The Role of Magnetic Resonance Imaging in Predicting Surgical Outcome in Patients with Degenerative Cervical Myelopathy

By

Aria Nouri, MD

A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto
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2015

Abstract

Magnetic resonance imaging (MRI) is commonly used to confirm a diagnosis of degenerative cervical myelopathy (DCM), however, its role in predicting outcome following surgical treatment remains unclear. Herein, it is hypothesized that quantitative preoperative MRI analysis can predict surgical outcome. Using data derived from a prospective and multicenter cohort of patients undergoing surgical treatment for DCM, multiple MRI parameters were assessed, including presence/absence of signal change on T1 and T2, T2 signal quantitative factors, and anatomical measurements. A dichotomized postoperative modified Japanese orthopedic association score at 6-months was then used to characterize patients with mild myelopathy (≥16) and those with substantial residual neurological impairment (<16). Using multivariate logistic regression analysis, the results indicate that assessment of maximum canal compromise, T1 signal change and baseline functional severity provide superior prognostic value than baseline functional severity alone. It is therefore concluded that MRI has a statistically significant role in predicting surgical outcome.
Acknowledgements

The success of an academic is often a function of his surroundings and those who have provided the support and means to permit the pursuit of their scientific enquiry. This has been no different for me and thus I would like to acknowledge the graduate coordinators, particularly Drs. Howard Mount and Cindi Morshead, as well as the staff at the Institute of Medical Science for their support and guidance. I would also like to acknowledge my program advisory committee members, Drs. Albert Yee, Aileen M. Davis and David Mikulis for their valuable input and direction.

As well, I would like to recognize the many members of the clinical and basic science research team, with particular acknowledgement to Lindsay Tetreault, Dr. Juan Zamorano, Dr. Kristian Dalzell, and Dr. Anoushka Singh for their contributions to this thesis. Lastly, I would like to extend my greatest gratitude to my mentor and thesis supervisor, Dr. Michael G. Fehlings, for his support as well as guidance, and without whom the culmination of this work would not have been achievable.

A lesson from an anecdote I shall never forget:
In discussing the struggles of residents in managing a complex sacral fracture in a homeless woman, Dr. Fehlings reminded his residents, “You should feel honored to take care of her, because it is a privilege to serve the most vulnerable in our society”.

I dedicate this work to my parents, my brother and my sister, who have been my strongest supporters and my greatest teachers.

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Contributions

Aria Nouri
Primary investigator of all MR imaging. Conceptualized study design and structured methodology. Interpreted results, drafted, reviewed, and finalized all relevant research contained. Sole writer of this thesis.

Michael G. Fehlings
Mentor and thesis supervisor. Provided significant guidance, contributions, and conceptual design for all parts of this thesis.

Lindsay Tetreault
Contributions in chapter 1 for the section on epidemiology of DCM and table 1.4. Significant contributions to chapter 3 in terms of statistical analysis, drafting and reviewing contents, figures and tables.

Kristian Dalzell
Significant contributions to MRI analysis and quantitative MRI methodology. Further contributions include drafting and reviewing of content in chapter 3.

Juan Jose Zamorano
Significant contributions to MRI analysis and quantitative MRI methodology. Further contributions include drafting and reviewing of content in chapter 3.

Anoushka Singh
Specific contributions related to epidemiology and etiology of DCM in chapter 1.

Spyridon Karadimas
Specific contribution to the discussion of the pathobiology of spinal cord compression in chapter 1.

Madeleine O'Higgins
Significant editorial support for various works within this thesis.

Program Advisory Committee - Albert Yee, Aileen M. Davis and David Mikulis
Provided significant guidance and assistance for approaching thesis aims. Provided experience and conceptual support, most notably for chapter 3.
# Table of Contents

Abstract ii  
Acknowledgements iii  
Contributions iv  
Table of Contents v-vii  
List of Figures viii  
List of Tables ix  
Description of Abbreviations x-xi  

<table>
<thead>
<tr>
<th>Preamble</th>
<th>1-2</th>
</tr>
</thead>
</table>

**CHAPTER 1 – Degenerative Cervical Myelopathy: A Comprehensive Review of Literature** 3-78  

1.1. Introduction 4-5  
1.2. Anatomy of the Spine 5-8  
1.2.1. Anatomy of the Spinal Cord 6-8  
1.2.2. Anatomy of the Cervical Spine 8  
1.3. Degenerative Cervical Myelopathy (DCM) 9-23  
1.3.1. Cervical Spondylotic Myelopathy and Degenerative Disc Disease 11-4  
1.3.2. Ossification, Hypertrophy, and Calcification of Spinal Canal Ligaments 15-7  
1.3.3. Pathobiology of Spinal Cord Compression 18-20  
1.3.4. Dynamic Injury Mechanisms and Degenerative Spondylolisthesis 21-2  
1.3.5. Degenerative Cervical Spine Deformity and Myelopathy 22-3  
1.4. Epidemiology of DCM 24-30  
1.4.1. Estimation of Incidence and Prevalence of DCM from Non-Traumatic Spinal Cord Injury Data 28  
1.4.2. Estimation of DCM Progression Rates from Studies on Osteoarthritis in the Spine 29  
1.4.3. Estimation by Hospital Admission Rates 29-30  
1.4.4. Survival 30  
1.5. Risk Factors Associated with DCM 31-44  
1.5.1. Hereditary and Genetic causes 31-7  
1.5.1.1. Cervical Spondylotic Myelopathy and Degenerative Disc Disease 33-4  
1.5.1.2. Ossification of the Posterior Longitudinal Ligament 35-6  
1.5.1.3. Ossification of the Ligamentum Flavum 37
1.5.2. Occupational, Personal and Other Associations 38-44
  1.5.2.1. Physical Transportation of Goods 38-9
  1.5.2.2. Cervical Spine Degeneration in High Performance Aviators and Astronauts 39-40
  1.5.2.3. Cervical Spine Degeneration in Athletes 40-1
  1.5.2.4. Personal Factors 41-2
  1.5.2.5. Motor Vehicle Accident Injury and DCM 42-3
  1.5.2.6. Other Associations 43-4
1.5.3. Congenital Disorders associated with DCM 45-9
  1.5.3.1. Down’s Syndrome 45
  1.5.3.2. Klippel-Feil Syndrome 46-7
  1.5.3.3. Congenital Spinal Stenosis 48
  1.5.3.4. Other Congenital Associations 49

1.6. Clinical Assessment 50-63
  1.6.1. Clinical Assessment Tools for Evaluating Disease Severity 50-3
  1.6.2. Medical Imaging 54-63
    1.6.2.1. Conventional Radiography 54-5
    1.6.2.2. Computerized Tomography 56-7
    1.6.2.3. Conventional MRI 58-61
    1.6.2.4. Advanced MRI techniques 62-3

1.7. Treatment of Degenerative Cervical Myelopathy 64-70
  1.7.1. Non-operative Management 64-5
  1.7.2. Surgical Management 65-8
  1.7.3. Pharmacological Treatment 69-70
    1.7.3.1. Riluzole: A Potential Therapeutic Adjunct to Surgical Management 70

1.8. Prognosis: Predicting Surgical and Non-Surgical Outcome 71-8
  1.8.1. Predictors of Myelopathy Development in patients with Cervical Spinal Cord Compression, Canal Stenosis and/or OPLL 72-3
  1.8.2. Comparison of Outcomes in Non-operative Management vs. Surgically Managed DCM Patients 73
  1.8.3. Clinical Predictors of Outcomes of Surgical Treatment 74-5
  1.8.4. Imaging Predictors of Surgical Outcome 75-8

CHAPTER 2 – Hypothesis, Research Objectives, & Rationale 79-80

CHAPTER 3 – The Role of Quantitative MRI Analysis in Predicting Surgical Outcome in Patients with Cervical Spondylotic Myelopathy 81-101

3.1. Introduction 82
3.2. Materials and Methods 83-92
  3.2.1. Study Data and Design 83-4
3.2.2. Quantitative MRI analysis 85-6
3.2.3. T2-WI MCC and MSCC 87-8
3.2.4. T2-WI Signal Measurements and Signal Change Ratio 89-90
3.2.5. Primary Clinical Severity Measure 91
3.2.6. Statistical Analysis 91-2

3.3. Results 93
3.4. Discussion 98-101
3.5. Limitations 101

CHAPTER 4 – General Discussion, Clinical Implications, and Knowledge Translation 102-119

4.1. Key Findings 103
4.2. Basis for MRI Analysis 103-4
4.3. Interpretation and Meaning of MRI Findings of Degenerative Changes 104-6
4.4. Approach and Rationale for the Use of MRI Measurement Techniques 106-11
4.5. Creating a Multivariate Model for Predicting Outcome 111-2
4.6. Clinical Implications 113-4
4.7. Knowledge Translation: Bringing Research Into Practice 114-6
  4.7.1. Identifying knowledge users 114-5
  4.7.2. Disseminating the knowledge 115-6
  4.7.3. Optimizing knowledge translation 116
4.8. Limitations 117
4.9. Conclusion 118-9

CHAPTER 5 – Future Directions 120-7

5.1. Introduction 121
5.2. Assessment of Reliability and External Validity 121
5.3. Combining the Predictive Capacity of Imaging and Clinical Parameters 121-2
5.4. An Approach for Defining T1 and T2 Weighted MRI Signal Changes Quantitatively 122-4
5.5. Advanced MRI Techniques and the Future of DCM Assessment 125-7
  5.5.1. Dynamic/Kinematic & Upright MRI 125-6
  5.5.2. Advanced MRI techniques: Diffusion Tensor MRI, BOLD, and Nuclear Magnetic Resonance (NMR) Spectroscopy 126-7

REFERENCES 128-143
APPENDIX 144
List of Figures

Figure 1.1 – A conceptual breakdown of Degenerative Cervical Myelopathy pathoetiological constituents.
Figure 1.2 – A T2-weighted MRI depicting general degenerative changes of the cervical spine in a patient with confirmed DCM.
Figure 1.3 – An artistic depiction of the multiple anatomical changes that may present in the cervical spine of patients with DCM.
Figure 1.4 – Ligamentous changes commonly observed on medical imaging of patients with DCM.
Figure 1.5 – MRIs and plain radiographs of 3 patients with KFS.
Figure 1.6 – A radiograph showing the canal to vertebral body ratio method for evaluation of cervical spine stenosis.
Figure 1.7 – Measurement of the maximum canal compromise (MCC) of the cervical spine on CT.
Figure 1.8 – T1 and T2 weighted MRIs of the same patient with the presence of signal changes and a confirmed diagnosis of DCM.
Figure 3.1 – A consort diagram indicating the clinical and imaging data available at baseline and upon follow-up at 6-months.
Figure 3.2 – MSCC and MCC measurement techniques illustrated on T2-WI MR.
Figure 3.3 – Quantitative signal change measurements illustrated on T2-WI MR.
Figure 3.4 – A receiver operator characteristic curve of the final model based on 3 predictors of outcome.
Figure 5.1 – A conceptual illustration of how T1-WI and T2-WI signal change could be defined quantitatively.
List of Tables

Table 1.1 – Ascending pathways and the sensory information that they mediate.
Table 1.2 – Descending pathways and the motor function they mediate.
Table 1.3 – Key pathobiological changes occurring in the setting spinal cord compression secondary to degenerative changes in the cervical spine.
Table 1.4 – Trends of patient characteristics and regional incidences of the various forms of degenerative pathologies.
Table 1.5 – Summary of genetic research conducted on CSM, DDD, OPLL as well as OLF.
Table 1.6 – A description of the modified Japanese Orthopedic Association score (mJOA) score and how it is tabulated.
Table 1.7 – Nurick Grade for the assessment of myelopathy severity
Table 1.8 – Correlation between MRI characteristic and pathobiological changes as well as current thoughts related to structure recovery potential after decompression surgery.
Table 1.9 – A list of conservative therapeutic approaches for the management of DCM.
Table 1.10 – A list of commonly performed anterior and surgical procedures for the treatment of DCM.
Table 1.11 – Evidence-based recommendations regarding the comparative effectiveness of anterior and posterior surgical techniques.
Table 1.12 – A summary of recent reviews that have evaluated the role of MRI characteristics in predicting surgical outcome in patients treated for DCM.
Table 3.1 – The table outlines, describes and discusses the various quantitative measures evaluated in the patient population. Respective validation of the methods has also been described.
Table 3.2 – General and MRI characteristics of patients for which MRI analysis was conducted.
Table 3.3 – Univariate and multivariate relation of MRI parameters and baseline mJOA with a dichotomized mJOA outcome (≥16, <16) at 6 months.
### Description of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AOSpine-NA</td>
<td>AOSpine-North America</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
</tr>
<tr>
<td>ASP</td>
<td>Adjacent Segment Pathology</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Receiver Operating Characteristic Curve</td>
</tr>
<tr>
<td>BIC</td>
<td>Bayesian Information Criterion</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-Oxygen-Level Dependent</td>
</tr>
<tr>
<td>BSCB</td>
<td>Blood Spinal Cord Barrier</td>
</tr>
<tr>
<td>CLF</td>
<td>Calcification of Ligamentum Flavum</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CSM</td>
<td>Cervical Spondylotic Myelopathy</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
</tr>
<tr>
<td>dtMRI</td>
<td>Diffusion Tensor MRI</td>
</tr>
<tr>
<td>DCM</td>
<td>Degenerative Cervical Myelopathy</td>
</tr>
<tr>
<td>DDD</td>
<td>Degenerative Disc Disease</td>
</tr>
<tr>
<td>dkMRI</td>
<td>Dynamic Kinematic MRI</td>
</tr>
<tr>
<td>DSL</td>
<td>Degenerative Spondylolisthesis</td>
</tr>
<tr>
<td>DS</td>
<td>Down's Syndrome</td>
</tr>
<tr>
<td>EDS</td>
<td>Ehlers–Danlos Syndrome</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional MRI</td>
</tr>
<tr>
<td>Gz</td>
<td>G-Force, Gravitational-Force</td>
</tr>
<tr>
<td>KFS</td>
<td>Klippel-Feil Syndrome</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>IVD</td>
<td>Intervertebral Disc</td>
</tr>
<tr>
<td>LF</td>
<td>Ligamentum Flavum</td>
</tr>
<tr>
<td>MCC</td>
<td>Maximum Canal Compromise</td>
</tr>
<tr>
<td>mJOA</td>
<td>Modified Japanese Orthopedic Association score</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSCC</td>
<td>Maximum Spinal Cord Compression</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>MVA</td>
<td>Motor Vehicle Accident</td>
</tr>
<tr>
<td>ntSCI</td>
<td>Non-Traumatic Spinal Cord Injury</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>OLF</td>
<td>Ossification of Ligamentum Flavum</td>
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<tr>
<td>OPLL</td>
<td>Ossification of Posterior Longitudinal Ligament</td>
</tr>
<tr>
<td>PLL</td>
<td>Posterior Longitudinal Ligament</td>
</tr>
<tr>
<td>pMRI</td>
<td>Upright-Neutral Position MRI</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>SCR</td>
<td>Signal Change Ratio</td>
</tr>
<tr>
<td>SEP</td>
<td>Sensory Evoked Potentials</td>
</tr>
<tr>
<td>SI</td>
<td>Signal Intensity</td>
</tr>
<tr>
<td>SN</td>
<td>Spinal Nerve</td>
</tr>
<tr>
<td>TA</td>
<td>Transverse Area</td>
</tr>
<tr>
<td>T1-WI</td>
<td>T1-Weighted Image</td>
</tr>
<tr>
<td>T2-WI</td>
<td>T2-Weighted Image</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D Receptor</td>
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PREAMBLE

Let us begin by considering a clinical vignette.

Mr. Smith is a healthy 68-year-old Caucasian male who has recently retired after long career as a carpenter. He frequents his family physician regularly and prides himself for working hard to stay in shape and living a well-balanced life. Upon his recent visit for a regular check-up, he was noted to walk with less confidence, using a wider gait pattern, and requiring the use of the handrail for taking a few steps up the stairs. Despite acknowledging these findings, Mr. Smith did not complain of any problems. His medical history has been otherwise unremarkable, with the exception of a diagnosis of urinary retention due to suspected benign prostatic hypertrophy at his last check-up; however, a digital rectal exam was unremarkable. Upon questioning, he indicated that he has become increasingly bothered by neck pain that began approximately 5 years ago and that is becoming less manageable with over-the-counter painkillers. He stated that he made the choice to retire, as he no longer felt comfortable handling tools and that this had impacted the quality of his work. He also stated that he felt that the natural aging process has caught up with him and that he wished to enjoy the remainder of his life. Concerned over his precipitous deterioration from his last visit 2 years ago, when this constellation of findings were absent, the family physician ordered imaging of the neck. A magnetic resonance imaging exam was remarkable for diffuse degenerative changes in the cervical spine, with severe narrowing of the spinal canal and frank compression of the spinal cord. Specifically, the report indicated that there are signal changes on T2-weighted imaging in the spinal cord spanning two vertebral levels in height. On the basis of these findings a referral to a spine surgeon was arranged.

While Mr. Smith is a fictional character and only serves to exemplify a case scenario, such a presentation in the elderly is very real; indeed, spinal cord compression due to degenerative changes in the spine represents the commonest cause of spinal cord dysfunction in this population segment worldwide. From this case we see that the disability arising from cervical spinal cord compression can
significantly impact the quality of life. If we look even closer, we can also see that early symptoms indicative of degenerative cervical myelopathy (DCM), such as problems voiding, began before the patient deteriorated to his current level and remained undetected – a problem that currently prevails for a number of reasons, including a general lack of awareness in the medical community to screen for signs of DCM and attribution of functional decline to the natural aging process by patients.

For Mr. Smith, an important decision will have to be made after consultation with a spine surgeon. Conservative management has limited utility in managing mild DCM, but this cannot be said with more advanced levels of disease, which is more consistent with his case. It is thus likely that Mr. Smith will be recommended to undergo surgery to decompress the spinal cord. At this point, one important question arises when considering the possibility of surgery: Doctor, what are my future prospects of health after treatment?

Although one would hope that the answer to this question should be fairly clear-cut, it is not. In recognition of this, one of the objectives of the recent AOSpine-North American prospective and multicenter study on cervical spondylotic myelopathy was to close this critical knowledge gap. Indeed, not long ago, a clinical prediction model derived from the AOSpine study data emerged and will help to address Mr. Smith’s question. However, this model was based on clinical parameters and did not fully consider the role of MRI analysis. Accordingly, it is the objective of this thesis to explore the role that preoperative MRI plays in predicting how patients such as Mr. Smith can expect to fare after surgical treatment.

As our study represents the only prospective and multicenter investigation on the subject to date, the findings herein provide the highest level of evidence currently available on the subject and therefore have direct implications on current practice. Consequently, it is the ultimate objective of this thesis to provide information that will help answer Mr. Smith’s question.
CHAPTER 1
Degenerative Cervical Myelopathy: A Comprehensive Review of Literature

The contents of sections 1.3-1.5 of this chapter derive from the manuscript:
1.1 Introduction

Degenerative Cervical Myelopathy (DCM) is an age-related disease of the cervical spine and represents one of the most common causes of spinal cord dysfunction worldwide (Tracy and Bartleson, 2010). Though genetic factors may be implicated in its development, it is generally recognized that the degenerative process is a function of two fundamental factors: advancing age, and the accumulative wear-and-tear on the cervical spine anatomy. As these two factors occur in all humans, it is quite understandable that a large portion of the elderly population, whether clinically myelopathic or not, will present with evidence of structural changes of the cervical spine on medical imaging (Tracy and Bartleson, 2010). From a diagnostic perspective, it has been particularly challenging to determine when degenerative changes should be considered significantly pathological and treated. Those who have symptoms due to spinal cord compression, present clinically with variable degrees of motor and sensory deficits. However, waiting for the onset of myelopathic symptoms to emerge before treatment is initiated may only prevent further deterioration and result in irreversible neurological deficits. Conversely, prophylactic treatment may result in unnecessary risks to the patient. Cervical spine surgery is an invasive procedure with significant risks of injury to the spinal cord and death at the extreme end of the spectrum, despite the fact that it is a commonly performed procedure that has been consistently performed without such sequelae.

To guide the management of DCM, clinical and imaging predictors of surgical outcome may be investigated to understand more about how these patients can expect to fare when treatment is instigated. The specific role of preoperative MRI in this regard, which is the central role of this thesis, is further explored in the following chapters. However, in beginning this discussion, it is appropriate to provide a comprehensive background on various topics surrounding DCM to set context.

In the following sections of this chapter, the anatomy and natural degeneration of the cervical spine, as well as DCM pathogenesis, epidemiology, clinical presentation, functional assessment, medical imaging, treatment, and finally,
current knowledge on predictors of surgical outcome will be explored. Collectively, these subjects will set the basis of current knowledge surrounding DCM.

1.2 Anatomy of the Spine

The spine is the central musculoskeletal structure in the human body, connecting the head and upper limbs superiorly, to the pelvis and lower limbs inferiorly. The typical spine is composed of 24 articulating vertebrae that are further segregated into 7 cervical, 12 thoracic and 5 lumbar vertebrae (Moore, 2009). In the adult, these sit on top of another 9 fused, or “false”, sacral and coccygeal vertebrae. As the spine descends caudally, the vertebrae increase in size to support the progressive increase in weight bearing (Moore, 2009).

Though the spine is often referred to as a column, it is actually shaped in curves, with a natural lordotic predisposition in the cervical and lumbar segments and kyphosis in the thoracic region.

All non-fused vertebral levels of the spine are connected to the next level by an intervertebral disc (IVD). IVDs are composed of a central nucleus pulposus that is comprised of gelatinous like tissue, and a surrounding annulus fibrosus, which is composed of several layers of fibrous cartilage. However, the cervical, thoracic, lumbar, as well as the first sacral vertebrae also form synovial zygapophysial joints via the inferior articular process of superior vertebrae with the superior articular process of the inferior vertebrae. With exception to the above, it should be noted that C1 articulates at its superior articular surface with the occipital condyles at the base of the skull.

Though one of the core functions of the spine is to provide structural support and mobility of the trunk, it also confers protection of the spinal cord, which runs through the spinal canal. The spinal canal is demarcated by the posterior longitudinal ligament (PLL) anteriorly, and by the vertebral arches, vertebral foramina as well as ligamentum flavum laterally and posteriorly (Moore, 2009).
1.2.1 Anatomy of the Spinal Cord

The spinal cord is an extension of the brain that descends through the foramen magnum at the inferior aspect of the skull and continues caudally through the spinal canal, commonly terminating at L1-L2 in adults. During its descent, the spinal cord gives rise to 31 spinal nerves (SN) that exit the spine through intervertebral foramina bilaterally. Each one of these SNs is comprised of a dorsal and ventral root, constituting primarily sensory inputs and motor outputs, respectively.

Grossly, the spinal cord varies in size and widens laterally in the cervical and lumbosacral regions. These enlargements are attributable to the increased number of lower motor neurons that constitute the origins of the nerves of the brachial plexus of the upper extremities and the lumbosacral plexus of the lower extremities (Waxman, 2009).

On transverse-section, the spinal cord shows an H-shaped internal mass of grey matter that is surrounded by white matter (Waxman, 2009). Located at its center is the central canal, which contains CSF and is lined by ependymal cells. As with the brain, the spinal cord is lined at its periphery by the meninges, comprised from inside to outside, the pia, arachnoid and dura layers, respectively.

Within the white matter, there are functionally related bundles of axons that form tracts, which are further broken down into ascending and descending (Ross et al., 2003). The ascending tracts represent the pathways that take sensory information from the body to the cerebrum or cerebellum. Disturbances in their function due to myelopathy can result in the loss of sensation and proprioception below the level of injury. Most of these pathways decussate or cross to the other side of the spinal cord as they travel rostral in the neuroaxis. Table 1.1 provides a list of the major ascending pathways and the sensory information that they mediate.

Descending tracts of the spinal cord carry autonomic as well as voluntary motor fibers from the brain to the viscera and muscles of the body. Disturbances in their function due to myelopathy will result in problems with motor control necessary for both voluntary and involuntary movement, as well as movement
coordination below the site of injury. **Table 1.2** presents a list of the major descending pathways and the motor function they mediate.

The gray matter of the spinal cord is segregated into three horns or columns: Dorsal (Posterior) Horn, Lateral (Intermediate) Horn and Ventral (Anterior) Horn. Within these, nerve bodies that are functionally related group together to form nuclei called Rexed laminae (Ross et al., 2003, Fix, 2001). Posterior horn gray matter receive and process sensory inputs, intermediary horn gray matter (present only in thorax and lumbar region) receive viscerosensory input, and anterior horn gray matter contain predominately motor nuclei (Fix, 2001).

**Table 1.1**
Ascending pathways and some of the sensory information that they mediate (Fix, 2001, Blumenfeld, 2010).

<table>
<thead>
<tr>
<th><strong>Ascending Tracts</strong></th>
<th><strong>Mediates</strong></th>
</tr>
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<tbody>
<tr>
<td>Medial Lemniscus Pathway</td>
<td>● Tactile discrimination, vibration, form recognition, joint muscle sensation and conscious proprioception</td>
</tr>
<tr>
<td>Ventral Spinothalamic Tract</td>
<td>● Light touch (perception from gentle cotton strokes)</td>
</tr>
<tr>
<td>Lateral Spinothalamic Tract</td>
<td>● Temperature and pain sensation</td>
</tr>
<tr>
<td>Dorsal Spinocerebellar Tract</td>
<td>● Unconscious proprioception to the cerebellum</td>
</tr>
<tr>
<td></td>
<td>● Fine coordination of posture and movement of individual muscles of the lower extremity</td>
</tr>
<tr>
<td>Ventral Spinocerebellar Tract</td>
<td>● Unconscious proprioception to the cerebellum</td>
</tr>
<tr>
<td></td>
<td>● Coordinated movement and posture of entire lower extremity</td>
</tr>
<tr>
<td>Cuneocerebellar Tract</td>
<td>● Upper-extremity equivalent of the dorsal spinocerebellar tract</td>
</tr>
<tr>
<td>Spinoreticular Tract</td>
<td>● Emotional and arousal aspects of pain</td>
</tr>
</tbody>
</table>
Table 1.2
Descending pathways and some of the motor information that they mediate (Fix, 2001, Blumenfeld, 2010).

<table>
<thead>
<tr>
<th>Descending Tracts</th>
<th>Mediates</th>
</tr>
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<tbody>
<tr>
<td>Lateral Corticospinal (pyramidal) pathway</td>
<td>• Somatic and visceral motor activities arising from the cerebral cortex or brainstem</td>
</tr>
<tr>
<td>Ventral Corticospinal Tract</td>
<td>• Control of axial muscles</td>
</tr>
<tr>
<td>Rubrospinal Tract</td>
<td>• Control of flexor tone</td>
</tr>
<tr>
<td>Vestibulospinal Tract</td>
<td>• Control of extensor tone, balance and positioning of the head and neck</td>
</tr>
<tr>
<td>Descending Autonomic Tracts</td>
<td>• Projections to sympathetic (T1-L3) and parasympathetic (S2-S4) centers in spinal cord</td>
</tr>
<tr>
<td></td>
<td>• Innervation of ciliospinal center (T1-T2)</td>
</tr>
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</table>

1.2.2 Anatomy of the Cervical Spine

The anatomy of the spine varies between the cervical, thoracic, lumbar and sacral divisions, but can also differ significantly within these regions. The cervical portion is composed of 7 segments, which comprise the smallest of the articulating vertebrae. The cervical region is also naturally lordotic and gives rise to 8 SNs between the cervical vertebrae, with the exception of the first SN, which arises between the occipitus and C1. As there are 7 cervical levels but 8 SNs arising out of the cervical region, SNs are numbered starting at 1 according to the corresponding vertebrae level below their origination, except for SN 8, which arises between C7-T1. The first 2 cervical vertebrae, the atlas and the axis, are more uniquely shaped than the rest of their counterparts as they bridge the connection between the head and the spine.

Anatomical variations between cervical levels and their articulations with adjacent vertebrae are related to function and permit varying degrees of mobility between segments. This is important, as dislocations are relatively more prone to occur in regions of greater flexibility.
1.3 Degenerative Cervical Myelopathy

Degeneration of tissue anywhere in the body occurs principally as a function of use intensity over time. Musculoskeletal structures that bear significant structural loads, however, may experience accelerated deterioration. In the cervical spine, these degenerative changes can be divided into spondylotic (or osteoarthritic) and non-osteoarthritic changes, with further subtype categorization (Figure 1.1). However, while these pathological changes have been segregated into separate clinical entities, there is a loose divergence between them in practical terms, as they are highly interrelated and oftentimes manifest concomitantly. Ultimately, the principal unifying problem is the propensity of degenerative changes to cause spinal canal stenosis, lead to compression of the spinal cord, and eventually, result in disability due to the development of myelopathy.

Pathophysiologically, symptomatic degenerative cervical myelopathies can result from static compression of the spinal cord, spinal malalignment leading to altered cord tension and vascular supply, and repeated dynamic injury owing to segmental hypermobility (Baptiste and Fehlings, 2006a, Ames et al., 2013). In terms of the latter, it has also been recognized that unstable spine segments may be responsible for chronic repetitive microtrauma upon the spinal cord not significantly large enough to be recognized as traumatic SCI. Additionally, patients with spinal stenosis who have experienced minor trauma to the neck may be at a substantial risk of developing myelopathy or experiencing deterioration of preexisting myelopathy (Yoo et al., 2010). Accordingly, some degree of trauma is likely to be contributory to the natural history of DCM development.

In the following section, the pathology of CSM and DDD will be discussed together, and separated from the discussion of the ossification, hypertrophy and calcification of spinal ligaments. The current understanding of the pathobiology of spinal cord compression will then be discussed as a consequence of these. Following this, degenerative spondylolisthesis (DSL) and evidence supporting dynamic injury mechanisms are briefly reviewed. Finally, emerging evidence to support cervical spine malalignment as a contributor to DCM pathogenesis will be discussed.
Figure 1.1
A conceptual breakdown of the pathoetiologial constituents of Degenerative Cervical Myelopathy (DCM). Predominant features form the basis of diagnosis, but more than one of these pathologies frequently present concomitantly. In addition, congenital anomalies may predispose to accelerated manifestation of DCM. CSS = Congenital Spinal Stenosis, KFS = Klippel-Feil syndrome, DS = Down’s syndrome, OPLL = Ossification of posterior longitudinal ligament; OLF = Ossification of ligamentum flavum.
1.3.1 Cervical Spondylotic Myelopathy and Degenerative Disc Disease

Each intervertebral disc (IVD) is comprised of an outer layer, the annulus fibrosus, and an inner layer called the nucleus pulposus. The nucleus pulposus is largely comprised of proteoglycans which, due to their hydrophilic nature, become encased in water molecules. The resulting viscoelastic nucleus pulposus converts axial load into hoop stress and is contained by the dense connective tissue of the annulus fibrosus which serves to provide structural integrity to the IVD. This construction provides a unique capacity to withstand high compressive loads and transfer of these forces longitudinally onto the cartilage endplates of vertebral bodies and radially onto the surrounding annulus fibrosus (Galbusera et al., 2014). With repeated use of everyday living, periods of trauma and excessive use, and other nutritional and environmental factors, the intervertebral discs begin to degenerate and the uncovertebral processes of the vertebrae become flattened, altering the weight-bearing and load-transferring functions of the intervertebral joint (Baptiste and Fehlings, 2006b). As a result, there is increased stress on the articular cartilage endplates and hypermobility in adjacent segments (Baptiste and Fehlings, 2006b, Galbusera et al., 2014). Uneven pressure forces exerted upon the vertebrae as a consequence of these structural changes are thought to encourage the formation of osteophytic spurs in an adaptive remodeling process meant to stabilize an unstable spine segment (Galbusera et al., 2014).

As DDD generally precedes the onset of osteophytosis (Karadimas et al., 2013b), severe cases of disk degeneration that result in significant migration of disk elements into the canal can be solely implicated in the development of myelopathy (Jacobs et al., 2011). However, more subtle forms of disk degeneration that are accompanied by progressive changes in the anatomical architecture of entire cervical joint, as is frequently observed in the elderly, present with a constellation of findings more consistent with CSM. A T2-weighted MRI of a patient with CSM and
DDD showing these changes is presented in Figure 1.2. Additionally, these changes are further illustrated in Figure 1.3.
Figure 1.2
A T2-weighted MRI depicting general degenerative changes of the cervical spine in a patient with confirmed DCM. The cervical vertebra bodies, most prominently seen in cervical vertebra “4”, have lost their height and have increased anterior to posterior length. Intervertebral disc elements have migrated in the spinal canal C3-C4 (thin arrow) as well as C4-C5 and are contributing to spinal cord compression. Hyperintensity signal change of the spinal cord is also clearly visible extending from C3-C5 (thick arrow).
Figure 1.3
An artistic depiction of the multiple anatomical changes that may present in the cervical spine of patients with DCM. Conceptual design by Aria Nouri, edits by Michael G. Fehlings and medical illustration by Diana Krysni. See Appendix.
1.3.2 Ossification, Hypertrophy and Calcification of Spinal Canal Ligaments

Age-related changes to spinal ligaments implicated in the development of cervical myelopathy involve the posterior longitudinal ligament (PLL) and the ligamentum flavum (LF). While hypertrophy and ossification of spinal ligaments may be influenced significantly by underlying genetics, their manifestation in older age as well as presumed multifactorial pathogenesis suggests a progressive and degenerative cause for their development (Ogata et al., 2002, Inamasu et al., 2006, Stapleton et al., 2011, Stetler et al., 2011, Kudo et al., 2011, Hayashi et al., 1997).

Stiffening and buckling of the LF has been suggested to occur as a consequence of natural cervical joint degenerative changes, including loss of IVD height (Kalsi-Ryan et al., 2013, Baptiste and Fehlings, 2006b). Similarly, prolapse of the nucleus pulposus has been implicated as an initiating stimulus for hypertrophy of PLL (Inamasu et al., 2006). Although this suggests that stiffening or hypertrophy may develop as a consequence of cervical joint degeneration, the recognition that their prevalence varies between spinal regions [OLF is more common in the thorax (Guo et al., 2010)] and the frequent manifestation without signs of DDD or CSM, supports additional pathomechanistic processes in their development. A T2-weighted MRI of spinal cord compression due to hypertrophy of the ligamentum flavum is displayed in Figure 1.4A.

It remains unclear how a normal ligament transitions into an ossified ligament, but it has been suggested that hypertrophy may be a precursor for ossification (Inamasu et al., 2006). Histologically, hypertrophy of PLL has been defined as “hyperplasia of nonfibrous cartilage with strong metaplasia in the PLL in more than two intervertebral spaces, with capillary hyperplasia and infiltration of the connective tissue” (Inamasu et al., 2006). It has been hypothesized that hypertrophy of PLL may be replaced by lamellar bone to become ossified when hypertrophy has potential systematic or genetic factors to induce secondary ossification (Mizuno et al., 2001). The role of genetic factors is reinforced by the frequent coexistence of cervical and thoracic OPLL and OLF disease (referred to as
tandem ossification) in which different segmental stresses still exhibit similar pathological changes in nearly one-third of patients (Park et al., 2008). This finding is also interesting as it suggests that although OPLL and OLF may have different natural histories, they share some form of pathological relationship (Inamasu et al., 2006, Ono et al., 1999, Yoshida et al., 1992). Figure 1.4B displays a CT scan of a patient with OPLL.

It has been stated that calcification of the ligamentum flavum (CLF) is a common finding on CT (Meyer et al., 2011); however, much remains unknown about this clinical entity. Given the limited amount of research on CLF, it has been challenging to definitively classify its common pathological features; however, reports have supported different histopathology from OLF (Miyasaka et al., 1983, Inoue et al., 2013). CLF has been described as occurring in degenerated and thickened ligaments and that the calcification has no continuity with the lamina (Miyasaka et al., 1983). Moreover, the superficial and deep layers of the ligamentum flavum are relatively preserved (Miyasaka et al., 1983). This is in contrast to OLF, which has been described as a metaplastic process in which endochondral ossification leads to lamellar bone formation (Ben Hamouda et al., 2003). More specifically, Miyasaka et al. (1983) state that in OLF cartilage forms an ossified bridge that extends from the upper and lower edges of two adjacent laminae.

Reports indicate that CLF may be more common in females and that it may be a manifestation of pseudogout (calcium pyrophosphate dihydrate deposition disease) (Meyer et al., 2011, Miyasaka et al., 1983, Cabre et al., 2001). However, a number of other potential associations have also been noted, including hypercalcemia, hyperparathyroidism, hemochromatosis and renal failure (Ruiz Santiago et al., 1997). Despite these reports, there remains a paucity of research on the subject and further investigation is necessary.
Figure 1.4
Ligamentous changes commonly observed on medical imaging of patients with DCM. A) A T2-WI MRI of a patient with LF hypertrophy that is resulting in significant posterior compression of the spinal cord (short arrow). B) A sagittal reconstructed computerized tomography (CT) image of a patient with OPLL (long arrows).
1.3.3 Pathobiology of Spinal Cord Compression

In comparison to traumatic forms of spinal cord injury (SCI), the pathophysiological sequelae of SCI in DCM have been considerably less investigated. Having said this, recent studies on CSM rodent models (Karadimas et al., 2013d, Klironomos et al., 2011) as well as on human spinal cords (Yu et al., 2011) of patients with CSM have uncovered a number of underlying phenomena related to chronic and progressive compression and have implicated chronic stretching in the development of important pathophysiological events. In particular, it has been demonstrated that chronic cervical spinal cord compression results in chronic reduction of the intraparenchymal spinal cord blood flow (Karadimas et al., 2013d, Karadimas et al., 2014). The resulting chronic ischemic injury, in conjunction with mechanical stretch, has been found to activate some key biological events and cause neural degeneration.

There is emerging evidence supporting that chronic intraparenchymal ischemia generates a unique immune response (Beattie and Manley, 2011, Karadimas et al., 2013c). Persistent activation of microglia and macrophage accumulation at the site of the compression is the main known components of this neuroinflammatory reaction (Karadimas et al., 2013b, Yu et al., 2011, Moon et al., 2014). However, the role of microglia/macrophage activation under the chronic compression of the cervical spinal cord has yet to be fully elucidated. Hirai et al (2013) demonstrated that both the M1 and M2 microglia phenotype are activated in CSM, indicating that microglia may be involved in promoting neural damage and in the repairing process. Interestingly, Moon et al (2014) demonstrated that riluzole attenuated the neuropathic pain in a rodent model of CSM that was associated with decreased levels of microglia activation. The neuroinflammatory story becomes more complex since it has recently been shown that chronic endothelial cell dysfunction and blood spinal cord barrier (BSCB) disruption are occurring even during the late stages of the compression (Karadimas et al., 2013d), phenomena that inevitably exaggerate the existing inflammatory process being propagated by peripheral immune cell infiltration.
This persistent hypoxic insult and the ongoing neuroinflammatory response during chronic spinal cord compression may be implicated in progressive neuronal and oligodendroglial cell death through activation of apoptotic pathways (Yu et al., 2011, Yu et al., 2009, Kalsi-Ryan et al., 2013, Karadimas et al., 2013b, Karadimas et al., 2010). Indeed, the levels of neuronal and oligodendroglial injury have been well associated with neurobehavioural dysfunction. As previously indicated by histological studies on human and experimental CSM tissue, the compression-mediated activation of the pathophysiological cascades described previously can lead to development of gliosis, cavity formation, degeneration of the main corticospinal tracts, interneuronal loss, and atrophy of the anterior horns associated with motoneuronal loss, the constellation of which is consistent with the principal neuroanatomical features of myelopathy (Karadimas et al., 2013a). A summary of the key pathobiological changes is outlined in Table 1.3.
Table 1.3
Key pathobiological changes occurring in the setting spinal cord compression secondary to degenerative changes in the cervical spine (Karadimas et al., 2014, Yu et al., 2011, Karadimas et al., 2013d, Moon et al., 2014).

<table>
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<tr>
<th>Pathobiological consequences of spinal cord compression</th>
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<tr>
<td>• Chronic reduction in spinal cord blood flow</td>
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<td>• Disruption of the microvascular network:</td>
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<td>Endothelial cell dysfunction</td>
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<td>Disruption of the vascular basement membrane</td>
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<tr>
<td>Loss of blood-spinal cord barrier integrity</td>
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<td>• Glutamate excitotoxicity</td>
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<td>• Microglia activation regulated by:</td>
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<td>CX3CR1:CX3CL1 axis</td>
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<tr>
<td>CD200:CD200R axis</td>
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<tr>
<td>• Neuronal and oligodendroglial apoptosis</td>
</tr>
<tr>
<td>• Demyelination</td>
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<tr>
<td>• Astrogliosis</td>
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<td>• Axonal degeneration</td>
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1.3.4 Dynamic Injury Mechanisms and Degenerative Spondylolisthesis

In addition to stretching and static compression, it is also recognized that the spinal cord may be injured through dynamic injury mechanisms (Matsunaga et al., 2002, Hayashi et al., 2014, Fengbin et al., 2013, Fujiyoshi et al., 2010). It has been proposed that dynamic injury may occur through instability (Jiang et al., 2011), increased range of motion (Fujiyoshi et al., 2010, Matsunaga et al., 2002), and through minor trauma in the setting of preexisting DCM (Fengbin et al., 2013).

Degenerative spondylolisthesis (DSL) results in regional instability of the spine that can manifest as an anterior or posterior subluxation of a vertebral segment and is due to a number of degenerative changes, including facet joint arthropathy, disc degeneration, and increased stretch of discs as well as ligaments (Jiang et al., 2011, Chaput et al., 2013). DSL occurs most frequently between C3-4 and C4-5, representing 46% and 49% of observed occurrences, respectively (Jiang et al., 2011). It has been suggested that this region may be preferentially affected due to greater degenerative changes occurring in the lower cervical spine, which result in excessive compensatory mobility in the upper cervical segments (Kawasaki et al., 2007). Although there is no clear grading system for delineating severity, it is generally accepted that patients with 3-3.5mm of horizontal translation have severe DSL (Kawasaki et al., 2007, Suzuki et al., 2013). When severe and unstable, DSL can result in narrowing of the spinal canal (Jiang et al., 2011) and potentially recurrent compression of the spinal cord. Indeed, a recent systematic review has reported that myelopathy or myeloradiculopathy was present in 64% of DSL patients referred for surgery (Jiang et al., 2011). However, static imaging can make it challenging to discover movement dependent subluxation and therefore patients with suspected DSL may benefit from kinematic MRI examination. Hayashi et al (2014) recently reported that spinal cord compression in the cervical spine of symptomatic patients (neck pain with or without neurological signs) was observed in 5.3% in the neutral position, but that missed dynamic stenosis was discovered in 8.3% in extension and 1.6% in flexion using kinematic MRI.
It has also been suggested that an increased range of motion in the cervical spine may result in dynamic injury to the cord. Matsunaga et al (2002) previously showed that OPLL patients with critical stenosis (<6mm) all had myelopathy and that no myelopathy was present in patients with canal diameters ≥14mm. However, when spinal canal size was >6mm but less <14mm in diameter, myelopathy preferentially developed in those with increased range of motion (Matsunaga et al., 2002). Given these results, the authors suggest that static compression cannot be solely implicated in myelopathy development and hypothesize that dynamic injury mechanisms play a role.

Recently, it has been shown that dynamic injury to the spinal cord may also occur in CSM patients in the setting of minor trauma. Fengbin et al (2013) has shown that patients with minor trauma, particularly in the setting of lower cervical instability, had a greater incidence of neurological deterioration and experienced less postoperative improvement than those without trauma.

It is clear, however, that further research on dynamic injury mechanisms in the setting of a degenerated cervical spine is warranted.

### 1.3.5 Degenerative Cervical Spine Deformity and Myelopathy

The cervical spine has a natural lordotic disposition, and age-related degeneration may result in hyperlordosis, scoliosis, and most notably kyphosis. Indeed, the cervical alignment in DCM patients must be taken into consideration during surgical planning, particularly to prevent the development or progression of kyphosis postoperatively. Interestingly, however, there is emerging evidence that cervical alignment also contributes to the pathogenesis and severity of cervical myelopathy (Ames et al., 2013, Mohanty et al., 2015, Smith et al., 2013). Ames et al (2013) hypothesize that the mechanism behind myelopathy development in patients with kyphosis can be attributed to the deformity forcing the spinal cord against the vertebral bodies. They further state that this results in anterior cord pathology as well as longitudinal cord tension due to the cord being tethered by the dentate ligaments and cervical nerve roots (Ames et al., 2013). Ultimately, spinal cord tethering is believed to increase intramedullary pressure that results in neuronal
loss, demyelination, and decreased blood supply due to the flattening of small blood vessels (Ames et al., 2013). These findings indicate that spinal cord compression due to canal stenosis may not be the only pathoetiological factor contributing to myelopathy. Furthermore, this supports the idea that the absence of frank spinal cord compression on medical imaging cannot exclude a diagnosis of DCM.

Recent research on patients with kyphotic deformity using kinematic MRI has also indicated that subtypes of kyphosis affect cervical spine mobility differently and that kinematic MRI may be better than standard supine MRI in investigating both the degree of instability and spinal cord compression (Ruangchainikom et al., 2014). The same authors also found that in patients with kyphosis, spinal cord compression was mostly located at C4-6, the apex in C-type, and the transition zone of S-type and R-type kyphotic deformities. However, the apex of the focal kyphotic deformities was also noted as a high-risk area for spinal cord compression (Ruangchainikom et al., 2014).
1.4 Epidemiology of Degenerative Cervical Myelopathy

Although degenerative cervical conditions are generally regarded as the most common cause of spinal cord impairment in the elderly, their global epidemiological trends remain challenging to evaluate. There are 3 main reasons for this: (1) the prevailing classification of degenerative conditions into separate clinical entities has resulted in segregation of their previous epidemiological investigation; (2) there is a general paucity of literature on the topic; and, (3) investigations that have been conducted have focused on particular world regions or populations. Current epidemiological data on the incidence and prevalence of degenerative pathologies from around the world are summarized in Table 1.4. In the following section incidence, prevalence, progression rates as well as survival will be further discussed.
**Table 1.4**
Epidemiological Trends and Patient Characteristics of the Various Forms of Degenerative Pathologies. Note that regarding OPLL regional incidence, authors have frequently used prevalence and incidence interchangeably. †Protrusion beyond the vertebral body causing cord compression. AP = Anterior-Posterior

<table>
<thead>
<tr>
<th>Type of Degenerative Pathology</th>
<th>Trends in Patient Characteristics</th>
<th>Regional Incidence</th>
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<tr>
<td>Spondylosis</td>
<td>Male:Female ratio is 3:2 (Tracy and Bartleson, 2010). Males present with a greater incidence of canal stenosis, more vertebral levels and more severe stenosis at the primary level of pathology (Hukuda and Kojima, 2002, Northover et al., 2012). The height and AP diameter of the vertebral body are larger in males (Hukuda and Kojima, 2002, Northover et al., 2012). Females present at a younger age and have a larger canal body ratio (Hukuda and Kojima, 2002, Northover et al., 2012).</td>
<td>The incidence of osteophyte development in the cervical vertebra of skeletons was greater in Caucasians than native Africans at all cervical levels studied in South Africa. Native Africans, however, had smaller midsagittal and transverse diameter at all cervical levels (Taitz, 1999).</td>
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<td>Disc Degeneration</td>
<td><strong>Asymptomatic volunteers</strong> (Ernst et al., 2005): Mild disc degeneration: 50% in subjects &lt;30 years, 75% in those aged 31-45 years and 100% in volunteers &gt;40 years. Severe disc herniation: 16.6% in subjects &lt;30 years, 8.3% in those aged 31-45 years, 56% in those aged 46-60 years and 100% in volunteers &gt;60 years. <strong>Japanese asymptomatic volunteers</strong> (Matsumoto et al., 1998): Evidence of disc degeneration in 17% of males and 12% of females in their 20s, rising to 86% and 89%, respectively, in patients over the age of 60 years.</td>
<td><strong>Asymptomatic volunteers</strong> (Ernst et al., 2005): Annular tears: 37% Bulging discs: 73% Protrusions: 50% Disc extrusions: rare Radiological signs of medullary compression: 13.3% <strong>Japanese asymptomatic volunteers</strong> (Matsumoto et al., 1998): Disc degeneration was the most frequent finding. Accompanied by either anterior (78%) or posterior (71%) protrusions (80% bulges, 20% prolapsed). Grade 2† posterior disc protrusion was identified in 7.6%.</td>
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<td>Type of Degenerative Pathology</td>
<td>Trends in Patient Characteristics</td>
<td>Regional Incidences</td>
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<td>Ossification of the ligamentum flavum (OLF)</td>
<td>Thoracic OLFs are more likely to present asymptptomatically than cervical (Al-Jarallah et al., 2012).</td>
<td><em>Kuwait</em>: 18.6% of patients with low back pain had evidence of OLF (Al-Jarallah et al., 2012).</td>
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<td><em>Southeast Asian</em>: Believed to be commonly afflicted, particularly males between 40-60 years of age (Wani et al., 2012).</td>
<td><em>South China (volunteers)</em>: 3.8% (Guo et al., 2010).</td>
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<td><em>Kuwait</em>: 63.2% present with single-level disease. 57.7% involved segments in the cervical spine (Al-Jarallah et al., 2012).</td>
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<td><em>South China (volunteers)</em>: Female predominant. Age dependent, with prevalence rising from 0.5% in subjects &lt;35 years, to 5% in the 35-45 years age group and to &gt;7% in volunteers &gt;45 years of age (Guo et al., 2010).</td>
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<td>Calcification of the ligamentum flavum</td>
<td><em>Japan</em>: Case series of 3 females with CLF predominately in the cervical spine at C5-C7 (Miyasaka et al., 1983).</td>
<td>Rare (Cabre et al., 2001). Predominantly reported in the Japanese (Cabre et al., 2001).</td>
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<td><em>French West Indies</em>: A case series on 6 patients identified 5 females and 1 male; average age 71.7 years (Cabre et al., 2001).</td>
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<tr>
<td>Type of Degenerative Pathology</td>
<td>Trends in Patient Characteristics</td>
<td>Regional Incidences</td>
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<td>Ossification of the posterior longitudinal ligament (OPLL)</td>
<td>Male predominant: At least two times more common in males than females (Ohtsuka et al., 1987, Harsh et al., 1987, Jeon et al., 2012, Kim et al., 2008, Saetia et al., 2011, Smith et al., 2011, Trojan et al., 1992, Wu et al., 2011). May occur in 20-25% of patients treated for cervical myelopathy in North America (Epstein, 1994). OPLL symptomatology: 50% in Japanese, 14% in non-Japanese Asians and 50.5% in Indian Caucasians (Jayakumar et al., 1996). <strong>Japan</strong>: Prevalence was 4.3% in males, 2.4% in females (Ohtsuka et al., 1987). Prevalence was 2.6% for patients in their 50s and 4.5% for patients in their 60s (Ohtsuka et al., 1987). Peak incidence in the 50-60 year age group (Harsh et al., 1987, Jeon et al., 2012, Kim et al., 2008, Ohtsuka et al., 1987, Tsuyama, 1984).</td>
<td><strong>Japan</strong>: 1-4.3% (Jayakumar et al., 1996, Ohtsuka et al., 1987, Ono et al., 1999, Trojan et al., 1992, Inamasu et al., 2006, Matsunaga and Sakou, 2012) <strong>United States of America</strong>: 0.1-1.3% (Matsunaga and Sakou, 2012) <strong>North America</strong>: 0.12% (Trojan et al., 1992) <strong>New York City</strong>: 0.7% (Trojan et al., 1992) <strong>Western Caucasians</strong>: 0.16% (Jayakumar et al., 1996) <strong>Non-Japanese Asians</strong>: 2-4% (Jayakumar et al., 1996) <strong>Indian Caucasians</strong>: 1-8% (Jayakumar et al., 1996) <strong>Korea</strong>: 0.6-3.6% (Kim et al., 2008, Inamasu et al., 2006, Matsunaga and Sakou, 2012, Smith et al., 2011) <strong>Taiwan</strong>: 2.1-3.0% (Smith et al., 2011, Matsunaga and Sakou, 2012) <strong>Singapore</strong>: 0.8% (Matsunaga and Sakou, 2012) <strong>Hong Kong</strong>: 0.4% (Matsunaga and Sakou, 2012) <strong>Philippines</strong>: 1.5% (Matsunaga and Sakou, 2012) <strong>Mongolia</strong>: 1.5% (Tsuyama, 1984) <strong>Non-Asian</strong>: 0.16% vs. Asia: 2.4% (Saetia et al., 2011) <strong>West Germany</strong>: 0.1% (Trojan et al., 1992) <strong>Italy</strong>: 1.7% (Matsunaga and Sakou, 2012)</td>
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1.4.1 Estimation of Incidence and Prevalence of DCM from Non-Traumatic Spinal Cord Injury Data

One potential way of estimating the incidence and prevalence of DCM is by looking at the reported rates of SCIs, which are generally broken down into traumatic and non-traumatic forms. DCMs represent non-traumatic forms of spinal cord injury (ntSCI) and, therefore, are included in such estimates. This classification, however, also includes motor neuron, infectious, inflammatory, and neoplastic disease as well as various other conditions (Farry and Baxter, 2010). In a recent review on non-traumatic spinal cord injury epidemiology, New et al (2014) indicated that degenerative disease of the spine make up 59% of ntSCI in Japan, 54% in the USA, 31% in Europe, 22% in Australia and between 4-30% in Africa. In this same review it was estimated that the regional incidence of ntSCI in North America, Europe and Australia were 76, 26 and 6 per million, respectively, and that the prevalence in Canada is 1,120/million and Kashmir region is 2,310/million. From these numbers, it can be estimated that the incidence and prevalence of ntSCI related to DCM in the North American region is at a minimum 41 and 605 per million, respectively. A number of important limitations of this estimate have to be considered, however. These include the general low level of quality of literature that was at the disposal to make these approximations, and the fact that patients recorded as ntSCI injury in countries with higher quality data, such as Canada (Farry and Baxter, 2010), included only the findings of those with paraplegia and quadriplegia and not those with less severe disability. The recognition that many myelopathic patients will have a milder clinical presentation indicates that the aforementioned figure is significantly underestimated and likely represents only those at the severe end of the spectrum of disease. On the other hand, it should also be noted that not all cases of ntSCI are cervical in nature.
1.4.2 Estimation of DCM Progression Rates from Studies on Osteoarthritis in the Spine

Despite the finding that radiographic evidence of osteoarthritis (OA) presents in the majority of people by 65 years of age and in about 80% of those over 75, the literature has primarily focused on OA rates of the hands, knee and hip (Arden and Nevitt, 2006), thus making it difficult to derive estimates for rates of spinal OA. One exception to this has been a report on the radiographic cervical spine osteoarthritis progression rates by Wilder et al (2011). In their longitudinal study, the authors found that progression of OA (as defined by the Kellgren and Lawrence ordinal scale; an increased grade denotes worse degeneration) (Kellgren and Lawrence, 1963), increased in males at all ages at a greater rate than in females. Furthermore, the authors report that the highest progression rates was present in men between 70-79 years of age at 12.5 cases per 100 patient-years and in women over the age of 80 at 9.3 cases per 100 patient-years. Unfortunately, in terms of DCM, this estimate is limited by the fact that it indicates patients at risk of myelopathy rather than clinically myelopathic patients and would also likely exclude patients considered to have OPLL and OLF. For those in whom progression leads to asymptomatic cord compression, clinically evidence of myelopathy has been shown to develop at approximately 8% at 1-year follow-up and 23% at a median of 44 month of follow-up (Wilson et al., 2013a).

1.4.3 Estimation by Hospital Admission Rates

Recently, 2 studies have emerged that estimated epidemiological trends for CSM based on hospital admission data. Boogaarts and Bartels (2013) estimated a prevalence of CSM of 1.6/100,000 inhabitants based on surgical cases at their hospital in the Netherlands. Wu et al (2013) retrospectively assessed a 12-year nationwide database and estimated an overall incidence of CSM-related hospitalization of 4.04/100,000 person-years.

When interpreting these findings, a number of limitations have to be taken into consideration, including the geographical basis (referral area), as well as the
fact that patients undergoing surgery most likely represented those at the severe end of the spectrum of disease; therefore, it is likely that these estimations undervalue actual epidemiological trends. Furthermore, while Wu et al (2013) included OPLL and disc pathologies as part of their CSM rate estimations, it is unclear if this was the case with the study by Boogaarts and Bartels (2013).

In addition to these studies, it has been proposed that the rate of surgical treatment for CSM is rising. Lad et al (2009) examined national trends in outcome for CSM in the USA and reported that annual admissions increased from 9,623 patients in 1993 to 19,212 in 2002 (approximately 3.73 to 7.88 per 100,000) based on the US national inpatient database. Moreover, the authors found that a near 7-fold increase in the number of spinal fusions for CSM took place between 1993 and 2002 in the US, representing an increase from 0.6 to 4.1 per 100,000 people (Lad et al., 2009). It should be noted that increases in fusion rates might be a reflection of the transition in the understanding of the pathophysiology of DCM from one simply based on static compression of the cord to one recognizing malalignment and dynamic injury as part of the disease process.

1.4.4 Survival

A study from Israel by Ronen et al (2004) assessed the survival of patients with ntSCI between 1962-2000. Though these data included all forms of ntSCI, information regarding the location and type of etiology for ntSCI were provided. The authors found that of 1066 patients with ntSCI, 32% were cervical in nature and that 62% of those with spinal stenosis were cervical. Patients with ntSCI of the cervical spine of any etiology had a median survival of 22.7 years and patients with spinal stenosis at any site had a survival of 17.6 years. Patients with ntSCI due to a herniated disk had a survival of 29 years; however, most of these were lumbar in nature.
1.5 Risk Factors Associated with Degeneration Cervical Myelopathy

Though the anatomical restructuring resulting from degeneration is a natural process of aging, the timing of its manifestation may be influenced by hormonal, metabolic, genetic and personal factors as well as congenital predispositions (Singh et al., 2012, Tracy and Bartleson, 2010, Ogata et al., 2002, Inamasu et al., 2006). Despite the fact that many of these risk factors have been proposed and seem logically relevant, there is a paucity of high quality evidence associating them with DCM. In the following sections, genetic, occupational, personal, congenital as well as other associated risk factors that have been discussed in literature are presented.

1.5.1 Hereditary and Genetic Causes

A number of studies in the literature discuss the genetic basis of degenerative spinal disease. Much of this academic enquiry however, has focused on OPLL and DDD, with relatively little research being conducted on CSM. Moreover, most studies seeking to elucidate an underlying genetic predisposition have been conducted in Asia, limiting global generalizability. It is evident from the literature however that OPLL, OLF, DDD and CSM all may entail some form of genetic or hereditary etiological component; albeit, the degree of evidence varies between the types. Some of the strongest potential genetic factors implicated include those related to MMP-2 and collagen IX for DDD (Erwin and Fehlings, 2013), and Collagen VI and XI for OPLL (Wilson et al., 2013c). Additionally, some of the candidate genetic variants have shown to cause predisposition to the development of more than one of these conditions, for example, genetic studies on the Vitamin D receptor (VDR) have been associated with both DDD and CSM (Erwin and Fehlings, 2013, Wang et al., 2010b). Likewise, it has been found that the collagen VI gene is potentially linked to both OPLL and OLF (Kong et al., 2007). These findings indicate the possibility of some pathomechanical alignment between these conditions. Table 1.5 summarizes current genes/genetic products that have been studied.
Table 1.5
Summary of genetic research conducted on CSM, DDD, OPLL as well as OLF. VDR = Vitamin D Receptor; MMP = Matrix Metalloproteinase; ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs BMP = Bone Morphogenetic Proteins; TSG-6 = Tumor Necrosis Factor alpha stimulated gene 6; IL = Interleukin.

<table>
<thead>
<tr>
<th>DCM Types</th>
<th>Studied Genes/Gene products</th>
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| **Cervical Spondylotic Myelopathy (CSM)**  
(Setzer et al., 2008, Wang et al., 2012, Wang et al., 2010b) | **Structural**: Collagen IX  
**Hormonal**: VDR  
**Other**: Apolipoprotein E |
| **Degenerative Disc Disease (DDD)**  
(Erwin and Fehlings, 2013) | **Structural**: Collagen IX  
**Enzymes**: MMP-2, MMP-3, MMP-9, ADAMTS  
**Hormonal**: VDR  
**Immunological**: IL-β, IL-1 receptor |
| **Ossification of Posterior Longitudinal Ligament (OPLL)**  
(Inamasu et al., 2006, Wilson et al., 2013c, Ogata et al., 2002, Kudo et al., 2011, Kim et al., 2012, Ikeda et al., 2005, Yoshizawa et al., 2004, Iwasawa et al., 2006, Ohishi et al., 2003) | **Structural**: Collagen VI and XI  
**Hormonal**: Retinoic X receptor, VDR, Parathyroid Hormone, Leptin Receptor, Estrogen Receptor  
**Immunological**: TSG-6, TNF-β1, IL-1 α and β, IL-15, Interferon-γ  
**Transcription factors**: RUNX2, Promyelotic Leukemia Zinc Finger, Msx2,  
**Growth Factors**: Insulin-like growth factor, Connective tissue growth factor, BMP 2 and 4, Growth-hormone-binding protein, platelet-derived growth factor  
**Other**: Nucleotide Pyrophosphatase, Endothelin-1, Prostaglandin I2 |
| **Ossification of Ligamentum Flavum (OLF)**  
(Liu et al., 2010, Kong et al., 2007, Kishiya et al., 2008) | **Structural**: Collagen VI  
**Hormonal**: VDR  
**Growth Factors**: BMP-2  
**Transcription factors**: RUNX2 |
1.5.1.1 Cervical Spondylotic Myelopathy and Degenerative Disc Disease

Early reports suggesting a genetic susceptibility for the development of CSM were published by Bull et al (1969) and Palmer et al (1984). In their research, both groups assessed and compared cervical radiographs of twin siblings. Though Bull et al (1969) found that there was a marked resemblance in the degenerative process between twins on imaging, Palmer et al (1984) observed the opposite, concluding instead that though anatomical similarities in twins may predispose them to similar degeneration over time, the incongruence of pathological findings amongst their subjects indicate that numerous other factors are likely at play, and thus preclude a simple genetic causation. One potential reason for discrepancy between their findings may be related to epigenetic factors, specifically, the transcriptional alterations in cells over time related to non-hereditary influences such as the environment.

More recently, Setzer et al (2008), Wang et al (2010b) and Wang et al (2012) have sought particular genetic determinants of CSM susceptibility, implicating the potential polymorphism of Apolipoprotein E, Vitamin D receptor (VDR) and Collagen 9 genes, respectively. Wilson et al (2013c) in their systematic review on the topic caution that though these studies did find significant genetic associations between single nucleotide polymorphisms (SNPs) and CSM, none of the findings have been validated in separate studies.

To date, the strongest indication for a genetic etiological component has been published by Patel et al (2012) who assessed a genealogical database of over 2 million Utah (USA) residents for excessive familial clustering, reporting the presence of significant (p<0.001) relatedness of those with CSM. Most notably, they determined that there was a significant relative risk of 5.21 (p<0.001) for the development of CSM among first-degree relatives (Patel et al., 2012).

In discussing genetic susceptibility for CSM, it is also important to account for genes that have been associated with the development of DDD, because it has been recognized that the pathogenesis of CSM is preceded by disk degeneration
(Karadimas et al., 2013b). Erwin and Fehlings (2013) recently summarized a number of such genes, including those related to metalloproteinases, collagen IX, VDR, and interleukins. Interestingly, genes related to VDR and collagen IX have been associated with both CSM and DDD, suggesting that these may be of particular importance in the natural course of CSM development. The recognition that multiple genes may be involved in the occurrence of these conditions indicates that there may be substantial heterogeneity between patients, their clinical manifestation, and the natural course of their progression.
1.5.1.2 Ossification of the Posterior Longitudinal Ligament

The search for an underlying genetic basis for OPLL has been carried out by a number of investigators. Suspicion for a genetic etiological component is supported by the fact that OPLL presents significantly more frequently in Asian populations than in Caucasians (Inamasu et al., 2006, Matsunaga and Sakou, 2012, Jayakumar et al., 1996, Ono et al., 1999, Saetia et al., 2011, Smith et al., 2011). Indeed, a nationwide survey in Japan revealed that 24% of 2nd degree or closer blood relatives and 30% of siblings of patients with OPLL had radiographically detectable OPLL (Matsunaga and Sakou, 2012).

At the present time, a number of candidate genes including those related to collagen VI and XI, BMP 2 and 4, TNF-alpha, TNF-Beta 1 and 3, nucleotide pyrophosphatase, retinoic X receptor, VDR, parathyroid hormone, IL-1B and IL-15, RUNX2, promyelotic leukemia zinc finger, connective tissue growth factor, prostaglandin I2, endothelin-1, leptin receptor, estrogen receptor 1, and interferon-gamma have been investigated (Inamasu et al., 2006, Kudo et al., 2011, Kong et al., 2007, Liu et al., 2010, Kim et al., 2012). However, despite the numerous investigations, a recent systematic review on the topic by Wilson et al (2013c) determined an overall low strength of evidence in support for a genetic association for OPLL development.

Investigation of OPLL as a single disease may be hindering attempts to attribute specific genetic factors with its development. Based on its pathological distribution, OPLL has been classified into 4 subtypes: localized (bridged or circumscribed); segmental; continuous and mixed, with segmental considered as the most common type (Stapleton et al., 2011, Mizuno and Nakagawa, 2006). Recently, Kudo et al (2011) looked at the genetic differences amongst these subtypes and proposed 2 categories for OPLL: continuous (include continuous and mixed) and segmental (include segmental and circumscribed). They concluded that cells of the OPLL continuous group had higher osteogenic differentiation potency in comparison to segmental group cells, and that a different genetic background between the groups also exists (Kudo et al., 2011). This finding is supported by
previous research that has found that patients with continuous and mixed OPLL types frequently experience progression of their ossification postoperatively, and that contrarily, progression is rare in patients with segmental OPLL (Hori et al., 2006, Kawaguchi et al., 2001). This is worthy of note since Kawaguchi et al (2001) indicated that 3 of their 45 patients developed neurological deterioration due to OPLL progression at 10-year follow-up. Thus, the recognition of potential etiological differences between OPLL types may have significant clinical ramifications.

A general limitation of the interpretation of the genetic studies, as is the case with OLF, is that studies assessing candidate genes have been conducted in Asia, and therefore may not be etiologically translatable to other populations.
1.5.1.3 Ossification of the Ligamentum Flavum

At the present time there is insufficient evidence available to support a genetic basis for the development of OLF in isolation. Having said this, a greater frequency of the disease in some regions, such as Asia, has given support to the idea of some form of genetic and/or environmental susceptibility (Ono et al., 1999). Additional support for an isolated genetic connection has also been demonstrated recently using a mouse model with homozygous mutation in the NPPS gene, which has been specifically linked with the development of OLF at C2/3 (Yu et al., 2009). However, few studies have looked at OLF in humans and have frequently studied OPLL in parallel. For example, Kong et al (2007) found that intron 33 (+20) as well as promoter (-572) SNPs of COL6A1 were associated with both OPLL as well as OLF in the Chinese Han population, although they also found that Haplotype 4 was associated with OLF but not with OPLL, and that Haplotype 1 was associated with OPLL but not with OLF. Other work by Liu et al (2010), has given support to a previously described genetic association related to the RUNX2 gene in OPLL patients (Kishiya et al., 2008), and has also found a similar association with OLF patients, concluding that genetic variants in the gene may be responsible for ectopic bone formation in spinal ligaments.

It is clear that further research needs to be conducted to establish whether a genetic susceptibility exists and if such susceptibility is genetically separate from OPLL as well as conditions with generalized spinal ligament ossification such as Diffuse Idiopathic Skeletal Hyperostosis (DISH).
1.5.2 Occupational, Personal and Other Associations

The development of DCM has been related to a number of personal and occupational risk factors. These factors may accelerate degeneration of the spine through mechanical stress (both dynamic and static) as well as underlying pathobiological processes. Also, the association between individual risk factors has been shown to vary between DCM types, potentially providing insight into differences in their pathomechanics.

1.5.2.1 Physical Transportation of Goods

Porters and coolies in less developed countries transport substantial amounts of goods by bearing weight on their heads and backs. A number of researchers have investigated the potential for this mode of transportation to accelerate cervical spondylosis (Jumah and Nyame, 1994, Echarri and Forriol, 2005, Jager et al., 1997, Joosab et al., 1994). However, as the types of load bearing and techniques may differ among the various populations, it is difficult to extract a collective conclusion on the precise biomechanical factors that may be at play. There is a general consensus among these studies that degenerative changes of the cervical spine in weight bearers is significantly more pronounced than what is observed in the general population, and that the C5-6 region is particularly affected (Jumah and Nyame, 1994, Echarri and Forriol, 2005, Jager et al., 1997, Joosab et al., 1994). Additionally, weight bearers more commonly complained of neck stiffness and pain (Echarri and Forriol, 2005).

Bista and Roka (2008) hypothesized that Nepalese porters using a “Namlo” (a particular type of carriage in Nepal where weight bearing occurs principally on backs) would promote cervical spondylosis as well. However, it was found that the prevalence of spondylosis was actually lower than that of controls (non-porters). The authors suggest that using this method, the orientation of the cervical spine requires isometric flexion of the neck and therefore may significantly reduce the risk of spondylosis compared to non-porters.
Given these findings, it appears that the method of transportation of goods can significantly impact the rate of spondylosis and this recognition may be useful in reducing this occupational hazard.

1.5.2.2 Cervical Spine Degeneration in High-Performance Aviators and Astronauts

The potential of an increased susceptibility for degenerative changes in fighter pilots emerged after reports of acute neck injuries during flight, and the recognition that Gz (G-force) place substantial axial force on the cervical spine (Schall, 1989). Upon neck movement during flight maneuvering, the ability of the cervical spine to withstand high compressive forces is substantially reduced and the IVDs are predominately affected, as they are the chief components of the spine that adapt to stress and have viscoelastic properties (Schall, 1989, Hamalainen et al., 1993). Investigations on fighter pilots have mostly supported that accelerated DDD and osteophytosis takes place (Petren-Mallmin and Linder, 2001, Petren-Mallmin and Linder, 1999, Hamalainen et al., 1993, Hendriksen and Holewijn, 1999, Landau et al., 2006).

One of the more comprehensive studies on the subject was conducted by Petrén-Mallmin and Linder (1999) & (2001). These authors studied an asymptomatic group of fighter pilots against controls (non-fighter pilots) for evidence of spinal degeneration and then assessed them again at a 5-year follow up. During their initial analysis of asymptomatic subjects, it was evident that significant acceleration in degeneration occurred in older fighter pilots compared to younger fighter pilots as well as age-matched controls without exposure to Gz; specifically, experienced pilots had significantly increased degeneration in the form of osteophytes, disk protrusions/herniations, cord compression and foraminal stenosis. Upon follow-up at 5 years, the authors noted that the difference between the groups diminished significantly, and they concluded that high performance flying results in cervical spine degeneration at a younger age compared with
controls; however, with increasing age, the difference between pilots and controls diminishes (Petren-Mallmin and Linder, 2001).

Astronauts frequently complain of back pain in microgravity (Sayson and Hargens, 2008) and have been recognized to be at risk for degenerative disease of the cervical spine (Johnston et al., 2010). It has been proposed that this may be attributable to the physiological changes as a result of weightlessness, including spine elongation and loss of thoracic and lordotic curvatures (Johnston et al., 2010). Recently, it was reported that astronauts have a significantly higher incidence of nucleus pulposus herniation than controls (Johnston et al., 2010). The incidence of herniation was reported to be highest within the first year after return from a space mission, a striking 35.9 times the risk compared to matched (age, sex, body mass index) controls (Johnston et al., 2010). It was also particularly interesting to note that the incidence of cervical herniation was 21.4 times higher in astronauts (Johnston et al., 2010). The authors postulate that prolonged abnormal posture during space missions, exposure to both low and high Gz environments, predisposition to injury due to post flight dysfunction of the neurovestibular system, and changes within the disc structures may be responsible for these findings (Johnston et al., 2010).

1.5.2.3 Cervical Spine Degeneration in Athletes

Athletes engaging in significant physical contact have been shown to present with accelerated cervical degeneration. This has been demonstrated in rugby players who have been studied by Berge et al (1999), Scher (1990) and Silver (2002). There is a general consensus that accelerated cervical degeneration in this group is likely attributable to the high force placed upon the cervical spine, particularly in rugby forwards. Scher (1990) postulates that the forces in the rugby scrum which can generate up to 1.5 tons upon the cervical spine, coupled with rapid changes in direction and intensity of thrust, likely results in repeated minor trauma. In addition to this, in a series of 47 rugby players and 40 age-matched controls, Berge et al (1999) noted increased rates of disc herniation, disc degeneration and reduction of spinal canal diameter as well as other factors amongst rugby players. Much like
rugby players, American football players are also exposed to potentially injurious energy inputs directed at the cervical spine (Nyland and Johnson, 2004). Though protective equipment such as helmets may diminish some of these forces, players in sports in which great force is repeatedly exerted on the cervical spine will likely experience accelerated degeneration.

Cervical spine pain is also a common complaint across other high performance athletes including cyclist and triathlon participants (Villavicencio et al., 2007). Chronic neck pain (≥3 months) was reported in 15.4% of triathlon respondents in a recent study, and it has been suggested that this is possibly due to discogenic injury and overuse (Villavicencio et al., 2007). While it would seem intuitive to believe that such athletes may be predisposed to accelerated degenerative disease of the spine due to increased work intensity, research on weight-lifters and participants of various other sports has shown that high performance athletic activities are not harmful (Mundt et al., 1993). Indeed, it has been postulated that participation in most sports may exert a protective effect against IVD herniations (Mundt et al., 1993).

1.5.2.4 Personal Factors

Patient factors have been implicated in the development of both CSM as well as OPLL. Wang et al (2012) assessed the impact of smoking status on disease development in their study of 172 Chinese subjects. They found that patients who smoked were at increased risk of CSM development, and that the risk increased in patients who carried tryptophan alleles of collagen IX. Indeed, it has been well reported that smoking impacts bone metabolism, decreases bone mineral density and increases fracture risk (Yoon et al., 2012). Furthermore, the effect on bones has been shown to be influenced by dose and duration of smoking as well as body weight (Yoon et al., 2012). Animal studies have shown that smoking has a considerable effect on collagen structure, increases chondrocyte degeneration, and is related to cell necrosis and fibrosis in the nucleus pulposus (Abate et al., 2013). However, given that other research has indicated that cigarette smoking may
actually reduce the occurrence of osteoarthritis (Abate et al., 2013, Felson et al., 1997), further research is necessary to substantiate a potential relationship.

Early reports indicating that there is a high incidence of diabetes in patients with OPLL were discussed by Tsuyama (1984) and Takeuchi et al (1989). More recently, Kobashi et al (2004) in their sex- and age-matched study in Japanese subjects, found that excessive weight gain between 20 and 40 years of age and diabetes were independent risk factors for the development of OPLL. It has also been reported that general ossification of spinal ligaments is associated with non–insulin dependent diabetes mellitus (Kobashi et al., 2004). Though it has been suggested that insulin has implications on bone formation, the precise mechanism by which diabetes and weight influence the development OPLL, if at all, remains to be investigated (Karasugi et al., 2013).

Recently, 2 reports have described deficiency of vitamin B12 as a potential contributor to the pathology in CSM patients (Xu et al., 2013, Miyazaki et al., 2014). Indeed, vitamin B12 deficiency by itself can result in subacute combined degeneration of the spinal cord, which can present with an inverse V-shaped T2-weighted MRI hyperintensity on axial view (Miyazaki et al., 2014). Although it is likely to be a rare phenomenon, this finding does suggest that when MRI findings are equivocal, an assessment of vitamin B12 deficiency should be considered.

### 1.5.2.5 Motor Vehicle Accident Injury and DCM

Motor vehicle accidents (MVAs) represent one of the most frequent causes of traumatic SCI worldwide (Singh et al., 2014), and it has been suggested that spinal canal stenosis and degenerative disc disease render individuals more susceptible to neck injury and reduces injury thresholds (Pettersson et al., 1995, Zhou et al., 2010). However, the long-term effects of soft tissue injury surrounding the cervical spine including neck strains (muscle-tendon overloading) and sprains (ligamentous and capsular damage) that frequently occur with MVAs in the absence of acute damage to neural elements remains less clear (Zhou et al., 2010, Otremski et al., 1989). The biomechanical effects on the cervical spine during MVAs are complex and depend on the type of accident (e.g. rear-end, side impact) and, therefore, multiple injury
mechanism are likely relevant. In terms of whiplash injuries, it has been reported that disc pathology may be responsible for persistent symptoms which may lead to neurological impairment later on (Jonsson et al., 1994, Pettersson et al., 1997). However, Matsumoto et al (2010) in their 10-year prospective follow-up on whiplash patients and controls found that while some evidence of disc degeneration was significantly more common in patients with whiplash injury, no patients in their study developed myelopathy or required surgery.

1.5.2.6 Other Associations

There are a number of less defined associations with DCM. In a study of 30 patients with schizophrenia, Matsunaga et al (2008a) reported a finding of OPLL in 20% of these patients, noting that this represents nearly 5 times the reported incidence in the general Japanese population. However, it is unclear how these patients were selected and thus these findings may be subject to bias. The authors suggest a potential connection between the conditions via calcineurin, which has been linked with susceptibility for schizophrenia development and has been shown to partake in osteogenesis by osteoblast activation (Matsunaga et al., 2008a). Although this would suggest a biochemical etiology, it is unclear whether perhaps aberrant kinetics such as dystonias or other movement abnormalities, which may appear in some people with schizophrenia because of neuroleptic use, may be contributory. Indeed, other aberrant kinetics, as are seen in patients with Parkinson’s disease, for example, may contribute to accelerated degeneration as well. Parkinson’s patients who have chronic dystonia and who have not benefited from medical or botulinum toxin treatment should be reassessed for complex cervical dystonia with tonic posture and phasic movements (Krauss et al., 2002). These patients can rapidly develop progressive myelopathy secondary to their dyskinesias and dystonia with generalized movement (Krauss et al., 2002). Additional noteworthy conditions with associated movement abnormalities that have been implicated with accelerated cervical spondylosis were described by Wong et al (2005) and include cerebral palsy, torticollis and Tourette syndrome. In particular, patients with cerebral palsy who exhibit severe involuntary movements of the head and neck have shown a
propensity to develop significant degenerative changes in the cervical spine at an early age (Kim et al., 2014).

Additional potential population groups associated with OPLL development include patients with hypoparathyroidism, hypophosphatemic rickets, and short sleeping hours (Inamasu et al., 2006).
1.5.3 Congenital Disorders Associated with Degenerative Cervical Myelopathy

Although congenital disorders do not generally cause DCM directly, they can indirectly accelerate the pathological process or result in earlier clinical manifestation. This may occur through various gross as well as microstructural anatomical aberrations of the cervical spine, including congenitally fused vertebral segments (Pizzutillo et al., 1994, Nouri et al., 2015), congenital spinal stenosis (Singh et al., 2012), or structural abnormalities leading to hypermobility syndromes (McKay et al., 2012).

1.5.3.1 Down’s Syndrome

Patients with trisomy 21 or Down’s syndrome (DS) have been recognized to be at a predisposition for developing degenerative cervical disease (Bosma et al., 1999, Olive et al., 1988, Ali et al., 2006). This can occur due to a litany of congenital factors including atlantoaxial instability, odontoid abnormalities, atlanto-occipital abnormalities and hypoplasia of the posterior arch of C1 (Bosma et al., 1999). Atlantoaxial instability has been estimated to occur in 10-20% of DS patients, of which 1-2% present with symptomatic spinal cord compression (Ali et al., 2006). Unfortunately, while it has been recognized that spondylosis is common in DS patients, specific epidemiological data do not currently exist. The significance of this knowledge gap from a clinical perspective is evinced by the approximately 5400 children with DS born in the USA per year and their increasing lifespan, which has increased from a median age of death from 25 years in 1983 to 49 years in 1997 (Shin et al., 2009). As the occurrence of degenerative changes in the cervical spine are naturally progressive and seems to manifest at a younger age in patients with DS (Ali et al., 2006, Bosma et al., 1999), this trend suggests that an increase in DCM arising from this population can be anticipated over the years.
1.5.3.2 Klippel-Feil Syndrome

Klippel-Feil syndrome (KFS) patients are diagnosed by the “hallmark” finding of congenital fusion of cervical vertebrae and have been described by a clinical triad encompassing a short neck, low posterior hairline and restriction of neck motion (Samartzis et al., 2006, Giampietro et al., 2013). Most occurrences of KFS are thought to occur sporadically, but autosomal dominant, autosomal recessive and X-linked forms have also been described (Giampietro et al., 2013). Recently, Rosti (2013) implicated mutations in the MEOX1 gene as the culprit behind autosomal recessive forms of KFS and Tassabehji et al (2008) implicated a GDF6 gene locus in familial and sporadic cases of KFS. Examples of KFS on MRI and plain radiographs are demonstrated in Figure 1.5.

Patients with KFS may be at increased predisposition for the development of cervical joint degeneration (Pizzutillo et al., 1994, Nouri et al., 2015). Although the mechanism for such a relationship has not been fully elucidated, the postulation that patients who undergo surgical fusion of cervical vertebrae may be at risk for the development of adjacent segment pathology (Bartolomei et al., 2005, Ishihara et al., 2004, Lawrence et al., 2012), supports the supposition that increased biomechanical stress on non-fused segments may be contributory (Nouri et al., 2015). In a recent prospective and multicenter study on a surgical cohort of patients treated for CSM, it was discovered that the prevalence of KFS among surgical patients was nearly 4%, and that MRI features in patients with KFS were generally worse than in CSM patients without KFS (Nouri et al., 2015). Given that the prevalence of KFS in the general population has been estimated at 0.71% (Brown et al., 1964), this suggests that patients with KFS may be at a substantial predisposition for DCM. Further research will be necessary to fully uncover the relationship between these conditions, and whether the clinical approach to their management should differ from the general population.
Figure 1.5
MRIs and plain radiographs of 3 patients with KFS. The arrowheads point to the fused vertebrae. The arrows indicate the presence of hyperintensity changes of the spinal cord on T2-WI MRI. The images shown here have been adapted and modified from (Nouri et al., 2015).
1.5.3.3 Congenital Spinal Stenosis

Congenital cervical spinal stenosis has been widely recognized as a predisposing factor for the development of DCM (Countee and Vijayanathan, 1979, Bernhardt et al., 1993, Singh et al., 2012) and has been defined as a sagittal canal diameter of <13mm (Bajwa et al., 2012), or a ratio of less than 0.82 using the Torg-Pavlov (Pavlov et al., 1987) measure (canal diameter/vertebral body diameter). It is believed that a reduction of the spinal canal size will render the spinal cord vulnerable to compression even from minor encroachment of tissue into the canal (Countee and Vijayanathan, 1979). It has also been suggested that a narrow canal reduces the effect size of cerebrospinal fluid and will impair cushioning of kinetic energy in the setting of minor trauma (Del Bigio and Johnson, 1989), and presumably other dynamic injury mechanisms. However, variability in the transverse area of the spinal cord between individuals (Kameyama et al., 1994) indicates that cervical canal size should be related with the size of the spinal cord when evaluating risk for injury.

It has been estimated that spinal canal stenosis is present in approximately 250,000-500,000 people in the USA, of which 20-25% are cervical (Bajwa et al., 2012). Moreover, the prevalence in the USA is expected to increase substantially over the next decade (Bajwa et al., 2012). These patients, and in particular those with conditions that are known to present with a predilection for the occurrence of cervical spinal stenosis, such as achondroplasia (King et al., 2009), should be monitored regularly for the early onset of myelopathic symptoms.
1.5.3.4 Other Congenital Associations

It is important to recognize that a number of other congenital conditions resulting in gross structural malformations of the spine may be of importance in DCM development. Giampietro et al (2013) have published an extensive list of conditions related to congenital vertebral malformations that may be highly relevant. In addition, more generalized congenital aberrations such as those related to collagen structure may be of importance in DCM development as well. A particularly noteworthy group includes patients with significant generalized hypermobility. Patients with Ehlers-Danlos Syndrome (EDS), for example, experience a substantial joint instability secondary to widespread ligament and tendon laxity, and resulting joint pain and orthopedic complications are common (Raff and Byers, 1996). Furthermore, it has been suggested that chronic subluxation in these patients renders them susceptible to osteoarthritis (Raff and Byers, 1996). Although limited, there is some evidence linking EDS with atlantoaxial instability, in particular (Halko et al., 1995). Given these findings, it seems reasonable to assume that EDS patients may have a substantial risk for both accelerated spine degeneration and spinal cord trauma. In terms of surgical treatment, this emphasizes that stabilization of the spine to correct hypermobility should be a key objective if myelopathy is suspected. However, discussion on the impact of hypermobility syndromes on DCM and spinal cord trauma in general requires substantially more investigation.
1.6 Clinical Assessment

Myelopathy secondary to degenerative changes in the cervical spine is a clinical phenomenon almost exclusive to the elderly patient. Indeed, the average age of patients presenting with CSM has been estimated at 64 (Kalsi-Ryan et al., 2013). To arrive at a diagnosis of DCM a careful history should be taken, followed by a detailed clinical examination.

As with OA in any other joints in the body, degenerative changes in cervical spine articulations will impact mobility and anatomical function. As a result, patients may complain of decreased range of motion, stiffness, and pain related to neck movement. Additionally, degenerative changes such as those outlined earlier in section (1.3) have the propensity to reduce spinal canal space, inflict neural damage, and ultimately result in motor, sensory as well as autonomic nervous system dysfunction. Clinically, patients may therefore present with variable degrees of weakness, paresthesia and complaints of urinary dysfunction. Movement coordination may also be impaired and patients may present with difficulty in performing everyday tasks such as buttoning-up their shirt, difficulty handling utensils and walking. Clinical examination may also elicit a positive L’hermitte, Babinski and Hoffman sign. Ultimately, these manifestations have a profound effect on the patient’s quality of life.

1.6.1 Clinical Assessment Tools Evaluating Disease Severity

Although a clinical examination may elicit the constellation of signs and symptoms consistent with a diagnosis of myelopathy, there is a spectrum of severity within which patients may fall. Some patients may have subtle symptoms while others may suffer from more serious debilitation. It is therefore necessary to determine the level of impairment and this can be achieved through the use of assessment tools. In addition to this, the application of assessment tools over time provides an opportunity to evaluate progression of signs and symptoms of DCM, and if treatment is instigated, serve as a means by which the relative efficacy of various treatment options can be objectively compared.
In the absence of a gold standard measure, multiple tools have been employed to assess patients with DCM. Some assessment tools such as the patient reported Short Form-36, provide a general assessment of well-being and have been used to evaluate how much the neurological impairment is affecting the quality of life of DCM patients. Though these measures are subjective, they provide information regarding the general health of the patient. More specific tools such as the modified Japanese Orthopedic Association Score (mJOA) as well as Nurick grade are utilized by physicians, and evaluate the level of impairment related to neurological dysfunction (Table 1.6 and Table 1.7). Indeed, the mJOA score is becoming widely accepted as the standard for assessing the functional status of DCM patients (Tetreault et al., 2013c). It is an 18-point scale that scores upper and lower extremity motor function, sensation, and sphincter control. Although it has been widely used, there has been little investigation to evaluate its measurement properties until recently. Kopjar et al (2014) found that the mJOA had moderate internal consistency (Cronbach’s alpha = 0.63), correlated moderately with the Nurick grade (r=0.62), and was responsive to change as demonstrated by a Cohen’s effect size of 1. The authors did not however investigate inter- and intra-rater reliability of the mJOA and indicate that this remains a current knowledge gap. The authors concluded that their findings validate existing literature and that there is justification for the use of this assessment tool in research studies going forward (Kopjar et al, 2014).
Table 1.6
A description of the modified Japanese Orthopedic Association score (mJOA) score and how it is tabulated. The mJOA is a modified version of the JOA scale and was developed by Benzel et al (1991). It assesses the level of functional impairment in DCM patients by evaluating motor functions of the upper and lower limbs, sensory function of the upper extremities, and urinary function by assessing sphincter control.

<table>
<thead>
<tr>
<th>mJOA Definitions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Dysfunction Score of the Upper Extremities</strong></td>
<td></td>
</tr>
<tr>
<td>Inability to move hands</td>
<td>0</td>
</tr>
<tr>
<td>Inability to eat with a spoon, but able to move hands</td>
<td>1</td>
</tr>
<tr>
<td>Inability to button shirt, but able to eat with a spoon</td>
<td>2</td>
</tr>
<tr>
<td>Able to button shirt with great difficulty</td>
<td>3</td>
</tr>
<tr>
<td>Able to button shirt with slight difficulty</td>
<td>4</td>
</tr>
<tr>
<td>No dysfunction</td>
<td>5</td>
</tr>
<tr>
<td><strong>Motor Dysfunction Score of the Lower Extremities</strong></td>
<td></td>
</tr>
<tr>
<td>Complete loss of motor and sensory function</td>
<td>0</td>
</tr>
<tr>
<td>Sensory preservation without ability to move legs</td>
<td>1</td>
</tr>
<tr>
<td>Able to move legs, but unable to walk</td>
<td>2</td>
</tr>
<tr>
<td>Able to walk on flat floor with a walking aid (i.e., cane or crutch)</td>
<td>3</td>
</tr>
<tr>
<td>Able to walk up and/or down stairs with hand rail</td>
<td>4</td>
</tr>
<tr>
<td>Moderate to significant lack of stability, but able to walk up and/or down stairs without hand rail</td>
<td>5</td>
</tr>
<tr>
<td>Mild lack of stability but walks with smooth reciprocation unaided</td>
<td>6</td>
</tr>
<tr>
<td>No dysfunction</td>
<td>7</td>
</tr>
<tr>
<td><strong>Sensory Dysfunction Score of the Upper Extremities</strong></td>
<td></td>
</tr>
<tr>
<td>Complete loss of hand sensation</td>
<td>0</td>
</tr>
<tr>
<td>Severe sensory loss or pain</td>
<td>1</td>
</tr>
<tr>
<td>Mild sensory loss</td>
<td>2</td>
</tr>
<tr>
<td>No sensory loss</td>
<td>3</td>
</tr>
<tr>
<td><strong>Sphincter Dysfunction Score</strong></td>
<td></td>
</tr>
<tr>
<td>Inability to micturate</td>
<td>0</td>
</tr>
<tr>
<td>Marked difficulty with micturition</td>
<td>1</td>
</tr>
<tr>
<td>Mild to moderate difficult with micturition</td>
<td>2</td>
</tr>
<tr>
<td>Normal micturition</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total Max score</strong></td>
<td>18</td>
</tr>
</tbody>
</table>
Table 1.7
Nurick Grade for the assessment of myelopathy severity. A higher grade denotes increasing neurological impairment (Nurick, 1972).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Spinal Root Signs</th>
<th>Spinal Cord Disease</th>
<th>Walking Impairment</th>
<th>Social Independence</th>
<th>Ability to Work Full-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Least Severe)</td>
<td>Yes</td>
<td>No</td>
<td>Unremarkable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Unremarkable</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Substantial</td>
<td>Mildly Impaired</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Requires Assistance</td>
<td>Moderately Impaired</td>
<td>No</td>
</tr>
<tr>
<td>5 (Most Severe)</td>
<td>Yes</td>
<td>Yes</td>
<td>Chair/Bedridden</td>
<td>Severely Impaired</td>
<td>No</td>
</tr>
</tbody>
</table>

**Nurick Grade, as originally published in 1972**

**Grade 0:** Signs or symptoms of root involvement but without evidence of spinal cord disease.

**Grade 1:** Signs of spinal cord disease but no difficulty in walking.

**Grade 2:** Slight difficulty in walking which did not prevent full-time employment.

**Grade 3:** Difficulty in walking which prevented full-time employment or the ability to do all housework, but which was not so severe as to require someone else’s help to walk.

**Grade 4:** Able to walk only with someone else's help or with the aid of a frame.

**Grade 5:** Chairbound or bedridden.
1.6.2 Medical Imaging

In the setting of suspected myelopathy, patients initially undergo a thorough clinical examination. However, since a number of conditions can result in neurological impairment and may manifest similarly, medical imaging is ultimately required to confirm a preliminary clinical diagnosis. In the following section, the various neuroimaging modalities available for the assessment of DCM are discussed.

1.6.2.1 Conventional Radiography

Radiographs are the oldest form of medical imaging available to the physician. They are created by the detection of ionizing radiation that has either passed or failed to pass through (absorbed) the patient upon external emission of X-rays. Radiation that is absorbed by the patient is not detected on the radiograph and appears as white; conversely, X-rays that are not absorbed by patient pass through and appear black. Generally, most of the radiation passes through human tissue, with the notable exception of bones, due to their large calcium composition. Radiographs are usually the first modality used at the general practitioners office for the assessment of patients with suspected neurological dysfunction of the neck. These images allow for the analysis of bone structures and may be able to detect aberrant ossification of ligaments within the spine, listhesis, and uncover congenital malformations. Their depiction of the spine is limited to 2-dimensional space and therefore multiple radiographs are required to observe different spatial orientations. Oftentimes, lateral view cervical spine flexion and extension radiographs are ordered; however, this procedure may not be appropriate in patients with severely unstable spine segments.

In addition to viewing the radiographs, specific measurements to assess DCM may be performed. One of the most relevant measurements, the canal to vertebral body ratio, was developed by Torg et al (1986) and Pavlov et al (1987), and is a measure of cervical spinal canal stenosis. Figure 1.6 displays an example of how the canal to vertebral body ratio is measured. Radiographs are limited, however, since imaging in any given plane superimposes all radiodense structures from one plane
into a single image and because they do not allow for the effective assessment of soft tissue structures.

Figure 1.6
A radiograph showing the canal to vertebral body ratio method for evaluation of cervical spine stenosis [Developed by Torg et al (1986) and Pavlov et al (1987)]. A ratio of 1 is considered to normal; a ratio of less than 0.82 indicates significant cervical spine stenosis.
1.6.2.2 Computerized Tomography

Computerized tomography (CT) is a technique that utilizes tomographic data to formulate a 3-dimensional view of the spine, and additionally, permits the individual analysis of transverse, sagittal and coronal anatomical planes. In contrast to simple radiographs that superimpose all radiodense structures from one plane into a single image, CT generates individual “slices” of adjustable thickness. This allows for the careful analysis of spine restructuring manifesting in DCM patients, including osteophytosis, vertebral hourglass reshaping, anterior or posterior vertebral displacement, as well as potential ossification of soft tissue structures (e.g. ligamentum flavum, posterior longitudinal ligament - see Figure 1.4B). As with conventional radiography, contrast between tissues is dependent on the electron density of tissue (hindering the passage of electromagnetic radiation). On CT, this is measured in terms of Hounsfield units where water is assigned the value 0; denser values (such as bone) range upwards of +500 or more; and less dense structures (such as fat and air) range downwards of -500 or less (Novelline, 2004). The higher the Hounsfield unit the brighter the tissue on imaging, such that dense tissue appears white, less dense tissue appears dark, and air appears black (Novelline, 2004). Despite this, soft tissue structures such as the spinal cord are not delineated well on CT.

One of the most relevant measurement techniques using CT in patients with DCM is the assessment of maximum canal compromise (MCC) described by Fehlings et al (1999). The method for assessing MCC via CT is demonstrated in Figure 1.7. Information regarding the utility of MCC is discussed in chapters 3 & 4 of the thesis.

In addition to using conventional CT for the assessment of DCM, contrast may be injected into the spine to provide better visual delineation between the spinal cord and surrounding tissue – this method is referred to as a CT myelography. Magnetic resonance imaging has largely replaced CT myelography. However, the latter remains a useful alternative in patients with contraindications to MRI examination, most notably those with ferromagnetic implants (e.g. aneurysm clips, pacemakers).
Figure 1.7
Measurement of the maximum canal compromise (MCC) of the cervical spine on CT. MCC is measured by dividing the canal diameter at the region of interest (Di) by the average of the normal canal diameter size above (Da) and below (Db) (Fehlings et al., 1999). More information about the calculation is described in Table 3.1. Note the vertebrae bodies of level 5 and 6 appear to have a fused.
1.6.2.3 Conventional Magnetic Resonance Imaging (MRI)

While many of the anatomical features consistent with a degenerated spine can be demonstrated by the aforementioned imaging techniques, they do not allow for the clear inspection of the spinal cord. MRI is the gold standard imaging modality for the analysis of soft tissue structures, including the nervous system, and is the principal method for analysis of the spinal cord. Like CT, MRI can acquire multi-planar imaging of tissue that facilitates the assessment of regions of interest from multiple angles. Unlike CT however, MRI uses radiofrequency instead of ionizing radiation to formulate medical imaging (Runge et al., 2014).

Although a number of complex methods have been developed that extend the utility of MRI beyond assessing anatomy [i.e. functional MRI (fMRI) techniques], basic diagnostic MRI methods rendering T1-weighted imaging (T1-WI) and T2-weighted imaging (T2-WI) remain the basic techniques applied in clinical practice for the assessment of suspected myelopathy. MRI is also useful for the assessment of anatomical aberrations in spine structure, including those identifiable by CT as well as degenerative pathologies involving soft tissues (i.e. IVDs and ligaments).

MRI technology is based on a complex application of both classical theory and quantum physics that extend beyond the scope of the current discussion. However, as the role of MRI is being studied and discussed throughout this thesis, some background into how these images are created using this technology is appropriate.

MR exploits the inherent magnetic properties of the most abundant atoms in our body, the hydrogen atom. In the MRI machine, a static magnetic field is created that orients the hydrogen atoms in the body into parallel alignment with the magnetic field. In this direction, the atoms wobble (or precess) at a frequency known as the Larmor frequency. When a radio pulse is used to perturb the hydrogen atoms at the same frequency (i.e. the Larmor frequency), hydrogen atoms absorb energy, begin to orient themselves perpendicular (transverse) to the magnetic field and cohere with the frequency direction (in-phase). When this occurs, signal is given off which is detected by a coil. Once the pulse is stopped, the magnetization of the
atoms begins to fall back into alignment with the magnetic field due to loss of energy to surrounding atomic nuclei. The time it takes for 63% of hydrogen atoms to lose their energy and reorient to the initial magnetic field is termed the T1 relaxation time. Coherence of magnetization from the hydrogen atoms decays over time. The time it takes to lose 63% of this coherence is called the T2 relaxation time.

In order for imaging to possess clinical utility, contrast between tissues must be demonstrated. MR achieves this by depicting areas of high signal (bright) versus areas of low signal (dark). With CT imaging, tissues are discriminated based on only one metric, x-ray attenuation, which has a tight range for soft tissues and makes soft tissue discrimination poor. By contrast, tissue discrimination in MRI is based on two independent metrics, T1 and T2 relaxation, which have wide variation in soft tissues and thereby enable superior discrimination.

In individuals without pathology, the spinal cord generally demonstrates a homogenous signal intensity (grey appearance) on both T1-WI and T2-WI. However, patients with DCM may present with hypointense (dark) signal changes on the spinal cord on T1-WI, and more commonly, hyperintense (bright) signal changes on T2-WI. Examples of these changes are presented in Figure 1.8. There are multiple methods to assess these signal changes, specifically via T2-WI, and these are discussed in further detail in the methods section of chapter 3.

Attempts have been made to correlate specific histopathology of DCM and signal changes on MRI. Table 1.8 summarizes current thoughts on MRI characteristics seen in patients with DCM and their histopathological correlation.
Figure 1.8
T1 and T2 weighted MRIs of the same patient with the presence of signal changes and a confirmed diagnosis of DCM. A) A T1 weighted MRI with hypointensity changes in the cervical spinal cord. B) A T2 weighted MRI with hyperintensity changes in the cervical spinal cord.
Table 1.8
Correlation between MRI characteristic and pathobiological changes as well as current thoughts related to structure recovery potential after decompression surgery. T2-WI signal hyperintensity changes are nonspecific and may represent both reversible and irreversible structural alterations. It should be noted that patients might have a combination of both weak and strong T2-WI signal hyperintensity elements. T1-WI signal hypointensity changes more specifically represent frank neural tissue loss (Tetreault et al., 2013a, Chen et al., 2001, Karpova et al., 2013a, Al-Mefty et al., 1988, Mehalic et al., 1990).

<table>
<thead>
<tr>
<th>MRI Characteristics</th>
<th>Likely Pathobiological Correlation</th>
<th>Structural change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T2-WI</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Weak* Signal Hyperintensity (brighter than spinal cord but darker than CSF signal intensity) appearing: Bright, fuzzy, diffuse, without clear border/delineation | • Edema  
• Wallerian Degeneration  
• Demyelination  
• Ischemia  
• Gliosis | Considered Reversible  |
| **Strong** Signal Hyperintensity (approaching isointensity with CSF) appearing: Bright, focal, sharp, clear border/delineation | • Cavitation  
• Neural tissue loss  
• Myelomalacia  
• Necrosis  
• Spongiform changes in gray matter | Considered largely Irreversible  |
| **T1-WI**                                |                                                                                                    |                            |
| Remarkable presence of signal hypointensity (approaching isointensity with CSF) appearing: Dark, focal, faint | • Cavitation  
• Neural tissue loss  
• Myelomalacia  
• Necrosis  
• Spongiform changes in gray matter | Considered largely Irreversible  |
1.6.2.4 Advanced MR Functional Imaging Techniques

The advent of functional imaging techniques based on MRI technology have brought about a plethora of capabilities that may integrate into the diagnostic and prognostic evaluation of patients with DCM in the future. Having said this, accessibility to such potential technologies will likely be limited. Unlike conventional MRI, which facilitates the detailed inspection of anatomical structures, more advanced imaging techniques, allow for the evaluation of function, more detailed anatomical structure, and physiology. A couple of these, diffusion tensor MRI (dtMRI) and fMRI - specifically the BOLD (Blood-Oxygen-Level Dependent) sequence - are particularly interesting for the investigation of the spinal cord.

Diffusion weighted MRI assesses the amount of diffusion of water molecules in various tissues and is the technology behind dtMRI. In areas with restricted boundaries, such as membranes or ligaments, the motion of water molecules is restricted. The net displacement of water molecules across a tissue area over time (seconds) is termed the apparent diffusion coefficient (Westbrook et al., 2011). The diffusion gradient can be applied in any direction to assess the directional motility of water. This enables 3D reconstruction of fibers and specific visualization of white matter tracts in the central nervous system.

Recent work using dtMRI has indicated diagnostic utility by showing that damage to white matter tracts can be identified before signal changes appear on a T2-WI (Jones et al., 2013). Fractional anisotropy values and fiber tract ratios have also shown significant correlation to surgical outcome, indicating a prognostic value as well (Tetreault et al., 2013a, Nakamura et al., 2012, Jones et al., 2013) However, the clinical application of dtMRI remains largely limited by long processing times and user dependency of fiber tracking (Runge et al., 2014).

Blood-Oxygen-Level dependent MRI is another technology that has a potential application in the evaluation of myelopathy. It takes advantage of the different levels of magnetization between oxygen-bound hemoglobin and unbound hemoglobin in the blood. During BOLD examination, increased blood flow, and subsequent oxygenation, is observed during neuronal activation of moving fingers
for example (Runge et al., 2014). When increased blood flows to the area of interest, the difference in magnetization in the blood, though small, can be appreciated and evaluated.

Though BOLD has great potential to become an important assessment tool for uncovering pathobiological mechanisms underlying spinal cord injury, its application at the present time remains fundamentally investigational.
1.7 Treatment of Degenerative Cervical Myelopathy

Treatment of DCM can be approached either non-operatively, or through surgical management that is focused on spinal cord decompression. The relative difference of efficacy between these two options has been difficult to conclusively demonstrate due to a dearth of literature on the subject and a lack of randomized control trials. From the evidence that has arisen through a systematic review by Rhee et al (2013), it appears that non-operative management for myelopathic patients can be cautiously considered in those who are believed to be mildly myelopathic. Conversely, in patients with more severe myelopathy, non-operative management has been shown to be less effective than surgery with respect to functional outcome, pain, and neurological function (Rhee et al., 2013). Ultimately, it is the objective of both of these approaches to prevent further neurological deterioration, slow disease progression, and improve neurological function as well as quality of life. In the following sections the role of both non-operative and surgical management for the treatment of DCM is discussed.

1.7.1 Non-operative Management

Non-operative management includes exercise therapy, anti-inflammatory medication and promotion of lifestyle changes, such as discouragement of high-risk activities and encouragement of intermittent bed rest. Table 1.9 outlines a more extensive list of the non-operative management techniques reported in literature.

How rigorously non-operative management is instituted may play an important role in treatment efficacy. Yoshimatsu et al (2001) reported that rigorous management in those with severe myelopathy (mJOA<13) is more efficacious than nonrigorous management. The authors defined rigorous management as an initial 1-3 month of traction (Good-Samaritan method), cervical spine immobilization, drug as well as exercise therapy, and orthosis, thermal and drug therapy during regular visits to the outpatient clinic thereafter. Though presumably less intensive, nonrigorous non-operative therapy was not described. However, despite the possibility to achieve more favorable results with more rigorous non-operative
management, surgically treated patients still achieved better results in their study (Yoshimatsu et al., 2001, Rhee et al., 2013).

Given that DCM is a progressive disorder, non-operative management is limited in that it does not adequately address the underlying issue, but there are instances in which surgery is not a viable option (i.e. risks to surgery outweigh the potential benefits). Such a situation may arise in patients with significant comorbidities or advanced age. Other times, patients may simply refuse surgical treatment. Accordingly, in addition to close follow-up these patients may benefit from non-operative management. Having said this, however, current evidence-based recommendations on the subject indicate that there is insufficient evidence to support the use of non-operative treatment (Rhee et al., 2013).

Table 1.9 A list of non-operative therapeutic approaches for the management of DCM. NSAID = Nonsteroidal anti-inflammatory drug (Kadanka et al., 2002, Kadanka et al., 2011, Yoshimatsu et al., 2001, Sampath et al., 2000).

<table>
<thead>
<tr>
<th>Non-operative Management Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Therapy</strong></td>
</tr>
<tr>
<td>• Pharmacological therapy (e.g. Steroids, NSAIDs, Narcotics)</td>
</tr>
<tr>
<td>• Thermal therapy</td>
</tr>
<tr>
<td>• Orthosis therapy</td>
</tr>
<tr>
<td>• Exercise therapy</td>
</tr>
<tr>
<td>• Cervical traction therapy (e.g. Good-Samaritan method)</td>
</tr>
<tr>
<td>• Local spinal injections (i.e. nerve blocks, facet blocks, epidural steroids)</td>
</tr>
<tr>
<td><strong>Lifestyle Adjustments</strong></td>
</tr>
<tr>
<td>• Bed rest</td>
</tr>
<tr>
<td>• Discouragement of high-risk activities</td>
</tr>
<tr>
<td>• Avoidance of risky environments (e.g. slippery surfaces, spine manipulation therapies)</td>
</tr>
</tbody>
</table>

1.7.2 Surgical Management

The purpose of surgical treatment of DCM is cord decompression, spine stabilization, and prevention of further insult to the cord. Although the objective is
clear, the means of achieving decompression is much more complex. As was outlined earlier in the pathogenesis section, patients with DCM can present with a wide ranging set of degenerative changes, and thus, there presents no one surgical approach that is appropriate for all patients. While multiple studies have attempted to synthesize an ideal algorithm that surgeons may use in the treatment of DCM patients, they have fallen short (Lawrence et al., 2013b). Table 1.10 outlines surgical methods commonly used to treat DCM.

The surgical method requires a number of considerations that have been well described in a consensus statement of the surgical management of DCM by Lawrence et al (2013b). They state that the following factors should be included in surgical decision-making:

- Sagittal alignment
- Anatomical location of the compressive pathology
- Number of levels of compression
- Presence or absence of instability or subluxation
- The type of compressive pathology (e.g. Spondylosis, OPLL)
- Neck anatomy
- Bone quality
- Surgeon experience and preference

After considering these factors, the surgeon must decide if they are to approach the spine from the anterior, posterior, or a combination of the two (two-step surgery). A posterior approach is often chosen when multiple spinal levels are involved (Lawrence et al., 2013b). However, the choice of surgical approach is still largely dependent on the location of the compressive force. While there is an insufficient level of evidence to indicate that one approach is superior to the other in terms of JOA score improvement, there is moderate strength of evidence favoring posterior surgery over anterior surgery with regards to increasing sagittal canal diameter (Lawrence et al., 2013a). In their systematic review, Lawrence et al (2013a) make the following evidence-based clinical recommendation: “We recommend a individualized approach when treating patients with CSM accounting for pathoanatomical variations (ventral vs. dorsal, focal vs. diffuse, sagittal, dynamic
instability), as there appears to be similar outcomes between the anterior and posterior approaches in regards to effectiveness and safety.”

Along with deciding the surgical approach, the surgeon must also decide what technique to use. For posterior approaches, there are a few methods at the disposal to the surgeon, but two procedures are most often performed: Laminoplasty, and laminectomy with fusion. The relative efficacy between these procedures was assessed by a systematic review by Yoon et al (2013). For anterior approaches, there are also a number of potential procedures that can be performed. The comparative effectiveness between these anterior surgical options were assessed by Shamji et al (2013) in a separate systematic review. The evidence-based recommendations based on the findings of these authors are presented in Table 1.11.
Table 1.10
A list of commonly performed anterior and posterior surgical procedures for the treatment of DCM.

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Discectomy</td>
<td>• Laminectomy</td>
</tr>
<tr>
<td>• Corpectomy</td>
<td>• Laminectomy and Fusion</td>
</tr>
<tr>
<td>• Discectomy-Corpectomy Hybrid Approach</td>
<td>• Laminoplasty</td>
</tr>
<tr>
<td>• Arthroplasty</td>
<td>• Skip Laminectomy</td>
</tr>
<tr>
<td>• Oblique Minimally Destructive Corpectomy</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.11
Evidence-based recommendations regarding the comparative effectiveness of anterior and posterior surgical techniques.

<table>
<thead>
<tr>
<th>Evidence-Based Clinical Recommendations</th>
<th>Recommendation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes After Laminoplasty vs. Laminectomy and Fusion (Yoon et al., 2013).</td>
<td>&quot;For CSM, evidence suggests that laminoplasty and laminectomy-fusion procedures can be similarly effective. We suggest that surgeons consider each case individually and take into account their own familiarity and expertise with each procedure.&quot;</td>
</tr>
<tr>
<td></td>
<td>Strength of Evidence = Low</td>
</tr>
<tr>
<td></td>
<td>Strength of Recommendation = Weak</td>
</tr>
<tr>
<td>Anterior Surgical Options for CSM. (Shamji et al., 2013).</td>
<td>Recommendation:</td>
</tr>
<tr>
<td></td>
<td>&quot;When pathoanatomically appropriate with minimal retrovertebral disease, we recommend the selection of multiple discectomy over corpectomy or discectomy-corpectomy hybrid procedures.&quot;</td>
</tr>
<tr>
<td></td>
<td>Strength of Evidence = Low</td>
</tr>
<tr>
<td></td>
<td>Strength of Recommendation = Strong</td>
</tr>
</tbody>
</table>
1.7.3 Pharmacological Treatment

Pharmacological treatment of DCM beyond pain control and anti-inflammatory medication does not presently exist. However, the growing understanding of the underlying pathobiological factors involved in the development of SCI, as was discussed in greater detail earlier in the chapter, have opened the possibility for the investigation of two notable types of therapeutic agents for the treatment of DCM: (1) Neuroprotective agents aimed at mitigating secondary injury mechanisms; and (2) Neuroregenerative agents aimed at promoting repair and regeneration of axons as well as the supporting cellular matrix (Wilson et al., 2013b).

Neuroprotective drugs, such as Methylprednisolone and Riluzole (discussed further in the following section), may be useful in patients who are experiencing ongoing compression of the spinal cord, or are at high risk of injury. The mechanisms of these drugs differ and therefore their potential therapeutic application and treatment windows may vary considerably. In general however, it is the objective of neuroprotective agents to contain the epicenter of trauma, and therefore, starting treatment either prior or immediately after injury is desirable (Wilson et al., 2013b). Additionally, these drugs may also play a role in reducing reperfusion injury after decompression surgery.

Neuroregenerative agents may play a useful role in patients with debilitating neurological dysfunction and in whom substantial neurological recovery is unlikely. Neuroregenerative agents include both drugs (e.g. Gangliosides or GM-1) and stem cells (various types including human embryonic stem cells) (Wilson et al., 2013b). These agents have been specifically investigated for the treatment of traumatic SCI, but no discernable effectiveness has currently been shown in human trials. Having said this, it could be conjectured that if such treatment was efficacious, it could likewise be useful in treating DCM. Despite their exciting potential, however, these agents remain largely investigational for the time being.
1.7.3.1 Riluzole: A Potential Therapeutic Adjunct to Surgical Management

Riluzole is an FDA-approved therapeutic agent for the treatment of Amyotrophic Lateral Sclerosis and has been shown in animal models to exert its function by decreasing sodium and glutamate-mediated secondary injury (Fehlings et al., 2013a). It is currently believed that part of the pathobiology of DCM is related to excessive local release of the excitatory neurotransmitter glutamate and that this results in local excitotoxicity and subsequent cell death in the spinal cord (Fehlings et al., 2013a). On the basis of these findings, Riluzole is currently being investigated in Phase III clinical trials (CSM-Protect Trial1) for its safety and therapeutic potential in patients with DCM undergoing surgical treatment. Specifically, patients have been randomized to receive Riluzole or a placebo 28 days before surgical decompression.

1 https://clinicaltrials.gov/ct2/show/NCT01257828
1.8 Prognosis: Predicting Surgical and Non-Surgical Outcome

In counseling patients regarding their treatment, an essential point of discussion is how they can expect to fare given their therapeutic choice, and how they can expect to fare if no treatment is instigated at all. Unfortunately, with regards to DCM, answering these questions using high levels of evidence has been a great challenge. Although there are clinical as well as imaging measures that have been shown to be predictive of outcome, many of them still need to be validated.

A general consensus on predictors of outcome does exist in the form of expert opinion however. In a recent survey of members of the international AOSpine community by Tetreault et al (2014), there was consensus that both clinical and imaging factors were predictive. Most notably, preoperative age and a low mJOA score were important factors that related to poor outcome. Moreover, members from all geographical locations with the exception of Europe indicated that the top two predictors of outcome were duration of symptoms and the preoperative severity score (in Europe presence of myelopathic symptoms was rated higher than baseline severity). In terms of imaging predictors, there was international consensus that MRI is an important prognostic tool and that the presence/absence of signal change on the spinal cord on T2-WI and T1/T2-WI are the most important of these (Tetreault et al., 2014). However, findings of the survey have to be taken into consideration cautiously. In some cases, the collective opinion of respondents was erroneous based on current literature, as Techy and Benzel (2014) pointed out.

In the following section, discussion of predictors of outcome in the surgical setting will be divided into those derived from clinical assessment and those obtained through medical imaging, specifically via MRI analysis. However, not all patients with spinal cord compression present with myelopathy. Therefore, predictors of the natural progression in the non-operative setting will be explored first.
1.8.1 Predictors of Myelopathy Development in Patients with Cervical Spinal Cord Compression, Canal Stenosis and/or OPLL

Patients with degenerative changes of the spine and compression of the cord may present with or without myelopathy. In those patients who do present with symptoms, 20-62% will deteriorate neurologically at 3-6 years of follow-up if treated non-operatively (Fehlings et al., 2013b). However, no specific disease or patient characteristics have been shown to predict the course of this progression reliably (Fehlings et al., 2013b). In nonmyelopathic patients with spinal cord compression secondary to degenerative changes, the rate of myelopathy development approximates 8% and 23% at 1 year and 4 years of follow-up, respectively (Fehlings et al., 2013b).

In a recent systematic review, Wilson et al (2013a) discussed specific predictors of neurological dysfunction in nonmyelopathic patients with degenerative spine disease. The authors identified two studies by Bednarik et al (2008) & (2011) on a prospective cohort of CSM patients without clinically evident myelopathy. In the first of these, the presence of radiculopathy, T2-WI cervical cord hyperintensity, and prolonged somatosensory- and motor-evoked potentials were independent predictors of subsequent myelopathy development (Wilson et al., 2013a, Bednarik et al., 2008). Interestingly, Bednarik et al (2008) found that the absence of T2-WI spinal cord hyperintensity on MRI was independently predictive of myelopathic development at ≤12 months follow-up in subjects with asymptomatic cervical spinal cord compression and that the presence of T2-WI signal change was related with late development (>12months). The meaning of this finding is difficult to explain and exemplifies the difficulty with relating MRI findings with the state of myelopathic disease. In their second study, Bednarik et al (2011) investigated the risk of symptomatic myelopathy after minor trauma in patients with asymptomatic compression after conducting a questionnaire and data file analysis. They concluded, “SCI after minor trauma of the cervical spine in patients with asymptomatic cord compression appeared to be low provided risky activities in these individuals is restricted”.
Wilson et al (2013a) also identified 3 articles on the frequency of myelopathy development in OPLL patients (Fujiyoshi et al., 2010, Matsunaga et al., 2008b, Matsunaga et al., 2004), and found that the progression to myelopathy in this group of patients ranged between 0-61.5%. The authors of one of these articles, Matsunaga et al (2008b), identified canal stenosis (≥60%), laterally deviated OPLL, and increased cervical range of motion as significant predictors of myelopathy development in their prospective multicenter investigation (Wilson et al., 2013a).

1.8.2 Comparison of Outcomes in Non-operative Management vs. Surgically Managed DCM Patients

In a recent systematic review, Rhee et al (2013) investigated the efficacy of non-operative treatment vs. surgery. Though their review was limited by the relative small amount of research that has been conducted on the subject, some interesting findings were reported. They indicate that low strength of evidence derived from Kadanka et al (2002) & (2011) supports that patients with mild cervical myelopathy treated non-operatively may fare as well as those who undergo surgery - this was demonstrated by a comparable mJOA score between the groups throughout a 10-year follow-up period. Rhee et al (2013) caution however, that patients who underwent surgical treatment did not improve from their baseline status as much as patients from other surgical studies, which could potentially explain the lack of difference. In terms of patients with moderate or severe DCM, Rhee et al (2013) identified two separate studies (Sampath et al., 2000, Yoshimatsu et al., 2001) that found that surgical treatment results in a significant improvement of outcome when compared to non-operated patients. Both studies demonstrated not only that patients with surgery improved from baseline but also that patients treated conservatively deteriorated. Collectively, these findings provide low strength of evidence that baseline severity seems to play a predictive role in terms of how patients can expect to fare with or without surgical intervention.
1.8.3 Clinical Predictors of Outcomes of Surgical Treatment

The role of clinical parameters in predicting surgical outcome in patients with DCM has been investigated by a number of researchers. Evidence derived from two recent systematic reviews (Holly et al., 2009, Tetreault et al., 2013b), and a recent prediction model based on clinical parameters (Tetreault et al., 2013c), supports their utility and form the basis of current knowledge on the subject.

In their review, Holly et al (2009) identified Class II evidence to support that sensory evoked potentials (SEPs) have a role in predicting surgical outcome. Specifically, they state “normal preoperative median nerve potentials and/or normalization of potentials in the early decompression period appear to be associated with a more favorable outcome”. Holly et al (2009) also identified Class III evidence to support age, duration of symptoms as well as preoperative neurological function as predictive parameters.

In the more recent systematic review, Tetreault et al (2013b) determined that the most important predictors of outcomes were preoperative disease severity (established through clinical assessment measures) as well as duration of symptoms – indicating that patients with prolonged symptoms and greater preoperative dysfunction are more likely to have an unfavorable surgical outcome. Additionally, the authors pointed to a number of other potential predictors, including age, specific clinical manifestations (e.g. hyperreflexia, gait impairment), comorbidities (e.g. diabetes, psychological impairment), and smoking status that merit further investigation.

Information derived from these reviews provided the scientific prelude for the synthesis of a clinical prediction rule by Tetreault et al (2013c). Using prospective and multicenter population data derived from the AOSpine-NA study, the authors describe a model which included 6 clinical and 1 imaging parameter, including: Age (OR = 0.97, 95% CI = 0.94-0.99), duration of symptoms (OR = 0.78, 95% CI = 0.61-1.00), smoking status (OR = 0.46, 95% CI = 0.21-0.98), impairment of gait (OR = 2.66, 95% CI = 1.17-6.06), psychological comorbidities (OR = 0.33, 95% CI = 0.15-0.69), baseline mJOA score (OR = 1.22, 95% CI = 1.05-1.41), and the
preoperative transverse area of the spinal cord measures on MRI (OR = 1.02, 95% CI = 0.99-1.05) (Tetreault et al., 2013c). Using these factors, the authors developed a model that discriminates a “successful” and “failed” postsurgical outcome (mJOA ≥16 and mJOA <16 as defined by the authors) at 1-year with an area under the receiver operating curve of 0.79.

1.8.4 Imaging Predictors of Surgical Outcome

The potential of imaging factors to predict the outcome of patients with DCM undergoing surgical decompression has been assessed by numerous investigators over the years. Unfortunately, findings from these studies have been inconsistent. The reasons for this are multifold but can be largely attributed to (1) the utilization of different methods for analyzing MRIs, (2) correlation of MRI findings with diverse clinical assessment measures, (3) investigations at single centers, and (4) lack of external validation. In an effort to provide clarity with regards to how imaging factors can be utilized in prognostication, four recent reviews have evaluated literature assessing the role of MRI in predicting surgical outcome (Tetreault et al., 2013a, Li et al., 2011, Karpova et al., 2013a, Vedantam and Rajshekhar, 2013). The summary of their results is displayed in Table 1.12. Collectively, the conclusions of these papers form the foundation of the present knowledge on the subject.

In their systematic review on MRI predictors of outcome in DCM patients, Karpova et al (2013a) conclude that there seems to be good evidence to suggest transverse area (TA) of the spinal cord correlates with recovery ratio but not with post-operative functional scores as assessed by JOA/mJOA. The authors’ findings are also supportive of the predictive value of signal intensity (SI) changes (in terms of presence on T2-WI, extent, brightness and presence on both T1/T2-WIs) on surgical outcomes as measured by the original or modified version of JOA, Nurick grade, or Neurosurgery Cervical Spine scale (Karpova et al., 2013a). However, in a prospective single center study published by Karpova et al (2013b) in the same year, neither TA nor signal changes (on T1-WI and T2-WI) were associated with surgical outcome in patients with DCM – though TA did correlate with baseline functional status. In the systematic review by Tetreault et al (2013a) on MRI
characteristics that affect treatment decision making and prediction of clinical outcome, the authors concluded based on low strength of evidence that there are 3 negative predictors of outcome: Number of SI segments on T2-WI, presence of combined T1/T2-WI signal change, and a high SI ratio on T2.

Li et al (2011) conducted a meta-analysis on the role of T2-WI hyperintensity to predict surgical outcome. The authors conclude that patients with hyperintensity changes of the spinal cord on T2-WI had worse postoperative recovery (measured using the JOA recovery ratio) than patients without signal change. However, they acknowledged that their conclusions are limited given the relatively small number (n=5) of articles available on the subject. The authors also caution that various other factors that could possibly affect prognosis were not controlled for in their analysis, and that further high quality investigation is necessary to substantiate their results (Li et al., 2011).

In their recent review, Vedantam & Rajshekhar (2013) noted the challenge of interpreting results from studies assessing the role of T2-WI signal hyperintensity on surgical outcome, corroborating Karpova et al (2013a). However, the authors concluded that Level II evidence supports that multisegmental T2-WI hyperintensity and sharp, intense T2-WI hyperintensity are associated with poorer surgical outcome, and that regression of T2-WI postoperatively correlates with better functional outcomes (Vedantam and Rajshekhar, 2013).

Despite many attempts to elucidate the role of MRI in predicting surgical outcome as evinced by the outlined reviews above, the findings have been challenging to translate into practice. Specifically, at the present time the key knowledge gaps include:

1) There remains no strong recommendation to guide how MRI factors can be related to outcome.
2) There have been no multicenter studies that have attempted to investigate the role of MRI factors in predicting outcome.
3) Multiple MRI factors have not been adequately investigated in a multivariate fashion.
### Table 1.12
A summary of recent reviews that have evaluated the role of MRI characteristics in predicting surgical outcome in patients surgically treated for DCM.

<table>
<thead>
<tr>
<th>Reviews on MRI characteristics and their ability to predict surgical outcome</th>
<th>Most Important Findings</th>
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<tr>
<td>Systematic review of magnetic resonance imaging characteristics that affect treatment decision making and predict clinical outcome in patients with cervical spondylotic myelopathy. <em>(Tetreault et al., 2013a)</em></td>
<td>The authors identified 3 imaging assessment measures that demonstrated a negative association with outcome based on low-quality evidence, including (1) multiple hyperintensity segments on T2-WI, (2) presence of combined T1-WI and T2-WI signal change, and (3) deviations in signal change ratios. While other evaluated MRI parameters may be important, there was an insufficient amount of evidence to provide a recommendation. The authors provide the following evidence-based recommendation: “T2 signal may be a useful prognostic indicator when used in combination with low SI change on T1-WI, or as a ratio comparing compressed with noncompressed segments, or as a ratio of T2 compared with T1-WI. We suggest that if surgeons use MRI signal intensity to estimate the risk of a poor outcome after surgery, they use high SI change on T2WI in combination with other signal intensity parameters, and not in isolation.” Strength of Evidence: Low Strength of Recommendation: Weak</td>
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<tr>
<td>Assessment of spinal cord compression by magnetic resonance imaging--can it predict surgical outcomes in degenerative compressive myelopathy? A systematic review. <em>(Karpova et al., 2013a)</em></td>
<td>The authors were not able to conclude based on their review that compression of the cord in terms of transverse area or as a compression ratio was predictive of surgical outcome. The authors conclude: “SI changes defined by (1) its presence on T2-WI, (2) its extent (focal or multisegmental), (3) its brightness, and (4) its presence on both T1-/ T2WI can predict surgical outcomes in degenerative compressive myelopathy.” Level of Evidence for conclusion: 2</td>
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<td>Table 1.12 (continued)</td>
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<td><strong>“A meta-analysis showing that high signal intensity on T2-weighted MRI is associated</strong></td>
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<td><strong>with poor prognosis for patients with cervical spondylotic myelopathy.”</strong></td>
<td></td>
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<tr>
<td><strong>(Li et al., 2011)</strong></td>
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<tr>
<td>The authors conducted a meta-analysis using 5 studies and determined that the JOA recovery ratio was lower in patients with T2-WI hyperintensity than patients without T2-WI signal hyperintensity. Their results suggests that T2-WI is a negative predictor of surgical outcome.</td>
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| **“Does the type of T2-weighted hyperintensity influence surgical outcome in patients with cervical spondylotic myelopathy? A review.”** |
| **(Vedantam and Rajshekhar, 2013)**                                                     |
| In their review, the authors conclude “Both multisegmental T2-WI SI and sharp, intense T2-WI SI are associated with poorer surgical outcome. The regression of T2WI SI postoperatively correlates with better functional outcomes”. |
| Level of Evidence: Class II |
CHAPTER 2
Hypothesis, Research Objectives, and Rationale
**Hypothesis:**
It is the principal hypothesis that MRI features encountered in patients with DCM preoperatively, including anatomical alterations (canal stenosis and cord compression) as well as signal intensity changes of the spinal cord on T1 and T2 weighted imaging (size and degree of deviation) will be predictive of surgical outcome as determined by functional assessment using the mJOA.

**Research Objective:**
Using data derived from patients enrolled in the prospective, multicenter CSM-North America study, it is the objective to investigate the prognostic role of preoperative MRI features in patients undergoing surgical treatment for DCM.

**Specific Objectives:**
1) To quantitatively assess pathological MRI features in DCM using three approaches, (1) T1-weighted signal analysis, (2) T2-weighted signal analysis, including size and intensity deviation, and (3) anatomical pathologies (canal stenosis and spinal cord compression), and determine the association with surgical outcome as assessed by the mJOA score.

2) To develop a prediction model that can discriminate between patients into those with mild myelopathy and those with substantial residual neurological impairment based on a dichotomized (>16, ≤16) postoperative mJOA score.

**Rationale:**
The constellation of MRI characteristics manifesting in patients with DCM can be assessed quantitatively using multiple methods. While these MRI measurements are useful in confirming the clinical diagnosis, their utility in predicting surgical outcome remains unclear. The AOSpine-NA study is the first prospective and multicenter study assessing the efficacy of treatment of surgical decompression in DCM patients, and provides a platform to investigate the role of MRI in predicting surgical outcome.
CHAPTER 3
The Role of Quantitative MRI Analysis in Predicting Surgical Outcome in Patients with Cervical Spondylotic Myelopathy

The contents of this chapter have been published in the journal Spine:
3.1 Introduction

Cervical Spondylotic Myelopathy (CSM) is one of the leading causes of DCM and is the most common cause of spinal cord dysfunction in the elderly worldwide (Karpova et al., 2013b). The development of CSM is associated with age-related degeneration of the cervical spine anatomy that progresses with time. Myelopathy in these patients arises from compressive forces exerted upon the spinal cord from the aberrant migration of tissue into the spinal canal. Although asymptomatic degeneration of the cervical spine is common in the elderly (Tracy and Bartleson, 2010), when these changes lead to myelopathy, patients are at risk of motor, sensory and autonomic dysfunction, as well as a reduction in quality of life (Karadimas et al., 2013b).

Although CSM patients with mild symptoms are often managed conservatively, surgical decompression is increasingly recommended as the treatment strategy for the full spectrum of myelopathy severity. As demonstrated by Fehlings et al (2013a), surgical decompression is effective as it not only prevents further neurological decline but also improves neurological function. However, surgery of any kind, particularly involving the cervical spine, does not always result in perfect outcome and is associated with risks.

Outcome prediction in this setting is therefore valuable as surgeons can use this information to discuss with patients how they are likely to fare after surgical intervention and to manage their expectations. In recent work by Tetreault et al (2013c), a clinical prediction rule was constructed to predict functional status at 1-year follow-up using a combination of clinically relevant and routinely-collected variables. This model, however, did not assess the role of MRI in predicting outcome. While a number of studies have attempted to assess this relationship, a recent systematic review (Tetreault et al., 2013a) demonstrated that the overall body of evidence is low and that the results do not provide clear guidance regarding the utility of MRI in predicting surgical outcome.
3.2 Materials and Methods

3.2.1 Study Data and Design

The current study utilized data from the AOSpine CSM-NA multicenter study. That study was primarily undertaken to assess the safety and efficacy of surgical decompression in patients with mild, moderate or severe myelopathy (Karpova et al., 2013a). A secondary objective was to evaluate the association between various preoperative MRI characteristics and postoperative functional status. Research ethics board approval was granted at each study site.

At 12 participating sites, 278 patients with clinically confirmed CSM were enrolled and underwent surgical decompression of the cervical spine. The approach, number of operated levels, and whether or not to use instrumentation varied case by case and was at the discretion of the surgeon. Extensive patient data were collected at baseline and at 6, 12, and 24 months postoperatively, including demographic information, surgical summary, medical history, functional status and patient-reported quality of life. As per standard of care, all patients also received a MRI or CT scan preoperatively. One hundred and fourteen patients had MRIs available for research purposes, 102 of which had complete data required for quantitative analysis and predictive modeling Figure 3.1.
Inclusion Criteria:
≥18 yr, symptomatic CSM with ≥1 clinical sign of myelopathy, imaging evidence of cord compression, no previous surgery for the condition.

Exclusion Criteria:
Asymptomatic CSM, active infection, neoplastic disease, rheumatoid arthritis, ankylosing spondylitis, concomitant lumbar stenosis.

Figure 3.1
A consort diagram indicating the clinical and imaging data available at baseline and upon follow-up at 6-months.
3.2.2 Quantitative MRI Analysis

MRIs were performed using 1.5 Tesla magnets. Image analysis of DICOM (Digital Imaging and Communications in Medicine) formats was carried out using OsiriX (open access software, http://www.osirix-viewer.com). Quantitative measurement techniques were primarily chosen based on findings from previously published systematic reviews on imaging characteristics that predict surgical outcome (Tetreault et al., 2013a, Karpova et al., 2013a). The images were reviewed by 3 investigators (Aria Nouri – postdoctoral trainee, Kristian Dalzell – orthopedic spine fellow, Juan Zamorano – orthopedic spine fellow) to identify the mid-sagittal slice on T2-WI, the level of maximum spinal cord compression (MSCC) as well as maximum canal compromise (MCC), and the presence/absence of signal change on T1-WI and T2-WI. If two mid-sagittal slices approximated the midline with equal distance, the mid-sagittal slice with greatest compression on the axial plane on T2-WI was used for measurement. Disagreement among the investigators was resolved with consensus. Aria Nouri then conducted quantitative measurements and ratio calculations. Table 3.1 summarizes the various quantitative methods of analysis conducted.
Table 3.1
The table outlines, describes and discusses the various quantitative measures evaluated in the patient population. Respective validation of the methods has also been described. MSCC = Maximum Spinal Cord Compression, MCC = Maximum Canal Compromise, SCR = Signal Change Ratio, ROI = Region of Interest, CSF = Cerebral Spinal Fluid, ICC = Interclass Correlation Coefficients.

<table>
<thead>
<tr>
<th>Quantitative MRI Measurement</th>
<th>Formula</th>
<th>Description</th>
<th>Reliability</th>
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<tr>
<td><strong>Maximum Spinal Cord Compression</strong></td>
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<tr>
<td>Fehlings et al (1999)</td>
<td>MSCC = (1 - \frac{\text{di}}{(\text{da} + \text{db})/2}) X 100</td>
<td>Measures the most compressed spinal cord diameter (di) seen on midsagittal MRI against non-compressed diameter references from above (da) and below (db).</td>
<td>The intra- and interobserver ICCs were previously reported as 0.76 +/- 0.08 and 0.79 +/- 0.09 for T2 MSCC, respectively (Karpova et al., 2013c).</td>
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<tr>
<td><strong>Maximum Canal Compromise</strong></td>
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<td>Fehlings et al (1999)</td>
<td>MCC = (1 - \frac{\text{Di}}{(\text{Da} + \text{Db})/2}) X 100</td>
<td>Measures the greatest reduction of spinal canal diameter (Di) seen on midsagittal MRI based on non-reduced diameter references from above (Da) and below (Db).</td>
<td>The intra- and interobserver ICCs were previously reported as 0.88 +/- 0.1 and 0.75 +/- 0.04 for the T1 MCC, respectively (Karpova et al., 2013c).</td>
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<td><strong>Signal Change Ratios</strong></td>
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<td>Arvin et al (2011)</td>
<td>SCR(Arvin) = (\frac{\text{ROI}}{\text{CSF Ref}}) X 100</td>
<td>Computes a ratio of for ROIs against a CSF signal intensity reference obtained from behind the dens.</td>
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<td>Wang et al (2010a) &amp; Zhang et al (2010)</td>
<td>SCR(Wang/Zhang) = (\frac{\text{ROI (0.05cm}}{\text{B}}}{\text{Ref B}})</td>
<td>Computes a ratio based on a fixed ROI of 0.05cm² against a reference point on the spinal cord in the region of C7/T1.</td>
<td>Reliability unknown.</td>
</tr>
<tr>
<td>New Ratio</td>
<td>SCR(New) = (\frac{\text{ROI (0.05cm}}{\text{2}}}{(\text{Ref A+Ref B)/2}})</td>
<td>Computes a ratio based on a fixed ROI of 0.05cm² against an average reference point on the spinal cord approximating C7/T1 and C2.</td>
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3.2.3 T2-WI MCC and MSCC

MCC and MSCC were measured using previously described methods originally designed to assess patients with cervical SCI (Fehlings et al., 1999). Canal compromise and cord compression were computed using the mid-sagittal diameter of the most compressed region of the canal (Di) and cord (di). These diameters were then measured as a percentage of the non-compressed areas (calculated using references above and below the compression regions: Da, Db, and da, db for the spinal canal and the spinal cord, respectively), Figure 3.2. The borders of the canal were defined by the limits of visible CSF both anterior and posterior to the spinal cord.
Figure 3.2.
MSCC and MCC measurement techniques illustrated on T2-WI MR. A) T2-WI of a patient with clinically confirmed CSM without measurements. B) Displays the measurements required for MCC and MSCC calculation. Di, Da and Db measure the diameter of the spinal canal at the site of compression and at the normal site above and below, respectively; di, da and db indicate the diameter of the spinal cord at the site of compression and at the normal site above and below, respectively.
3.2.4 T2-WI Signal Measurements and Signal Change Ratio

For patients with a signal hyperintensity on T2-WI, the region of interest (ROI) area, sagittal extent, and average intensity within the planar ROI were measured. Another fixed area of 0.05cm² was measured for average intensity from within the ROI or at the level of greatest cord compression in patients without a hyperintensity signal change. Baseline measurements were taken from the CSF (between the dens and the spinal cord) and at two spinal cord sites (approximating C2 and C7/T1), measuring an estimated area of 0.05cm², 0.15cm² and 0.15cm², respectively Figure 3.3.

T2-WI signal change ratios (SCR) were computed by comparing the spinal cord ROI against a baseline intensity measurement taken from the same image (CSF or “normal cord” depending on the method). SCRs were measured using 3 different methods; two of these have been previously published and the other is a modified method developed during our investigation (Arvin et al., 2011, Wang et al., 2010a, Zhang et al., 2010).
Figure 3.3
Quantitative signal change measurements illustrated on T2-WI MRI. A) T2-WI of a patient with clinically confirmed CSM without measurements. B) ROI indicates the circumscribed T2-WI signal change from which the area and average ROI intensity were obtained. An additional circle within the ROI area approximating 0.05cm² provides the ROI(0.05cm²) utilized for signal ratio calculations using Wang's and the author's method. Sagittal extent measures the maximum height of the signal change parallel to the spinal cord. Ref A, Ref B and CSF Ref provide the average signal intensity reference points of the spinal cord above and below, and from the CSF behind the dens, respectively.
3.2.5 Primary Clinical Severity Measure

The mJOA scale was used as the primary measure to assess preoperative and postoperative functional status. It is an 18-point CSM-specific scale that separately scores upper (5) and lower (7) extremity motor function, sensation (3) and sphincter control (3), and was discussed in greater detail in the first chapter (Benzel et al., 1991). A dichotomized mJOA at 6-months follow-up was used to discriminate between patients with mild myelopathy postoperatively (≥16) and those with substantial residual neurological impairment at 6 months following surgery (<16) (Tetreault et al., 2013c). The 6-months follow-up period was used as it represented the first postoperative encounter with patients.

3.2.6 Statistical Analysis

The distribution of all continuous variables was visualized using histograms and normality was assessed using the Shapiro-Wilk test. Descriptive statistics were computed for all MRI parameters and relevant clinical variables: continuous variables were assessed using means, standard deviations and ranges, including SCRs, MCC, MSCC and baseline mJOA, and categorical variables were described using frequencies, including T1-WI signal hypointensity (dichotomous), T2-WI hyperintensity (dichotomous), sagittal extent (cm) of signal hyperintensity on T2-WI (Ordinal: 0, <0.2, ≥0.2 and <0.35, ≥0.35) and ROI area (cm²) of signal hyperintensity (Ordinal: 0, <0.75, ≥0.75 and <1.50, ≥1.50).

We conceptually divided the MRI variables into three groups: (1) T1-WI signal analysis; (2) T2-WI signal analysis, including signal size and intensity ratio; and (3) anatomical measurements (based on T2-WI). Univariate analyses were used to evaluate the relationship between these MRI parameters and baseline mJOA with functional outcome at 6-months. Along with baseline mJOA, the lowest p-value from each group was then used to select variables for multivariate logistic regression modeling (Group 2 was subdivided into 2 categories and therefore provided 2 variables: one for T2-WI signal size and one for signal intensity). This preliminary multivariate model was then simplified by manual backward elimination based on
practical and statistical considerations (including Akaike information criterion, AIC; Bayesian information criterion, BIC) with an objective to create the most parsimonious model. Collinearity of all variables was assessed by calculating tolerance.

The final model was compared to a model containing only baseline mJOA using a likelihood ratio test as baseline neurological function has been consistently shown to be predictive of outcome (Tetreault et al., 2013c, Holly et al., 2009, Tetreault et al., 2013b).
3.3 Results

Our subset of patients with partial and complete MRI data analysis (n=114) had similar demographics as the complete cohort as reported by Fehlings et al (2013a): Average age (55.75±11.84 vs. 56.33 ± 11.71), female sex (37.72% vs. 40.65%), and baseline mJOA severity (12.81±2.74 vs. 12.85±0.32).

Review of MR imaging for signal changes revealed that T2-WI signal hyperintensity was present in 67.6% (75/111) and T1-WI signal hypointensity was present in 26.9% (29/108) of patients at baseline. T2-WI signal change was present in 86.2% (25/29) of patients with T1-WI hypointensities. On average, patients had a MSCC of 33.9% (-4.60-64.86) and MCC of 49.2% (16.12-75.33) preoperatively. Complete patient characteristics are presented in Table 3.2.

In univariate analyses, a worse outcome at 6-months was associated with a lower or more severe baseline mJOA (p<0.001), greater MCC (p=0.03), a greater T2-WI hyperintensity area (p=0.04) and sagittal extent (p=0.03) (Table 3.3). In addition, a higher SCR, as assessed by Wang’s ratio (Wang et al., 2010a) and our new methodology also predicted a worse outcome, although neither of these relationships reached statistical significance (p=0.07, p=0.11, respectively). T1-WI hypointensity (p=0.26), T2-WI hyperintensity (p=0.17), Arvin’s ratio (Arvin et al., 2011) (p=0.26) and MSCC (p=0.27) were not related to outcome univariately.

A multivariate logistic regression model was constructed using a single variable to describe both T1-WI signal change (+/- of hypointensity) and anatomical measurements (MCC), and two variables to describe T2-WI signal characteristics (signal intensity, Wang’s SCR (Wang et al., 2010a); and signal hyperintensity size, sagittal extent). These four imaging variables, along with baseline mJOA, yielded an area under the receiver operating characteristic curve (AUC) of 0.85. Reduction of variables to create parsimony resulted in a final model including T1-WI hypointensity (OR=0.24; CI=0.07-0.87), MCC (OR=0.94; CI=0.90-0.98) and baseline mJOA (OR=1.74; CI=1.35-2.24). According to this image-based model, a worse outcome was best predicted by presence of T1-WI hypointensity, a greater MCC and a more severe baseline mJOA score. This model had an AUC of 0.84 (Figure 3.4) and
a reduced AIC and BIC compared to the initial five-variable model (AIC = 94.78 vs. 98.29; BIC = 104.78 vs. 113.29).

In comparison to the above model, the AUC for the baseline mJOA-only model was 0.81. The likelihood-ratio test indicated superior performance of the full model compared with the baseline mJOA-only model (p<0.0001).
Table 3.2
General and MRI characteristics of patients for whom MRI analysis was conducted. Continuous variables are presented as means and standard deviations, with the range in parentheses. MSCC = Maximum Spinal Cord Compression; MCC = Maximum Canal Compromise.

<table>
<thead>
<tr>
<th>General Characteristics (n=114)</th>
<th>x±SD (Range), unless otherwise indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.75±11.84 (29-86)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>71/43</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>26.55±34.24 (1-240)</td>
</tr>
<tr>
<td>Baseline mJOA</td>
<td>12.81±2.74 (5-18)</td>
</tr>
<tr>
<td>Smoking status (Y/N)</td>
<td>30/84</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>T2-WI Hyperintensity (Y/N)</td>
<td>75/36</td>
</tr>
<tr>
<td>T1-WI Hypointensity (Y/N)</td>
<td>29/79</td>
</tr>
<tr>
<td>Arvin’s Signal Change Ratio</td>
<td>0.43±0.13 (0.21-0.92)</td>
</tr>
<tr>
<td>Wang’s Signal Change Ratio</td>
<td>1.49±0.41 (0.91-3.1)</td>
</tr>
<tr>
<td>New Signal Change Ratio</td>
<td>1.42±0.38 (0.89-2.97)</td>
</tr>
<tr>
<td>MSCC (%) (n=108)</td>
<td>33.91±15.34 (-4.60-64.86)</td>
</tr>
<tr>
<td>MCC (%) (n=108)</td>
<td>49.24±12.95 (16.12-75.33)</td>
</tr>
<tr>
<td>Sagittal Extent of T2-signal change (n=111)</td>
<td></td>
</tr>
<tr>
<td>Group 1 = 0 (n=36)</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 &gt;0, ≤0.75cm2 (n=23)</td>
<td>0.58±0.12</td>
</tr>
<tr>
<td>Group 3 &gt;0.75, ≤1.50cm2 (n=24)</td>
<td>1.15±0.20</td>
</tr>
<tr>
<td>Group 4 &gt;1.50cm2 (n=28)</td>
<td>2.17±0.74</td>
</tr>
<tr>
<td>Area of T2-signal change (n=111)</td>
<td></td>
</tr>
<tr>
<td>Group 1 = 0 (n=36)</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 &gt;0, ≤0.20cm2 (n=33)</td>
<td>0.13±0.04</td>
</tr>
<tr>
<td>Group 3 &gt;0.20, ≤0.35cm2 (n=22)</td>
<td>0.26±0.04</td>
</tr>
<tr>
<td>Group 4 &gt;0.35cm2 (n=20)</td>
<td>0.51±0.16</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>mJOA at 6-months (n=101)</td>
<td>15.16±2.73 (2-18)</td>
</tr>
<tr>
<td>≥16</td>
<td>55 (54.46%)</td>
</tr>
<tr>
<td>&lt;16</td>
<td>46 (45.54%)</td>
</tr>
</tbody>
</table>
Table 3.3
Univariate and multivariate relationship of MRI parameters and baseline mJOA with a dichotomized mJOA outcome (≥16, <16) at 6 months. Odds ratios indicate the odds of having an mJOA of ≥16 in light of the corresponding MRI findings.

<table>
<thead>
<tr>
<th>Imaging Predictor (Univariate)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-WI Hyperintensity (n=98)</td>
<td>0.55 (CI: 0.23, 1.28)</td>
</tr>
<tr>
<td>T1-WI Hypointensity (n=95)</td>
<td>0.59 (CI: 0.23, 1.50)</td>
</tr>
<tr>
<td>T2 signal hyperintensity sagittal extent (n=98)</td>
<td>0.67 (CI: 0.48, 0.95)</td>
</tr>
<tr>
<td>T2 signal hyperintensity area (n=98)</td>
<td>0.67 (CI: 0.46, 0.99)</td>
</tr>
<tr>
<td>New signal change ratio (n=98)</td>
<td>0.42 (CI: 0.15, 1.21)</td>
</tr>
<tr>
<td>Wang’s Ratio (n=98)</td>
<td>0.41 (CI: 0.16, 1.09)</td>
</tr>
<tr>
<td>Arvin’s Ratio (n=98)</td>
<td>0.18 (CI: 0.01, 3.57)</td>
</tr>
<tr>
<td>Maximum spinal cord compression, MCC (n=96)</td>
<td>0.98 (CI: 0.96, 1.01)</td>
</tr>
<tr>
<td>Maximum canal compromise, MCC (n=96)</td>
<td>0.96 (CI: 0.93, 1.00)</td>
</tr>
</tbody>
</table>

**Final Model Predictors (Multivariate) n = 90**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mJOA</td>
<td>1.74 (CI: 1.35, 2.24)</td>
</tr>
<tr>
<td>T1 signal hypointensity</td>
<td>0.24 (CI: 0.07, 0.87)</td>
</tr>
<tr>
<td>Maximum canal compromise, MCC</td>
<td>0.94 (CI: 0.90, 0.98)</td>
</tr>
</tbody>
</table>

**mJOA-only Model n = 90**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mJOA</td>
<td>1.64 (CI: 1.33, 2.04)</td>
</tr>
</tbody>
</table>
**Figure 3.4**

A receiver operator characteristic curve of the final model based on 3 predictors of outcome: T1 hypointensity (OR=0.242; CI=0.07-0.87), spinal canal compromise (OR=0.94; CI=0.90-0.98) and baseline mJOA, (OR=1.743; CI=1.35-2.24). The area under the curve of this model (~0.84) indicates a “very good” ability to discriminate between a dichotomized mJOA postsurgical outcome (≥16, <16).
3.4 Discussion

In the typical CSM patient, MRI of the cervical spine provides static images of spinal cord compression. This manifestation is the consequence of degenerative anatomical changes that have resulted in the aberrant migration of soft tissue as well as bone structures (i.e. osteophytes) into the spinal canal. Insult to the cord may be further exacerbated by dynamic compression resulting from hypermobility and cervical joint instability. Myelopathic changes are frequently observable as hyperintense changes on T2-WI and have been suggested to represent necrosis, microcavities, or spongiform changes when well-defined borders are present and edema, demyelination, and Wallerian degeneration when signal changes are diffuse (Karpova et al., 2013a). Such changes were present in approximately 67.6% of patients in the present study. Less frequently, and generally present in more severe case of CSM, patients may also display T1-WI hypointensity changes, indicating cavitation, ischemia and frank loss of neuronal tissue (Tetreault et al., 2013a). Approximately 26.9% of patients presented with such changes.

Numerous investigators have assessed the association between various preoperative MRI parameters and postsurgical outcome in CSM patients; however, their collective results have provided an unclear picture in terms of predictive value and practical application (Tetreault et al., 2013a, Vedantam and Rajshekhar, 2013, Li et al., 2011). Despite this, international spine care professionals agree that MRI is an important prognostic tool (Tetreault et al., 2014). Evidence to support this notion has recently been published in a systematic review and indicates that factors, such as combined T1-/T2-signal change, multilevel signal change and SCRs, are significant predictors of surgical outcome (Tetreault et al., 2013a). Having said this, there are several limitations in methodology that impact the interpretation of current literature. Issues of particular note include variability in approaches used to analyze and quantify structural changes as well as a lack of accepted standard protocols with respect to MRI assessment methodology. Taking these factors into consideration, in the present study, MRI analysis was conducted with a focus on
quantitative approaches and with a goal of establishing a reproducible and effective protocol for MRI assessment.

Though most of the quantitative MRI parameters assessed in the present study displayed a tendency towards significance (p<0.20), only three of these (MCC and T2-WI hyperintensity sagittal extent and area) were significant (p<0.05) predictors of surgical outcome at 6 months following univariate analysis. Interestingly, both measurements of T2-WI signal hyperintensity size (sagittal extent and area) were significantly associated with surgical outcome, indicating that the larger the signal change the lower the odds of achieving an mJOA ≥16. The finding that SCRs were not predictive of outcome indicates that perhaps such analysis is dependent on specific MRI protocols, may be dependent on technical factors, and may vary due to truncation, chemical shift, cerebrospinal fluid flow, or motion artifacts (Karpova et al., 2013c). Therefore, it cannot be concluded that these methods have no practical utility. The finding that the average patient had a much greater MCC (49.2%) than MSCC (33.9%) is understandable given that excess spinal canal space occupied by cerebral spinal fluid can allow for some migration of structures into the canal without cord compression. Therefore, patients with a narrower spinal canal, as seen in patients with congenital spinal stenosis, are likely to be at a predisposition for myelopathy development (Singh et al., 2012).

It is noteworthy that the method of analysis for MCC was a modified method that may serve to more accurately assess the level of compromise in patients with degenerative conditions. The original method was created for traumatic SCI patients and bases the degree of MCC on the diameters from the posterior margin of the vertebral body anteriorly and the anterior portion of the lamina posteriorly as seen on CT or T1-WI MRI (Fehlings et al., 1999, Fehlings et al., 2006). Compression of the spinal cord in degenerative conditions may however arise as a result of soft tissue structures that are more clearly visible on T2-WI, and therefore, assessment of diameter size between bone structures may present a false picture of canal size if osteogenic restructuring is not involved. It is therefore recommended that patients with degenerative cervical myelopathy be assessed with the modified measurement as described in the present study.
While individual parameters are useful in predicting outcome, a multivariate approach is required to assess CSM patients due to the heterogeneity of pathological manifestations. Additionally, a combinatorial assessment of MRI parameters may yield a greater predictive performance than individual parameters. Following this view, a multivariate model was constructed and included the most predictive parameters from three MRI assessment groups as well as baseline mJOA severity. The grouping of MRI parameters into these categories is based on the concept that: (1) measurements therein are usually conducted separately, (2) parameters from each group represent different pathological findings, and (3) each group is generally investigated separately in literature. The initial model had an AUC of 0.85 and included T1-WI signal change, MCC, Wang’s SCR (Wang et al., 2010a) and T2-WI signal hyperintensity sagittal extent. However, more parsimonious models are likely to reduce complexity and improve information gain and therefore the model was simplified. Accordingly, assessment of comparable efficacy from this nested model indicated that T1-WI signal analysis, MCC, and baseline mJOA severity provided greater parsimony while maintaining a similar predictive capacity (AUC=0.84) to the initial five-variable model. The inclusion of the baseline mJOA in the model is necessary to avoid regression to the mean, also, neurological function is a strong predictor of postsurgical outcome (Holly et al., 2009, Tetreault et al., 2013b), and therefore it necessitates a comparison of the final MRI-based model with one based solely on mJOA baseline severity. As measured by the likelihood-ratio test the final model provided a greater predictive capacity than the baseline-only model. Thus, on the basis of these findings, quantitative MRI analysis has a significant role in predicting surgical outcome in patients undergoing decompressive surgery for CSM.

Although external validation is necessary to confirm these results, recently published systematic reviews have associated T1-WI hypointensity with postsurgical outcome (Tetreault et al., 2013a), and indicated that patients with cervical spine stenosis are predisposed for myelopathy development (Wilson et al., 2013a). These findings conceptually support the inclusion of both T1-WI signal change and MCC in the final model and their independent efficacy in improving the predictive capacity.
Going forward, the application of newer techniques and technologies in the assessment of surgical outcome in CSM patients may allow for improvement of prediction models. Methods described by Zhang et al (2011) for example may be interesting to evaluate in the future. Furthermore, newer MRI technologies such as diffusion tensor (Jones et al., 2013, Nakamura et al., 2012) as well as upright and dynamic/kinematic MRI (Jinkins et al., 2005) may uncover additional information from which prognostic insights may be derived.

### 3.5 Limitations

There are a few limitations of this study. Though the multicenter basis of this study offers an opportunity to determine which MRI assessment methods are valid across different centers, SCRs are likely dependent on the type of MRI protocol used and therefore our insignificant findings for some these measurements may reflect technical variability. As well, patients received different types of surgical procedures, as is consistent with current practice, and this has prevented standardized treatment of patients. Additionally, MRI data was only available for a subset of the entire study population. Furthermore, MRI assessment was conducted for a sample of patients who had clinically confirmed CSM and underwent surgical treatment. Lastly, the characterization of patients with mild myelopathy and those with substantial neurological impairment using our dichotomized mJOA may marginalize patients bordering this demarcation. These patients may have had their mJOA score impacted by advancing age or alternatively may be considered to have moderate impairment.
CHAPTER 4
General Discussion, Clinical Implications, and Knowledge Translation
4.1 Key Findings

To date, there have been no prospective multicenter studies to investigate the role of MRI in predicting outcome in patients undergoing surgical treatment for DCM. The research undertaken in the previous chapter was conducted to address this knowledge gap and has demonstrated the following:

1. On univariate analysis, MCC, T2-WI hyperintensity (in terms of sagittal extent as well as area), and baseline mJOA severity are statistically significantly related with mJOA outcome at 6-months postoperatively.

2. A multivariate regression model of MRI features incorporating assessment of T1-WI signal hypointensity, MCC, and baseline mJOA severity yielded an AUC of 0.84 and offers a very good ability to predict whether patients will have an mJOA score of ≥16 or <16 at 6-month after surgery.

3. The multivariate model had a higher predictive capacity than a model solely based on baseline mJOA severity, indicating that while baseline severity is a strong predictor of outcome, MRI assessment has a significant role in predicting surgical outcome.

4.2 Basis for MRI Analysis

It has been well recognized that wear occurs in the spine of all individuals over time. This natural progression can be accelerated in some individuals, but is generally considered a part of normal physiological and adaptive changes in response to chronic use with age (Galbusera et al., 2014). Given this, imaging of elderly patients will generally depict some signs of degeneration. Indeed, in a recent review, Tracy and Bartleson (2010) indicated that over 50% of the asymptomatic population aged 40 and older may present with MRI evidence of disc degeneration or space narrowing at 1 or more levels, and another 40% may present with bone spurs. These changes can result in symptoms that are similar to those appreciated with osteoarthritic changes in other body sites such as the knee or hand, and may include
pain and restriction of movement. The multiple articular layers that comprise the spinal column, however, do not simply function to confer movement of the torso and neck, but also harbor the passage of the nervous system from the brain to the periphery via the spinal cord. As a consequence, degenerative changes of the spine may result in the failure of 2 functions of the spine: Biomechanical, and protection of the spinal cord. Compression of neural roots or individual spinal nerves can cause substantial clinical symptoms, but compression of the spinal cord and resulting myelopathy at the cervical level damages the neural pathway at an early course away from the brain, and can result in debilitation severe enough to prevent social independence. These symptoms can include motor and sensory deficits of both upper and lower limbs and also impact involuntary motor function necessary for urinary and bowel control. However, symptoms that present in patients with degenerative cervical myelopathy can also occur in a number of other neurological conditions and it is therefore necessary that a suspicion of the diagnosis be confirmed via medical imaging, with the gold standard being MRI.

4.3 Interpretation and Meaning of MRI Findings of Degenerative Changes

Given that damage to the cord is preceded by changes in the surrounding spine structure, it would be reasonable to assume that imaging evidence that depicts the cord under compression would justify intervention to prevent myelopathic symptoms from progressing. Unfortunately however, given current literature, it is not so clear that this is the case. Despite high prevalence rates of cervical spine stenosis on postmortem examination due to spondylosis or OPLL, clinical experience indicates that only a small percentage of these patients seek medical care for symptomatic myelopathy and require surgical intervention (Lee et al., 2007, Wilson et al., 2013a). In a recent systematic review by Wilson et al (2013a), it was noted that 22.6% of nonmyelopathic patients with MRI signs of cord compression due to spondylosis will develop clinical evidence of myelopathy at a median of 44-months. While some predictive factors where identified and may be used to
anticipate the development of myelopathy in these patients, the review also recognized that the majority of patients remain stable and require only conservative management.

Ambiguity with regards to the meaning of remarkable degenerative changes on MRI is, however, not only limited to patients with asymptomatic spinal cord compression. As was evident in our study, the degree of spinal cord compression varied widely, with a number of patients without frank MRI evidence of spinal cord compression despite a clinical diagnosis of CSM. There are a number of reasons for why this may be the case. Conventional MRI, though the most useful tool for evaluating patients with suspected DCM, only provides static imaging. However, hypermobile or dynamic factors may be additional mechanisms responsible for compressing the spinal cord. It is also challenging to determine the extent of insult placed upon the spinal cord using conventional MRI due to the patient’s position. When lying supine, as is routinely the case, the patient is not bearing the same weight upon the spine as they would during an upright orientation. This means that during a typical MRI exam, there is decreased downward force placed upon the intervertebral discs as well as between facet joints. Accordingly, this may result in less soft tissue migration into the spinal canal or less listhesis, and ultimately, portray an inaccurate representation of canal patency.

In contrast to the unclear relationship between image evidence of spinal cord compression and the state of myelopathy, when signal intensity changes present on T1-WI or T2-WI it is clear that an intrinsic pathological process has occurred in the spinal cord. Hyperintensity changes on T2-WI may represent a wide range of pathologies depending on the characteristics and have been proposed to indicate (1) microcavities, spongiform changes when well-defined borders are present, and (2) edema, demyelination, and Wallerian degeneration when signal changes are diffuse (Karpova et al., 2013a, Mehalic et al., 1990, Chen et al., 2001). Hypointensity changes on T1-WI appear less frequently, are more difficult to evaluate, and are believed to represent frank loss of neuronal tissue or cavitation (Tetreault et al., 2013a, Al-Mefty et al., 1988). While most patients will present with signal changes, as is supported with our findings, many do not; therefore, the
absence of signal intensity changes does not preclude a diagnosis of DCM. There may be a few reasons for why this may be the case. Compelling arguments could be made that patients without signal change may represent those at early stages of myelopathy, or perhaps represent those who experience symptoms due to dynamic forces rather than persistent or static compression. These, however, remain speculations.

In a recent survey of spine care professionals there was consensus that both clinical and imaging factors are predictive of outcome in patients surgically treated for CSM. In terms of the imaging predictors, there was international consensus that MRI is an important prognostic tool and that the presence of signal change on the spinal cord on T2-WI and combined T1/T2-WI are the most important of these (Tetreault et al., 2014).

4.4 Approach and Rationale for the Use of MRI Measurement Techniques

Understanding that degeneration of the spine can present with great heterogeneity sets the basis for creating parameters that assess the wide spectrum of changes that may appear on MRI of patients with DCM. Given the literature and methods at our disposal, MR imaging of these patients was investigated in 3 capacities: (1) anatomical changes including spinal canal size as well as spinal cord compression, (2) T1-WI signal intensity change, and (3) T2-WI signal intensity change, including the quantitative analysis of its size and relative intensity.

Anatomical changes in terms of reduction in the canal size and compression of the spinal cord have been effectively measured previously using methods described by Fehlings et al (1999) for the assessment of patients with traumatic SCI. The original method assessed MCC using CT and MSCC using MRI. Subsequent investigation by Fehlings et al (2006) assessed the intrarater and interrater reliability of these methods and additionally assessed MCC using T1-WI. Their findings indicated that the interclass correlation coefficients (ICC) in terms of intrarater reliability were quite high, ranging between 0.90-0.97 for MCC and MSCC.
Contrarily, the interrater reliability demonstrated disparity between investigator measurements, ranging between 0.35-0.56. More recent work by Karpova et al (2013c) assessed the reliability of MSCC and MCC specifically in patients with DCM. Their findings showed intra- and interobserver ICCs of 0.76 ± 0.08 and 0.79 ± 0.09 for T2-WI MSCC, respectively, and intra- and interobserver ICCs of 0.88 ± 0.1 and 0.75 ± 0.04 for T1-WI MCC, respectively. Overall, these findings indicate that MCC and MSCC methods have acceptable measurement reliability.

In recognizing that these methods were originally devised for the investigation of patients with traumatic SCI, some modification to the methodology is necessary, specifically for the measurement of MCC. The canal diameters on CT and T1-WI were originally measured from the posterior margin of the vertebral body to the anterior portion of the lamina. Compression of the spinal cord in degenerative conditions may however arise as a result of soft tissue structures that are more clearly demarcated on T2-WI, and therefore, assessment of diameter size between bone structures may present a false picture of canal size if soft tissue structures are chiefly involved. In the publication by Arvin et al (2011), T2-WI were used for the analysis of MCC in patients with CSM, and it appears that measurement of canal size was done in this modified fashion, although this was not specifically indicated. As was described in chapter 3, our analysis of MCC was based on this modification and was conducted on T2-WI. This is especially noteworthy as MCC was one of the two MRI parameters included in our final prediction model (the other being T1-WI hypointensity). In our model, an increased MCC was related with a worse surgical outcome, and specifically, the odds for a good outcome (mJOA ≥16) decreased 6% for every 1% increase in MCC.

In our analysis, the MSCC methods, contrary to MCC, were unaltered and conducted on T2-WI. In terms of its prognostic value, MSCC did not relate to outcome univariately, and was not included in our final model. Indeed, while not directly addressing our method of measuring MSCC, a current systematic review by Karpova et al (2013a) determined that the relationship between spinal cord compression using various methods and surgical outcome remains unclear. Given that compression of the spinal cord is a fundamental pathological component
responsible for the development of myelopathy, this finding is somewhat perplexing, and perhaps serves to illustrate that the various methods used to assess spinal cord compression do not reliability represent the pathological state of patients. Karpova et al (2013a) offer a number of compelling reasons for why this may be the case including that DCM may appear as a multilevel disease with varying degrees of cord compression through the course of the cervical spine. They suggest that techniques assessing accretive effects of compression should be considered for future investigation instead of assessment at a single level (Karpova et al., 2013a).

Perhaps it should also be considered that compression arising from different tissue might exert different degrees of force upon the spine. While this remains speculative, compressive forces arising from soft tissue may demonstrate greater compliance than forces arising from solid structures such as bone.

Another set of MRI assessment techniques measure signal intensity changes present in the spinal cord on T1-WI and T2-WI. In our investigation, T1-WI signal hypointensity was the second of two MRI parameters (the other being MCC) that was included in the final prediction model. Presence of T1-WI signal hypointensity indicated that patients are likely to have a worse outcome than those without a signal change. This prognostic effect was independent of T2-WI signal hyperintensity, since it was not represented by a parameter in the final model. The recognition that T1-WI indicates a frank loss of neural tissue (Tetreault et al., 2013a, Al-Mefty et al., 1988), suggests that these patients are likely to experience less improvement in their neurological dysfunction. Therefore, it is not surprising that the presence of T1-WI signal hypointensity in our model was related with an outcome that suggests substantial residual neurological impairment (mJOA <16) after surgery. The relatively low prevalence of T1-WI signal change in patients with DCM (26.9% in our study) makes this parameter particularly clinically relevant for those in whom it presents.

T2-WI signal hyperintensity on the spinal cord has been much more thoroughly investigated by researchers than T1-WI signal hypointensity. In general, T2-WI signal hyperintensity can be broken down in two categories of parameters, those measuring size, and those measuring the degree or quality of signal intensity.
Size measurements have been typically conducted in terms of assessing the area and the number of cervical levels involved on sagittal view. Given that a greater size of signal change indicates more anatomical involvement, it would seem reasonable to assume that a larger size would indicate more extensive pathology. Indeed, during our investigation, univariate analysis showed that both area and sagittal extent (measured in cm) could be used to predict surgical outcome at 6-months; however, neither of these contributed to additional predictive capacity of our final prediction model and therefore were not included. Recent reviews that have discussed findings based on the size (in terms of area and sagittal extent) of T2-WI signal changes have provided unclear conclusions regarding the utility of these parameters and their ability to predict outcome (Tetreault et al., 2013a, Karpova et al., 2013a, Vedantam and Rajshekhar, 2013). The studies included in these reviews have mostly focused on evaluating whether patients have focal or multisegmental (extending multiple vertebral levels) T2-WI signal change. However, in the absence of a quantitative assessment of the sagittal extent, there remains ambiguity in the delineation between focal and multisegmental involvement. In our investigation, sagittal extent was measured quantitatively in cm rather than classifying signal changes as focal or multisegmental. Our approach is recommended for future investigation as it provides a more objective measurement of extent and retains the ability for specific size categorization thereafter. Measurement of signal intensity size in terms of sagittal area has not been routinely reported. There may be many reasons for this and it can be speculated that this may be the result of difficulty in demarcating areas of signal change that appear fuzzy or faint. Furthermore, it may be difficult to establish which MRI sagittal slice to use as the signal hyperintensity may span across multiple slices. Therefore, ambiguity and decreased reliability may arise. To overcome such problems in our study, we devised a specific approach that was discussed in section 3.2.2, and used three investigators who reviewed and agreed upon which slice was most appropriate before measurements were performed. It would be recommended that future analysis by investigators would likewise adopt a consistent approach for such measurements, as it is likely to increase the reliability.
Though interesting work has come from the investigation of T2-WI signal hyperintensity size (sagittal area/extent), a large focus has also been placed on assessing the degree of deviation of hyperintensity signal away from what is considered to be normal, as well as the qualitative nature of the signal intensity change. In a recent review by Vedantam and Rajshekhar (2013), a number of qualitative categorization methods derived from other authors were summarized. While the categorization methods differed and have not been validated, there appeared to be a general consensus that T2-WI hyperintensities can either present as highly intense, focal and well circumscribed, or less hyperintense, diffuse and without a clear margin. In recognizing this distinction, many have proposed that these changes not only represent different pathological states, but also indicate different recovery potentials after spinal cord decompression (Tetreault et al., 2013a). As mentioned earlier in the thesis, less hyperintense and diffuse changes are considered to represent milder changes and potentially present an opportunity for regeneration. Conversely, focal and hyperintense changes are believed to represent cavitation and necrosis (Tetreault et al., 2013a, Al-Mefty et al., 1988). These associations are supported by the findings that very hyperintense T2-WI focal changes appear to be isointense with CSF and that they are frequently accompanied by hypointense T1-WI changes, which are considered to represent cavitation and loss of neuronal tissue. Defining and categorizing through visual inspection which T2-WI signal changes are less or more hyperintense, and those that are focal or diffuse, is however a subjective endeavor. As a consequence, the potential subjectivity and differences in classification may serve as an explanation that despite the many indications that signal changes can be related to outcome by single center studies, a consensus on their utility has not been definitively substantiated upon replication. More recent research, including that undertaken by us, has attempted to address these concerns by assessing T2-WI signal change objectively through quantitative methods that measure the degree of T2-WI intensity deviation (Arvin et al., 2011, Wang et al., 2010a, Zhang et al., 2010, Zhang et al., 2011). Though slightly different methods were used, the premise behind most of these studies was to assess the T2-WI signal hyperintensity at the region of interest against baseline
values from various non-pathological reference sites (spinal cord or CSF). In addition to these methods, in our study we also recorded a parameter that represented a simple absence or presence of signal change. Despite these various methods, none of the measures indicated a statistically significant univariate (or multivariate) relationship with surgical outcome, although Wang’s and our modified SCR method approached statistical significance. There are many reasons for why this may be the case: (1) Signal changes may demonstrate different functional impairment based on their anatomical site; (2) signal intensity measurements are based on a single slice and therefore do not take into account volume; (3) multiple discontinuous signal intensity changes may present; and, (4) signal intensity changes are unlikely to represent a linear relationship with disease severity. These factors make it challenging to relate signal intensity changes with a pathological state and, therefore, may be limited in their ability to predict surgical outcome using current approaches.

4.5 Creating a Multivariate Prediction Model for Predicting Surgical Outcome

In order to evaluate the role of any of the MRI parameters in predicting surgical outcome, it is necessary to objectively assess the functional change that has occurred between the preoperative state, and postoperatively, when the effect of surgery can be measured. Indeed, there are a few assessment tools that are at the disposal to clinicians for evaluating functional status of DCM patients and a number of these are frequently used in concert in clinical practice. Of these, the mJOA has emerged as a widely accepted standard for assessing the functional status (Tetreault et al., 2013c). The clinical examination assesses motor, sensory as well as autonomic function out of a maximum score of 18. Although patients can technically range in scores from 18 to 0, substantial debilitation arises after the loss of only a few points on the scale. In their clinical prediction model of surgical outcome in CSM patients, Tetreault et al (2013c) used a dichotomized outcome to indicate if patients had an optimal or suboptimal surgical outcome using an mJOA score dichotomized at 16,
and this method was likewise adopted in this study. The interpretation of this outcome was that a mJOA score of ≥16 represented patients with mild impairment, whereas a score of <16 represented those with substantial residual functional impairment. However, since a single point can sway a patient between groups, there remains a limitation to such categorization.

The construction of our prediction model was based on incorporating the best MRI parameters, which we considered to be the ones that had the lowest p-value on univariate analysis. The categorization of MRI parameters into three groups of T1-WI signal analysis, T2-WI signal analysis, including signal size and intensity ratio, and anatomical measurements (based on T2-WI) yielded four initial MRI parameters: T1-WI hypointensity, Wang's SCR (Wang et al., 2010a), sagittal extent of T2-WI and MCC. The initial model with the inclusion of baseline mJOA provided an AUC of 0.85. While the AUC represents a very good ability to discriminate between our dichotomized outcome, it is necessary to evaluate whether the model can be simplified while offering a similar predictive capacity. This is because simpler models are easier to use and are less prone to measurement error. We therefore used the Akaike and Bayesian information criterions to assess the tradeoff between predictive capacity and complexity of variables in the model. In doing so, we were able to create a more parsimonious model that was comprised of 3 variables (MCC, T1-WI hypointensity, mJOA0) that had comparable predictive discrimination in terms of AUC (AUC=0.84 vs. 0.85) while reducing both the AIC and BIC (AIC = 94.78 vs. 98.29; BIC = 104.78 vs. 113.29).

In using the mJOA as the principal outcome measure, it was necessary to include the preoperative severity of patients into the prediction model. In doing so, however, it also necessitated that our final model be compared to one that considered the predictive capacity of only baseline mJOA, so that role of MRI could be clearly demonstrated. Using the likelihood-ratio test, we were able to demonstrate that there was a significant statistical difference between the models and that indeed a greater predictive capacity existed for the model including MRI features. This finding demonstrates that the MRI parameters had a distinct prognostic role.
4.6 Clinical Implications

The purpose of this research was to provide information that would help predict how patients can expect to fare after surgical treatment. Now that it has been shown that MRI can indeed provide such information, what are the clinical implications? First and foremost, the research has provided clear support that all patients, in the absence of contraindications, should undergo an MRI examination of their cervical spine. Secondly, at minimum, the MRI should be quantitatively assessed to provide the parameters that were found to be predictive of outcome in the model presented in chapter 3.

When conducting the MRI assessment, the surgeon can obtain an objective estimation on how the patient can expect to fare (based on the mJOA score) after surgical treatment. A suboptimal outcome (<16 mJOA) is best predicted by the presence of T1-WI hypointensity, a greater MCC and a more severe baseline mJOA score. Patients with findings indicating that a suboptimal outcome is likely, may be weary of surgery, but should be informed that they can still benefit from surgical treatment as it can slow or arrest the disease process. On the other hand, patients who are likely to achieve an optimal outcome based on their MRI findings may be more inclined to undergo surgical treatment. Given these results, surgeons may feel more confident in providing recommendations for these patients. However, it is important to emphasize that the baseline severity of patients is an essential component of the model presented and stresses that MRI findings need to be closely related with the clinical context.

Indeed, given the strong predictive contribution of baseline severity to the prediction model, it is worthy to also question the clinical relevance of the additional predictive performance garnered from the inclusion of MRI features. In terms of probability, the improvement between the baseline severity model and the model including MRI features (without rounding the AUC) was 0.807 to 0.845, representing an improvement in predictive probability close to 0.04 (0.038). Viewed another way, this suggests that approximately 20% [(0.038/0.194)*100] or 1 in 5 patients who would have received incorrect guidance with the mJOA-only model
could have received correct guidance using the MRI-based model. In terms of its clinical significance, if we were to conservatively estimate that 20,000 individuals received surgical treatment for DCM per year in North America and all were evaluated by both models, the mJOA-only model would correctly estimate 16,140 outcomes \((20,000 \times 0.807)\), while the MRI-based model would correctly estimate the outcome for 16,900 \((20,000 \times 0.845)\). This means that 760 individuals per year who would have received incorrect guidance based on the mJOA-only model could have received correct guidance using the MRI-based model.

Of course, it is clear that our prediction model cannot substitute good clinical judgment, but these tools do provide objective estimates that can be used to inform the surgeon and help guide patient expectations. It is also evident from previously reported literature that the general population will present with abnormal findings on MRI without having symptoms of DCM, and therefore, it remains essential that MRI examinations be undertaken after an extensive clinical examination.

Since most patients will receive a MRI examination for diagnostic purposes and have it read by a radiologist, it would take perhaps an additional 5 minutes to perform the quantitative measurements outlined. Therefore, the adoption of these findings is practical and represents a feasible means of improving patient care.

### 4.7 Knowledge Translation: Bringing Research Into Practice

Since this research can potentially impact clinical care by providing information that improves surgical decision-making and management of patient expectations, a natural progression is to translate the findings of this research into clinical practice. Accordingly, in the following sections further information on identifying knowledge users, methods for dissemination of the research, and optimizing knowledge translation are discussed in greater detail.

#### 4.7.1 Identifying Knowledge Users

Generally speaking, knowledge users of research can encompass managers of health care resources, policy decision-makers and clinicians amongst others \((\text{CIHR, 2014})\). In order to effectively translate findings from research to the bedside it is essential
to identify the correct individuals who are the gatekeepers for the implementation and clinical application of the knowledge. The research that we have brought forth is relevant most specifically to individuals who read MRIs and are involved in the medical care of DCM patients. Broadly speaking this group includes radiologist, neurosurgeons, orthopedic surgeons, neurologists and rehabilitation specialists. However, since the research also provides insight into the prognosis after surgical treatment, healthcare funders may also have a keen interest in learning of the impact of the research as it relates to determining the likelihood for treatment efficacy.

4.7.2 Dissemination of Knowledge

Disseminating the key findings brought forth in the thesis can be done through multiple avenues. Conventionally, early on, research is presented at national and international conferences that are focused on the main subject area of the work. For our research, such conferences would include those surrounding the area of spine, radiology and neuroscience. Presenting the research provides not only a means to disseminate the information to the most critical knowledge users (including neurosurgeons, radiologists and orthopedic surgeons), but potentially also to policymakers and managers of health care resources.

Commonly, research should then be peer-reviewed and published to communicate the purpose, what has been learned, and how it can impact status quo medical care. Publication of work in a journal and listing on databases such as PubMed provides access to the research and allows for its detailed review by those who are interested. Once the work is readily available, efforts to encourage readership and application of the findings should follow. This may be achievable through the engagement of media and through promotion by authorities in the field; however, the efficacy of such promotion would largely depend on interest in the subject. To stimulate this interest, dissemination through social media (e.g. twitter) with links to the research is possible but depends on a previously developed social media presence or through sponsorship, with the latter likely requiring significant funds. In addition to this, readership may also be improved through the publication
of research as open-access, which remains an option in most journals even after publication.

Less commonly, but also possible, is the creation of learning modules. For the research presented within this thesis, detailed teaching of the methods for the quantitative analysis of MRI in DCM patients to knowledge users, namely radiologists, neurosurgeons, neurologists and orthopedic surgeons, may be highly effective in translating the research from academia into practice. In addition to disseminating the key learning points, such sessions can also provide valuable feedback from the knowledge user, which can be used to improve knowledge translation and identify ongoing knowledge gaps.

4.7.3 Optimizing Knowledge Translation

To translate knowledge into practice it is essential to convey to the knowledge users the potential for the research for improving patient care. To achieve this, it is necessary to describe the findings of the research and how it will impact the clinical decision-making process. Our findings that T1-WI hypointensity and MCC are important in determining outcome, for example, should be well communicated so that reasons for the uptake of these assessment techniques into practice can be appreciated. Unfortunately, it is however widely recognized that translating evidence-based medicine into practice is often met with great challenges (Bradley et al., 2004). Therefore, to facilitate and optimize the uptake of our research, it may serve well to start by introducing the additional MRI analysis methods through a pilot program. This may serve to uncover practical issues, deficiencies in communicating the knowledge transfer, and potential administrative roadblocks for the application of the research in the clinical practice. The pilot program may serve as a valuable way to identify problems before efforts for wider knowledge dissemination are undertaken.
4.8 Limitations

As previously outlined at the end of chapter 3, there are a number of limitations that have to be taken into consideration. MR images may not be obtained routinely worldwide and there are substantial costs associated with acquiring them. Additionally, image acquisition and quality may differ between centers and may result in technical challenges and hinder generalizability. Conventional MRIs are also limited in their ability to detect dynamic pathoetiologies and do not account for degenerative changes in the spine that may occur when patients are standing upright and bearing the weight of their head.

Interpretation of the findings must also take into consideration that patients with DCM present with heterogeneous anatomical changes of the spine and therefore multiple surgical treatment strategies were used. Furthermore, the dichotomization of the mJOA outcome into two groups may marginalize patients that border the demarcation. Additional, noteworthy limitations include the following:

1) **Model Comparison** - The final MRI model was only compared to a model containing baseline mJOA, and although it demonstrated that it is superior to the mJOA-only model, this assessment does not provide information on whether it would be superior to a multivariable clinical-based model.

2) **Inclusion of baseline mJOA** – The final model was not only based on imaging factors but also included baseline mJOA. While this is noteworthy, the inclusion of baseline mJOA is necessary to address the statistical phenomenon of regression to the mean.

3) **Dichotomous mJOA outcome** – Prediction of patient outcomes was not assessed linearly in terms of change. Looking at differences in the mJOA would be useful to observe whether subtle changes not large enough to move patients between the dichotomous groups could be predicted. However, the ceiling effect of the mJOA and the recognition that not all points on the mJOA score carry equal weight makes this a challenging endeavor when using linear regression modeling.
4.9 Conclusion

In counseling patients who are considering surgical treatment for DCM, it is necessary to provide information on their anticipated recovery. Since MRI is routinely conducted to confirm a diagnosis of DCM, information regarding surgical outcome derived from its assessment provides a unique opportunity to ascertain additional guidance. In recognizing this, it was the principal objective of this thesis to investigate what role MR imaging plays in predicting the surgical outcome of patients treated for DCM. To study this relationship we evaluated a cohort of patients from the AOSpine-NA prospective and multicenter study, and hypothesized that MRI characteristics would be prognostic of outcome. In conducting our analysis, we created a protocol to facilitate the systematic review of MR images based on previously published and modified methods. Through univariate analysis we indicated that a greater MCC and greater T2-WI hyperintensity size, in terms of both area as well as sagittal extent, was significantly associated with substantial residual neurological impairment at 6-months after surgery. We further demonstrated using multivariate logistic regression, that the presence of T1-WI signal change and degree of MCC, in addition to baseline functional impairment, provided a very good ability (AUC of 0.84) to discriminate between our dichotomous outcome (mJOA <16, ≥16). Furthermore, this model demonstrated superior predictive capacity than a model based solely on baseline functional impairment and supports that MRI has a separate and distinct role.

Our study represents the only prospective and multicenter study to date to investigate the role of MRI in predicting surgical outcome. We have utilized a large number of MRI measuring techniques and have determined through multivariate analysis that MRI factors have a distinct capacity to provide information on how patients can expect to fare. This information is pivotal for both patients, who must decide whether to undergo surgical treatment, and for clinicians, who are tasked with making therapeutic recommendations. Therefore, it is strongly recommended that a detailed MRI analysis with particular emphasis on MCC measurement and
evaluation of T1-WI signal hypointensity be conducted in all surgical candidates to help guide clinical decision-making and manage patient expectations.
CHAPTER 5
Future Directions
5.1 Introduction

While considerable efforts have been made in this thesis to address the present knowledge gap regarding the role of MRI in predicting surgical outcome, there remains ample opportunity to investigate this subject further. In the following sections, a number of worthy future directions of this research are explored.

5.2 Assessment of Reliability and External Validity

It would be a valuable contribution to the field to establish the measurement reliability of the quantitative MRI methods outlined in this thesis, as it will determine whether these measurements are effective tools that can be translated from academic centers into clinical practice. In conducting this research, it would be imperative to have a team of experts agree on a protocol for MRI assessment.

The reliability of the quantitative MRI measurements can be estimated by assessing the intraclass and interclass correlation coefficients of multiple investigators. It would be preferred that this undertaking would include a diverse group of specialists coming from different global regions. The results can identify methods that are effective and indicate how they can be improved going forward.

In addition, if baseline clinical severity assessment (via the mJOA) were collected when conducting such research, there would be a unique opportunity to externally validate the prediction model presented in this thesis.

5.3 Combining the Predictive Capacity of Imaging and Clinical Parameters

Predicting surgical outcome of DCM patients can also be achieved using clinical parameters. As discussed earlier in the thesis, a clinical prediction model based on the full AOSpine North America study cohort was published by Tetreault et al (2013c) very recently. Given the findings presented in chapter 3, it would be interesting to pursue future research that incorporated the combined predictive capacity of clinical and imaging factors. Since such work will likely entail an investigation of multiple parameters, it may become necessary to investigate a much
larger cohort of patients to adequately present the diverse clinical pictures that patients may manifest with. Additionally, as parsimonious models are preferred, it is plausible that some of the many previously established predictors would be removed from a combined model. This may be beneficial however, as it may lead to the retention of highly predictive parameters. A combined model may result in a comparable or even superior predictive capacity than either a clinical or imaging model in isolation.

5.4 An Approach for Defining T1 and T2 Weighted MRI Signal Changes Quantitatively

Current assessment for determining the presence or absence of signal change on T1-WI and T2-WI is largely based on visual inspection. Though there are merits to this method as it can save time, particularly in cases where signal intensity is distinctly contrasted from adjacent tissue and is well circumscribed, it can be challenging to classify a definitive presence of signal change when the intensity differences are weak and appear fuzzy or diffuse. This difficulty becomes clinically relevant when assessing patients for anatomical evidence of myelopathy, since prognostic information is commonly conveyed in terms of the binary classification of presence or absence.

In lieu of visual inspection, it may be possible to develop quantitative measurement techniques. This may be achievable by analyzing the signal intensity of the entire sagittal plane of the cervical spinal cord (C2-C7) and plotting the distribution of signal intensity. It would be expected that the signal intensity would distribute normally and therefore deviations of intensity frequencies (i.e. hyperintensity regions on T2-WI and hypointensity regions on T1-WI) could be statistically evaluated. The concept is visually described in Figure 4.1. Moreover, this process could serve as a potential tool to define a quantitative level of signal intensity deviation that is necessary to constitute a definitive region of altered signal intensity. Comparing the frequency of signal change voxels to the overall amount of voxels could also estimate the size of signal intensity change relative to the entire
cervical spinal cord. This could be calculated by comparing the quantity of voxels under the normal curve to the quantity of voxels under the distribution of the abnormal signal intensity curve.

Finally, if signal intensity changes are converted into signal change ratios as we have shown in chapter 3, there is an opportunity to assess whether different degrees of deviation represent different anatomical pathologies. Since intensity changes do not represent anatomical changes through a linear relationship, future analysis of signal change ratios may be better evaluated through cluster analysis methods. It may also be appropriate to conduct such analysis using true T2 MRI sequences instead of T2 weighted sequences, as this would reflect a more accurate T2 image of the spinal cord.
Figure 5.1
A conceptual illustration of how T1-WI and T2-WI signal change could be defined quantitatively. Using a sagittal MR image the signal intensity on T1-WI and T2-WI of the cervical spine region can be measure from C2-C7. Additionally, a region of interest can be circumscribed. When signal intensity values from each voxel in the whole area are plotted in terms of frequency, it would be expected that they would distribute normally. Signal intensity changes (hypointense, closer to 0; hyperintense, further away from 0) would form separate distributions and the deviations of these means from the norm (M1, M2) can be statistically assessed.
5.5 Advanced MRI Techniques and the Future of DCM Assessment

Over the years, with improvement in technology both in terms of hardware as well as software, additional novel application have emerged that have increased the functional utility of MRI. These improvements include the ability to obtain volumetric data, to obtain dynamic/kinematic MR imaging, and the ability of MR to provide physiological as well as chemical information. These technologies may offer a new set of approaches that can assist in a more sensitive and specific assessment of DCM. It should be taken into consideration that these technologies remain largely within the realm of research and their potential clinical application may be many years away. In the following sections, a few of these technologies and their potential utility are briefly discussed.

5.5.1 Dynamic/Kinematic & Upright MRI

One of the chief limitations to conventional MRI in evaluating DCM is that it provides static imaging. In addition to this, images are also almost exclusively obtained while the patient is lying down. To overcome these limitations future analysis of DCM may be conducted using upright-neutral position (pMRI) as well as dynamic/kinematic MR imaging (dkMRI).

When using a pMRI, the patient is upright as opposed to lying supine during image acquisition, thereby allowing for the assessment of the spine during axial loading. This is relevant for patients being assessed for DCM as IVDs function to absorb considerable compressive loads from carrying structures above the spine segments. In the setting of DDD, when a disc may have lost the structural integrity of the annulus fibrosis, potential migration of disc elements into the canal may be load-dependent. Accordingly, pMRI may serve to unmask occult disease (Jinkins et al., 2005).

dkMR obtains imaging while the patient is moving and therefore allows for the assessment of kinematic-dependent disease (Jinkins et al., 2005). During movement involving the cervical spine, patients may demonstrate hypermobility of spine segments or listhesis, which may contribute to repetitive insult upon the
spinal cord. Such a pathomechanism would be impossible to capture during static MR imaging.

Ultimately, these imaging techniques may provide essential pre- and post-operative information that have implications not only on improving prognostic guidance but also on surgical planning. Additionally, these technologies confer the ability to scan the patient in the position of clinically relevant signs and symptoms (Jinkins et al., 2005).

5.5.2 Advanced MRI Techniques: Diffusion Tensor MRI, Blood-Oxygen-Level Dependent (BOLD), and Nuclear Magnetic Resonance (NMR) Spectroscopy

There are a number of advanced MRI techniques that may offer additional methods by which patients with DCM may be assessed in the future. The most exciting of these, dtMRI, was briefly noted in chapter 1. The ability for dtMRI to map fiber tracts is of particular value for patients with DCM as it can help identify interruption of neural tract wiring due to cavity formation or Wallerian degeneration for example. A particularly interesting finding described by Jones et al (2013) was their ability to discover pathological changes in the cord prior to the finding of hyperintensity T2-WI signal changes. This finding requires additional inquiry and validation as it may help determine patients at risk for further SCI. Also, knowledge of the evolution of signal change will allow for better understanding of the underlying disease process. It is therefore likely that substantially more work in this area will appear in the near future.

Another technique, which was also discussed briefly in chapter 1, is Blood-Oxygen-Level Dependent (BOLD) MRI. BOLD may provide useful information regarding functional and damaged neural tissue in the spinal cord. Therefore, assessing differences in pre- and post-operative BOLD may be useful in determining the potential for neurological recovery. However, while there is great potential for its clinical application, BOLD remains in the realm of investigation.
Yet another technique with potential future application for the DCM assessment is Nuclear Magnetic Resonance (NMR) Spectroscopy. Two commonly used methods for conducting NMR spectroscopy are: Single voxel spectroscopy and chemical shift imaging. Both methods allow for the analysis of the chemical environment in a region of interest on MRI (Runge et al., 2014). At the present time, NMR spectroscopy can specifically detect and assess the abundance of a number of specific chemical compounds including glutamate, N-acetylaspartate and choline (Runge et al., 2014). Given that trauma to the spinal cord is thought to be followed by a secondary injury process involving glutamate excitotoxicity and other molecular changes at the region of interest, NMR spectroscopy may serve as a unique tool for providing chemical correlations with structural changes seen on imaging.

Although many MRI techniques are being investigated and others may still emerge in the coming years, many challenges (e.g. economical and academic) for their integration into clinical practice lie ahead. Therefore, excitement over these innovations should be appreciated cautiously.
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APPENDIX

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