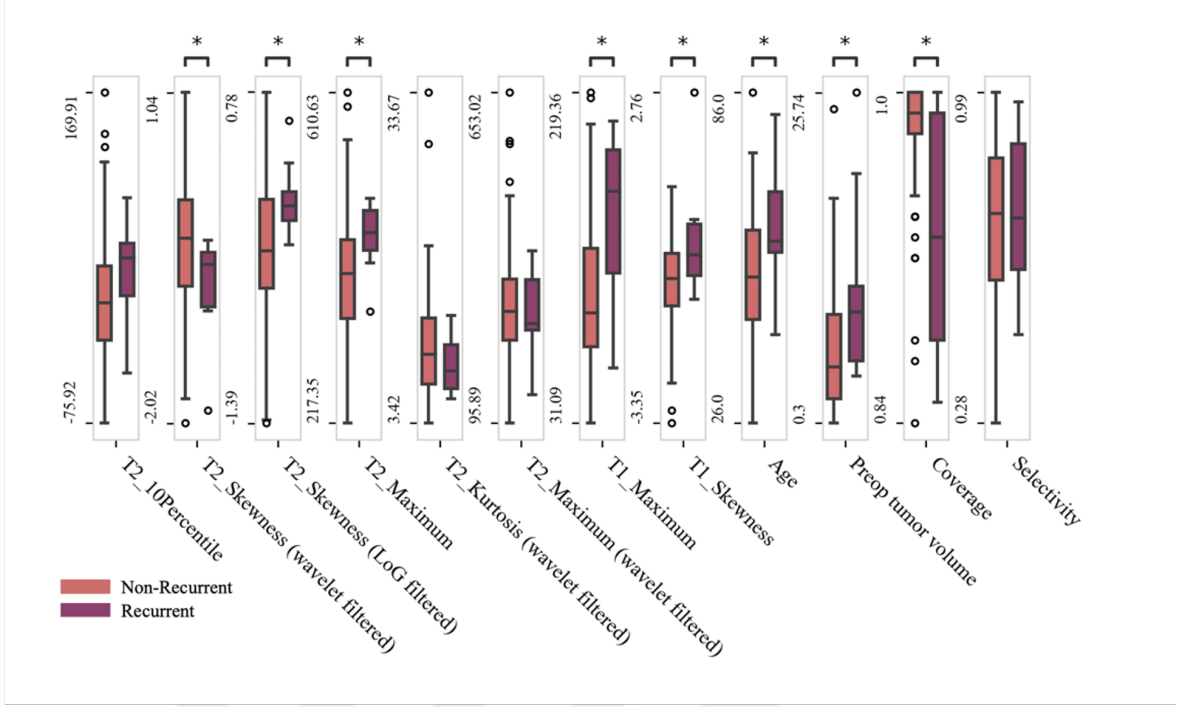


Figure 4.4 The distributions of selected radiomics and clinical features in the recurrent and non-recurrent PFM (*P:0.05).

Table 4.2 shows the results of univariable and multivariable Cox analyses for RFS of PFM. Univariable Cox analysis associated higher maximum and skewness of T1 lesion volume, age, pre-op TV, and lower coverage ($P < 0.05$ for all) with shorter RFS. On the other hand, lower skewness of T2 lesion volume (with LoG filtering), and higher coverage and selectivity were significantly associated with a longer RFS in multivariable Cox analysis ($P < 0.05$ for all, Figure 4.5).

4.4 Discussion

4.4.1 Prediction of NF2-Loss

In the present study, we found that CE T1-w radiomic models might be helpful for the prediction of the meningioma subset with NF2-L. Previous studies reported that radiomics had the potential to estimate tumor grades and histological subtypes of meningiomas [224]. Since radiomics analysis extracts a large number of predictive

Table 4.2

Univariable and multivariable Cox proportional hazards regression for RFS following GK treatment in PFM (*P:0.05).

Covariate	Univariable		Multivariable	
	HR (95%CI)	P	HR (95% CI)	P
T2_10Percentile	1.25(0.70,2.23)	0.46	11.96(0.66,218.32)	0.09
T2_Skewness (wavelet filtered)	0.63(0.34,1.4)	0.13	0.10(0.01,1.02)	0.05
T2_Skewness (LoG filtered)	3.80(0.94,1.9)	0.07	11.11(1.53,80.53)	0.02*
T2_Maximum	1.55(0.86,2.80)	0.14	7.17(0.52,98.83)	0.14
T2_Kurtosis (wavelet filtered)	0.70(0.31,1.59)	0.40	0.42(0.06,2.77)	0.36
T2_Maximum (wavelet filtered)	0.81(0.41,1.61)	0.55	0.22(0.03,1.84)	0.16
T1_Maximum	2.06(1.16,3.68)	0.01*	2.85(0.76,10.69)	0.12
T1_Skewness	1.79(1.10,2.92)	0.02*	1.15(0.28,4.71)	0.84
Age	2.18(1.08,4.38)	0.03*	0.67(0.15,2.92)	0.59
Sex	1.24(0.67,2.30)	0.50	1.38(0.29,6.50)	0.68
Pre-op tumor volume	1.66(1.07,2.58)	0.02*	3.56(0.89,14.25)	0.07
Multiple lesion	1.33(0.76,2.32)	0.32	1.15(0.33,4.06)	0.82
Coverage	0.53(0.36,0.78)	<0.005*	0.12(0.02,0.58)	0.01*
Selectivity	1.05(0.52,2.09)	0.90	0.02(0.00,0.44)	0.01*

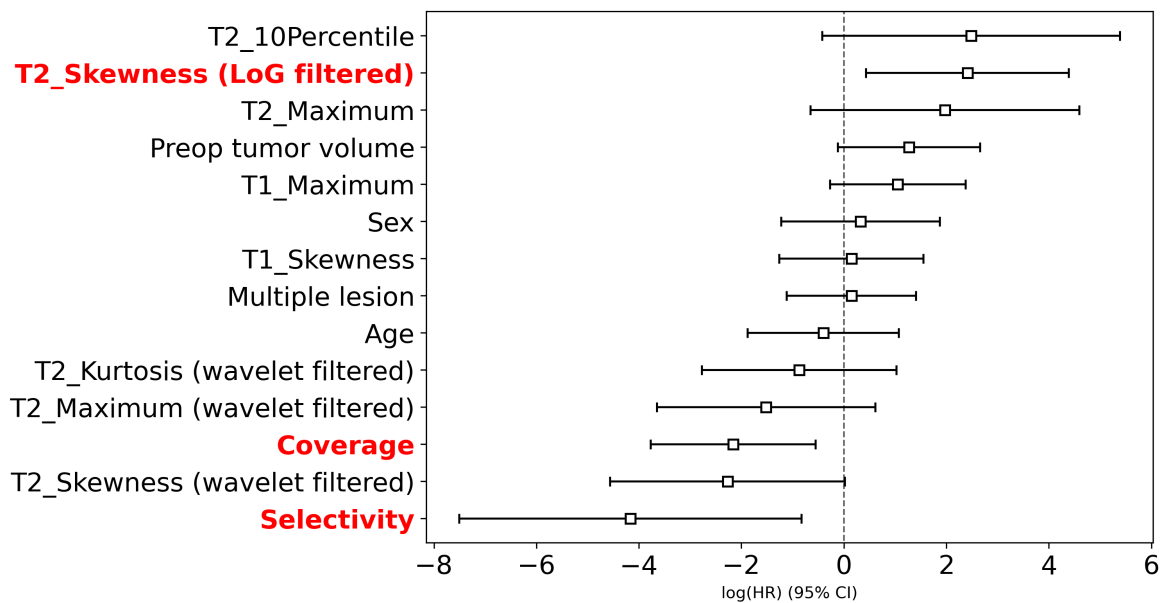


Figure 4.5 The impact of the selected radiomics and clinical features on RFS in multivariable Cox analysis (red: P< 0.05).

features from imaging data, a well-functioning feature selection process was necessary [225]. In our case, Lasso selected six important radiomic features while minimizing diversity over 100 repetitions, which enabled generalization of the feature selection process. Malignancy in tumors has been associated with intra-tumoral spatial heterogeneity, which is usually captured by texture and intensity-based radiomic features [226]. Therefore, radiomic features have the potential to quantify the characteristics of the tumor microenvironment that are imperceptible to the human eye.

4.4.2 Prediction of Recurrence

The combination of radiomics features extracted from the pre-GK anatomical MRI and the clinical parameters were associated with recurrence in patients with PFM after GK radiosurgery. In the literature, standard MRI findings, such as an irregular tumor shape [227], high peritumoral edema [228], and the extent of tumor resection [229] have been associated with recurrence; however, quantitative assessment of MR images may add valuable information about the patient prognosis. Thus, radiomics offer objective and quantitative features to build prognostic models. A previous multi-modal study showed that the radiomics features, such as T1 max probability, T1 cluster shade, and apparent diffusion coefficient (ADC) correlation, could predict recurrence in skull base meningiomas [230]. In our study, higher T1 maximum, T1 skewness, age, pre-op tumor volume, and lower coverage were associated with shorter PFS. A higher T1 maximum may be a clue of bleeding, which appears as hyperintense in T1w MRI, whereas higher T1 skewness could indicate intensity asymmetry from a normal distribution. On the other hand, lower T2 skewness and higher coverage and selectivity were associated with longer RFS.

4.5 Conclusion

Current findings indicate that the meningioma molecular subset with NF2-L has strong radiomics correlates on CE T1w MRI. The combination of radiomics and

clinical features might help to identify PFM patients with a high risk of recurrence after GK and could improve clinical decision-making.



5. CONCLUSION

This thesis aimed to explore the potential of radiomics in several areas, including assessing the quality of Gamma Knife treatment plans, evaluating treatment outcomes in vestibular schwannomas, predicting IDH mutations and prognosis in gliomas, and estimating NF2 loss and recurrence in meningiomas.

Through the application of radiomics-based methods, we found that shape-based radiomics played a significant role in Gamma Knife dose planning, but did not significantly impact treatment outcomes. Furthermore, our radiomics models showed potential for identifying IDH mutation, which is one of the most important prognostic factors, as well as estimating overall survival in gliomas. Finally, we were able to estimate a key genetic marker of meningiomas, NF2 alterations, and recurrence-free survival preoperatively using MRI derived radiomics.

The results of this thesis highlight the strength of radiomics analysis in the decision-making framework, providing new insights into neurooncology. One of the key challenges in the application of radiomics to brain tumors is the standardization of imaging protocols and feature extraction methods. Variability in MRI acquisition parameters and differences in image processing techniques can lead to inconsistencies in radiomic features. Multi-center studies and the development of standardized protocols are essential to validate and generalize radiomics based decision-making models.

In conclusion, MRI-based radiomics offers a powerful tool for the noninvasive characterization of brain tumors, particularly vestibular schwannomas, gliomas and meningiomas. By extracting and analyzing quantitative imaging features, radiomics can offer valuable insights into tumor biology, guide treatment decisions, and predict patient outcomes. Ongoing advancements in imaging techniques, standardization efforts, and integration into clinical practice will further enhance the clinical utility of radiomics in neuro-oncology. However, implementing these models in clinical practice

will require large, annotated datasets and multicentric validation.



REFERENCES

1. National Institutes of Health, “Vestibular Schwannoma (Acoustic Neuroma) and Neurofibromatosis.” <https://www.nidcd.nih.gov/health/vestibular-schwannoma-acoustic-neuroma-and-neurofibromatosis>.
2. Whitfield, B. T. and Huse, J. T., “Classification of adult-type diffuse gliomas: Impact of the world health organization 2021 update,” *Brain Pathology*, Vol. 32, no. 4, p. e13062, 2022.
3. Hanna, C., Willman, M., Cole, D., Mehkri, Y., *et al.*, “Review of meningioma diagnosis and management,” *Egyptian Journal of Neurosurgery*, Vol. 38, p. 16, Apr. 2023.
4. Dimitriadis, A. and Paddick, I., “A novel index for assessing treatment plan quality in stereotactic radiosurgery,” *J Neurosurg*, Vol. 129, no. Suppl1, pp. 118–124, 2018. Edition: 2018/12/14.
5. Shapey, J., Kujawa, A., Dorent, R., Wang, G., *et al.*, “Segmentation of vestibular schwannoma from MRI, an open annotated dataset and baseline algorithm,” *Scientific Data*, Vol. 8, no. 1, p. 286, 2021.
6. Gore, S., Chougule, T., Jagtap, J., Saini, J., *et al.*, “A review of radiomics and deep predictive modeling in glioma characterization,” *Academic Radiology*, Vol. 28, no. 11, pp. 1599–1621, 2021.
7. Fernandes, R. T., Teixeira, G. R., Mamere, E. C., Bandeira, G. A., *et al.*, “The 2021 world health organization classification of gliomas: an imaging approach,” *Radiologia Brasileira*, Vol. 56, pp. 157–161, 2023.
8. Lyndon, D., Lansley, J. A., Evanson, J., and Krishnan, A. S., “Dural masses: meningiomas and their mimics,” *Insights into imaging*, Vol. 10, no. 1, p. 11, 2019.
9. Mayerhoefer, M. E., Materka, A., Langs, G., Häggström, I., *et al.*, “Introduction to radiomics,” *Journal of Nuclear Medicine*, Vol. 61, no. 4, pp. 488–495, 2020.
10. Saad, M., Lee, I. H., and Choi, T. S., “Are shape morphologies associated with survival? A potential shape-based biomarker predicting survival in lung cancer,” *J Cancer Res Clin Oncol*, Vol. 145, no. 12, pp. 2937–2950, 2019.
11. Reinhold, J. C., Dewey, B. E., Carass, A., and Prince, J. L., “Evaluating the impact of intensity normalization on MR image synthesis,” 2018. <https://arxiv.org/abs/1812.04652>, Version Number: 1.
12. National Cancer Institute, “Cancer of the Brain and Other Nervous System - Cancer Stat Facts,” June 2024. <https://seer.cancer.gov/statfacts/html/brain.html>.
13. Ilic, I. and Ilic, M., “International patterns and trends in the brain cancer incidence and mortality: An observational study based on the global burden of disease,” *Heliyon*, Vol. 9, p. e18222, July 2023.
14. IJzerman-Korevaar, M., Snijders, T. J., de Graeff, A., Teunissen, S. C., *et al.*, “Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review,” *Journal of Neuro-Oncology*, Vol. 140, pp. 485–496, 2018.

15. Cioffi, G., Waite, K. A., Edelson, J. L., Kruchko, C., *et al.*, “Changes in survival over time for primary brain and other CNS tumors in the United States, 2004–2017,” *Journal of Neuro-Oncology*, Vol. 160, no. 1, pp. 209–219, 2022.
16. Hertler, C., Felsberg, J., Gramatzki, D., Le Rhun, E., *et al.*, “Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY Brain Tumor Funders’ Collaborative Consortium (EORTC 1419),” *European Journal of Cancer*, Vol. 189, p. 112913, 2023.
17. Louis, D. N., Perry, A., Wesseling, P., Brat, D. J., *et al.*, “The 2021 WHO classification of tumors of the central nervous system: a summary,” *Neuro-Oncology*, Vol. 23, no. 8, pp. 1231–1251, 2021. Publisher: Oxford Academic.
18. Perry, A. and Brat, D. J., “1 - neuropathology patterns and introduction,” in *Practical Surgical Neuropathology: A Diagnostic Approach (Second Edition)* (Perry, A. and Brat, D. J., eds.), pp. 1–17, Elsevier, second edition ed., 2018.
19. Komori, T., “Grading of adult diffuse gliomas according to the 2021 WHO Classification of Tumors of the Central Nervous System,” *Laboratory Investigation*, Vol. 102, no. 2, pp. 126–133, 2022.
20. Carlson, M. L. and Link, M. J., “Vestibular schwannomas,” *New England Journal of Medicine*, Vol. 384, no. 14, pp. 1335–1348, 2021.
21. Matthies, C. and Samii, M., “Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation,” *Neurosurgery*, Vol. 40, no. 1, pp. 1–10, 1997.
22. Warren, C., James, L. A., Ramsden, R. T., Wallace, A., *et al.*, “Identification of recurrent regions of chromosome loss and gain in vestibular schwannomas using comparative genomic hybridisation,” *Journal of Medical Genetics*, Vol. 40, no. 11, pp. 802–806, 2003.
23. Tan, N. C.-W., Macfarlane, R., Donnelly, N., Mannion, R., *et al.*, “A 2 and 5-year longitudinal analysis of 671 consecutive patients diagnosed with unilateral vestibular schwannoma,” *Otology & Neurotology*, Vol. 43, no. 6, pp. 702–708, 2022.
24. Halliday, J., Rutherford, S. A., McCabe, M. G., and Evans, D. G., “An update on the diagnosis and treatment of vestibular schwannoma,” *Expert Review of Neurotherapeutics*, Vol. 18, no. 1, pp. 29–39, 2018.
25. Brun, L., Mom, T., Guillemin, F., Puechmaille, M., *et al.*, “The recent management of vestibular schwannoma radiotherapy: A narrative review of the literature,” *Journal of Clinical Medicine*, Vol. 13, no. 6, p. 1611, 2024.
26. Larsson, B., Leksell, L., and Rexed, B., “The use of high energy protons for cerebral surgery in man,” *Acta Chirurgica Scandinavica (Sweden)*, Vol. 125, 1963.
27. Betti, O. and Derechinsky, V., “Hyperselective encephalic irradiation with linear accelerator,” in *Advances in Stereotactic and Functional Neurosurgery 6: Proceedings of the 6th Meeting of the European Society for Stereotactic and Functional Neurosurgery, Rome 1983*, pp. 385–390, Springer, 1984.
28. Ostrom, Q. T., Cioffi, G., Waite, K., Kruchko, C., *et al.*, “CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018,” *Neuro-Oncology*, Vol. 23, no. Supplement_3, pp. iii1–iii105, 2021. Publisher: Oxford University Press US.

29. Dang, L., White, D. W., Gross, S., Bennett, B. D., *et al.*, “Cancer-associated IDH1 mutations produce 2-hydroxyglutarate,” *Nature*, Vol. 462, no. 7274, pp. 739–744, 2009.
30. Yan, H., Parsons, D. W., Jin, G., McLendon, R., *et al.*, “IDH1 and IDH2 mutations in gliomas,” *New England Journal of Medicine*, Vol. 360, no. 8, pp. 765–773, 2009. Publisher: Mass Medical Soc.
31. Ceccarelli, M., Barthel, F. P., Malta, T. M., Sabedot, T. S., *et al.*, “Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma,” *Cell*, Vol. 164, no. 3, pp. 550–563, 2016.
32. Eckel-Passow, J. E., Lachance, D. H., Molinaro, A. M., Walsh, K. M., *et al.*, “Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors,” *New England Journal of Medicine*, Vol. 372, no. 26, pp. 2499–2508, 2015. Publisher: Mass Medical Soc.
33. Lan, Z., Li, X., and Zhang, X., “Glioblastoma: An update in pathology, molecular mechanisms and biomarkers,” *International Journal of Molecular Sciences*, Vol. 25, no. 5, p. 3040, 2024.
34. Akyerli, C. B., Yüksel, Ş., Can, Ö., Erson-Omay, E. Z., *et al.*, “Use of telomerase promoter mutations to mark specific molecular subsets with reciprocal clinical behavior in IDH mutant and IDH wild-type diffuse gliomas,” *Journal of Neurosurgery*, Vol. 128, pp. 1102–1114, Apr. 2018.
35. Weller, M., van den Bent, M., Preusser, M., Le Rhun, E., *et al.*, “Eano guidelines on the diagnosis and treatment of diffuse gliomas of adulthood,” *Nature Reviews Clinical Oncology*, Vol. 18, no. 3, pp. 170–186, 2021.
36. Baldi, I., Engelhardt, J., Bonnet, C., Bauchet, L., *et al.*, “Epidemiology of meningiomas,” *Neurochirurgie*, Vol. 64, no. 1, pp. 5–14, 2018.
37. Whittle, I. R., Smith, C., Navoo, P., and Collie, D., “Meningiomas,” *The Lancet*, Vol. 363, no. 9420, pp. 1535–1543, 2004.
38. Harter, P. N., Braun, Y., and Plate, K. H., “Classification of meningiomas—advances and controversies,” *Chinese Clinical Oncology*, Vol. 6, no. Suppl 1, pp. S2–S2, 2017.
39. Kros, J., de Greve, K., van Tilborg, A., Hop, W., *et al.*, “NF2 status of meningiomas is associated with tumour localization and histology,” *The Journal of Pathology*, Vol. 194, no. 3, pp. 367–372, 2001.
40. Berghoff, A. S., Hielscher, T., Ricken, G., Furtner, J., *et al.*, “Prognostic impact of genetic alterations and methylation classes in meningioma,” *Brain Pathology*, Vol. 32, no. 2, p. e12970, 2022.
41. Juratli, T. A., Thiede, C., Koerner, M. V., Tummala, S. S., *et al.*, “Intratumoral heterogeneity and tert promoter mutations in progressive/higher-grade meningiomas,” *Oncotarget*, Vol. 8, no. 65, p. 109228, 2017.
42. Goldbrunner, R., Minniti, G., Preusser, M., Jenkinson, M. D., *et al.*, “Eano guidelines for the diagnosis and treatment of meningiomas,” *The Lancet Oncology*, Vol. 17, no. 9, pp. e383–e391, 2016.
43. Rowe, J., Grainger, A., Walton, L., Silcocks, P., *et al.*, “Risk of malignancy after gamma knife stereotactic radiosurgery,” *Neurosurgery*, Vol. 60, no. 1, pp. 60–66, 2007.

44. Yu, C. and Shepard, D., "Treatment planning for stereotactic radiosurgery with photon beams," *Technology in Cancer Research & Treatment*, Vol. 2, no. 2, pp. 93–104, 2003.
45. Novotný, J., "Leksell gamma knife-past, present and future," *Lékař a technika-Clinician and Technology*, Vol. 42, no. 3, pp. 5–13, 2012.
46. Acosta, R., "Computing isodose curves for radiotherapy treatment plans," *Computer Science Honors Theses*, no. 8, 2005.
47. Chen, G. T., "Dose volume histograms in treatment planning," *International Journal of Radiation Oncology*Biophysics*, Vol. 14, no. 6, pp. 1319–1320, 1988.
48. Shaw, E., Kline, R., Gillin, M., Souhami, L., *et al.*, "Radiation therapy oncology group: radiosurgery quality assurance guidelines," *International Journal of Radiation Oncology*Biophysics*, Vol. 27, no. 5, pp. 1231–1239, 1993.
49. Torrens, M., Chung, C., Chung, H. T., Hanssens, P., *et al.*, "Standardization of terminology in stereotactic radiosurgery: report from the Standardization Committee of the International Leksell Gamma Knife Society," *J Neurosurg*, Vol. 121, pp. 2–15, Dec. 2014.
50. Larson, D. A., Bova, F., Eisert, D., Kline, R., *et al.*, "Consensus statement on stereotactic radiosurgery quality improvement," *International Journal of Radiation Oncology*Biophysics*, Vol. 28, no. 2, pp. 527–530, 1994.
51. Paddick, I., "A simple scoring ratio to index the conformity of radiosurgical treatment plans - Technical note," *J Neurosurg*, Vol. 93, pp. 219–222, 2000.
52. Paddick, I. and Lippitz, B., "A simple dose gradient measurement tool to complement the conformity index," *J Neurosurg*, Vol. 105, pp. 194–201, 2006.
53. Lomax, N. J. and Scheib, S. G., "Quantifying the degree of conformity in radiosurgery treatment planning," *Int J Radiat Oncol Biol Phys*, Vol. 55, pp. 1409–19, Apr. 2003.
54. Wu, Q.-R. J., Wessels, B., Einstein, D., Maciunas, R., *et al.*, "Quality of coverage: conformity measures for stereotactic radiosurgery," *Journal of Applied Clinical Medical Physics*, Vol. 4, no. 4, pp. 374–381, 2003.
55. Thomas, E. M., Popple, R. A., Wu, X., Clark, G. M., *et al.*, "Comparison of plan quality and delivery time between volumetric arc therapy (RapidArc) and Gamma Knife radiosurgery for multiple cranial metastases," *Neurosurgery*, Vol. 75, no. 4, pp. 409–418, 2014.
56. Stojadinovic, S., Yan, Y., Leiker, A., Ahn, C., *et al.*, "Considerations of target surface area and the risk of radiosurgical toxicity," *PLOS ONE*, Vol. 14, no. 10, p. e0224047, 2019.
57. Laing, R. W., Bentley, R. E., Nahum, A. E., Warrington, A. P., *et al.*, "Stereotactic radiotherapy of irregular targets: a comparison between static conformal beams and non-coplanar arcs," *Radiother Oncol*, Vol. 28, pp. 241–246, 1993.
58. Schoonbeek, A., Monshouwer, R., Hanssens, P., Raaijmakers, E., *et al.*, "Intracranial radiosurgery in the Netherlands. A planning comparison of available systems with regard to physical aspects and workload," *Technol Cancer Res Treat*, Vol. 9, no. 3, pp. 279–289, 2010.

59. Flickinger, J. C., Kondziolka, D., Niranjan, A., and Lunsford, L. D., "Results of acoustic neuroma radiosurgery: an analysis of 5 years' experience using current methods," *Journal of Neurosurgery*, Vol. 94, pp. 1–6, Jan. 2001.
60. Loeffler, J. S., Larson, D. A., Shrieve, D. C., and Flickinger, J. C., "Radiosurgery for the treatment of intracranial lesions," *Important Adv Oncol*, pp. 141–56, 1995. Edition: 1995/01/01.
61. Balagamwala, E. H., Suh, J. H., Barnett, G. H., Khan, M. K., *et al.*, "The importance of the conformality, heterogeneity, and gradient indices in evaluating gamma knife radiosurgery treatment plans for intracranial meningiomas," *International Journal of Radiation Oncology* Biology* Physics*, Vol. 83, no. 5, pp. 1406–1413, 2012.
62. Wagner, T. H., Yi, T., Meeks, S. L., Bova, F. J., *et al.*, "A geometrically based method for automated radiosurgery planning," *Int J Radiat Oncol Biol Phys*, Vol. 48, no. 5, pp. 1599–1611, 2000.
63. Yu, C., Luxton, G., Jozsef, G., Apuzzo, M. L., *et al.*, "Dosimetric comparison of three photon radiosurgery techniques for an elongated ellipsoid target," *International Journal of Radiation Oncology* Biology* Physics*, Vol. 45, no. 3, pp. 817–826, 1999.
64. Chin, L. S. and Regine, W. F., *Principles and Practice of Stereotactic Radiosurgery*, New York, NY: Springer, 2010.
65. Collins, S. P., Coppa, N. D., Zhang, Y., Collins, B. T., *et al.*, "Cyberknife® radiosurgery in the treatment of complex skull base tumors: analysis of treatment planning parameters," *Radiation Oncology*, Vol. 1, pp. 1–10, 2006.
66. Ellingson, B. M., Bendszus, M., Boxerman, J., Barboriak, D., *et al.*, "Consensus recommendations for a standardized brain tumor imaging protocol in clinical trials," *Neuro-Oncology*, Vol. 17, no. 9, pp. 1188–1198, 2015.
67. Law, M., "Advanced imaging techniques in brain tumors," *Cancer Imaging*, Vol. 9, no. Special issue A, p. S4, 2009.
68. Hentschel, M., Scholte, M., Steens, S., Kunst, H., *et al.*, "The diagnostic accuracy of non-imaging screening protocols for vestibular schwannoma in patients with asymmetrical hearing loss and/or unilateral audiovestibular dysfunction: a diagnostic review and meta-analysis," *Clinical Otolaryngology*, Vol. 42, no. 4, pp. 815–823, 2017.
69. Roland Goldbrunner, M., Michael Weller, M., Jean Regis, M., Morten, L.-J., *et al.*, "Eano guideline on the diagnosis and treatment of vestibular schwannoma," *Neuro-Oncology*, 2019.
70. Stuckey, S. L., Harris, A. J., and Mannolini, S. M., "Detection of acoustic schwannoma: use of constructive interference in the steady state three-dimensional MR.," *American Journal of Neuroradiology*, Vol. 17, no. 7, pp. 1219–1225, 1996.
71. Pope, W. B. and Brandal, G., "Conventional and advanced magnetic resonance imaging in patients with high-grade glioma," *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, Vol. 62, Sept. 2018.
72. Scott, J., Brasher, P., Sevic, R., Rewcastle, N., *et al.*, "How often are nonenhancing supratentorial gliomas malignant? a population study," *Neurology*, Vol. 59, no. 6, pp. 947–949, 2002.

73. Patel, S. H., Poisson, L. M., Brat, D. J., Zhou, Y., *et al.*, "T2-FLAIR mismatch, an imaging biomarker for IDH and 1p/19q status in lower-grade gliomas: a TCGA/TCIA project," *Clinical Cancer Research*, Vol. 23, no. 20, pp. 6078–6085, 2017.
74. Zhang, J., Liu, H., Tong, H., Wang, S., *et al.*, "Clinical applications of contrast-enhanced perfusion MRI techniques in gliomas: Recent advances and current challenges," *Contrast Media & Molecular Imaging*, Vol. 2017, no. 1, p. 7064120, 2017.
75. Maia, A. C., Malheiros, S. M., da Rocha, A. J., da Silva, C. J., *et al.*, "MR cerebral blood volume maps correlated with vascular endothelial growth factor expression and tumor grade in nonenhancing gliomas," *American Journal of Neuroradiology*, Vol. 26, no. 4, pp. 777–783, 2005.
76. Emblem, K. E., Nedregård, B., Nome, T., Due-Tønnessen, P., *et al.*, "Glioma grading by using histogram analysis of blood volume heterogeneity from MR-derived cerebral blood volume maps," *Radiology*, Vol. 247, no. 3, pp. 808–817, 2008.
77. Lev, M. H., Ozsunar, Y., Henson, J. W., Rasheed, A. A., *et al.*, "Glial tumor grading and outcome prediction using dynamic spin-echo MR susceptibility mapping compared with conventional contrast-enhanced MR: confounding effect of elevated rCBV of oligodendrogliomas," *American Journal of Neuroradiology*, Vol. 25, no. 2, pp. 214–221, 2004.
78. Kickingereder, P., Sahm, F., Radbruch, A., Wick, W., *et al.*, "IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma," *Scientific Reports*, Vol. 5, no. 1, p. 16238, 2015.
79. Andronesi, O. C., Kim, G. S., Gerstner, E., Batchelor, T., *et al.*, "Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy," *Science Translational Medicine*, Vol. 4, no. 116, pp. 116ra4–116ra4, 2012.
80. McKnight, T. R., Lamborn, K. R., Love, T. D., Berger, M. S., *et al.*, "Correlation of magnetic resonance spectroscopic and growth characteristics within grades II and III gliomas," *Journal of Neurosurgery*, Vol. 106, no. 4, pp. 660–666, 2007.
81. Wang, Q.-p., Lei, D.-q., Yuan, Y., and Xiong, N.-x., "Accuracy of ADC derived from DWI for differentiating high-grade from low-grade gliomas: Systematic review and meta-analysis," *Medicine*, Vol. 99, no. 8, p. e19254, 2020.
82. Han, C., Huang, S., Guo, J., Zhuang, X., *et al.*, "Use of a high b-value for diffusion weighted imaging of peritumoral regions to differentiate high-grade gliomas and solitary metastases," *Journal of Magnetic Resonance Imaging*, Vol. 42, no. 1, pp. 80–86, 2015.
83. Osborn, A. G., Hedlund, G., and Salzman, K., "Neoplasms cysts and tumor like lesions," *Osborns Brain Imaging Pathol Anatomy*, Vol. 1, pp. 443–514, 2013.
84. Hakyemez, B., Erdogan, C., Bolca, N., Yildirim, N., *et al.*, "Evaluation of different cerebral mass lesions by perfusion-weighted MR imaging," *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, Vol. 24, no. 4, pp. 817–824, 2006.
85. Lin, M.-C., Li, C.-Z., Hsieh, C.-C., Hong, K.-T., *et al.*, "Preoperative grading of intracranial meningioma by magnetic resonance spectroscopy (1H-MRS)," *PLOS ONE*, Vol. 13, no. 11, p. e0207612, 2018.

86. Nagar, V., Ye, J., Ng, W., Chan, Y., *et al.*, “Diffusion-weighted MR imaging: diagnosing atypical or malignant meningiomas and detecting tumor dedifferentiation,” *American Journal of Neuroradiology*, Vol. 29, no. 6, pp. 1147–1152, 2008.
87. “Meningioma Recurrence,” Oct. 2023. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/meningioma-recurrence/>.
88. Nakasu, S., Nakasu, Y., Nakajima, M., Matsuda, M., *et al.*, “Preoperative identification of meningiomas that are highly likely to recur,” *Journal of Neurosurgery*, Vol. 90, no. 3, pp. 455–462, 1999.
89. Spille, D. C., Adeli, A., Sporns, P. B., Heß, K., *et al.*, “Predicting the risk of postoperative recurrence and high-grade histology in patients with intracranial meningiomas using routine preoperative MRI,” *Neurosurgical Review*, Vol. 44, pp. 1109–1117, 2021.
90. Ildan, F., Erman, T., Göçer, A. İ., Tuna, M., *et al.*, “Predicting the probability of meningioma recurrence in the preoperative and early postoperative period: a multivariate analysis in the midterm follow-up,” *Skull Base*, Vol. 17, no. 03, pp. 157–171, 2007.
91. Lambin, P., Rios-Velazquez, E., Leijenaar, R., Carvalho, S., *et al.*, “Radiomics: Extracting more information from medical images using advanced feature analysis,” *European Journal of Cancer*, Vol. 48, no. 4, pp. 441–446, 2012.
92. Gillies, R. J., Kinahan, P. E., and Hricak, H., “Radiomics: images are more than pictures, they are data,” *Radiology*, Vol. 278, no. 2, pp. 563–577, 2016.
93. Ranjbarzadeh, R., Bagherian Kasgari, A., Jafarzadeh Ghouschi, S., Anari, S., *et al.*, “Brain tumor segmentation based on deep learning and an attention mechanism using MRI multi-modalities brain images,” *Scientific Reports*, Vol. 11, no. 1, pp. 1–17, 2021.
94. Walsh, J., Othmani, A., Jain, M., and Dev, S., “Using U-Net network for efficient brain tumor segmentation in MRI images,” *Healthcare Analytics*, Vol. 2, p. 100098, 2022.
95. Kumar, V., Gu, Y., Basu, S., Berglund, A., *et al.*, “Radiomics: the process and the challenges,” *Magnetic Resonance Imaging*, Vol. 30, no. 9, pp. 1234–1248, 2012.
96. Haralick, R. M., Shanmugam, K., and Dinstein, I., “Textural features for image classification,” *IEEE Transactions on Systems, Man, and Cybernetics*, Vol. SMC-3, no. 6, pp. 610–621, 1973.
97. Galloway, M. M., “Texture analysis using gray level run lengths,” *Computer graphics and image processing*, Vol. 4, no. 2, pp. 172–179, 1975.
98. Thibault, G., Fertil, B., Navarro, C. L., Pereira, S., *et al.*, “Texture indexes and gray level size zone matrix. application to cell nuclei classification,” in *10th International Conference on Pattern Recognition and Information Processing, PRIP 2009*, pp. 140–145, 2009.
99. Amadasun, M. and King, R., “Textural features corresponding to textural properties,” *IEEE Transactions on Systems, Man, and Cybernetics*, Vol. 19, no. 5, pp. 1264–1274, 1989.
100. Sun, C. and Wee, W. G., “Neighboring gray level dependence matrix for texture classification,” *Computer Vision, Graphics, and Image Processing*, Vol. 23, no. 3, pp. 341–352, 1983.

101. Kumar, V., Gu, Y. H., Basu, S., Berglund, A., *et al.*, “Radiomics: the process and the challenges,” *Magn Reson Imaging*, Vol. 30, no. 9, pp. 1234–1248, 2012.
102. AIM-Harvard, Pyradiomics Team, “Welcome to pyradiomics documentation!,” Oct. 2024. <https://pyradiomics.readthedocs.io/en/latest/>.
103. Kunicatsu, A., Yasaka, K., Akai, H., Sugawara, H., *et al.*, “Texture analysis in brain tumor MR imaging,” *Magnetic Resonance in Medical Sciences*, Vol. 21, no. 1, pp. 95–109, 2022.
104. Wang, K., An, Y., Zhou, J., Long, Y., *et al.*, “A novel multi-level feature selection method for radiomics,” *Alexandria Engineering Journal*, Vol. 66, pp. 993–999, 2023.
105. Suh, H. B., Choi, Y. S., Bae, S., Ahn, S. S., *et al.*, “Primary central nervous system lymphoma and atypical glioblastoma: differentiation using radiomics approach,” *European Radiology*, Vol. 28, pp. 3832–3839, 2018.
106. Morin, O., Chen, W. C., Nassiri, F., Susko, M., *et al.*, “Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure, and overall survival,” *Neuro-Oncology Advances*, Vol. 1, no. 1, p. vdz011, 2019.
107. Gao, X.-Y., Wang, Y.-D., Wu, S.-M., Rui, W.-T., *et al.*, “Differentiation of treatment-related effects from glioma recurrence using machine learning classifiers based upon pre-and post-contrast T1WI and T2 FLAIR subtraction features: A two-center study,” *Cancer Management and Research*, Vol. Volume 12, pp. 3191–3201, May 2020.
108. Alis, D., Bagcilar, O., Senli, Y., Isler, C., *et al.*, “The diagnostic value of quantitative texture analysis of conventional MRI sequences using artificial neural networks in grading gliomas,” *Clinical radiology*, Vol. 75, no. 5, pp. 351–357, 2020.
109. Vamvakas, A., Williams, S., Theodorou, K., Kapsalaki, E., *et al.*, “Imaging biomarker analysis of advanced multiparametric MRI for glioma grading,” *Physica Medica*, Vol. 60, pp. 188–198, 2019.
110. Zhou, H., Vallières, M., Bai, H. X., Su, C., *et al.*, “MRI features predict survival and molecular markers in diffuse lower-grade gliomas,” *Neuro-Oncology*, Vol. 19, no. 6, pp. 862–870, 2017.
111. Bahrami, N., Hartman, S. J., Chang, Y.-H., Delfanti, R., *et al.*, “Molecular classification of patients with grade II/III glioma using quantitative MRI characteristics,” *Journal of Neuro-Oncology*, Vol. 139, pp. 633–642, 2018.
112. Lewis, M. A., Ganeshan, B., Barnes, A., Bisdas, S., *et al.*, “Filtration-histogram based magnetic resonance texture analysis (MRTA) for glioma IDH and 1p19q genotyping,” *European Journal of Radiology*, Vol. 113, pp. 116–123, 2019.
113. Chaddad, A., Desrosiers, C., and Toews, M., “Radiomic analysis of multi-contrast brain MRI for the prediction of survival in patients with glioblastoma multiforme,” in *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 4035–4038, IEEE, 2016.
114. Kickingereder, P., Burth, S., Wick, A., Götz, M., *et al.*, “Radiomic profiling of glioblastoma: identifying an imaging predictor of patient survival with improved performance over established clinical and radiologic risk models,” *Radiology*, Vol. 280, no. 3, pp. 880–889, 2016.

115. Sanvito, F., Castellano, A., and Falini, A., "Advancements in neuroimaging to unravel biological and molecular features of brain tumors," *Cancers*, Vol. 13, no. 3, p. 424, 2021.
116. Lin, K., Cidan, W., Qi, Y., and Wang, X., "Glioma grading prediction using multiparametric magnetic resonance imaging-based radiomics combined with proton magnetic resonance spectroscopy and diffusion tensor imaging," *Medical Physics*, Vol. 49, no. 7, pp. 4419–4429, 2022.
117. Yan, P.-F., Yan, L., Hu, T.-T., Xiao, D.-D., *et al.*, "The potential value of preoperative MRI texture and shape analysis in grading meningiomas: a preliminary investigation," *Translational Oncology*, Vol. 10, no. 4, pp. 570–577, 2017.
118. Laukamp, K. R., Shakirin, G., Baekler, B., Thiele, F., *et al.*, "Accuracy of radiomics-based feature analysis on multiparametric magnetic resonance images for noninvasive meningioma grading," *World Neurosurgery*, Vol. 132, pp. e366–e390, 2019.
119. Niu, L., Zhou, X., Duan, C., Zhao, J., *et al.*, "Differentiation researches on the meningioma subtypes by radiomics from contrast-enhanced magnetic resonance imaging: a preliminary study," *World Neurosurgery*, Vol. 126, pp. e646–e652, 2019.
120. Liu, X., Wang, Y., Han, T., Liu, H., *et al.*, "Preoperative surgical risk assessment of meningiomas: a narrative review based on MRI radiomics," *Neurosurgical Review*, Vol. 46, no. 1, p. 29, 2022.
121. Zhang, Y., Chen, J.-H., Chen, T.-Y., Lim, S.-W., *et al.*, "Radiomics approach for prediction of recurrence in skull base meningiomas," *Neuroradiology*, Vol. 61, pp. 1355–1364, 2019.
122. Leksell, L., "Stereotactic radiosurgery," *J Neurol Neurosurg Psychiatry*, Vol. 46, pp. 797–803, 1983.
123. Régis, J., Delsanti, C., Roche, P.-H., Thomassin, J.-M., *et al.*, "Functional outcomes of radiosurgical treatment of vestibular schwannomas: 1000 successive cases and review of the literature," *Neuro-Chirurgie*, Vol. 50, pp. 301–311, June 2004.
124. Lunsford, L. D., Niranjan, A., Flickinger, J. C., Maitz, A., *et al.*, "Radiosurgery of vestibular schwannomas: summary of experience in 829 cases," *Journal of Neurosurgery*, Vol. 102 Suppl, pp. 195–199, Jan. 2005.
125. Kollová, A., Liščák, R., Novotný, J., Vladyka, V., *et al.*, "Gamma Knife surgery for benign meningioma," *Journal of Neurosurgery*, Vol. 107, pp. 325–336, Aug. 2007.
126. Elaimy, A. L., Mackay, A. R., Lamoreaux, W. T., Demakas, J. J., *et al.*, "Clinical outcomes of gamma knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma," *World Neurosurgery*, Vol. 80, pp. 872–878, Dec. 2013.
127. Sansur, C. A., Chin, L. S., Ames, J. W., Banegura, A. T., *et al.*, "Gamma knife radiosurgery for the treatment of brain metastases," *Stereotactic and Functional Neurosurgery*, Vol. 74, no. 1, pp. 37–51, 2000.
128. Wu, Q. J. and Bourland, J. D., "Morphology-guided radiosurgery treatment planning and optimization for multiple isocenters," *Med Phys*, pp. 2151–2160, 1999.
129. Kawashima, M., Hasegawa, H., Shin, M., Takahashi, W., *et al.*, "Long-term outcomes of gamma knife radiosurgery for treating vestibular schwannoma with a lower prescription dose of 12 Gy compared with higher dose treatment," *Otology & Neurotology*, Vol. 41, pp. e1314–e1320, Dec. 2020.

130. van Griethuysen, J. J. M., Fedorov, A., Parmar, C., Hosny, A., *et al.*, “Computational radiomics system to decode the radiographic phenotype,” *Cancer Res*, Vol. 77, no. 21, pp. E104–E107, 2017.
131. Aerts, H. J., Velazquez, E. R., Leijenaar, R. T., Parmar, C., *et al.*, “Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach,” *Nat Commun*, Vol. 5, p. 4006, 2014. Edition: 2014/06/04.
132. Limkin, E. J., Reuze, S., Carre, A., Sun, R., *et al.*, “The complexity of tumor shape, spiculatedness, correlates with tumor radiomic shape features,” *Sci Rep*, Vol. 9, 2019.
133. Wu, Q. R., Wessels, B. W., Einstein, D. B., Maciunas, R. J., *et al.*, “Quality of coverage: conformity measures for stereotactic radiosurgery,” *J Appl Clin Med Phys*, Vol. 4, no. 4, pp. 374–81, 2003.
134. Chagas Saraiva, C. W., Cardoso, S. C., Groppo, D. P., De Salles, A. A. F., *et al.*, “Gamma Knife radiosurgery for vestibular schwannomas: Evaluation of planning using the sphericity degree of the target volume,” *PLOS ONE*, Vol. 15, no. 1, p. e0225638, 2020.
135. Fedorov, A., Beichel, R., Kalpathy-Cramer, J., Finet, J., *et al.*, “3D Slicer as an image computing platform for the Quantitative Imaging Network,” *Magn Reson Imaging*, Vol. 30, no. 9, pp. 1323–1341, 2012.
136. Seabold, S. and Perktold, J., “Statsmodels: Econometric and statistical modeling with Python,” in *Proceedings of the 9th Python in Science Conference* (van der Walt, S. and Millman, J., eds.), pp. 92–96, 2010.
137. Terpilowski, M., “scikit-posthocs: Pairwise multiple comparison tests in Python,” *J Open Source Softw*, Vol. 4, no. 36, p. 1169, 2019.
138. Tibshirani, R., “Regression shrinkage and selection via the Lasso,” *J R Stat Soc Series B Stat Methodol*, Vol. 58, no. 1, pp. 267–288, 1996.
139. Kohavi, R. and John, G. H., “Wrappers for feature subset selection,” *Artif Intell*, Vol. 97, no. 1-2, pp. 273–324, 1997.
140. Shepard, D. M., Yu, C., Murphy, M. J., Bussière, M., *et al.*, “Treatment planning for stereotactic radiosurgery,” in *Principles and Practice of Stereotactic Radiosurgery* (Chin, L. S. and Regine, W. F., eds.), pp. 73–94, New York, NY: Springer New York, 2015.
141. Grady, C., Wang, H., Schnurman, Z., Qu, T., *et al.*, “Predicting growth trajectory in vestibular schwannoma from radiomic data using supervised machine learning techniques,” *Neurosurgery*, Vol. 66, no. Supplement_1, 2019.
142. Langenhuizen, P. P. J. H., Sebrechts, S. H. P., Zinger, S., Leenstra, S., *et al.*, “Prediction of transient tumor enlargement using MRI tumor texture after radiosurgery on vestibular schwannoma,” *Med Phys*, Vol. 47, no. 4, pp. 1692–1701, 2020.
143. Narayanasamy, G., Zhang, G., Siegel, E., Campbell, G., *et al.*, “Radiomic assessment of the progression of acoustic neuroma after gamma knife stereotactic radiosurgery,” *J Solid Tumors*, Vol. 9, p. 1, 2019.
144. D’Amico, N. C., Sicilia, R., Cordelli, E., Valbusa, G., *et al.*, “Radiomics for predicting CyberKnife response in acoustic neuroma: a pilot study,” in *2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pp. 847–852, 2018.

145. Menon, S. V., Paramu, R., Bhasi, S., and Nair, R. K., "Evaluation of plan quality metrics in stereotactic radiosurgery/radiotherapy in the treatment plans of arteriovenous malformations," *J Med Phys*, Vol. 43, pp. 214–220, Oct. 2018.
146. Stanley, J., Breitman, K., Dunscombe, P., Spencer, D. P., *et al.*, "Evaluation of stereotactic radiosurgery conformity indices for 170 target volumes in patients with brain metastases," *J Appl Clin Med Phys*, Vol. 12, no. 2, pp. 245–253, 2011.
147. Stanley, D. N., Covington, E. L., Liu, H., Alexandrian, A. N., *et al.*, "Accuracy of dose-volume metric calculation for small-volume radiosurgery targets," *Med Phys*, Vol. 10.1002, p. mp.14645, 2020. Edition: 2020/12/10.
148. Nakamura, J. L., Verhey, L. J., Smith, V., Petti, P. L., *et al.*, "Dose conformity of gamma knife radiosurgery and risk factors for complications," *International Journal of Radiation Oncology*Biophysics*, Vol. 51, pp. 1313–1319, Dec. 2001.
149. Albano, L., Deng, H., Wei, Z., Vodovotz, L., *et al.*, "The longitudinal volumetric response of vestibular schwannomas after Gamma Knife radiosurgery," *Journal of Neurosurgery*, pp. 1–8, Sept. 2022.
150. Smith, D. R., Saadatmand, H. J., Wu, C. C., Black, P. J., *et al.*, "Treatment outcomes and dose rate effects following Gamma Knife stereotactic radiosurgery for vestibular schwannomas," *Neurosurg*, Vol. 85, pp. E1084–E1094, Dec. 2019. Edition: 2019/07/05.
151. Brown, M., Ruckenstein, M., Bigelow, D., Judy, K., *et al.*, "Predictors of hearing loss after Gamma Knife radiosurgery for vestibular schwannomas: Age, cochlear dose, and tumor coverage," *Neurosurgery*, Vol. 69, pp. 605–614, Sept. 2011.
152. Lindquist, C. and Paddick, I., "The Leksell Gamma Knife Perfexion and comparisons with its predecessors," *Neurosurgery*, Vol. 62, Feb. 2008.
153. Paddick, I., Cameron, A., and Dimitriadis, A., "Extracranial dose and the risk of radiation-induced malignancy after intracranial stereotactic radiosurgery: is it time to establish a therapeutic reference level?," *Acta Neurochirurgica*, Vol. 163, pp. 971–979, Apr. 2021.
154. Wolpert, D. H., "The relationship between PAC, the statistical physics framework, the Bayesian framework, and the VC framework," in *The Mathematics Of Generalization*, Vol. 20, pp. 117–214, Boca Raton: CRC Press, 1995.
155. Chen, Q., Meng, Z. P., Liu, X. Y., Jin, Q. G., *et al.*, "Decision variants for the automatic determination of optimal feature subset in RF-RFE," *Genes (Basel)*, Vol. 9, June 2018.
156. "Glioma," Nov. 2024. <https://braintumourresearch.org/pages/types-of-brain-tumours-glioma/>.
157. Çelik, S., Öven, B. B., Demir, M. K., Yılmaz, E. Ç., *et al.*, "Magnetic resonance imaging criteria for prediction of isocitrate dehydrogenase (IDH) mutation status in patients with grade II-III astrocytoma and oligodendroglioma," *Clinical Neurology and Neurosurgery*, Vol. 207, p. 106745, Aug. 2021.
158. Perizzolo, M., Winkfein, B., Hui, S., Krulicki, W., *et al.*, "IDH mutation detection in formalin-fixed paraffin-embedded gliomas using multiplex PCR and single-base extension," *Brain Pathology (Zurich, Switzerland)*, Vol. 22, pp. 619–624, Sept. 2012.

159. Katzendobler, S., Do, A., Weller, J., Dorostkar, M. M., *et al.*, “Diagnostic yield and complication rate of stereotactic biopsies in precision medicine of gliomas,” *Frontiers in Neurology*, Vol. 13, p. 822362, 2022.
160. Li, Y., Qin, Q., Zhang, Y., and Cao, Y., “Noninvasive determination of the IDH status of gliomas Using MRI and MRI-based radiomics: Impact on diagnosis and prognosis,” *Current Oncology*, Vol. 29, pp. 6893–6907, Sept. 2022.
161. Pérez-Beteta, J., Molina-García, D., Martínez-González, A., Henares-Molina, A., *et al.*, “Morphological MRI-based features provide pretreatment survival prediction in glioblastoma,” *European Radiology*, Vol. 29, pp. 1968–1977, Apr. 2019.
162. Qi, S., Yu, L., Li, H., Ou, Y., *et al.*, “Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms,” *Oncology Letters*, Vol. 7, pp. 1895–1902, June 2014.
163. Fyllingen, E. H., Bø, L. E., Reinertsen, I., Jakola, A. S., *et al.*, “Survival of glioblastoma in relation to tumor location: a statistical tumor atlas of a population-based cohort,” *Acta Neurochirurgica*, Vol. 163, pp. 1895–1905, July 2021.
164. Wang, Y., Wang, K., Li, S., Wang, J., *et al.*, “Patterns of Tumor Contrast Enhancement Predict the Prognosis of Anaplastic Gliomas with *IDH1* Mutation,” *American Journal of Neuroradiology*, Vol. 36, pp. 2023–2029, Nov. 2015.
165. Dubinski, D., Won, S.-Y., Rauch, M., Behmanesh, B., *et al.*, “Association of Isocitrate Dehydrogenase (IDH) Status With Edema to Tumor Ratio and Its Correlation With Immune Infiltration in Glioblastoma,” *Frontiers in Immunology*, Vol. 12, p. 627650, 2021.
166. Pope, W. B., Sayre, J., Perlina, A., Villablanca, J. P., *et al.*, “Mr imaging correlates of survival in patients with high-grade gliomas,” *American Journal of Neuroradiology*, Vol. 26, no. 10, pp. 2466–2474, 2005.
167. Ma, H., Zeng, S., Xie, D., Zeng, W., *et al.*, “Looking through the imaging perspective: the importance of imaging necrosis in glioma diagnosis and prognostic prediction - single centre experience,” *Radiology and Oncology*, Vol. 58, pp. 23–32, Mar. 2024.
168. Malik, D. G., Rath, T. J., Urcuyo Acevedo, J. C., Canoll, P. D., *et al.*, “Advanced MRI protocols to discriminate glioma from treatment effects: State of the art and future directions,” *Frontiers in Radiology*, Vol. 2, p. 809373, Apr. 2022.
169. Xing, Z., Zhang, H., She, D., Lin, Y., *et al.*, “IDH genotypes differentiation in glioblastomas using DWI and DSC-PWI in the enhancing and peri-enhancing region,” *Acta Radiologica*, Vol. 60, pp. 1663–1672, Dec. 2019.
170. McCullough, B. J., Ader, V., Aguedan, B., Feng, X., *et al.*, “Preoperative relative cerebral blood volume analysis in gliomas predicts survival and mitigates risk of biopsy sampling error,” *Journal of Neuro-Oncology*, Vol. 136, pp. 181–188, Jan. 2018.
171. Xiong, J., Tan, W.-L., Pan, J.-W., Wang, Y., *et al.*, “Detecting isocitrate dehydrogenase gene mutations in oligodendroglial tumors using diffusion tensor imaging metrics and their correlations with proliferation and microvascular density,” *Journal of Magnetic Resonance Imaging*, Vol. 43, no. 1, pp. 45–54, 2016.

172. Saksena, S., Jain, R., Narang, J., Scarpace, L., *et al.*, “Predicting survival in glioblastomas using diffusion tensor imaging metrics,” *Journal of Magnetic Resonance Imaging*, Vol. 32, no. 4, pp. 788–795, 2010.
173. Ozturk-Isik, E., Cengiz, S., Ozcan, A., Yakicier, C., *et al.*, “Identification of *IDH* and *TERTp* mutation status using ^1H -MRS in 112 hemispheric diffuse gliomas,” *Journal of Magnetic Resonance Imaging*, Vol. 51, pp. 1799–1809, June 2020.
174. Sacli-Bilmez, B., Danyeli, A. E., Yakicier, M. C., Aras, F. K., *et al.*, “Magnetic resonance spectroscopic correlates of progression free and overall survival in “glioblastoma, *IDH*-wildtype, WHO grade-4”,” *Frontiers in Neuroscience*, Vol. 17, p. 1149292, June 2023.
175. Zhang, X., Tian, Q., Wang, L., Liu, Y., *et al.*, “Radiomics strategy for molecular subtype stratification of lower-grade glioma: Detecting *IDH* and *TP53* mutations based on multimodal MRI,” *Journal of Magnetic Resonance Imaging*, Vol. 48, pp. 916–926, Oct. 2018.
176. Park, C. J., Choi, Y. S., Park, Y. W., Ahn, S. S., *et al.*, “Diffusion tensor imaging radiomics in lower-grade glioma: improving subtyping of isocitrate dehydrogenase mutation status,” *Neuroradiology*, Vol. 62, pp. 319–326, Mar. 2020.
177. Calabrese, E., Villanueva-Meyer, J. E., and Cha, S., “A fully automated artificial intelligence method for non-invasive, imaging-based identification of genetic alterations in glioblastomas,” *Scientific Reports*, Vol. 10, p. 11852, July 2020.
178. Peng, H., Huo, J., Li, B., Cui, Y., *et al.*, “Predicting isocitrate dehydrogenase (*IDH*) mutation status in gliomas using multiparameter MRI radiomics features,” *Journal of Magnetic Resonance Imaging*, Vol. 53, pp. 1399–1407, May 2021.
179. Lu, J., Xu, W., Chen, X., Wang, T., *et al.*, “Noninvasive prediction of *IDH* mutation status in gliomas using preoperative multiparametric MRI radiomics nomogram: A multicenter study,” *Magnetic Resonance Imaging*, Vol. 104, pp. 72–79, Dec. 2023.
180. Foltyn-Dumitru, M., Schell, M., Sahm, F., Kessler, T., *et al.*, “Advancing noninvasive glioma classification with diffusion radiomics: Exploring the impact of signal intensity normalization,” *Neuro-Oncology Advances*, Vol. 6, p. vdae043, Jan. 2024.
181. Tan, Y., Mu, W., Wang, X.-c., Yang, G.-q., *et al.*, “Improving survival prediction of high-grade glioma via machine learning techniques based on MRI radiomic, genetic and clinical risk factors,” *European Journal of Radiology*, Vol. 120, p. 108609, Nov. 2019.
182. Yan, J., Zhang, B., Zhang, S., Cheng, J., *et al.*, “Quantitative MRI-based radiomics for noninvasively predicting molecular subtypes and survival in glioma patients,” *npj Precision Oncology*, Vol. 5, p. 72, July 2021.
183. Santinha, J., Matos, C., Papanikolaou, N., and Figueiredo, M. A. T., “Improving Generalizability to Out-of-Distribution Data in Radiogenomic Models to Predict *IDH* Mutation Status in Glioma Patients,” in *2022 IEEE International Symposium on Medical Measurements and Applications (MeMeA)*, (Messina, Italy), pp. 1–5, IEEE, June 2022.
184. Foltyn-Dumitru, M., Schell, M., Rastogi, A., Sahm, F., *et al.*, “Impact of signal intensity normalization of MRI on the generalizability of radiomic-based prediction of molecular glioma subtypes,” *European Radiology*, Vol. 34, pp. 2782–2790, Apr. 2024.

185. Orlhac, F., Boughdad, S., Philippe, C., Stalla-Bourdillon, H., *et al.*, “A postreconstruction harmonization method for multicenter radiomic studies in pet,” *Journal of Nuclear Medicine*, Vol. 59, no. 8, pp. 1321–1328, 2018.
186. Calabrese, E., Villanueva-Meyer, J., Rudie, J., Rauschecker, A., *et al.*, “The University of California San Francisco Preoperative Diffuse Glioma MRI (UCSF-PDGM),” Apr. 2023. <https://wiki.cancerimagingarchive.net/x/5pAiBw>.
187. Baid, U., Ghodasara, S., Mohan, S., Bilello, M., *et al.*, “The RSNA-ASNR-MICCAI BraTS 2021 benchmark on brain tumor segmentation and radiogenomic classification,” 2021. <https://arxiv.org/abs/2107.02314>.
188. Tustison, N. J., Avants, B. B., Cook, P. A., Yuanjie Zheng, *et al.*, “N4ITK: Improved N3 Bias Correction,” *IEEE Transactions on Medical Imaging*, Vol. 29, pp. 1310–1320, June 2010.
189. Isensee, F., Schell, M., Pflueger, I., Brugnara, G., *et al.*, “Automated brain extraction of multisequence MRI using artificial neural networks,” *Human Brain Mapping*, Vol. 40, pp. 4952–4964, Dec. 2019.
190. Fortin, J.-P., Cullen, N., Sheline, Y. I., Taylor, W. D., *et al.*, “Harmonization of cortical thickness measurements across scanners and sites,” *NeuroImage*, Vol. 167, pp. 104–120, Feb. 2018.
191. Jain, A., Duin, P., and Jianchang Mao, “Statistical pattern recognition: a review,” *IEEE Transactions on Pattern Analysis and Machine Intelligence*, Vol. 22, pp. 4–37, Jan. 2000.
192. Du, P., Chen, H., Lv, K., and Geng, D., “A survey of radiomics in precision diagnosis and treatment of adult gliomas,” *Journal of Clinical Medicine*, Vol. 11, p. 3802, June 2022.
193. Sartoretti, E., Sartoretti, T., Wyss, M., Reischauer, C., *et al.*, “Amide proton transfer weighted (APTw) imaging based radiomics allows for the differentiation of gliomas from metastases,” *Scientific Reports*, Vol. 11, p. 5506, Dec. 2021.
194. Cheng, J., Liu, J., Yue, H., Bai, H., *et al.*, “Prediction of glioma grade using intratumoral and peritumoral radiomic features from multiparametric MRI images,” *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, pp. 1–1, 2020.
195. Sun, C., Fan, L., Wang, W., Wang, W., *et al.*, “Radiomics and qualitative features from multiparametric MRI predict molecular subtypes in patients with lower-grade glioma,” *Frontiers in Oncology*, Vol. 11, p. 756828, Jan. 2022.
196. Wang, Z.-h., Xiao, X.-L., Zhang, Z.-T., He, K., *et al.*, “A radiomics model for predicting early recurrence in grade II gliomas based on preoperative multiparametric magnetic resonance imaging,” *Frontiers in Oncology*, Vol. 11, p. 684996, Sept. 2021.
197. Li, G., Li, L., Li, Y., Qian, Z., *et al.*, “An MRI radiomics approach to predict survival and tumour-infiltrating macrophages in gliomas,” *Brain*, Vol. 145, pp. 1151–1161, Apr. 2022.
198. Bangalore Yogananda, C. G., Wagner, B. C., Truong, N. C. D., Holcomb, J. M., *et al.*, “MRI-based deep learning method for classification of IDH mutation status,” *Bioengineering*, Vol. 10, p. 1045, Sept. 2023.

199. Claes, A., Idema, A. J., and Wesseling, P., "Diffuse glioma growth: a guerilla war," *Acta Neuropathologica*, Vol. 114, pp. 443–458, Nov. 2007.
200. Qazi, M., Vora, P., Venugopal, C., Sidhu, S., *et al.*, "Intratumoral heterogeneity: pathways to treatment resistance and relapse in human glioblastoma," *Annals of Oncology*, Vol. 28, pp. 1448–1456, July 2017.
201. Sakai, Y., Yang, C., Kihira, S., Tsankova, N., *et al.*, "MRI radiomic features to predict IDH1 mutation status in gliomas: a machine learning approach using gradient tree boosting," *International Journal of Molecular Sciences*, Vol. 21, no. 21, p. 8004, 2020.
202. Arita, H., Kinoshita, M., Kawaguchi, A., Takahashi, M., *et al.*, "Lesion location implemented magnetic resonance imaging radiomics for predicting IDH and TERT promoter mutations in grade II/III gliomas," *Scientific Reports*, Vol. 8, no. 1, p. 11773, 2018.
203. Niu, L., Feng, W.-h., Duan, C.-f., Liu, Y.-c., *et al.*, "The value of enhanced MR radiomics in estimating the IDH1 genotype in high-grade gliomas," *BioMed Research International*, Vol. 2020, no. 1, p. 4630218, 2020.
204. Li, Y., Ammari, S., Lawrance, L., Quillent, A., *et al.*, "Radiomics-based method for predicting the glioma subtype as defined by tumor grade, idh mutation, and 1p/19q codeletion," *Cancers*, Vol. 14, no. 7, p. 1778, 2022.
205. He, J., Ren, J., Niu, G., Liu, A., *et al.*, "Multiparametric MR radiomics in brain glioma: models comparison to predict biomarker status," *BMC Medical Imaging*, Vol. 22, no. 1, p. 137, 2022.
206. Ren, Y., Zhang, X., Rui, W., Pang, H., *et al.*, "Noninvasive prediction of IDH1 mutation and ATRX expression loss in low-grade gliomas using multiparametric MR radiomic features," *Journal of Magnetic Resonance Imaging*, Vol. 49, no. 3, pp. 808–817, 2019.
207. Wang, J., Hu, Y., Zhou, X., Bao, S., *et al.*, "A radiomics model based on DCE-MRI and DWI may improve the prediction of estimating IDH1 mutation and angiogenesis in gliomas," *European Journal of Radiology*, Vol. 147, p. 110141, 2022.
208. Lu, C.-F., Hsu, F.-T., Hsieh, K. L.-C., Kao, Y.-C. J., *et al.*, "Machine learning-based radiomics for molecular subtyping of gliomas," *Clinical Cancer Research*, Vol. 24, no. 18, pp. 4429–4436, 2018.
209. Kim, M., Jung, S. Y., Park, J. E., Jo, Y., *et al.*, "Diffusion-and perfusion-weighted MRI radiomics model may predict isocitrate dehydrogenase (IDH) mutation and tumor aggressiveness in diffuse lower grade glioma," *European Radiology*, Vol. 30, pp. 2142–2151, 2020.
210. Ibrahim, A., Lu, L., Yang, H., Akin, O., *et al.*, "The impact of image acquisition parameters and combat harmonization on the predictive performance of radiomics: A renal cell carcinoma model," *Applied Sciences*, Vol. 12, no. 19, p. 9824, 2022.
211. Orhlac, F., Eertink, J. J., Cottureau, A.-S., Zijlstra, J. M., *et al.*, "A guide to combat harmonization of imaging biomarkers in multicenter studies," *Journal of Nuclear Medicine*, Vol. 63, no. 2, pp. 172–179, 2022.
212. Liu, X., Li, Y., Qian, Z., Sun, Z., *et al.*, "A radiomic signature as a non-invasive predictor of progression-free survival in patients with lower-grade gliomas," *NeuroImage: Clinical*, Vol. 20, pp. 1070–1077, 2018.

213. Park, C. J., Han, K., Kim, H., Ahn, S. S., *et al.*, “Radiomics risk score may be a potential imaging biomarker for predicting survival in isocitrate dehydrogenase wild-type lower-grade gliomas,” *European Radiology*, Vol. 30, pp. 6464–6474, 2020.
214. Wang, J., Zheng, X., Zhang, J., Xue, H., *et al.*, “An MRI-based radiomics signature as a pretreatment noninvasive predictor of overall survival and chemotherapeutic benefits in lower-grade gliomas,” *European Radiology*, Vol. 31, pp. 1785–1794, Apr. 2021.
215. American Brain Tumor Association, “Meningioma,” June 2024. https://www.abta.org/tumor_types/meningioma/.
216. Wang, Y.-C., Chuang, C.-C., Wei, K.-C., Chang, C.-N., *et al.*, “Long term surgical outcome and prognostic factors of atypical and malignant meningiomas,” *Scientific Reports*, Vol. 6, p. 35743, Oct. 2016.
217. Yaylim, I., Azam, S., Farooqi, A. A., Küçük Hüseyin, Ö., *et al.*, “Critical molecular and genetic markers in primary brain tumors with their clinical importance,” in *Neurooncology - Newer Developments* (Agrawal, A., ed.), InTech, July 2016.
218. Youngblood, M. W., Miyagishima, D. F., Jin, L., Gupte, T., *et al.*, “Associations of meningioma molecular subgroup and tumor recurrence,” *Neuro-Oncology*, Vol. 23, pp. 783–794, May 2021.
219. Goutagny, S. and Kalamarides, M., “Meningiomas and neurofibromatosis,” *Journal of Neuro-Oncology*, Vol. 99, pp. 341–347, Sept. 2010.
220. Aboukais, R., Zairi, F., Baroncini, M., Bonne, N.-X., *et al.*, “Intracranial meningiomas and neurofibromatosis type 2,” *Acta Neurochirurgica*, Vol. 155, pp. 997–1001, June 2013.
221. Pinzi, V., Fariselli, L., Marchetti, M., Scorsetti, M., *et al.*, “Stereotactic radiotherapy for parasagittal and parafalcine meningiomas: Patient selection and special considerations,” *Cancer Management and Research*, Vol. Volume 11, pp. 10051–10060, Nov. 2019.
222. Hasegawa, T., Kida, Y., Yoshimoto, M., Iizuka, H., *et al.*, “Gamma Knife surgery for convexity, parasagittal, and falcine meningiomas: Clinical article,” *Journal of Neurosurgery*, Vol. 114, pp. 1392–1398, May 2011.
223. Slicer, “A multi platform, free and open source software package for visualization and medical image computing,” Oct. 2019. <https://www.slicer.org/>.
224. Park, Y. W., Oh, J., You, S. C., Han, K., *et al.*, “Radiomics and machine learning may accurately predict the grade and histological subtype in meningiomas using conventional and diffusion tensor imaging,” *European Radiology*, Vol. 29, pp. 4068–4076, Aug. 2019.
225. Delzell, D. A. P., Magnuson, S., Peter, T., Smith, M., *et al.*, “Machine Learning and Feature Selection Methods for Disease Classification With Application to Lung Cancer Screening Image Data,” *Frontiers in Oncology*, Vol. 9, p. 1393, Dec. 2019.
226. O’Connor, J. P., Rose, C. J., Waterton, J. C., Carano, R. A., *et al.*, “Imaging Intratumor Heterogeneity: Role in Therapy Response, Resistance, and Clinical Outcome,” *Clinical Cancer Research*, Vol. 21, pp. 249–257, Jan. 2015.
227. İldan, F., Erman, T., Göçer, A., Tuna, M., *et al.*, “Predicting the probability of meningioma recurrence in the preoperative and early postoperative period: A multivariate analysis in the midterm follow-up,” *Skull Base*, Vol. 17, pp. 157–171, May 2007.

228. Hwang, W. L., Marciscano, A. E., Niemierko, A., Kim, D. W., *et al.*, “Imaging and extent of surgical resection predict risk of meningioma recurrence better than WHO histopathological grade,” *Neuro-Oncology*, Vol. 18, pp. 863–872, June 2016.
229. Nanda, A., Bir, S. C., Konar, S., Maiti, T., *et al.*, “Outcome of resection of WHO Grade II meningioma and correlation of pathological and radiological predictive factors for recurrence,” *Journal of Clinical Neuroscience*, Vol. 31, pp. 112–121, Sept. 2016.
230. Zhang, Y., Chen, J.-H., Chen, T.-Y., Lim, S.-W., *et al.*, “Radiomics approach for prediction of recurrence in skull base meningiomas,” *Neuroradiology*, Vol. 61, pp. 1355–1364, Dec. 2019.

