Surgery versus nonsurgical treatment of cervical radiculopathy

Randomized studies of anterior cervical decompression and fusion followed by physiotherapy versus structured physiotherapy alone

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You can have your own opinions, but you can’t have your own facts.

To Maria and Ida
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1 LIST OF PAPERS


II. Physical function outcome in cervical radiculopathy patients after physiotherapy alone compared with anterior surgery followed by physiotherapy: a prospective randomized study with a 2-year follow-up.


III. Factors affecting the outcome of surgical versus nonsurgical treatment of cervical radiculopathy: a randomized, controlled study.


IV. A 5-8 years randomized study on treatment of cervical radiculopathy: anterior cervical decompression and fusion plus physiotherapy versus physiotherapy alone.

Submitted
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACDF</td>
<td>Anterior Cervical Decompression and Fusion</td>
</tr>
<tr>
<td>ADR</td>
<td>Artificial Disc Replacement</td>
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<tr>
<td>AROM</td>
<td>Active Range Of Motion</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CR</td>
<td>Cervical Radiculopathy</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<td>DRAM</td>
<td>Distress Risk Assessment Method</td>
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<td>DTR</td>
<td>Deep Tendon Reflex</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>EQ-5D</td>
<td>5-dimensional health-scale of the EuroQol</td>
</tr>
<tr>
<td>MET</td>
<td>Medical Exercise Therapy</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimal Important Change</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NDI</td>
<td>Neck Disability Index</td>
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<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<tr>
<td>PT</td>
<td>Physiotherapy</td>
</tr>
<tr>
<td>ROM</td>
<td>Range Of Motion</td>
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<tr>
<td>RR</td>
<td>Risk Ratio</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SES</td>
<td>Self-Efficacy Scale</td>
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<td>TE</td>
<td>Treatment Effect</td>
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<td>TEM</td>
<td>Treatment Effect Modifier</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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3 ABSTRACT

Background and aims
Cervical radiculopathy (CR) is a symptom complex comprising neck pain and radiating arm pain due to compression of one or more cervical nerve roots, caused by spondylotic narrowing of the intervertebral foramina, intervertebral disc herniation or both. Anterior cervical decompression and fusion (ACDF) is a common surgical procedure to treat CR, but the evidence supporting use of this method versus nonsurgical treatment is scarce. The main aims of this thesis were to evaluate the additive value of ACDF when combined with physiotherapy (PT) in regard to disability, pain, patient satisfaction, health outcome and recovery of function, and to find patient-related factors that may predict the outcome of surgery and PT.

Patients and methods
Sixty-three patients were included in the study. They were all evaluated prior to treatment and two years after treatment start, while 59 were also evaluated 5-8 years after treatment. Patients were randomized into two groups: ACDF followed by a structured PT program or the same PT program alone. Outcome measures at 2 years were disability using the Neck Disability Index, (NDI), pain intensity, patient global assessment and objective function. At 5-8 years, health outcome (EQ-5D) was also analyzed, but function was not. Based on the outcomes of the NDI and pain intensity at one year, possible patient-related modifiers of treatment outcome such as age, gender, smoking and psychological factors were analyzed.

Results
During the first two years, the only significant differences between treatment groups were that the operated patients had less neck pain throughout the entire period, while at one year, the patient global assessment of the treatment effect was superior in the surgery group. After 5-8 years, the surgical patients fared significantly better concerning NDI, neck pain and global assessment. No significant differences were seen regarding arm pain, health outcome or function.
Factors that significantly altered the treatment effect between the two treatment groups in favor of surgery regarding one or more of the outcome measures were: duration of neck and arm pain < 12 months, low EQ-5D index, female sex, high levels of anxiety due to neck/arm pain, low SES
score and high DRAM score. No factors were found to be associated with better outcome from PT alone.

**Discussion**

The studies in this thesis represent the first scientific evidence to support use of ACDF for treatment of cervical radiculopathy, based on a randomized study of surgical versus nonsurgical treatment. From the results of the studies, it is reasonable to recommend a trial of structured physiotherapy in the early phase of CR, before deciding upon surgery. However, for patients with substantial residual symptoms, ACDF is a good option for achieving greater and more rapid improvement, which can also be expected to last at least throughout a 5-8 year time span. Patients should not be disqualified from surgical treatment due to gender, poor health or a high level of distress and/or anxiety. When surgery is deemed necessary, better treatment outcomes can be expected when the procedure is performed within one year of onset of CR symptoms.
Bakgrund och syfte

Cervical radikulopati (CR) är ett symptomkomplex bestående av nacksmärta med utstralade armsgärta, som orsakas av tryck på en eller flera nervrötter i halsryggen. Orsaken kan vara diskbråck, benpålagringar eller en kombination av dessa. Främre diskutrymmare och steloperation av ett eller flera kotpar är det mest utförda kirurgiska ingreppet för att behandla CR, men trots detta är de vetenskapliga beläggen för dess effekt jämfört med icke-kirurgisk behandling ringa. Syftet med denna avhandling var att utvärdera effekten av denna operation med efterföljande sjukgymnastik jämfört med enbart sjukgymnastik, med avseende på subjektiv funktionsnedläggning, smärta, patientnöjdhet, allmän hälsa och objektiv fysisk funktion. Ett ytterligare syfte var att finna faktorer hos patienterna som kan hjälpa oss att bättre välja de patienter som kommer att ha mest nytta av respektive behandling.

Patienter och metoder


Resultat

Under de första två åren var de enda statistiskt säkerställda skillnaderna mellan grupperna att de opererade patienterna hade mindre nacksmärta under hela perioden och att patienternas egen gradering av behandlingeffekten var till fördel för operation efter ett år. Efter 5-8 år hade de opererade patienterna bättre resultat avseende subjektiv funktionsförbättring, minskning av nacksmärta och självskattad gradering av behandlingsresultatet. Ingen statistiskt säkerställd skillnad fanns avseende armsgärta, allmän hälsa eller objektiv fysisk funktion. Faktorer som gjorde behandlingsresultatet för opererade patienter bättre jämfört med enbart sjukgymnastik var smärtduration <12 månader före...
operationen, kvinnligt kön, sämre allmän hälsa och tilltro till egen funktionsförmåga före operationen samt större förekomst av ångest/oro relaterat till nack/armbesvären.

**Diskussion**

5 INTRODUCTION

5.1 Background
Cervical radiculopathy (CR) is a symptom complex of neck pain and radiating arm pain due to compression of one or more cervical nerve roots. The impingement is caused by spondylotic narrowing of the intervertebral foramina, by intervertebral disc herniation or by both.\(^1\) In the classic study of a cohort of 561 patients in Minnesota by Radhakrishnan et al,\(^2\) annual incidence was reported to be 83.2/100,000 with a larger proportion of men (107.3/100 000) than women (63.5/100,000). Mean age at diagnosis was 47.9 years. Total prevalence has been reported to be 0.35% with a peak prevalence of 2.2% in the 50-59 year age spans.\(^3\) This condition was first recognized in 1817\(^4\) and the pathology has subsequently been clarified over time.\(^5\) The natural history of CR is said to be favorable, but surprisingly little literature exists to confirm this statement.

Anterior cervical decompression and fusion (ACDF) is considered to be the gold standard surgical procedure for CR. Artificial disc replacement (ADR) instead of fusion has gained popularity over the last decade, but the clinical outcome seems to be similar to fusion.\(^6\)–\(^8\) According to the National Board of Health and Welfare and the Swedish spine registry (Swespine), about 500 ACDFs and 20 ADRs due exclusively to radiculopathy were performed in Sweden in 2013. Despite these figures, very little is known about the effects of anterior surgery compared with nonsurgical treatment. In fact, the only prospective, randomized study on the subject, only found small differences in outcome at 3 months and none at 15 months when compared with different nonoperative approaches.\(^9\) However, that study excluded pure soft disc herniations. The most recent Cochrane update concerning surgery for cervical radiculopathy only considered that study, and concluded that there was no reliable evidence that surgery for CR was effective.\(^10\) A few studies have applied similar approaches to lumbar radiculopathy, but were not entirely successful for various reasons, such as inconsistent randomization, drop outs and cross over.\(^11,12\)

5.2 Anatomy and pathology
5.2.1 Anatomy of the cervical spine
The most common section of the spine involved in the etiology of CR stretches from the third cervical vertebra to the first thoracic vertebra (C3-
T1). Each segment consists of two vertebrae and the intervertebral disc between them. The vertebrae comprise a vertebral body, a vertebral arch, a spinous process and various smaller processes involved in articulations or serving as attachment sites for various ligaments and muscles (figure 1). The vertebral arteries pass through vertebral canals defined by the foramina transversaria. The facet joints are formed by the superior and inferior articular processes while the uncinate processes (uncus= hook) arise from the lateral, superior parts of the vertebral bodies. Together with the convex inferior lateral parts of the vertebra above, the uncinate processes form the uncovertebral joints (joints of Luschka), which are essentially pseudo-joints without cartilage or real joint capsules. The intervertebral foramina containing the cervical nerve roots are located between the uncovertebral and the facet joints, and these two joints, along with the intervertebral discs, are involved in the degenerative processes of the cervical spine that cause CR (figure 2).

**Figure 1. Anatomy of a subaxial cervical vertebra.**

### 5.2.2 Intervertebral discs

The intervertebral discs have a soft consistency that permits angular movement and allows them to act as shock absorbers between the vertebral bodies. The discs consist of the semi-gelatinous, proteoglycan- and water-rich nucleus pulposus surrounded by the annulus fibrosus, made of collagen, cartilage and proteoglycans. The discs are firmly attached
to the end plates of the vertebrae, which consist of cortical, subchondral bone, covered by a thin layer of hyaline cartilage. The discs are predominantly avascular and the blood supply extends mainly to the vertebral end plates.

Figure 2. Anatomy of a subaxial cervical vertebral segment

5.2.3 Nerve roots and brachial plexus
The C3-C8 subaxial cervical nerve roots are most commonly referred to in terms of CR. The C3 and C4 nerve roots innervate the neck and shoulder. The brachial plexus arises from the C5 to T1 cervical nerve roots, which pass through the intervertebral foramina between C4-C5 and T1-T2. These nerve roots form a complex web of junctions ending in the musculocutaneous, axillary, radial, median and ulnar nerves, which innervate the sensory and motor functions of the arm. Each nerve root corresponds to a dermatome of sensory function in the arm. Due to the many junctions in the brachial plexus and to different anatomical variations, there may be considerable overlap among dermatomes.

5.2.4 Degenerative disease of the cervical spine
Degenerative disease of the cervical spine consists of cervical disc disease and/or cervical spondylosis and incidence increases with age. In a study of 497 asymptomatic individuals, about 20% had disc degeneration but less than 5% had foraminal stenosis at age 30. In individuals over age 60,
more than 80% had disc degeneration and about 15% had foraminal stenosis. The biochemical structure of the discs changes with increasing age, leading to an increase in collagen content and a decrease in water and glycosaminoglycans, causing discs to become less elastic and more fibrotic, while also reducing disc height. Reduced intradiscal pressure in the nucleus pulposus due to endplate damage increases stress on the anulus fibrosus, which may lead to disc bulging or herniation. In addition to normal aging, genetic and toxic factors, autoimmune and infectious conditions as well as mechanical factors have been implicated in disc degeneration.

Cervical spondylosis is most likely to be secondary to changes in biomechanics due to disc disease, since disc degeneration is present in almost every case of foraminal stenosis. The reduction in disc height causes the facet and uncovertebral joints to be slightly incongruent, which may initiate the degenerative process. In this sense, the two entities could be regarded as a single continuous disease process.

Cervical radiculopathy appears as the result of nerve root compression at the entry site to, or within the intervertebral foramina which arises in response to disc prolapse and/or osteophytes of the facet and uncovertebral joints (figure 3). The levels of disc degeneration/spondylosis that most commonly cause CR, in order, are C5-C6, C6-C7 and C4-C5.

Figure 3. Anatomic basis for the origin of cervical radiculopathy.
5.3 Symptoms and diagnosis of cervical radiculopathy

5.3.1 Clinical manifestation and testing

The symptoms of CR are pain in the neck and/or one or both upper extremities accompanied by paresthesias and/or sensory and motor disturbances. The onset may be sudden in cases of acute disc herniation, or slow in cases of gradual foraminal narrowing due to spondylosis and/or disc degeneration. Typically, neck pain is present along with restricted range of motion (ROM), radiating arm pain and sensory disturbance, often aggravated by neck extension and rotation of the head toward the affected side (Spurling test). Symptomatic relief may occur with shoulder abduction and traction/neck distraction. The Spurling test, traction/neck distraction test and shoulder abduction test all share high specificity, but low sensitivity, which means they are more effective for verifying the condition than for ruling it out. Weakness and altered deep tendon reflexes (DTRs) occur in about 70% of cases, and scapular pain in about 50%. Sensory function and DTRs of the upper extremity are evaluated to confirm findings and to further specify the level of suspected nerve root compression. In this context, the substantial overlap of cervical nerve roots in the brachial plexus must be taken into account; therefore clinical findings can only be moderately precise. Patient history as well as testing of sensory function and DTRs in the lower extremities are also essential to rule out concomitant myelopathy.

5.3.2 Differential diagnosis

Since the predominant symptoms of CR are pain and/or neurologic deficit in the neck and arms, any conditions that can cause such symptoms must be considered when examining the patient. Common differential diagnoses include peripheral nerve compression (e.g. carpal tunnel syndrome and ulnar nerve compression at elbow or wrist), epicondylalgia and shoulder impingement. Neuritis, demyelinating disease and tumors should also be considered.

5.3.3 Electromyography

Electromyography (EMG) is a technique for evaluating the electrical activity of skeletal muscles, and thereby indirectly the function of the nerves controlling them. A small needle electrode is placed in a specific muscle and electrical activity is recorded and analyzed for abnormalities. EMG can be used both to confirm a diagnosis of CR and to differentiate
this condition from peripheral neuropathies such as carpal tunnel syndrome. While specificity is high, sensitivity ranges from 50-71% in various studies. Agreement between EMG and MRI findings has been reported to be 60%. 

5.3.4 Imaging

Magnetic Resonance Imaging (MRI) has become the standard investigation for cervical nerve root compression. This non-invasive procedure has rapidly become more accessible over the past 10–15 years in Sweden, as well as in many other parts of the world. Although computed tomography (CT) remains a good option for elucidating bony structures, MRI has the advantage of being able to visualize the soft tissue of intervertebral discs and nerve roots, as well as intramedullary edema and spinal tumors. The MRI predecessor, CT myelography, is now used only when MRI examination is not possible, such as in a patient with a pacemaker or cerebral shunt.

It is well known that protruding discs may be seen on MRI in up to 50% of asymptomatic individuals, depending on age\textsuperscript{13,17,29}; therefore findings must always be correlated with the clinical picture when making treatment decisions.

5.4 Natural history of cervical radiculopathy

Although the natural history of CR is generally considered to be favorable, little high-quality literature exists to confirm this opinion. Lees and Turner conducted the first study in 1963, in which 41 patients were followed for at least 10 years.\textsuperscript{30} Forty-six per cent had no further trouble, 29% had intermittent symptoms and 27% had moderate or severe symptoms. Likely the most cited study on this subject is the 1976 epidemiological survey carried out in Rochester, Minnesota by Radhakrishnan et al.\textsuperscript{2} At the 6-year follow-up 90.5% of the 561 patients with CR were “normal or only mildly incapacitated,” but 31.7% had experienced recurrent CR. It is important to note that 26% of the patients underwent surgery during the follow-up period, and since they are also included in the follow-up, the study does not just reflect the natural history of the disease. A short-term follow-up of 96 patients 28 days after non-structured physiotherapy found that 53% of patients could be regarded as having a “successful” course.\textsuperscript{31} A study of 205 patients with a history of CR of less than one month found that the intensity of neck and arm pain, as measured by VAS, decreased from 60-80 to 20-30 at 6 months, regardless of whether patients were randomized to physiotherapy,
cervical collar or a “wait and see policy”. Another study followed 205 patients with “neck pain” for 10 years and found that 43% were pain-free, 79% experienced a decrease in pain and 32% had moderate or severe residual pain. In a randomized study comparing plasma disc decompression (percutaneous disc coblation) with conservative treatment, the 53 patients in the conservative treatment group received various non-structured analgesic and manual therapy treatments. These patients experienced a 36 mm decrease in VAS (pain) and a 12 score percent reduction in NDI (disability) at the one-year follow-up, leaving a mean residual pain score of 39 and an NDI score of 55, which according to Vernon should be considered as “severe disability.”

5.5 Treatment

5.5.1 Nonsurgical treatment

The scientific evidence for different conservative treatment modalities for CR is generally scarce. Immobilization in a soft cervical collar has been shown to produce better results than no treatment after six weeks, but not after six months and the results were equal to physiotherapy or surgery after 15 months. Concerning patient education a 2009 Cochrane review concluded that no reliable evidence was available to support these methods.

5.5.1.1 Medical therapy

Analgesics are often used in the early phase. Commonly used drugs include non-steroidal anti-inflammatories (NSAIDs), paracetamol, and various opioids. Evidence to support use of these drugs is weak. In a randomized study, treatment of radiculopathy patients with pregabalin resulted in significantly greater reduction in pain, as well as symptoms of depression and anxiety, than treatment of a comparable group with various analgesics. One study showed that administration of high-dose oral prednisolone (50 mg/day) for five days followed by tapering resulted in better short-term pain relief than placebo. Randomized studies showed that treatment with transforaminal or epidural steroids was no better than local anesthetics alone, although other studies found that repeated injections of epidural steroids may be associated with a 24-100% decrease in the need for surgery among “potential surgical candidates.” However, the potential for serious complications from spinal injections must be taken into account.
5.5.1.2 Physiotherapy

Physiotherapy (PT) administered to patients suffering from radiculopathy may vary significantly. Many therapists seem to have a fear of worsening the condition with too aggressive exercise, which may lead to an overcautious program that doesn’t help the patient. Passive treatment modalities can be used during the early phase to reduce pain and decrease muscle tension, while active modalities are used to regain ROM, muscle strength and function. Passive modalities include heat, massage, ultrasound, acupuncture, mechanical traction and transcutaneous electrical nerve stimulation (TNS). Active modalities include general exercise, as well as ROM exercises, isometric and dynamic strength training. Evidence in support of any specific program is weak. Saal et al treated 26 CR patients with soft disc herniations using traction, targeted physiotherapy and patient education. While two patients underwent surgery during the course of the study, 20 achieved good or excellent outcomes at one year according to the Odom criteria. However, the study is biased by narrow inclusion and exclusion criteria. A systematic literature review in 2011 concluded that “potential benefits were indicated in the provision of manual therapy and exercise and behavioral change approaches to reduce pain.” General physiotherapy and traction were no more effective than “comparators” in reducing pain. Randomized studies on structured PT programs are lacking.

5.5.2 Surgical treatment

5.5.2.1 Background

The first attempt to treat CR surgically was undertaken by Horsley in the late 1800s. The anterior approach for decompression and fusion was developed by Cloward, Smith and Robinson in the 1950s. They used either autogenous bone transplants from the iliac crest or allogenous bone transplants to replace the disc and achieve fusion. Due to reports of frequent early and chronic complications from the iliac crest donor site, various artificial implants were tried to avoid autologous bone harvesting, and were proven to produce similar, or even better, results than autologous bone. The possible risk that fusion may induce more rapid degeneration of adjacent vertebral levels has also been discussed. In recent years, various motion-preserving devices have been tried in order avoid this risk. These devices have produced adequate clinical results, but have not been shown to be significantly superior to ACDF in reviews/meta-analyses. In a recent meta-analysis comparing fusion and disc replacement, no significant difference was found in reoperation rate due to adjacent-level disease, although long-term studies concerning adjacent-level pathology are still lacking.
5.5.2.2 Surgical technique and complications
When undergoing ACDF, the patient is under general anesthesia and placed in a supine position. The skin incision is usually transverse and the dissection is continued through the platysma. The trachea and esophagus are retracted medially and the internal jugular vein and carotid artery laterally. Damage to any of these structures is rare but potentially lethal. Care must be taken to preserve the recurrent laryngeal nerve that emerges from the vagus nerve at the level of the arcus aortae, where it divides into one branch on either side of the vertebral column. The incidence of symptomatic recurrent nerve palsy has been reported to be between 3.1% and 8.3%, with an additional asymptomatic vocal cord palsy in 15.9% of patients undergoing anterior cervical spine surgery. The longus colli muscles are elevated from the vertebrae and the correct level or levels verified by fluoroscopy. Under microscopic magnification, the disc, posterior osteophytes from the vertebrae and uncovertebral joints and, if necessary, the posterior longitudinal ligament are removed and the disc is replaced with a bone graft or metal cage. The benefit of using anterior plates is controversial. Typically, plate reinforcement yields better radiological outcomes, albeit with little or no clinical difference compared with cage or bone graft alone in single-level surgery. However, a few studies do show somewhat better outcome using plates when surgery involves two levels. The most common complication of ACDF is dysphagia and the reported incidence varies widely from 3-83% in different studies, although 10-15% seem to be most commonly reported. Worsening of preexisting radiculopathy or myelopathy has been reported in less than 1% of cases and the specific C5 palsy leading to deltoid muscle weakness in 2-4% following anterior surgery.

5.5.2.3 Surgical treatment outcome
Several studies report surgical treatment outcomes, but only one included a nonsurgically treated control group in which no differences were detected at the 15-month follow-up among any of the three groups treated with surgery, cervical collar or non-structured physiotherapy. This is the only CR study included in the latest Cochrane review, which states that there is little or no evidence supporting the benefits of surgery. Many of the studies describing outcome from surgery alone are retrospective; outcome measures and statistics vary considerably (see below), which often makes comparison difficult. For example, VAS for pain intensity can be evaluated based on “worst” possible neck, arm or head pain, or to describe the pain currently “present.” NDI is sometimes given as a number value, and sometimes as a percentage of achieved
“clinical success,” which is usually defined as an improvement of 15 to 20 score percent, although there is no general agreement on which of these values to use. Nevertheless, almost all papers report improvement in terms of change from baseline concerning both NDI and pain intensity where typical levels of improvement 2-6 years postoperatively are 0-30 score % for NDI and 23-53 mm on the VAS scale. Furthermore, 75-95% of the patients report a good/excellent outcome according to the Odom criteria or global assessment. The two studies with the longest follow-up periods were presented by Gore et al., a study in which 32 of 50 patients (64%) remained pain-free after 21 years, and by Noriega et al., whose study found that 82% of patients had good or excellent outcomes by the Odom criteria after 22 years. Unfortunately, the lack of nonsurgically treated control groups in these studies makes it impossible to differentiate improvement due to surgery from improvement due to other treatment and/or natural history of the condition.
6 AIMS

The overall aim of this thesis was to evaluate both the subjective and functional outcome of anterior cervical decompression and fusion (ACDF) for treatment of patients with cervical radiculopathy (CR).

Specific aims were:

- To study the 2-year outcomes for patients with CR randomized to either ACDF followed by structured physiotherapy, or to structured physiotherapy alone, with respect to disability (NDI), neck/arm pain and patient global assessment.

- To analyze the differences in baseline characteristics between patients included in the study and those who were eligible to participate, but declined.

- To evaluate 2-year functional outcomes between study groups, regarding active neck range of motion, neck muscle endurance and hand function.

- To analyze patient-related treatment effect modifiers that may impact outcome regarding NDI and neck/arm pain in the two study groups.

- To study the long-term effect (>5 years) of the treatments in the two study groups regarding health state (EQ-5D), NDI, neck/arm pain and patient global assessment.
7 PATIENTS AND METHODS

7.1 Patient population

All papers are based on the same randomized study, but with different aims and methods and slightly different patient populations. Inclusion and exclusion criteria are listed in table 1.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<td>Pain (with or without sensory and motor deficit) in one or both arms indicating nerve-root involvement, caused by disc herniation with or without osteophytes, or by stenosis due to osteophytes, and confirmed by MRI.</td>
<td>History of neck distortion (Whiplash Associated Disorder) or “generalized” muscle pain (i.e. fibromyalgia).</td>
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<td>Symptom duration of eight weeks to five years.</td>
<td>Slight, intermittent signs of myelopathy (“mild myelopathy”) without objective findings.</td>
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<td>One or two symptomatic disc levels.</td>
<td>Obvious myelopathy.</td>
</tr>
<tr>
<td>Of working age (18-65 years).</td>
<td>Indication for different type of surgery, i.e. vertebral body resection or foraminotomy.</td>
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<tr>
<td>Malignancy, inflammatory joint disease or psychiatric disorder.</td>
<td>Difficulty understanding Swedish.</td>
</tr>
<tr>
<td>Concomitant disease causing work disability.</td>
<td>Other spinal disease causing pain or neurologic deficit during the last year.</td>
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<tr>
<td>Previous cervical spine surgery.</td>
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Table 1. Inclusion and exclusion criteria.

A total of 68 patients consented to participate in the study and were randomized to ACDF followed by physiotherapy or the same physiotherapy program alone. First, the patient was examined and the baseline questionnaire was filled out. Randomization was then carried out by a secretary at one of the centers who consecutively opened previously
randomly distributed envelopes with equal numbers for each treatment group. All follow-ups were conducted by an observer who was not involved in the treatment of the patients. Immediately after randomization, five patients declined further participation. Four of these patients had been randomized to surgery and one to nonsurgical treatment. These patients had not yet participated in any kind of treatment in the study and were excluded at this early stage, leaving a total of 63 patients who were included in the study. The study design and number of patients who completed the subjective follow-ups at various times are summarized in figure 4.

7.2 Treatment

7.2.1 Physiotherapy treatment

The PT treatment program was developed by physiotherapists with extensive experience in research and treatment of radiculopathy patients. The aim was to improve neck and arm range of motion, muscle strength and endurance, as well as to educate patients on different ways of coping with pain.

Treatment was administered by physiotherapists who had undergone a 1-day education in delivering the program. The program was initiated six weeks after inclusion, in accordance with surgery in the surgical group. First, patients received guidance in sensory-motor control exercises, relaxation techniques and postural correction. Next, the medical exercise therapy (MET) program was initiated along with the coping program. The program comprised both exercises and a cognitive-behavioral approach and progressed individually for at least 14 weeks depending on the patient’s personal circumstances. A flow-chart of the program is shown in figure 5. Week 1 represents the start of the program six weeks after inclusion.

Patients participated in MET twice a week, where they focused on thoracic mobilization, neck stabilization and endurance, strengthening of the scapular muscles and stretching of neck and shoulder muscles. Patients who experienced dizziness were also instructed in vestibular rehabilitation.

Pain management education was conducted once a week, with the aim of enhancing adaptive and active coping strategies, as well as self-efficacy in activities. Patients learned about stress, exercise, ergonomics, pain physiology, breathing techniques and pain management techniques, as well as how to pace themselves (recognizing personal limits and using their resources wisely). Some of these sessions were conducted as group activities.
Following the initial program, patients were encouraged to continue the neck-specific exercises and to increase their general level of physical activity. Additional appointments with the physiotherapist were made individually.

Figure 4. Flow-chart of the study design. Figures in brackets represent the number of patients. Five patients dropped out before the start of treatment and were excluded. Four of these had been randomized to surgery. Eight patients in the nonsurgical group had surgery during the study, including 1 after the 6-month follow-up, 4 after the 12-month follow-up and 3 after the 24-month follow-up. Seven of the crossover patients were included in the 5-8 year follow-up of 59 patients.
Figure 5. Flow chart of the physiotherapy program. Week 1 represents the start of the program six weeks after inclusion.

<table>
<thead>
<tr>
<th>Week</th>
<th>Type of intervention</th>
<th>Goals of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>Relaxation training</td>
<td>Introduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proprioceptive skills</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain management</td>
</tr>
<tr>
<td>2-4</td>
<td>Education about pain physiology, coping, self-efficacy, breathing techniques and relaxation</td>
<td>Four appropriate MET exercises (at least one neck muscle specific exercise)</td>
</tr>
<tr>
<td></td>
<td>Pacing</td>
<td>Understand mechanisms and pain physiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased body awareness</td>
</tr>
<tr>
<td>5-6</td>
<td>Education about pain physiology, coping with stress and importance of self-efficacy</td>
<td>Initiate self management in coping with stress and increasing self-efficacy</td>
</tr>
<tr>
<td></td>
<td>Relaxation training</td>
<td>Improved coping with pain</td>
</tr>
<tr>
<td></td>
<td>MET</td>
<td>Appropriate MET program with at least four neck muscle specific exercises</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased body awareness</td>
</tr>
<tr>
<td>7-8</td>
<td>Education about pain physiology, coping with stress and self-efficacy</td>
<td>Progression of MET program</td>
</tr>
<tr>
<td></td>
<td>Relaxation training</td>
<td>Improved physical activity</td>
</tr>
<tr>
<td></td>
<td>MET</td>
<td>Progression of MET program</td>
</tr>
<tr>
<td>9-10</td>
<td>Lessons and implications in coping with stress and self-efficacy</td>
<td>Increased body awareness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased body awareness</td>
</tr>
<tr>
<td>11-14</td>
<td>Education, discussion and implications in ergonomy</td>
<td>Increased skills in coping with pain and stress and self-efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coping with pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased body awareness</td>
</tr>
<tr>
<td>15-20</td>
<td>Relaxation training</td>
<td>Progression of MET program</td>
</tr>
<tr>
<td></td>
<td>Increased/ altered physical activity</td>
<td>Maintained disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Managing activities in everyday life including work and relaxation time</td>
</tr>
<tr>
<td>21-52</td>
<td>Prescribed physical activity</td>
<td>Physical training/ activity on their own</td>
</tr>
</tbody>
</table>
7.2.2 Surgical treatment

ACDF was the surgical procedure used in this study. The study began in 2003 when disc replacement was not generally considered to be a reliable option. For single-level fusion, a cylindrical titanium implant (BAK/C®, Zimmer, Minneapolis, MN, USA) was chosen to avoid donor site complications from iliac crest bone harvesting. This device has been shown to provide results that are at least equal to classic fusion using iliac crest autografts, although it has been associated with kyphosis when used for two-level fusions. Therefore, two rectangular metal cages were used in two-level fusions, along with an anterior plate to achieve primary stability. No iliac crest grafts or other bone substitutes were used. Three months post-surgery, patients began participation in the same physiotherapy program provided to the nonsurgical group. The three-month time span prior to physiotherapy was chosen to allow the fusion to heal.

7.3 Outcome measures

7.3.1 Subjective outcome measures

7.3.1.1 Neck Disability Index

The Neck Disability Index was described by Vernon et al in 1991. The NDI was modified from the Oswestry Low Back Pain Index to make it suitable for cervical spine conditions. It consists of 10 questions about pain and the patient ability to perform various activities of daily living. Each question has 6 checkbox answers, which are graded from 0-5 points. The total sum of the points from the 10 questions is multiplied by 2, thereby creating a score from 0-100, usually referred to as score percent. If any single question is left unanswered (i.e., the patient does not drive a car), it is replaced with the mean value for the other questions. This decreases the risk of excluding NDI score values due to a single omitted answer in the questionnaire. Vernon divided the score into five categories, where 0-8 score % = no disability, 10-29 = mild, 30-49 = moderate, 50-69 = severe and over 70 = complete disability. The Swedish version of the NDI was validated in 2002. The cut-off value for recovery has been suggested to be 15 and the mean score in an average population is 7. The North American Spine Society recommended the NDI as a primary outcome measurement tool for CR in 2011.

7.3.1.2 Visual Analogue Scale (assessment of pain)

The Visual Analogue Scale (VAS) was introduced by Clark et al. in 1964. It was not initially used for pain, but has come into widespread
use as an instrument for pain assessment in the clinical setting, as well as for research purposes. We used a 100 mm horizontal scale graded from 0 (no pain) to 100 (worst pain imaginable). Arm pain and neck pain were recorded separately and the figures represent patient self-assessment of “present pain.”

7.3.1.3 Patient global assessment
To assess their overall opinion of their neck and arm problems following treatment patients were asked: “After the treatment, my neck/arm problems are: ‘much better, better, unchanged, worse, much worse’.” In the analyses, answers were dichotomized into two groups: much better/better or unchanged/worse/much worse.

7.3.1.4 Health state (EQ–5D and EQ VAS)
The EuroQol five dimension (EQ-5D) health outcome protocol was developed by the EuroQol group in 1990. It is a non-disease-specific instrument for measuring health-related quality of life, which allows different diseases to be compared. The questionnaire consists of five questions with three (EQ5D-3L) or five (EQ-5D-5L) different response options ranging from “no problems” to “extreme problems.” This study used the 3L version. The five evaluated dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The combination of various responses results in 243 possible health states, which are computed into a global health index. Adjustment for regional differences are made based on national or regional surveys. In the absence of a Swedish tariff, the British tariff was used in the present study. It has previously been used for large Swedish general health surveys. The scale ranges from -0.584 – 1, where 1 is defined as the “best possible health state.” Since 0 is defined as the “worst possible health state” or “diseased,” values below zero are considered to be “conditions worse than death.” Some authors therefore prefer to set the lower boundary of the scale to 0, while others do not. In any case, values below zero are extremely rare and the present study makes use of the full scale. The average Swedish 45-54 year-old citizen has an EQ-5D score of 0.83. The EuroQol instrument also includes the EQ-VAS, which is a thermometer-style scale for patients to rate their own global health state. It ranges from 0-100 where 0 is the “worst possible health state” and 100 is the “best possible health state”. The average rating for Swedish 45-54 year-olds is 84.
7.3.2 Functional outcome measures

7.3.2.1 Neck active range of motion (neck AROM)

Neck AROM was measured in a sitting position using a plastic “helmet”\(^\text{113-114}\) (Performance Attainment Associates, Roseville, MN). Flexion, extension, rotation and lateral flexion were recorded. The test is shown in figure 6.

![Figure 6. Test of neck AROM.](image)

7.3.2.2 Neck muscle endurance (NME)

Patients were placed in a supine position for ventral neck muscle tests and in a prone position for dorsal muscle tests. For the dorsal muscle test, a weight of 2 kg for men and 1 kg for women was applied using a strap. Patients were instructed to maintain their neck position for as long as possible, and to stop for exhaustion or radiating arm pain. Measurements were recorded in seconds, with a maximum value of 120.\(^\text{114}\) The tests are shown in figure 7.

![Figure 7. Tests of neck muscle endurance.](image)
### 7.3.2.3 Hand strength

Tests were performed using a Jamar hand dynamometer (Sammons Preston Inc. Bolingbrook IL) with the right hand first. The peak value of an 8 second squeeze was recorded in kilograms.\textsuperscript{115,116} The test is shown in figure 8.

![Test of hand strength](image)

*Figure 8. Test of hand strength.*

### 7.3.2.4 Manual dexterity

The Purdue Pegboard Test was used to assess fine manual dexterity. Patients were asked to move one peg at a time from a cup to a hole in the board as fast as possible for 30 seconds. The test was performed with one hand at a time and then with both hands together.\textsuperscript{117} Next, an assembly test was performed. Patients grasped pegs with their dominant hand, and washers with the other hand and were asked to put as many as possible together during a 60-second period, after which the number of completed assemblies was recorded. The test is shown in figure 9.

![Test of manual dexterity](image)

*Figure 9. Test of manual dexterity.*
7.3.2.5 Arm elevation during neck extension

A board with eight large nuts was placed on the wall with the middle of the board aligned with the top of the patient’s head. The task was to unscrew the nuts and place them in a box. Patients were permitted to alternate hands, but could only use one hand at a time. They were told to track the working hand with their gaze at all times. This task is difficult for many CR patients and not all were able to unscrew all nuts even though there was no time limit. Therefore, the total working time was recorded regardless of whether or not all nuts were unscrewed. In addition, the number of seconds per unscrewed nut was registered. This means that if two patients had the same number of seconds per nut but one worked for a longer period of time, he or she was able to unscrew more nuts, which accordingly represents a better result. The test is shown in figure 10.

Figure 10. Test of arm elevation during neck extension.

7.4 Patient populations and study methods

7.4.1 Study I

All 63 patients completed the study at the two-year follow-up; 31 had been randomized to surgery and 32 to nonsurgical treatment. Missing values for certain patients at the 6-month (8 patients) and 12-month (3 patients) follow-ups were due to the ± 10% selected time span for follow-up to be considered valid. This translates to ± 18 days for the 6-month and ± 36 days for the 12-month follow-ups, which increased the risk that patients failed to return the questionnaire in time at these follow-ups. During the first two years, five patients originally randomized to
nonsurgical treatment were operated at their own request, due to persistent or worsening pain. One had surgery between the 6-month and 12-month follow-ups and four after the 12-month follow-up. The data for these patients were kept in the nonsurgical group according to the “intention-to-treat” principle. No patients originally randomized to surgery had additional surgery during the study period.

Figure 2 summarizes the study design and number of patients who completed the subjective follow-ups at different times. The follow-ups were conducted at 6, 12 and 24 months after treatment start by an observer who was not involved in the treatment of patients. The main outcome was disability (NDI) and the secondary outcomes were pain intensity, patient global assessment and use of analgesics.

A group of 37 patients who were found eligible for the study, but declined participation was also compared with the participants regarding baseline data such as age, gender, smoking, pain levels and disability.

### 7.4.2 Study II

Study II included 49 of 63 patients who consented to participate in functional testing by a physiotherapist at 3, 6, 12 and 24 months. Most patients who declined testing cited time constraints and/or travel as reasons for declining participation. Among participants, 24 were randomized to surgery and 25 to nonsurgical treatment. Participants had significantly shorter duration of pain than nonparticipants. There were no other differences in baseline data between the 49 participants and the 14 nonparticipants, nor were there any differences at baseline between the two treatment groups.

The two treatment groups were compared on the four follow-up occasions. Outcomes were the objective function tests: neck active range of motion, neck muscle endurance, handgrip strength, manual dexterity and arm elevation during neck extension.

### 7.4.3 Study III

The 60 patients who completed the 12-month follow-up were included in the study. The 12-month follow-up was chosen, as far as possible, to avoid the effects of crossover from nonsurgical to surgical treatment. At the 12-month follow-up, only one patient originally randomized to physiotherapy alone had been operated, and the data were kept in the nonsurgical group according to the “intention-to-treat” principle.

Twenty-four potential modifiers of treatment outcome were identified, including baseline data such as sex, age, smoking, duration of pain and NDI. Since other factors might be able to influence outcome, different scales pertaining to individual patient-related factors were used, including
the Zung depression scale,\textsuperscript{119} the Self-Efficacy Scale (SES) for assessment of self-belief in coping with different activities and problems\textsuperscript{120} and the Distress and Risk Assessment Method (DRAM) to identify distress and risk of poor outcome.\textsuperscript{121} Patients also completed a “symptom index” questionnaire that included shoulder pain, back pain, headache, hand numbness, hand weakness, sleeping problems, and anxiety due to neck/arm pain, which could be answered by “never,” “occasionally,” “every day,” or “always.” The effects of these possible “treatment effect modifiers” on the differences in outcome between surgically and nonsurgically treated patients were evaluated in relation to the three outcome measures NDI, neck pain and arm pain.

7.4.4 Study IV
Fifty-five of 63 patients answered the questionnaire sent to them 5-8 years after inclusion in the study, while an additional four answered the questions by phone. Consequently, 59 patients could be analyzed in the 5-8 year follow-up. Four of the five patients who crossed over between treatment groups before the 2-year follow-up were included in this late follow-up. An additional three patients in the nonsurgical group had cervical spine surgery between two and 5-8 years. Thus a total of seven patients (24%) crossed over from the nonsurgical to the surgical group. In the analyses, the data for these patients remained in the nonsurgical group in accordance with the “intention-to-treat” principle.

The outcome measures in the 5-8 year follow-up were NDI, neck and arm pain intensity, patient global assessment and health state as assessed by the EQ-5D and EQ-VAS.

7.5 Statistics
All analyses were two-sided and the significance level was set at $p=0.05$.

7.5.1 Study I
Differences at baseline between participants and nonparticipants as well as between treatment groups were analyzed using the Pearson $\chi^2$ test on categorical data and the independent sample $t$-test on interval-level data. To compare within-treatment-group change with baseline, the paired samples $t$-test was used. The Bonferroni correction was used to control the familywise error rate of multiple pairwise comparisons. To address 63 cases of internal missing values (6.7\%) for VAS, NDI and patient global assessment (total for baseline and the three follow-ups), multiple imputation\textsuperscript{122} was used to fill the gaps and to allow for repeated
measurement ANOVA to analyze treatment-group differences in change over time. NDI and pain intensity were predicted using multiple linear regression models, while global assessment was predicted using multiple logistic regression models. NDI, neck pain intensity and patient global assessment were used as both predictors and outcome variables in the models, while treatment group was entered as a predictor. The purpose of this method is to reflect the assumed distribution of the missing values as closely as possible. The multiple imputation procedure was repeated 100 times and a pooled data set was used for all analyses.

Differences between treatment groups regarding NDI and pain intensity (VAS) for neck and arm pain separately were analyzed using repeated measures analysis of variance (ANOVA). The Bonferroni correction was used because of multiple pairwise comparisons.

To address treatment group differences in global assessment, risk ratios (RRs) with corresponding confidence intervals (CIs) were calculated and significance tested using z-statistics.

7.5.2 Study II

Differences between the treatment groups over time were analyzed using repeated measurement ANOVA. To address variables where differences occurred over time, the different follow-ups were further analyzed using the paired samples t-test with the Bonferroni correction.

7.5.3 Study III

To compare baseline data between participants and nonparticipants, the independent samples t-test was used on parametric data and the Fischer’s exact test or Pearson $\chi^2$ test on nonparametric data. For the main analysis between treatment groups, change in the three outcome measures NDI, neck pain, and arm pain between baseline and 12 months was calculated, and defined as treatment effect (TE). Differences in TE were assessed using either surgical or nonsurgical treatment as a fixed factor. Separate two-way, full-factorial ANOVAs on each outcome measure were analyzed, using treatment method plus one additional variable as fixed factors. The two-way interaction between treatment and the additional variable was defined and interpreted as a treatment effect modifier (TEM), provided that the interaction effect was significant. In addition, estimated marginal means were calculated on the interaction effect to analyze the treatment effect difference within each TEM group. Positive values favored surgery, while negative values favored nonsurgical treatment.
7.5.4 Study IV
Differences at baseline as well as differences in changes from baseline to 5-8 years between the two treatment groups were analyzed using the Pearson $\chi^2$ test on categorical data and the independent sample $t$-test on interval-level data. Differences within groups from baseline to 5-8 years, as well as between 2 and 5 years were analyzed using the paired samples $t$-test. Risk ratios (RR) with corresponding 95% confidence intervals (CI) were calculated for treatment group differences in the patients’ global assessment and significance tested using z-statistics.

7.6 Ethical considerations
All patients had a good understanding of the Swedish language, received written and oral information about the study, and were informed that there was no reliable evidence in favor of either treatment option. All patients provided written informed consent prior to inclusion in the study. Patients understood that they had the right to withdraw from the study at any time without specifying any reason, and without any effect on their future treatment. All studies were performed in accordance with the principles of the Helsinki declaration. The study was approved by the Regional Ethical Review Board at the Faculty of Health Sciences in Gothenburg, and the experiments complied with current Swedish law (Dnr S 222-02).
## 8 RESULTS

### 8.1 Study I

**Baseline data**

Table 3 presents baseline data for the 63 participants as well as for 37 patients who were eligible for the study but declined participation. The nonparticipants had significantly higher pain intensity levels for both neck and arm pain, and a shorter duration of symptoms.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Surgical group (SG) n=31</th>
<th>Nonsurgical group (NSG) n=32</th>
<th>Non-participants (NP) n=37</th>
<th>SG vs NSG p-value †</th>
<th>SG+NSG vs NP p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49 (8)</td>
<td>44 (9)</td>
<td>44 (8)</td>
<td>&lt;0.05</td>
<td>N.S.</td>
</tr>
<tr>
<td>Duration of neck symptoms, months</td>
<td>15 (12)</td>
<td>21 (19)</td>
<td>11 (9)</td>
<td>N.S.</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of arm symptoms, months</td>
<td>13 (10)</td>
<td>17 (16)</td>
<td>11 (9)</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Duration of sick leave, months</td>
<td>8 (6)</td>
<td>10 (11)</td>
<td>7 (5)</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>NDI before treatment, score %</td>
<td>37 (14)</td>
<td>40 (14)</td>
<td>43 (15)</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Neck pain before treatment, VAS 0-100</td>
<td>50 (25)</td>
<td>47 (23)</td>
<td>63 (25)</td>
<td>N.S.</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arm pain before treatment, VAS 0-100</td>
<td>43 (26)</td>
<td>46 (22)</td>
<td>61 (19)</td>
<td>N.S.</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

| Male, %               | 45                       | 59                         | 51                          | N.S.                | N.S.                 |
| Smoker, %             | 32                       | 25                         | 27                          | N.S.                | N.S.                 |
| Living alone, %       | 25                       | 16                         | 14                          | N.S.                | N.S.                 |
| Employed, %           | 89                       | 81                         | 92                          | N.S.                | N.S.                 |
| Sick leave (full- or part-time), % | 82                       | 70                         | 50                          | N.S.                | <0.05                |
| Change of work due to neck problems, % | 13                       | 12                         | 32                          | N.S.                | <0.05                |

*p-value ‡ | p-value ‡

Table 3. Baseline data. Values presented as means (SD) unless otherwise noted. P-values represent differences between groups. † Significance was calculated with the t-test. ‡ Significance was calculated with the chi-square test.
**NDI and pain intensity**

No difference was detected between treatment groups in outcome of the ANOVA analysis over the entire study period regarding NDI (p=0.23) or arm pain (p=0.58). Regarding neck pain, there was a difference in favor of surgery throughout the entire study period (p=0.04). The difference was greatest at 6 and 12 months and then decreased. These data are presented in table 4.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDI, Score % 0-100</td>
<td>39 (13)</td>
<td>27 (18)</td>
<td>25 (18)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
<td>56 (26)</td>
<td>18 (24)</td>
<td>19 (22)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
<td>49 (28)</td>
<td>25 (29)</td>
<td>21 (25)</td>
<td>28 (30)</td>
</tr>
<tr>
<td><strong>Nonsurgical group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDI, Score % 0-100</td>
<td>44 (11)</td>
<td>34 (17)</td>
<td>36 (18)</td>
<td>32 (20)</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
<td>52 (23)</td>
<td>31 (25)</td>
<td>36 (27)</td>
<td>32 (29)</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
<td>50 (22)</td>
<td>32 (26)</td>
<td>30 (26)</td>
<td>30 (26)</td>
</tr>
</tbody>
</table>

**Comparison of difference between treatment groups (p-value, ANOVA)**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Surgical group</th>
<th>Nonsurgical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDI, Score % 0-100</td>
<td>0.23</td>
<td>N.S.</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
<td>0.04</td>
<td>N.S.</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
<td>0.6</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Comparison of difference between treatment groups (p-value, t-test)**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Surgical group</th>
<th>Nonsurgical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDI, Score % 0-100</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Table 4.** Neck disability index and pain intensity from baseline to 24 months. Table displays mean values (SD). P values for ANOVA represent change throughout the entire study period and p-values for the t-test represent change between baseline and the specific follow-ups.
Patient global assessment and use of analgesics

In the surgical group, 81-87% of patients rated their symptoms as “better” or “much better” at the various follow-up times, compared with 62-69% in the nonsurgical group. The difference between treatment groups was significant only at the 12-month follow-up. These data are presented in table 5. No difference in use of analgesics was detected between treatment groups.

Patient global assessment at 6-24 months

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Surgical group</th>
<th>Nonsurgical group</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worse</td>
<td>Better</td>
<td>Risk</td>
</tr>
<tr>
<td>6 mo</td>
<td>5</td>
<td>26</td>
<td>0.84</td>
</tr>
<tr>
<td>12 mo</td>
<td>4</td>
<td>27</td>
<td>0.87</td>
</tr>
<tr>
<td>24 mo</td>
<td>6</td>
<td>25</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Table 5. Patient global assessment of treatment effect after 6-24 months. Figures display number of patients and risk within each treatment group at follow-up. Between-group difference was calculated with risk ratio (95% CI) and significance tested using z-statistics.

Worse = unchanged/worse/much worse, Better = better/much better

Within group comparisons

Significant improvement compared with baseline was found in NDI, pain intensity and patient global assessment within both groups and at all follow-ups.

8.2 Study II

When comparing the two treatment groups, there were no significant differences regarding any of the five outcome measures neck AROM, NME, hand strength, manual dexterity or arm elevation at baseline or in the ANOVA analysis for the 2-year study-period. Improvement in the whole patient population was seen for NME, manual dexterity and arm elevation, and all improvement occurred before the 6-month follow-up. Regarding neck AROM and hand strength, no significant improvement was observed. An alternative analysis of the affected side (instead of right and left side) was made for manual dexterity and handgrip strength and showed no significant differences between the treatment groups. The significance data are presented in table 6.
### Functional outcome at 24 months

<table>
<thead>
<tr>
<th>Measurement</th>
<th>p between groups</th>
<th>p over time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neck AROM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion</td>
<td>0.31</td>
<td>0.52</td>
</tr>
<tr>
<td>Extension</td>
<td>0.19</td>
<td>0.96</td>
</tr>
<tr>
<td>Lateral flexion right</td>
<td>0.44</td>
<td>0.56</td>
</tr>
<tr>
<td>Lateral flexion left</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Rotation right</td>
<td>0.72</td>
<td>0.70</td>
</tr>
<tr>
<td>Rotation left</td>
<td>0.91</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Neck Muscle Endurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral</td>
<td>0.62</td>
<td>0.01*</td>
</tr>
<tr>
<td>Dorsal</td>
<td>0.86</td>
<td>0.006*</td>
</tr>
<tr>
<td><strong>Hand Strength</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0.83</td>
<td>0.01*</td>
</tr>
<tr>
<td>Left</td>
<td>0.71</td>
<td>0.20</td>
</tr>
<tr>
<td>Affected side</td>
<td>0.91</td>
<td>0.0001*</td>
</tr>
<tr>
<td><strong>Manual Dexterity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0.59</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Left</td>
<td>0.92</td>
<td>0.03*</td>
</tr>
<tr>
<td>Both</td>
<td>0.63</td>
<td>0.01*</td>
</tr>
<tr>
<td>Affected side</td>
<td>0.70</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Assemblies</td>
<td>0.77</td>
<td>0.0001*</td>
</tr>
<tr>
<td><strong>Arm Elevation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seconds</td>
<td>0.28</td>
<td>0.74</td>
</tr>
<tr>
<td>Seconds per nut</td>
<td>0.32</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

*Table 6. Functional outcome measures at 24 months. Figures under “p between groups” show the comparison between surgical and nonsurgical treatment. Figures under “p over time” show the difference for all patients between baseline and all follow-ups until 24 months. Significance was calculated with repeated measurements ANOVA. * = significant difference detected (p<0.05)*
8.3 Study III

Factors that significantly altered the treatment effect (TE) between treatment groups in favor of surgery (p<0.05) for one or more of the outcome measures were: duration of neck pain < 12 months, duration of arm pain < 12 months, female sex, low EQ-5D index, high levels of anxiety due to neck/arm pain, low SES score and high DRAM score. Other trends that favored surgery (p<0.1) included: frequent headaches, frequent hand numbness, frequent shoulder pain and duration of neck pain < 12 months. Factors that did not affect outcome included age, smoking, type of disc herniation, preoperative pain levels and depression according to the Zung scale. These data are presented in table 7. No factors were found that were associated with better outcome from physiotherapy alone.
## Difference between treatment group outcomes for treatment effect modifiers

<table>
<thead>
<tr>
<th>Treatment effect modifier (at baseline)</th>
<th>p-value for difference in treatment effect between treatments groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outcome: NDI</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (under 48)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of neck pain &lt; 12 months</td>
<td>0.1</td>
</tr>
<tr>
<td>Duration of arm pain &lt; 12 months</td>
<td>0.4</td>
</tr>
<tr>
<td>Neck pain intensity &gt; 50</td>
<td>0.9</td>
</tr>
<tr>
<td>Arm pain intensity &gt; 50</td>
<td>0.7</td>
</tr>
<tr>
<td>Frequent shoulder pain</td>
<td>0.4</td>
</tr>
<tr>
<td>Frequent back pain</td>
<td>0.6</td>
</tr>
<tr>
<td>Frequent headache</td>
<td>1.0</td>
</tr>
<tr>
<td>Frequent hand numbness</td>
<td>1.0</td>
</tr>
<tr>
<td>Frequent hand weakness</td>
<td>1.0</td>
</tr>
<tr>
<td>Frequent sleeping problems</td>
<td>0.2</td>
</tr>
<tr>
<td>Frequent anxiety due to neck/arm problems</td>
<td>0.02*</td>
</tr>
<tr>
<td>Soft disc herniation only</td>
<td>0.4</td>
</tr>
<tr>
<td>High expectations of returning to work</td>
<td>0.9</td>
</tr>
<tr>
<td>High expectations of good treatment effect</td>
<td>0.3</td>
</tr>
<tr>
<td>NDI &gt; 40 at baseline</td>
<td>0.3</td>
</tr>
<tr>
<td>Zung score &quot;at risk&quot;</td>
<td>0.3</td>
</tr>
<tr>
<td>EQ-5D score &lt;0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>EQ-VAS &lt; 50</td>
<td>0.8</td>
</tr>
<tr>
<td>Arm pain &gt; neck pain</td>
<td>0.3</td>
</tr>
<tr>
<td>SES &lt; 128</td>
<td>0.05*</td>
</tr>
<tr>
<td>DRAM &quot;at risk&quot; or &quot;distress&quot;</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

**Table 7. Significance of difference between treatment group outcomes associated with treatment effect modifiers in relation to the three outcome measures. Difference in TE between TEM groups was analyzed with two-way full-factorial ANOVA.**

* = Significant difference between groups (p<0.05) detected
8.4 Study IV

NDI, pain intensity and health state

A difference between the two treatment groups in favor of surgical treatment was found for NDI (p=0.03) and neck pain (p=0.01), but not for arm pain (p=0.1) or health state assessed with EQ-5D (p=0.1) and EQ-VAS (p=0.6). These data are presented in table 8.

<table>
<thead>
<tr>
<th>Outcome and group comparison at 5-8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Surgical group</strong></td>
</tr>
<tr>
<td>NDI, Score % 0-100</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
</tr>
<tr>
<td>EQ-5D score (-0.584-1)</td>
</tr>
<tr>
<td>EQ-VAS (0-100)</td>
</tr>
<tr>
<td><strong>Nonsurgical group</strong></td>
</tr>
<tr>
<td>NDI, Score % 0-100</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
</tr>
<tr>
<td>EQ-5D score (-0.584-1)</td>
</tr>
<tr>
<td>EQ-VAS (0-100)</td>
</tr>
<tr>
<td><strong>Comparison of difference between treatment groups (p-value)</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Mean difference</td>
</tr>
<tr>
<td>NDI, Score % 0-100</td>
</tr>
<tr>
<td>Neck pain VAS 0-100</td>
</tr>
<tr>
<td>Arm pain VAS 0-100</td>
</tr>
<tr>
<td>EQ-5D score (-0.584-1)</td>
</tr>
<tr>
<td>EQ-VAS (0-100)</td>
</tr>
</tbody>
</table>

Table 8. Neck disability index, pain intensity, EQ-5D and EQ-VAS at baseline and 5-8 years shown as mean values (SD). Significance was calculated using the independent samples t-test.
Patient global assessment

In the surgical group, 93% of patients rated their symptoms as “better” or “much better” at the 5-8 year follow-ups, compared with 62% in the nonsurgical group. The difference between treatment groups was significant (p=0.005). There was also a difference in the distribution of answers within the group of patients who responded “better” or “much better,” in which a significantly larger number of patients rated themselves as “much better” in the surgical group than in the nonsurgical group (p=0.02). These data are presented in table 9.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Surgical group</th>
<th>Nonsurgical group</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worse</td>
<td>Better</td>
<td>Risk</td>
</tr>
<tr>
<td>5-8 years</td>
<td>2</td>
<td>28</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Table 9. Patient global assessment of treatment effect at 5-8 years. Figures show number of patients and risk within each treatment group at follow-up. Between-group-difference was calculated using risk ratio (95% CI) and significance tested using z-statistics. Worse = unchanged/worse/much worse, Better = better/much better

Comparison between 2 and 5-8 years

When outcome differences between 2 and 5-8 years were compared, there was still significant improvement in the surgical group regarding NDI, arm pain and EQ-VAS, but not regarding neck pain and EQ-5D. In the nonsurgical group, no significant change was detected between these two follow-ups. However, a comparison between the two treatment groups over this time span found no significant differences.

Within-group comparisons

Significant improvement compared with baseline was seen for all outcome measures in both groups at the 5-8 year follow-up.
9 DISCUSSION

9.1 Performance of the study
Planning for this study began in 2002. Scientific evidence based on randomized studies supporting the benefits of ACDF for cervical radiculopathy was limited to one small study, which excluded pure soft disc herniations and showed no difference in outcome between treatment groups, i.e. no supportive evidence. A few similar approaches had been tried on lumbar spine problems. Limitations to these studies, such as inconsistent randomization and a non-structured nonsurgical treatment option, were identified and rectified in the present study. The study was designed to avoid the placebo effects of treatment as far as possible by including a comprehensive physiotherapy program for both groups, while one group also received surgical treatment. All follow-ups were conducted by an observer who was not involved in the treatment of the patients. However, we refrained from trying to blind the observer from knowing which treatment the patients had received. This decision was based on an assumed strong risk that patients would reveal their treatment group at follow-up, even if the area for the skin incision were to be covered, which would have resulted in “pseudo blinding.” Enrollment of patients began in 2003 and because of the difficulty in enrolling patients who accepted randomization to either surgical or nonsurgical treatment, enrollment continued until 2009. The limited number of patients, 63, could be considered a drawback and is also the main limitation of the study. Nevertheless, this study still represents the largest material of its kind published to date. In fact, no similar studies have been published over the 13 years that have transpired since planning began.

In addition to the outcomes presented in this thesis, plans had been made to assess the social security cost-benefit and how these treatments affected the ability of patients to return to work. However, these aims had to be abandoned due to a major restructuring of the Swedish social security system following the 2006 national elections.

9.2 Participants versus nonparticipants
Selection bias must always be considered a risk in a study with randomization that is as demanding for patients as surgical versus nonsurgical treatment. Consequently, assessed nonparticipants had significantly more intense arm and neck pain than participants. However, duration of neck pain was shorter and they used less sick leave. The exact effect on treatment results stemming from the selection of a group with
lower pain intensity and longer pain duration cannot be precisely evaluated. However, since patients with a shorter duration of pain fared better with surgical treatment in study III and because previous reports that high preoperative pain levels lead to better surgical results, the effect of this patient selection would probably be consistent with smaller differences between treatment groups in regard to the studies in this thesis.

9.3 Improvement due to treatment versus natural history

The studies in this thesis mainly focus on the difference in treatment effects between the surgical and nonsurgical treatment groups, with surgery as the only difference in treatment between the groups. From a scientific standpoint, the ideal situation would have included an untreated control group in addition to the two treatment groups in this study, which would have allowed us to assess for improvement over the natural course of disease. However, such an option would be impossible on ethical grounds.

Many papers on cervical radiculopathy point to a favorable natural history. However, the literature on the subject is far from comprehensive, and many papers referring to “natural history” actually include interventions of various kinds, making it difficult to differentiate treatment effects from the natural course of disease. Regarding the outcome measures and follow-ups in the present study where surgical patients fared better than nonsurgical patients, it is reasonable to conclude that at least the additional improvement in operated patients supersedes improvement due to natural history. Considering that even the patients in the nonsurgical group had already improved in all subjective outcomes by the 3-month follow-up, despite a mean symptom duration of 15 to 18 months, it is plausible that all patients in the study experienced improvement above and beyond that expected from the natural history of the disease. The persistent improvement at 5-8 years makes it less likely that the placebo effect was a factor in either group.

9.4 Subjective outcomes

At the last follow-up 5-8 years after treatment start, surgical patients experienced a better outcome regarding NDI, neck pain and patient global assessment than patients treated with physiotherapy alone, though no differences in arm pain or health outcome were seen. In the early phase of the study, differences were greater at 6 months and at 1 year than after 2 years, which was especially apparent regarding arm pain, for which the surgically treated patients deteriorated markedly between the 12 and 24-
month follow-ups, only to improve again by the last follow-up. The reason for this is unknown and early speculation focused on adjacent-level disease, but given the improvement between 2 and 5-8 years, this seems unlikely. Since the study material is limited, the effects of substantial deterioration among a relatively small group of patients could also affect the outcome. The difference in NDI between the treatment groups ranged from 3 to 10 at the various follow-ups. Even when significant, the clinical importance of these values could be subject to debate. Recent studies have calculated that the smallest difference that patients detect as an improvement (minimal important change (MIC)) is a change of 5 to 9 units, but earlier reports have cited an MIC of more than 30 score %.

The difference in treatment effect on neck pain between treatment groups was generally larger than that on arm pain due to the somewhat surprisingly limited improvement in the latter among surgically treated patients at 24 months and the rather low baseline values for arm pain. Some earlier reports state that surgery alone has a greater effect on neck pain than on arm pain, but the majority report a greater effect on arm pain than on neck pain within a cohort of operated patients. However, according to our studies, which compare surgery and PT with PT alone, relief of neck pain should be considered to be at least as important to a surgical decision as relief of arm pain. Despite the lack of significant differences in either health outcome or arm pain and considering the rather small differences in NDI, the surgically treated patients reported superior results at the 1 and 5-8 year follow-ups, and at the last follow-up, there was also a significant difference in favor of surgery regarding the distribution of answers between “much better” and “better.” This could be interpreted either as an aggregate effect of various small improvements, or mainly as an effect of the difference in neck pain. A strong correlation between pain relief and patient satisfaction has previously been reported among patients suffering from CR.

9.5 Functional outcomes

There were no significant differences between the treatment groups regarding any of the five evaluated functional outcomes at any of the follow-ups. Improvement compared with baseline was seen for NME and manual dexterity, although improvements in manual dexterity were very small. Considering the comprehensive nature of the PT program, which was maintained for at least three months, and that patients experienced improvement in pain during the first six months, it must be concluded that the potential to improve neck-related functional outcome through exercise and/or surgery in patients with CR seems limited. On the other hand,
patients in both groups improved regarding disability, for which some of the tested skills seem likely to be important. Because the patient population in study II is smaller than in the other studies, the higher risk of type II errors has to be considered. However, since the changes in the assessed outcomes are so small, missing a significant difference between groups would likely be of little or no clinical consequence. Therefore, based on the results of the present study, improvement in functional outcome should not be a consideration in the decision-making process between surgical and nonsurgical treatment for patients with CR, nor should it be the sole objective of physiotherapy.

### 9.6 Predicting treatment outcome

Factors associated with a better outcome from surgery were female sex, high DRAM score, low health and self-efficacy scores, duration of pain of less than 12 months and high levels of anxiety due to neck/arm pain. These results do not point to a clear pattern. Superior surgical outcome for patients with shorter pain duration has previously been reported in various nonrandomized studies, and is probably the least controversial finding.\(^{133-135}\) Patients with low health and SES scores may have achieved better outcomes because these individuals generally have more pain, which has previously been associated with better surgical outcome.\(^{61}\) Better outcomes for surgical treatment than for nonsurgical treatment in female patients contrasts with earlier reports of no gender differences or better outcomes for men.\(^{61,134,136}\) Regarding DRAM, our results also contrast with earlier reports of no predictive effects or better surgical outcomes with lower DRAM scores.\(^{121,137,138}\) The important difference between these papers and the present study is the lack of a nonsurgically treated control group in the earlier studies. It is important to remember that a better outcome from surgery compared with nonsurgical treatment does not necessarily mean a better outcome for these patients within the surgically treated cohort, but when choosing between surgical and nonsurgical treatment, these factors must still be considered. The present study indicates that female sex, high levels of distress or anxiety or poor health status should not discourage a surgical option if otherwise indicated.

### 9.7 Limitations

The main limitation of the study is clearly the small size. Since the spread and MIC for the outcome measures in this patients group were not very well-established, power analyses when planning the study had to be based on assumptions and were therefore only estimates. Based on assumed standard deviations of just above 20, 90% power for detecting a difference
of 10 steps on a VAS or NDI scale would have required 90-100 patients in each group and 80% would have required 70. Since we were unable to reach such figures despite six years of inclusion, a calculation of observed power was made in paper I. The number of patients enrolled would have required a difference of 15-20 steps on the scales to reach a power of 80% in that study. The observed differences are of course still valid, but the risk of type II errors must be acknowledged, especially since almost all outcomes at all follow-ups favored surgical treatment, even when nonsignificant. However, many of those nonsignificant trends would be unlikely to reflect clinical significance since the differences were very small.

A second limitation is that the patients enrolled in the study were different from those who chose not to participate. Nonparticipants had significantly higher pain levels and shorter duration of pain than study participants, which makes generalization of the results to a population with these characteristics less certain.

9.8 Summary and clinical recommendations

The studies in this thesis represent the first scientific evidence, based on a randomized study design between surgical or nonsurgical treatment, to support use of ACDF for the treatment of cervical radiculopathy. Based on the results of the studies, it is reasonable to recommend a trial of structured physiotherapy in the early phase of CR, before making any surgical decision. However, for patients who have substantial residual symptoms, ACDF provides a good alternative for greater and more rapid improvement, which can also be expected to last for at least 5-8 years. The studies also indicate that, compared with structured physiotherapy, the potential for surgery to relieve neck pain is greater than to relieve arm pain, which should be considered when informing the patients of the expected treatment results, as should the limited effects on functional outcome. Patients should not be disqualified from surgical treatment due to gender, poor health status or a high level of distress and/or anxiety. Optimal timing for surgery remains to be determined, but a better treatment outcome can be expected when any necessary surgery is performed within one year of onset of CR symptoms.
10 CONCLUSIONS

In a 5-8 year time span, anterior cervical decompression and fusion followed by physiotherapy was more effective than physiotherapy alone in reducing disability and neck pain. ACDF also resulted in a superior self-rating by patients regarding treatment outcome.

ACDF also produced faster relief of neck pain and a better patient-reported global outcome in the first postoperative year, but at the 2-year follow-up, those differences were less, resulting in a difference in neck pain relief only for the first two-year period as a whole.

Regarding health outcome, relief of arm pain and functional outcome, there were no significant differences between surgical and nonsurgical treatment.

Structured physiotherapy alone resulted in significant improvement among a majority of patients after 3-6 months regarding pain, disability and patient global assessment, even in patients with longstanding symptoms, but how the natural history of disease affected this outcome is unknown.

To improve surgical outcome, ACDF should be performed within one year of onset of cervical radiculopathy symptoms.

Patients should not be disqualified from surgical treatment for cervical treatment due to gender, poor health status, or a high level of distress and/or anxiety.
11  FUTURE

Bearing in mind that the main limitation of this study is the relatively small study population, it would be reasonable to propose that larger studies of the same kind be conducted. However, given the difficulties we encountered when enrolling patients for such a challenging randomization process, the hope for that to happen has to be set low. Other researchers in the lumbar spine field have experienced massive problems with crossover and dropouts, which may be a somewhat inevitable consequence of large-scale multicenter studies on this subject. True noninterventional studies of the natural history of CR would also be valuable, but are impossible to conduct from an ethical point of view since we cannot deny treatment to patients suffering from pain.

In light of the situation at large, the following subjects for further research should be considered:

- Prospective studies on patient-related factors affecting outcome within a cohort of patients undergoing surgery are easier to perform and could add valuable information that can be used when selecting patients for surgical treatment, or making a prognosis of the outcome.

- Well-designed, randomized studies on the effects of physiotherapy are needed to evaluate the specific value of different treatment modalities for patients suffering from CR and could serve as a basis for recommending a more uniform structured PT program for this group of patients.

- Studies on the possible added benefits of physiotherapy among patients undergoing surgery could optimize postoperative rehabilitation for this group of patients.
12 ACKNOWLEDGEMENTS

It is impossible to produce a PhD thesis without a great deal of help and support from supervisors, co-authors, colleagues, friends and family. Therefore, it is my pleasure to express my sincere gratitude to all those who have contributed:

**Bengt Lind**, associate professor, MD, PhD, main supervisor, for all your support and encouragement and for sharing your vast knowledge in the field.

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Isak Engquist, my brother, for – as with everything else regarding academic accomplishments – being 19 years ahead of me with your thesis. But now, who’s the real doctor?

and finally my family, Maria and Ida, for encouragement, support and for being the meaning of my life. Ida, you are probably the first child who knew the word “nackdiskbråck” at the age of five.
13 REFERENCES


Errata

Study I, page 7, discussion:

In this study, to achieve a power of 80%, a 10% difference in NDI was necessary regarding pain intensity, and the difference had to be 15 to 20 mm to reach a power of 80%.

In this study, to achieve a power of 80%, a 10 score % difference in NDI was necessary, and regarding pain intensity, the difference had to be 15 to 20 mm to reach a power of 80%.