Meningioma Relational Database Curation Using A Pacs-Integrated Tool For Collection Of Clinical And Imaging Features

Ryan Mclean

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Meningioma Relational Database
Curation Using a PACS-Integrated Tool
for Collection of Clinical and Imaging Features

Ryan McLean
YSM Class of 2024

Thesis Written in Fulfillment of Graduation Requirements for MD Degree
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i. Acknowledgements

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I. Abstract

Meningiomas are the most common primary intracranial neoplasm seen in adults, and despite the largely benign nature of these tumors, they are associated with significant morbidity and mortality\(^1\). Physicians specialized in CNS pathologies, such as neurosurgeons, neuroradiologists, and neuro-oncologists rely on multiparametric MRI (mpMRI) for diagnosis, guidance of management, and response to therapy of CNS lesions. Today, in the era of artificial intelligence, with high-throughput computing and accessibility to massive amounts of data, we see the emergence of new fields in translational science. Proteomics, genomics, metabolomics, and more recently, radiomics are quantitative and analytical fields that are driven by the accumulation of data. Advancements in these areas, as well as computer and data science in general, have resulted in the development of automated, objective, and quantitative tools that can provide non-invasive assessments of tumors. However, the accessibility to large amounts of medical imaging data for machine learning (ML) and deep learning (DL) purposes is limited, resulting in a shortage of such tools for meningiomas. To bridge this gap, in this thesis we specifically focus on contributing to the development of automated segmentation tools by building a database of meningiomas.

The Brain Tumor Segmentation (BraTS) Challenge has formed a multi-institutional coalition to increase the accessibility of automated segmentation tools for CNS tumors. To do this, the BraTS network aims to compile the largest annotated multilabel meningioma dataset. This dataset will serve as the training dataset for participants in the challenge to develop automated segmentation models for meningiomas. Models will then be validated using standardized metrics. The ultimate goal of this challenge is to provide a resource of segmentation tools and to facilitate
incorporation of this technology into clinical practice to improve the care and outcomes of meningioma patients.

This thesis will have two primary aims. First, compile a series of manually segmented and annotated MR scans of meningioma patients treated at Yale-New Haven Hospital to contribute to the BraTS Challenge. Second, outline a method of database curation that accommodates the storage, organization, and secure transfer of clinical, genomic, and imaging data to streamline. The ultimate objective is to reduce the time and labor burden on researchers interested in data collection and organization for prediction algorithm development via machine learning or deep learning.

To accomplish the second aim, we utilized Fast Healthcare Interoperability Resources (FHIR) webforms, a customizable questionnaire that can be integrated into a picture archiving and communication system (PACS). A PACS-integrated tool serves as a bridge between the electronic medical record (EMR) and PACS, where patient medical imaging is organized and stored. This is advantageous in the context of research and data collection because it can reduce or eliminate the requirement of external software that is typically used for the storage of clinical variables. Utilization of external software, particularly in the context of a large research group, can often result in a disjointed workflow and errors making the management of large amounts of data challenging. This approach provides an avenue for researchers interested in developing ensemble models that use image-based measurements and features to augment traditional clinical-only/clinical-weighted staging and treatment response prediction algorithms.
II. Overview of Meningiomas.

IIa. Background

Meningiomas have been described in the literature dating back to 1614 when a lesion, likely to be a meningioma, was reported by Felix Platter, a Swiss physician\(^2\). The nomenclature surrounding these lesions was highly contested in the early 19\(^{th}\) century, with terms such as ‘tumeurs fongueuses’, ‘fungus durae matris’, myeloid tumors, ‘acervuloma’, and ‘tumeur fibro-plastique’\(^3,4\). Eventually, ‘meningioma’, popularized by Harvey Cushing, became the accepted term to describe the dural-based lesions\(^4,5\). As a pioneer in neurosurgery, Dr. Harvey Cushing documented over 300 meningioma cases he treated throughout his career. In the absence of neuroimaging, early cases highlighted the challenge of neurosurgical intervention. Starting in 1914, and in conjunction with Louise Eisenhardt, Cushing began writing one of the most highly regarded texts in neurosurgery, *Meningiomas, Their Classification, Regional Behavior, Life History, and Surgical End Results*\(^4\). An endeavor of over 20 years, the text was completed and published in 1938 during Cushing’s retirement at Yale\(^6\).

Meningiomas are the most common tumors of the central nervous system (CNS), accounting for 37.6% of primary CNS tumors and 53.6% all benign CNS tumors\(^7\). Meningiomas can occur throughout the CNS, though most occur in the cerebral meninges (80.3%)\(^7\). Meningiomas originate from meningotheelial cells, which are found in the choroid plexus, tela choroidea, as well as the arachnoid villi\(^8\). Generally, these cells serve as physical and immune protection for the CNS and can vary in anatomical location.
depending on embryological origin. Importantly, meningiomas that arise from the different variants of meningothelial cells exhibit distinct features histologically and are associated with different sets of somatic mutations. There are currently 15 histologic subtypes of meningioma that have been identified (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacytic-rich, metaplastic, atypical, clear cell, choroid, anaplastic, rhabdoid, and papillary). The most frequent subtype is meningothelial (syncytial).

Similar to other cancers, the incidence of meningioma increases with age. The median age at diagnosis is 66, and evidence suggests the incidence of meningiomas in patients older than 70 is up to 3.5 times higher in comparison to younger patients of both sexes. There is also considerable variation in incidence between age groups (18.69 per 100,000 in patients over 40 years versus 0.16 per 100,000 in patients younger than 20 years), between sexes (incidence ratio of 2.33 in females versus 1.12 in males), and races (incidence ratio of 1.18 in White populations versus 1.52 in Black populations).

In most cases, meningiomas are sporadic tumors and are likely multifactorial in their development. In fact, the etiology of meningiomas is still not fully understood. Possible risk factors reported in the literature, however, include ionizing radiation (IR), head trauma, viruses (polyoma SV40 and adenovirus), obesity, sex hormones, advanced age, and genetic mutations (hereditary and somatic).

Obesity and history of prior radiation are two well-documented associations with meningioma risk. Positive associations of obesity and meningioma risk are thought to be consequence of a state of chronic inflammation as well as upregulation of signaling pathways, specifically adipokine-mediated, insulin, and insulin-like growth factor (IGF)
signaling pathways\textsuperscript{19}. A study investigating the association of obesity and meningioma risk reported a dose-dependent relationship; for every 5 kg/m\textsuperscript{2} increase in BMI the associated relative risk was 1.19\textsuperscript{20}. Although the relationship between obesity and cancer risk is not entirely understood, obesity can be attributed to 4-8\% of all cancers, many of which originate outside of the CNS, including breast cancer, colorectal, endometrial, kidney, esophageal, pancreatic, liver, and gallbladder\textsuperscript{21}. Abnormalities in obesity involving fatty acid metabolism, extracellular matrix remodeling, adipokines, sex hormones, anabolic hormones, immune dysregulation, and chronic inflammation have all been implicated in the oncogenesis of obese patients\textsuperscript{21}. Diet, however, does not appear to be related to meningioma risk\textsuperscript{22}.

Ionizing radiation (IR) is another example of a well-documented risk factor in meningioma development. In fact, meningiomas are the most common CNS lesion to occur secondary to IR exposure\textsuperscript{23}. Radiation has been extensively documented as dose-dependent with higher morbidity in patients exposed to higher levels. Moreover, there several associated CNS adverse effects in addition to the development of tumors (e.g., vasculopathy, visual and hearing changes, necrosis, calcifications)\textsuperscript{23,24}. Radiation doses as low as 1-2Gy have been linked to increased meningioma risk, particularly if the exposure occurs in childhood\textsuperscript{15,16}. The dose-dependent relationship of IR and cancer is also readily apparent in the context of the aftermath of the Hiroshima and Nagasaki in 1945 and Chernobyl nuclear accident of 1986\textsuperscript{25-28}. Survivors closer to the epicenter (and those that were children at the time) of the explosions in Hiroshima and Nagasaki had an increased risk of meningioma development than survivors further away\textsuperscript{29}. Overall,
increases in incidence in patients exposed to IR vary, with reports of up to a tenfold increase in risk of meningioma\textsuperscript{24}.

Many meningiomas also express progesterone receptors\textsuperscript{30,31}. Evidence suggests high progesterone receptor expression is associated with low histological grades, lower likelihood of recurrence, and favorable prognoses\textsuperscript{32,33}. Somatostatin receptors are also frequently present (70-100\%)\textsuperscript{34}. Interestingly, the presence of these receptors can be leveraged for radiological assessment. Radiolabeled galium-68 octreotide analogue (DOTA-TATE), a somatostatin receptor ligand, can be used to detect meningioma tissue on PET imaging\textsuperscript{35}. Due to the high specificity of DOTA-TATE for somatostatin receptor 2, this approach has been shown to be a useful tool in guiding postoperative radiotherapy of meningiomas, ultimately reducing radiation treatment volumes\textsuperscript{36}. The role of hormones and associated receptors is an active area of research with a focus on identifying prognostic biomarkers and their biological significance.

\textbf{IIb. Genetics and Anatomy}

\textit{GENETICS.} Genetics represents a crucial component to understand the etiology, behavior, and prognosis of meningiomas. The cytogenetics of meningiomas can be divided into two categories: somatic mutations and familial syndromes. Familial syndromes account for a small portion of meningiomas, though there are several notable examples that are associated with increased risk of meningioma development\textsuperscript{37}. Examples include neurofibromatosis type 2 (autosomal dominant germline NF2 mutation on chromosome 22q12)\textsuperscript{38,39}, Gorlin syndrome (autosomal dominant syndrome causing aberrant sonic hedgehog signaling pathway)\textsuperscript{37,40}, Cowden syndrome (autosomal dominant
mutation in PTEN, a component of the mTOR pathway influencing cell proliferation, survival, and metabolism\textsuperscript{41}), and Werner syndrome (autosomal recessive mutation in the WRN on chromosome 8, resulting in a dysfunctional DNA helicase\textsuperscript{37}) among others. Other mutations found in familial syndromes include breast cancer (BRCA)1-associated protein 1 (BAP1)\textsuperscript{42} as well as SMARCB1 and SMARCE1 (subunits of the SWI/SNF group of ATP-dependent chromatin remodelers\textsuperscript{37}). Notably, meningiomas are also found in patients with Li-Fraumeni, Turcot, Gardener, von Hippel-Landau, Rubenstein-Taybi, and multiple endocrine neoplasia type I (MEN1), though in these cases meningiomas are just one of several associated neoplasms\textsuperscript{37,43,44}.

Familial syndromes vary greatly in associated meningioma risk as well as the behavior of the lesions, if present. Over 50\% of patients with NF2 mutations develop one or more meningiomas in their lifetime (mean age of 30 years old of meningioma diagnosis)\textsuperscript{45}. These tumors tend to be more aggressive than sporadic lesions\textsuperscript{1,46}. There are a number of mutations in the NF2 gene that were found to be drivers in meningioma tumorigenesis. Initially thought to have a prevalence of about 1:200,000, more recent estimates are about 1:33,000 worldwide\textsuperscript{39,47}. Patients with mutations that result in a truncated Merlin protein and mutations towards the 5’ end of the gene exhibit higher morbidity and mortality\textsuperscript{48}. In contrast to NF2-mutated meningiomas, Cowden syndrome and Gorlin syndrome are associated with much lower risk of meningioma (8.25\% and 5\% of patients, respectively)\textsuperscript{37,41}.

The somatic mutations in meningioma can be further divided into two major molecular subgroups: meningiomas with NF2 mutations and meningiomas with non-NF2 mutations. Neurofibromatosis type 2 is an example of a syndrome that can occur via two
pathways. The first pathway is a germline mutation of the NF2 gene that is inherited in an autosomal dominant fashion\textsuperscript{38}. As such, affected individuals have a 50\% chance of transmitting the mutated allele to their offspring. The second pathway accounts for 50-60\% of NF2 cases and is the consequence of \textit{de novo} mutations in patients with no family history\textsuperscript{49}. NF2 is a tumor suppressor gene located on chromosome 22 that encodes for the Merlin protein, a structural component that bridges receptors in the plasma membrane to intracellular effectors\textsuperscript{49,50}. The targets of these effectors are oncogenic pathways involved in several hallmarks of cancer: proliferation, cell survival, cellular architecture, intercellular interactions, and cell migration\textsuperscript{51}. The Ras/mitogen-activated kinase (MAPK) is an example of an oncogenic pathway that becomes hyperactive in the absence of the Merlin protein and highlights the interconnectedness of signaling pathways, given that many pathologies arise as a result of dysregulation in this pathway\textsuperscript{49}. Genetic syndromes with dysregulated Ras signaling are known as “RAS-opathies” (e.g., Noonan syndrome\textsuperscript{52}, LEOPARD syndrome\textsuperscript{53}, hereditary gingival fibromatosis\textsuperscript{54}, neurofibromatosis 1 (NF1)\textsuperscript{55}, arteriovenous malformations\textsuperscript{56}, Costello syndrome\textsuperscript{57}, autoimmune lymphoproliferative syndrome\textsuperscript{58}, cardio-facio-cutaneous syndrome [CFC]\textsuperscript{59}, and Legius syndrome\textsuperscript{60}). The phosphoinositide 3-kinase (PI3K)/AKT, mTOR, Notch, and Hippo pathways also become dysregulated in NF2 mutations\textsuperscript{49}. Although NF2 mutations are present in large percentage of all meningiomas, it is important to note that these tumors are typically low-grade subtypes (75\% of atypical, 80\% of fibrous and transitional, and 30\% of meningothelial)\textsuperscript{61}. Non-NF2 mutations are a diverse set of genes that account for the remaining 40-50\% of meningiomas\textsuperscript{46}. Interestingly, many of these mutations share cellular pathways
and regulate one another under physiological conditions (Figure 1). Genomic analysis has identified several non-NF2 mutations implicated in meningioma tumorigenesis: TNF receptor-associated factor 7 (TRAF7), Kruppel-like factor 4 (KLF4), v-Akt murine thymoma viral oncogene homolog 1 (AKT1), RNA polymerase subunit II A (POLR2A), Telomerase reverse transcriptase (TERT), smoothened/frizzled class receptor (SMO), and Phosphadidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha (PIK3CA)\textsuperscript{1,46,61-63}.

Figure 1. Diagram of the epidermal growth factor (EGF) signaling pathway highlighting the interconnectedness of meningioma driver mutations.
Within this group, there is a degree organization to the presence or absence of co-mutations. In general, most non-NF2 mutations occur exclusively in the absence of NF2 mutations and monosomy 22\textsuperscript{63,64}. TRAF7 mutations are found in 25% of all meningiomas and is the most common denominator in co-mutations, frequently co-occurring with KLF4, AKT1, and PIK3CA mutations\textsuperscript{46,65}. Under physiological circumstances, non-NF2 mutations contribute to crucial functions in the cell. As a result, many are implicated in the development of other neoplasms and syndromes\textsuperscript{65,66}. The majority of non-NF2 somatic mutations (TRAF7, KLF4, POL2RA, SMO, and PIK3CA) are associated with low-grade meningiomas\textsuperscript{61,63,67,68}. Although AKT1 mutations are found in a small percentage of high-grade tumors (WHO grade 2 and 3) and TERT mutations can be present in all grades (1.7%, 5.7%, and 20%, respectively)\textsuperscript{46,69}. A summary of somatic and chromosomal mutations with the associated grade and histological subtype is summarized in Table 1.
Table 1. Somatic and chromosomal mutations in relation to the World Health Organization (WHO) grade and histological subtype. Figure adapted from Ogasawara et al.¹
It is widely understood that cancer risk is not limited to environment exposures and coding in the genome, but rather the regulation of the genome itself is also a critical factor in tumorigenesis. Molecular profiling is powerful tool for classifying meningiomas, detection of biomarkers, and can provide prognostic information to guide therapy\textsuperscript{70}. Similar to the subgroups of mutations classically found in meningiomas, epigenetic subgroups with distinct features have also been identified\textsuperscript{71}. DNA methylation is a chemical modification of cytosine wherein a methyl group is attached at the C-5 position on the cytosine ring, by DNA methyltransferase (DMNT) enzymes (mainly DNMT1, DNMT3A, and DNMT3B)\textsuperscript{72-73}. DNA methylation is involved in processes affecting the genome: gene expression, imprinting, X-chromosome inactivation (formation of Barr bodies), transposon silencing, and maintenance of genomic stability\textsuperscript{74}. Methylation can also occur on histone proteins (Figure 2). Similar to DNA methylation, methylation of lysine residues on histone proteins results in gene repression. However, a key difference between histone and DNA methylation is the reversibility of the modification. DNA methylation is a highly stable modification that can result in long-term gene repression while histone methylation is readily reversible and provides a more labile form of gene regulation\textsuperscript{75}.

In general, when applied to the promoter region of a gene, DNA methylation results in repression at that site. Repression of transcription is observed in DNA methylation as a consequence of steric hindrance wherein proteins involved in transcription are physically unable to interact with the DNA\textsuperscript{76}. This effect can be reversed by removal of the methyl group by demethylases. In contrast, histone acetylation, another form of epigenetic modification, typically results in increased expression of the affected
gene\textsuperscript{77}. Aberrations in DNA methylation have been identified in a number of cancers\textsuperscript{78}. The changes in methylation pattern seen in cancer varies. For example, genome-wide hypomethylation causes chromosomal instability, reverses repression of imprinted genes and retrotransposons, and overall abnormal gene expression\textsuperscript{78-80}. Retrotransposons insert into promoter regions of genes and can result in drastic changes of that gene's expression. The $MET$ promoter, once affected by the long interspersed nuclear element 1 ($LINE1$) retrotransposon, becomes a driver in the development of skin, genitourinary, and renal cancers\textsuperscript{81}. In contrast, hypermethylation in promoter regions of tumor suppressor genes can also result in tumorigenesis. Important examples of the effects of aberrant hypermethylation include sporadic breast and ovarian cancers (loss of $BRCA1$) and malignancies associated von Hippel-Landau syndrome (loss of $VHL$ tumor suppressor$^{82,83}$).
Information on the methylation status in the genome is obtained through the generation of DNA methylation profiles. Single-cell methylation profiling can be completed with base-conversion methods where cytosine or methyl cytosine is modified and detected as thymine by sequencing (reduced representation bisulfite sequencing [RRBS], whole-genome bisulfite sequencing [WGBS], methylation-sensitive reaction enzymes [MSRE]) or conversion-free methods (methyl-CpG-binding domain sequencing [MIB-seq] and methylated DNA immunoprecipitation sequencing [MeDIP-seq])

Bisulfite conversion is the gold standard and preferred by researchers due to its high conversion efficiency.

The use of DNA methylation profiles has been a profound tool in the study of meningiomas. As discussed below, the predictability of meningiomas relies heavily on classification information provided by the CNS WHO grading scale. This scale focuses on genetic and histological criteria to classify tumors and predict behavior. Although the CNS WHO grading scale has been updated to incorporate new data, there is still a degree of variability in predicting meningioma behavior. In fact, studies suggest information provided by epigenetics be a superior approach to predicting meningioma behavior. In a retrospective analysis by Sahm et al., six unique meningioma methylation profiles were identified from 497 meningioma samples. The study showed that meningioma DNA methylation profiles can be used as a method to distinguish these tumors by comparing results 309 samples from histologically similar non-meningioma skull tumors (hemangiopericytoma, schwannoma, malignant peripheral nerve sheath tumors, chordoma, chondrosarcoma, fibrous dysplasia, and hemangioblastoma).
Of the six methylation classes identified in this study, further analysis of the
samples identified histological subtypes, cytogenetics, and gene expression patterns
associated with each class. Three of the methylation classes were predominantly
associated with CNS WHO grade 1 tumors, one class correlated with CNS WHO grade 3
tumors, but the distribution of CNS WHO grade 2 tumors was scattered across all
methylation classes. Finally, the outcome prediction potential of methylation classes was
compared to WHO grading. Results that were validated on an additional cohort suggested
that classification by histology, cytogenetics, and associated mutations combined with
methylation profiles provided more precise prognostication of progression-free survival
compared to WHO grading at 10-year follow-up\textsuperscript{86}.

\textbf{ANATOMY.} Anatomically, meningiomas present in all intracranial regions. Using an
axial view of the skull, regions can be divided into anterior, middle, and posterior regions
for location grouping with specific mutations characteristically found within each region.
As a whole, however, the three intracranial locations with the high frequency of
meningioma are the skull base (43-51%), middle cranial fossa (9-36%), and the lateral
hemisphere (20-37%); rarer locations (\leq5% of all meningiomas) include the foramen
magnum (3%), ectopic locations (<1%), tentorium cerebelli (2-4%), cerebellar convexity
(5%), orbital (<1-2%), and interventricular regions (1-5%)\textsuperscript{1,87,88}. In general, low-grade
meningiomas tend to localize to the lateral and posterior regions of the skull base, while
high-grade meningiomas are more likely to be found in the parasagittal and
interventricular regions\textsuperscript{67,89} (\textbf{Figure 3}).
Clinical manifestations, as a consequence of genetic composition, are intertwined with the anatomical location of a tumor. Oftentimes, however, the signs and symptoms associated with CNS tumors are nonspecific and can range in severity or frequency. Presenting symptoms include headache, seizure, altered mental status, cranial nerve deficits, ataxia and sensory changes (i.e., visual, olfactory), syncope, weakness, and vertigo. The most frequently reported symptoms of this group are: headache (33.6-36.7%), nerve deficit (28.8-31.3%), and seizure (16.9-24.6%) with the most uncommon being syncope (1.0%).\textsuperscript{87,89} Once a CNS tumor is suspected, specific symptoms can often provide insight into the location of the lesion and vice versa. Some symptoms, such as focal neurological deficits, may be easier to associate with a specific region while causes of seizures, which are multifactorial, may not be associated with one area. Anterior skull base meningiomas (i.e., anterior falcine, olfactory groove, or orbitofrontal regions) can present with psychomotor symptoms and behavior disturbances.\textsuperscript{90} More specifically, parasellar/medial sphenoid wing meningiomas can cause visual disturbances while lesions in the cavernous sinus and petrous-ridge can result in ophthalmoplegia or trigeminal dysesthesia.\textsuperscript{91} Posterior lesions can disrupt circulation of the CSF due to the proximity of a lesion to the ventricles resulting in obstructive hydrocephalus.\textsuperscript{91} A subset of patients (<10%), however, are asymptomatic and have a meningioma detected as an incidental finding.\textsuperscript{87} Spinal meningiomas, which most commonly occur in the cervical and thoracic regions, can be symptomatic on presentation and symptoms are dependent on the location of meningioma within the spine. Thoracic lesions present with progressive spastic paresis which may or may not have associated radicular or nocturnal pain.\textsuperscript{91} Meningiomas of the cervical spine and cranio-cervical junction also present with
spastic paresis, specifically spastic quadriplegia with or without low bulbar signs (e.g., dysphagia, dysarthria, flaccid paresis, atrophy, and muscle fasciculations)\textsuperscript{91}.

Patients with larger tumors (>4cm) were reported to have more pronounced deficits in comparison to smaller tumors (<4cm), likely as a consequence of greater compression and disruption of local structures\textsuperscript{92}. Importantly, in the same study at 1-year postoperative follow-up, patients demonstrated significant improvement on neuropsychological examination (preoperative patients exhibited lower performance at baseline in comparison to controls). Neurocognitive assessments of executive, motor, and parietal function\textsuperscript{92-94} were conducted in healthy volunteer controls and meningioma patients and demonstrated that preoperative patients performed significantly worse than healthy volunteer controls\textsuperscript{92}.

Meningiomas are highly vascular lesions and although it is a rare clinical presentation (0.5\%-2.4\%), patients with meningiomas are at risk of spontaneous intracerebral hemorrhage\textsuperscript{95}. Intracerebral hemorrhage carries a very high mortality rate of 40-50\% within 30 days\textsuperscript{96}. A meta-analysis found that at baseline, the mortality rate for patients with spontaneous meningioma hemorrhages is about 1 in 5, but drastically increases to 75\% for patients that are unable to regain consciousness before surgical intervention\textsuperscript{97}. 
Figure 3. Anatomical locations of meningiomas and corresponding mutations in the axial.
(A) and coronal (B) views.

IIc. Grading and Staging

**GRADING.** Methods to classify tumors and predict behavior are rapidly evolving, though a few older approaches are still utilized today. Historically, meningiomas have been graded according to the CNS World Health Organization (WHO) grading scale, *Classification of Tumours of the Central Nervous System*. The first edition, released in 1979, was the first official WHO publication in the series. The first edition built upon previous classification attempts dating back to 1952 from the *Armed Forces Institute of Pathology (AFIP) Fascicle – Tumors of the Central Nervous System*. The first four editions (released in 1979, 1993, 2000, and 2007, respectively) relied exclusively on histological criteria to stratify tumors. In contrast, an updated fourth edition (2016) and later a fifth edition (2021) incorporated genetic data in addition to histological criteria. Important nomenclature changes to note in the fifth edition include the use of Arabic numeral (previously Roman) and grading of neoplasms is now within types, as opposed to across different tumor types.

The fifth edition is a more comprehensive approach to defining tumors and utilizes a layered approach, each layer designated to characterize a specific feature of the tumor. Layer 1 is the final integrated diagnosis, Layer 2 is the histological classification, Layer 3 is the WHO grade, and Layer 4 provides molecular information on the tumor. Using a meningioma as an example, the layer approach may be as follows: Layer 1, anaplastic meningioma; Layer 2, anaplastic meningioma with cellular anaplasia and numerous mitotic figures (**Figure 4**); Layer 3, WHO Grade 3; Layer 4, NF-2 deletion on
chromosome 22q12.2. WHO grade in addition to the extent of surgical resection (Simpson grade) have historically been strong predictors for tumor recurrence\textsuperscript{106,107}. Generally, higher WHO grades correlate with higher rates of recurrence. Confidence in the predictive accuracy of this scale, however, begin to break down in subsets of patients with WHO grade 1 meningiomas that experience early recurrence and a population of WHO grade 3 meningiomas that ultimately do not recur at all\textsuperscript{108}. As a result, in these groups, treatment planning may be more challenging in the absence of more information.

**Figure 4. Example of the layered approach to CNS tumor classification introduced in the fifth edition of the WHO Classification of Tumors of the CNS (WHO CNS5)\textsuperscript{103}.

The vast majority of meningiomas typically fall within Grade 1 (80-85%), which are low-grade benign tumors\textsuperscript{109}. In most cases, these are slow-growing tumors, with a growth rate of 2-4 mm/year in asymptomatic meningiomas\textsuperscript{43}. WHO grading criteria for grade 1 are as follows: (i) Mitotic rate <4 per 10 high-power field (HPF) and (ii) no brain invasion\textsuperscript{109}. Generally speaking, the prognosis of low-grade meningiomas is drastically better than high grade lesions. Patients with low-grade meningiomas in favorable
locations that are amendable to extensive surgical resection (e.g., convexities) have been shown to have a higher probability of cure and improved recurrence-free survival\textsuperscript{110}. The ten-year survival rate for nonmalignant meningiomas is 83.7\% versus 61.7\% for malignant meningioma\textsuperscript{7}. Grade 1 meningioma subtypes include: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, lymphoplasmacytic-rich, and metaplastic (Figure 5). Other tumors in this grade include craniopharyngioma, chordoma, ganglioglioma, gangliocytoma, and pilocytic astrocytoma. Images and histological interpretation in panel B of Figures 5-7 are courtesy of Dr. Anita Huttner, MD.

**Figure 5.** (A) Axial and coronal cross-sections of a grade 1 meningothelial subtype meningioma. (B) Histological slide of meningothelial meningioma with lobular architecture, syncytium-like appearance (due to ill-defined borders) and prominent whorl formation.

Similar to Grade 1 tumors, Grade 2 meningiomas are the ‘atypical’ group and have more variability in behavior. WHO grading criteria for atypical meningiomas include: (i) Mitotic rate 4-19 per 10 HPFs or (ii) brain invasion or (iii) \( \geq 3 \) of 5
histological features (i.e., spontaneous or geographic necrosis, disorganized sheet-like growth, prominent nucleoli, high cellularity, small cells with high nuclear: cytoplasmic ratio)\textsuperscript{109}. Grade 2 meningiomas account for 15-20\% of all meningiomas and have a higher chance to both recur as well as progress to higher grades. Ten-year survival rates for grade 2 meningiomas is 53\%\textsuperscript{7,43}. Meningioma subtypes that are classified as Grade 2 include atypical, choroid, and clear cell meningiomas (Figure 6). Other tumors to note in this category are pineocytoma, “diffuse” astrocytoma, and pure oligodendroglioma.

Figure 6. (A) Axial and coronal post-contrast MRI image of a grade 2 atypical meningioma. (B) Histological image of an atypical meningioma, demonstrating sheetlike growth with a focus of spontaneous necrosis and elevated proliferative activity.

Meningiomas can only be classified as grade 3 and below, though the CNS WHO grading system goes up to grade 4. Both groups represent the more aggressive tumors that are characterized by rapid progression with histological features that demonstrate evidence of malignancy (i.e., nuclear atypia and increased mitotic activity). Specific
criteria for grade 3 includes a mitotic rate >20 per 10 HPFs or histology consistent with papillary or rhabdoid subtypes\textsuperscript{109}. On magnetic resonance imaging (MRI), these tumors will often show evidence of necrosis (Figure 7). Grade 3 meningioma is composed of three subtypes: rhabdoid, papillary, and anaplastic meningiomas. For completeness, examples of Grade 4 tumors include anaplastic ependymoma, anaplastic astrocytoma, and anaplastic oligodendroglioma. These are the most malignant tumors that demonstrate rapid proliferation and are aggressive. Moreover, grade 4 lesions are highly infiltrative, prone to recurrence, and can be necrotic.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image.png}
\caption{(A) Axial post-contrast MRI image of a grade 3 anaplastic meningioma. (B) Histological slide of an anaplastic (malignant) meningioma with high mitotic activity and markedly atypical cells.}
\end{figure}

\textbf{STAGING.} Tumor grade is an invaluable tool to categorize malignancies, especially CNS neoplasms. However, it is important to also address tumor staging, another method of tumor characterization that considers different parameters to provide insight on tumor behavior. Tumor staging refers to the anatomic spread of disease from its point of origin. In general, staging can be divided in four categories: Stage I (tumor is present only within
the organ of origin and no evidence of nodular or vascular spread), II (extension of tumor invasion into local tissues and involvement of regional lymph nodes), III (extensive and deeper invasion of local tissues and lymph nodes), and IV (evidence of distant metastasis from organ of origin)\textsuperscript{111}.

Tumor staging has been historically done using the tumor-node-metastasis (TNM) system, though the utility of this structure, on an individual level, is questioned in light of the evolution of cancer biology. Now in its eighth iteration, the AJCC Cancer Staging Manual has prioritized inclusion of molecular factors and the adoption of a more “personalized” approach to cancer staging, as opposed to previous versions that were population-based\textsuperscript{112}. Still, it is important to address the parameters in this scale, which include size of the tumor (T), involvement of lymph nodes (N), and presence or absence of distant metastases (M). Each of these parameters are organized into rank to reflect the size of the tumor (TX, T0, T1, T2, T3, T4), degree of lymph node involvement (NX, N0, N1, N2), and whether or not there is evidence of metastasis (MX, M0, M1)\textsuperscript{112} (Table 2).

Therefore, a patient with a newly diagnosed meningioma may have a tumor staging with the following results after a proper workup has been completed: T2N0M0, a tumor of moderate size with no evidence of lymph node involvement or metastasis.

The eighth edition of the AJCC Cancer Staging Manual now considers prognostic factors and biomarkers for staging, citing advances in molecular biology as a driving force towards a more individualized approach to staging. These categories are organized into new sections of the manual. New sections include: The Prognostic Factors Required for Stage Grouping (prognostic factors that strongly correlation with prognosis) and The
Emerging Factors for Clinical Care (factors that are not yet routinely recommended due to insufficient evidence to support clinical benefit)\textsuperscript{112}.

In previous versions of the AJCC Cancer Staging Manual, brain tumors, including meningiomas, were staged using the TNM system. However, following the fourth edition this classification method has been withdrawn and replaced with Collaborative Staging, a code-based system that encompasses the TNM, SEER Extent of Disease (EOD), and SEER Summary Stage (SS) systems to provide more comprehensive staging\textsuperscript{113}. For meningiomas, the severity of the tumor is determined by the grade. According to the World Health Organization, these lesions can be classified as grade 1, 2, or 3, with grade 3 representing the most aggressive category of meningiomas\textsuperscript{103}. WHO grade 4 tumors are the most aggressive and severe category and does not include meningiomas.

<table>
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<td>Primary tumor cannot be found</td>
<td>The higher the number after T, the larger and more extensive the tumor</td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>Cancer in nearby lymph nodes cannot be measured</td>
<td>No cancer in nearby lymph nodes</td>
<td>The higher the number after the N, the more lymph nodes contain cancer</td>
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<tr>
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<td>No metastasis</td>
<td>Cancer has spread to distant parts of the body</td>
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<td>*The M parameter only goes up to 1</td>
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\textit{Table 2. Characteristics and features associated with TNM staging scale.}
Diagnostics and Treatment

DIAGNOSTICS. Standard magnetic resonance (MR) imaging and computed tomography (CT) are two major diagnostic tools for detecting and diagnosing intracranial pathologies. These are highly favorable imaging methods that produce high resolution images noninvasively. MR and CT are often used as complements to one another. On unenhanced CT (no contrast), meningiomas are homogenous and hyperdense masses with consistent homogeneity following contrast administration\textsuperscript{114}. Intra-tumoral calcifications in meningiomas are a common radiologic finding that is best visualized on CT. Another strength of CT is the detection of bony changes. In meningiomas, bony changes may present as hyperostosis, osteolysis, or pneumosinus dilatans\textsuperscript{114}. Hyperostosis is the most common of these findings and may signify invasion of nearby osseous structures. Tumor invasion of osseous structures is radiologically similar to reactive hyperostosis, though strong enhancement is more suggestive of invasion\textsuperscript{114}. As previously discussed, meningiomas are highly vascularized lesions and have a small risk of hemorrhaging. In the hyperacute phase (<12 hours), non-contrast CT is the gold standard imaging approach for detecting intracranial bleeding due to its high sensitivity. However, MR is more sensitive after 12-24 hours\textsuperscript{115}. In the context of intracranial hemorrhage, the speed of CT scans relative to MR is an important consideration.

For diagnosis, MR is the gold standard for meningiomas because of the superior resolution soft-tissues as well as the absence of radiation exposure to patients\textsuperscript{116}. Provided there are no contraindications (e.g., end-stage renal disease, cochlear implants, pacemakers, aneurysm clips), contrast enhanced study is recommended. In scenarios where there are contraindications, contrast-enhanced CT or non-contrast MRI with thin slice imaging on T2 can be used as an alternative technique\textsuperscript{117}. Meningiomas are strongly
enhancing lesions. Enhancement occurs as a result of increased vascularization throughout a lesion. Gadolinium-based contrast is the most common agent used for clinical imaging. It can be administered intravenously (at a standard dose of 1 mmol/kg body mass) and provides enhancement by increasing the T1 signal. This effect can be augmented by increasing the concentration or by lengthening the time between administration of the contrast and subsequent imaging. However, caution is required when increasing contrast concentrations due to nephrotoxicity.

MR sequences can be divided into four categories: spin echo (SE), gradient echo (GRE), inversion recovery (IR), and echoplanar imaging (EPI). Basic MR sequences include T1-weighted images (T1w) and T2-weighted images (T2w). MR is particularly strong for visualizing and distinguishing structures within soft tissue. On T1, substances that demonstrate low signal (e.g., water) are hypointense and appear gray on imaging, while hyperintense substances (e.g., fat) appear white. Depending on the structure being imaged, there are a number of other sequences available that are adept at detecting specific features: fat suppressed sequences, fluid attenuated (FLAIR), susceptibility weighted imaging (SWI), proton density weighted sequences, and flow sensitive sequences (MR angiography and venography, CSF flow studies).

Unlike other CNS lesions, meningiomas can be diagnosed with imaging alone. The characteristic radiological findings of enhancing well-circumscribed dural-based lesions associated with dural tail are useful features for meningioma diagnosis. Although, diagnosis can be challenging radiologically due to lesions that present similarly to meningiomas, such as cerebral metastases which are the most common brain tumors in adults. Dural metastases are found in approximately 9% of patients with terminal stage
IV cancer and manifest as a solitary intracranial lesion in about 5% of cases\textsuperscript{121}.

Meningiomas of the cerebral hemispheres can be difficult to distinguish from brain metastases from other cancers (e.g., prostate, lung, kidney, or breast)\textsuperscript{116,122}, tumors within the CNS (e.g., primary glial lesions, hemangiopericytomas)\textsuperscript{123,124}, or even humoral malignancies (e.g., lymphomas)\textsuperscript{125}. These mimics reduce the reliability and specificity of findings classically associated with meningiomas, such as dural tails, which are present in 52-78\% of meningioma cases\textsuperscript{126}. Positron emission tomography (PET)/MRI, other advanced MR imaging techniques such as MR spectroscopy, functional MRI (fMRI), diffusion-weighted imaging/diffusion tensor imaging (DWI/DTI), and perfusion imaging can be used to provide diagnostic information not available by standard MR imaging\textsuperscript{127}.

\begin{figure}[h]
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\caption{MRI images of a grade 1 meningothelial meningioma on (A) pre-contrast T1-weighted imaging, (B) post-contrast T1-weighted imaging, (C) fluid attenuated inversion recovery (FLAIR), and (D) diffusion-weighted imaging (DWI).}
\end{figure}

\textbf{TREATMENT.} The treatment of meningiomas is highly dependent on both the patient as well as the tumor. Fortunately, outcomes for meningioma patients continue to improve. With the exception of grade 3 lesions, patients are experiencing better long-term outcomes, retreatment free survival, and overall survival. The best predictors for
outcomes are the histological grade of the tumor and the extent that the tumor can be resected\textsuperscript{106,107}. According to the CBTRUS Statistical Reports (2012-2016), benign spinal meningiomas, benign cerebral meningiomas, and WHO grade 1 meningiomas as a whole have the highest 10-year survival rates of 95.6\%, 83.2\%, and 83.7\%, respectively\textsuperscript{7}. In contrast, malignant spinal, malignant cerebral, WHO grade 2, and WHO grade 3 meningiomas had much poorer outcomes with 10-year survival rates of 73.4\%, 55.7\%, 53\%, and 0\%, respectively\textsuperscript{7}.

Options for management include observation, surgical resection, radiotherapy, chemotherapy, and in tumors that do not respond to conventional methods (e.g., surgery or radiotherapy), salvage systemic therapy. Observation is a conservative approach that attempts to minimize potential morbidity in patients that are asymptomatic and/or have a small tumor that is incidentally diagnosed\textsuperscript{128}. In the observation period, routine MR imaging is the test of choice for monitoring tumor growth. According to recommendations by European Association of Neuro-Oncology (EANO), following the initial diagnosis of a meningioma, patients that are to be observed should receive MR imaging 6 months post-diagnosis and, if the patient remains asymptomatic, annually for the following 5 years\textsuperscript{129}. After 5 years of annual monitoring, patient scans can be spread out to every 2 years. The EANO recommends MR studies be performed with gadolinium contrast-enhanced T1-weighted imaging or T2-weighted imaging as an option for small tumors\textsuperscript{129}. Patients can be observed until they become symptomatic or may be preemptively treated if a tumor grows too large. Importantly, patients that are diagnosed with a benign meningioma and have a short life expectancy due to age or other comorbidities can forgo observation altogether\textsuperscript{129}.  

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Surgery is the mainstay choice of treatment for patients that are either symptomatic, can no longer be safely observed, or have large tumors that may become problematic. Fortunately, 70-80% of meningiomas can be cured by resection\(^69\). The surgical management of meningiomas can be summarized according to the Simpson scale, which is divided into 5 grades. Simpson grades 1-3 fall under the umbrella of gross surgical resection and grades 4 and 5 are classified as subtotal resection\(^107\). Grade 1 represents the most extensive example of gross resection (i.e., resection of tumor, dural attachment, and involved bone). At the other end, grade 4 is a partial resection of the tumor and grade 5 is a biopsy. Five-year recurrence rate following Simpson grade 1-3 resection are 7-23% in CNS WHO grade 1 meningiomas, 50-55% in grade 2, and 72-78% in grade 3\(^7,109\).

As previously discussed, meningiomas occur throughout the CNS, including regions that are not easily accessible surgically. In the context of surgical intervention, there are important considerations\(^128\): (i) surgical benefits, (ii) surgical risks, (iii) biological characteristics of the tumor, (iv) symptoms and mass effect, (v) patient wishes. Within surgical risks, tumor location and patient comorbidities are important considerations. In general, older patients and sicker patients will not tolerate surgery as well. Meningiomas involving the dural sinuses, blood vessels, or cranial nerves are challenging to resect\(^128\). Convex meningiomas are considered low risk. Tumors located in the olfactory sulcus, adjacent to the sagittal sinus, intraventricular, cerebellopontine angle, and the falx cerebrum are moderate risk. Finally, high risk locations include the clinoid process, cavernous sinus, and tuberculum sellae\(^128,130\).
Radiation therapy can be used in two approaches for the treatment of meningiomas: stereotactic radiosurgery (SRS) or fractionated radiation therapy (FRT). These approaches differ in the number of fractions, or radiotherapy treatment sessions. SRS was introduced in 1951 by Lars Leksell as an alternative approach to whole-brain radiotherapy, which is associated with significant neurotoxicity\textsuperscript{131}. SRS is a precise method of radiation therapy that targets the tumor while minimizing damage to surrounding normal brain parenchyma. SRS delivers high energy x-rays, gamma rays, or protons. In oncology, SRS is used to treat smaller tumors\textsuperscript{129}. In contrast, FRT is used in instances where a tumor cannot be treated with a single fraction, and therefore delivers radiation in multiple smaller doses over the course of a treatment cycle. Given that recurrence is frequently a concern, even after Simpson grade I resection of a meningioma, adjuvant radiotherapy is often integrated in the management of meningiomas with a high likelihood of recurrence. The aim is that radiation will destroy neoplastic cells that remain following surgical resection. It is recommended that WHO grade 2 meningiomas that have undergone subtotal resection (Simpson grade 4 or 5) receive FRT and WHO grade 3 receive adjuvant radiation regardless of the resection extent\textsuperscript{129}. It is generally accepted that radiation therapy is not standard practice for WHO grade 1 meningiomas, except under circumstances that render a tumor unresectable. Radiotherapy, in addition to chemotherapy and immunotherapy, and its role in the management of meningiomas is an active area of research. At this time, all three categories of therapy have numerous clinical trials underway.
III. The Brain Tumor Segmentation (BraTS) Challenge

The primary method for diagnosing meningiomas is MR imaging which produces high-resolution images and can provide information on tumor volume, location, and intra- or peritumoral features (i.e., necrosis, calcifications, edema). There still is, however, a need to improve the radiological assessment and evaluation of meningiomas. Traditional MR cannot reliably provide information on tumor grade, aggressiveness, likelihood of recurrence, or predictions on overall survival\textsuperscript{116}. Improvement to the assessment of diagnostic imaging in an effort to fill these gaps will facilitate a more patient-specific approach to management.

Tumor segmentation is a tool routinely used in treatment planning and post-treatment monitoring by neurosurgeons, neuroradiologists, and radiation oncologists. Segmentation refers to the process of creating a 3-dimensional outline for a tumor in PACS. Segmentation can provide data on tumor volume and is useful method for monitoring tumor size in the long term. Manual segmentation is a time-intensive process that is also prone to bias. More recently, automated segmentation has shown potential as a clinically viable option for providing objective assessments of tumor volume to aid in treatment planning. Automated segmentation, however, is an algorithm-based process that requires representative training data for machine learning and is tumor-specific. Most tumor segmentation models and studies to date have primarily focused on gliomas\textsuperscript{132}. In short, glioma models would not function properly or its full potential if applied to meningioma MR scans. Meningiomas differ radiologically from gliomas and require another set of technical considerations for segmentation (i.e., extra-axial location, multiplicity, and higher likelihood of involving the skull base)\textsuperscript{132}. 
The Medical Image Computing and Computer Assisted Intervention (MICCAI) Brain Tumor Segmentation (BraTS) challenges are a series of initiatives that focus on developing open-source CNS tumor segmentation tools. This is accomplished by building a retrospective multi-institutional database that accrues annotated medical images for a specific lesion or group of lesions. Challenge participants then develop segmentation algorithms that are evaluated for performance using standardized quantitative metrics, which are used across all BraTS challenges for that year. Since 2012, the BraTS Challenge has been a leader in machine learning methods to segment adult glioblastomas.

In 2023 several BraTS challenges have been published: Focus on Pediatrics (CBTN-CONNECT-DIPGR-ASNR-MICCAI BraTS- PEDs)\textsuperscript{133}, Brain Metastasis Segmentation on Pretreatment MRI\textsuperscript{134}, Intracranial Meningioma\textsuperscript{132}, Glioma Segmentation in Sub-Saharan Africa Patient Population (BraTS-Africa)\textsuperscript{135}, and Brain MR Image Synthesis for Tumor Segmentation (BraSyn)\textsuperscript{136}. We contributed to the meningioma challenge by providing annotated and segmented cases where they will be consolidated into a training dataset used for model development of an automated segmentation tool specifically for preoperative meningiomas. As a result of this work, I have been listed as third co-author in Data Descriptor publication\textsuperscript{137} for the dataset as well as a co-author in The ASNR-MICCAI Brain Tumor Segmentation (BraTS) Challenge 2023: Intracranial Meningioma publication\textsuperscript{132}. As discussed in further detail in a later section, submitted cases for this project pre-contrast T1-weighted, post-contrast T1-weighted, T2-weighted, and T2-weighted FLAIR series. Meningioma sub-regions of interest included enhancing tumor, non-enhancing tumor core, and surrounding FLAIR hyperintensity (Figure 9).
IV. Data, Medicine, and Radiomics

Robust imaging-based databases are critical for development of novel artificial intelligence algorithms that analyze medical imaging. In recent decades, there has been a drastic increase in computational power and accessibility to medical mega-data, which have facilitated the growth of AI and its applications in medicine. According to estimates by the Organization for Economic Cooperation and Development, in the United States alone approximately 80 million CT and 34 million MRI scans are performed yearly\textsuperscript{138}. As trends to improve the efficiency and accessibility to medical imaging continue, these figures are likely to grow. On one hand, this increase in volume can put a strain on practicing radiologists, resulting in burnout\textsuperscript{139,140}. A silver lining, however, is that from the perspective of AI access to such volume of images can be advantageous and provide an avenue to better manage trends of increasing imaging volume.
Similar to proteomics, genomics, and metabolomics, radiomics is a large-scale quantitative approach to medical imaging. Specifically, radiomics is the extraction of features from medical images that are then used to gather clinically relevant information. Medical images harbor hundreds to thousands of features that are invisible to the naked eye and quantitative analysis of these features can be used for diagnosis, prognostication, disease monitoring, or characterization. Extracted features can be divided into classes: statistical, shape-based, model-based, texture-based, and transform-based. As it relates to AI, methods of DL and ML are commonly used in radiomics pipelines. Preset algorithms are trained using images that are representative examples of a specific radiologic findings (e.g., glioma, meningioma, brain metastases) that include shape, intensity, and texture. Imaging data can be two-dimensional (e.g., ultrasound images) or multi-section volumetric (e.g., CT, MRI, PET).

Interest in radiomics has skyrocketed over the last several years. A query for ‘radiomics’ on PubMed found 2,831 and 2,882 results in 2022 and 2023, respectively. In contrast to 524 results just five years ago in 2018. Applications of radiomics are seen across specialties and disciplines in medicine (e.g., immunotherapy, gastroenterology, and neurology) and providing predictions on prognostics, outcomes, and etiology. Radiomics has also been extensively utilized in oncology as a complimentary tool to improve cancer diagnosis, treatment evaluation, and prognosis predictions.

Machine learning is the most common approach to radiomic-based prediction models and is a field of AI that focuses on developing algorithms to best represent data. Machine learning commonly follows a workflow of three overarching steps are: Data
Processing, Modeling, and Deployment (Figure 10). In the context of radiomics, different terminology is used but the same general principle is the same. For radiomics, this workflow is as follows: (i) data acquisition and preprocessing; (ii) tumor segmentation; (iii) feature extraction; and (iv) model construction. A paper published by Avery et al. provides an overview on the workflow and analysis process in radiomics.\textsuperscript{144}

![Figure 10. Schematic of machine learning workflow.](image)

For model development each step is dependent on the one that precedes it, as such data acquisition and preprocessing represent the most critical steps in the process. Originally, data for radiomics came from CT images, but has since expanded to other modalities (e.g., MR, PET, and ultrasound).\textsuperscript{145} Acquiring enough data to draw a reliable conclusion can be challenging, especially in the context of medical images. Logistically, manually collecting medical images is a time-consuming process and may be a limiting factor if there is insufficient volume at an institution. To overcome this, data sharing and access to big data for research is warranted. Examples of large-scale data sharing available for public use include The Cancer Genome Atlas Program (TCGA)\textsuperscript{146} and ImageNet Large Scale Visual Recognition Challenge (ILSVRC)\textsuperscript{147}. 
Once enough raw images are acquired from a target population, the region of interest (ROI) or volume of interest (VOI) can be annotated for two- and three-dimensional data of brain tumors, respectively. Segmentation can be accomplished manually, though automated segmentation tools for specific lesions, as previously discussed, are in development and well-documented in the literature\textsuperscript{148-150}. Common software used include 3D Slicer, FreeSurfer, ITK-SNAP, ImageJ, as well as deep learning-based algorithms such as U-Net, and iW-Net\textsuperscript{144}. Many of these software are also commonly used to automated image pre-processing. This is a critical step to increase the reproducibility of the model given research groups may use different imaging protocols and scanning equipment. Pre-processing can include interpolation to isotropic voxel spacing, range re-segmentation, intensity outlier filtering, and discretization of voxel intensities\textsuperscript{144}.

There are hundreds to thousands of radiomics features that can quantify characteristics of a medical image. The guidelines by the Image Biomarker Standardization Institute are commonly used as a standard used by researchers\textsuperscript{151}. The Image Biomarker Standardization Initiative (2020) validated reference values for 169 radiomics features thus providing a benchmark for validation of radiomics software\textsuperscript{151}. It is also important to note that depending on the research question, only a portion of the radiomics features will be applicable. The process of feature filtering and selection is referred to as dimensionality reduction. Features that are ultimately excluded are those that correlate with other features and features that lack reproducibility. Standards for evaluating feature relevance and reproducibility are also available for this step\textsuperscript{152}. 

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Finally, model construction is the step that utilizes image data in machine learning. Supervised learning is a common approach for ML\textsuperscript{153}. Other approaches in ML include unsupervised learning and reinforcement learning\textsuperscript{154}. Supervised learning (e.g., regression and classification tasks) approaches in ML use data with known input-output behavior to train a system to identify patterns and desired relationships when applied to new data. The accuracy of radiomics-based models can be evaluated by the receiver operating characteristic (ROC) of the area under the curve (AUC). A system is ‘learning’ if the accuracy of the model on the training set and validation set are both increasing and converging\textsuperscript{153}. The validation set is a separate dataset but is ideally similar to the training dataset. This is analogous to practice questions as preparation for an examination that tests performance using a different set of questions on the same concepts. This is a critical step in assessing the generalizability and robustness of a model.

Radiomics is a popular topic in the literature with several applications in image-based disciplines with both DL and ML approaches. However, as a field, there are challenges and limitations that require consideration. First, radiomics is an analytical technique that requires large dataset for the training process. This is especially true for DL-based models, which, in general, requires more datapoints to accomplish complex tasks\textsuperscript{155,156}. Moreover, in order for a model to be clinically applicable, it must be generalizable. Generalizability is dependent on many factors throughout the radiomics process, including data acquisition and image processing which do not have a standardized protocol\textsuperscript{144}. While there are common guidelines that are followed for different stages, a lack of standardization limits the reproducibility as well as the generalizability of a prediction model\textsuperscript{151,152}. Other important inconsistencies that can
negatively affect model performance are image quality (e.g., a patient moving during a
scan) or the usage of different scanning equipment between institutions or research
groups. To minimize such effects, accepted standards for image acquisition, data
processing, and internal/external validation protocols in radiomics-based studies are
warranted.

V. Statement of Research Methods

The first aim of this thesis is to compile a representative cohort of meningioma
patients with annotated MRI scans to contribute to the training dataset for the BraTS
challenge. Patients in this cohort were treated with surgical resection for meningiomas at
Yale-New Haven Hospital. Following surgical resection, patient tumors were
subsequently analyzed and assigned a CNS WHO grade as well as a pathology report.
Documentation of grade and pathology reports were compiled by a collaborating research
group into a parent Excel spreadsheet along with the genetic composition of the tumor
and patient demographics.

A secondary goal of this thesis was to develop an approach for relational database
curation using an EMR-linked PACS-integrated tool that allowed for organization and
storage of patient-specific clinical and image-based data.

Va. Patients

In this HIPAA-compliant IRB-approved retrospective study, medical records
from 583 meningioma patients treated with surgical resection from 2008-2022 were
reviewed. Clinical parameters of interest included age at diagnosis, sex, CNS WHO grade, and histological subtype of resected tumors.

Vb. Image Acquisition and Preprocessing

The requisite images for pre-processing were preoperative pre- and post-contrast T1-weighted (T1w) and Fluid-Attenuated Inversion Recovery (FLAIR) sequences on MR. MRI studies that lacked these sequences or were incomplete were not segmented. Imaging studies were viewed in Visage 7.1.18 Client (64-bit, build 3822) PACS and could be accessed through the EPIC medical record. If a study met the inclusion criteria, it was then transferred as DICOM files from the clinical Visage server to the Visage research server used by our lab group. Transferred DICOM studies were automatically deidentified with a de-identified alphanumeric code unique to each patient. In a separate document, patient medical record numbers (MRNs) were matched with the corresponding de-identified code for organization purposes and later entry of clinical variables.

Vc. Segmentation and Annotation

3-dimensional image segmentation was generated using Visage Client 7.1.18 (64-bit, build 3822) PACS software. Segmentations were on pre-/post-contrast T1w and FLAIR images in the axial view. T1 sequences included higher resolution magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) gradient recovery/inversion recovery (GR/IR) or T1 spin echo (SE). The thickness for MP-RAGE sequence slices ranged from 0.9mm to 1mm and slices for T1 SE sequences ranged from 2.5mm to 5mm.
Segmented regions of interest (ROIs)/volumes of interest (VOIs) included tumor core alone and tumor core with peritumoral edema. The tumor core was segmented in the MP-RAGE or T1-post contrast SE sequences and labeled accordingly. Tumor core in MP-RAGE sequences were labeled as “Core_PGGE” while the segmented tumor core in the SE sequences was labeled as “Core_PGSE”. The abbreviations “PGGE” and “PGSE” refer to the corresponding sequence: post-gadolinium gradient echo and post-gadolinium spin echo, respectively. On FLAIR, peritumoral edema in addition to the tumor core was segmented and designated “Whole_FLAIR” (Figure 11).
**Figure 11.** Axial tumor segmentations of (A) tumor core on post-contrast T1-weighted imaging and (B) tumor core plus peritumoral edema on FLAIR.
Vd. Clinical Data Questionnaire

The clinical questionnaire created for integration into the Visage research server was created using the Form Builder for LHC-Forms/FHIR Questionnaire through the Lister Hill National Center for Biomedical Communications (LHNCBC) of the National Library of Medicine website (Figure 12). As a pilot questionnaire for data entry in future relational database projects, clinical variables available for documentation in the questionnaire are as follows: Genomic mutations, MRN, accession number, surgery state, date of birth, race, ethnicity, sex, zip Code, weight, deceased (i.e., yes/no), diagnosis date, diagnosis age (i.e., age of the patient when diagnosed), genetic predisposition (i.e., congenital genetic disorders predisposing the individual to meningioma formation), anatomic location, axial location, coronal location, tumor volume, edema, prior radiation, radiation induced, neoadjuvant radiation, post-operative radiation, extent of resection (i.e., gross total resection or subtotal resection), Simpson grade, CNS WHO grade, histology, brain invasion, mitotic count, increased cellularity, spontaneous necrosis, small cells with high N/C ratio (i.e., nucleus/cytoplasmic ratio), macro-nucleoli, sheet-like growth, Ki-67, recurrence, last imaging date, time to last imaging (i.e., time from Date of Surgery to Last Imaging Date), last datum (i.e., date of last confirmed interaction with patient), lost to follow-up, progression-free survival, overall survival, radiology report, pathology report, and radiation oncology report.
VI. Statement on Results

In this thesis we aimed to contribute as many quality segmentations as possible to the BraTS Challenge to aid in the development of meningioma-specific segmentation tools. Of the 583 patients in the parent dataset provided by one of our collaborators, 390 patients met the inclusion criteria for segmentation. After submitting the cases to the BraTS Challenge, our aim was to use a radiomics approach to extract features from these studies in an effort to identify a radiologic biomarker that could be used to predict the proliferative potential of meningiomas.
In tandem with our work on the meningioma segmentation project, we also
dedicated time towards creating a workflow for developing a relational database with our
meningioma dataset. The result of that project is a novel approach of a FHIR-based
PACS-integrated tool for data collection that increases the feasibility of generating
datasets large enough for deep learning purposes (Figure 13).

The final result of these two projects is an EMR-linked relational database of 390
annotated meningioma MRI scans with a PACS-integrated tool for clinical data
collection of preoperative variables. In total, 390 patients included in the annotated parent
dataset, with a mean age at diagnosis was 57.32 ±13.68 years and a composition of 280
females (71.8%) and 110 males (28.2%). The CNS WHO grades distribution was as
follows: Grade 1, 266 patients (68.2%); grade 2, 122 patients (31.3%); and grade 3, 2
patients (0.51%). The three most common histological subtypes were meningothelial (87
patients, 22%), atypical (92 patients, 24.9%), and transitional (36, 9.2%).

Of the 390 cases that were annotated, 230 were included in the final BraTS
dataset. The cases were subsequently split into a training set (160, 70%), validation set
(23, 10%), and a testing set (47, 20%). The median age in this cohort was 57 years with a
range of 20-92 years and had a composition of 69 males and 161 females. The CNS
WHO grade distribution was grade 1, 157 patients (68.2%) and grade 2, 71 patients
(30.9%) (Table 3).
Table 3. Preliminary clinical and demographic data for the 2023 BraTS Meningioma Dataset cohort. Site abbreviation are as follows: DUKE (Duke University); JEFF (Thomas Jefferson University); MISS (Missouri University); PENN (University of Pennsylvania); UCSF (University of California, San Francisco); YALE (Yale University). Values for cells labeled “N/A” have not yet been determined. Table adapted from LaBella et al\textsuperscript{137}.

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<th>Validation Set</th>
<th>Testing Set</th>
<th>Age (Median; Min-Max)</th>
<th>Male: Female</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>1424</td>
<td>1000 (70%)</td>
<td>141 (10%)</td>
<td>283 (20%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>DUKE</td>
<td>452</td>
<td>315 (70%)</td>
<td>46 (10%)</td>
<td>91 (20%)</td>
<td>65 (19-96)</td>
<td>115:337</td>
<td>115</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>JEFF</td>
<td>338</td>
<td>236 (70%)</td>
<td>34 (10%)</td>
<td>68 (20%)</td>
<td>60 (19-90)</td>
<td>114:224</td>
<td>292</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>MISS</td>
<td>181</td>
<td>132 (73%)</td>
<td>16 (9%)</td>
<td>33 (18%)</td>
<td>64 (14-89)</td>
<td>38:143</td>
<td>171</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>PENN</td>
<td>44</td>
<td>31 (70%)</td>
<td>4 (9%)</td>
<td>9 (20%)</td>
<td>59 (21-87)</td>
<td>21:23</td>
<td>0</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>UCSF</td>
<td>180</td>
<td>126 (70%)</td>
<td>18 (10%)</td>
<td>35 (19%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>YALE</td>
<td>230</td>
<td>160 (70%)</td>
<td>23 (10%)</td>
<td>47 (20%)</td>
<td>57 (20-92)</td>
<td>69:161</td>
<td>157</td>
<td>71</td>
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</tr>
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VII. Discussion

VIIa. FHIR Webforms

Fast Healthcare Interoperability Resources (FHIR) is a standard developed by the Health Level 7 (HL7) organization and is a set of rules that define specifications for exchange of data in electronic health records (EHRs). FHIR resources are healthcare concepts with a known location and defined meaning. Resources refers to exchangeable discrete units of data and represents the building blocks of FHIR. There are currently 145 resource types supported by FHIR (e.g., XML, JSON). For this thesis, we leveraged the use of LHC-forms, which can be integrated into our PACS to facilitate curation of a...
relational database. LHC-Forms is an open-source JavaScript widget that creates data input forms using the Logical Observation Identifier Names and Codes (LOINC) model. LOINC is a terminology system for identifying health measurements, observations, and documents. This system is an international standard funded by United States federal agencies and organizations. For healthcare interoperability, data input to LHC-Forms can be exported as either a JSON structure or as FHIR resources, which is accessible on any device regardless of the operating system (e.g., Windows, Android).

Figure 14. Schematic overview of FHIR resources serving as a bridge between PACS and the EMR.

By leveraging the flexibility of FHIR resources, we provide an avenue for developing an EMR-linked relational database where DICOM images can be securely transferred and stored with associated patient-specific clinical variables within a PACS research server. With this method, we are able to reduce, or eliminate, the need for external software that are traditionally used for clinical data entry (e.g., Excel). Utilization of this software for the manual entry and storage of clinical data is inefficient, prone to errors, and results in a disjointed workflow given that multiple users cannot simultaneously interact with the data in real-time. This approach also increases the
feasibility of using image-based measurements and features to augment traditional clinical-only/clinical-weighted staging and treatment response prediction algorithms (Figure 15).

![Diagram of ensemble model development of clinical data augmented with image-based measurements.](image)

**Figure 15.** Schematic overview of ensemble model development of clinical data augmented with image-based measurements.

**VIIIb. The BraTS Challenge**

AI is a broad term that refers to a branch of computer science that deal with machines performing complex tasks that other require human intelligence. As it pertains to healthcare, Mascarenhas et al. succinctly outline the goals of AI$^{135}$: (i) offer patients more personalized healthcare; (ii) improve diagnostic/prognostic accuracy; (iii) reduce human error in clinical practice; and (iv) reduce time burdens on clinicians improve overall efficiency of healthcare.

Machine learning and deep learning (DL) are subsets of AI. DL is an extension of machine learning that is modelled on the structure of neurons in the brain. Through
artificial neural networks with “hidden” layers, DL models are able to continually learn and incorporate acquired knowledge to improve performance and solve complex problems. DL models have provided state-of-the-art-performance in medical image-based tasks, such as classification, image segmentation, and object detection. DL, in general, is the most demanding branch of AI in terms of data. Models are highly effective when the training dataset is large. For the ImageNet Large Scale Visual Recognition Challenge (ILSVRC), contained over a million images available to train DL image recognition models. In reality, the data requirement for DL can be a severe limitation in accessibility. Medical datasets tend to be relatively small, oftentimes containing only hundreds to thousands of data entries. In radiology, these limitations are readily apparent in pathologies with a low incidence. There are few methods to circumvent or overcome insufficient data, but one of the most practical solutions is the emergence of open-source datasets that can be expanded by contributions across the country. Although not open-source, databases such as the ACS National Surgical Quality Improvement Program (NSQIP) and PearlDiver are examples of large-scale national data aggregation. The BraTS Challenge takes a similar approach, though for CNS lesions.

The purpose of the BraTS challenge is to provide a repository of standardized, representative data to develop automated segmentations tools optimized for a specific lesion. This is achieved through a crowd-sourcing and collaborative method. Since its inception in the early 2010, BraTS challenges have been a premier resource for CNS tumor imaging data. As more attention is drawn to automated segmentation, datasets for machine, and clinical applicability, resources such as BraTS will increase in their utility.
Up until now, many tumor segmentation studies have focuses on gliomas. However, these tools are not readily applicable for the segmentation of meningiomas, which are more circumscribed, more likely to present as multiple lesions, and have a propensity for extension into the skull. When taken into consideration, these factors raise technical challenges for segmentation, which are foundational to radiomics-based studies.

As discussed, traditional MRI are insufficient in determining tumor grade or expected clinical course. Given that MRI is the primary diagnostic tool for meningiomas, which can often be diagnosed with imaging alone, the reliance on the information obtainable by radiologists from this modality drastically increases. Therefore, improvement to the radiographic assessment of meningiomas is needed, as it can benefit patient care by providing a more individualized approach. This also underscores the importance of developing tools to help facilitate radiomics studies to better understand quantifiable features that are invisible to the naked eye. The ability to predict meningioma behavior, such as aggressiveness in a preoperative setting would greatly benefit surgical planning as maximal resection is the gold standard for treatment that minimizes likelihood of recurrence\textsuperscript{132,166}. To bridge this gap, substantial effort is still required at the ground level: increasing accessibility to large-scale medical imaging data to facilitate the development of tools with downstream clinical implications.

Data collection for the meningioma challenge was a multi-institutional effort, with participating institutions that included Duke University, Yale University, Thomas Jefferson University, University of California, San Francisco (UCSF), Missouri University, and University of Pennsylvania. The approximate case contribution for each participating site, respectively, was as follows: 450, 400, 350, 200, 200, and 50, for an
approximate total of 1650 meningioma cases. The analysis results for model performance in the 2023 meningioma challenge have not been released yet, but participation and engagement in previous challenges are encouraging\textsuperscript{167}.

VIIc. Challenges and Limitations

There were several challenges and limitations in our study. Manual tumor segmentation on MR scans is a time-consuming process. For each of the 390 cases included in this project, each imaging study contained multiple sequences to be segmented (pre- and post-contrast T1-weighted images and T2/FLAIR), resulting in approximately 1000 structures being segmented. Manual segmentation is also more prone to errors and inter-operator variability. Automated segmentation reduces the observer bias and increases segmentation speed, though manual oversight is still required. Moreover, if segmentations are completed by students or other non-radiologist personnel, verification of the segmentation quality and accuracy by a board-certified radiologist is required. In a large-scale dataset, the verification process alone requires a significant time investment (Figure 16).

From a technical perspective, there are significant challenges in radiomics related to data acquisition and processing. Currently there is no standardized procedure for data acquisition and analysis, which can introduce difficulties with reproducibility and subsequent variation. Another technical challenge involved image acquisition and patient MR scans. The sequences that were segmented for this thesis are typical of a standard MR protocol (T1-weighted and T2/FLAIR), though the quality of the studies, as well as the completeness, varied. While reviewing patient’s EMR, a number of studies,
particularly the earliest in the dataset had MR sequences missing from the study or no documentation for a preoperative MR. This was likely a consequence of the patient having exams completed at outside facilities. Secondly, in a subset of studies the quality of the images were low, usually due to patient movement distorting the images. These studies were excluded from segmentation.

**Figure 16.** Overview of developing the meningioma relational database with a PACS-integrated tool for organization of clinical variables with the corresponding patient-specific imaging.

**VIId. Future Directions**

The future directions for this project can be summarized by the following steps: (i) completion of segmentations; (ii) segmentation corrections and approval; (iii) model development; (iv) radiomics feature extraction; and (v) develop meningioma-specific prediction model. The first step is to finish segmentations of the cases in the parent dataset. In addition to segmenting all the necessary sequences, it can be valuable to perform a second pass of the dataset to ensure all cases that meet the criteria are included.
and to reduce the number of cases that may have been discarded in error. The time investment for the manual segmentation of these sequences varies, with large tumors that demonstrate a range of signal intensities on MR and FLAIR sequences demanding the greatest amount of time and effort. Depending on the experience and number of annotators, this step can be completed in about two weeks, provided no additional cases are added to the dataset.

Following the completion of segmentations, it is imperative that a ground truth of the segmentations is established based off the consensus of two board-certified neuroradiologists. Manual segmentation, as previously discussed, is prone to bias, particularly inter-observer bias. Due to the observational nature of image segmentation, wherein the nuances of what may constitute as tumor, edema, or necrosis may vary slightly by annotator, this can lead to inconsistencies across annotations in a dataset. To limit the effects of this bias, two neuroradiologists are required to review, correct, and approve each of the preliminary annotations. The approval process is accomplished following an established model used in prior BraTS challenges. For cases where inaccuracies are identified by one of the reviewing radiologists, the case can be subsequently assigned to a different annotator or returned to the case pool for revisions and feedback concerning any possible remaining inaccuracies. If necessary, this can be repeated until segmentations meet the approval criteria of the reviewing radiologists. Manual corrections for this step can be accomplished using ITK-SNAP, an open-source software application used to segment structures in 3D medical imaging.

Once the parent dataset of annotated images is complete and has undergone necessary corrections for approval, a segmentation algorithm must be developed to
automate the segmentation process. This can be accomplished by training the nnU-Net semantic segmentation model, or the original model, U-Net. The nnU-Net (“no new U-Net”) model is a deep learning convolutional neural network method that has been validated as an accurate tool for 2D or 3D imaging modalities. In addition to the object identification and image segmentation capabilities common to both U-Net and nnU-Net, an advantage of nnU-Net is the increased generalizability. In general, U-Net models are specific and require a greater amount of manual input regarding design elements for a given segmentation task, resulting in a more computationally demanding process. In contrast, nnU-Net analyzes training datasets and automatically configures a matching U-Net-based architecture segmentation pipeline, thereby reducing the expertise requirement of the researcher. For the development of an nnU-Net meningioma segmentation tool, this will require the parent dataset of annotated images to be divided into training, validation, and testing datasets. To limit the possibility of bias, the data must be split randomly. Due to the importance of having sufficient amounts of data for the training phase, 70% of the dataset will be training data, 10% will be validation data to evaluate model performance, and 20% will be a testing dataset, which can used for performance evaluation on validated models that were trained using external datasets.

To ultimately develop a prediction algorithm using the meningioma dataset, radiomics features must first be extracted. There are thousands of radiomics features that can be extracted from the segmented images. Feature extraction can be performed using PyRadiomics, an open-source python package for the extraction of radiomics features from medical imaging. Common categories of radiomics features include first-order, shape-based, gray-level matrices (co-occurrence, run length, size zone, dependence), and
neighboring gray tone difference matrix. To streamline this process, PyRadiomics can also be integrated into the Visage PACS client for feature extraction on previously segmented images. It is important to note that segmentation can also be done within PACS using a separate algorithm\textsuperscript{171}.

Among the array of extracted features, a subset can be redundant or non-reproducible and must be discarded. Relevant features will need to be identified and validated for robustness by confirming the same features can be extracted at different time points\textsuperscript{171}. Zero error, or differences in extracted features, among these separate extraction steps would support the reproducibility and robustness of the associated features. Given that this dataset can be expanded as more patient studies are identified, a PACS-integrated tool may be a favorable approach to facilitate this growing library of annotated meningioma studies. These studies can provide additional training data for current models or be reserved in a library as testing data as new models trained on external data becomes available. In conjunction with the integrated FHIR questionnaire, this can create a readily expandable, comprehensive database for future projects that leverage image-based measurements in addition to clinical data.

Finally, using machine learning algorithms, we can use the existing dataset to develop a model to predict Ki-67 and WHO grade of meningiomas. While the vast majority of meningiomas are low-grade\textsuperscript{7}, this parameter cannot be readily determined by imaging alone. Similarly, levels of Ki-67, an immunohistochemical biomarker for cell proliferation, cannot be determined radiologically. As a biomarker, Ki-67 can be an important prognostic parameter for recurrence and progression in meningioma patients, both of which can be important factors that influence management\textsuperscript{172}. By leveraging the
information obtained from extracted radiomics features, we can develop a model to predict these parameters by using a training dataset where these values are known. There are numerous machine learning approaches for classification and prediction, with common examples including decision trees, random forests, support vector machines, k-nearest neighbors, neural networks, linear and logistic regression, naïve Bayes, and ensembles\textsuperscript{154}. For this project, extreme gradient boosting (XGBoost)\textsuperscript{173}, a decision tree-based machine learning algorithm that is compatible with python, can be used. Ideally, in the training phase, the algorithm will develop an input-output relationship specifically for Ki-67 and WHO grade such that on a validating dataset the model is able to demonstrate high prediction accuracy and overall robustness. In this scenario, because of the high dimensionality of radiomics features, the speed and use of parallel decision trees for model optimization makes XGBoost a favorable option.

**VIII. Conclusion**

Computational tools for the analysis and automated segmentation of meningiomas are lacking. In this thesis we curated and manually segmented 390 preoperative MR scans of patients treated for meningioma at Yale-New Haven Hospital. We also contributed the imaging in HIPAA compliant de-identified and skull stripped manner to the multi-institutional BraTS Challenge for development of generalizable algorithms that are applicable to different institutions. This work has resulted in co-authorship for two publications associated with the meningioma BraTS challenge\textsuperscript{132,137}.

Segmented regions include the tumor core on T1-weighted imaging and peritumoral edema on FLAIR. These segmentations will be used in the training of
computational models via machine learning to ultimately automate this process while demonstrating high accuracy for detection of the tumor regions. This, in turn, will improve segmentation speed for future meningioma-specific research and model development. Finally, we have presented a novel approach for constructing datasets that combine imaging features and clinical characteristics. This will bridge the gap between PACS and EMR and thus improve the feasibility of large-scale projects. Additionally, FHIR webform will provide research groups with unique flexibility by allowing for the exclusive collection and storage of variables with relevance to the research question. We believe this approach will foster safe transfer of clinical data by eliminating the need for external software for storage and will increase the feasibility of creating and utilizing large datasets that are needed for clinically relevant deep learning applications.
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