Outcome after anterior cervical discectomy: from inferential statistics to Machine Learning

Goedmakers, C.M.W.

Chapter 1

Introduction and general outline

Introduction and general outline

With a prevalence of approximately 30%, neck pain is the fourth most common cause of physical disability worldwide. In 50% of patients acute neck pain develops into chronic neck pain [1]. The most common causes of chronic neck pain are the progressive degenerative changes that affect all components of the cervical spine [2].

These degenerative changes gradually induce a decline in the functioning of (parts of) the spine and loss of normal structure of the vertebrae, intervertebral discs and surrounding tissue [3]. Sagittal misalignment, radiculopathy and myelopathy among others, can all be correlated with cervical degeneration [4-6]. The most common degenerative change in the cervical spine, leading to neurological symptoms, is the herniated disc, which can cause a cervical radiculopathy.

Anterior cervical discectomy and fusion (ACDF) is the standard surgical treatment for cervical radiculopathy. First described in the 1950s, this procedure enables direct exposure to the disc and subsequently to the disc herniation and results in less soft tissue damage than the posterior approach [4-6]. During the procedure a discectomy is performed to decompress the neural structures, followed by insertion of a cage in the intervertebral disc space to maintain foraminal height and cervical alignment. Subsequently, the spinal segments will fuse by natural bone ingrowth, creating a stable construct.

ACDF is widely considered, by spine surgeons, a procedure with high clinical success rates. In the studies that initially reported on the technique, success rates as high as 80-90% were reported, based on the alleviation of arm pain [7-10]. Though the efficacy of the procedure for the alleviation of arm pain remains unchallenged, current studies show around 25% of patients report low satisfaction at follow-up [11-13]. The discrepancy between the high clinical success rates and the lower patient-perceived recovery scores can be partially attributed to the greater significance patients assign to the reduction of neck disability in their perceived recovery, as opposed to the mere alleviation of arm pain [14, 15]. This highlights the necessity of integrating neck disability assessments into the evaluation of patient-perceived recovery. Nevertheless, no study yet has been able to identify why these patients demonstrate a lower perceived recovery than the other 75% of patients undergoing anterior cervical spine surgery. In order to preoperatively predict perceived recovery after surgery, the underlying factors driving the difference need first to be identified.

Different underlying pathologies have been hypothesized to play a role in the postoperative functional ability of patients undergoing anterior cervical spine surgery. One hypothesis is that differences in implanted hardware may cause differences in functional outcome. Theoretically, fusion increases the stress-load on the levels adjacent to the index disc, which can cause pain and decrease in functionality on the short term and recurrent nerve compression on the long-term (adjacent segment disease; ASD). The cervical disc prosthesis was introduced to keep the index level mobile and to avoid ASD. A randomized controlled trial from our institution previously investigated whether implanting a cervical disc prosthesis (anterior cervical discectomy and arthroplasty, ACDA) would provide superior clinical outcome after anterior discectomy [16]. During an anterior discectomy the cervical spinal root is decompressed in order to relieve radicular symptoms in the arm. The short-term purpose of a prosthesis, additional to the purpose of maintaining height, is to mimic the non-degenerated mechanical properties of the cervical spine segment and therefore decrease neck disability postoperatively. ACDA was hypothesized to provide lower Neck Disability Index (NDI) scores postoperatively, as compared to anterior cervical discectomy with (ACDF) and without a cage (ACD). However, one and two years after surgery the prosthesis did not reach the predefined criterium for clinical superiority of a 20-point lower NDI score (on a 100 point scale) [16]. Although implanting a prosthesis did not provide superior clinical outcome in the short term, long-term data could provide different results. Adjacent segment disease is defined as new radiculopathy symptoms, corresponding to degenerative radiographic changes on the level adjacent to the index surgery. What makes ASD clinically relevant is the need for reoperation [17]. However, ASD has long been a radiographic diagnosis, and was typically reported to occur after longer follow-up [18]. Therefore it seems relevant to study long-term results in patients undergoing anterior discectomy to treat cervical radiculopathy.

Another hypothesis is that mental health influences patient-perceived recovery scores in patients undergoing ACDF. In patients suffering from pain and chronic disease, depression and anxiety are common psychological conditions. The estimated mean prevalence of major depression in patients suffering from pain due to orthopedic and rheumatologic disease is 56% [19]. Additionally, in patients being treated for pain, clinical outcome is known to be influenced by depressive symptoms; reporting an increase in pain episodes, more intense pain, more amplification of pain symptoms, and longer duration of pain [20-23]. Moreover, patients that report both anxiety and depressive symptoms have a lower self-perceived recovery rate and are more likely to report persistent pain [23-26]. In a systematic review on the relation between psychological disorders and spine surgery, it was concluded that patients subjected to spine surgery suffer from higher rates of spinal pain, postoperative complications and worsened functional outcomes [27]. Specifically, in patients with lumbar radiculopathy it was demonstrated that better mental health at baseline was significantly associated with lower disability after surgery [28]. In the cervical spine however, the relation between mental health and functional outcome after surgery is less well investigated. One study showed statistically significant improvement in postoperative neck pain after one year in patients who received concomitant treatment for their anxiety compared those who had not [29]. However, longer follow-up on these patients demonstrated that this significant difference did not persist 24 months after surgery [30]. Another study that described the impact of depression on outcome after posterior cervical fusion demonstrated that depressed patients reported less improvement in postoperative quality of life [31], which could, however, not be confirmed in a later study [32]. The true dimension of the effect of mental health on functional outcome after cervical spine surgery thus remains to be unknown. Ultimately, not just the effect size of mental health on functional outcome is of interest, but it is particularly interesting to discover how the association can be used to effectively counsel patients preoperatively.

Finally, in line with the hypothesized role of ASD, the preoperative degree of degeneration of the cervical spine is hypothesized to influence postoperative functional outcome in patients undergoing anterior cervical discectomy. In previous studies on ASD after cervical discectomy physiological, age-related occurrence of degeneration at the adjacent levels was not consistently accounted for. Hilibrand et al. demonstrated in a large retrospective study on patients that were subjected to ACDF that in 25.6% of patients degenerative changes were present at the adjacent level ten years after surgery. They concluded that adjacent segment degeneration occurred at a relative constant incidence of 2.9% annually [18]. This finding was received with skepticism. The study did not report on the baseline degree of degeneration, therefore it could not be ruled out whether the changes diagnosed at 10 years follow-up were already present at baseline, or not. Moreover, they reported that adjacent segment disease was less in patients that had ACDF at two levels, which is contra-intuitive and actually supports the idea that baseline degeneration is important in the analysis of ASD development after ACDF.

With the current pressure on healthcare, the ageing population and the relatively high prevalence of spinal degenerative disease, there is an increasing demand on image analysis [1]. However, radiological analysis is a time consuming task which has to be done carefully, as diagnostic and treatment decisions are based on the outcomes. In addition, there is an inter-observer variability of 30 % on average, which leaves room for improvement. Automating parts of the radiological analysis using artificial intelligence (AI) could support the medical specialists to provide a more consistent outcome, with an increased time efficiency [33].

Artificial intelligence (AI) is a rapidly evolving field in medical research. Over the last decade, it has become increasingly popular. Within the field of AI, Machine Learning (ML) algorithms seem to have great potential for computer aided diagnostics (CAD), as it is applicable to classification and regression problems [34-37]. An ML algorithm ”learns”, which means that the model can improve its performance on a specific task, through provided data. After training with high volumes of data, this enables the model to analyze unseen data, without explicitly being programmed to do so.

Deep Learning is a subset of ML that mimics the learning process of the human brain, predominantly using a type of algorithm that is structured in layers, called an artificial neural network. Neural networks are algorithms that are made up of many simple processing nodes that are connected to each other. The nodes work together to find patterns in the data and make predictions. When the network is active, each node receives a number from the nodes connected to it and multiplies it by a weight. It then adds these products together and decides whether to pass the information to the next layer. During training, the network's weights and thresholds are adjusted until it consistently produces accurate predictions. A particular type of neural network is the convolutional neural network (CNN). When research focusses on computer vision, use of a CNN is preferred, as this type of deep learning model can be used for image analysis and feature extraction. Traditional image analysis methods used to involve picking out predefined features of the image and then using those features to make a prediction. Different from these traditional methods of predefined feature extraction coupled with a classifier as predictor, CNNs use the imaging data to achieve a unified hierarchical representation of the visual information. Simplified, this means that a CNN is able to look at the entire image and create a sort of "map" of the important parts. The interconnected layers of nodes, or chained convolutional layers, transform the input images as vectors into a high dimensional feature space to derive the hierarchical feature representations. This creates a detailed representation of the image and is done by breaking down the image into tiny pixels and analyzing them one by one. The model then puts all the information together to make a prediction. Essentially, it enables the performance of statistical testing on imaging data through translating pixels into series of numbers and ultimately performing a form of regression on those number series.

In this thesis both classical statistical methods on clinical data and Machine Learning on medical imaging data will be used to answer the questions; 'what drives differences in perceived functional outcome after anterior cervical discectomy for radiculopathy', and 'how can AI be harnessed to improve the diagnostic and prognostic process'?

Aims and outline of this thesis:

1. Previously published reviews and meta-analyses on the comparison between fusion and prosthesis in the treatment of cervical radiculopathy mainly analyze studies including patients with a herniated disc resulting in either radiculopathy, myelopathy, or a combination. We consider the latter to be 'mixed patient populations'. Myelopathy, as opposed to radiculopathy, is generally occurring in patients with more degenerated spines and demonstrate different clinical symptoms. Moreover, surgical indications and treatment goals for myelopathy patients are fundamentally different from those for radiculopathy patients. Comparing clinical outcome in patients exclusively suffering from radiculopathy is therefore a more valid method to compare the true clinical effect of the prosthesis to that of fusion surgery. The first aim is therefore to assess clinically relevant differences in clinical outcome after cervical arthroplasty (ACDA), as compared to fusion (ACDF) after anterior cervical discectomy in patients exclusively suffering from radiculopathy, and to evaluate differences with mixed patient populations (Chapter 2).
2. Defining clinically meaningful success criteria from patient-reported outcome measures (PROMs) is crucial for clinical audits, research and decision-making. The second aim is to define criteria for a successful outcome 3 and 12 months after surgery for cervical degenerative radiculopathy on recommended PROMs (Chapter 3).
3. The third aim is to draw a conclusion on the alleged clinical superiority of ACDA, with improved power, by combining data from two RCTs, performed in two academic hospitals. Both trials compare clinical outcomes for ACDA and ACDF, while adding a comparison to the less-studied alternative; ACD. This combined study aimed to investigate whether the ACDA procedure offers superior clinical results 2 years after surgery, to either ACDF or ACD without instrumentation, in the entire group of patients or in a particular subgroup of patients (Chapter 4).
4. Depression and anxiety are common mental disorders among patients with chronic pain. It is hypothesized that patients suffering from these disorders benefit less from cervical spine

surgery than mentally healthy patients. The fourth aim is hence to quantify the effect of mental health status on functional outcome after anterior cervical discectomy in a post-hoc analysis on RCT data (Chapter 5).

5. As adjacent segment disease is typically reported to occur after longer follow-up, it is essential to study long-term results in patients undergoing anterior discectomy to treat cervical radiculopathy. Therefore the fifth aim is to evaluate the long-term clinical outcome in patients with cervical radiculopathy due to a herniated disc undergoing ACDA, ACDF or ACD (no cage, no plate) measured in PROMs and clinically relevant adjacent segment disease (Chapter 6).
6. Healthcare has enormous potential to take advantage of artificial intelligence (AI) for the analysis of big data. Machine Learning, a fundamental driver of current-generation AI, feeds on big data to identify underlying patterns to improve its model performance on predefined tasks. With an explosion of healthcare data ranging from basic science, clinical, numerical, language-based, and imaging data to vast amounts of administrative and economic data, artificially intelligent computer programs are well positioned to harvest, manage, analyze, and interpret this data to optimize healthcare delivery. However, the rise of big data and related technologies has led to an increased reliance on computer algorithms and a decline in direct human involvement and oversight. This shift raises ethical concerns in healthcare, as the machine-driven automation of processes, that were previously guided by human intelligence, creates new challenges. A sixth aim is to describe a pathway for the ethical application of Machine Learning in healthcare (Chapter 7).
7. Automating parts of the radiological image analysis process using Machine Learning could provide more accurate and consistent assessment, eliminating interobserver variability with an increased time efficiency. Therefore, the seventh aim is to create an overview of the available Machine Learning methods for automated analysis of cervical spine characteristics on radiological imaging (Chapter 8).
8. Identifying patients who will develop ASD remains challenging for clinicians. The eighth aim is to develop and validate a deep learning algorithm capable of predicting ASD by using only preoperative cervical MRI in patients undergoing single-level anterior cervical diskectomy and fusion (ACDF) (Chapter 9).
9. Not all patients benefit from surgical treatment and predicting who will and who will not, is difficult. For that reason the final aim of this thesis was to develop and validate a deep learning algorithm capable of predicting clinical success one year after surgery for cervical disc herniation, solely based on preoperative radiographs, and identify which image features are important for the algorithms decision-making (Chapter 10).

References

1. Cohen SP. Epidemiology, diagnosis, and treatment of neck pain. Mayo Clin Proc. 2015;90(2):284-99.
2. Kuo DT, Tadi P. Cervical Spondylosis. BTI - StatPearls.
3. Peng B, DePalma MJ. Cervical disc degeneration and neck pain. J Pain Res. 2018;11:2853-7.
4. Cloward RB. The anterior approach for removal of ruptured cervical disks. J Neurosurg. 1958;15(6):602-17.
5. Dereymaeker A, Mulier J. [Vertebral fusion by a ventral approach in cervical intervertebral disk disorders]. Rev Neurol (Paris). 1958;99(6):597-616.
6. Robinson R. Anterolateral disc removal and interbody fusion for cervical disc syndrome. Bull Johns Hopkins Hosp. 1955;96:223-4.
7. Robinson RA, Smith GW. ANTEROLATERAL CERVICAL DISC REMOVAL AND INTERBODY FUSION FOR CERVICAL DISC SYNDROME. BULLETIN OF THE JOHNS HOPKINS HOSPITAL. 1955;96(5):223-4.
8. Simmons Eh Fau - Bhalla SK, Bhalla SK. Anterior cervical discectomy and fusion. A clinical and biomechanical study with eight-year follow-up. (0301-620X (Print)).
9. Gore DR, Sepic SB. Anterior Cervical Fusion for Degenerated or Protruded Discs: A Review of One Hundred Forty-Six Patients. Spine. 1984;9(7).
10. Bohlman HH, Emery SE, Goodfellow DB, Jones PK. Robinson anterior cervical discectomy and arthrodesis for cervical radiculopathy. Long-term follow-up of one hundred and twenty-two patients. JBJS. 1993;75(9).
11. Hessler C, Boysen K, Regelsberger J, Vettorazzi E, Winkler D, Westphal M. Patient Satisfaction After Anterior Cervical Discectomy and Fusion Is Primarily Driven by Relieving Pain. The Clinical Journal of Pain. 2012;28(5).
12. Andresen AK, Paulsen RT, Busch F, Isenberg-Jørgensen A, Carreon LY, Andersen MØ. Patient-Reported Outcomes and Patient-Reported Satisfaction After Surgical Treatment for Cervical Radiculopathy. Global spine journal. 2018;8(7):703-8.
13. Wichmann TO, Rasmussen MM, Einarsson HB. Predictors of patient satisfaction following anterior cervical discectomy and fusion for cervical radiculopathy. Clinical Neurology and Neurosurgery. 2021;205:106648.
14. Jawahar A, Cavanaugh DA, Kerr EJ, Birdsong EM, Nunley PD. Total disc arthroplasty does not affect the incidence of adjacent segment degeneration in cervical spine: results of 93 patients in three prospective randomized clinical trials. SPINE JOURNAL. 2010;10(12):1043-8.
15. Divi SN, Goyal DKC, Woods BI, Nicholson KJ, Salmons HI, Galetta MS, et al. How Do Patients With Predominant Neck Pain Improve After Anterior Cervical Discectomy and Fusion for Cervical Radiculopathy? (2211-4599 (Print)).
16. Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, Goedmakers CMW, Bosscher L, Peul W, et al. The NECK trial: Effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomized controlled trial. The Spine Journal. 2019;19(6):965-75.
17. Donk RD, Verhagen WIM, Hosman AJF, Verbeek A, Bartels RHMA. Symptomatic Adjacent Segment Disease After Anterior Cervical Discectomy for Single-level Degenerative Disk Disease. Clinical Spine Surgery. 2018;31(1).
18. Hilibrand AS, Carlson GD, Palumbo MA, Jones PK, Bohlman HH. Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. J Bone Joint Surg Am. 1999;81(4):519-28.

19. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity: A Literature Review. Archives of Internal Medicine. 2003;163(20):2433-45.

20. Lamb SE, Guralnik JM, Buchner DM, Ferrucci LM, Hochberg MC, Simonsick EM, et al. Factors that modify the association between knee pain and mobility limitation in older women: the Women's Health and Aging Study. Ann Rheum Dis. 2000;59(5):331-7.

21. Wells KB, Golding JM, Burnam MA. Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. General Hospital Psychiatry. 1989;11(5):320-7.

22. Betrus PA, Elmore SK, Hamilton PA. Women and somatization: Unrecognized depression. Health Care for Women International. 1995;16(4):287-97.

23. Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial Predictors of Outcome in Acute and Subchronic Low Back Trouble. Spine. 1995;20(6).

24. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. PAIN. 2001;92(1).

25. Potter RG, Jones JM. The evolution of chronic pain among patients with musculoskeletal problems: a pilot study in primary care. Br J Gen Pract. 1992;42(364):462-4.

26. Reis S, Hermoni D, Borkan JM, Biderman A, Tabenkin C, Porat A. A new look at low back complaints in primary care: a RAMBAM Israeli Family Practice Research Network study. J Fam Pract. 1999;48(4):299-303.

27. Jackson KL, Rumley J, Griffith M, Agochukwu U, DeVine J. Correlating Psychological Comorbidities and Outcomes After Spine Surgery. Global Spine Journal. 2019;10(7):929-39.

28. Edwards RR, Klick B, Buenaver L, Max MB, Haythornthwaite JA, Keller RB, et al. Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes. Pain. 2007;130(1-2):47-55.

29. Adogwa O, Elsamadicy AA, Cheng J, Bagley C. Pretreatment of Anxiety Before Cervical Spine Surgery Improves Clinical Outcomes: A Prospective, Single-Institution Experience. World Neurosurg. 2016;88:625-30.

30. Elsamadicy AA, Adogwa O, Cheng J, Bagley C. Pretreatment of Depression Before Cervical Spine Surgery Improves Patients' Perception of Postoperative Health Status: A Retrospective, Single Institutional Experience. World Neurosurgery. 2016;87:214-9.

31. Alvin MD, Miller JA, Sundar S, Lockwood M, Lubelski D, Nowacki AS, et al. The impact of preoperative depression on quality of life outcomes after posterior cervical fusion. Spine J. 2015;15(1):79-85.

32. Toru D, Hideki N, Koji N, Shima H, Yusuke S, So K, et al. Effect of depression and anxiety on health-related quality of life outcomes and patient satisfaction after surgery for cervical compressive myelopathy. Journal of Neurosurgery: Spine SPI. 2019;31(6):816-23.

33. Urrutia J, Zamora T, Yurac R, Campos M, Palma J, Mobarec S, et al. An Independent Inter- and Intraobserver Agreement Evaluation of the AOSpine Subaxial Cervical Spine Injury Classification System. Spine (Phila Pa 1976). 2017;42(5):298-303.

34. Xu Y, Hosny A, Zeleznik R, Parmar C, Coroller T, Franco I, et al. Deep Learning Predicts Lung Cancer Treatment Response from Serial Medical Imaging. Clin Cancer Res. 2019;25(11):3266-75.

35. Zhang Y, Lobo-Mueller EM, Karanicolas P, Gallinger S, Haider MA, Khalvati F. CNN-based survival model for pancreatic ductal adenocarcinoma in medical imaging. BMC Medical Imaging. 2020;20(1):11.

36. Tabibu S, Vinod PK, Jawahar CV. Pan-Renal Cell Carcinoma classification and survival prediction from histopathology images using deep learning. Sci Rep. 2019;9(1):10509.

37. Nam KH, Seo I, Kim DH, Lee JI, Choi BK, Han IH. Machine Learning Model to Predict Osteoporotic Spine with Hounsfield Units on Lumbar Computed Tomography. J Korean Neurosurg Soc. 2019;62(4):442-9.