The comparison of outcome after arthroplasty or fusion in single level cervical disc disease

by

Jarle Sundseth

Department of Neurosurgery
Oslo University Hospital
Rikshospitalet
&
Institute of Clinical Medicine
Faculty of Medicine
University of Oslo

2017
CONTENTS

CONTENTS........................................................................................................................................3

ACKNOWLEDGMENTS .......................................................................................................................7

ABBREVIATIONS .............................................................................................................................11

LIST OF PUBLICATIONS ..................................................................................................................13

1. INTRODUCTION ............................................................................................................................15

1.1 Anatomy and physiology .............................................................................................................15
  1.1.1 Cervical vertebral column and intervertebral discs .................................................................15
  1.1.2 Spinal nerves ...........................................................................................................................17
  1.1.3 Blood supply ............................................................................................................................18

1.2 Pathophysiology ..........................................................................................................................19
  1.2.1 Disc degeneration and herniation .........................................................................................20
  1.2.2 Cervical radiculopathy and radicular pain ............................................................................20
  1.2.3 Myelopathy ...........................................................................................................................22

1.3 Epidemiology ...............................................................................................................................23

1.4 Clinical presentation .....................................................................................................................23
  1.4.1 Cervical radiculopathy and radicular pain ............................................................................23
  1.4.2 Myelopathy ...........................................................................................................................25
  1.4.3 Headache ................................................................................................................................26

1.5 Duration of symptoms and consequences ...................................................................................26

1.6 Diagnosis .......................................................................................................................................27
  1.6.1 Physical examination .............................................................................................................27
  1.6.2 Radiographic investigation .....................................................................................................29
  1.6.3 Electrophysiology ..................................................................................................................30

1.7 Natural course of cervical radiculopathy and radicular pain ......................................................31

1.8 Treatment ...................................................................................................................................32
  1.8.1 Non-operative treatment .......................................................................................................32
  1.8.2 Non-operative versus operative treatment ..............................................................................34
1.8.3 Indication for surgical treatment ............................................. 35
1.9 Surgical historical perspective .................................................. 35
1.10 Complications ........................................................................ 39
  1.10.1 Mortality ........................................................................... 39
  1.10.2 Perioperative complications ................................................. 40
  1.10.3 Postoperative complications ............................................... 42
2. AIMS OF THE THESIS .................................................................. 43
3. METHODS ...................................................................................... 45
  3.1 Participants ............................................................................... 45
  3.2 Intervention .............................................................................. 48
    3.2.1 General surgical procedure ................................................. 48
    3.2.2 Anterior cervical disectomy and arthroplasty ....................... 49
    3.2.3 Anterior cervical disectomy and fusion ................................. 50
  3.3 Assessments .............................................................................. 51
    3.3.1 Paper I .............................................................................. 51
    3.3.2 Paper II .............................................................................. 52
    3.3.3 Paper III ............................................................................ 54
    3.3.4 Paper IV ............................................................................ 56
  3.4 Statistics .................................................................................... 56
    3.4.1 Paper I .............................................................................. 57
    3.4.2 Paper II .............................................................................. 57
    3.4.3 Paper III ............................................................................ 57
    3.4.4 Paper IV ............................................................................ 58
  3.5 Ethical considerations ............................................................... 58
4. SUMMARY OF RESULTS ............................................................. 61
  4.1 Paper I ..................................................................................... 61
  4.2 Paper II ..................................................................................... 62
  4.3 Paper III ................................................................................... 62
ACKNOWLEDGMENTS

This study was based upon a collaboration between all the neurosurgical departments in Norway, including: Department of Neurosurgery and Department of Neuroradiology, Oslo University Hospital; National Advisory Unit of Spinal Disorders and Department of Orthopaedic Surgery, Clinic of Orthopaedics and Rheumatology, St. Olavs Hospital, Trondheim University Hospital; Faculty of Medicine, University of Oslo and Norwegian University of Science and Technology, Trondheim; Department of Biostatistics, Epidemiology and Health Economics, Oslo University Hospital; Department of Neurosurgery, University Hospital of Trondheim (St. Olavs Hospital); Department of Neurosurgery, Haukeland University Hospital, Bergen; and the Department of Neurology and FORMI, Oslo University Hospital Ullevål.

Nine years have passed between writing the trial protocol and the completion of this thesis. The research was carried out mainly in addition to my work as a consultant neurosurgeon at Oslo University Hospital Rikshospitalet. I received financial funding from the South-Eastern Norway Regional Health Authority (#2012009). Finally, the neurosurgical department facilitated the completion of the thesis.

There are many people I would like to thank for their input and assistance. Without your unique contributions, it would not have been possible to complete this thesis.

First of all, I would like to express my sincere gratitude to all the patients who participated.

Further, my profound gratitude to my supervisor, John-Anker Zwart, for including me at the very beginning of the Norwegian Cervical Arthroplasty Trial (NORCAT). Your support and wise counselling have been extraordinary, your constructive criticism, patient guidance, and experience have been invaluable.
To my dear friend, colleague, and co-supervisor Frode Kolstad, your patience, composure, and insightful reflections have made arduous periods easier. Your extensive knowledge and eminent surgical skills have inspired me both in research and in the operating theatre.

To Vigdis Skogly and Torun Gillebo, what would I have done without you? One thing is for sure, this study would not have taken place without your invaluable support and meticulous work over many years. Your thorough overview and impressive follow-up of our patients have been essential for the completion of this research.

To Øystein P. Nygaard, for your impressive knowledge and research experience, and for inviting me to be a part of the NORCAT from the start. Thank you for your critical, but well-founded, comments. Hege Andresen, you have always had exceptional discipline, and coordinated this study with impressive steadiness. You are organized, always helpful, and have been a great support to me on many occasions.

Oddrun Anita Fredriksli, I could not have wished for a better research partner. You are thorough and precise and have greatly contributed to solving many challenges during our work together. Lars Gunnar Johnsen, your eminent research skills and knowledge on health-related quality of life assessments have been of invaluable help.

To Sissel Reinlie and Angelika Sorteberg, for facilitating my research and the completion of this thesis. Angelika, you have been an invaluable support when I needed it.

Further, I would like to thank the Department of Neuroradiology at Oslo University Hospital Rikshospitalet, where most of the radiological investigations were conducted. A special thanks to Eva Astrid Jacobsen, for your friendly helpfulness and professional expertise. Jorun Roos, thank you for organizing the radiological follow-up.
Per Kristian Hol and the Intervention Center at Oslo University Hospital Rikshospitalet, for facilitating a radiological investigation at the very beginning of the trial.

Statistics is a difficult field. Luckily, I met you, Are Hugo Pripp, thanks to my dear colleague and friend Milo Stanisic. Despite having completed the mandatory PhD courses, my knowledge of statistics was very limited. You have taught me so much, and you became an essential part of my research.

To my dear friend and colleague Mark Züchner, who I can always count on. You are honest and dependable, and have been an important source of support on many occasions.

I would also like to thank my dear colleagues Karl Ove Skaanes and Bjarne Lied, for recruiting me to neck surgery, and teaching me the basic tricks of the trade.

Kari Toverud, your artistic medical illustrational skills have been an important part of my publications as well as this thesis.

I want to thank Gidske and Peder Jacob Sørensens Research Foundation for their financial support.

Finally, to my family who mean everything to me! My profound gratitude goes to my parents for always supporting me with their love, wisdom and knowledge, and for teaching me what is important in life. To my sister and my brother-in-law, for always being there for me.

Antje, the love of my life and my very best friend. The importance of your heartfelt support is difficult to describe. You encourage me every day and light up the grey moments. You have taught me that yesterday is history and tomorrow is a mystery, but that every moment is a wonderful gift. Your patience and faith in me have brought me safely ashore. My dear children Endre and Eline, you remind me every day what is most important in life!
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACDA</td>
<td>Anterior cervical discectomy and arthroplasty</td>
</tr>
<tr>
<td>ACDF</td>
<td>Anterior cervical discectomy and fusion</td>
</tr>
<tr>
<td>ASD</td>
<td>Adjacent segment disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COR</td>
<td>Center of rotation</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>Computed tomography</td>
</tr>
<tr>
<td>DDD</td>
<td>Degenerative disc disease</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>EuroQol-5 Dimension-3 Level</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HAD-A</td>
<td>Hospital anxiety and depression scale for anxiety</td>
</tr>
<tr>
<td>HAD-D</td>
<td>Hospital anxiety and depression scale for depression</td>
</tr>
<tr>
<td>HO</td>
<td>Heterotopic ossification</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICBG</td>
<td>Iliac crest bone graft</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental component scale</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NDI</td>
<td>Neck Disability Index</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCM</td>
<td>Porous Coated Motion</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical component scale</td>
</tr>
<tr>
<td>PEEK</td>
<td>Polyetheretherketone</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RLNP</td>
<td>Recurrent laryngeal nerve palsy</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36</td>
</tr>
<tr>
<td>VA</td>
<td>Vertebral artery</td>
</tr>
</tbody>
</table>
LIST OF PUBLICATIONS


1. INTRODUCTION

Cervical disc disease may cause ailments detrimental to one’s physical health. When conservative treatment fails, the gold standard surgical treatment for symptomatic cervical disc disease is anterior cervical disectomy and fusion (ACDF). Anterior cervical disectomy and arthroplasty (ACDA), aiming to preserve physiological motion at the operated level, was introduced as an alternative to fusion, and over the last decade it has attracted growing interest among surgeons. This thesis explores differences in clinical outcome between the two treatment modalities two years after surgery, and investigates post-surgery radiographic challenges with the motion preserving arthroplasty device.

1.1 Anatomy and physiology

1.1.1 Cervical vertebral column and intervertebral discs

The cervical section of the spine consists of seven vertebrae numbered C1 to C7 (Figure 1).

Figure 1. Sagittal T2-weighted cervical spine MRI with illustration
Atlas (C1) lacks a vertebral body, and instead articulates with the dens (odontoid process) of axis (C2). Caudally, the atlas also articulates with the axis by horizontal, flat, and wide facets. The facets’ anatomic structure allows for rotation, which is the predominate motion at C1/C2. The cervical spine permits 90° rotation from the midline, of which 25° to 30° takes place at the atlantoaxial junction. Thereafter, the motion occurs at the subaxial segments C3 to C7. Each motion segment in the subaxial spine consists of five articulations; the intervertebral disc, two facet joints, and two uncovertebral joints (Figure 2). Between the anterior located uncovertebral joints and the posterior located facets, the nerve roots exit laterally (Figure 2).

**Figure 2. Axial illustration of the cervical vertebrae C3 to C6**

The vertebrae are separated by discs consisting of nucleus pulposus and annulus fibrosus. Each disc is unique in structure and represents a response to local mechanical conditions. Its function is to spread the load on the vertebrae.

The structure of the annulus fibrosus of the cervical spine differs from that of the lumbar spine. In the lumbar spine, the collagenous fibers of the annulus are arranged in concentric laminae, while those in the cervical spine are arranged in a thick mass at the anterior part of the disc, with decreasing thickness laterally towards the uncinate processes. At the posterolateral part, the annulus consists only
of a thin layer of vertically oriented fibers, and the posterior longitudinal ligament acts as reinforcement in this area.\(^3\)

1.1.2 Spinal nerves

Thirty-one pairs of spinal nerves emanate from the spinal cord, eight of them in the cervical region. Each nerve consists of a dorsal sensory and a ventral motor root (Figure 2).

The function of each spinal nerve is based on its specific sensory and motor distribution. Unlike in the lumbar spine, the cervical spinal nerves exit above the level of the corresponding pedicle, and the numbering of the nerves is based on the lower cervical vertebrae. For instance, the C5 nerve roots exit at the C4/C5 disc space. An exception is the lowest cervical nerve, C8, that runs between C7 and the first thoracic vertebrae.

The cervical nerves C1 to C4 serve the back of the head and the neck.

- The suboccipital nerve C1 innervates the muscles at the skull base.
- C2 and C3 provide sensation to the back of the head through the greater occipital nerve, and the area behind the ear through the lesser occipital nerve. In addition, there are multiple nerves emanating from C2 and C3, providing both motor and sensory control of the neck.
- The phrenic nerve emanates mainly from C3 and C4, but also from C5. It innervates the diaphragm, enabling breathing. Damage to the spinal cord above C3 can threaten spontaneous breathing.

The brachial plexus, consisting of the nerves C5 to C8 and the first thoracic nerve, Th1, serves the upper back and upper limbs. It is a very complex composition of nerves with minimal variation from person to person.
Table 1. Spinal nerves C5 to C8

<table>
<thead>
<tr>
<th>Root</th>
<th>Root pain distribution</th>
<th>Weakness</th>
<th>Sensory loss</th>
<th>Reflex loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Medial scapular border, lateral upper arm to elbow</td>
<td>Deltoid, supraspinatus, infraspinatus</td>
<td>Lateral upper arm</td>
<td>Supinator (brachioradialis)</td>
</tr>
<tr>
<td>C6</td>
<td>Lateral forearm, thumb, and index finger</td>
<td>Biceps, brachioradialis, wrist extensors</td>
<td>Thumb and index finger</td>
<td>Biceps</td>
</tr>
<tr>
<td>C7</td>
<td>Medial scapula, posterior arm, dorsum of forearm, third and fourth fingers</td>
<td>Triceps, wrist flexors, finger extensors</td>
<td>Posterior forearm, third and fourth fingers</td>
<td>Triceps</td>
</tr>
<tr>
<td>C8</td>
<td>Shoulder, ulnar side of forearm, fifth finger</td>
<td>Thumb flexors, abductors, intrinsic hand muscles</td>
<td>Fifth finger</td>
<td>--------</td>
</tr>
</tbody>
</table>

1.1.3 Blood supply

Blood supply to the posterior fossa and the cerebral occipital lobes is provided by the vertebral artery (VA). In addition, it supplies the extradural content of the canal, the cervical vertebral bodies and, through the anterior and posterior spinal arteries, the dura and spinal cord. The VAs usually originate from the superior posterior part of the subclavian arteries.

In about 95% of cases, the VA enters the vertebral column via the foramen transversarium at C6 (Figure 3). An abnormal entrance has been observed in approximately 5% of cases, where an entry at C5 is the most frequent. The VA runs alongside the cervical vertebral column and discs through the foramina transversaria. It enters through the dura for a further intradural course at level C1. At the lower border of the pons, it joins the contralateral VA to form the basilar artery.
1.2 Pathophysiology

Cervical disc disease may affect one or more levels of the cervical spine. The most common conditions are disc herniation and degeneration with excessive osteophyte formation (Figure 4).

Figure 4. Sagittal (left) and axial (right) illustration of disc herniation and degeneration with excessive osteophyte formation
1.2.1 Disc degeneration and herniation

Before the age of 20 years, few morphologic changes occur in the intervertebral disc. From the third decade of life, however, the disc’s water content declines. In patients under 30 years of age, the disc consists of 90% water, while in the eighth decade of life the water content is 70%.

The disc’s decreasing ability to retain water results in it drying out and losing height. Combined with the strain caused by motion, disc protrusion may occur. This protrusion most often occurs in the posterior part of the disc, in the zone of least resistance, where the arrays of collagen fibers of the annulus fibrosus are very thin. The bulging or herniation of the disc may cause the compression of nervous structures like spinal nerves, the roots of the nerves or the spinal cord (Figure 5). The disc levels C6/C7 and C5/C6 are most prone to the impact of movement.

A reduction in disc height, caused by declining water content and degeneration, may lead to approximation of the vertebral bodies, which again may cause the posterior longitudinal ligament to bulge towards the spinal canal and cause a narrowing of the canal. In addition, the reduced disc height leads to the facet joint capsules being folded, resulting in a narrowing of the root canal. When two vertebral bodies get closer, it may also initiate a reactive process resulting in excessive osteophytes forming around the disc margins and uncovertebral joints (Figure 4).

1.2.2 Cervical radiculopathy and radicular pain

Cervical radiculopathy and radicular pain are caused by degenerative disc disease (DDD) in 70-75% and disc herniation in 20-25% of cases, while infections and tumors are less frequent causes.

Cervical radiculopathy caused by direct compression or compromise of the axons leads to sensory or motor loss. The pathophysiological mechanism of pain, however, is different because compression of axons alone does not elicit pain.
Howe and colleagues showed that compression of a lumbar nerve root did not elicit activity in nociceptive afferent fibers, something compression of the dorsal root ganglion did. Thus, radicular pain caused by cervical nerve root compression alone, only occurs if it involves the dorsal root ganglion. The nature of radicular pain reflects the afferent fibers that are activated due to compression, namely myelinated A-fibers and unmyelinated C-fibers. There are, however, factors other than pure mechanical nerve encroachment that are likely to contribute. Kang and colleagues reported that herniated discs produce increased amounts of matrix metalloproteinases, nitric oxide, prostaglandin E2, and interleukin-6, and that their production could be important in the pathophysiological mechanism of disc degeneration as well as of radiculopathy.

**Figure 5.** Sagittal T2-weighted cervical spine MRI with illustration of C6/C7 disc herniation (top). Axial T2-weighted cervical spine MRI (bottom left) and illustration (bottom right) with disc herniation to the left.
1.2.3 Myelopathy

A reduced volume of the spinal canal is often caused by progressive spondylosis or disc herniation, and patients with a congenitally narrow spinal canal (10-13 mm) are predisposed to cervical myelopathy.\textsuperscript{13}

Myelopathy is a neurological deficit caused by interruption of the normal transmission of neural signals in the spinal cord. Causes of myelopathy may be trauma, inflammation, autoimmune disorders, or tumors. However, the most frequent cause is degeneration, resulting in either disc herniation or in spondylosis with spinal cord compression (cervical spondylotic myelopathy [CSM]) (Figure 6). CSM is the most common cause of cervical myelopathy, and may involve one or several levels of the cervical spine. The degenerative nature of the condition usually leads to a slow progression of symptoms.\textsuperscript{14}

\textbf{Figure 6.} Sagittal T2-weighted cervical spine MRI with C5/C6 disc herniation with spinal cord compression (left). Sagittal cervical spine illustration of spondylosis and disc herniation causing spinal cord compression (right).

The exact pathophysiology underlying cervical myelopathy remains uncertain, but it is agreed that it involves both static and dynamic factors. Static factors are developmental or acquired stenosis of the cervical spinal canal, while dynamic factors are repetitive injuries of the spinal cord through motion. These mechanical
factors lead to neuron and glia cell injury as well as ischemia and apoptosis.\textsuperscript{15} It is unclear why some patients develop severe symptomatology, while others have few or no symptoms despite radiologic evidence of a similar degree of spinal cord compression.\textsuperscript{16}

### 1.3 Epidemiology

In the population-based study carried out between 1976 and 1990 in Rochester, Minnesota, the average annual age-adjusted incidence rates for cervical radiculopathy were 107.3 for men, and 63.5 for women per 100 000 members of the population, with a peak at 50 to 54 years of age.\textsuperscript{7} A recent study investigating the incidence of cervical radiculopathy in the US military from 2000 to 2009, found an incidence of 1.79 per 1000 person-years.\textsuperscript{17}

Risk factors for cervical disc disease and corresponding radiculopathy are white race, cigarette smoking and, as shown by Radhakrishnan and colleagues, prior lumbar radiculopathy in 41%\textsuperscript{7, 18} Further risk factors include the occupations of aviator\textsuperscript{19} and professional driver, and the operation of vibrating equipment.\textsuperscript{20} However, one study reported that only 14.8% of cases had a history of physical exertion or trauma preceding the onset of symptoms.\textsuperscript{7}

### 1.4 Clinical presentation

#### 1.4.1 Cervical radiculopathy and radicular pain

In most cases, acute symptoms due to disc herniation occur without any history of preceding trauma. Only 14.8% of patients have been shown to have reported a trauma.\textsuperscript{7} Spondylosis is associated with more slowly progressive ailments.

Unlike patients with isolated axial neck pain, patients with cervical radiculopathy usually present unilateral symptoms, typically neck pain radiating
into the ipsilateral arm. Cervical radiculopathy and radicular pain should be differentiated from each other, since radiculopathy is a neurological condition where a spinal nerve or its roots are blocked, causing neurological deficits.\textsuperscript{21} Typically, cervical radiculopathy is characterized by a combination of motor loss, sensory loss and impaired reflexes.\textsuperscript{9} However, none of these symptoms constitute pain. Pain, on the other hand, does not reflect loss of function.\textsuperscript{9} Radicular pain may be experienced as a shooting, stabbing, or shocking (A-fibers), and/or burning (C-fibers) feeling,\textsuperscript{9} and follows a myotomal pattern,\textsuperscript{11} while loss of sensation, burning or tingling symptoms and paresthesia usually follow a dermatomal pattern (Figure 7). Even though the pathophysiology of cervical radiculopathy and radicular pain is different, they commonly occur together.\textsuperscript{22}

\textbf{Figure 7. Cervical and cervicothoracic dermatomes}

Patients often experience symptom relief when the affected arm is raised above the head and rotated away from the affected side while looking down. Symptoms are aggravated when the patient rotates or bends the head towards the symptomatic side.\textsuperscript{11} Patients may also experience shoulder girdle, interscapular, or
trapezial pain regardless of which nerve is compressed, and without radiating symptoms.\textsuperscript{23}

1.4.2 Myelopathy

Cervical spondylotic myelopathy (CSM) is the most usual cause of cervical myelopathy, and the condition commonly develops slowly. Gradual aggravation of symptoms with sudden worsening with or without preceding trauma is typical, however, patients may have long periods of stable clinical status. Onset of symptoms usually occurs between 50 and 70 years of age.

The clinical findings vary between patients.\textsuperscript{24, 25} Symptoms often include a combination of axial neck pain and limited range of motion. The lower extremities are usually affected first. Dysfunction of the dorsal columns of the spinal cord may lead to reduced proprioception, accompanying gait changes, reduced motor strength and spasticity.\textsuperscript{26} As the condition progresses, lower motor neuron findings in the upper extremities, such as loss of strength, atrophy, and difficulty in fine finger movements, may present.\textsuperscript{26} Typical symptoms are problems with carrying out fine motor tasks such as buttoning buttons, opening jars, using a cell phone or a computer keyboard, and writing. Compression of the spinal cord may result in upper motor neuron findings such as hyperreflexia. In advanced cervical myelopathy, bowel and/or bladder dysfunction may be present.\textsuperscript{27, 28}

Cervical myelopathy may also have a more sudden or acute onset of symptoms. Acute non-traumatic myelopathy may be caused by soft disc herniation,\textsuperscript{29} or by tumors, myelitis, infections, and vascular lesions causing ischemia or hematoma.\textsuperscript{30}
1.4.3 Headache

Headache is common among patients with cervical radiculopathy and radicular pain. Persson and colleagues found this association in 161 out of 275 patients.\textsuperscript{31} In addition, patients with cervical radiculopathy and headache reported higher pain intensity in the neck, shoulder, and arm compared to patients without headache.\textsuperscript{31}

Headache arising from pathology in the cervical spine has typically been termed “cervicogenic headache”.\textsuperscript{32} Bogduk, however, suggested that this type of headache should instead be termed “referred pain from the cervical spine”.\textsuperscript{33} Occipital headache can be explained by compression of the upper cervical nerves C2 and C3, which may create symptoms related to the major occipital nerve.

Bogduk explained the referred pain from the neck to the head due to an association between the upper three cervical spinal nerves and nociceptive afferent fibers from the trigeminal nerve, where they converge into second order neurons in the trigeminocervical nucleus located in the upper cervical spinal cord. Because of this convergence, pain signals from the neck may be referred to regions of the head which are innervated by the trigeminal or cervical nerves.\textsuperscript{32}

Headache associated with the lower cervical nerves, however, cannot be explained, and the pathogenic mechanism is unclear.\textsuperscript{31, 32}

1.5 Duration of symptoms and consequences

Delayed diagnosis or treatment of symptomatic cervical disc disease may have an impact on the outcome.\textsuperscript{34, 35} Burneikiene and colleagues recently investigated this relationship in patients undergoing surgery for cervical disc disease with symptom duration of less than or more than 6 months, and concluded that patients with a shorter duration of symptoms had significantly better improvement in radiculopathy.\textsuperscript{35} Besides this recent study, there are few reports on the impact of time on outcome after surgery for cervical radiculopathy. However, regarding lumbar radiculopathy and lumbar spine
surgery, there are some reports showing that a shorter duration of symptoms before surgery resulted in improved clinical outcome.\textsuperscript{34, 36-38}

1.6 Diagnosis

The diagnosis of symptomatic cervical disc disease is based on a thorough patient anamnesis, physical examination, and radiographic assessment.

1.6.1 Physical examination

Many provocative tests have been proposed for the diagnosis of cervical radiculopathy, but the reliability and diagnostic accuracy of these tests are poor.\textsuperscript{39, 40} Five tests, however, have been reported to be useful.

- The Spurling test can reproduce symptoms in the ipsilateral arm through simultaneous extension, rotation to the affected side, lateral bending, and vertical compression. Tong HC et al. found that the test had a sensitivity of 30\% and a specificity of 93\%, and concluded that it is not sensitive, but very specific for cervical radiculopathy.\textsuperscript{41} Thus, this test is not useful as a screening test, but can be used to confirm cervical radiculopathy.

- The shoulder abduction test was initially described by Spurling as the “shoulder abduction relief test”,\textsuperscript{42} as shoulder abduction by lifting the arm above the head often relieves symptoms. The test is valuable for differentiating cervical pathology from other causes of shoulder and arm pain.

- The neck distraction test is performed by the examiner holding the patient’s head under the occiput and chin, and pulling upward, applying axial traction, which results in relief of radicular symptoms.\textsuperscript{43}
• The *Valsalva maneuver* increases intraspinal pressure and may thereby reproduce radiculopathy or radicular pain caused by nerve root encroachment. The patient sits and is instructed to take and hold a deep breath, then attempt to exhale over a 2-3-second period with gradually increasing force.\(^{39}\)

• *Elvey's upper limb tension test* has formerly been called the brachial plexus tension test.\(^{44}\) The patient is in a supine position and the affected arm is placed on the body. In the first step, the examiner abducts the arm passively, and the patient's forearm is pronated and flexed. In the second step, the forearm is extended and supinated, and in the third and final step, the patient's hand is extended from the wrist. Reproduction of radiculopathy or radicular pain in any step is considered a positive sign.

Several findings on physical examination may be suggestive of myelopathy.

• *Hyperreflexia* is often present with increased lower limb reflexes and possibly clonus.\(^{28}\) *Sustained clonus*, meaning a series of more than 3 involuntary and rhythmic contractions and relaxations of muscles as a response to stimulation, can be detected, and has a beat frequency of 5 to 8 Hz.\(^{45}\) Hyperreflexia may, however, be absent in concomitant peripheral nerve disease as cervical or lumbar nerve root compression, spinal stenosis or diabetes.

• The *inverted radial reflex*, also called the *inverted supinator reflex*, introduced by Babinski in 1910,\(^{46}\) may give rise to suspicion of stenosis at level C5/C6, and is considered by some as pathognomonic of cervical cord compression causing myelopathy.\(^{47}\) The test is positive if tapping on the distal brachioradialis tendon triggers ipsilateral finger flexion.\(^{47}\)
- Spontaneous flexion of the index finger and/or thumb due to snapping or tapping of the distal phalanx of the middle or ring finger is called the *Hoffmann's sign*.\(^{48}\)

- The *Babinski sign* is the pathological response to stimulation of the sole of the foot resulting in extension of the big toe.\(^{47, 49}\) Houten and colleagues found the Babinski sign in 83% of their patients with cervical myelopathy.\(^{50}\)

1.6.2 Radiographic investigation

1.6.2.1 Plain X-ray

In order to get an impression of the overall configuration of the spine, conventional X-rays are often useful. They also provide an impression of the degree of degeneration or spondylosis. Functional images with flexion and extension views are important to reveal any instability that cannot be seen on a static X-ray.\(^{51}\) However, disc herniation and spinal cord compression are difficult to verify.\(^{52, 53}\)

1.6.2.2 Myelography

In myelography, intrathecal contrast medium is used to evaluate nerve roots, the spinal cord and meninges. Unfortunatley, this method has several disadvantages. A major concern is that it is an invasive investigation. Furthermore, it can be difficult to distinguish between osteophytes and soft disc herniation. Honet and colleagues compared preoperative myelography findings with perioperative findings, and found an overall accuracy rate of 85%.\(^{54}\) However, when myelography is combined with computed tomography (CT) (CT myelography), the diagnostic accuracy rate increases to more than 90%.\(^{55}\)
1.6.2.3 Computed tomography

CT is the most sensitive method of assessing the bony structures of the spine, and can be useful in distinguishing foraminal encroachment, the extent of bony spurs, and ossification of the posterior longitudinal ligament. However, the use of CT alone is of limited value in establishing the diagnosis of cervical disc disease and nerve root compression. Combined with intrathecal contrast medium, its accuracy is similar to that of magnetic resonance imaging (MRI).

1.6.2.4 Magnetic resonance imaging

MRI is considered the ideal screening method for investigation of patients with cervical radiculopathy or myelopathy. It is preferred to CT and myelography due to its high soft tissue contrast discrimination, and its ability to provide excellent multiplanar images of neural structures, the subarachnoid space, and the intervertebral discs. MRI is a non-invasive and radiation-free diagnostic procedure with high accuracy in detecting disc herniation and spinal stenosis.

In 1991, Wilson and colleagues performed MRI in the preoperative evaluation of patients with radiculopathy, and found an accuracy rate of 92% compared to the perioperative findings regarding herniated discs and/or spondylosis. They concluded that MRI is the only preoperative imaging technique necessary in most cases of cervical radiculopathy. Brown and colleagues compared preoperative MRI findings to perioperative findings in patients with radiculopathy and myelopathy, and found that pathology was predicted in 88% with MRI, in 81% with CT myelography, and in 50% with CT alone.

1.6.3 Electrophysiology

Electrophysiological testing may play an important role in the diagnosis of cervical radiculopathy/radicular pain when anamnesis, physical examination, and imaging
studies are not sufficient to provide an adequate explanation for the patients’ symptoms.\textsuperscript{11} Furthermore, needle electromyography (EMG) is the only objective method to detect nerve root dysfunction.\textsuperscript{62,63} EMG is most valuable in patients with motor deficits or focal neurologic deficit, such as muscle reflex asymmetry, where it may provide information regarding duration and severity of the pathology.\textsuperscript{63} Abnormal electrophysiologic activity in the limb muscles of the associated myotome is typically present from three weeks after onset of nerve root encroachment.\textsuperscript{64} EMG without imaging, however, has been shown to be a relatively poor diagnostic tool with only 42\% of EMG findings correlating to perioperative findings.\textsuperscript{62}

1.7 Natural course of cervical radiculopathy and radicular pain

It is uncertain to what extent and at what time spontaneous recovery occurs after cervical nerve root encroachment and radiculopathy, and radicular pain.\textsuperscript{11}

One of the first studies to assess the natural course of cervical radiculopathy was published by Spurling and Segerberg in 1953.\textsuperscript{65} One hundred and ten patients with lateral intervertebral lesions were treated with bed rest and traction for 7 to 10 days, and followed for 23 months. Definite improvement was seen in 77\% of the patients. Within the first month, 12\% of the patients were referred to surgical treatment. However, none of those who responded to bed rest and traction within the first month were operated.

An epidemiologic study from Rochester, assessing cervical radiculopathy, followed 561 patients over 4.9 years.\textsuperscript{7} During the observation period, 31.7\% of the patients had a recurrence of symptoms, and 26\% underwent surgical treatment. At the last follow-up, 90\% of the patients were asymptomatic or only mildly bothered by their radiculopathy.\textsuperscript{7}

In a recent review on the natural course and prognosis of cervical disc disease with radiculopathy, substantial improvement tended to occur within 4 to 6
months after onset of symptoms, and 83% of the patients experienced complete recovery within 24 to 36 months.\textsuperscript{66} While others have reported good to excellent outcomes in up to 90% of the patients with non-operative management of cervical radiculopathy.\textsuperscript{67} Thus, it is the belief of many investigators that cervical radiculopathy is, in most cases, a self-limiting condition.\textsuperscript{68}

1.8 Treatment

1.8.1 Non-operative treatment

The aims of treatment of symptomatic cervical disc disease are to improve pain and neurologic function as well as to prevent recurrent symptoms.\textsuperscript{69} Conservative treatment is recommended when there is no significant motor deficit and/or myelopathy.\textsuperscript{11} Different treatment modalities are immobilization, physical therapy, traction, manipulation, medication, and steroid injection.\textsuperscript{23}

\textit{Immobilization} – For a period immediately after the symptom onset, a soft collar can be attempted to minimize motion, thereby reducing nerve root irritation.\textsuperscript{70} However, immobilization with a collar for a longer time period is not recommended, since it may lead to deconditioning of the neck musculature and tissue damage. Active interventions are favored in the literature.\textsuperscript{70-72}

\textit{Physiotherapy} – In the first weeks after symptom onset, the focus should be on stretching and gentle range-of-motion exercises. In addition, massage and heat therapy can be used, although their long-term benefits have not been proven.\textsuperscript{73} When the patient’s symptoms improve, treatment should focus on reducing the risk of recurrence, involving active range-of-motion exercises and aerobic conditioning, like walking or using a stationary bicycle. This regimen may then be followed by isometric (performed without changing the length of muscles), and progressive-resistive exercises, where the weak or injured muscle is strengthened by increasing the resistance on the muscles normal function.\textsuperscript{11} These recommendations are,
however, not supported by evidence from clinical trials, and some authors even believe that physical therapy does not change the natural course of radiculopathy.

- **Traction** is the administration of a distracting force to the neck in order to separate the segments of the cervical column, and thereby relieve the compression of nerve roots caused by intervertebral discs. Traction can be conducted in minutes or for up to one hour, using various techniques. However, randomized controlled trials (RCTs) have shown similar results in patients who did and did not receive cervical traction. Care must be taken in patients with myelopathy, as traction may result in stretching the spinal cord over a compressive lesion.

- **Manipulation** is a “hands on” treatment, moving muscles and joints by gentle pressure and resistance. However, the literature supporting the use of manipulative treatment in cervical radiculopathy is of low to very low quality. The uncertain benefits of manipulation must therefore be weighed against the potential of complications, especially regarding injury of the craniocervical arteries. Although such injuries are rare, and the causal relationship is uncertain, the potential for serious complications should be taken into consideration.

**Medication** to alleviate cervical radiculopathy may be difficult to adapt to the individual patient, and its use is based on anecdotal experience only. Medical therapy usually includes opioids and non-steroidal anti-inflammatory drugs (NSAID). In some patients with acute pain, a short course of prednisone may be advocated.

**Steroid injection** allows for local delivery of a high dose of corticosteroids. The symptom and pain relief is likely due to factors such as reduction in nerve root inflammation and in nociceptive input from somatic nerves, stabilization of neural membranes, and blocking of the synthesis of pain-mediating neuropeptides and of C-fiber activity in the dorsal root ganglion. Both retrospective and
prospective cohort studies have shown up to 60% long-term relief of radiculopathy and neck pain after translaminar or transforaminal epidural injections. There is, however, a potential risk for serious complications.

There are almost no randomized, placebo-controlled trials regarding the abovementioned commonly used non-operative treatment options in symptomatic cervical disc disease. Therefore, the potential risks and individual patients’ preferences should be taken into account in the planning of non-operative management of cervical radiculopathy.

1.8.2 Non-operative versus operative treatment

Persson and colleagues prospectively assessed the results of conservative treatment with physiotherapy, with a collar alone, or with surgical intervention, and found that only the surgery group experienced an improvement in mean current pain at 2- and 4-months follow-up. At 1 year, however, there was no significant difference in experienced pain between the groups.

Recently, another Swedish group presented their results from a prospective RCT assessing the outcome after surgery and physiotherapy versus after physiotherapy alone in patients with cervical radiculopathy. After 1 year, 87% of the patients who received surgery reported being better or much better compared to 62% in the non-surgery group. At 2 years, the difference between the groups decreased and was no longer significant. Neck Disability Index (NDI), neck pain, and arm pain improved significantly from baseline values in both groups at 2 years. The 5- and 8-year follow-up data from the same patient population still showed a difference in favor of surgery regarding better NDI and neck pain scores, but no significant difference regarding arm pain and health-related quality of life outcomes.
1.8.3 Indication for surgical treatment

There is no consensus-based agreement regarding indications for surgery in patients with symptomatic cervical disc disease.\textsuperscript{23, 51} Fast surgical intervention must be considered in those with progressive neurological deficits, symptoms consistent with myelopathy, or signs of cervical instability.\textsuperscript{90} Surgery is often recommended when there is 1) correspondence between nerve root encroachment visualized on MRI or CT myelography and the patient’s ailments, and 2) persistence of pain or radiculopathy despite non-operative treatment for at least 6 to 12 weeks.\textsuperscript{11} How long non-operative management should be attempted is unclear, as most patients improve substantially within the first 4 to 6 months after symptom onset.\textsuperscript{66} However, a recent study showed that symptom duration of more than 6 months before surgical intervention resulted in worse postoperative outcome.\textsuperscript{35} Consequently, the authors recommended a cut-off of 6 months for non-operative management.\textsuperscript{35} A RCT to clarify the optimal time of surgery is underway,\textsuperscript{91} but currently 6-12 weeks of observation are commonly recommended before patients are scheduled for surgery.\textsuperscript{11}

1.9 Surgical historical perspective

For a long time, laminectomy was the only surgical treatment option for patients with symptomatic cervical disc disease, even when the pathology was located anterior to the spinal cord.\textsuperscript{92} In 1952, Brain and Wilkinson distinguished between acute lesions due to herniation of the nucleus pulposus and chronic lesions arising from degenerative spondylosis.\textsuperscript{93} Between the 1950s and 1960s, Rogers performed laminectomy with opening of the dura and section of the dentate ligament to decrease tension and to improve retraction of the spinal cord, allowing the surgeon to identify and excise the herniated disc.\textsuperscript{94} Laminectomy and extradural approach was another alternative, but then often with the sacrifice of the nerve root.\textsuperscript{92} As knowledge of the cervical spine pathophysiology and anterior access evolved, posterior approaches for the treatment of cervical disc disease were gradually
abandoned. The first description of the anterior approach to the cervical spine was by Lahey and Warren, who used the technique to expose esophageal diverticula. Robinson and Smith applied the technique for treating symptomatic cervical disc disease, and reported their first 14 operations in 1958, using a horseshoe-shaped tricortical autologous bone graft from the crista iliaca for enhanced bone fusion during anterior cervical reconstruction. Cloward followed later the same year, inserting a cylindrical graft to achieve anterior cervical fusion. Cloward, Robinson, and Smith used a longitudinal incision along the anterior border of the sternocleidomastoid muscle to access the cervical spine.

Although anterior cervical discectomy with various fusion techniques was increasingly applied during the 1960s, studies advocated performing the procedure without interbody bone grafting. Rosenørn and colleagues found discectomy without grafting to be superior to the procedure with interbody bone grafting. Watters and colleagues, using a tricortical crista graft, concluded that neither procedure was ideal. Discectomy alone was associated with decreased hospital costs and surgical morbidity, while implantation of an iliac crest bone graft (ICBG) resulted in more rapid resolution of radicular pain. ICBG harvesting was, however, associated with complications such as harvest site pain, infection, iliac crest fractures, and hematomas.

Watters and colleagues’ ideal vision of the future was a low-cost biomaterial implant that would result in successful arthrodesis. However, the work with artificial cervical implants, in order to avoid donor site morbidity, had already begun. In 1979, Wagner and Bagby published the results of implanting a stainless-steel cage, the Bagby basket, between adjacent vertebrae in 12 horses with Wobblers syndrome, a condition involving spinal cord compression in horses. The method was a direct modification of Cloward’s procedure, and in 1988 Bagby presented a modified version of his implant for possible future use in the human cervical spine. Even though artificial implants were already used in the cervical spine in the 1980s, the first implant in the lumbar spine based on Bagby’s design was in 1992. During the 1990s, a modification of the Bagby implant was adapted
to the cervical spine. Since then, multiple different stand-alone implants have been available, offering safe and positive long-term fusion results.

In Norway, ICBG was used as standard cervical interbody implant to achieve fusion until around 2003-2004. In the last decade, artificial polyetheretherketone (PEEK) cages have been preferred over ICBG, and are now the gold standard implant used in ACDF procedures in Norway. Titanium was, however, the first material used in artificial interbody implants in the 1980s, but since the 1990s, PEEK cages have been produced as an alternative to titanium.

Early publications on ACDF procedures mainly focused on the high grade of clinical success, and fusion rates of 90-97%. Adjacent segment degeneration and adjacent segment disease (ASD) as unintended consequences of fusion were discussed in the late 1970s and 1980s, even though the issue had already been presented in 1959 by Scoville in his criticism of Cloward’s fusion technique. The question has been increasingly debated in recent years, especially by Hilibrand and colleagues. They described adjacent segment degeneration as “radiographic changes seen at levels adjacent to a previous spinal fusion procedure that do not necessarily correlate with any clinical findings”, and ASD as “the development of new radiculopathy or myelopathy referable to a motion segment adjacent to the site of a previous anterior cervical arthrodesis”.

There is controversy regarding whether cervical ASD is a consequence of altered biomechanics, or if it is actually related to the natural course of cervical spondylosis in the aging spine. The natural degeneration process has been shown by Gore, who examined asymptomatic individuals with normal plain X-rays and followed them for 10 years, finding the development of radiographically assessed DDD in 34%. At the same time, McGrory and colleagues assessed pediatric patients, operated with cervical fusion procedures due to fractures and dislocations, and found a high level of adjacent segment osteoarthritic changes in 8 out of 12 patients 20 years after the initial surgery. Likely, ASD is caused by a combination of biomechanical stress related to fusion and the natural course of degeneration.
According to the literature, the incidence of symptomatic ASD is approximately 3% per year.\textsuperscript{122, 129} Furthermore, Hilibrand and colleagues found that patients operated with ACDF had a 26% 10-year risk of developing symptomatic ASD.\textsuperscript{122} The prevalence of ASD after cervical fusion requiring surgical treatment has been reported to be between 9% and 17% after 4.5-6 years,\textsuperscript{115, 118, 134} corresponding to an annual incidence of 1.5 to 4%.\textsuperscript{121} Chang and colleagues\textsuperscript{135} recently presented their results on symptomatic ASD based on a review of the literature, and found that adjacent level surgery was necessary in 3.1% and 6.0% after arthroplasty and fusion, respectively, in the time range of 24-80 months.

Regardless of the underlying cause, ASD has led to the development of cervical arthroplasty, with the aim of ensuring virtually physiological motion at the operated level, thus preventing increased strain on adjacent levels.\textsuperscript{133} In many ways, the growing interest in ACDA as a replacement for fusion follows the development from hip arthrodesis, as the gold standard treatment before the 1960s, to hip arthroplasty.\textsuperscript{133} In contrast to hip arthroplasty, where joint stability to a great extent depends on the ligamentous structures, stability in the cervical spine largely depends on the disc itself. This places great demands on the construction of the arthroplasty devices, in order to maintain balance in the facet joints, as well as maintaining the posterior aspect of the disc space as the instantaneous axis of rotation.\textsuperscript{133}

The first attempt to use a cervical arthroplasty device in humans was described in 1966 by Fernstrøm.\textsuperscript{136} Unfortunately, the spherical design of the implant caused segmental hypermobility, and subsidence with the device tending to migrate into the superior endplate.\textsuperscript{133} The poor results were admitted by Fernstrøm himself, and the procedure was abandoned in favor of cervical fusion.\textsuperscript{133} During the 1980s, however, lumbar arthroplasty paved the way for new enthusiasm regarding ACDA, and before the first clinical trial in 1991, several prototypes were constructed. The first cervical arthroplasty device used in a human clinical trial was the Cummins-Bristol artificial joint, and the results were presented in 1998.\textsuperscript{137} Even though no adjacent segment degeneration was observed in the mean 2.4 years
follow-up, there were complications resulting from the screws being used as anchoring points into the vertebrae cranial and caudal to the disc space. A further development of the Cummins-Bristol artificial joint was the Frenchay artificial cervical joint with optimized physiological motion and a better screw locking mechanism. The results of a pilot study using this implant were published in 2002, and showed better outcome regarding the device itself, without dislocations and few screw complications. The first prospective RCT comparing ACDA using the Frenchay disc with fusion with ICBG was initiated in 2000, and preliminary results favored the arthroplasty device. The Frenchay disc was later renamed the Prestige® LG cervical disc (Medtronic Spinal and Biologics, Memphis, TN). A prospective, randomized controlled US investigational device exemption study was initiated in 2002, and 2-year, 5-year, and 7-year results demonstrated clinical outcome in favor of the arthroplasty device. Several other prospective RCTs, using different arthroplasty devices, as well as meta-analyses have been published in the last decade, and show favorable outcomes of arthroplasty, while others show similar results for the 2 treatment modalities.

1.10 Complications

Complications may occur during the surgical access to the vertebral column, during discectomy and decompression of encroached nerve structures, and in the postoperative phase.

1.10.1 Mortality

Complications related to ACDF and ACDA may be serious. Mortality has been reported to be 0.1% in patients with an overall morbidity rate of 8.4%. Joseph and colleagues assessed 49300 patients after anterior cervical fusion procedures, and reported 0.1% in-hospital mortality in those without postoperative dysphagia.
and 0.6% in those with dysphagia.\textsuperscript{157} Patients with dysphagia had significantly higher comorbidity.

\subsection*{1.10.2 Perioperative complications}

During the surgical access to the cervical vertebral column, damage to blood vessels, the esophagus, and nerve structures may occur.

Carotid artery injury is extremely rare, and the incidence is not calculable.\textsuperscript{158} Only a few cases have been reported in the literature, where the authors describe thrombosis and stroke due to postoperative hematoma and prolonged retraction of the artery.\textsuperscript{159-161} The first case of carotid artery dissection during a cervical arthroplasty procedure was reported in 2013.\textsuperscript{162} Iatrogenic injury to the vertebral artery, although also very rare, was reported in 0.3% of 1976 anterior cervical spine procedures,\textsuperscript{163} and in 0.07% in a series of different cervical procedures.\textsuperscript{164} Injury to the internal jugular vein resulting in thrombosis is only described once in the literature.\textsuperscript{165}

Perforating injury to the esophagus is unusual. Fountas and colleagues reported 3 cases in 1015 patients, 1 with fatal outcome,\textsuperscript{156} while Lied and colleagues did not have any injuries in 390 procedures.\textsuperscript{166} A recent review of the literature is based on 65 publications from 1980 through 2015 including 153 patients. Most patients were operated due to trauma and fractures of the cervical spine, and only 10 due to cervical disc herniation. Most perforations of the esophagus were due to implant complications or erosion caused by plates and screws, and only 19% were intraoperative injuries caused by retraction and tools.\textsuperscript{167}

A more frequent complication is recurrent laryngeal nerve palsy (RLNP) with an incidence of 3.2-3.3%.\textsuperscript{156,168} Interestingly, in one study the incidence of RLNP fell from 6.8% to 2% when the endotracheal tube cuff pressure was lowered after retractor placement.\textsuperscript{168} Jung and colleagues performed preoperative and postoperative laryngoscopy, finding an incidence of 8.3% of clinically symptomatic
RLNP,\textsuperscript{169} and 15.9\% of asymptomatic RLNP without hoarseness. After 3 months, the incidence was 2.5\% and 10.8\%, respectively.\textsuperscript{169} Kilburg and colleagues did not find any significant association between RLNP and the side of the surgical approach.\textsuperscript{170} Horner’s syndrome (miosis, ptosis, anhydrosis, enophthalmus) is rare with an incidence of 0.1-1.1\%,\textsuperscript{156,171,172} and is caused by compression or injury of the cervical sympathetic trunk.\textsuperscript{173} Lied and colleagues reported Horner’s syndrome in 1 patient (0.3\%).\textsuperscript{166} In all of the above-mentioned cases, the deficit was temporary.

During discectomy and decompression of encroached nerve structures, cerebrospinal fluid (CSF) leak, nerve root damage, and injury to the spinal cord may occur.

CSF leak due to injury of the dura mater occurred in 0.3\% in the study by Fountas and colleagues.\textsuperscript{156} Bertalanffy and colleagues\textsuperscript{171} reported accidental dural injury in 1.8\%, where 1 patient (0.2\%) developed a cutaneous fistula resulting in meningitis. In the study by Lied and colleagues,\textsuperscript{166} dural tear occurred in 2 patients (0.5\%).

Injury to nerve roots or the spinal cord resulting in neurological deterioration was reported in 5 patients (1.2\%) by Lied and colleagues.\textsuperscript{166} In a recent meta-analysis, C5 nerve root palsy after anterior C4/C5 decompressive surgery occurred in 5.2\% of the patients.\textsuperscript{174} Fountas and colleagues reported spinal cord contusion and worsening of pre-existing myelopathy in 0.2\% of the patients.\textsuperscript{156} Flynn assessed neurologic complications after ACDF by sending questionnaires to 1358 neurosurgeons.\textsuperscript{175} Out of 82114 procedures, major neurologic complications were reported in 0.4\%.

The literature is sparse regarding “wrong level surgery”, which is probably underreported. Lied and colleagues reported surgery on the wrong level in 1 patient (0.3\%).\textsuperscript{166}
1.10.3 Postoperative complications

Fountas and colleagues reported dysphagia as the most common postoperative complication in 9.5% of the patients, but it was resolved within 2 to 7 days in 92 out of 97 patients. Dysphagia is, however, a subjective symptom and may vary between patients. It can be caused by hematoma, esophageal perforation, or implant dislocation, but in some cases the exact pathophysiological mechanism is unknown. Bazaz and colleagues reported the incidence of dysphagia at 1, 2, 6, and 12 months to be 50.2%, 32.2%, 17.8%, and 12.5%, respectively, while Wu and colleagues recently reported it to be 10.9%, 6.4%, and 2.7% at 1-5 days, 3, and 6 months. In this study, higher level and multilevel disc surgery were risk factors for postoperative dysphagia.

The second most reported complication by Fountas and colleagues was postoperative hematoma in 5.6% of the patients. The patients presented symptoms including severe dysphagia, respiratory problems, and painful swelling of the neck, and 2.4% needed emergency reoperations. In the study by Lied and colleagues, 1.2% of the patients developed postoperative hematoma, all of whom were reoperated within 6 hours.

Implant dislocation may occur with both arthroplasty and stand-alone fusion. Ozbek and colleagues reported dislocation of the implanted arthroplasty devices in 5 out of 163 patients (3.1%). Implant instability or loosening of the device was found in 2 out of 81 patients (2.5%) in the study by Skeppholm and colleagues. Others, however, reported no dislocation at 5-year follow-up using another arthroplasty device. Lied and colleagues reported dislocation of stand-alone fusion implants in 4 patients (1%), all of whom were operated with ICBG. Dislocation of stand-alone PEEK cages was not seen in this study, which is consistent with other reports.

Postoperative wound infection is quite uncommon and has been reported to be 0.2%. Patients operated with ICBG may develop iliac crest donor site morbidity, which is beyond the scope of this thesis.
2. AIMS OF THE THESIS

With this thesis, we wanted to explore the clinical outcome after anterior cervical discectomy and implantation of an arthroplasty device (ACDA) with that of the standard surgical procedure, stand-alone interbody cage implant (fusion, ACDF), in patients with C5/C6 or C6/C7 nerve root encroachment, and corresponding radiculopathy. Furthermore, we wanted to assess the radiological aspects of the motion preserving arthroplasty device, and the correlation of the NDI with quality of life and mental health measures.

**Paper I**

To assess 2-year clinical outcome after arthroplasty versus stand-alone fusion in patients suffering from symptomatic single-level cervical disc disease.

**Paper II**

To assess the degree of heterotopic ossification (HO) at index level 2 years after arthroplasty, and to evaluate the clinical outcome related to the degree of HO.

**Paper III**

To investigate the extent of artifact induced by the arthroplasty device, and how it limits interpretation of the MRI in a 1.5 compared with a 3 Tesla magnet.

**Paper IV**

To evaluate the relationship between the NDI and health-related quality of life (HRQoL) and mental health questionnaires in patients with symptomatic single-level cervical disc disease.
3. METHODS

All papers are based on the NORCAT, a prospective, single-blinded, randomized, controlled multicenter study comparing motion preserving cervical arthroplasty with fusion (Table 2). The study was conducted at the neurosurgical departments of Oslo University Hospital, Trondheim University Hospital (St. Olavs Hospital), Haukeland University Hospital in Bergen, and the University Hospital of North Norway in Tromsø. Patients were included in the trial from November 2008 to January 2013.

**Table 2. Data basis of papers I to IV**

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>3 months</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

3.1 Participants

The trial was designed to include 146 patients. Inclusion and exclusion criteria are presented in Table 3. The patients were assessed in the neurosurgical outpatient clinics of the five participating hospitals. One principal investigator at each study site had the main responsibility for inclusion.

After written informed consent was obtained, the patients were included in the study. Enrollment is shown in Figure 8. The patients were randomized to either arthroplasty or fusion. Randomization was stratified according to center, and blocked using the Unit of Applied Clinical Research website (www.ntnu.edu/dmf/akf/randomising), in order to ensure equality in the groups.
An envelope with the result of randomization was kept in a locked cabinet in the operating theatre until the day of surgery. Both arthroplasty and fusion implant systems were available in the operating theatre. The surgical team was blinded to the result of randomization until decompression of the encroached nerve root was completed as the last step of the operation. The patients were blinded to the treatment modality until the last follow-up. Follow-up visits were scheduled at 3 months, 1 year, and 2 years. At 6 months, the patients answered the questionnaires by mail.

Table 3. Inclusion and exclusion criteria
Reprinted with permission from Eur Spine J. 2017; 26: 1225-35

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 25 to 60 years</td>
<td></td>
</tr>
<tr>
<td>Clinical C6 or C7 root radiculopathy with corresponding radiologic findings with or without neurological symptoms</td>
<td></td>
</tr>
<tr>
<td>Mechanical provoked pain which aggravates with physical activity or positive Spurling test</td>
<td></td>
</tr>
<tr>
<td>Radiological nerve root compression on the basis of disc herniation or spondylosis</td>
<td></td>
</tr>
<tr>
<td>NDI ≥ 30%</td>
<td></td>
</tr>
<tr>
<td>The patient has not responded to non-operative treatment and has had no clinical improvement in the 6 weeks prior to surgery</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant spondylosis involving more than one level</td>
<td></td>
</tr>
<tr>
<td>Intramedullary changes on MRI</td>
<td></td>
</tr>
<tr>
<td>Ankylosis at adjacent level</td>
<td></td>
</tr>
<tr>
<td>Clinical suspicion of myelopathy</td>
<td></td>
</tr>
<tr>
<td>Chronic generalised pain syndrome</td>
<td></td>
</tr>
<tr>
<td>Infection or active cancer</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis involving the cervical spine</td>
<td></td>
</tr>
<tr>
<td>Previous trauma involving the cervical spine</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Allergy against contents of cage/prosthesis</td>
<td></td>
</tr>
<tr>
<td>Previous neck surgery</td>
<td></td>
</tr>
<tr>
<td>Mental or somatic illness which makes the patient unsuitable for the study</td>
<td></td>
</tr>
<tr>
<td>The patient does not understand oral or write Norwegian</td>
<td></td>
</tr>
<tr>
<td>Abuse of medication/narcotics</td>
<td></td>
</tr>
</tbody>
</table>
Figure 8. Eligibility, randomization and follow-up of the patients

Reprinted with permission from Eur Spine J. 2017; 26: 1225-35

---

a 1 patient withdrew consent before surgery. 1 patient’s MRI was too old; a new preoperative MRI was impossible due to claustrophobia. 1 patient had a short neck, making visualization of the index level C6/C7 with fluoroscopy impossible. For 1 patient the prostheses were not available in the operating theater at time of surgery due to a misunderstanding. In 1 patient the surgeons had to convert to fusion with anterior plating fixation due to instability. b Short necks made visualization of the index level C6/C7 with fluoroscopy impossible. c 1 patient did not receive the allocated intervention due to problems with positioning of the arthroplasty device, resulting in conversion to fusion. d 4 patients in each group did not attend the follow-up and did not return the questionnaires. e 11 patients in the arthroplasty group and 14 patients in the fusion group did not return the questionnaires. f 5 patients in the arthroplasty group and 6 patients in the fusion group did not attend the follow-up and did not return the questionnaires. g 2 patients did not attend the follow-up and did not return the questionnaires, 1 patient attended the follow-up without returning the questionnaires, and 1 patient had undergone brain surgery that resulted in postoperative problems with hand writing. h 1 patient did not attend the follow-up and did not return the questionnaires.
3.2 Intervention

3.2.1 General surgical procedure

The surgical procedures were carried out by 2 senior surgeons at each hospital. Under general intubation anesthesia, the patient was placed in a neutral supine position. Preoperative fluoroscopy was used to visualize the index level, and thus to ensure correct placement of the skin incision. A paramedian skin incision facilitated the anterolateral approach (Figure 9), where the carotid sheath was luxated laterally to access the prevertebral space.

![Figure 9. Location of the skin incision](image)

Intraoperative lateral fluoroscopy was used once more to confirm the correct cervical level. To determine the center of the disc space, a midline pin was introduced into the disc, and the location was verified with anteroposterior fluoroscopy. A standard discectomy was performed mainly with sharp curettes, and in some cases with the help of a high-speed diamond bur. Posterior osteophytes were removed, and a symmetrical central decompression with opening of the longitudinal ligament was performed to visualize the dura mater in width and height of the discectomy. Optimal decompression of the nerve root was achieved with preservation of as much of the uncovertebral joint as possible, and without compromising the decompression of nerve structures. The procedure until decompression of the nervous structures was identical for all patients.
Before preparing the endplates in order to facilitate insertion of the implant, the patient was randomized to either arthroplasty or fusion. An independent nurse in the operating theatre opened the randomization envelope and presented the result to the surgeon. At that point, the surgeon was not able to further decompression of the nerve root. Only preparation of the endplates to ensure optimal positioning of the arthroplasty device or cage was allowed at this stage of the operation.

3.2.2 Anterior cervical discectomy and arthroplasty

The DISCOVER® Cervical Arthroplasty Disc Replacement System (DePuy Spine Inc., Raynham, MA) is an advanced, unconstrained prosthesis, designed to imitate the normal functional movements of the patient’s neck (Figure 10). The DISCOVER® disc prosthesis is comprised of a superior titanium alloy endplate with an ultra-high molecular weight polyethylene core mechanically fixed to the inferior titanium alloy endplate.

**Figure 10. Illustration of the DISCOVER® disc prosthesis (top), and motion with flexion (bottom left) and extension (bottom right)**
The disc space was prepared by slight distraction and endplate flattening to match the prosthesis’ lordotic geometry. The appropriate size of the prosthesis was determined with the use of templates, and intraoperative anteroposterior and lateral fluoroscopy. The implant was placed under continually lateral fluoroscopy until the desired depth was reached. Before closure of the incision, anteroposterior and lateral fluoroscopy were performed, and images printed to confirm the placement of the prosthesis.

Problems with positioning of the arthroplasty device resulted in conversion to fusion.

3.2.3 Anterior cervical disectomy and fusion

CERVIOS® (Synthes GmbH, Eimattstrasse 3, CH-4436, Oberdorf) is a radiolucent cage system for anterior cervical interbody fusion (Figure 11). The cage is made of PEEK, and is curved or wedge-shaped to accommodate endplate shape variance. The central hole is prefilled with synthetic β-tricalcium phosphate, which is converted to vital bone within 6 to 18 months.

Figure 11. Illustration of the CERVIOS® (left) and the cage in place (right)

The appropriate size of the CERVIOS® cage was determined preoperatively using templates that best matched the prepared endplates. The procedure was performed as stand-alone fusion, meaning without anterior plating.
3.3 Assessments

Follow-ups were scheduled at 3 and 6 months, and 1 and 2 years (Tables 2 and 4). The clinical follow-up was carried out by one of the 2 surgeons who performed the operation. A study secretary handed out the questionnaires, which the patients answered at the study site. All questionnaires and completed radiologic investigations were sent to the principal study coordinator at Trondheim University Hospital St. Olav.

Table 4. Postoperative follow-up oversight

<table>
<thead>
<tr>
<th></th>
<th>Clinical examination</th>
<th>Questionnaires</th>
<th>X-ray</th>
<th>MRI</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

3.3.1 Paper 1

The baseline data recorded were age, sex, height, weight, body mass index, index level (C5/C6 or C6/C7), duration of arm and neck pain, if the patient was able to attend work until the day of surgery, duration of sick leave, level of education (primary/secondary or higher education [college and university]), marital status, smoking, and co-morbidity (heart disease, hypertension, diabetes).

The NDI, a self-rated questionnaire developed for patients with neck disability, was our primary outcome variable. We used the validated Norwegian version184 (appendix 10.1). The questionnaire consists of 10 items, of which 7 are related to activities of daily life (personal care, lifting, reading, work/daily activities, driving, sleep, and recreation), 2 to pain (pain, headache), and 1 to concentration.
Each item ranges from 0 to 5, and the summary score from 0 to 50, with lower scores indicating less severe symptoms. In our study, we expressed the summary scores as percentages.

We assessed several secondary outcomes. Arm and neck pain were evaluated with the one-dimensional Numeric Rating Scale (NRS 11)\(^{1,85}\) ranging from 0 (“no pain at all”) to 10 (“worst imaginable pain”) (appendix 10.2). HRQoL was assessed using the Short Form 36 (SF-36)\(^{1,86}\) and the EuroQol-5 Dimension-3 Level (EQ-5D-3L).\(^{1,87}\) SF-36 consists of 8 dimensions (physical function, role limitations due to physical problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems, and mental health), and 2 summary scores (physical component summary [PCS] and mental component summary [MCS]). The score ranges from 0 to 100, where higher scores relate to better health. We used the validated Norwegian (chronic) version 2.0\(^{1,88}\) (appendix 10.3). The EQ-5D-3L provides a simple descriptive profile of the health status. It consists of 5 dimensions (mobility, self-care, activities of daily life, pain, and anxiety/depression), and the score ranges from -0.59 to 1, with higher scores indicating better health status. We used the validated Norwegian version\(^{1,89}\) (appendix 10.4) and syntax files obtained from the EQ-5D society, using the UK time trade-off tariff to calculate the utility index.\(^{1,90}\) Dysphagia was assessed using the Dysphagia Short Questionnaire\(^{1,91}\) (appendix 10.5), consisting of 5 subscores (ability to swallow, incorrect swallowing, globus sensation, involuntary weight loss, and pneumonia). The score ranges from 0 to 18, where lower scores represent milder symptoms.

Finally, we registered the duration of surgery and anesthesia, the total blood loss, and major perioperative complications (dural tear, damage of n. laryngeus recurrens, index level nerve, esophagus, trachea or large vessel).

3.3.2 Paper II

This paper is based on all patients operated with the DISCOVER\(^{®}\) disc prosthesis at Oslo University Hospital Rikshospitalet. A CT of the index level was performed at
2-year follow-up, using a multidetector scanner with bone algorithm, dFOV 15–18 cm, 80 to 100 mA, 120 kV, and 1 mm increment with coronal and sagittal reconstructions. Two experienced neuroradiologists, blinded to the patients’ clinical outcomes, evaluated the images twice and reached agreement by consensus. They graded the degree of HO according to the classification system by Mehren and colleagues,\textsuperscript{192} based on the lumbar classification system by McAfee and colleagues\textsuperscript{193} and adapted to the cervical spine. Cervical HO was graded from 0 (no HO) to IV (complete fusion) (Figure 12), with grades 0 to II defined as low-grade and grades III to IV as high-grade HO.\textsuperscript{194} Clinical outcomes were assessed using the NDI, NRS-11 for arm and neck pain, SF-36 PCS and MCS, and EQ-5D-3L.

**Figure 12. Grading of HO demonstrated by CT and illustrations**

Reprinted with permission from Eur Spine J. 2016; 25: 2271-8
This paper is based on the first 10 patients operated with the DISCOVER® disc prosthesis at Oslo University Hospital Rikshospitalet. At 1-year follow-up, the patients underwent standard MRI according to the study protocol with default setting of the magnet. Both 1.5 Tesla (Siemens Symphony, Erlangen, Germany) and 3 Tesla (Achieva, Philips Healthcare, Best, The Netherlands) MRI was performed with all 10 patients. The settings for the 1.5 Tesla magnet were: TSE; 3 mm slice thickness 552/13 (repetition time msec/echo time msec) for sagittal T1 and for sagittal and oblique T2 4500/97, 4 mm axial MEDIC (me2d) with 891/27, 3 mm axial T2 4000/119; matrix size 512 9 384 for sagittal T1, matrix size 256 9 512 for sagittal and oblique T2, matrix size 256 9 256 for axial T2, matrix size 256 9 192 interpolated to 512 for MEDIC (me2d); bandwidth 130 Hz/ px for sagittal and oblique T2, 150 for sagittal T1, 190 for axial T2 and 195 for Medic (me2d). For the 3 Tesla magnet, the settings were: Turbo-Spin-Echo (TSE); 3 mm slice thickness; 618/7.8 (repetition time msec/echo time msec) for sagittal T1, 3196/100 for sagittal T2, 4057/100 for oblique T2 and 4109/100 for axial T2; matrix size 312 9 312 for sagittal T1 and for sagittal and oblique T2 and 188 9 187 for axial T2; bandwidth 410.9 Hz/px for T1, 406.4 for sagittal T2, 434.8 for oblique T2 and 404.7 for axial T2.

The degree of artifacts around the DISCOVER® disc prosthesis, when using the 1.5 or 3 Tesla magnet, was compared (Figure 13). The images were evaluated by 2 experienced radiologists and agreement was achieved by consensus. The spinal cord was interpreted on the basis of sagittal T1 and T2 sequences. For evaluation of the nerve roots and root canals, the oblique and axial images were primarily used. Finally, the “blur artifact ratio”, defined as the height of the blur artifact divided by the height between 2 vertebrae, both measured at midline on sagittal T1 images (Figure 14), was compared between the 2 magnets.
**Figure 13.** Artifacts on sagittal T2-weighted 1.5 Tesla (A) and 3.0 Tesla (B) MRI with DISCOVER® prosthesis at level C6/C7

Reprinted with permission from Eur Spine J. 2013; 22: 2296-302

**Figure 14.** Calculation of the “blur artifact ratio” using sagittal T1-weighted 1.5 Tesla (A) and 3.0 Tesla (B) MRI

Reprinted with permission from Eur Spine J. 2013; 22: 2296-302
3.3.4 Paper IV

At baseline and before the surgical intervention, we assessed NDI, SF-36, and EQ-5D-3L in all patients. The Hospital Anxiety and Depression Scale (HADS)\(^{195}\) (appendix 10.6) became part of the assessment measures 1 year after patient inclusion started. HADS consists of 14 items, 7 related to anxiety (HAD-A), and 7 to depression (HAD-D). A score of 8-10 points is considered a possible case of anxiety or depression, and a score of $\geq 11$ is a definite case.\(^{195}\)

3.4 Statistics

A difference of 10\% in NDI score was considered to be the minimal level required for clinical important change.\(^{196,197}\) To detect this difference, the trial was planned to have a power of 80\%. Using a significance level of 0.05, a standard deviation (SD) of 18, and correcting for 40\% lost to follow-up, the sample size was calculated to be 146 participants.

Continuous data are presented as means and SD or 95\% confidence intervals (CI) for normally distributed data, and medians and interquartile ranges (IQR) for non-parametric data. Between-group differences for normally distributed data were tested with independent \(t\)-tests, and for non-parametric data with Mann-Whitney \(U\) tests. Change in outcome variables over time was determined by paired-sample \(t\)-tests for normally distributed data, and Wilcoxon signed rank tests for non-parametric data. Categorical data are described as frequencies and percentages, and between-group differences were tested with $\chi^2$ tests or Fischer exact tests, as appropriate. A \(p\) value of $< 0.05$ was used as level of significance.

PASW (Predictive Analytics SoftWare) Statistics 18 (IBM Corporation, Armonk, NY) was used for statistical analyses in paper I, and SPSS version 18.0 (IBM Corporation, Armonk, NY) in papers II, III, and IV.
3.4.1 Paper I

Outcomes were analyzed according to the intention-to-treat principle. Repeated measurements after intervention were assessed using linear mixed models with a random intercept adjusted for the baseline score. Follow-up time-points, treatment modality, and baseline scores were included as fixed main effects together with interaction terms between follow-up time-points and treatment modality. The linear mixed model analysis was not described in the original study protocol, but applied to adjust for the difference in baseline NDI between the 2 treatment groups.

A sensitivity analysis, including the 7 patients who were randomized and excluded from the trial, was performed based on the intention-to-treat principle with extreme values, meaning best possible scores for all outcome measures.

Possible effects or differences between the 5 neurosurgical departments were evaluated, but neither the statistical assessment nor the trial design indicated that any multicenter effect should be taken into account in our final statistical analysis.

3.4.2 Paper II

Patients were classified into a low-grade and a high-grade HO group, and demographics and outcomes were compared between the groups.

3.4.3 Paper III

An independent t-test was used to compare the mean “blur artifact ratio” between the 1.5 and 3 Tesla magnets.
3.4.4 Paper IV

To rule out differences between the patients who were included the first year after study enrollment, and thus did not answer the HADS questionnaire, and those who did, baseline demographics and HRQoL variables were compared.

Simple linear regression analyses were performed to explore the relationship between increasing NDI scores and SF-36 subscores, SF-36 summary scores, EQ-5D-3L, HAD-A, and HAD-D as independent variables. We provided regression coefficients (R) and CI, and calculated the R square to assess how much of the total variation in the NDI score could be explained by the independent variables. We performed multiple regression analyses to investigate the relationship between NDI and SF-36 summary scores, EQ-5D-3L, HAD-A, and HAD-D. Stepwise elimination was done to assess which of the independent variables best predicted the NDI score.

The relationship between SF-36 MCS and HADS was assessed using a Pearson product-moment correlation coefficient, and the strength of the relationship was interpreted in the manner suggested by Cohen.198

3.5 Ethical considerations

The trial was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway and the Data Protection Official for Research. The trial was registered at www.clinicaltrials.gov (NCT 00735176.19).

All patients were informed both orally and in writing through a comprehensive information letter, and gave their written informed consent prior to participation. Participants were free to withdraw from the study at any time, and without any need for explanation.

Participation in the study had no benefits, except for follow-up beyond 3 months after surgery, which is the standard procedure for all patients after ACDF.
Study participants were aware that they had to go through repeated radiological examinations, which are not standard after uncomplicated ACDF.

All authors vouched for the accuracy of the study according to the study protocol, and all agreed unanimously to submit the manuscripts for publication.

The NORCAT received a grant from DePuy Synthes Spine. However, the sponsor was not involved in the study design, conducting the trial, writing or reviewing the manuscripts.
4. SUMMARY OF RESULTS

4.1 Paper I

The Norwegian Cervical Arthroplasty Trial (NORCAT): 2-year clinical outcome after single-level cervical arthroplasty versus fusion—a prospective, single-blinded, randomized, controlled multicenter study

In all, 3922 patients with cervical radiculopathy were screened at specialist outpatient clinics at all study sites, and 143 were eligible for inclusion in the study. Seven patients had to be excluded for several reasons after randomization. At baseline, 136 patients were included, 68 in each group. The 2-year follow-up was attended by 120 patients (Figure 8).

There was significant improvement in NDI scores from baseline to all follow-up time points for both treatment modalities, but no difference between the groups. Both groups achieved significant mean reduction in NDI scores from baseline to 2 years, from 45.7 (95% CI 42.9–48.6) to 25.0 (95% CI 20.1–29.9) for arthroplasty (P<0.001), and from 51.2 (95% CI 48.0–54.4) to 21.2 (95% CI 16.7–25.6) for fusion (P<0.001).

Regarding NRS for arm and neck pain, SF-36 PCS and MCS, and EQ-5D-3L, there was significant improvement from baseline to all follow-up times (P<0.001), but no difference between the groups.

Linear mixed models for repeated measurements, correcting for baseline differences, dropouts and missing data, showed, however, a mean difference of 5.9% in NDI score, P=0.049, and of 1.0 in NRS arm pain, P = 0.03, in favor of fusion after 2 years. There was a longer duration of surgery (P<0.001) and a higher frequency of reoperations (P=0.03) with arthroplasty.

There were no major complications in either group, and no between-group differences in the dysphagia score. In the arthroplasty group, 10.9% and 6.6% of the
patients had dysphagia at 6 and 12 months, respectively, in the fusion group 18.6% and 5.5%.

4.2 Paper II

Heterotopic ossification and clinical outcome in nonconstrained cervical arthroplasty 2 years after surgery: the Norwegian Cervical Arthroplasty Trial (NORCAT)

Out of 136 patients attending the trial, 79 were included at Oslo University Hospital Rikshospitalet. Of these, 39 were operated with the DISCOVER® disc prosthesis. In 2 patients, the arthroplasty device had to be removed before the 2-year follow-up due to loosening and anterior migration. This paper is based on the remaining 37 patients.

All patients had developed HO at 2-year follow-up. Fourteen patients (37.8%) were classified as having grade II HO. High-grade HO was found in 23 patients (62.2%), of whom 6 patients (16.3%) had complete fusion. There were no significant baseline differences between those with low-grade and high-grade HO. The mean NDI scores (±SD) after 2 years were 27.0 (±19.6) in patients with low-grade HO, and 26.8 (±20.3) in patients with high-grade HO. Neither this difference, nor differences in NRS-11 for arm and neck pain, SF-36 PCS and MCS, or EQ-5D-3L were statistically significant after 2 years.

4.3 Paper III

Magnetic resonance imaging evaluation after implantation of a titanium cervical disc prosthesis: a comparison of 1.5 and 3 Tesla magnet strength

1.5 and 3 Tesla MR images demonstrated a number of artifacts, however, the character of these artifacts was entirely different for each of the magnets. Evaluation
of the spinal cord at index level was impossible in both magnets. Artifacts also made the root canals difficult to assess, and were more pronounced in the 3 Tesla magnet. At the adjacent levels, the spinal cord and root canals were completely visualized in all patients using both magnets.

With the 1.5 Tesla magnet, the “blur artifact ratio” was 47.0% (range 39.2%–58.2%), and with the 3 Tesla magnet, it was 54.2% (range 30.1%–71.4%). The difference was not statistically significant.

4.4 Paper IV

The Neck Disability Index (NDI) and its correlation with quality of life and mental health measures among patients with single-level cervical disc disease scheduled for surgery

All of the 136 study participants answered the SF-36 and EQ-5D-3L questionnaires, and 92 completed the HADS questionnaire. There were no differences in baseline data between the patients who did and did not answer the HADS questionnaire.

Simple linear regression analyses demonstrated a significant correlation between NDI and EQ-5D-3L (R=-0.64, 95% CI -0.64– -0.198, P<0.001), and to a lesser extent between NDI and SF-36 PCS (R=-0.49, 95% CI -0.49– -0.58, P<0.001) and SF-36 MCS (R=-0.25, 95% CI -0.25– -0.09, P=0.004). We also found a significant positive correlation between NDI and HAD-D (R=0.26, 95% CI 0.21– 1.73, P=0.01). Multiple linear regression analysis was performed to assess the independent variables’ ability to predict the level of the NDI score. The correlation was most pronounced for EQ-5D-3L (R=-0.64, 95% CI -0.64– -0.79, P<0.001), intermediate for SF-36 PCS (R=-0.41, 95% CI -0.41– -0.23, P=0.001), and lowest for SF-36 MCS (R=-0.36, 95% CI -0.36– -0.15, P=0.001).
5. GENERAL DISCUSSION

Cervical disc surgery is one of the most common spinal procedures. In the US, approximately 550,000 patients were operated between 2005 and 2008, and in Norway, the number of surgical procedures for cervical DDD has increased from 711 in 2008 to 1356 in 2014. During this time period, 6511 procedures were performed, 79% due to cervical radiculopathy. Since the anterior approach to the cervical spine was introduced in the late 1950s, ACDF has been the gold standard surgical treatment. However, concerns about ASD have led to increasing use of motion preserving ACDA. So far, most RCTs have shown clinical results in favor of ACDA, but there is limited knowledge regarding the significance of HO and radiographic challenges after arthroplasty.

5.1 Paper I

The NORCAT showed excellent clinical results for both ACDF and ACDA at 3 months, which were sustained until the final follow-up at 2 years. We did not find significant differences between the 2 treatment modalities in any outcome measures at the scheduled follow-ups. This is not consistent with most RCTs, or a study on available registry data, reporting clinical outcome in favor of arthroplasty. In contrast, by performing repeated measurement analyses we revealed a 5.9% difference in NDI score in favor of fusion after 2 years. However, the difference was small and the statistical significance weak, and therefore, the result must be interpreted with caution. It is unclear whether this difference can be considered to be clinically important, as there is no clear consensus-based agreement on how large the between-group difference should be. The minimal clinically important improvement of at least 10% in NDI score was reached by 70% of the patients in the arthroplasty group, and 78% of those in the fusion group. Even though the difference was not statistically significant, the result did not favor arthroplasty. There are several possible explanations for the different results of our study compared with previous trials, like
study methods, length of follow-up, device design, fusion technique, and the impact of funding by arthroplasty manufacturers.

Only 2 of the previous RCTs described blinding of their patients,\textsuperscript{142, 145} however, only until after surgery and not during follow-up. Blinding procedures are important in order to reduce expectation bias among the patients, but should also include the treating surgeons. In addition to the NORCAT, only the Swedish study by Skeppholm and colleagues\textsuperscript{181} blinded the surgical team until after decompression of the compressed nerve root was completed.

The length of follow-up might have an influence on the clinical outcome, especially regarding development of HO and ASD. HO will be addressed later, while ASD is beyond the scope of this thesis. In our study, however, we found little change in clinical outcome from 3 months to 2 years, consistent with the results presented by Gornet and colleagues,\textsuperscript{205} and the study on registry data by Staub and colleagues, showing a quite stable postoperative course of patient-reported outcomes from 2 to 5 years.\textsuperscript{202}

The various arthroplasty devices have different biomechanical performances.\textsuperscript{206} Most devices are “semiconstrained”, allowing physiological movement, or “nonconstrained”, without a mechanical stop and allowing a maximum range of motion determined by perispinal soft tissue and inherent compression across the disc space.\textsuperscript{207} In this respect, the nonconstrained DISCOVER\textsuperscript{®} disc prosthesis can be compared with the Bryan\textsuperscript{®} cervical disc (Medtronic Spine and Biologics, Memphis, TN),\textsuperscript{142-144} and the Porous Coated Motion (PCM) artificial cervical disc (Cervitech Inc., Rockaway, NJ).\textsuperscript{145} The semiconstrained design of the Prestige\textsuperscript{®} ST cervical disc system (Medtronic Spine and Biologics, Memphis, TN)\textsuperscript{139, 140} on the other hand, differs from the DISCOVER\textsuperscript{®} not only in the degree of movement restriction, but also in relation to the implantation technique, as this device is fixed to the vertebrae with screws. In addition to the degree of constraint, arthroplasty devices may also differ in the design of the articulating surfaces, affecting the range of motion (ROM). The ball-and-socket design of the DISCOVER\textsuperscript{®} has a different influence on the ROM than
the design of the Bryan® and PCM devices. Different implant design has also been shown to cause different intradiscal pressure on adjacent levels.206

The applied stand-alone fusion technique with the CERVIOS® cage in the NORCAT differs from most previous RCTs performing anterior plating in combination with an allograft,139, 140, 142-145 or ICBG.181 Two-year fusion rates of the techniques are, however, similar with 92% to 97.5% for allograft and anterior plating,139, 142, 145 and 92% for a stand-alone PEEK cage.208

In the NORCAT, there was a higher reoperation rate after arthroplasty, which contrasts with previous results.139, 140, 143 Possible explanations could be related to incorrect size of the implanted device or suboptimal implantation technique. However, all patients were operated at a time-point when all study surgeons had good experience with the DISCOVER® disc prosthesis. A recent study by Skeppholm and colleagues, using the same arthroplasty device, showed instability and accompanying neck pain after ACDA in 8% of the patients, all of whom underwent revision surgery.209

Arthroplasty manufacturers have been involved in numerous RCTs comparing outcome between cervical arthroplasty and fusion, as was the case in the NORCAT. The impact of funding and outcome discrepancy between previous RCTs was recently addressed by Alvin and colleagues.210 They assessed whether there was a greater probability of results in favor of arthroplasty in trials funded by device manufacturers, and found lower complication rates with arthroplasty when a conflict of interest was reported, but no impact on HRQoL outcomes.210

5.2 Paper II

At 2-year follow-up, all our patients had developed HO, 62% even had high-grade ossification. There were no differences in clinical outcome between those with high-grade and low-grade ossification.
The reason for using ACDA instead of ACDF is the preservation of motion at the operated level. However, HO is an unwanted consequence of arthroplasty. Skeppholm and colleagues recently showed very limited motion due to HO in 8%, and lack of motion due to complete fusion in 5% of patients. A meta-analysis found HO after 24 to 96 months in 38% to 62% of the patients operated with nonconstrained devices. Yi et al. found HO after 20 months in 21% and 53% of the patients operated with the nonconstrained devices Bryan® and Mobi-C® cervical disc (LDR Medical, Sainte-Savine, France), respectively, and with the semiconstrained ProDisc® C Total Disc Replacement (Synthes, West Chester, PA) in as many as 71% of the patients. Skeppholm and colleagues used the same arthroplasty device as in the NORCAT, and found HO causing complete fusion or very limited motion in 5% and 8% of patients, respectively, after 40 months. Interestingly, other authors did not report any HO after 32 months when using the DISCOVER® in 2-level disc surgery. Possible explanations for differences in the reported degree of HO may be related to device design, suboptimal placement and incorrect size of the device, and surgical technique. Park and colleagues found that use of a fluted ball-type burr instead of a diamond burr to trim the endplates resulted in a significantly higher frequency of HO. In the NORCAT, only diamond burrs were used, nevertheless, HO was seen in all patients.

Another possible contributing factor in the development of HO may be related to the use of NSAIDs after surgery. The positive effects of NSAIDs in the prevention of HO after total hip replacement have previously been reported. One study has reported a trend toward decreased HO formation in patients using NSAIDs after ACDA compared with those who did not, but the difference was not statistically significant. NSAIDs were not routinely used in the NORCAT.

Male gender has previously been associated with HO formation, which could not be confirmed in our study.

The instantaneous axis of rotation is the point of rotation of one vertebral body on the other at a given time, and will change when motion of the vertebrae consists of both translational and rotational components. Arthroplasty devices
should be able to restore the physiologic ROM and disc height, and to transmit axial loading forces from the superior to the inferior vertebral body.\textsuperscript{219} Implants like the DISCOVER\textsuperscript{®} and ProDisc\textsuperscript{®} C have a ball-and-socket single-articulating design with a fixed center of rotation (COR). With such devices, a posterior positioning of the implant in the disc space is important in order to mimic the kinematics of the normal spine. Other arthroplasty devices like the Bryan\textsuperscript{®} have double articulation surfaces and independent translation and thus allow for a mobile COR, meaning that various positions of the device may theoretically maintain physiologic kinematics.\textsuperscript{220} Whether an altered COR due to implantation of an arthroplasty device has long-term clinical consequences is yet unknown. However, an imprecise position of the implant may influence HO formation. Koller and colleagues found that ideal surgical preparation and positioning of the implant are most important in order to preserve the segmental COR and balance.\textsuperscript{221}

Regardless of the underlying causes of HO, the degree of ossification did not influence the clinical outcome in the NORCAT, which was not consistent with a recent meta-analysis, demonstrating that patients with high-grade HO actually had less pain than patients with low-grade HO.\textsuperscript{194} According to our results, the role of preserved motion at the operated level is of limited relevance with respect to the clinical outcome.

5.3 Paper III

Both 1.5 and 3 Tesla MR images produced a number of artifacts in patients operated with the DISCOVER\textsuperscript{®} disc prosthesis, making the evaluation of root canals and the spinal cord at index level difficult or impossible.

Not all patients achieve symptom relief after surgery, and postoperative investigation with MRI may be necessary. The alloy composition of the arthroplasty device is highly important regarding the artifacts induced in the magnet. Sekhon and colleagues compared the image quality of the ProDisc\textsuperscript{®} C and PCM ferromagnetic
cobaltchrome metal devices with the Bryan® and Prestige® LP titanium devices, and found that ferromagnetic cobaltchrome metal alloys caused the image quality to significantly deteriorate.\textsuperscript{222} Titanium implants are thus recommended in patients who may need further MRI.\textsuperscript{223} Even though a titanium implant was used in the NORCAT, artifacts were found in all patients, restricting the diagnostic evaluation at the operated level. Possible explanations may be related to the magnet field strength and the MR sequence parameters.

The present study demonstrated that a higher magnet field strength produced more artifacts and an increased artifact ratio. These results are consistent with those of Antosh and colleagues who compared 1.5 with 0.2 Tesla strength.\textsuperscript{224} Even though visualization of root canals at index level was almost impossible in the NORCAT, others found this possible in 1.5 Tesla MRI after implantation of a titanium device.\textsuperscript{225} Sekhon and colleagues visualized both root canals and the spinal cord in T2 weighted images using a 1.5 Tesla magnet.\textsuperscript{222} The use of different MR sequence parameters may explain the discrepancy between the results of the NORCAT and previous studies.

In particular, the axial MEDIC sequence causes artifact in the presence of metal. This sequence is performed for good evaluation of disc protrusion and the CSF space, avoiding CSF flow disturbance, but at the cost of inducing more artifacts. The spinal cord was, however, assessed with standard T2 sequences in the abovementioned studies. In order to produce fewer artifacts, MR sequences should be adjusted accordingly. Spin-echo sequences reduce the size of the artifact, and frequency encoding direction, slice thickness, bandwidth, and echo-time will influence the extent of artifacts. In our study, these factors were not investigated.

\textbf{5.4 Paper IV}

In the present study, we found a correlation between NDI score and EQ-5D-3L, SF-36 sumscores, and HAD-D in patients with single-level disc disease and corresponding radiculopathy.
Selecting the “right” patient for surgery may be difficult. However, questionnaires may help to get the best possible impression of the patient’s overall health status. The questionnaires chosen for this purpose should be easy and quick to complete, but at the same time provide as much information as possible. In our study, we found the NDI with its simple and easy profile to be correlated to more complicated HRQoL and mental health questionnaires, demonstrating that it not only captured the patient’s self-reported neck disability, but also HRQoL and mental health aspects. The present results were consistent with previous reports assessing the correlation between NDI and EQ-5D, SF-36, and HAD-D.

5.5 Methodological considerations

5.5.1 Participants

The NORCAT is a multicenter study, conducted at 5 neurosurgical departments in Norway. Seventy-nine out of 136 patients were included at Oslo University Hospital Rikshospitalet. Approximately half of all anterior cervical discectomies annually in Norway are performed at Rikshospitalet.

One or 2 senior investigators at each attending hospital evaluated all patient referrals from general practitioners and the specialist health care services, before patients were assessed for eligibility at the neurosurgical outpatient clinics. At Rikshospitalet, the treating surgeon screened all patients for inclusion in the study. At the other hospitals, colleagues not involved in the trial, but also evaluating patients with cervical radiculopathy, were informed about the study and asked to notify the study investigators about potential participants. Accordingly, one cannot exclude the possibility that potential candidates with cervical radiculopathy might have been missed for eligibility screening (selection bias).

During the first year of enrollment, the NDI score for inclusion was >30%. This was changed to NDI≥30% in order to increase the number of eligible patients.
for the study. Thus, some patients with an NDI score=30% were lost for inclusion the first study year.

The study protocol could have been more specific regarding the radiographic parameters for evaluation of the degree of spondylosis, since severe spondylosis, defined as bridging osteophytes, loss of disc height greater than 50%, or absence of motion (<2°), has been considered a contraindication for ACDA. Therefore, one cannot exclude the possibility that some patients who did not meet the criteria for arthroplasty may have been included into the study, which could have biased the study in favor of the fusion group.

The strict blinding procedure of the NORCAT is unique compared with previous RCTs, and the discharge reports, addressed to the patients’ general practitioners and referring authorities, did not contain information regarding the surgical procedure, which is otherwise common procedure. However, to what extent the patients actively sought to gain information about their surgical procedures is unknown.

5.5.2 Intervention

Stand-alone ACDF is one of the most commonly performed surgical procedures and all study surgeons had extensive experience with the fusion procedure. ACDA, on the other hand, was a less common procedure, which is the reason why all study surgeons had to perform 5 arthroplasty procedures with the DISCOVER® disc prosthesis before the enrollment of patients started in November 2008. Nevertheless, the study surgeons never got to the same level of experience with ACDA as with ACDF. Therefore, one cannot exclude the possibility of suboptimal implantation technique and size of the arthroplasty device. In addition, the longer duration of ACDA may partly be due to a lower level of experience.
5.5.3 Assessments

The follow-up of the patients was performed unblinded by one of the treating surgeons, and not by an independent and blinded investigator, thus, expectation bias cannot be excluded. The completed questionnaires were, however, collected by an independent study secretary before the clinical evaluation. At baseline, the questionnaires were completed 1 to 3 days prior to surgery. Accordingly, one cannot exclude the possibility that factors such as anxiety about the operation itself might have influenced the baseline responses.

The use of questionnaires in clinical research requires that their measurement properties, like reliability, validity and responsiveness, be assessed and found adequate for their purpose. Reliability is the ability of a test to reproduce a result. The reliability of a test is derived from its internal consistency, test-retest reliability and interrater reliability. The internal consistency of a test measures to what extent different items of the test correlate. Test-retest reliability is an expression of the consistency of test results at different time points, given the same test conditions and the same rater. Interrater reliability assesses to what degree a test’s results are consistent between two or more raters. Validity refers to a test’s ability to measure what it claims, and is divided into criterion, content and construct validity. Criterion validity describes the correlation between one test and other tests known to be valid and measuring the same characteristics. Content validity refers to the extent to which a test measures all aspects of the content to be measured, and construct validity to whether the construct of the test is measured adequately. Responsiveness describes a test’s ability to measure change over time or between treatments in the same subject.

Different questionnaires have been developed in order to measure pain and disability in patients with cervical radiculopathy and neck pain, and NDI is the most widely used in clinical settings. Self-reported assessment instruments like the NDI should be able to capture a patient’s actual level of disability, the extent to which the disease affects daily activities, and to detect change in function over time.
Several studies have assessed the measurement properties of the NDI, but most of these were conducted in patients receiving physiotherapy for neck pain and whiplash injuries, and only a few in patients with cervical radiculopathy or those treated surgically. The validity of NDI is well documented, and has a fair test-retest reliability and adequate responsiveness. A systematic review of the measurement properties of the NDI supported its status as the most commonly used self-report measure for neck pain. However, other questionnaires measuring neck pain like the Neck Outcome Score, have been found to be superior in terms of reliability, validity, and responsiveness. The Patient Specific Functional Scale has also been found to be superior to the NDI.

McCarthy and colleagues assessed patients with neck pain in an outpatient setting, and found that the NDI had good reliability and validity, and correlated well with the SF-36, making the use of both questionnaires unnecessary in the clinical setting. This is in accordance with the results from paper I.

In paper II, the degree of HO around the DISCOVER disc prosthesis was assessed using CT. We used a classification based on the McAfee classification system for HO related to arthroplasty in the lumbar spine, which has been found to be reliable. However, we neither assessed motion at the operated level, nor to what extent it was restricted by HO.

In paper III, the imaging parameters in both the 1.5 and 3 Tesla magnets were mainly set as standard sequences, and not optimized in order to reduce the number of artifacts. In addition, the use of different axial sequences made it impossible to compare the evaluation of root canals between the magnets.

5.5.4 Statistics

Paper II is only based on the 39 patients who were operated with the DISCOVER disc prosthesis at Rikshospitalet. Paper III was a small pilot study of the first 10
patients included at Rikshospitalet. The number of patients is limited in both studies, and may preclude firm conclusions.

In papers II and III, 2 independent neuroradiologists evaluated the images and reached agreement by consensus. Ideally, they should have evaluated the images independently, and the interrater agreement should have been measured with Kappa statistics.

Regarding paper IV, the HADS questionnaire became part of the assessment instruments approximately 1 year after patient enrollment started. Thus, only 92 out of 136 patients answered this questionnaire. However, there were no baseline differences between the patients who did answer the questionnaire and those who did not.
6. CONCLUSIONS

**Paper I**
The study showed excellent clinical outcome for both arthroplasty and fusion, and no significant between-group difference at any scheduled follow-up. However, the rate of index level reoperations was higher, and the duration of surgery longer, with arthroplasty.

**Paper II**
High-grade HO including spontaneous fusion was seen in more than half of the patients 2 years after surgery. However, the degree of ossification did not influence the clinical outcome.

**Paper III**
The DISCOVER® disc prosthesis induced artifacts in both 1.5 and 3 Tesla MRIs to such an extent that index level visualization of the root canals was difficult and evaluation of the spinal cord was impossible. MR sequences should be adjusted in order to produce the least amount of artifacts possible.

**Paper IV**
There was a significant correlation between the NDI and different quality of life and mental health measures in patients with single-level cervical disease and radiculopathy. The NDI may provide a simpler and broader understanding of the patients’ overall health situation.
7. FURTHER PERSPECTIVES

Several studies have shown favorable outcome after arthroplasty in patients with symptomatic single-level cervical disc disease, while others have shown similar results for arthroplasty and fusion. In our study, we did not find significant differences between the 2 treatment modalities up to 2-year follow-up. There are several aspects that should be considered more thoroughly before cervical arthroplasty is offered to patients to a greater extent.

The main premise of using ACDA over ACDF is the preservation of index level motion. Since several trials including the NORCAT have shown a disturbingly high level of HO, more studies should focus on the underlying reasons for HO development. The role of NSAIDs postoperatively and the surgical technique are probably important aspects to be evaluated.

Expectations of a lower ASD incidence, as a consequence of maintained motion, is the reason for choosing ACDA over ACDF. Likely, ASD is caused by a combination of biomechanical stress related to fusion and the natural course of degeneration. More studies are needed to answer the question regarding ASD after ACDA or ACDF, and the NORCAT 5-year results will address this important topic.

Relatively few studies have assessed the cost-effectiveness of ACDA versus ACDF. Radcliff and colleagues recently presented their results, and concluded that single-level ACDA was less costly and more effective over a 7-year time period than ACDF with allograft bone and anterior plating. Ament and colleagues found ACDA to be more expensive than ACDF in 2-level disc surgery at 2 and 5 years follow-up, but suggested it to be a highly cost-effective treatment option because of higher total quality-adjusted life years. Further health economic studies including radiological and clinical outcome are needed. The NORCAT 2-year cost-effectiveness analyses will be presented in the near future.
Previous RCTs reported index level reoperations to be higher with fusion,\textsuperscript{139, 140, 143} which contrasts with the NORCAT 2-year results. Further long-term results from other studies and the 5-year follow-up results from the NORCAT may elucidate this topic.

It has been shown that high-grade ossification around a cervical arthroplasty device will affect motion.\textsuperscript{247} However, more studies assessing the degree to which motion is restricted by the degree of HO are probably needed.

New implant designs and material composition will doubtless be developed, hopefully minimizing artifacts in postoperative MRI.
8. REFERENCES


75. Fritz JM, Thackeray A, Brennan GP, Childs JD. Exercise only, exercise with mechanical traction, or exercise with over-door traction for patients with cervical radiculopathy, with or without consideration of status on a previously described subgrouping rule: a randomized clinical trial. *J Orthop Sports Phys Ther*. 2014; 44: 45-57.


166. Lied B, Sundseth J, Helseth E. Immediate (0-6 h), early (6-72 h) and late (>72 h) complications after anterior cervical discectomy with fusion for cervical disc degeneration; discharge six hours after operation is feasible. Acta Neurochir (Wien). 2008; 150: 111-8.


9. ERRATA

The affiliation nr. 3 “Department of Neuroradiology, Oslo University Hospital Rikshospitalet, Oslo, Norway”, of the last author John-Anker Zwart in paper II (Heterotopic ossification and clinical outcome in nonconstrained cervical arthroplasty 2 years after surgery: the Norwegian Cervical Arthroplasty Trial (NORCAT), is wrong and should say nr. 2 “Faculty of Medicine, University of Oslo, Oslo, Norway”.

99
10. APPENDIX

10.1 Neck Disability Index – Norwegian version

<table>
<thead>
<tr>
<th>Funksjonsscore (NDI)</th>
<th>4. Lesing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg har ingen smerte akkurat nå</td>
<td>Jeg kan lese så mye som jeg ønsker, uten at det gir smerte i nakken</td>
</tr>
<tr>
<td>Smertene er svært svake akkurat nå</td>
<td>Jeg kan lese så mye som jeg ønsker, men med svake smerte i nakken</td>
</tr>
<tr>
<td>Smertene er moderate akkurat nå</td>
<td>Jeg kan lese så mye som jeg ønsker, men med moderate smerten i nakken</td>
</tr>
<tr>
<td>Smertene er koså sterke akkurat nå</td>
<td>Jeg kan ikke lese så mye som jeg ønsker, på grunn av koså sterke smerten i nakken</td>
</tr>
<tr>
<td>Smertene er meget sterke akkurat nå</td>
<td>Jeg kan omtrent ikke lese i det hele tatt, på grunn av meget sterke smerten i nakken</td>
</tr>
<tr>
<td>Smertene er de vane tankeige akkurat nå</td>
<td>Jeg kan ikke lese i det hele tatt på grunn av smerten i nakken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Personlig stell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg kan stelle meg som normalt, uten at det gir ekstra smerten</td>
</tr>
<tr>
<td>Jeg kan stelle meg selv som normalt, men det gir ekstra smerten</td>
</tr>
<tr>
<td>Det er smertefullt å stelle seg selv, og jeg er langsom og forskjellig</td>
</tr>
<tr>
<td>Jeg trenger noe hjelp, men klarer mesteparten av mitt personlige stell</td>
</tr>
<tr>
<td>Jeg trenger hjelp hver dag med mesteparten av mitt personlige stell</td>
</tr>
<tr>
<td>Jeg klarer ikke på meg, har vansker med å vaske meg og holde meg i sengen</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Letting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg kan laate tunge ting uten å få smerten</td>
</tr>
<tr>
<td>Jeg kan laate tunge ting, men får smerten</td>
</tr>
<tr>
<td>Smertene hindrer meg i å laate tunge ting opp fra gulvet, men jeg greier det hvis det som skal lasset er gunstig plassert, for eksempel på et bord</td>
</tr>
<tr>
<td>Smertene hinder meg i å laate tunge ting, men jeg klarer det lett hvis det er gunstig plassert</td>
</tr>
<tr>
<td>Jeg kan bare laate noe som er veldig lett</td>
</tr>
<tr>
<td>Jeg kan ikke laate eller bare noe i det hele tatt</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Hodepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg har ikke hodepine i det hele tatt.</td>
</tr>
<tr>
<td>Jeg har svak hodepine som kommer nå og da</td>
</tr>
<tr>
<td>Jeg har moderat hodepine som kommer nå og da</td>
</tr>
<tr>
<td>Jeg har moderat hodepine som kommer jevnlig</td>
</tr>
<tr>
<td>Jeg har sterk hodepine som kommer jevnlig</td>
</tr>
<tr>
<td>Jeg har hodepine nesten hele tiden</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Konsentrasjon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg kan koncentrer meg uten vansker</td>
</tr>
<tr>
<td>Jeg kan koncentrer meg små vansker</td>
</tr>
<tr>
<td>Jeg har nokså store vansker med å koncentrer meg</td>
</tr>
<tr>
<td>Jeg har store vansker med å koncentrer meg</td>
</tr>
<tr>
<td>Jeg har svært store vansker med å koncentrer meg</td>
</tr>
<tr>
<td>Jeg kan ikke koncentrer meg i det hele tatt</td>
</tr>
</tbody>
</table>
7. Arbeid (eller daglige gjøremål)
- Jeg kan gjøre så mye arbeid jeg ønsker
- Jeg kan gjøre litt vanlige arbeid, men ikke mer
- Jeg kan gjøre mesteparten av mitt vanlige arbeid, men ikke mer
- Jeg kan ikke gjøre litt vanlige arbeid
- Jeg kan omtrent ikke gjøre noe arbeid i det hele tatt
- Jeg kan ikke gjøre noe arbeid i det hele tatt

8. Bilkjøring
- Jeg kan kjøre en bil uten at det gir smert i nakken
- Jeg kan kjøre en bil så lenge som jeg ønsker, men med svake smert i nakken
- Jeg kan kjøre en bil så lenge som jeg ønsker, men med moderate smert i nakken
- Jeg kan ikke kjøre en bil så lenge som jeg ønsker, på grunn av roks sterke smert i nakken
- Jeg kan omtrent ikke kjøre bil i det hele tatt, på grunn av meget sterke smert i nakken
- Jeg kan ikke kjøre bil i det hele tatt, på grunn av smert i nakken

9. Søvn
- Jeg har ikke problemer med å sove
- Søvn min er litt forstyrret (mindre enn 1 times savnløshet)
- Søvn min er noe forstyrret (1-2 timers savnløshet)
- Søvn min er moderat forstyrret (2-3 timers savnløshet)
- Søvn min er sterkt forstyrret (3-5 timers savnløshet)
- Søvn min er fullstendig forstyrret (5-7 timers savnløshet)

10. Fritid
- Jeg er i stand til å drive med alle mine fritidsaktiviteter uten at det gir smert i nakken overhodet
- Jeg er i stand til å drive med alle mine fritidsaktiviteter, men med noe smert i nakken
- Jeg er i stand til å drive med de feste av, men ikke alle, mine fritidsaktiviteter på grunn av smert i nakken
- Jeg er bare i stand til å drive med noen få av mine vanlige fritidsaktiviteter på grunn av smert i nakken
- Jeg kan omtrent ikke drive med fritidsaktiviteter på grunn av smert i nakken
- Jeg kan ikke drive med fritidsaktiviteter i det hele tatt
10.2 Numeric Rating Scale

<table>
<thead>
<tr>
<th>Hvor sterke smertene har du hatt i nakken i løpet av den siste ukene? (Sett ring rundt ett tall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingen smerten</td>
</tr>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Så vondt som det går an å ha</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hvordan vil du gradere smertene du har hatt i armen (en eller begge) i løpet av den siste ukene? (Sett ring rundt ett tall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingen smerten</td>
</tr>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Så vondt som det går an å ha</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hvordan vil du gradere de smertene du har hatt i hodet i løpet av den siste ukene? (Sett ring rundt ett tall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingen smerten</td>
</tr>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Så vondt som det går an å ha</td>
</tr>
</tbody>
</table>
10.3 Short Form 36 – Norwegian version

**SF-36 Spørreskjema om helse**

Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine gjenrein.


1. **Stort sett, hvordan vil du si din helse er?**
   - [ ] Utskrivet
   - [ ] Meget god
   - [ ] God
   - [ ] Nokså god
   - [ ] Dårlig

2. **Sammenlignet med for et år siden, hvordan vil du si din helse er nå?**
   - [ ] Mye bedre nå enn for et år siden
   - [ ] Litt dårligere enn for et år siden
   - [ ] Litt bedre nå enn for et år siden
   - [ ] Mye dårligere enn for et år siden
   - [ ] Omtrent det samme som for et år siden

3. **De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?**

<table>
<thead>
<tr>
<th>Slett kryss</th>
<th>Ja, begrenser meg mye</th>
<th>Ja, begrenser meg litt</th>
<th>Nei, begrenser meg ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Anstrengende aktiviteter som å løpe, latte tunge gjenstander, ditta i anstrengende idrett</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Moderate aktiviteter som å flyte et bord, stavsuge, gå en tur eller saue med nagearbeid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Leve eller bære en handelkurv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Gå opp trappen flere etapper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Gå opp trappen et eneste</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Børge deg eller sitte på huk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>Gå mer enn to kilometer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>Gå noen hundre meter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Gå hundre meter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>Vanske eller kle på deg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. **I løpet av de siste 4 ukene, har du hatt noen av tilgjengelige problemer i ditt arbeid eller i andre av dine daglige gjerning på grunn av din fysiske helse?**

<table>
<thead>
<tr>
<th>Skrifte kryss</th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Du har måttet redusere tiden du har brukt på arbeid eller på andre pågjemål</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Du har utrettet mindre enn du hadde ønsket</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Du har vært hindret i å utføre visse typer arbeid eller gjerning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Du har hatt problemer med å gjennomføre arbeid eller andre gjerning (for eksempel fordi det krevede ekstra anstrengelser)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. I løpet av de siste 4 ukene, har du hatt noen av følgende problem i ditt arbeid eller i andre av dine daglige gjøremål på grunn av fysiskesmussige problemer (som for eksempel å føle deg deprimert eller engstlig)?

<table>
<thead>
<tr>
<th>Sett kryss</th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du har måttet reduser tiden du har brukt på arbeid eller andre gjøremål</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Du har utrettet mindre enn du hadde ønsket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmussige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

<table>
<thead>
<tr>
<th>Innlevering</th>
<th>Ikke i det hele tatt</th>
<th>Litt</th>
<th>En del</th>
<th>Mye</th>
<th>Svingt mye</th>
</tr>
</thead>
</table>

7. Hvor sterke knokkelssmerter har du hatt i løpet av de siste 4 ukene?

<table>
<thead>
<tr>
<th>Innlevering</th>
<th>Ikke i det hele tatt</th>
<th>Litt</th>
<th>En del</th>
<th>Mye</th>
<th>Svingt mye</th>
</tr>
</thead>
</table>

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gerer både arbeid utenfor hjemmet og husarbeid)

<table>
<thead>
<tr>
<th>Innlevering</th>
<th>Ikke i det hele tatt</th>
<th>Litt</th>
<th>En del</th>
<th>Mye</th>
<th>Svingt mye</th>
</tr>
</thead>
</table>

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål vennlig velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Felt deg full av liv?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Felt deg veldig nervøs?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Været så langt nede at ingen ting har kunnet mønke deg opp?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Felt deg rolig og harmonisk?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Hatt mye overskudd?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Felt deg nødfor og trist?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g) Felt deg sliten?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Felt deg glad?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Felt deg trett?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmussige problemer påvirket din sosiale omgang (som det å besøke venner, skikning, osv.)

<table>
<thead>
<tr>
<th>Innlevering</th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i et hele tatt</th>
</tr>
</thead>
</table>

11. Hvor RIKTIG eller GAL er hver av de følgende påstandene for deg?

<table>
<thead>
<tr>
<th>Sett kryss</th>
<th>Helt riktig</th>
<th>Delvis riktig</th>
<th>Vet ikke</th>
<th>Delvis gal</th>
<th>Helt gal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Det virker som om jeg blir syk lottere enn andre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Jeg er like trissom de fleste jeg kjener</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Jeg bor holen min vil forveres</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Jeg har utmerket heise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10.4 EuroQol-5 Dimension-3 Level – Norwegian version
### 10.5 Dysphagia Short Questionnaire

<table>
<thead>
<tr>
<th>Dysfagiscore</th>
<th>3. Klumpfølelse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vanskeligheter med å svelge</td>
<td>Jeg opplever ingen klumpfølelse i halsen</td>
</tr>
<tr>
<td>□ Jeg har ingen vanskeligheter med å svelge</td>
<td>□ Jeg opplever ingen klumpfølelse i halsen</td>
</tr>
<tr>
<td>□ Det hender noen ganger at mat setter seg fast i svelgut hvis jeg ikke tygger ordentlig</td>
<td>□ Jeg opplever øverst klumpfølelse i halsen</td>
</tr>
<tr>
<td>□ Jeg har vanskeligheter med å svelge fast fade</td>
<td>□ Jeg opplever hele tiden klumpfølelse i halsen</td>
</tr>
<tr>
<td>□ Jeg har vanskeligheter med å svelge flytende fade</td>
<td>□</td>
</tr>
<tr>
<td>□ Jeg har vanskeligheter med å svelge mitt spyt</td>
<td>□</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. &quot;Feileveljing&quot;</th>
<th>4. Ufrivillig vekttap</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Jeg opplever ikke at jeg svelger feil</td>
<td>Jeg har ikke tapt vekt den senere tid</td>
</tr>
<tr>
<td>□ Jeg har en følelse av å svelge feil iblant, uten å måtte hoste</td>
<td>□ Jeg har tapt 1-2 kg i den senere tid</td>
</tr>
<tr>
<td>□ Det hender iblant at jeg hoster når jeg svelger</td>
<td>□ Jeg har tapt mere enn 2 kg i vekt den siste tiden</td>
</tr>
<tr>
<td>□ Det hender ofte jeg hoster når jeg svelger</td>
<td>□</td>
</tr>
<tr>
<td>□ Jeg får alltid et hosteanfall når jeg svelger</td>
<td>□</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Lungebetennelse</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Jeg har ikke hatt noen lungebetennelse fordi jeg svelger feil</td>
<td>□ Jeg har hatt noen &quot;enstaka&quot; lungebetennelser fordi jeg svelger feil</td>
</tr>
<tr>
<td>□ Jeg har hatt gjentagende lungebetennelser fordi jeg svelger feil</td>
<td>□</td>
</tr>
</tbody>
</table>
### Hospital Anxiety and Depression Scale – Norwegian version

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For det meste</td>
<td>Avgjort like mye</td>
<td>Helt sikker å svært ille</td>
<td>Like mye som jeg alltid har gjort</td>
<td>Veldig ofte</td>
<td>Aldri</td>
<td>Ja, helt klart</td>
<td>Nesten hele tiden</td>
<td>Ikke i det hele tatt</td>
<td>Ja, helt klart</td>
<td>Utente til svært ofte</td>
<td>Ofte</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofte</td>
<td>Ikke fullt så mye</td>
<td>Ja, men ikke så veldig ille</td>
<td>ikke mye nå som før</td>
<td>Ganske ofte</td>
<td>Noen ganger</td>
<td>Vanligvis</td>
<td>Svært ofte</td>
<td>Ikke i det hele tatt</td>
<td>Jeg bryr meg ikke så mye som jeg burde</td>
<td>Ganske ofte</td>
<td>Gratis til annen</td>
<td>Fra tid til annen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noen ganger</td>
<td>Bare lite grann</td>
<td>Litt ille, men det bekymrer meg ikke så mye</td>
<td>Avgjort ikke så mye nå som før</td>
<td>Ganske ofte</td>
<td>Ganske ofte</td>
<td>Ikke så ofte</td>
<td>Fra tid til annen</td>
<td>Ikke i det hele tatt</td>
<td>Jeg bryr meg ikke så mye som jeg burde</td>
<td>Ikke i det hele tatt</td>
<td>Ikke så ofte</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ikke i det hele tatt</td>
<td>Ikke i det hele tatt</td>
<td>Ikke i det hele tatt</td>
<td>Ikke i det hele tatt</td>
<td>Svært ofte</td>
<td>Ikke i det hele tatt</td>
<td>Ikke så ofte</td>
<td>Ikke i det hele tatt</td>
<td>Svært sjelden</td>
<td>Jeg bryr meg ikke så mye som jeg burde</td>
<td>Ikke i det hele tatt</td>
<td>Ikke så ofte</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. Papers I-IV