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SUPRACLAVICULAR APPROACH FOR RIB-SPARING TREATMENT OF NEUROGENIC THORACIC OUTLET SYNDROME AND QUALITY OF LIFE IN NTOS PATIENTS

Niina Ruopsa

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ABSTRACT

Thoracic outlet syndrome (TOS) is a compression of nerves or vessels in the passageway from the lower neck to the armpit. TOS usually causes pain in the shoulder and neck, numbness or tingling in the fingers, and weakness in the hand. TOS is divided into four subgroups: neurogenic, venous, arterial, and true neurogenic TOS. It can result from various factors, for instance, anatomical abnormalities, cervical trauma, or repetitive movements of the hand. Treatment options include physical therapy and, in severe cases, surgery to relieve the compression.

This dissertation includes a systematic literature review and meta-analysis of surgical outcomes in patients with scalenotomy, our own study of long-term surgical outcomes of NTOS patients treated with scalenotomy, development of a new quality-of-life scale (QoL) for NTOS patients (the Thoracic Outlet Syndrome Index, TOSI), and evaluation of the convergent validity of TOSI.

Systematic review and meta-analysis was conducted based on previous findings from research on scalenotomy. Of the 1345 studies, we included 18. Patients in each study ranged in number from 11 to 179, with approximately 80% women. Mean age of these patients at surgery was 35.8 years. No randomized research concerned scalenotomy. The mean follow-up time in months was 48.7, and mean sample size of the studies was 58 patients. A total of 14 studies met the eligibility criteria for meta-analysis. Patient's reported outcome was the variable among the studies used for meta-analyses. Pooled estimate for success of operation was 70.6%.

Our own patient series comprised 94 NTOS patients treated with scalenotomy. These patients we studied in regard to their main outcomes for pain, numbness, weakness, and upper-extremity function. The Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) survey, the Cervical-Brachial Symptom Questionnaire (CBSQ), and a numerical rating system served as functional outcome measures. Mean follow-up was 12.9 years. Surgical outcome was reported as good or excellent by 87% of the women and 57% of the men. Self-reported NRS pain diminished by 3.2, numbness by 3.4, and weakness by 3.5. We found that, after scalenotomy, pain, numbness, weakness, and daily harm significantly decreased.

For patients with TOS, no validated scales exist specifically for measuring QoL and functioning level. Our cross-sectional survey examined whether some items adopted from validated QoL scales could prove suitable for patients with TOS. To find an optimal TOS index, a panel of 14 TOS specialists evaluated the relevance of 19 items adopted from scales used in other upper-extremity

syndromes. After undergoing surgery for TOS, 52 patients rated the relevance of those items that experts found relevant. Of the 19 items, 15 were considered by the panelists relevant for TOS, with an overall test content validity index of 0.93. The internal consistency of these 15 items was excellent. An exploratory factor analysis accompanied by a parallel analysis confirmed the uni-dimensionality of the TOSI. All 15 items that the panelists considered relevant were also items that, on an 11-point scale of relevance, the patients gave scores exceeding 7 points.

We also assessed the convergent validity of the TOSI when compared with the QDASH, the CBSQ, and the painNRS after supraclavicular rib-sparing decompression for NTOS. Our 67 TOS patients, mean age 36.5 years at surgery, we evaluated clinically for a mean 13.2 years after rib-sparing surgery. They completed the QDASH, the CBSQ, the pain NRS, and the TOSI questionnaires. Correlations between TOSI total score and QDASH, CBSQ total scores, and the painNRS were strong: 0.67 for TOSI vs. QDASH; 0.75 for TOSI vs. CBSQ; and 0.65 for TOSI vs. painNRS. The TOSI demonstrated good convergent validity.

NTOS treatment seems effective for rib-sparing scalenotomy. We recommend high-quality and multicentred, randomized controlled research to confirm these findings.

TOSI is the first TOS-related QoL index. In future we recommend testing the psychometric properties of the TOSI, including its reliability in different populations.

TIIVISTELMÄ

Rintakehän yläaukeaman oireyhtymä (TOS) on tila, jossa hermot ja/tai verisuonet joutuvat puristuksiin kulkiessaan kaulalta kainaloon. TOS aiheuttaa yleensä kipua olkapäässä ja niskassa, tunnottomuutta tai pistelyä sormissa ja heikkoutta kädessä. TOS on jaettu neljään alaryhmään: neurogeeninen TOS, laskimo- ja valtimo -TOS sekä hyvin harvinainen todellinen neurogeeninen TOS. TOS voi johtua useista tekijöistä, esimerkiksi anatomisista poikkeavuuksista, kaularangan traumasta tai toistuvista käden liikkeistä. Hoitovaihtoehtoja ovat fysioterapia ja vaikeissa tapauksissa leikkaus puristuksen lievittämiseksi.

Tämä väitöskirja sisältää systemaattisen kirjallisuuskatsauksen ja meta-analyysin skalenotomialla hoidettujen potilaiden leikkaustuloksista, oman tutkimuksemme skalenotomialla hoidettujen NTOS-potilaiden pitkäaikaisista leikkaustuloksista, uuden elämänlaatumittarin kehittämisen NTOS-potilaalle (Thoracic Outlet Syndrome Index, TOSI) ja TOSI:n konvergentin validiteetin arvioinnin.

Systemaattinen katsaus ja meta-analyysi tehtiin aiempien skalenotomialeikkausten tuloksia käsittelevien tutkimusten perusteella. Mukaan hyväksyttiin 18 artikkelia 1354 tutkimuksesta. Potilaiden määrä tutkimuksissa vaihteli 11:stä 179:ään, ja noin 80 % potilaista oli naisia. Potilaiden keski-ikä oli 35,8 vuotta. Keskimääräinen seuranta-aika oli 48,7 kk, ja tutkimusten keskimääräinen otoskoko oli 58 potilasta. Satunnaistettuja tutkimuksia aiheesta ei löytynyt. Yhteensä 14 artikkelia täytti meta-analyysin kelpoisuusvaatimukset. Potilaan raportoima tulos leikkauksen onnistumisesta oli ainoa muuttuja, mitä meta-analyyseissä pystyttiin käyttämään. Meta-analyysin perusteella onnistumisprosentiksi saatiin 70,6.

Tutkimme myös oman potilasaineiston avulla skalenotomian pitkäaikaistuloksia. 94 potilaalla arvioitiin leikkaustuloksina kipua, tunnottomuutta, heikkoutta ja yläraajojen toimintaa. Toiminnallista tulosta ja elämänlaatua arvioitiin The Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) -mittarilla, the Cervical-Brachial Symptom Questionnaire (CBSQ) -mittarilla ja Numeric Rating Scale -luokitusjärjestelmällä. Keskimääräinen seuranta-aika oli 12.9 vuotta. Leikkauksen tulos oli hyvä tai erinomainen 87 %:lla naispotilaista ja 57 %:lla miespotilaista. NRS:n perusteella potilaiden itse raportoima kipu väheni 3,2, tunnottomuus 3,4 ja heikkous 3,5 pistettä. Tutkimuksen perusteella tunnottomuus, heikkous ja päivittäiset haitat vähenivät merkittävästi skalenotomian jälkeen.

Erityisesti TOS-potilaille suunnattuja validoituja elämänlaatumittareita ei ole kehitetty. Poikkileikkaustutkimuksessamme tutkittiin, voisivatko

jotkin validoitujen QoL-mittareiden kysymykset sopia myös TOS-potilaille. Optimaalisen TOS-indeksin löytämiseksi 14 TOS-asiantuntijan paneeli arvioi 19:n muista yläraajojen oireyhtymien elämänlaatumittareista löytyvän kysymyksen soveltumista myös TOS-potilaiden elämänlaadun mittaamiseen. TOS-leikkauksen jälkeen puolestaan 52 potilasta antoi oman arvionsa asiantuntijoiden valitsemien kysymysten osalta. Heidän mielestään näistä 15 oli merkityksellistä kuvastamaan oireita TOS:n osalta. Näiden pohjalta luotiin 15 kysymystä sisältävä TOSI-elämänlaatumittari. Testin sisällön validiteetti-indeksiksi saatiin 0,93. Näiden 15 kohdan sisäinen konsistenssi oli erinomainen. TOSI:n yksiulotteisuus vahvistettiin eksploratiivisen faktorianalyysin ja rinnakkaisanalyysin avulla. Kaikki 15 kohtaa, joita panelistit pitivät merkityksellisinä, olivat myös kohteita, jolle potilaat antoivat yli 7 pistettä 11-portaisessa asteikossa.

Arvioimme myös TOSI:n konvergenttia validiteettia verrattuna QDASH:iin, CBSQ:hen ja kipuNRS:ään NTOS:n skalenotomian jälkeen. 67 TOS-potilastamme, joiden keski-ikä oli 36,5 vuotta leikkaushetkellä, arvioitiin kliinisesti keskimäärin 13,2 vuoden kuluttua leikkauksesta. He täyttivät QDASH-, CBSQ-, kipu-NRS- ja TOSI-kyselylomakkeet. Korrelaatiot TOSI:n kokonaispisteiden ja QDASH:n, CBSQ:n kokonaispisteiden ja kipuNRS:n välillä olivat vahvat: 0,67 TOSI vs. QDASH; 0,75 TOSI vs. CBSQ; ja 0,65 TOSI vs. painNRS. TOSI osoitti hyvää konvergenttia validiteettia.

Ilman kylkiluun poistoa tehtävä skalenotomia vaikuttaa olevan tehokas hoitomuoto NTOS-potilaille. Suosittelemme jatkossa korkealaatuista satunnaistettua kontrolloitua monikeskustutkimusta näiden tutkimustulosten vahvistamiseksi.

TOSI on ensimmäinen TOS-potilaille kehitetty elämänlaatumittari. Jatkossa suosittelemme testaamaan TOSI:n psykometrisiä ominaisuuksia, mukaan lukien sen luotettavuutta eri väestöryhmissä.

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Lempäälä, June 2024

Niina Ruopsa

ABBREVIATIONS

ATOS	arterial thoracic outlet syndrome
BPI	brief pain inventory
BTX	botulinum toxin
CBSQ	cervical brachial symptom questionnaire
CRPS	complex regional pain syndrome
CVI	content validity index
CVR	content validity ratio
DASH	disabilities of the arm, shoulder, and hand questionnaire
I-CVI	item-level content validity index
NPMS	neurogenic pectoralis minor syndrome
NTOS	neurogenic thoracic outlet syndrome
NRS	numeric rating scale
PSS	Paget-Schroetter syndrome
QoL	quality of life
ROM	range of motion
S-CVI	scale-level content validity index
SANE	Single Assessment Numeric Evaluation
TN-TOS	True neurogenic TOS
TOS	thoracic outlet syndrome
VTOS	venous thoracic outlet syndrome
WORC	Western Ontario rotator cuff index

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LIST OF ORIGINAL PUBLICATIONS

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III Vastamäki M, Ruopsa N, Vastamäki H, Laimi K, Ristolainen L, Saltychev M. Validity and internal consistency of the thoracic outlet syndrome index for patients with thoracic outlet syndrome. Shoulder Elbow Surg. 2020 Jan;29(1):150-156. doi: 10.1016/j.jse.2019.05.034. Epub 2019 Aug 29. PMID: 31474322

IV Ruopsa N, Vastamäki H, Ristolainen L, Vastamäki M, Saltychev M. Convergent validity of Thoracic Outlet Syndrome Index (TOSI). Physical Activity and Health 6.1 (2022): 16–25.

The publications are referred to in the text by their roman numerals.
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1 INTRODUCTION

The passageway from the lower neck to the armpit is called the thoracic outlet. If nerves or blood vessels are compressed in this space, we call this group of disorders thoracic outlet syndrome, TOS. It causes, in the upper limb, pain, numbness, and lack of grip strength. The most common form of TOS is neurogenic (>90%) (1, 2, 6). The other forms of TOS are venous TOS (VTOS) (2%-3%) (3), arterial TOS (ATOS) (1%) (3), and a very rare true neurologic TOS (<1%), which is thought to result from compression of the lower trunk in the brachial plexus (4).

The usual TOS treatment is physiotherapy and guided self-training. If these prove ineffective, surgical treatment can be considered. The problem is that we have no clinical or mechanical tests to confirm a TOS diagnosis or to predict surgical outcome. Systematic reviews and meta-analysis concerning NTOS are rare. It has been difficult to select patients with NTOS who will truly benefit from surgical management, and for differing methods, data on long-term results are also rare. These facts explain at least part of the reason why surgeons find that the surgical management of NTOS has been a controversial topic.

NTOS patients often feel that their quality of life has decreased. They have problems at work, in daily living, and in sports activities. Because patients' own observations on alterations in their health status are important measures of treatment success, quality of life surveys provide a framework by which to survey their point of view on functioning, outcome, and health. Measuring QoL may be particularly useful in syndromes such as TOS with its limited treatment options despite its infliction of daily limitations.

Even if no specific QoL tools have existed for TOS itself, various instruments allow measurement of QoL via other upper-extremity symptoms, especially in patients with shoulder pain. The Western Ontario Rotator Cuff (WORC) index (7), the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire (8), and the Cervical Brachial Symptom Questionnaire (CBSQ) (9), are specifically aimed for patients with upper-extremity disorders. What is unknown, however, is whether these more generic or shoulder-specific tools are suitable for TOS, even though some of their questionnaire items would also apply to TOS symptoms.

2 REVIEW OF THE LITERATURE ON THORACIC OUTLET SYNDROME

2.1 History

The roots of TOS go back a long way, as the cervical rib was already known at the time of Galen around 150 AD (1). The first well-documented case of a thoracic outlet patient was reported in 1861 (2). Coote wrote about a 26-year-old woman who had anomalous bone growth causing compression and disturbance of the circulation and loss of sensation in the corresponding extremity, and the patient underwent surgery. In 1912, T. Wingate Todd reported that the first rib can cause the symptoms of a cervical rib, and the carrying position may relieve the stretching (3). Stopford and Telford reported in 1919 on a group of patients with weakness of intrinsic muscles, loss of grip strength and problems with sensation in the area of the lower trunk of the brachial plexus (4). One of the pioneers was Adson at the Mayo Clinic, who began to treat patients by removing the anterior scalene muscle (5). Anatomical anomalies of the thoracic outlet syndrome also became more widely analysed. For instance, Milliez and Poitevin made an analysis of the thoracic outlet syndrome in regard to muscle biochemistry and to fibre type (6). Peet et al. first initially launched the term "thoracic outlet syndrome" in 1956 (7).

The first rib resection (FRR) was described by O. Theron Clagett in 1962 (8). Roos reported in 1966 a study of removal of the first thoracic rib done by a transaxillary method (9). His study included 15 patients, and this procedure became the standard operation in the 1970s. In 1976, Roos described the abnormal fibres and bands he had found in thoracic-outlet operations and inspired the understanding that we should also recognize the other associated abnormalities besides the first rib (10).

Though the diagnosis became year by year more usual, there was still a lack of objective clinical tests and of common criteria for diagnosis. In 2009 came the founding of The Consortium for Outcomes Research and Education on Thoracic Outlet Syndrome (CORE-TOS). Its purpose was to create the criteria for diagnosis and offer principles on how to compare treatment outcomes. A Cochrane systematic review appeared in 2010 (11), and the first comprehensive textbook concerning TOS was released in 2013 by Illig et al (12). In 2016, the Society for Vascular Surgery reported their standards for thoracic outlet syndrome (13). According to this report, NTOS can go diagnosed when three of these four criteria are present: symptoms and signs of pathology

occurring at the thoracic outlet (tenderness and/or pain); symptoms suggest nerve compression (distal neurologic changes, especially worsening with arms overhead or dangling); no other pathology potentially explains these symptoms; and a scalene-muscle test block is positive

2.2 Epidemiology

Due to non-uniform methods to diagnose any disease, epidemiology has attracted little research. The true prevalence of TOS still remains unclear. The major TOS textbook is that of Illig, and it estimates the incidence of TOS to be from 3 to 80 / 1000 (12). According to Illig, incidence of NTOS is an annual 2 to 3 / 100,000; incidence of VTOS seems to be 0.5 to 1/100,000; and ATOS manifests itself as sporadic. TOS typically affects females at the ages of 20 to 50, but also case series exist of adolescent patients (14, 15).

2.3 Anatomy

The passageway from the lower neck to the armpit makes up a space called the thoracic outlet, and it is traversed by the subclavian vessels and the brachial plexus. The volume of its space changes because of the impact of movement of the upper limbs, thorax, and neck. Four osseus structures regulate its size: the first rib, the transverse processes, the cervical vertebrae, and the clavicle. The scalene and prevertebral muscles as well as fibrous structures also affect this area's size.

The thoracic outlet area can be divided into three anatomical spaces involved in the possibility to cause compression of nerves or vessels: the scalene triangle, the costoclavicular space, and the pectoralis minor space. The neurovascular bundle (brachial plexus and subclavian artery and vein) traverses from the scalene triangle into the costoclavicular space to pass next through the pectoralis minor space. The C5 and C6 roots branch into the long thoracic and dorsal scapular nerves and enter then the scalene triangle. The phrenic nerve is located on the medial side of the scalene triangle. Cervical ribs arise from the seventh vertebral body. Studies reveal multiple bands and ligaments attached to the first rib (10). For the anatomy of the thoracic outlet syndrome see Figure 1.

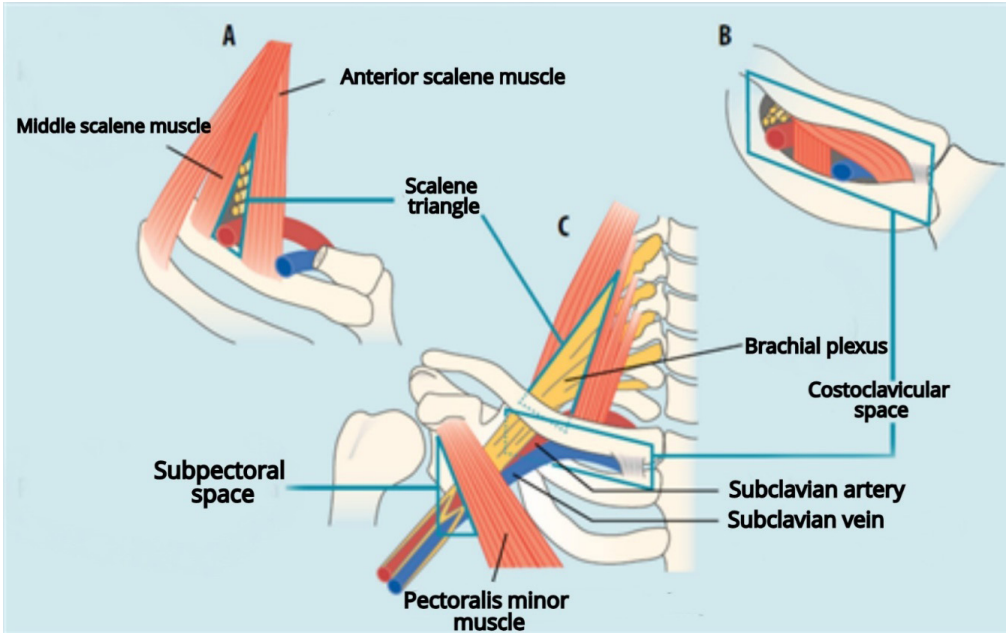

Figure 1. Anatomy of the thoracic outlet syndrome. Reprinted with permission of Duodecim. Original publication: Rintakehän yläaukeaman oireyhtymä - toiminnallinen yläraajavaiva; Arokoski et al., Lääketieteellinen Aikakauskirja Duodecim; 2017;133(11):1043-51.

Three anatomical spaces are important concerning the anatomy of the thoracic outlet: the scalene triangle, the costoclavicular space, and the pectoralis minor space. The subclavian artery and brachial plexus are located in the scalene triangle, above the clavicle. Inside the scalene muscle is located the long thoracic nerve. The phrenic nerve crosses the anterior scalene muscle. The anterior border of the costoclavicular space consists of the middle third of the clavicle, and the posteromedial side is formed by the first rib. The anterior wall of the pectoralis minor space consists of the deep surface of the pectoralis minor muscle, whereas the posterior wall consists of the subscapularis muscle. The apex of the space is formed by the clavicle and the floor of the second rib.

2.4 Pathogenesis

Most of the TOS cases are diagnosed in early adulthood (ages 20-40 years) and are more common in women (16-19). TOS can emerge after a cervical or shoulder trauma (20). Ellison reported that 49% of TOS patients indicated one single traumatic episode which precipitated TOS (21). Heneghan, in his systematic review and data synthesis, found evidence of an association between whiplash disorder and NTOS (22). Kai also reported on NTOS after whiplash injury (23). Sanders (24) found that even as high as 92% of NTOS patients reported

an aetiology of trauma. Repeated trauma to the shoulder joint, and exhibiting an abnormal posture can also cause TOS, including positions required to play bowed instruments (25).

Anomalies of the 1st rib and cervical rib are quite common causes of TOS (26-28). Henry found that a cervical rib was significantly more common in patients with TOS than in healthy individuals (29). Muscular anomalies have been described as causing TOS, as well (17, 18, 30). Machleder (31) found histological changes in the anterior scalene muscle of a TOS patient, for instance tonic contracting fibre predominance.

2.5 Disease classification

Thoracic outlet syndrome has been classified into four types: 1) neurogenic TOS (NTOS), 2) venous TOS (VTOS or Paget-Schroetter syndrome, PSS), 3) arterial TOS (ATOS), and 4) true neurologic TOS (TN-TOS).

2.5.1 NTOS

Compression of the brachial plexus in the scalene triangle or in the pectoralis minor space causes NTOS. In the literature, compression of the pectoralis minor space is called also neurogenic pectoralis minor syndrome (NPMS) (13). NTOS is the most common type of TOS, occurring in over 90% of TOS patients (13, 29), but is the hardest to diagnose (13). According to Klaassen, NTOS involves primarily, but not exclusively, the lower trunk of the brachial plexus (32) and occurs more frequently in women; it typically presents between the ages of 20 and 40 years (12).

Among its wide spectrum of presenting symptoms, the most common peripheral symptoms are numbness, weakness in the upper extremity and tingling in the hands and forearms, being worse with the arms raised overhead (13). Local symptoms are usually irritation or inflammation at the site of the scalene triangle in the case of NTOS, and at the pectoralis insertion site in the case of NPMS (13). The symptoms can range from mild to severe. In addition to the upper limb, pain can be felt in the neck, armpit, chest area, neck-shoulder area, between the shoulder blades, and even in the head.

Especially working with the arm overhead, driving, and daily activities worsen the symptoms (12, 13). Some have difficulty sleeping because of symptoms and may describe feeling the upper limb ‘’as dead.” Patients should be asked about any history of trauma with a single episode or repetitive motion injury to the area of the upper limb or neck. Previous operations on the shoulder or clavicle area should also be determined.

2.5.2 VTOS (Paget-Schroetter syndrome)

VTOS or Paget Schroetter syndrome (PSS) is caused by compression of the subclavian vena at the costoclavicular space or pectoralis minor space, and is the second most common type of TOS, including 2% to 3% of TOS patients (12). Usually, VTOS patients have experienced a repetitive subclavian mechanical trauma caused by compression in the costo-clavicular space, leading to an acute thrombosis in the subclavian or axillary vein (13). The costoclavicular space, which is formed between the first rib, the clavicle, and the anterior scalene muscle, narrows with one's arms raised. Repeated compression in that space can cause intra-luminal or extra-luminal scar tissue to form in the subclavian vein (13). Rarely, the cause of the compression can also be the pectoralis minor space. Such compression can be intermittent, involving a normal vein (McCleery syndrome); intermittent, leading to a damaged vein; or can result in thrombosis of the vein at presentation (33).

Patients with intermittent positional venous obstruction usually have as symptoms episodic arm discoloration and swelling; 60% to 80% of patients report a history of vigorous exercise or activity involving the upper extremities (33). Those PSS patients who have acute thrombosis have a sudden onset of symptoms and a classical clinical presentation with a swollen, cyanotic, and painful arm. Most of the patients are young, and VTOS is twice as common in men. Some patients with PSS experience pulmonary embolism (34, 35).

Duplex ultrasound imaging is usual for diagnosis, though it has its limitations (36, 37). Additionally useful in diagnosis are a conventional venogram, computed tomography, venography, and magnetic resonance imaging (38). Venography is both diagnostic and often therapeutic (33).

Catheter-directed thrombolysis is the standard first step in all patients who have acute effort thrombosis in the absence of significant contraindications (33), and it has a success rate of 62% to 84% (39, 40). After thrombolysis, patients are maintained with systemic anticoagulation to prevent early recurrent thrombosis. It is generally accepted that what should follow thrombolysis is surgical decompression of the costoclavicular junction; however, its correct method and timing are still under discussion (33). If surgical decompression is not performed, re-thrombosis within 30 days has occurred in as many as one-third of patients (41, 42). Molina stated that the standard of care for acute obstruction of the subclavian vein is catheter-directed thrombolytic therapy, followed immediately by surgical intervention by an anterior subclavicular approach (43). He achieved with this protocol a long-term patency rate of 100%.

2.5.3 ATOS

ATOS, in turn, is caused by compression of the subclavian artery by the first or cervical rib or by anomalous bone or ligamentous structures. ATOS among TOS patients appears in 1% (44). Arterial pectoralis minor compression has never been reported. ATOS can be symptomatic, causing ischaemia or embolization or can be asymptomatic, causing an aneurysm, occlusion, or silent embolization (13). Patients can have at-rest pain in the arm, hand, or fingers, paresthesias, ischaemia of the hand, ulcerations, or colour changes in the hand and arm. The pulse in the arm can be weak or missing.

The diagnosis of ATOS is possible by Duplex arteriography, CT angiography, or MR angiography. Chest radiography is performed routinely to identify rib anomalies, osseous malformations, or other bone lesions that may cause ATOS. CT or MRI may even be necessary to find the causative agent for ATOS.

Management of ATOS depends on aetiology. Conservative therapy is appropriate for mild symptoms. Surgical treatment of ATOS consists of three phases: repair or replacement of the damaged subclavian artery, correction of the original cause of the thoracic outlet syndrome, and correction of any distal embolic or other problems. Catheter-directed thrombolysis can prove useful, if the duration of symptoms is only for days. Surgical management may include endoluminal intervention, arterial repair, replacement, or bypass or distal embolectomy. Fasciotomy may be necessary (13), as also may be cervical rib-, first rib- and scalene resection (45).

Pitcher stated that after surgical treatment of ATOS, 14% of ATOS patients experienced postoperatively chronic upper extremity pain in long-term follow-up (46). Vemuri found in his study that, after surgical ATOS treatment, QDASH decreased from 39.1 to 19.2 and CBSQ from 44.3 to 18.4 (47).

2.5.4 TN-TOS

TN-TOS is very rare, affecting fewer than 1% of TOS patients (48). The cause is suggested to be compression of the lower trunk of the brachial plexus (T1 - C8 roots) with a fibrous band, which has been called the Gillatt-Sumner hand; the initial description of TN-TOS having been by Gilliatt (48). It manifests in ENMG as a severely depressed median compound muscle action potential and as the loss of sensory nerve action potential of the medial antebrachial cutaneous nerve (49). Patients show atrophy of their abductor pollicis brevis, hypothenar, and interossei muscles, weakness of their radial digital flexors, and mild numbness in the medial forearm (12). Clinical examination and treatment follow the same pattern as for NTOS. Restoration of motor function is rarely

achieved, but Goeteyn reported 23.5% of patients having a ≥50% decrease in their NRS score for muscle weakness (50).

2.6 Physical examination

Although many tools exist to aid with the diagnosis of TOS, what is still lacking are dependable tests for diagnosis. Evidence on the validity of clinical tests in making the diagnosis of TOS is weak (51).

The patient's posture should be noticed, also the scope of movement of both arm and shoulder, with possible muscle atrophy checked on (13). The cervical spine is evaluated. Presence of Tinell's sign should be examined along the median, radial, and ulnar nerves and also at the plexus area. Point tenderness should be examined and reported at the scalene triangle or pectoralis minor insertion site and axillary area. Elevated-arm stress, the so-called Roos' test for one minute, should be done, marking the time of the onset of symptoms and the time to dropping the hand, as well as any possible hand pallor.

The Adson test is performed with the patient standing. In our own modification, the examiner raises the relaxed upper limb to 90 degrees of abduction with the palm up and asks the patient to take a deep breath and turn the head to the direction of the opposite hand. Any weakening or disappearance of the radial pulse is recorded, and a stethoscope allows possible murmurs caused by compression of the subclavian artery to be heard. Arm swelling and pain raise suspicion of VTOS. Symptoms of ATOS may cause changes in hand temperature (52).

Other diagnoses should be carefully taken into consideration. TOS can limit the movement of the upper limb, especially of the shoulder. The shoulder range of motion (ROM) should be measured with an angle meter, and the patient's ability in extension, abduction, and pro-supination of the shoulder needs registering. All findings should be compared to those of the contralateral healthy shoulder ROM. Shoulder pathology and shoulder injury must be taken into account in evaluation of any patient suspected of having thoracic outlet syndrome (53, 54). For instance, malunion of a fractured clavicle may lead to TOS (55). A local anaesthetic test of the scalene or pectoralis minor muscle can be useful. Needle electromyography serves to rule out compression of other nerves, for instance the median nerve. Usually, TN-TOS alone is found by needle electromyography.

The most difficult symptom for the patient can be pain. TOS patients usually feel much pain, especially after exertion. Pain evaluation can be according to the numerical rating scale (NRS) where 0 means a painless condition and 10 is the worst imaginable pain. Among other ways to estimate

pain is by the VAS (visual analogue scale). The patient marks the pain intensity by a crossbar (56). The everyday harm may also be estimated by the amount of analgesics required.

The grip strength and force of the pinch grip should be tested and compared with the healthy side's measured values. Usually, the force of the dominant side is approximately 10% greater. TOS patients often have lower grip strength, and grip is affected by prolonged inactivity of the upper limb.

2.7 Radiology

2.7.1 Native x-ray

An x-tray of the cervical spine should be routine for TOS patients (13). A native x-ray can show the presence or absence of bony structures, for instance a cervical rib or elongated C7 transverse process.

2.7.2 Ultrasound

Ultrasound in the diagnosis of TOS has been considered a potentially valuable technique especially for VTOS and ATOS. Aranyi et al. (57) found that it is possible to see the anomalous fibromuscular bands causing TOS by ultrasound before surgery. However, Pesser et al. (58) found that ultrasound provided no conclusive information for their NTOS diagnosis for the exclusion of a differential diagnosis. In VTOS, venous damage, compression of the vena during abduction of the upper limb, and thrombosis can all be seen in Doppler ultrasound. In ATOS, the associated osseous abnormality or anomalous rib is visible.

2.7.3 Magnetic resonance imaging

In cases of suspected NTOS, what is recommended is MRI of the brachial plexus (59). The role of MRI is mainly to exclude other conditions and find anatomical abnormalities, and it can function in combination with the clinical assessment. Hardy found that MRI identified a structure potentially responsible for TOS in 71% of patients; the false-negative rate was 29% (60). Demirbag stated that MRI findings prove most valuable in the diagnosis of TOS when the scan takes place with patients in a position provoking the symptom during the scan (61). He also showed that findings are in accord with findings from any physical evaluation tests.

2.8 Quality of life (QoL)

Quality of life has begun to be measured more and more generally when studying the effectiveness of surgeries and revealing the real benefits of treatment in the patient's daily life. There exists no definition of what should be included in the QoL indicator, however. In general, three areas are measured: physical, mental, and social, and measurement can involve very different approaches. Measures of QoL can be general or disease-specific. Disease-specific indicators aim to determine the effects of a particular disease on specific problems. General indicators can reveal more general comparisons between diseases and treatments. One of the most used generic QoL indicators in Finland is 15D, a 15-dimensional measure of health-related QoL (62).

NTOS causes pain and reduced work capacity and limits the activities of daily living. Many authors divide the results of TOS surgeries into four categories: excellent, good, fair, and poor (16, 63). Excellent means complete relief of all symptoms; good, relief of major symptoms; fair, partial relief but persistence of some major symptoms; poor means no improvement. Sanders used what is called a life-table method to describe the results of surgery on differing timelines (24, 64, 65).

The scales for evaluating TOS-patient outcome focus mostly on pain or functional limitations and are patient-reported outcome measures (PROMs) such as the Cervical Brachial Symptom Questionnaire (CBSQ) (14, 66), the short form of the Disabilities of the Arm, Shoulder and Hand (QuickDASH) (14, 67, 68), and the pain numeric rating scale (NRS).

The QuickDASH has a maximum score of 100 and is an 11-item survey scored on a 0–5 scale designed and validated for use in a variety of upper-extremity musculoskeletal disorders to quantify degree of disability (69). It is based on 30-item DASH survey (69). The CBSQ is a 14-item survey scored on a 0–120 scale, developed for evaluation of patients with NTOS and related disorders to measure functional disturbances resulting from performance of certain activities (70). The CBSQ and DASH are both valid tools in estimating the quality of life, but DASH is currently being used as scoring of the whole extremity and musculoskeletal conditions (71). The NRS is a widely used standard method for assessment of pain, consisting of a series of numbers with verbal anchors representing the entire possible range of pain intensity (72). The numerical scale is most commonly 0 to 10, with 0 being no pain, and 10 being the worst pain imaginable. The Neck Disability Index (NDI) is also used when examining upper-limb symptoms (73). It was originally developed for patients with a whiplash injury. It is a 10-item questionnaire (maximum score 50), that measures a patient's self-reported neck pain and disability.

2.9 Differential diagnosis of TOS

The diagnosis of TOS can be challenging, and has no certain test to indicate definitely the disease. Diagnosis is based on symptoms, clinical examination, and the ruling out of other causes. Several other neurological and musculoskeletal diagnoses must be considered. Median or ulnar nerve compression may cause the same kind of pain and numbness as TOS causes. ENMG is important with differential diagnosis. For TOS, the sensitivity and specificity of electrophysiological assessments both are poor (74).

Some neural tumours, for instance schwannomas, or other tumours like lipomas, can cause similar symptoms (75, 76). Patient with complex regional pain syndrome (CPRS) can have similar symptoms, such as increased sensitivity, dystonia, swelling, and discoloration that may resemble symptoms of TOS. CPRS causes later contractures and doesn't usually respond to NTOS therapy or interventions. Cervical spine disorders, for instance disc disease and arthritis, can cause pain and numbness in the upper extremity. Problems of the shoulder, including rotator cuff pathology, frozen shoulder, and arthrosis, may cause pain in the upper limb. Suprascapular nerve impingement may cause shoulder pain and shoulder weakness (77). Parsonage Turner Syndrome, PTS, also "brachial neuritis," is a neurological disorder of the brachial plexus. The typical onset of its symptoms is with sudden shoulder pain and subsequent weakness and paraesthesia in the upper extremity; it may have symptoms similar to those of NTOS (78). A patient having bilateral chronic pain in the upper and lower limbs should also be considered to possibly have fibromyalgia. Injecting botulinum toxin (BTX), local anaesthetic, or steroids into the scalene muscles can assist in diagnosis (13).

2.10 Conservative treatment of TOS

Conservative therapy is usually the first treatment, and it is recommended for all patients with NTOS (79, 80). It comprises physical therapy which focuses on the mobility of the upper part of the body and guided exercises. Scalene- and pectoralis-muscle-stretching exercises are guided. If postural changes exist, they should be corrected (81). Shoulder mobility should be maintained well (7). Kenny described a graduated resisted shoulder elevation exercise program, which significantly improved the symptoms of thoracic outlet patients (82). Ergonomics in the workplace should undergo checking. The initial course of therapy is usually for 6 to 8 weeks and will continue as long as progress is observable. Analgesics and inflammatory agents are also useful.

BTX has been a medicine used for a variety of medical conditions over the last 20 years. It causes muscular paralysis from temporary chemo-denervation and also affects pain neurotransmitters and the autonomic nervous system. It has a variable onset and duration of action depending upon dose and location. Torriani found that, with BTX, 69% of TOS patients experienced symptom relief (83). Christo stated that, after BTX injection, pain decreased for three months (84). Povlsen found that BTX significantly improved paresthesias at six months' follow-up, but failed to find a significant difference in terms of pain relief or performance when compared to placebo (79). Kök reported that BTX may provide short-lasting symptom relief in some NTOS patients (85). Response to BTX injections has also shown a positive correlation when considering long-term surgical outcome in NTOS patients (86).

2.11 Surgical treatment of TOS

If the patient fails to improve with physical therapy, surgical treatment should be considered. Usually an at least six-month conservative-treatment period is the choice before surgery. The most popular surgical methods for treatment of NTOS are four: transaxillary first-rib resection, supraclavicular first-rib resection, supraclavicular rib-sparing scalenotomy, and arthroscopic release. No clear guidelines indicate which method is best suited for each patient. Indications for NTOS surgery include chronic upper extremity pain, numbness, and weakness, and failure of a physical therapy program to relieve symptoms adequately.

Historically, TOS surgery focused on cervical-rib and first-rib resection. Later, the technique in which the scalenus anterior muscle was divided, and no rib was removed (scalenotomy) started to become common. It was recognized that all cases were not managed by scalenotomy and might need a rib resection. Today, first-rib resection is still apparently more common than rib-sparing surgery.

The approach can involve several methods. 1) the supraclavicular approach: an incision is made solely above the clavicle, 2) the infraclavicular approach: an incision solely below the clavicle, 3) the paraclavicular approach: two incisions, one above and one below the clavicle, 4) the transaxillary approach: an incision in the axilla, and 5) the posterior approach: any approach through the posterior structures. Pectoralis minor tenotomy is included in some techniques, as well. The first-rib resection can be done by a transaxillary approach, supraclavicular approach, or thoracoscopic approach.

2.11.1 Supraclavicular first-rib-sparing brachial plexus release

Scalenotomy without FRR was first published by Adson in 1927 (5). It is usually performed via a supraclavicular approach as described by Sanders (87). The incision of 4 to 5 cm is made 2 to 3 cm above the clavicle. The sternocleidomastoid muscle is mobilized and retracted medially. The external jugular vein is protected. The scalenus anterior is exposed beneath the prescalene fat. The phrenic nerve is identified on the anteromedial surface of the scalenus, and care is taken not to damage it, for instance, by stretching it too much. Scalenotomy is performed, and the nerve roots of the plexus are checked and freed by dissecting all compressive elements, if necessary, also the scalenus medius partially or completely. Bleeding during the procedure is usually minimal so that no drain is necessary. The wound is closed in two layers. After surgery, hand mobilization is free, but any heavy lifting overhead should be avoided during the first post-operative week.

2.11.2 First-rib resection

Roos described FRR combined with scalenotomy in 1966 (9). The several techniques for FRR include an open supraclavicular (88) or transaxillary approach (9, 89), and also available are mini-invasive techniques (90) and robot-assisted operations (91, 92).

2.11.2.1 Transaxillary approach

The transaxillary technique is the most common FRR method, first described by Roos (9). In the transaxillary first rib resection, the patient is placed with the operation-side up. The arm is elevated with a retractor and positioned with elbow in flexion, and the patient in the lateral decubitus position. A transverse skin incision is made between the posterior part of the pectoralis major muscle and the latissimus dorsi muscle. The serratus muscle is identified, and blunt dissection is made until the second rib is identified, and after that the artery and vena subclavia, the first rib, and brachial plexus nerve roots are identifiable. After division of the anterior scalene muscle, the first rib is partially or completely resected. The patient starts on 8- to 12-week physical therapy exercises. Postoperative complications include pneumothorax, nerve injuries, injuries to the subclavian artery and vein and lymphatics leaks, and also postoperative infections.

2.11.2.2 Supraclavicular approach

By the supraclavicular approach it is possible to perform anterior and middle scalenotomy or scalenectomy, pectoralis minor tenotomy, first-rib resection, and brachial-plexus neurolysis. This technique was first described by Sanders

et al. in 1985 (93). The patient is placed with upper body elevated 30 degrees and the legs flat. To improve surgical visibility, the neck should be extended. A transverse incision is made about 2- to 3-cm above the clavicle in the supraclavicular fossa. The incision should extend to the anterior part of the trapezius muscle, starting at the lateral side of the sternocleidomastoid muscle. After mobilization of the fat pad, the long thoracic nerve becomes visible, and the middle scalene muscle can also be viewed. After the anterior and medial scalenectomy, the first rib is resected, and what is ensured is that the nerve roots of the plexus are no longer under any compression. Pectoral minor tenotomy can be combined, as well. A drain is necessary, and the wound closure includes suture of the scalene fat attaching it to its normal position and suturing the wound in two layers. Possible complications include intraoperative haemorrhage, postoperative infection, lymphatic leak, nerve damage, and paraesthesia and persistent pain or CRPS.

2.11.2.3 Thoracoscopic approach

A less invasive method of surgery for NTOS is the transthoracic approach using a thoracoscope either video-assisted or robot-assisted. Both supraclavicular and transaxillary techniques occur. The studies reporting transthoracic first rib resection are still few, but they show no difference from other methods in success rate. The operation times are longer than with traditional open techniques earlier on, but improve with the learning curve; the complication rate is, however, a bit lower (91, 94-97).

2.12 Treatment outcomes of NTOS

2.12.1 Outcomes of conservative treatment

Good studies on conservative treatment of TOS are surprisingly few, considering that it is always the preferred method of treatment. The quality of physiotherapy and the experience of the physiotherapist certainly have an impact on the end result. Intensive hospital-based rehabilitation has been found to be effective even after private-practice physiotherapy had failed (98).

Mailis (99) did a prospective study of 32 patients and found that very good self-estimated pain relief was achieved in only 20% of the conservatively treated patients. Lindgren did a prospective study with 119 patients with two-year follow-up and stated that 88% of the patients were satisfied with the outcome of conservative treatment (82). Vanti found no difference in outcomes between placebo, no treatment, or different conservative treatments in his

literature review (100). Landry compared conservative treatment to FRR and found that surgery did not significantly improve functional outcome (101).

Any factors that would predict to whom conservative treatment should be directed have been little studied. Novak found that obesity, workers' compensation, and associated carpal or cubital tunnel syndrome were linked to a poor outcome (102). Studies are also few on the impact of conservative treatment on QoL. Goeteyn ran a randomised clinical trial which compared surgery and conservative treatment of NTOS and found a statistically significant difference in DASH scores at three months (103). Transaxillary FRR group had a mean 45.15 DASH score compared to DASH score 64.92 in conservative group.

2.12.2 Outcomes of rib-sparing surgery

There are no meta-analyses of the results of rib-sparing surgeries. The first operative outcomes are from the Sixties (104, 105). Data from more than 100 patients can be found in three studies (24, 65, 106). The follow-up period ranges from 3 to 180 months. Bhattacharya reported 52.7% of patients having a good result (16). Ciampi found a success rate of 83% (18). Woods reported 75% of patients as having a good result in his 90-patient study (107).

Outcome measures differ. Sanders has used a life-table method, with which he has measured the result of surgery nine times in three years, and his long-time outcome has been good or excellent in 66% to 69% (24, 64, 65). Some quantitative validated outcome scores used in the follow-up of scalenotomies are QuickDASH, VAS, SANE (the Single Assessment Numeric Evaluation), CBSQ, and NRS (14, 67, 108). Ransom reported a decrease in VAS from 7.5 to 1.8 and an increase in SANE from 28.9 to 85.4. Glynn found median DASH scores pre- and postoperatively of 68.5 and 36.0.

Reported complications include pleural injury, pneumothorax, pleural effusion, n. thoracicus longus injury, Horner syndrome, lymphatic injury, and wound infection, but few studies reported the interventions used to manage the complications. Yin, in his systematic review of patients with rib-sparing surgery, reported a complication rate of 12.6% and no permanent brachial plexus injury (109).

Most of the studies do not report any factors affecting the outcome of scalenotomy. Cheng found that patients with symptoms for less than two years had a 83% successful result, while those with symptoms for more than two years had a success rate of 68% (17). Glynn reported significant improvement in post- versus preoperative DASH scores for patients without a history of trauma (67). Sanders noticed that patients with work-related TOS had poorer results (65).

2.12.3 Outcomes of supraclavicular and transaxillary FRR

Results of supraclavicular FRR was found to be represented in a moderate amount. Yin reported in his systematic review a mean success rate of 77% and a complete relief rate of 57% (109). Sanders achieved improved short-term outcome with 92% of the patients and long-term outcome with 72% of the patients evaluated by his life-table method (64). Maxey reported that 63.9% of patients showed complete resolution of their symptoms, 23.6%, partial resolution, and 12.5% no resolution at all (110). He reported an 8.3% complication rate.

Balderman compared conservative treatment with supraclavicular FRR (109). He found that 90% of patients can receive significant relief from their symptoms by supraclavicular FRR, but only 27% received satisfactory improvement with physical therapy alone (111). He reported the mean change in QuickDASH scores for physical therapy to be -15.6, compared with -29.8 as their outcome from surgery. Jammed reported that improvement in QDASH scores was 21 after supraclavicular FRR with recurrent NTOS (112).

Several datasets exist for more than 150 patients concerning transaxillary FRR (113-117). Altobelli reported 46% primary and 64% secondary success (113). In his study, the patient was considered to have primary success when the success was uninterrupted, with no procedure having been performed on the operative side, whereas secondary success could be maintained by the secondary operation even after the primary failure. Jamieson stated that 78% patients had postoperative improvement (114). Lindgren achieved good or fair results in 59% of patients (116). Over 90% of patients, according to Sellke, had relief from their symptoms (117). Goeteyn reported a significant drop in DASH and CBSQ score after transaxillary FRR in a 12-month follow-up (103). Pesser reported a decrease in DASH score from 53.15 to 31.72 and CBSQ score from 75.65 to 37.40 in a 24-month follow-up in his 274 patients' prospective observational cohort study (118).

No clear predictors of surgical outcome have emerged for FRR. Altobelli found that if the patient had two risk factors of three (workers' compensation, duration of symptoms of a minimum 2 years, and at least one previous surgery), the primary success rate was significantly reduced. If the patient had all three risk factors, the primary success rate was significantly reduced (113). Goff reported that it was unlikely that employees would achieve a good outcome from their supraclavicular FRR surgery (119). Yavuzer stated that patients with less than 24 months' duration of symptoms or ulnar nerve conduction velocity values below 55 m/s had a significantly worse surgical outcome (120). He found also that the presence of a cervical rib had a significantly unfavourable effect on surgical outcome. Green stated that the presence of an anatomic abnormality had no effect on surgical results (121). He found instead that if the patient had

fixed joint abnormalities or had neurologic findings in the upper extremity, the risk of poor outcome in surgery was increased. Furthermore, any hobby or job in which the hands were used a lot, or any situation in which the patient had extensive insurance available, each predicted a bad outcome.

Lately also in use are mini-invasive techniques. George published in 2017 a small series of studies involving 10 patients who underwent totally endoscopic FRR; at follow-up, 9 of these patients had complete resolution of their main symptoms. Gharagozloo (122) made a study of robot-assisted FRR in 39 patients and found QDASH score to decrease from 60.3 preoperatively to 3.5 at six months. Nuutinen, doing the first long-term-outcome study, found 83.3% of patients showing a good or excellent result in the transaxillary group and 77.3% in the video-assisted thoracoscopic surgery group (123). Between these groups he found no differences in patient-reported outcome measures.

2.12.4 Comparison of rib-sparing surgery and FRR

In 1995, Cheng compared the results of rib resection (supraclavicular anterior and middle scalenectomy and first rib resection) with rib-sparing (supraclavicular anterior and middle scalenectomy alone) operations (17). He found no difference between these groups in long-term results (69% and 76% at two years). His only significant observation was that patients with symptoms for less than two years had a more successful result.

In 2014, Povlsen updated a Cochrane systematic review published in 2010 (79). He found three randomized controlled trials, but only two of them had a follow up of six months or more. He found very low-quality evidence that transaxillary FRR reduced pain more than did supraclavicular neuroplasty, but found no randomized evidence that either is better than no treatment.

Yin, in a systematic review in 2019 (109), found that scalenotomy had a high probability of success, at a rate greater than 80%; transaxillary and supraclavicular FRR had high probabilities of a success rate greater than 70% but only low probabilities of a success rate greater than 80%. The mean success rate found was 76% for transaxillary FRR, 77% for supraclavicular FRR, and 85% for scalenotomy. He found a complication rate for transaxillary FRR of 22.5%, for supraclavicular FRR of 25.9%, and for scalenotomy of 12.6%, so scalenotomy seemed to be associated with the least risks from surgery. The most frequently reported complications were pleural injury, pneumothorax, and temporary neurological injury.

Blondin made a meta-analysis in 2023 (124); he found that the mean difference between preoperative and postoperative DASH score significantly differed when comparing rib-sparing scalenectomy (43.0), transaxillary FRR

(26.8), and supraclavicular FRR (21.8). Scalenotomy had a better success rate, being 97.4% based on Derkash score compared to supraclavicular FRR (93.2%) and transaxillary FRR (87.9%). The mean differences in DASH scores and Derkash scores were therefore significantly better for scalenotomy. Transaxillary FRR had the highest complication rate: 14.5%, compared to supraclavicular FRR at 8.7% and scalenotomy at 3.6%.

3 AIMS OF THE PRESENT STUDY

The aims of the present study were:

I to summarize and compare the long-term outcomes of rib-sparing surgery for NTOS

II to report clinical long-term outcome and detect factors predicting responsiveness to surgical treatment for NTOS without rib resection

III to examine whether some items adopted from validated QoL scales could be suitable for patients with TOS, and to create a novel TOS-specific QoL scale

IV to assess the convergent validity of the Thoracic Outlet Syndrome Index (TOSI) when compared with QuickDASH, CBSQ, and pain numeric rating scales after supraclavicular rib-sparing decompression for NTOS

4 PATIENTS AND METHODS

4.1 Systematic review and meta-analysis (Study I)

To discover the earlier results concerning scalenotomy for NTOS patients, we performed a systematic review and meta-analysis. This study was registered on PROSPERO (CRD42015026255) and created in accordance with the PRISMA guidelines for reporting systematic reviews and meta-analyses (125). The Pubmed, EMBASE, Web of Science, Scopus, Central, and the references were reviewed for English-, Swedish-, or German-language human studies published between the inception of the databases and October 2022. Also "related articles" functions in PubMed and reference lists of retrieved articles served to identify articles not found in the original search.

Our inclusion criteria were these five: (1) rib-sparing supraclavicular scalenotomy; (2) studies in the English, Swedish, or German language; (3) studies with postoperatively described subjective and possibly objective outcomes; (4) sample size at least 10 patients; and (5) average follow-up duration of (at least) ≥1 years. Exclusion criteria were: (1) no full text available; (2) paediatric research; (3) research concerning rib resection or endoscopic-assisted surgery; and (4) studies performed on nonhumans or cadaveric specimens. If the study concerned both scalenotomy and first-rib resection, the separate data of the outcomes were required.

Each abstract was independently assessed by two authors. Analysis covered each full text. Any differences of opinion arising were resolved through discussion with the third author. We excluded some articles from the meta-analysis if the results were described ambiguously, or if it was unclear what percentage of patients were cured. For a flowchart of the study, see Figure 2. Of the 1354 studies, 18 that we identified through database searching we included in the systematic review. A total of 14 studies met the eligibility criteria for meta-analysis.

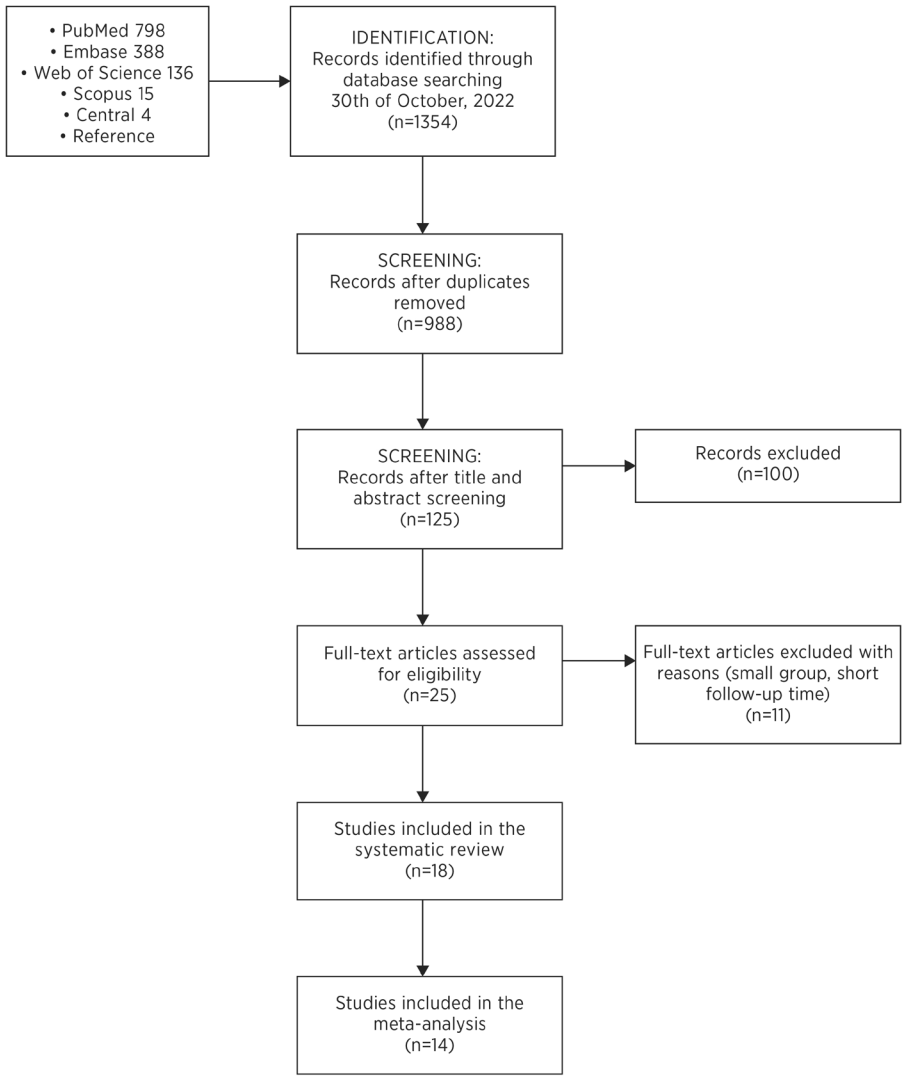

Figure 2. Study I flowchart.

4.2 Long-term outcome of NTOS (Study II)

Study II involved retrospective research on patients with surgically treated NTOS, excluding patients with ATOS and VTOS. All the patients were operated on by one individual surgeon. Fewer than 10 patients had severe consistent paleness in Roos' test. These were referred to thoracic surgeons and were also excluded from our series.

A total of 210 scalenotomies was operated in our facility between 1997 and 2011, with 94 (47%) of these patients agreeing to take part in our study. Of the remaining patients, we contacted 47 by phone. Five patients (5.3%) had a later rib resection because of residual symptoms. A flowchart concerning patient selection is Figure 3. Our final study group comprised 89 patients, of whom 83% were female, and overall age was a mean 48.5 years.

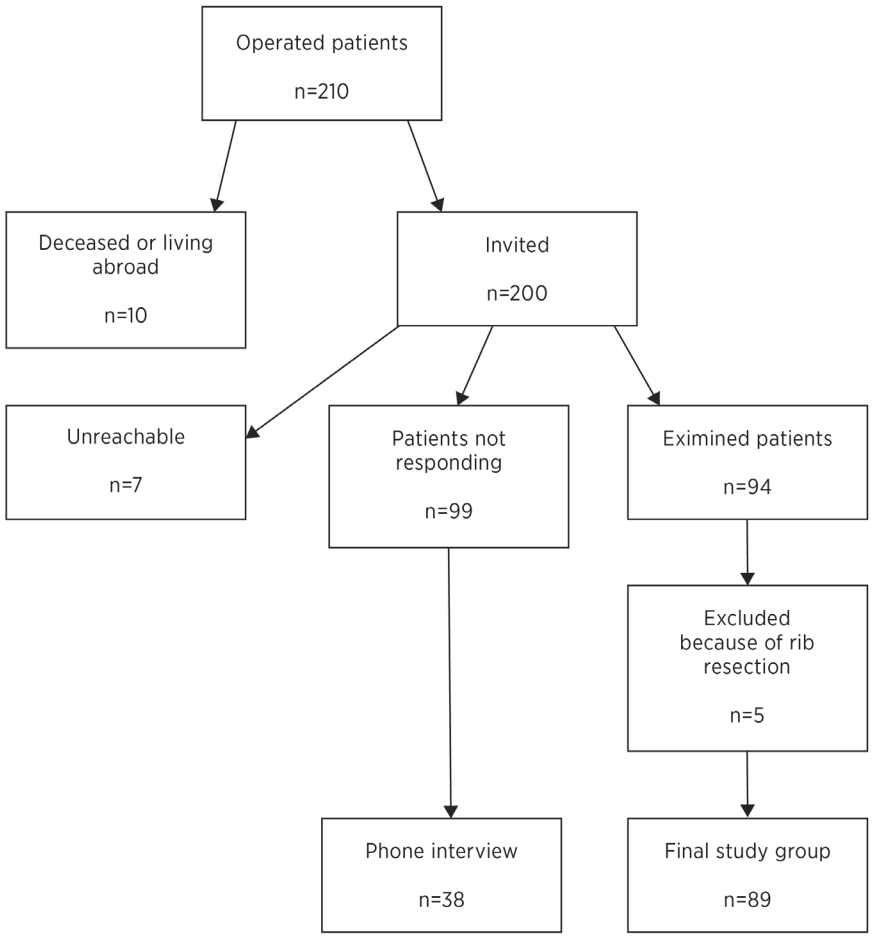

Figure 3. Study II flowchart.

Medical records of all the patients were carefully reviewed, including the reports of physiotherapy. Each patient had undergone adequate examinations, including electrophysiologic tests and imaging examinations, to rule out other diseases. All surgical reports were analysed in detail. The diagnosis of NTOS was set according to the principles described by Sanders (44), and scalenotomy

was also by a technique described by Sanders (65). Of our 89 patients, 13 (15 %) had a bilateral sequential operation.

Mean follow-up was 12.9 years. All patients underwent a clinical postoperative examination, in which they completed the QuickDASH and the CBSQ questionnaires and the 11-point numeric rating scale (NRS) for pain. They also completed a study questionnaire. Patients underwent the Roos and Adson tests; grip- and key-pinch strength were measured. In addition, supraclavicular tenderness- and compression tests of the brachial plexus and Tinel sign were performed.

4.3 Thoracic outlet syndrome index (TOSI) (Study III)

Our third study was a cross-sectional survey-based study in patients with NTOS. It consisted of three phases according to Kirkley (126). At first, we made a literature search to identify which already-existing, disease-specific questionnaires could be related to the TOS Quality of Life Survey. We explored three validated upper-extremity scales: the WORC index, QuickDASH, and CBSQ, without any symptom diagram. We ended with 19 items possibly relevant for assessing QoL in TOS patients.

The first author suggested 14 items among those above for a new thoracic outlet syndrome index (TOSI) scale and received the approval of other panelists with the addition of three items from the three aforementioned scales. Two more items we added of our own choice outside these scales. The final group consisted of 19 items, with 9 extracted from the WORC index (items 1, 3, 7, 9-13, and 15), 7 from the QuickDASH questionnaire (1, 2, 7, 8, 11, 14, and 19), and 5 from the CBSQ (6, 9, and 16-18). Some items came from two or three of these scales.

Secondly, we interviewed 14 health-care providers familiar with treatment of TOS (11 specialists in hand surgery, vascular surgery, or physical and rehabilitation medicine and 3 physiotherapists) to discover their opinions on important items for inclusion. Each of these experts had treated many NTOS patients (median, 115 patients) and worked with them for a lengthy period (median, 30 years). Our expert panel independently evaluated all 19 items. Their estimations of the validity were by a 4-point scale: 1 point, not relevant; 2, somewhat relevant; 3, quite relevant; and 4, highly relevant.

Thirdly, we interviewed patients with NTOS by selecting 52 patients from the same patient group as in Study II. These patients evaluated the relevance of the 19 items chosen by the expert panel. The patient survey used an 11-point numerical rating scale, with 0 points denoting not relevant at all, and 10 points denoting highly relevant for TOS.

4.4 Convergent validity of TOSI (Study IV)

In Study IV, we wanted to test how well TOSI measures TOS patients' quality of life and to compare the results it gives compared with other quality-of-life-indicators. We collected cross-sectional data from 67 consecutive patients, taken in part from Study II. The patients filled out questionnaires containing the TOSI, the CBSQ, the QDASH, and the pain NRS. We compared the total scores of TOSI, QDASH, CBSQ, and painNRS by using the Spearman correlation coefficient with the Bonferroni correction for multiple correlations. We considered a correlation according to Lawshe ≥0.70 be very strong, 0.40 to 0.69 to be strong, 0.30 to 0.39 to be moderate, 0.20 to 0.29 weak, and 0.01 to 0.19 as being no correlation or a negligible one. (127). These estimates were accompanied by 95% confidence intervals (95% CIs).

4.5 Statistical analysis

In Study I, the MetaXL version 5.3 (EpiGear International Pty Ltd., Queensland, QLD, Australia) served for meta-analysis, and the SAS System for Windows version 9.4 for metaregression (SAS Institute Inc., Cary, NC, USA). If substantial heterogeneity (I2 > 50%) was observable, meta-regression served to test the moderating effect of sex, age, and disease duration. The risk of publication bias we also examined using funnel plots and Egger's test for asymmetry.

In Study II, SPSS® statistics version 26.0 (IBM Corp. Released 2019, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA) served for statistical analysis. The paired sample t-test served for testing each patient´s subjective outcome before the operation and during the follow-up. Logistic regression explained the correlations between pre-and intraoperative outcomes. One-way ANOVA was determined between variables. All data we considered statistically significant at $p < 0.05$.

In Study III, the content validity ratio (CVR) for individual scale items we calculated, and the cutoff point for an excellent CVR we set at 0.78 or greater (Lawshe 1975). The content validity index (CVI) was also calculated for each scale item. Values of I-CVI of ≥0.78 and S-CVI ≥ 0.90 we considered excellent, and κm was calculated and value < 0.40 considered poor; ≥ 0.40, fair; ≥ 0.60 good; and > 0.74, excellent.

In Study IV, the Spearman correlation coefficient with the Bonferroni correction for multiple correlations was used. A correlation of ≥0.70 we considered very strong, 0.40 to 0.69 strong, 0.30 to 0.39 moderate, 0.20 to 0.29 weak, and 0.01 to 0.19 as none or a negligible correlation (127). The estimates

were accompanied by 95% confidence intervals. Stata/IC Statistical Software version 16 served for analysis.

4.6 Ethical aspects

The patients included in Studies II, III, and IV provided their written informed consent for the study. The Helsinki University Hospital ethics committee and the institutional review board approved all the studies (approval number 1755/2017). No personal data was published in any of the studies.

5 RESULTS

5.1 Results of systematic review and meta-analysis (Study I)

Our systematic review search yielded 1354 articles. A total of 18 studies met the eligibility criteria (14, 16-19, 24, 63-65, 67, 104-108, 128-130), and we identified the number of patients, follow-up time and method, gender, outcome measures, quantitative outcome scores, patient's subjective opinion, complications, and results. The number of patients in each study ranged from 11 to 179, and approximately 80% were female. The mean age of these patients at surgery was 35.8 years.

All the studies reported long-term outcomes. No randomized research concerned scalenotomy. The mean follow-up time in months was 48.7 months, and mean sample size of the studies included 58 patients. Outcomes were many and differing, with pain and numbness reported in most of them. The patient's own self-assessed outcome was reported in almost all studies (16-19, 24, 63-65, 104-107, 128-130), and this allowed for a meta-analysis in each. A summary of the studies makes up Tables 1 and 2.

Table 1. Articles included in the systematic review.

Article	First author	Year of publication	Journal
The scalenius anticus syndrome and the results of its operative treatment	Ahonen	1962	Ann Chir Et Gyn Fenn
Exercise-induced scalenus syndrome	Baltopoulos	2008	Am J Sports Med
Outcome following surgery for thoracic outlet syndrome	Bhattacharya	2003	Eur J Vasc Endovasc Surg
Neurogenic thoracic outlet decompression: rationale for sparing the first rib	Cheng	1995	Cardiovasc Surg
Surgical outcomes of thoracic outlet syndrome in young adults: single centre experience with minimum three-year follow-up	Ciampi	2011	Int Orthop
The results of supraclavicular brachial plexus neurolysis (without first rib resection) in management of post-traumatic ''thoracic outlet syndrome''	Dellon	1993	J Reconstruct Microsurg

Supraclavicular scalenectomy for thoracic outlet syndrome—functional outcomes assessed using the DASH scoring system	Glynn	2012	Vasc Endovascular Surg
Long-term results of primary scalenotomy in the treatment of thoracic outlet syndrome	Gockel	1994	J Hand Surg Br
Thoracic outlet syndrome: evaluation of clinical features and long-term outcomes after scalenotomy	Jasinskas	2017	Eur J Plast Surg
Effect of scalenotomy in the so-called scalenus anticus syndrome	Kallio	1964	Acta Orthop Scand
Intermediate and long-term outcomes following surgical decompression of neurogenic thoracic outlet syndrome in an adolescent patient population	Ransom	2022	Hand
Neurogenic thoracic outlet syndrome with supraclavicular release: long-term outcome without rib resection	Ruopsa	2021	Diagnostics
Scalenectomy versus first rib resection for treatment of the thoracic outlet syndrome	Sanders	1979	Surgery
The treatment of thoracic outlet syndrome: a comparison of different operations	Sanders	1989	J Vasc Surg
Results of the surgical treatment for thoracic outlet syndrome	Sanders	1996	Semin Thorac Cardiovasc Surg
Scalenotomy in patients with and without cervical ribs: analysis of surgical results	Shenkin	1963	Arch Surg
Surgical treatment of thoracic outlet syndrome: a randomized trial comparing two operations	Sheth	2005	J Neurosurg Spine
Thoracic outlet syndrome	Woods	1978	West J Med

Most of the studies reported trauma to be a significant factor causing TOS (14, 17, 19, 24, 64, 65, 106-108). Overuse was also reported to raise the risk for TOS (14). The 4.5% of NTOS patients who had a cervical rib matches the figures given by Sanders (64). Operative findings were reported in six studies (14, 17-19, 63, 130) including, for instance, hypertrophy of the scalenus anticus muscle, anterior and middle scalene anomalies, and a long C7 transverse process and abnormal first rib. Scarring of the brachial plexus, lower trunk, and the C8 and T1 roots also occurred.

Quantitative validated outcome scores used were VAS (14), SANE (14), QuickDASH (14, 67, 130), CBSQ (14, 130), NRS (130), and the NTOS index (14), with 14 using no quantitative validated outcome scores. Patients' subjective

opinion and satisfaction was clarified in 15 reports, with the life-table method used by three (24, 64, 65).

Factors affecting the outcome we studied in four articles (17, 65, 67, 130). The duration of symptoms before the operation seemed to affect the outcome so that patients with symptoms of less than two years showed a better result (17). After supraclavicular scalenotomy, a scalene-muscle block seemed to be an important factor determining clinical outcome, with a good response to scalenotomy occurring in 80% of those patients who had good responses to a scalene muscle block (24). A significant improvement was apparent in postoperative versus in preoperative DASH scoring for those patients without a history of trauma, and postoperative DASH scores were significantly better than the preoperative scores for those who did not smoke (67). Patients with work-related TOS seemed to have poorer post-operative results (65).

Return to work was estimated in four studies (17, 106, 108, 130). The retirement frequency increased from 6% to 33% during follow-up and was highest among factory workers, according to Gockel (106). Patients who didn't work before surgery were unlikely to start to work (108). Cheng found in his study that 63% of patients returned to work after scalenotomy (17).

Complications were reported in 11 studies (14, 16-18, 63, 64, 67, 106, 107, 128, 130). No operative mortality occurred. Reported complications were for instance intraoperative pleural injury, pneumothorax, pleural effusions/ atelectasis, long thoracic nerve injury, Horner's syndrome, lymphatic injury, and wound infection. Their occurrence ranged from 1% to 40%, but percentage of complications was overall fairly low.

Table 2. Articles including systematic analyses, with details.

First author	Number of procedures/ patients	Surgical success (excellent/ good, out of the full patient sample)	Surgical success (excellent/ good, out of the full patient sample) %	Female patients out of the full patient sample	Mean patient age at time of surgery (range)	Mean follow-up time in months (range)	Quantitative validated outcome scores
Ahonen	34/32	18	56.25%	50%	(32–65)	mean not reported (8–144)	none
Baltopoulos	12/12	12	100.00%	33%	27.9 (17–46)	36 (range not reported)	none
Bhattacharya	23/23	12	52.17%	86.96%	37 (18–57)	43 (4–102)	none
Cheng	43/43	27	62.79%	79.07%	36 (18–60)	28 months follow-up time (mean or range not reported)	none

Ciampi	20/20	15	75.00%	80.00%	29 (20–47)	54 (36-72)	none
Dellon	11/11	10	90.91%	81.82%	37.7 (26–49)	26 (range not reported)	none
Glynn	26/21	not reported	not reported	72.3%	38 (17–64)	60 (27–90)	QuickDASH
Gockel	107/107	67	62.6%	80.37%	41.9 (16–59)	49 (24–132)	none
Jasinskas	100/77	63	81.82%	79.22%	39.9 (18–90)	50.3 (26–89)	none
Kallio	51/51	35	68.63%	47%	not reported	not reported (12–108)	none
Ransom	61/54	not reported	not reported	77.7%	17.2 (13–21)	69.5 (24–180)	VAS, SANE, QuickDASH, CBSQ, NTOS index
Ruopsa	82/82	61	74.39%	83.15%	48.5	155(range not reported)	QuickDASH, CBSQ, NRS
Sanders	179/179	123	68.72%	73.74%	37.5	mean not reported (3–60)	none
Sanders	77/77	71	92.21%	71.43%	34 (16–84)	mean not reported (3–180)	none
Sanders	124/124	81	65.32%	not reported	not reported	mean not reported (120–180)	none
Shenkin	17/17	9	52.94%	88.24%	35 (25–51)	mean not reported (36–156)	none
Sheth	25/25	not reported	not reported	85%	37 (18–58)	37 (3–138)	VAS, active scale score
Woods	90/90	67	74.44%	71.11%	not reported	4 (4–84)	none

Patient's reported outcome excellent/good was reported in 15 studies (16-19, 24, 63-65, 104-107, 128-130), and it was the only variable among the studies that could serve for meta-analyses. One article concerned only young athletes' NTOS and was excluded from meta-analysis because those patients we considered to represent only a limited group (63). Three articles we excluded because they lacked the same conversion variable (14, 67, 108). Pooled estimate for success of operation was 70.6% (95% CI 64.4% to 76.4%, I2=73.0%). The forest plot of relevant studies is in Figure 4.

Meta-regression served to test the moderating effect of sex, age, and disease duration. Neither sex (p=0.971), age (p=0.816), nor disease duration (p=0.560) was a statistically significant moderator, so the heterogeneity was

not explained by these factors. The funnel plot shown in Figure 5 did not suggest any publication bias (Egger regression, p=0.802). In sensitivity analysis excluding one study (Sanders and Pearce 1989), results remained similar, and no substantial heterogeneity was detectable (pooled estimate for success of operation 68.5%, 95% CI 63.8% to 72.9%, I2=46.1%).

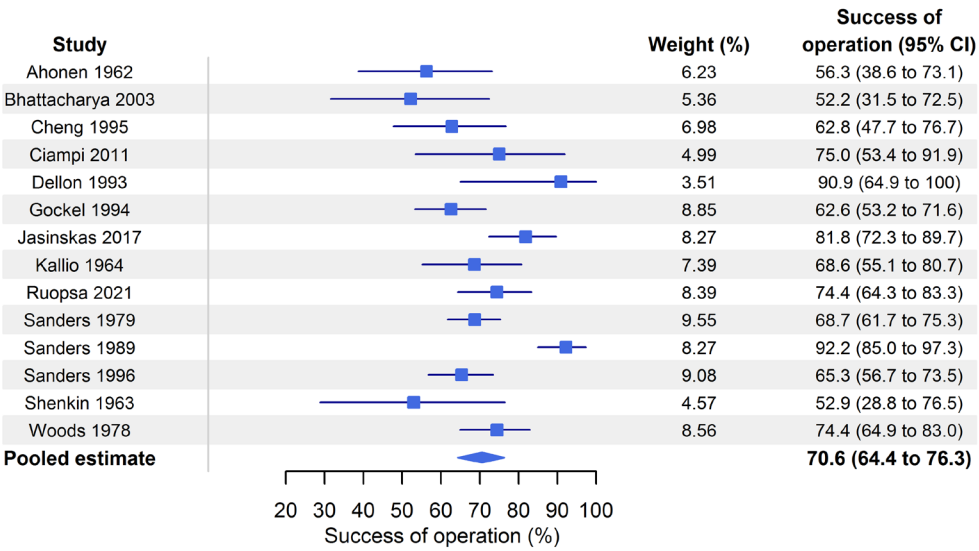

Figure 4. Forest plot of Study I.

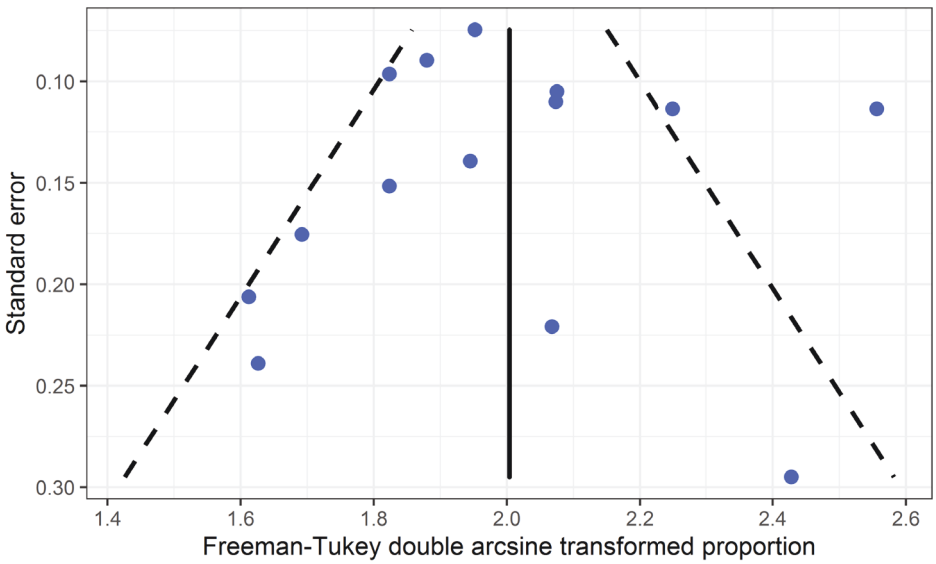

Figure 5. Funnel plot of Study I.

5.2 Results of long-term follow-up (Study II)

This Study comprised 94 NTOS patients. Five patients (5.3%) had later a rib resection due to residual symptoms. The outcome of surgery was reported as good or excellent by 87% of female patients and 57 % of male patients, and 82% of all the patients would choose the same surgery again. Scalenotomy had effects on pain, numbness, problems with working with hands in a raised position, headache, and grip strength. However, the key pinch remained unchanged. Self-reported NRS pain diminished by 3.2, numbness by 3.4, and weakness by 3.5 (each, $p < 0.001$). The results of the operation are presented in the Table 3.

Table 3. Results of the operation.

SYMPTOMS	Before operation	At follow-up	p-value
Daily pain	81%	18%	p<0.001*
Numbness of the hands during the night	57%	16%	p<0.001*
Problems working with hands in raised position	94%	34%	p<0.001*
Headache (at least once a weak)	57%	30%	p=0.021*
Grip strength, mean	26.2 kg	32.2 kg	p<0.001*

* paired sample t-test in patients, differences between before operation and during follow-up questionnaire time.

The surgery also had an impact on quality of life. NRS daily harm diminished by 4.0 ($p < 0.001$). At follow-up, CBSQ averaged 51.5 and QuickDASH 37.1. At follow-up, 79% of men and 54% of women were still working full time. Of the patients, 73% were helped by surgery very much for at least a mean 9.9 (SD 6.1) years. Men were at higher risk for worse self-reported long-term outcome (OR 4.4, 95% CI 1.4–14.2). Physician-reported complication rate was 5.6%.

We found no factors dependent on the patient that could predict the outcome of the surgery. Neither BMI, smoking, nor age at surgery was associated with long-term outcome. In addition, no explanatory or predictive factor was found among the changes observed during clinical examination or surgery. Clinical test (Roos, Adson, Tinell, or plexus compression test) did not appear to have any predictive value.

5.3 Results of the validity and internal consistency of the thoracic outlet syndrome index for patients with TOS (Study III)

Analysis of the replies of the expert panelists showed that, of the 19 items, 15 proved relevant (I-CVI ≥0.78). The content validity of the questionnaire is in Table 4.

Table 4. Content validity of questionnaire.

Item no.	Number of experts who rated item as 3 or 4 points*	Modified ϰ	I-CVR	I-CVI
1	11	0.79	0.57	0.79
2	14	1.00	1.00	1.00
3	13	0.93	0.86	0.93
4	11	0.79	0.57	0.79
5	7	0.50	0.00	0.50
6	10	0.71	0.43	0.71
7	14	1.00	1.00	1.00
8	13	0.93	0.86	0.93
9	14	1.00	1.00	1.00
10	12	0.86	0.71	0.86
11	12	0.86	0.71	0.86
12	10	0.71	0.43	0.71
13	9	0.64	0.29	0.64
14	14	1.00	1.00	1.00
15	13	0.93	0.86	0.93
16	14	1.00	1.00	1.00
17	13	0.93	0.86	0.93
18	12	0.86	0.71	0.86
19	14	1.00	1.00	1.00

I-CVI, content validity index for each scale item; I-CVR, content validity ratio for each scale item.

*Four-point scale (1 point, not relevant; 2 points, somewhat relevant; 3 points, quite relevant; 4 points, highly relevant)

Table 5 shows the final 15 questions included in the thoracic outlet index TOSI. Of those questions, 6 came from the WORC index, 5 from the QuickDASH questionnaire, 3 from the CBSQ, and one was our own question. We included

only items with a CVR value of 0.78 or greater, so the S-CVI was 0.94. In five items, CVR values were less than 0.78. We still thought that the items were considered relevant because of the excellent κ^m values (≥0.78). The S-CVI for the entire 19-item test was 0.87. After the items with I-CVI values of 0.78 or greater were retained, the S-CVI for the 15-item test was 0.93. Further analysis on internal consistency and construct validity was performed on these 15 retained items.

Table 5. The final 15 questions included in thoracic outlet index TOSI.

Pain and physical symptoms
1. How much pain do you experience in your shoulder and upper extremity?
2. How much pain do you experience in your axilla, thorax, neck, or cheek?
3. How much weakness do you experience in your upper extremity?
4. How much numbness/tingle do you experience in your upper extremity?
5. How much does your hand/upper extremity become sore and get tired when using it, especially overhead?
6. How much does your hand/upper extremity get numb or tingle when you are awakening from sleep or how much do those sensations increase when you wake up?
7. How much is your hand clumsy or weak while trying to hold onto objects or while attempting to open jars, use a key to open a lock, pull a zipper, or button clothing?
Sports and recreation
8. How much does TOS disturb you in daily activities about the house or yard?
9. How much does TOS disturb you in your recreational activities?
Work
10. How much difficulty do you experience in working above your head?
11. How much do you use your uninvolved arm to compensate for your injured one?
12. How much does TOS disturb your work in your job?
13. How much does TOS disturb your heavy household chores (washing windows, spring cleaning)?
Lifestyle
14. How much does TOS disturb your sleep?
Emotions
15. How worried or concerned are you about the effect of TOS on your occupation or work?

Face validity: All 15 remaining items judged essential by the panelists were also marked with relevancy scores over 7 points by the patients (from 0 to 10 points, in which a level of 10 points is highly relevant).

Internal consistency: The Cronbach α was excellent, 0.98, with a 1-sided 95% confidence limit of 0.97 or greater.

Construct validity: On exploratory factor analysis, only one factor had an eigenvalue greater than 1.0 (eigenvalue of 12). Parallel analysis confirmed the uni-dimensionality. After varimax rotation, the items' loadings on the 15 retaining factors ranged widely from 0.36 to 0.85.

5.4 Results of the convergent validity of the thoracic outlet syndrome index (TOSI) (Study IV)

After statistical analysis, we found that correlations between the TOSI, the QDASH, and the CBSQ were strongly positive. The correlations were mostly strong or very strong especially between individual items of all the scales. Pain severity measured by an NRS had strong correlations in the TOSI in all items. Table 6 shows the number of questions for each domain between TOSI, QDASH, and CBSQ.

Table 6. Number of questions for each domain between TOSI, QDASH, and CBSQ.

DOMAIN	TOSI	CBSQ	QDASH
Pain and physical symptoms			
Pain	3	5	1
Weakness	1	0	0
Tingling, numbness	2	5	1
Clumsiness	1	1	0
Swelling	0	1	0
Sports and recreation	**2**	**0**	**2**
Work	**4**	**0**	**2**

TOSI = Thoracic Outlet Syndrome Index, QDASH = Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire, CBSQ= Cervical Brachial Symptom Questionnaire

Correlations between the CBSQ and the TOSI were slightly more common than for the QDASH vs. the TOSI. All the items showed some positive and significant correlations with at least two items of the CBSQ. For the QDASH, the score of each item was also positively and significantly interconnected with several items of the TOSI. QDASH item #1 was the only one that showed no connection to any TOSI items. TOSI item #2 was correlated with a single item of the QDASH. TOSI items #6 and #15 had no correlation with any of the QDASH items. The total score of TOSI correlated positively and mostly strongly with both the QDASH and the CBSQ total scores.

6 DISCUSSION

6.1 Long-term outcomes of scalenotomy in the treatment of NTOS (Studies I & II)

One purpose of this overall study was to discover the long-term outcomes of scalenotomy. The literature shows no consensus on what constitutes the definition of short-term and long-term studies. In our systematic review and meta-analysis, we defined a long-term study as a follow-up period of at least one year. In Study II, the mean follow-up was 12.9 years.

Based on systematic analyses, there exist no randomized control trials concerning scalenotomies. Overall, the number of large-scale long-term follow-up studies is limited. We found only 18 studies (14, 16-19, 24, 63-65, 67, 104-108, 128-130) that met our inclusion criteria. It was possible only to conduct a meta-analysis on patient-reported outcomes. Previous NTOS meta-analyses have studied both scalenotomies and rib-resections and compared their results with each other.

Peek's systematic review and meta-analysis examined ATOS, VTOS, and NTOS in his study that included 12 papers (131). This found that QDASH scores improved by 28.3 points after treatment of NTOS surgically. The Yin (109) systematic review included NTOS patients with transaxillary first-rib resection, supraclavicular first-rib resection with scalenectomy, and scalenotomy. It revealed that scalenotomy has a high probability of a success rate greater than 80%. Lingyun (132) reported a meta-analysis of NTOS including ten studies, and patients had either sclerotomy or transaxillary first-rib resection. Their meta-analysis showed that scalenotomy is better in improving Derkash's classification in the long term. The excellent and good rate of scalenotomy was 1.34 times as great as the rate of first-rib resection. Blondin's meta-analysis (124) included five studies on scalenotomy and showed that DASH gave significantly different results when comparing scalenotomy (43.0), transaxillary first-rib resection (26.8), and supraclavicular first-rib resection (21.8).

We found in meta-analysis that the pooled estimate for operation success after scalenotomy was 71% (95% CI 64.4% to 76.4%, I2 = 73.0%). Nuutinen reported a good or excellent outcome in 83.3% of patients in the transaxillary group and 77.3% in the video-assisted thoracoscopic first-rib-resection group (123).

Our complication rate was 5/89 (5,6%), at the same level as in previous studies on scalenotomy (14, 18). Based on meta-analyses, the number of complications has been lower in scalenotomies than in rib-removal surgeries.

Blondin (124) reported complication rates of 8.7% for supraclavicular first rib resection, 14.5% for transaxillary first rib resection, and 3.6% for scalenotomy. Yin (109) reported complication rates depending on the surgical technique thus: transaxillary first rib resection 22,5%, supraclavicular first rib resection with scalenectomy 25,9%, and supraclavicular release leaving the first rib intact 12,6%.

We found no predicting factors that would aid in finding those patients who will benefit from surgery. Glynn (67) reported that non-smokers had better postoperative DASH scores than did those who smoked, but we found no differences between smokers and non-smokers. Cheng (17) found that those patients whose symptom-duration was less than two years had better operation success, but we found no consistency between symptom-duration and surgical outcome. Ohman (133) found that patient's BMI had no influence on the outcome of surgery, a conclusion that our research supported. Nor did we discover any intraoperative findings that could predict the final result.

Our Study II revealed that, after scalenotomy, pain, numbness, weakness, and daily harm significantly decreased. According to systematic analyses, meta-analyses, and our study, scalenotomy provides to the majority of patients good or excellent results.

6.2 Measuring the quality of life in NTOS patients (Studies II, III, & IV)

Measuring the change in quality of life in patients undergoing surgery is one good way to explore the benefits of surgery. No TOS-specific QoL index has existed before now. NTOS studies have used QuickDASH (14, 67, 134, 135), DASH (136, 137), Short-Form 12 (SF-12) (66, 136-138), CBSQ (14, 66, 70, 134), or the Brief Pain Inventory (BPI) (66) for measuring QoL. All these indicators have, however, been developed for other diseases.

We developed TOSI, a QoL index especially for NTOS patients, which is a 15-item questionnaire that measures pain, work, lifestyle, physical symptoms, emotions, and sports. It contains some items common also to QDASH, the WORC index, and CBSQ, and one totally new question. Although they are the most commonly used QoL indexes, neither QDASH nor CBSQ measures loss of strength, unlike TOSI. QDASH and CBSQ do not include questions about emotions, but TOSI has one such question. TOSI, CBSQ, and QDASH all include questions about tingling and numbness, but the number of such questions varies. Unlike the other two, CBSQ has no questions concerning functioning. TOSI has four question concerning working, which is more than in other metrics.

By developing a disease-specific indicator, we will gain better information specifically on the impact of TOS-caused symptoms on patients' quality of life. If only a single metric is used in a study, the comparability of its results improves.

In Study IV, we found the TOSI scale internally consistent as well as face- and content-valid for NTOS patients. When we compared it to pain intensity as measured by NRS, it also again showed strong correlations, which also indicates that pain is the main symptom of NTOS. We found TOSI to be able to find the following symptoms better than did either CBSQ or QDASH: tingling or numbness, and pain in axilla, thorax, neck, or cheek, and in upper extremity. Those symptoms are typical for NTOS, so it is important that the score is able to indicate them. We also found that TOSI could replace the CBSQ. However, QDASH still provided additional information on NTOS patients.

6.3 Effects of scalenotomy on Quality of Life in NTOS patients (Studies I & II)

We had no preoperative figures for QoL in our Study II. Postoperative QuickDASH was 31 for men and 39 for women, $p<0.326$. Glynn (67) found median QuickDASH 68,5 preoperatively and 36 postoperatively. Ransom (14) reported postoperatively a QuickDASH score of 11,4. Balderman (111) compared QuickDASH after physiotherapy and after supraclavicular decompression with or without pectoralis minor tenotomy. He reported the mean change in QuickDASH scores for physical therapy as being -15.6 ± 3.0 compared with -29.8 ± 2.4 for surgery ($p=0.001$).

Postoperative CBSQ was 52 in our study for men and 51 for women, $p<0.927$, the same level as Caputo reported (68). Ransom (14) had a CBSQ score of 27,4 postoperatively. In Ransom's study, the patients were between the ages of 13 and 21 years, which may affect the results. Johansen found a 90.9% success rate in rib-sparing scalenotomy and pectoralis minor discision (139). In that study, the mean preoperative QuickDASH score of 62.6 dropped to 25.2 postoperatively. Nuutinen reported a CBSQ score of 26,7 and DASH 21.1 in a long-term outcome study of FRR patients (140).

6.4 Limitations of the study

Our research does have several limitations. Our systematic review contained no randomized controlled trial studies, because no such TOS studies were found. Only 18 studies met our criteria, and only 3 had a population of more than 100 patients, which indicates that further studies are needed, with a sufficiently

large number of patients. The quality of some studies was poor or moderate, and objective data was difficult to find from some studies. Quantitative validated outcome scores had only been used in a few studies (14, 67, 108, 130). It is obvious that the available data on long-term outcomes are few, with a high risk of bias. Due to lack of objective data, no meta-analyses seem to exist that involve long-term outcomes. Moreover, we were only able to perform a meta-analysis of one variable.

Our own research on long-term outcomes was a retrospective follow-up without any control group. We had a large drop-out; we could perform a clinical examination only for 47% of the patients. For the others, we had to settle for a telephone interview. No validated scores were used preoperatively, so we could not compare postoperative results with preoperative ones, and in terms of QoL results, research remains incomplete. We had to exclude five patients who later had a rib resection. It would have been important to know their clinical condition before another operation. We were aiming for a long follow-up period. However, it brought with it issues. Patients had problems in remembering their preoperative symptoms, and on the other hand, at the follow-up, they had difficulty distinguishing which of the current symptoms were caused by TOS.

To find a large enough number of patients with NTOS for Study III, we collected the patients from Study II datasets. However, more than 80% of these patients were women, and at the time of Study III, the mean age of all patients was 48.5 years. Distribution of age and gender of the patients may distort any correlations with populations. In theory, there may be differences in the behaviour of TOSI between different nationalities and in other patient groups.

6.5 Strengths of the study

We maintained strict inclusion criteria in the systematic analysis. This allowed us to find enough heterogeneity between studies, which allowed us to conduct a meta-analysis of the results of scalenotomy, to our knowledge, for the very first time. In Study II, all the patients were examined clinically. Our research group was large, and the follow-up time was long, if we compare both with those of other international studies.

In Study III, we were able to create a new index TOSI, the Thoracic Outlet Syndrome Index. We believe that it is important to have one's own disease-specific quality-of-life index for NTOS. In the future, this could be the only form used to study QoL in patients with TOS.

In Study IV, we were able to show that the TOSI demonstrated good convergent validity. This should encourage further research into the use of TOSI.

6.6 Recommendations and future perspectives

NTOS causes pain, lowers work ability, and reduces quality of life. No clear international treatment policy exists for NTOS on its best method of operative care. Our systematic literature review and meta-analysis show that rib-sparing scalenotomy is effective in NTOS treatment. Our research on the long-term outcomes of scalenotomy surgery supports this. However, high-quality and multicentred, randomized controlled research is essential to confirm these findings.

TOSI is the first TOS-related QoL index. In future we recommend testing the psychometric properties of the TOSI, including its reliability in different populations. Moreover, TOSI's behaviour before and after conservative treatment and in the context of various surgical techniques needs examination. The Rasch analysis and item response could also prove useful in testing TOSI (141).

7 CONCLUSIONS

1. According to Derkash's excellent/good classification in treatment of NTOS patients, scalenotomy achieved the level of 71%. Pain, weakness, numbness, and daily harm decreased significantly. Our surgical results were similar to those of the other surgeries included in the systematic review.

2. No preoperative or intraoperative factors that could predict the outcome of surgery emerged from our retrospective research. Patients who would choose the same surgery again amounted to 82%.

3. We created a new quality of life index, the Thoracic Outlet Syndrome Index (TOSI), developed specifically for NTOS patients to measure their QoL and functional level.

4. The new TOSI scale showed, in our study, good face- and content validity. In the future, it may be possible to use only TOSI to explore TOS patients' QoL. Further research is necessary to determine the usefulness of the TOSI scale in different patient groups, including pre-operative studies.

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**The article was included in the systematic review and meta-analysis.*

APPENDICES

Appendix 1. Thoracic Outlet Syndrome Index (TOSI) Questionnaire

TOSI Quality of Life Questionnaire (**T**horacic **O**utlet **S**yndrome **I**ndex 24/11/2019)

Date _____ ID _____

TOS Patient Last Name _____ First Name _____

We use a new validated 15-item questionnaire to determine the quality of life of a TOS patient before and after TOS surgery or before and after conservative treatment of TOS (physiotherapy etc.).

Side □ right □ left

The following questions concern the average discomfort/limitations you have experienced due to your thoracic outlet syndrome (TOS). In all cases, please enter the average degree of severity of the symptoms you have experienced in the **last week**. (Please mark your answers with an "X")

Pain and physical symptoms

1. How much pain do you experience in your shoulder and upper extremity?
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10
No pain Extreme pain

2. How much pain do you experience in your axilla, thorax, neck, or cheek?
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10
No pain Extreme pain

3. How much weakness do you experience in your upper extremity?
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10
No weakness Extreme weakness

4. How much numbness/tingle do you experience in your upper extremity?
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10
No numbness/tingle Extreme numbness/tingle

5. How much does your hand/upper extremity become sore and get tired when using it, especially overhead?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all sore/tired Extremely

6. How much does your hand/upper extremity get numb or tingle when you are awakening from sleep or how much do those sensations increase when you wake up?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all numb/tingle Extremely

7. How much is your hand clumsy or weak while trying to hold onto objects or while attempting to open jars, use a key to open a lock, pull a zipper, or button clothing?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all clumsy/weak Extremely

Sports and recreation

8. How much does TOS disturb you in daily activities about the house or yard?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Constantly

9. How much does TOS disturb you in your recreational activities?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Constantly

Work

10. How much difficulty do you experience in working above your head?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

No difficulty Extreme difficulty

11. How much do you use your uninvolved arm to compensate for your injured one?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Constantly

12. How much does TOS disturb your work in your job?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Constantly

13. How much does TOS disturb your heavy household chores (washing windows, spring cleaning)?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Constantly

Lifestyle

14. How much does TOS disturb your sleep?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Extremely much

Emotions

15. How worried or concerned are you about the effect of TOS on your occupation or work?

□ 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

Not at all Extremely worried/concerned