

**QUANTITATIVE SUSCEPTIBILITY WEIGHTED
IMAGING (SWI) IN GRADING OF INTRACRANIAL
MASS LESIONS AND ASSESSMENT OF ACUTE
ISCHEMIC STROKE PENUMBRA**

RUPSA BHATTACHARJEE



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

OCTOBER 2021

Indian Institute of Technology Delhi (IITD), New Delhi, 2021

**QUANTITATIVE SUSCEPTIBILITY WEIGHTED
IMAGING (SWI) IN GRADING OF INTRACRANIAL
MASS LESIONS AND ASSESSMENT OF ACUTE
ISCHEMIC STROKE PENUMBRA**

by

RUPSA BHATTACHARJEE

CENTRE FOR BIOMEDICAL ENGINEERING

Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

OCTOBER 2021

Dedicated to,

Baba, Maa, Aju & Tarun!



CERTIFICATE

This is to certify that the thesis entitled, “**Quantitative susceptibility weighted imaging (SWI) in grading of intracranial mass lesions and assessment of acute ischemic stroke penumbra**”, submitted by **Ms Rupsa Bhattacharjee (2016BMZ8112)** for the award of the degree of the **Doctor of Philosophy**, to the Centre for Biomedical Engineering, Indian Institute of Technology Delhi, is a record of the bonafide research work carried out by her under my supervision and guidance. She has fulfilled the requirements for submission of this thesis, which to the best of my knowledge, has reached the requisite standard. The contents of this thesis have not been submitted in part or full to any other university or institute for the award of any other degree or diploma.

(Dr. Anup Singh)

Associate Professor

Centre for Biomedical Engineering

Indian Institute of Technology Delhi

New Delhi – 110016, India

Date:

New Delhi

Acknowledgements

I would like to take this opportunity to set aside the focus from the scope of the thesis and put the spotlight on some of those very important people. I will start by thanking my supervisor Dr Anup Singh. Sir didn't just guide me in the research by framing the critical questions or interpreting the outcome of our analysis, he rather stood beside me as a friend when I needed to hear words of encouragement, inspired us with his example, took us to tea and pizza breaks whenever we were tired of long hours in the lab. Sir always has provided me with a fresh new perspective/feedback of every piece of work and shown confidence in my capabilities, which I believe has shaped my thesis in unexpected but impactful ways. I would like to thank Kiran Maám and Vihaan for hosting us at odd hours always with the biggest smile, largest spread of snacks and nonstop hours of conversions and stories at their nest.

I would hereby extend my heartfelt thanks to the committee members. Prof. Veena Koul has always inspired us to believe we can achieve as much as women in science by working equally or doubly hard if need be, without any excuses. Prof. Kedar Khare has been the most inquisitive person on the committee with always asking questions I didn't know. It made me go back and study harder to be better prepared for the next meetings. Prof Amit Mehndiratta has constructively criticized my work in progressive years of SRC meetings to make it sounder technically and clinically, with questions and suggestions which led the overall work to a much solid outcome. I would also like to express my gratitude to all the faculty and staff members in our department.

I am especially indebted to Dr Rakesh Kumar Gupta, HOD and Director of Radiology Department in Fortis Memorial Research Institute. He has always taught me to start with the clinical idea or need/existing gaps in current research frameworks, to think about how these works can lead to outcomes that are necessary for radiologists to use and has provided me with real-time honest feedback and guidance, crucial for a novice researcher. I would be always thankful to Mr Karthick Raj, my friend and first reporting manager for the duration in Philips Healthcare, who has been extremely patient in guiding and mentoring me into understanding MRI when I first entered this domain eight years back. I am thankful to Dr Indrajit Saha, Clinical Scientist, Diagnostic Imaging, Philips India Limited and for being the toughest critic and mentor, providing wonderful suggestions both professionally and personally. His wife Dr Barnali Saha has been the elder sister for me in this city away from home, always feeding me her delicacies with immense

love. I would also like to express my gratitude to all my colleagues in Philips India Ltd., who over the past eight years have provided me with the friendliest and resourceful working environment and have honestly pat my back for every small achievement I have ever made.

I cannot thank my friends/colleagues in IIT MedImg and Fortis enough: Prativa, Sneekha, Rafeeq, Dharmesh, Sameer, Banasmita, Mamta, Anandh, Suhail, Archana, Neha, Ayan, Eshadi, Anirban, Virender, Rakshit, Sandeep, Ankit and Raufiya. I have shared many wonderful conversations, enjoyable and affectionate moments, innumerable WhatsApp chats and intense research discussions with them over a cup of tea or a slice of pizza, those have made my time in research colorful and every bit worth remembering. A special mention to Dinil, who has been a brother, a fellow friend for the last five years. We have solved problems, enjoyed paper acceptances (and rejections too), have had thoughtful discussions beyond research and progressed together. He has always been a phone call/text away whenever I needed his support for anything.

I have been encouraged, sustained, inspired, and tolerated by the greatest group of people and cheerleaders in my life than anyone ever had. My little brother, Aju, has been my arch-nemesis and my favorite person under the sky both at the same time. I have no words of gratitude for my dear husband, Tarun. I have truly been lucky to have him holding my hand in this tough PhD journey, always believing in me, in “us”, ever putting me and my priorities first, ever diluting all my problems with the poorest joke under the sun. This thesis is his as much as mine. Nupur, my best friend, has always been there putting many hats of a guide, a sister, a travel partner, a philosopher and a therapist, a teacher and whatnot. Her presence has given me the comfort of being understood, being home. My pseudo-family: Samapika, Sudipta, Saheli, Jackson, Mudasir, Peeyush and Prateek who have had more faith in my abilities than I can ever imagine. My extended family, in-laws, uncles, aunts and cousins have applauded me even for my smallest achievements.

In the end, I thank my parents, Baba, and Ma for building me up literally from ground zero into the person I am today. Baba has taught me the value of truth, integrity, kindness and stimulating conversations, that there is always room for progress at whatever I do. Ma has led me by the example of a perfect working woman balancing all the tough balls putting up the largest smile on her face. Like Sheldon Cooper would have hoped me saying, I know I haven't been the student, friend, wife or daughter you deserve. But I want you to know in my way, I love you all.

Abstract

This PhD thesis aims to explore the novel potentials of one of the advanced MRI methods known as Susceptibility Weighted Imaging (SWI), to develop quantitative biomarkers from SWI and to finally validate their implication in routine clinical setting particularly for specific disease conditions: glioma, primary cerebral nervous system lymphoma (PCNSL), and acute ischemic stroke. The scope of this thesis results in finding unmet benefits in terms of diagnostic accuracy, confidence as well as in reducing scan time and contrast dosage. It aims for better treatment prognosis, planning and management that can benefit the patients.

The second chapter of the thesis proposes a noninvasive segmentation based quantitative approach to analyze intra tumoral susceptibility signal (ITSS) from SWI and finally calculate ITSS vasculature volume (IVV) within grades of glioma. The proposed method scores over the existing semiquantitative method in terms of ITSS estimation and grading accuracy. The current study also evaluates the role of quantitative susceptibility mapping (QSM) for segmentation of ITSS into hemorrhage and vasculature; compute QSM based IVV and compare the results with R_2^* based IVV for glioma grading. A high correlation between both these methods is found. Therefore, QSM can be used interchangeably with R_2^* to calculate IVV for differentiation between grade II vs III and grade II vs IV. For grade III vs IV, R_2^* based IVV scores better. True biological classification of ITSS is necessary to understand the tumor viability, aggressiveness, and angiogenesis. This study develops a novel quantitative approach that combines SWI, R_2^* relaxivity and DCE MRI parameters for segmenting ITSS and its further classification into biological behaviour-based subcategories.

The third chapter of the thesis, our findings suggest SWI to be the most useful sequence in the glioma grading as it contributes to calculating the IVV metric, which can singlehandedly improve the glioma grading much further when combined with radiomic analysis used in combination with PCA feature reduction and random forest ML classifier. In the case of patients where contrast injection is impossible due to renal impairments, non-contrast way of glioma grading based on radiomic analysis use of SWI alone can provide almost as good accuracy as using the combinational approach of FLAIR and SWI. This chapter explores the differences between

hemorrhage and vasculature ITSS masks regions within the tumor, assessed by SWI images involving radiomic features extraction and machine learning-based classification. This chapter also focuses on evaluating the performance of texture-based features of SWI in improved differentiation of PCNSL from grade IV gliomas which proves to be a better standalone classification method.

Objectives of the fourth chapter of the thesis are to enhance the Prominent hypo-intense vein sign (PHVS) visibility in SWI, automatically segment and quantify stroke penumbra volume from it and calculate the mismatch ratio between PHVS(SWI) and DWI. The proposed approach demonstrates a high correlation with the gold standard ASL method, suggesting that PHVS and SWI based penumbra quantification has the potential to be used as an alternative for perfusion-based methods in stroke therapy setups. It could save the scan time, does not require any contrast dose to be injected and therefore should be beneficial for acute stroke therapy management.

The author believes that the work in the thesis can help the clinicians (radiologists, neurosurgeons, and neurologists) in improved diagnosis and overall treatment planning of the patients and will also benefit the patients suffering from neuro-diseases (glioma, PCNSL, acute ischemic stroke) to be benefited from no harmful contrast dosage, lesser scan time with expected outcomes. The author sincerely hopes her work will help humanity in general.

सार

इस थीसिस का उद्देश्य विशिष्ट रोग जैसे कि ग्लिओमा, लिम्फोमा और तीव्र एक्सकेमिक स्ट्रोक के नैदानिक उपचार व्यवस्था में एसडब्ल्यूआई से विकसित मात्रात्मक बायोमार्कर की उपयोगिता की खोज करना है। इस थीसिस का परिणाम नैदानिक उपचार की सटीकता, स्कैन समय और कंट्रास्ट की खुराक को कम करने के सन्दर्भ में परिलक्षित होता है। यह थीसिस उपचार पूर्वानुमान, योजना और प्रबंधन में सहायक है, जो रोगियों के उपचार में अतिआवश्यक उपयोगिता को दर्शाता है।

द्वितीय अध्याय, एक गैर-विभेदक विभाजन आधारित दृष्टिकोण का प्रस्ताव करता है, जिसकी सहायता से इंफ्रा ट्यूमरल संवेदनशीलता संकेत (आईटीएसएस) का विश्लेषण और ग्लियोमा के ग्रेड के भीतर आईटीएसएस वास्कुलर वॉल्यूम (आईवीवी) की गणना की गयी है। प्रस्तावित पद्धति, अनुमान और ग्रेडिंग सटीकता के संदर्भ में अन्य पद्धतियों से श्रेष्ठ है। वर्तमान अध्ययन रक्तस्राव और वाहिका में आईटीएसएस के विभाजन के लिए क्यूएसएम की भूमिका का मूल्यांकन करता है। वर्तमान अध्ययन में रक्तस्राव और वाहिका में आईटीएसएस के विभाजन के लिए क्यूएसएम की भूमिका के मूल्यांकन के साथ-साथ, क्यूएसएम आधारित आईवीवी की गणना और ग्लियोमा ग्रेडिंग के लिए आर2* आधारित आईवीवी के साथ परिणामों की तुलना की गयी है। इन दोनों विधियों के बीच उच्च सहसंबंध पाया गया है। ग्रेड II बनाम III और ग्रेड II बनाम IV के लिए IVV की गणना के लिए क्यूएसएम का परस्पर उपयोग किया जा सकता है। इस अध्ययन में R2* आधारित IVV स्कोर ग्रेड III बनाम IV के लिए बेहतर पाया गया। ट्यूमर की व्यवहार्यता, आक्रामकता और एंजियोजेनेसिस को समझने के लिए आईटीएसएस का सही जैविक वर्गीकरण आवश्यक है। यह अध्ययन एक नया मात्रात्मक दृष्टिकोण विकसित करता है जो आईटीएसएस को विभाजित करने और जैविक व्यवहार-आधारित उपश्रेणियों में इसके आगे के वर्गीकरण के लिए एसडब्ल्यूआई, R2*रिलैक्सीविटी और डीसीई एमआरआई मापदंडों को जोड़ता है।

थीसिस का तृतीय अध्याय, ग्रेड IV ग्लिओमास से पीसीएनएसएल के बेहतर विभेदीकरण में एसडब्ल्यूआई की बनावट-आधारित विशेषताओं के प्रदर्शन का मूल्यांकन करने पर केंद्रित है जो एक बेहतर स्टैंडअलोन वर्गीकरण पद्धति साबित होती है। यह अध्याय ट्यूमर के भीतर रक्तस्राव और वास्कुलर आईटीएसएस मास्क क्षेत्रों के बीच के अंतरों की भी पड़ताल करता है, जिसका मूल्यांकन एसडब्ल्यूआई छवियों द्वारा किया जाता है जिसमें रेडियोमिक फीचर निष्कर्षण और मशीन लर्निंग आधारित वर्गीकरण शामिल है।

कुल मिलाकर, हमारे निष्कर्ष एसडब्ल्यूआई को ग्लियोमा ग्रेडिंग में सबसे उपयोगी और अपरिहार्य अनुक्रम होने का सुझाव देते हैं क्योंकि यह आईवीवी मीट्रिक की गणना करने में योगदान देता है। आईवीवी मीट्रिक और रेडिओमिक्स फीचर का संयुक्त विश्लेषण ग्लियोमा ग्रेडिंग को सुधार सकता है। वर्गीकरण के पहले रेडिओमिक्स फीचर का चुनाव पीसीए विधि का उपयोग करके किया गया। वर्गीकरण, रैंडम फारेस्ट विधि का उपयोग करके किया गया। उन रोगियों के मामले में जहां गुर्दे की खराबी के कारण कंट्रास्ट इंजेक्शन असंभव है, अकेले एसडब्ल्यूआई के रेडियोमिक विश्लेषण के आधार पर ग्लियोमा ग्रेडिंग का गैर-विपरीत तरीका (प्लेयर और एसडब्ल्यूआई का संयोजन) लगभग अच्छी सटीकता प्रदान कर सकता है।

थीसिस के चौथे अध्याय का उद्देश्य एसडब्ल्यूआई में पीएचवीएस दृश्यता को बढ़ाना, स्वचालित विभाजन, स्ट्रोक पेनम्ब्रा वॉल्यूम का मापन और पीएचवीएस (एसडब्ल्यूआई) और डीडब्ल्यूआई के बीच बेमेल अनुपात की गणना करना है। प्रस्तावित दृष्टिकोण स्टैण्डर्ड मानक एएसएल पद्धति के साथ उच्च सहसंबंध को प्रदर्शित करता है और यह सुझाव देता है कि पीएचवीएस और एसडब्ल्यूआई आधारित मात्रात्मक पेनम्ब्रा विधि, स्ट्रोक थेरेपी सेटअप में छिड़काव-आधारित विधियों के विकल्प के रूप में उपयोग की जा सकती है। इस विधि से स्कैन समय बचाया जा सकता है। इस विधि में कंट्रास्ट इंजेक्शन खुराक की आवश्यकता नहीं होती है और इसलिए यह विधि तीव्र स्ट्रोक थेरेपी प्रबंधन के लिए फायदेमंद है।

शोधकर्ता का मानना है कि थीसिस कार्य रोगियों के बेहतर निदान और समग्र उपचार योजना में चिकित्सकों (रेडियोलॉजिस्ट, न्यूरो-सर्जन और न्यूरोलॉजिस्ट) की मदद कर सकता है। थीसिस कार्य, न्यूरो-रोगों (ग्लियोमा, लिम्फोमा, तीव्र इस्केमिक) से पीड़ित रोगियों को भी लाभान्वित करेगा। शोधकर्ता को पूरा विश्वास है कि उसका कार्य सामान्य रूप से मानवता की मदद में सहायक होगा।

Content

Certificate	7
Acknowledgements	9
Abstract	11
Content	15
List of Figures	19
List of Tables	23
List of Abbreviations	25
Chapter-1: Introduction and Contents of the Thesis	28
1.1 Motivation behind the thesis	29
1.2 . Literature Review	32
1.2.1. Historical Background of MRI	
1.2.2. Basics of Magnetic Resonance Imaging	
1.2.3. Conventional image contrasts	
1.2.4. Advanced MR Imaging: Perfusion	
1.2.5. Susceptibility Weighted Imaging (SWI)	
1.3. Role of MR Imaging in specific context of diseases	68
1.3.1. Intracranial mass lesions: Glioma and PCNSL	
1.3.2. Current role of SWI in glioma grading and PCNSL detection	
1.3.3. Acute ischemic stroke: role of conventional and advanced MRI	
1.3.4. Current role of SWI in acute ischemic stroke	
1.4. Research gaps: utilization of SWI in disease specific context	73
1.4.1. Potential utility of quantitative SWI in grading and differentiation of intracranial mass lesions (glioma and PCNSL)	
1.4.2. Potential utility of quantitative SWI in acute ischemic stroke management	
1.5. Objective & Structure of thesis work	75
1.6. Datasets & computation information	77

1.6.1. Details of Intracranial mass lesion patients:	
1.6.2. Details of Stroke patients:	
1.6.3. MRI Protocol for intracranial mass lesion (glioma and PCNSL) patients:	
1.6.4. MRI Protocol for stroke patients:	
1.6.5. Details of software used in the framework development:	
Chapter-2: Quantitative ITSS and its application in glioma grading	84
2.1. Study-1: Quantitative versus semiquantitative assessment of ITSS in patients with different grades of glioma	85
2.1.1. Introduction	
2.1.2. Materials and Methods	
2.1.3. Results	
2.1.4. Discussion and Conclusion	
2.2. Study-2: Quantitative ITSS vasculature volume using QSM vs R_2^* approach for glioma grading	101
2.2.1. Introduction	
2.2.2. Materials and Methods	
2.2.3. Results	
2.2.4. Discussion and Conclusion	
2.3. Study-3: R_2^* & DCE Perfusion MRI based novel approach for classification of ITSS into hemorrhage, non-leaky vessels, and leaky vessels in GBM	109
2.3.1. Introduction	
2.3.2. Materials and Methods	
2.3.3. Results	
2.3.4. Discussion and Conclusion	
2.4. Conclusions of the Chapter	116
Chapter-3: Evaluating the role of radiomics analysis of SWI and machine learning in differentiation and classification of glioma and PCNSL	117
3.1. Study-1: On evaluating the role of Quantitative ITSS and Radiomics features	118

from SWI in glioma grading	
3.1.1. Introduction	
3.1.2. Materials and Methods	
3.1.3. Results	
3.1.4. Discussion and Conclusion	
3.2. Study-2: Differentiating hemorrhage and vasculature ITSS in SWI	138
magnitude images: machine learning based radiomic feature selection and	
classification approach for high grade glioma	
3.2.1. Introduction	
3.2.2. Materials and Methods	
3.2.3. Results	
3.2.4. Discussion and Conclusion	
3.3. Study-3: Differentiating PCNSL from grade IV glioma using SWI based	146
texture features	
3.3.1. Introduction	
3.3.2. Materials and Methods	
3.3.3. Results	
3.3.4. Discussion and Conclusion	
3.4. Conclusions of the Chapter	156
 Chapter-4: Stroke penumbra assessment using SWI: a novel alternative	 157
4.1. Introduction	
4.2. Materials and Methods	
4.3. Results	
4.4. Discussion	
4.5. Conclusions of the Chapter	186
 Chapter-5: Conclusions, Limitations and Future scopes of work	 188
5.1. Conclusion	
5.2. Major findings of the thesis	

5.3. Limitations and Future scopes of work

Reference	194
List of Publications	214
About the Author	217

List of Figures

Title	Page No.
Figure 1.1: ^1H proton in a static magnetic field B_0 , precessing at Larmor frequency. This Figure is adapted from the book titled “Basic Principles of MR Imaging” by Brook, et al. [doi: 10.1007/978-81-322-2098-5_21]	35
Figure 1.2: The precessing net magnetization M can be viewed as having two vector components: M_z in the longitudinal direction, M_{xy} in the rotating transverse plane. A) In equilibrium the magnetization M aligns with B_0 and there is no transverse component, B) Application of the B_1 field increases magnitude of M_{xy} , the detectable component of the magnetization. This figure is adapted from the book titled “Basic Principles of MR Imaging” by Brook, et al. [doi: 10.1007/978-81-322-2098-5_21]	37
Figure 1.3: Explanation of transverse and longitudinal magnetization figuratively along with T_1 and T_2 weighted images of human brain	40
Figure 1.4: Basic blocks of MRI scanning and image formation. Some of the components of this figure were adapted from the book titled “Basic Principles of MR Imaging” by Brook, et al.[doi: 10.1007/978-81-322-2098-5_21]	42
Figure 1.5: Example of a gradient echo pulse sequence. ADC = Analog to Digital converter or Receiver.	43
Figure 1.6: Example of a spin echo pulse sequence. ADC = Analog to Digital converter or Receiver.	44
Figure 1.7: T_1 weighted images (multiple slices) for a grade-4 glioma patient	46
Figure 1.8: T_2 weighted images (multiple slices) for a grade-4 glioma patient	48
Figure 1.9 : PD weighted images (multiple slices) for a grade-4 glioma patient	49
Figure 1.10: FLAIR images (multiple slices) for a grade-4 glioma patient	50
Figure 1.11: DWI ($b = 1000 \text{ s/mm}^2$) and corresponding ADC images (multiple slices) for a grade-4 glioma patient	51
Figure 1.12: A post-operative case of high-grade glioma showing recurrent tumor with foci of susceptibility in the mural nodule as well as blood fluid level in the cystic component (E, open arrow). The mural nodule is showing high CBV on DCE perfusion (E, thick arrow). The corresponding area shows relatively low CBV on	56

DSC perfusion MRI. Other foci with increased CBV seen posteriorly detected well on both DSC and DCE perfusion MRI (E and F, thin arrows). Artifactual increased CBV is seen within the cystic component of the tumor on DSC perfusion (F, thin arrow). Image is adapted from Saini, et al.[doi: https://doi.org/10.1371/journal.pone.0215400.g001]	
Figure 1.13: (a) pCASL pulse sequence design. (b) The sample CBF image of pCASL generated as the final output with blue-to-red color scheme applied. (c) pCASL controlled image, (d) pCASL tagged image, (e) subtraction and generation of pCASL CBF map (without blue-to-red colormap)	59
Figure 1.14: Example simulations done for determining the number of phase-mask multiplication. a) multiplied once, b) 4 times, c) 8 times and d) 16 times. Radius of circles varied from 1 to 16 pixels. All circles have same phase value of 0.3π . SNR of original magnitude image was 15:1. This image is adapted from Haacke, et al.[doi: 10.1002/mrm.20198]	65
Figure 1.15: Steps of SWI image formation. Image is adapted from Neelavalli, et al.[doi: https://doi.org/10.3174/ajnr.A1400]. The raw phase image is passed through the high-pass filter to generate the filtered phase, which then undergoes scaling to generate the phase mask. Phase mask is multiplied with the magnitude image with the optimized multiplication factor to finally generate the conspicuous SW image.	66
Figure 1.16: Summary of thesis	76
Figure 2.1: Flowchart of the proposed algorithm	90
Figure 2.2: Showing a sample case of chronic hemorrhage A: SWI magnitude image of the chronic hemorrhage area, B: Calculated R_2^* map, C: and D: Zoomed sections of the rectangular area highlighted in A and B respectively	92
Figure 2.3: A: SWI Magnitude image of glioma, B: Calculated R_2^* Map (Colormap scaling unit: 1/ms), C: Segmented ITSS D: Total ITSS Volume Map (TIV = Segmented ITSS X R_2^* Map) containing both hemorrhage and vessels (Colormap scaling unit: 1/ms), E: ITSS Vasculature Volume (IVV) Map	94
Figure 2.4: The comparative images of three different glioma grades with respect to the proposed methodology.	95
Figure 2.5: ROC Analysis to differentiate between three different grades of glioma	98

Figure 2.6: Grade IV glioma case, ITSS vasculature volume segmented and calculated based on R_2^* and QSM based approaches	105
Figure 2.7: Bland Altman and scatterplot correlation graphs between R_2^* based IVV and QSM based IVV	107
Figure 2.8: Grade IV glioma case, biological classification of ITSS	113
Figure 2.9: Scatterplot distribution: Grade IV glioma case, Biological classification of ITSS	114
Figure 3.1: Schematic diagram of the study workflow	120
Figure 3.2: Best possible and significant classification accuracies (out of RF, SVM and LR) are plotted on X-axis. For each classification scenario (CS1-5), FV14, FV17 and FV18 outperform other FVs.	133
Figure 3.3: Visual representation of multi sequence combination of feature vectors and performances (grading accuracies) for five different classification scenarios. Classification accuracies are plotted in Y-axis.	133-135
Figure 3.4: Flowchart of methodology	142
Figure 3.5: Feature importance plot in RF classifier. Cumulative histogram bars show importance of adding each feature to the mix. Total twenty-one significant ($p < 0.05$) features are shown. Out of 99 remaining non-significant features, two are plotted as example. These two do not improve the cumulative importance more than 1%.	143
Figure 3.6: Features are ranked in terms of increase in classification errors in RF classifier. Total twenty-one significant ($p < 0.05$) features are shown. Out of 99 remaining non-significant features, two are plotted as example. These two do not increase the classification error more than 1%.	144
Figure 3.7: Representative feature value comparisons between $SMag_{vasculature}$ and $SMag_{hemorrhage}$ for the top-ranked four features	145
Figure 3.8: Box and whisker plots for texture feature “Contrast”: lymphoma (pCNSL) vs grade IV glioma	152
Figure 3.9: ROC analysis to differentiate lymphoma (pCNSL) vs grade IV glioma	153
Figure 3.10: Top row: PCNSL patient: A. T_2 weighted image shows the lesion boundary, B: DWI image shows the cellular differences within the tumor boundary, C: FLAIR image represents the hyper intense region and heterogeneity, D: SWI image shows the corresponding tumor area, minimal vasculature, no	154

hemorrhages are seen. Bottom row: grade IV patient: E. T ₂ weighted image shows the lesion boundary, F: DWI image shows the cellular differences within the tumor boundary, G: FLAIR image represents the hyper intense region and heterogeneity, H: SWI image shows the corresponding tumor area, high amount of hemorrhage, vasculature and susceptibility changes are seen.	
Figure 4.1: Flowchart of proposed methodology for Penumbra quantification from MR SWI-DWI mismatch and its comparison with MR ASL PWI-DWI mismatch	166
Figure 4.2: Proposed methodology for Penumbra ROI selection.	170
Figure 4.3: Acute ischemic stroke Patient 1. 40 years old female, presented with left sided weakness. Onset time was 2 hours, NIHSS score at onset = 16. Row A and Row B contains images corresponding to pre and post intravenous thrombolysis rtPA therapy, respectively.	175
Figure 4.4: Acute ischemic stroke Patient 2: 31 years old male, presented with sudden onset of left sided weakness. Onset time was 3.5 hours, NIHSS score at onset=16. Row A and Row B contains images corresponding to pre and post mechanical thrombectomy in patient with right internal carotid artery occlusion, respectively.	176
Figure 4.5: a) Pearson's correlation plot of $MR_{\left(\frac{CBF}{ADC}\right)}$ and $MR_{\left(\frac{SWI}{ADC}\right)}$: positively correlated, correlation coefficient $r = 0.90$ ($p < 0.05$), b) Bland Altman plots of $A = MR_{\left(\frac{CBF}{ADC}\right)}$ and $B = MR_{\left(\frac{SWI}{ADC}\right)}$. Threshold lines above and below plots represent values that are ± 1.96 SD from the mean difference. Data is in logarithmic scale. $MR_{\left(\frac{CBF}{ADC}\right)}$ and $MR_{\left(\frac{SWI}{ADC}\right)}$ values are used after normality correction.	178
Figure 4.6: Box plot distributions of two mismatch ratios: $MR_{\left(\frac{CBF}{ADC}\right)}$ and $MR_{\left(\frac{SWI}{ADC}\right)}$ ($n = 25$) in Acute ischemic stroke patients. Data is in logarithmic scale.	179
Figure 4.7: Five representative acute ischemic stroke patients: A1-A5: Segmented Penumbra ROI color overlaid on SWI images. B1-B5: Boundary of segmented Ischemic core marked on ADC images. C1-C5: Hypo perfused penumbra area marked on CBF images representing potential penumbra area	183

List of Tables

Title	Page No.
Table 1.1: List of magnetic compounds and associated susceptibilities	60
Table 1.2: Summary of MRI intracranial mass lesions scan protocol used in this study	80
Table 1.3: Summary of the MRI protocol for stroke patients used in this study	82
Table 2.1: Semiquantitative classification of ITSS	85
Table 2.2: Patient Demographics	87
Table 2.3: Summary of mean semiquantitative ITSS scoring, TIV and proposed IVV among different grades of tumors	97
Table 2.4: Sensitivity and specificity for differentiating grades of glioma (WHO grade II, III and IV)	98
Table 2.5: Patient Demographics	102
Table 2.6: Summary of mean semiquantitative ITSS scoring, R_2^* based IVV and QSM based IVV among different grades of tumors	106
Table 2.7: Patient Demographics	110
Table 2.8: Classification of Hemorrhage & Vessel	112
Table 2.9: Classification of leaky and non-leaky vessels	112
Table 3.1: List of the radiomic features (N =120)	122
Table 3.2: List of the Feature Vectors	124
Table 3.3: Distribution of patient data for training and testing	127
Table 3.4: Performance of IVV as a standalone variable	129
Table 3.5: Classification accuracy for single sequence feature vectors	129
Table 3.6: Classification accuracy for multi sequence feature vectors	131
Table 3.7: Performance evaluation for multi sequence feature vectors	132
Table 3.8: Confusion matrix for RF classifier	144
Table 3.9: Patient Demographics	148

Table 3.10: Thirteen features and their expressions used in the study	150
Table 4.1: Clinical evaluation scores of twenty-five patients: (NIHSS = The National Institutes of Health Stroke, Scale, mRS = modified Rankin Scale)	161
Table 4.2: Clinical details of twenty-five patients	162
Table 4.3 : Summary of mean ICV, PPV, SPV, FLV, mean $MR_{(\frac{CBF}{ADC})}$, $MR_{(\frac{SWI}{ADC})}$, $MR_{(\frac{FLAIR}{ADC})}$ and the logarithmic transformation values of stroke patients (n = 25)	177
Table 4.4: Association of high SPV values (>20 ml) with occlusion/stenosis of affected vessels (n=25)	180
Table 4.5: Correlation between favorable mismatch ratios (>1) with functional outcome (last follow up mRS score: 0 and 1) (n = 15 for patients undergoing mechanical thrombectomy/IV-rTPA)	181
Table 4.6: Infarct growth comparison between first MRI vs follow up MRI (n = 11)	182

List of Abbreviations

EEG = Electro Encephalography
PET = Positron Emission Tomography
CT = Computed Tomography
MRI = Magnetic Resonance Imaging
SWI = Susceptibility Weighted Imaging
DWI = Diffusion Weighted Imaging
ADC = Apparent Diffusion Coefficient
EES = Extracellular Extravascular Space
HCT = Hematocrit
CNR = Contrast to Noise Ratio
SNR = Signal to Noise Ratio
FFE = Fast Field Echo
PADRE = Phase difference-enhanced imaging
EPI = Echo Planar Imaging
FLAIR = Fluid Attenuated Inversion Recovery
MRA = Magnetic Resonance Angiography
ITSS = Intra tumoral susceptibility signal
IVV = ITSS vasculature volume
TIV = Total ITSS volume
VEGF = Vascular endothelial growth factor
DSC = Dynamic Susceptibility Contrast
DCE = Dynamic contrast enhanced
ROI = Region of Interest
ROC = Receiver operator characteristic
AUC = Area under the curve
QSM = Quantitative susceptibility mapping
CBF = Cerebral blood flow