Diplomarbeit

Ultrasound in Carpal Tunnel Syndrome

Predictive value of baseline B-Mode and Power Doppler assessment for long-term functional outcome

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Graz, am 10.04.2015 *Alexander Marschall eh.*

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Zusammenfassung

Hintergrund: Das Karpaltunnelsyndrom (CTS) ist das häufigste Kompressionssyndrom peripherer Nerven und wird durch eine Schädigung des Nervus medianus durch Kompression in seinem Verlauf durch den Karpalkanal hervorgerufen. Der diagnostische Wert des Ultraschalls im Sinne der Vermessung der Querschnittsfläche des N. medianus (CSA) wurde bereits bestätigt. Sein Vorhersagewert war bisher jedoch Thema von nur wenigen früheren Studien mit widersprüchlichen Ergebnissen.

Zielsetzung: Es handelt sich um das Langzeit Follow-up einer Studie über den diagnostischen Wert von Ultraschall für CTS. Zweck dieses Follow-ups ist es, den prognostischen Wert des Baseline B-Mode und Power Doppler (PD) Ultraschalls bezüglich des funktionellen Langzeit Outcomes von CTS Patienten zu evaluieren.

Methoden: Prospektive Studie an 27 Patienten mit bestätigtem CTS, die sich sowohl einer ambulanten Baseline Visite, als auch zweier Kontrollen unterzogen. Dabei erfolgte die erste Kontrolle (short-term follow-up) nach einem Mittel von 3 Monaten und die zweite Kontrolle (long-term follow-up) nach einem Mittel von 26.8 Monaten. Bei jeder Visite wurden eine klinische, elektrophysiologische und sonografische Untersuchung durchgeführt. Der CSA des N. medianus wurde mithilfe eines Logiq E9 Ultraschall Gerätes an den folgenden anatomischen Landmarken des Arms und Handgelenks vermessen: (1) proximaler Rand des M. pronator quadratus (CsP) (2) Proximales Drittel des M. pronator quadratus (CsT) (3) Im Karpalkanal, auf Höhe des Tuberculum ossis scaphoidei und des os pisiforme (CsS). Die PD Signale wurden semiquantitativ von 0-3 graduiert. Das Outcome wurde anhand der klinischen Verbesserung der Patienten evaluiert, basierend auf (1) dem DASH-Fragebogen, (2) einer visuellen Analogskala, welche die Schwere von Schmerzsymptomen erfasst (painVAS) (3) einer visuellen Analogskala, welche die Schwere des klinischen Zustandes aus Sicht des Untersuchers erfasst (physVAS). Der prädiktive Wert des Ultraschalls wurde anhand multivariater binär logistischer Regressionsmodelle bestimmt, welche neben der in Frage stehenden Variablen (CSA und PD), die Parameter Alter, Geschlecht, BMI und Symptomdauer als unabhängige Variablen miteinbezogen.

Ergebnisse: Jeweils 42.2% und 33.3% der CTS Patienten zeigten eine mindestens 20% und 70% Verbesserung des painVAS, jeweils 53.3% und 42.2% präsentierten eine Verbesserung bezüglich des physVAS und jeweils 37.8% und 15.6% zeigten eine Verbesserung des DASH von Baseline zum Langzeit Follow-up. Patienten, die keine klinische Verbesserung zeigten, wiesen einen größeren CsS, CsS/CsP und CsS/CsT auf als jene, die sich klinisch verbesserten. In allen Regressionsmodellen, die sich auf eine Verbesserung von mindestens 20% beziehen, präsentierte sich CsS/CsP als signifikanter Prädiktor (OR: 0.000 – 0.012, $p < 0.05$). In Modellen, die eine Verbesserung von mindestens 70% vorhersagen, war CsS/CsP signifikant für painVAS und erreichte beinahe Signifikanz für physVAS und DASH ($p=0.069$ und $p=0.076$, respektive). Wir fanden ähnliche Resultate für CsS/CsT (signifikant in allen Regressionsmodellen, die sich auf eine Verbesserung von mindestens 20% bezogen) und CsS (signifikant in Modellen, die eine Verbesserung von mindestens 20% des painVAS und DASH und eine Verbesserung von mindestens 70% des painVAS vorhersagen). Das Ergebnis des PD Scores war bezüglich des klinischen Outcomes ohne prädiktiven Wert.

Schlussfolgerung: Ein größerer Baseline CSA sagt ein schlechteres klinisches Langzeit Outcome von CTS Patienten, durch VAS und DASH bestimmt, vorher. PD Ultraschall hat keinen prädiktiven Wert im Bezug auf das Outcome von CTS.

Abstract

Background: Carpal Tunnel Syndrome (CTS) is the most frequent syndrome of entrapment of peripheral nerves and is caused by an impairment of the median nerve due to compression as it passes through the Carpal Tunnel. The diagnostic value of ultrasound imaging in CTS by means of measurement of the Cross-sectional Area (CSA) of the median nerve has been established. However, reports on its prognostic value regarding the long term outcome are rare and contradictory.

Objectives: To investigate the prognostic value of baseline B-mode and Power Doppler (PD) ultrasound assessment of the median nerve in CTS patients regarding their long-term functional outcome.

Methods: Out of 136 patients with suspected CTS, we conducted a prospective study on 27 patients with confirmed CTS, who underwent baseline visit and two follow-up visits: short-term after 2.8 months, long-term after 26.8 months (mean). Clinical, neurophysiological (NCS) and sonographic evaluation was performed at each visit. Ultrasound was performed using a Logiq E9 ultrasound device with multifrequence linear transducer, measuring the CSA of the median nerve at the following anatomic levels: (1) proximal border of the Pronator quadratus muscle (CsP), (2) area of the proximal Third of the pronator quadratus muscle (CsT) and (3) in the carpal canal, level of the Scaphoid tubercle and pisiform bone (CsS). PD-signals were graded from 0-3. Clinical outcome was evaluated regarding patients clinical improvement, based on: (1) the DASH questionnaire, (2) the visual analogue scale for grading pain symptoms (painVAS), (3) the VAS for grading severity of the clinical condition, completed by the examiner (physVAS). We conducted multivariate inclusive logistic regression models (including age, gender, BMI, vascularisation and symptom duration as covariates) to determine the predictive value of CSA and PD for the binary dependent variable of outcome: improvement/no improvement of both at least 20% and 70%.

Results: 42.2% and 33.3% of the CTS patients showed improvement of at least 20% and 70%, respectively regarding painVAS from baseline to long-term follow-

up: 53.3% and 42.2% presented improvement of physVAS and 37.8% and 15.6% showed improvement of DASH. CsS, CsS/CsP and CsS/CsT were higher in patients without improvement compared to those with at least 20% or 70% improvement. CsS/CsP presented the most relevant predictive value for clinical improvement, being significant in all logistic regression models and yielding ORs of 0.000 – 0.012 ($p<0.05$) for an improvement of at least 20%. In models predicting an improvement of at least 70%, CsS/CsP showed to be significant for painVAS and almost reached significance for physVAS and DASH ($p=0.069$ and $p=0.076$ respectively). We found similar results for CsS/CsT (being significant in all regression models predicting an improvement of at least 20%) and CsS (being significant in models predicting an improvement of at least 20% of painVAS and DASH, and predicting an improvement of at least 70% of painVAS). PD scores were not linked with the clinical outcomes investigated.

Conclusions: A higher CSA at baseline predicts a worse clinical outcome of CTS patients as determined by VAS and DASH. PD examination has no predictive value regarding CTS outcomes.

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1 Introduction

1.1 Definition of the Carpal tunnel Syndrome

Carpal Tunnel Syndrome (CTS) is the most common syndrome of entrapment of peripheral nerves. It is caused by an impairment of the median nerve due to compression as it passes through the Carpal Tunnel. Diagnosis is usually based on characteristic symptoms including numbness and paresthesia of the hands during the night, and it is confirmed by nerve conduction studies (NCS). (1,2)

1.2 Relevant anatomy

In order to understand the pathophysiology, symptoms and treatment of CTS, a basic knowledge of the Carpal Tunnel anatomy is required. Furthermore, the performance of a proper ultrasound of the median nerve is based on orientation by anatomical landmarks. Thus, a discussion of the fundamental anatomy is indispensable:

At the distal forearm, the median nerve is found between the flexor digitorum superficialis and the flexor digitorum profundus muscle. As it courses distal, the median nerve moves superficially and slightly lateral to the tendons of the flexor digitorum superficialis muscle. As it reaches the Carpal Tunnel it passes between the latter muscle and the flexor carpi radialis tendon. (3)

At its dorsal aspect, the Carpal Tunnel is confined by several carpal bones. At its palmar aspect, it is bordered by the transverse carpal ligament, also known as the flexor retinaculum. At the radial side, the Carpal Tunnel is limited by the trapezium bone and the scaphoid tubercle, the landmarks for the ulnar boundary are the pisiform bone and the hook of the hamate. (4)

Within these borders, the following structures can be found: The tendons of the flexor digitorum superficialis, flexor digitorum profundus and flexor pollicis longus muscle, as well as the median nerve. (4)

The median nerve is mostly found as a single nerve within the Carpal Tunnel. However it can divide within the canal. This so called “bifid” nerve variation can be

found in 9-19% of individuals. A persistent median artery is observed in up to 11% of cases. (3,5,6)

1.3 Epidemiology

The prevalence of the characteristic symptoms of CTS, namely pain, numbness and tingling in the hands are found very often in the general population. According to a Swedish survey, these symptoms occur in 14.4% of the general population and 1 out of 5 symptomatic subjects is expected to suffer from CTS. (7) A Dutch study found a CTS prevalence of 9.2% in women and 0.6% in men. (8)
Although studies report varying results regarding the incidence of CTS (ranging from 180/100.000 to 276/100.000 person-years), there are consistent reports concerning the female: male ratio of 3:1. (9,10) The incidence of CTS peaks between the 5^{th} and 6^{th} decades and the 7^{th} and 8^{th} decades of life. (10)
The economical consequences of CTS are immense: 57% of all costs related to occupational upper-extremity disorders are caused by CTS. (11)

1.4 Etiology

The etiology of CTS is multifactorial. Systemic, anatomical and ergonomic factors could be relevant for the development of CTS. (12) Although in most cases the cause for CTS is unknown, many occupational and non-occupational risk factors could be identified as detailed below.

1.4.1 Occupational risk factors

Exposure to vibration, increased hand force and repetition represent the most significant occupational risk factors for the development of CTS. Thus, it is highly plausible that the Jobs with the highest risk of CTS include the meat- and fish-processing industry, forestry work with chain saws and electronic assembly work. (13,14) Van Rijn et al reported that CTS is associated with a requirement of > 4kg hand force and repetitiveness at work, which includes 50% of cycle time performing the same movements. (14) CTS was long considered to be associated with keyboard and computer work; however, a systematic review pointed out that

there is not enough evidence to prove this association. (15)

1.4.2 Non-occupational risk factors

Female gender is one of the most important non-occupational risk factors for CTS. The reason for this association is still unclear but it is assumed that a higher wrist-index, a higher body fat percentage in the extremities and a higher disposition in developing edema might play a role. (16)
Furthermore, diabetes mellitus, obesity and wrist circumference are additional non-occupational risk factors for CTS. (12,16,17)
Due to hormone fluctuations, fluid shifts and musculoskeletal changes, pregnant women are at a particular high risk for CTS development. Given the fact that the symptoms often improve under conservative treatment and are self-limiting after delivery, surgical treatment of CTS of pregnant women can usually be avoided. (18)

1.5 Pathogenesis

Although the detailed pathogenetic mechanism of CTS is not yet clear, it is the current understanding of the disease that mechanical factors such as injuries of or within the Carpal Tunnel play a significant role. Considering the limited space within the tunnel, increased pressure applied to the nerve may cause ischemic or direct mechanical injury of the nerve. (15,19)
Whereas in normal wrists the intra Carpal Tunnel pressure raises from 25 mmHg to 31 mm Hg during flexion and to 30 mmHg during extension, in CTS patients it increases up to 110 mmHg and 90 mmHg, respectively. This causes compression of the median nerve leading to a reduced epineural and endoneural blood flow as well as edema. In case of persistent pressure, the axonal transport and the intraneural blood flow decrease. Increased fibroblastic activity then causes fibrous scar formation in the nerve, resulting in conduction delay or even complete nerve block. (20)
The cellular damage causes an increased production of cytokines, especially interleukin-6 (IL-6). By stimulation of acute-phase proteins, IL-6 promotes cellular proliferation and angiogenesis leading to vascular proliferation and vascular

hypertrophy. (20,21)
These pathophysiological changes induce the morphological alterations of the median nerve that can be detected by sonographic evaluation.

1.6 Diagnosis

Due to its typical clinical presentation, in many cases CTS is already suspected by patient's history. This clinical presentation is characterized by numbness, pain and tingling of the hands, especially during night. With progression of the disease, symptoms also occur at daytime. Furthermore, patients may complain about clumsiness and weakness of the hands limiting everyday activities such as carrying shopping backs, uncapping jars or buttoning up a shirt. In advanced stages, a hypotrophy of the abductor pollicis brevis and opponens pollicis muscles may be observed. (2)

1.6.1 Clinical diagnosis

A systematic review found that the most frequently studied clinical test for CTS is the *Phalen's Test*, yielding an estimated 68% sensitivity and 73% specificity. (22)
The test is considered positive when symptoms can be reproduced by a full palmar flexion of the wrist with the elbow in full extension and the forearm in pronation. (23)
The *Tinel's Sign* was reported with a wide range of sensitivity (50-73%) and specificity (30-77%). The test is considered positive if paresthesia or electric shock-like sensations occur in the area supplied by the median nerve when percussion is performed over the course of the median nerve slightly proximal to the carpal tunnel. (22–24)
The *Carpal Compression Test* consists of application of direct pressure to the carpal tunnel and the underlying median nerve. It has a sensitivity of 64% and a specificity of 83%. (22,25)
Another systematic review investigating the effects of bias on the results of clinical diagnostic studies for CTS concluded that unbiased studies are scarce and that the value of confounded studies for clinical practice is limited. (26)

1.6.2 Nerve conduction studies

First mentioned by Simpson in 1956, Nerve Conduction Studies (NCS) are still the standard technique aiding the diagnosis of CTS. (27)
Demyelination of the median nerve leads to a reduced nerve conduction velocity that can be detected by NCS. Besides, we can also measure a decrease in the nerve conduction amplitude that is caused by axonal damage in advanced state of CTS. (2)
Measurement of the distal motor latency of the median nerve and its comparison to the motor latency of the ulnar nerve is also a reliable procedure for CTS diagnosis. This measurement should be performed at both sides including the course of the median nerve along the forearm. In case motor NCS findings reveal undetermined/borderline values, a sensory NCS is required. (2)
According to the American Association of Electrodiagnostic Medicine (AAEM), motor and sensory NCSs confirm CTS with a high sensitivity (>85%) and specificity (95%). (28) Therefore, NCS can be regarded as a reliable and sensitive tool in the diagnosis of CTS.

1.6.3 Sonography of the median nerve

Due to computerization, imaging techniques are evolving rapidly, with a pace that outnumbers the speed of development of electrodiagnostic methods for studying nerves and muscles. Particularly high resolution ultrasound is a promising diagnostic tool that may supplant current methods for the evaluation of nerves and muscles in the future. (29)
Ultrasound is portable, non-invasive, easy to use and has no contraindications. In contrast to NCS that is applied to investigate changes of the neurophysiological function, sonography is used to assess morphological changes of the median nerve. Considering the pathogenesis of CTS (see chapter 1.5), it is reasonable to consider the increment of the median nerve cross sectional area (CSA), the sonographic correlate of nerve swelling, as a sign of CTS. Furthermore, the Power Doppler (PD) technique can be applied for the assessment of hypervascularisation of the median nerve thus improving CTS classification. (30)
Considering the economical impact of CTS (mentioned in 1.3) and the possibility

to reduce costs by early diagnosis and treatment of CTS, the application of sonography as a first-line diagnostic test for confirmation of a clinical diagnosis of CTS may be cost-effective compared to electrodiagnostic testing as suggested by a level III economic analysis. (31)

Nevertheless, the routine implementation of sonography for CTS diagnosis is still a matter of ongoing debate. It has been argued that the diagnostic value of sonography for CTS is still unclear given that sensitivities (ranging from 65% to 97%) and specificities (73%-98%) largely differ among studies. Furthermore, there is no consensus about the threshold for the median nerve CSA defining an abnormal result and there are uncertainties about anatomical landmarks guiding median nerve measurement. (30,32)

In case secondary CTS is suspected, ultrasound is valuable to detect synovitis, tenosynovitis, calcified masses or tophaceus gout as possible space occupying lesions leading to median nerve compression. (33)

1.6.4 Magnetic resonance imaging (MRI)

Similar to the ultrasound, MRI relies on morphological changes of the median nerve for CTS diagnosis. Increased T2-signal, flattening of the median nerve and changes of the CSA are the most common abnormalities in CTS patients. A low availability, contraindications and higher costs; however, limit the routine use of MRI in the diagnosis of CTS. (34)

1.7 Therapy

Treatment of CTS is indicated in case of continuous or recurring symptoms. A pathologic finding in NCS or ultrasound alone, without a clinical correlate, is not an indication for therapy. In general, there are two therapeutic approaches that can be considered: conservative treatment and surgical intervention. (2)

The conservative management includes splinting, local or systemic application of glucocorticoids, NSAIDs, Vit. B and physiotherapy. Surgical treatment includes traditional open carpal tunnel release and minimal invasive techniques.(2)

1.7.1 Conservative management

Although non-surgical treatment is frequently offered to those patients with mild to moderate symptoms, the actual long-term effectiveness of these approaches in CTS is yet unknown. (35)

1.7.1.1 Splints

Splints are the first-line approach in mild to moderate CTS cases and are used to fix the wrist in a neutral position to prevent nerve compression due to wrist flexion during the night. The evidence for the efficacy of splints versus no treatment, however, is limited and long-term follow-up data are scarce. Therefore, we need more studies to evaluate the long-term benefit of this therapeutic approach even if splinting has already been established for CTS therapy in clinical practice. (36)

1.7.1.2 Corticosteroids

Corticosteroid treatment is effective in reducing inflammation and edema and therefore can improve symptoms of CTS patients. It should, however be mentioned that the limitation of tenocyte function, caused by corticosteroids, can lead to further degeneration of the nerve by reducing collagen and proteoglycan synthesis. (37)

A review of Marshall et al investigated the benefit of corticosteroid injections in the treatment of CTS. They found that local treatment provided greater improvement of symptoms than placebo; however, a significant benefit beyond one month was not observed. Comparing oral and local corticosteroid therapy, it was found that local injections are more effective than oral therapy. (38)

Direct comparisons between local corticosteroid injections with splinting as well as local therapy with surgery reported better results for splinting after 8 weeks and surgical decompression after 12-month of follow-up. (39)

1.7.1.3 Other non surgical approaches

There are several other non-surgical therapeutic approaches of CTS including use of NSAIDs, vitamin B, diuretics, nerve gliding exercises, yoga and local ultrasound application. For all these methods there is only limited data suggesting a short-term improvement only. (2,40)

1.7.2 Surgical intervention

Overall, surgical treatment of CTS is superior to conservative approaches regarding improvement of symptoms and function. Besides, patients that underwent surgical treatment are 2x more likely to have normal NCS results during follow-up than patients with conservative therapy. (41) Open CTR achieves good to excellent long-term results in 70-90% of CTS cases.

Surgical therapy is a common second-line strategy in patients with mild-moderate CTS not improving with conservative therapy. Besides, patients suffering from painful paresthesia or neurological deficits, progressive weakness of the hands or loss of stereoesthesia also undergo surgical release. (2) Surgical therapy may also be performed in cases with extreme CTS, as well as in pregnant patients resulting in good clinical and neurophysiological outcomes. (42,43)

Surgical intervention in CTS is based on pressure relive of the carpal tunnel, which is achieved by division of the transverse carpal ligament. Longitudinal incision technique, with a long curvilinear incision is frequently used and mostly considered as the standard procedure. However, the minimal invasive carpal tunnel release techniques provide statistically significant improvement compared to the traditional open technique. (44)

1.8 Follow-up

In order to evaluate the success of surgical and non-surgical treatment of CTS, NCS are frequently used together with the evaluation of clinical symptoms. In case of persistence or recurrence of symptoms in patients that underwent Carpal tunnel release (CTR), NCS are often requested to distinguish between CTS recurrence and a failure of surgical treatment. (45)

The value of electrophysiology for this purpose, however, is not clear:(45–47) Merolli et al for example reported in a prospective and in a retrospective study that the persistence of abnormal electrophysiological findings after CTR is common despite clinical improvement. This „electrophysiological scar“ of the median nerve limits the value of NCS for follow-up of CTS patients undergoing surgery. (45)
Other studies conclude that self-administered scales, such as the Levine's Questionnaire or the Boston Carpal Tunnel Syndrome Questionnaire reflecting patients' function and daily activities are of higher value than electrophysiological findings for the decision whether or not a revision surgery is needed. (48,49)
Given that sonography helps to detect morphological changes of the median nerve and the Carpal tunnel, this technique may be valuable for the follow-up of CTS patients, as well. A few prospective short-term (not exceeding 4 months) studies have been conducted to measure the median nerve of CTS patients by sonography before and after CTR. These studies provide the utility of the sonographic measurement of the CSA of the median nerve and suggest ultrasound as a useful assessment tool for clinicians, considering the correlation between symptom improvement and a CSA decrease after surgery. (50,51)

1.9 Prognosis

There are only few factors predicting the outcome of CTS patients. Risk factors for a worse outcome are co-morbid conditions, such as diabetes, poor health status, thoracic outlet syndrome, alcohol abuse and smoking. (52)
The predictive value of NCS has been investigated in various studies with discordant results. Large observational studies with a careful preoperative and postoperative assessment concluded that NCS is of no prognostic value regarding the outcome of CTS patients undergoing surgical treatment. (53–57) These studies, however, used a simple model dividing patients in two or three groups combining subgroups with good and poor outcome. Using a more complex model, a relation between preoperative NCS results and outcome of carpal tunnel decompression could be shown. (58)

1.10 Purpose of this research

The prognostic value of ultrasound regarding the outcome of CTS patients has rarely been studied revealing contradictory results: One study including 112 wrists found that patients with a large CSA at baseline had a better outcome after carpal tunnel surgery compared to those with a small CSA, whereas an Italian study of 67 patients concluded that a smaller CSA was linked to a higher chance of patient's satisfaction after CTR, as measured by the Boston Questionnaire. (59,60) In another study, the baseline CSA was not a significant predictor for the clinical outcome after carpal tunnel release. The lack of significance in this study, however, was attributed to the small sample size given the high number of covariates included in the logistic regression model. (61)

1.10.1 Research question

The aim of this study was to investigate the prognostic value of baseline B-mode and Power Doppler sonography of the median nerve for short (after 3 months) and long-term (>12 months) functional outcome of CTS patients.

2 Methods

2.1 Patients

This is the long-term follow-up of a study on the diagnostic value of ultrasound for CTS published previously. The methods regarding recruitment, investigational procedures and gold standard are reported elsewhere. (30) In brief, we conducted a prospective study between March 2010 and December 2011 on patients with suspected CTS undergoing a baseline and a follow-up visit after 3 months including clinical, electrophysiological and sonographic evaluation. Patients were included when presenting with at least one of the following symptoms at one or both wrists: (1) paresthesias, pain and/or sensory deficits in the hand in a median nerve distribution, (2) nocturnal/ early morning worsening of paresthesias with disturbed sleep, (3) paresthesias relieved by hand movement or shaking, (4) pain and/or paresthesias in a median nerve distribution provoked by monotone exercises, (5) weakness of fingers supplied by median nerve. Patients who met ≥ 1 of the following criteria were excluded: previously diagnosed CTS, conditions resulting in an increased risk of associated CTS such as former surgery at the wrist, recent wrist fracture, known inflammatory rheumatic disease or pregnancy, patients with known polyneuropathy, contraindications against electrophysiological testing. (30,62)

The diagnosis of CTS was established by the evaluating neurologist, based on NCS findings as well as on symptoms and clinical presentation of the patient's wrists at baseline and 3 months follow-up visit. Furthermore, the neurologist indicated his confidence in the diagnosis on a scale from 0-100% at each visit. A confidence >90% was considered to confirm the diagnosis of CTS, whereas CTS was excluded when confidence scored < 10%. Wrists deemed as possible CTS (>10%, <90% confidence) at baseline but were considered as CTS cases (>90% confidence) at follow-up or those undergoing carpal tunnel surgery, were regarded as confirmed CTS cases. The examining neurologist was unaware of ultrasound findings. Wrists deemed as possible CTS cases at the 3 month visit that underwent carpal tunnel surgery at a later time point, were also classified as CTS

cases.

For the purpose of the present study, we projected a long-term follow-up (> 12 months after baseline) of all patients included in the original project. All patients that underwent the baseline visit were contacted by phone (in January 2013) and asked whether they are willing to return for a clinical, electrophysiological and ultrasound investigation. 36 Patients agreed to participate in the long-term follow-up; visits were performed between January 2013 and June 2013 after an average of 27.9 months after baseline visit.

The study was approved by the institutional review board of the Medical University Graz and written informed consent was obtained by each patient.

2.2 Clinical evaluation

For subjective evaluation of symptoms, we used the following scales: Levine/Boston Questionnaire (BQ), Disabilities of the Arm Shoulder and Hand (DASH) and a visual analogue scale (VAS, range 0-100mm with 0=best and 100=worst) for the severity of pain.

The BQ is a self-administered questionnaire divided in two parts and assessing both the severity of hand symptoms (11 Items) as well as the functional status of the hand (8 Items) with each Item being scored 1-5 (1=best, 5=worst). Each score is calculated as the mean of the responses to the individual item. (63,64) The DASH is scored in two components: the disability/symptom section (containing 30 items, scored 1-5) and an optional sport/music or work section (containing 4 items, scored 1-5). The assigned values are summed and averaged and then transformed to a score out of 100. (65)

Furthermore, we used the historical-objective scale (Hi-Ob scale) to determine the severity of the disease for each individual wrist. The Hi-Ob scale includes items concerning the historical picture, objective clinical findings and a patient-orientated item such as pain, with a total score of 1-5 (1=best, 5=worst). (66)

Clinical examination included evaluation of muscular strength, trophism, sensory function and clinical provocation tests, such as the Phalen's, reverse Phalen's and

carpal tunnel compression test. In addition, the examiner graded the severity of the disease using a visual analogue scale (physVAS) (range 0-100mm with 0=best and 100=worst).

2.3 Clinical Outcome

The following items were used for determination of clinical outcomes at short (i.e. 3 months) and long-term clinical follow-up: DASH, physVAS and painVAS.
For both painVAS and physVAS, a change was only taken into consideration when it exceeded 10mm. This cut-off was chosen in order to prevent false positive results; especially in ranges of a low VAS value. Since there are no universally accepted criteria for response to treatment in CTS, analogue to other rheumatic diseases, a 20% improvement over baseline values was assumed to be minimum requirement for considering a therapeutic response. (67,68) Furthermore, we defined a second endpoint of at least 70% improvement.

2.4 Nerve conduction studies

Nerve conduction studies (NCS) were performed by two neurologists' at all visits, both unaware of ultrasound findings, using commercially available nerve conduction equipment (EMG/NLG/EP-system type Topas, Schwarzer, Munich, Germany). (30)
Median sensory nerve distal latencies of the symptomatic side(s) were measured and compared to the ulnar or radial sensory latencies applying a standard protocol. Antidromic sensory NCSs were used, which have the advantage of producing larger amplitude sensory nerve action potentials (SNAPs) compared with orthodromic stimulation. (69) Dorsal skin temperature of the hand was kept at 34°C, since higher temperatures may produce false positive results. (2) Furthermore, median motor NCSs were performed, determining the distal motor latency and the median motor compound muscle action potential.

2.5 Ultrasound protocol

Sonographic evaluations were performed by one of three rheumatologists experienced in musculoskeletal sonography (C.De. – 5 years, M.St. – 2 years, A.Fi. – 2 years experience) at the same day of clinical and neurophysiological investigation at baseline visit and at follow-up visits as previously described in detail (2). Briefly, we used a Logiq E9 ultrasound device (GE, Milwaukee, WI, USA) with a multifrequence linear transducer (6 – 15MHz) to examine patient's wrists, which were placed in a horizontal supine position on the examination table with fingers semi-extended. B-Mode ultrasound was performed with a frequency of 15.0 MHz and PD-settings were standardized with a frequency of 11.9 MHz, a pulse repetition frequency of 600 Hz and medium persistence. The PD-gain was optimized by increasing gain until noise appeared and then reduced just enough to suppress the noise. An ultrasound gel pad was used to minimize sampling errors (thickness 3.3mm; Sonar Aid®, Gestlich Pharma, Wolhusen, Switzerland)

Measurement of the Cross-sectional Area (CsA) of the median nerve was performed in the area between the distal forearm and the outlet of the carpal tunnel at 5 different levels: (1) Cross-**s**ectional area at the proximal border of the **P**ronator quadratus muscle (Cs**P**), (2) area of the proximal **T**hird of the pronator quadratus muscle (Cs**T**), (3) area of the **L**argest CSA of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet (Cs**L**), (4) carpal tunnel inlet defined as the margin of the flexor **R**etinaculum (Cs**R)** and (5) in the carpal canal, level of the **S**caphoid tubercle and pisiform bone (Cs**S**). PD-signals were graded from 0-3, with 0 representing no PD signal, 1=one single vessel within median nerve, 2=two or three single or two confluent vessels and 3= more than three single or more than two confluent vessels. (30)

See figure 1 and 2 for example images.

2.6 Statistical analysis

To investigate the prognostic value of baseline ultrasound for outcome of CTS patient, we focused in the final analysis on patients with confirmed CTS as defined above.

Statistical analysis was performed using IBM SPSS Statistics (v22.0). Descriptive statistics were used to summarize the data, depicting median and range for

continuous non-parametric data, while mean and standard deviation is presented for parametric data. Distribution of data was tested with the Kolmogorov–Smirnov test. We generated cross tables to analyse proportions and performed chi-square test to determine significance. In order to compare independent groups the Mann-Whitney U-test was used. Paired data were analysed with the Wilcoxon test for non-parametric data and the Friedman test was applied for multiple paired groups. Correlations were investigated using the Spearman's rank correlation test.

We conducted multivariate inclusive logistic regression models to investigate a possible association between baseline CSAs or CSA ratios of the median nerve and the clinical outcomes. In patients with bilateral CTS, we selected the dominant side as indicated by the HI-OB scale, choosing the wrist with the higher value. In case both wrists scored the same value, we used the mean of both sides for all variables. The following dependent variables were tested: (1) at least 20% improvement of DASH, physVAS or painVAS (2) at least 70% improvement of DASH, physVAS or painVAS. The CSAs and CSA ratios served as variables of primary interest and the following covariates were included in each logistic regression model: (1) age at inclusion, (2) symptom duration, (3) Body mass index (BMI), (4) gender, (5) median nerve vascularisation (PD score), dichotomized according to PD grading 0-1 and 2-3. For sensitivity analysis, we excluded high leverage cases as well as cases producing low/high DFBETAs and/or large Cook values.

3 Results

3.1 Patient characteristics

A total of 135 patients with suspected CTS were included in the study and underwent baseline evaluation. The first follow-up visit after 3 months was completed by 111 (82.2%) patients and a total of 36 (26.7%) patients returned for the second, long-term follow-up visit. The implicated loss to follow-up is due to unwillingness to return.

Table 1

	Baseline visit	Short-term follow-up	Long-term follow-up
Numberofpatients	135	111	36
Time period to follow up, months	-	2.84 (0.08) †	27.86 (0.93) †

†mean (standard deviation)

Out of the 270 wrists available for sonographic studies at baseline visit, 4 were excluded due to previous surgery and 22 had a bifid median nerve.

At baseline visit, the diagnosis of CTS was made in 122 (45.9%) wrists. 101 (38%) wrists were classified as no CTS and 43 (16.2%) wrists received the diagnosis of possible CTS. At 3 months, out of the 43 wrists with possible CTS, the final diagnosis of CTS was made in 14 wrists. For none of the remaining 29 wrists with possible CTS at baseline, the final diagnosis of CTS was made at the last visit, resulting in a total of 45 (62.5%) wrists diagnosed with CTS at long-term follow-up. The proportions of the two follow-up groups regarding their final diagnosis are depicted in Table 2. A detailed summary of demographic data and clinical characteristics of all patients is presented in Table 3 and 4.

Out of all patients, a total of 32 patients underwent surgery after baseline visit. 16 of them attended all three visits, resulting in a significantly higher representation of operated patients in the group of long-term follow-up (44%), compared with the short-term follow-up group (7.6%; $p < 0.001$).

No significant difference could be found between CTS patients that completed all

follow-up visits and CTS patients that did not attend all follow-up visits, regarding their age at inclusion (57.9 vs 54.0 years respectively, p=0.198), symptom duration (12.8 vs 13.2 months respectively, p=0.826), BMI (26.9 vs 27.9 respectively, p=0.052) and gender (70% vs 67% females respectively, p=0.837).

Table 2, diagnosis at each visit

	Baseline visit	**Short-term follow-up**	**Long-term follow-up**
CTS	122 (45.9)	111 (50)	45 (62.5)
No CTS	101 (38)	68 (30.6)	14 (19.4)
Possible CTS	43 (16.2)	43 (19.4)	13 (18.1)
Total	266	222	72

Number of wrists (%)

Table 3, Demographic data and clinical characteristics

Parameter	Baseline n=135	Short-term n=111	Long-term n=36	P-value
Age at inclusion [years] †	**51.9 (±14.5)**	**52.8 (±14.8)**	**57.5 (±9.0)**	**0.02**
Female, n (%)	**99 (73.3)**	**83 (72.8)**	**27 (75)**	**0.8**
Body mass index [kg/m2]†	**26.8 (±4.3)**	**26.8 (±4.3)**	**26.7 (±4.3)**	**0.9**
Symptom duration [months] ‡	**12 (1-362)**	**12 (1-362)**	**12 (2-121)**	**0.4**
ESR [mm/1st hour] †	**11.2 (±10)**	**11.64 (±10.4)**	**11.35 (±6.9)**	**0.89**
CRP [mg/l] ‡	**1.4 (0.6 – 26.2)**	**1.7 (0.6 – 26.2)**	**1.5 (0.6 – 26.2)**	**0.7**
Employment, n (%)				
a. blue-collarjobs	**51 (38.3)**	**44 (38.6)**	**14 (40)**	**0.9**
b. white-collarjobs	**49 (36.8)**	**41 (36)**	**11 (31.4)**	**0.56**
c. housewifes/charlady	**23 (17.3)**	**18 (15.8)**	**5 (14.3)**	**0.8**
d. pensioners	**4 (3)**	**4 (3.5)**	**3 (8.6)**	**0.23**
e. other	**6 (4.5)**	**5 (4.4)**	**2 (5.7)**	**0.77**
Manual Hobbies, n (%)	**79 (73.8)**	**70 (76.9)**	**24 (70.6)**	**0.47**

‡median (range); †mean (standard deviation), n, number of patients, ESR, erythrocyte sedimentation rate (normal values 1-10 mm/1st hour); CRP, C-reactive protein (normal values 0-5 mg/L)

Table 4, clinical characteristics of CTS-patients at different follow-up visits

	Baseline, n=81	Short-term follow-up, n=72	Long-term follow-up, n=29	p-value
painVAS†	54.18 (19.88)	39.26 (23.64)	39.33 (31.71)	0.146
physVAS†	47.39 (22.08)	51.14 (23.99)	34.24 (32.13)	0.017
DASH†	30.31 (20.00)	30.45 (20.24)	26.02 (23.14)	0.088

†mean (standard deviation)

3.2 Median nerve sonography

CsL, CsR and CsS showed to be significantly larger in wrists with confirmed CTS than in wrists without CTS at baseline visit ($p < 0.005$) as well as at short-term ($p < 0.005$) and long-term follow-up visits ($p < 0.05$)(see Table 5 for details). Furthermore all CSA ratios resulted to be significantly larger in wrists with confirmed CTS at all three visits ($p < 0.005$) (Table 6).

Comparing baseline CSAs and CSA ratios of wrists with confirmed CTS revealing clinical improvement at short and long-term follow-up visits to wrists without such an improvement, only CsS and its ratios (CsS/CsP, CsS/CsT) presented relevant differences. Larger CSAs and higher CSA ratios were observed in wrists that did not show clinical improvement. In that context, CsS/CsP resulted to be the most applicable variable, presenting significant differences between the groups of improvement and no improvement (of at least both 20% and 70%) of painVAS and DASH ($p < 0.05$) and almost reached significance for improvement/no improvement of 20% and 70% of physVAS.

CsS/CsT presented similar results, with the difference of falling slightly short of significance for the difference between groups of improvement/no improvement of at least 70% of painVAS ($p=0.074$). CsS on the other hand only reached significance ($p < 0.005$) for improvement/no improvement of at least 20% of DASH (with p-values ranging from 0.062 to 0.152 for the other variables in which CsS/CsP reached significance).

This finding is also reflected in the results of the binary logistic regression models (as presented below) and constitutes the reason for our focus on CsS/CsP when analysing the ultrasound's predictive value.

Table 5, Cross-sectional areas at different anatomical levels

	Baseline visit, n=42,14	Short-term follow-up, n=38,14	Long-term follow-up, n=45,14	p-value
CsP†				
• **CTS**	7.29 (±1.24)	7.47 (±1.54)	9.02 (±2.46)	0.000
• **No CTS**	7.50 (±1.16)	7.71 (±1.20)	9.29 (±2.27)	0.024
CsT†				
• **CTS**	7.52 (±1.20)	7.55 (±1.25)	9.67 (±2.55)	0.000
• **No CTS**	7.79 (±1.25)	7.86 (±1.10)	9.79 (±2.42)	0.002
CsL†				
• **CTS**	13.46 (±3.81)	13.74 (±3.49)	17.44 (±5.60)	0.000
• **No CTS**	10.07 (±2.62)	10.29 (±2.37)	13.36 (±3.52)	0.000
CsR†				
• **CTS**	12.76 (±3.06)	12.63 (±2.65)	16.29 (±5.25)	0.000
• **No CTS**	9.43 (±1.79)	10.14 (±2.10)	12.79 (±3.56)	0.000
CsS†				
• **CTS**	11.95 (±4.14)	12.03 (±3.69)	15.93 (±5.04)	0.000
• **No CTS**	9.50 (±2.53)	10.00 (±2.54)	12.79 (±3.53)	0.000

†mean (standard deviation); n= CTS, no CTS; CTS=confirmed CTS, no CTS=CTS excluded, p-value refers to differences between baseline and follow-up groups

Table 6, Ultrasound CSA Ratios at different anatomical levels

Ultrasound	Baseline visit n= 41, 14	Short-term follow-up n= 38, 14	Long-term follow-up, n= 45, 14	p-value
CsL/CsP†				
• **CTS**	1.84 (±0.43)	1.88 (±0.49)	1.99 (±0.66)	0.302
• **No CTS**	1.36 (±0.39)	1.35 (±0.32)	1.46 (±0.32)	0.093
CsR/CsP†				
• **CTS**	1.75 (±0.35)	1.74 (±0.42)	1.86 (±0.60)	0.169
• **No CTS**	1.27 (±0.25)	1.33 (±0.26)	1.39 (±0.27)	0.292
CsS/CsP†				
• **CTS**	1.64 (±0.50)	1.66 (±0.55)	1.83 (±0.62)	0.142
• **No CTS**	1.28 (±0.36)	1.31 (±0.35)	1.40 (±0.33)	0.199
CsL/CsT†				
• **CTS**	1.79 (±0.43)	1.83 (±0.44)	1.84 (±0.59)	0.763
• **No CTS**	1.32 (±0.46)	1.32 (±0.28)	1.38 (±0.28)	0.223
CsR/CsT†				
• **CTS**	1.70 (±0.37)	1.70 (±0.38)	1.72 (±0.55)	0.938
• **No CTS**	1.22 (±0.18)	1.30 (±0.23)	1.32 (±0.24)	0.679
CsS/CsT†				
• **CTS**	1.60 (±0.50)	1.62 (±0.52)	1.69 (±0.55)	0.979
• **No CTS**	1.25 (±0.43)	1.28 (±0.29)	1.33 (±0.29)	0.311

†mean (standard deviation); n= CTS, no CTS; CTS=confirmed CTS, no CTS=CTS excluded, p-value refers to differences between baseline and follow-up groups

3.3 Clinical outcome

Out of 72 wrists (45 with, 14 without and 13 with possible CTS) available for examination of long-term outcome, 42.2% and 33.3% of the CTS patients showed 20% and 70% improvement, respectively regarding painVAS, 53.3% and 42.2% of the patients, respectively presented improvement of their physVAS and 37.8% and 15.6% of cases, respectively showed improvement of their DASH outcome measure.

3.4 Correlations and logistic regression models

Using Spearman's rank test we found moderate correlations of the baseline CsS, CsS/CsP and CsS/CsT with the long-term change score of painVAS (baseline painVAS minus long-term follow-up painVAS) or DASH (baseline DASH minus long-term follow-up DASH), with patients with larger CSAs showing a worsening in painVAS and DASH. Details are depicted in Table 7.

Table 7, Correlations

Ultrasound value	**painVAS*: r_s**	**DASH outcome measure*: r_s**
CsS/CsP	-0.573 (0.010)	-0.516 (0.012)
CsS/CsT	-0.443 (0.057)	-0.536 (0.008)
CsS	-0.296 (0.219)	-0.413 (0.050)

*difference: score at Baseline Visit – long-term follow-up, r_s: spearman's correlation coefficient, (p-value)

In order to explore the value of CsS/CsP as predictor for the binary outcomes of improvement (of at least 20% or 70%) for painVAS, physVAS and the DASH, multivariate inclusive regression models were performed. The following variables were included in the model as covariates: (1) age at inclusion, (2) symptom duration, (3) Body mass index (BMI), (4) gender, (5) median nerve vascularisation. As depicted in Table 7 and Table 8, CsS/CsP showed to be significant ($p < 0.05$) in all models predicting an outcome of improvement of at least 20%. In models predicting an improvement of at least 70%, CsS/CsP reached significance regarding painVAS and almost reached significance for physVAS and the DASH

outcome measure. OR indicates that a higher CsC/CsP value results in a lower probability of improvement.
Sensitivity analyses (as described in M&M) did not change these findings.

Table 8, CsS/CsP as predictor for improvement of at least 20%

Covariate	schmVAS (20%)	physVAS (20%)	DASH (20%)
CsS/CsP, OR (p-value)	**0.000 (0.047)** †	**0.012 (0. 032)** †	**0.000 (0.018)** †

†OR= odds ratio, (p-value)

Table 9, CsS/CsP as predictor for improvement of at least 70%

Covariate	schmVAS (70%)	physVAS (70%)	DASH (70%)
CsS/CsP, OR (p-value)	**0.000 (0.043)** †	0.022 (0.069) †	0.002 (0.076) †

† OR= odds ratio, (p-value)

We found similar results using CsS or CsS/CsT as covariate instead of CsS/CsP in the same logistic regression models. Details are presented in Table 10.

Table 10, CsS and CsS/CsT as predictors for improvement of at least 20% and 70%

	CsS	CsS/CsT
20% Improvement, OR (p-value)		
• **painVAS**	**0.293 (0.038)**	**0.000 (0.050)**
• **physVAS**	0.660 (0.073)	**0.006 (0.030)**
• **DASH**	**0.388 (0.042)**	**0.000 (0.026)**
70% Improvement, OR (p-value)		
• **painVAS**	**0.265 (0.028)**	0.000 (0.067)
• **physVAS**	0.744 (0.178)	0.061 (0.116)
• **DASH**	0.579 (0.112)	0.002 (0.082)

† OR= odds ratio, (p-value)

The p-values of the insignificant independent variables in the 4 models in which CsS/CsP was significant had the following ranges: Age at inclusion (p-value: 0.073 – 0.917), vascularisation (0.078 – 0.491), gender (0.089 – 0.289), symptom duration (0.397 –0.977) and BMI (0.403 – 0.825).

4 Discussion

Our data indicates that ultrasound B-mode imaging by means of measurement of CSAs of the median nerve can be a useful prognostic tool in CTS Patients. We found that a larger baseline CSA in the carpal canal (CsS) and a higher ratio of the CSA at this region compared to a pre-defined anatomic location at the forearm (where the median nerve is expected to be normal even in CTS patients) - CsS/CsP and CsS/CsT - predicted a worse long-term functional outcome of CTS patients as determined by VAS and DASH.

Since the prognostic value of ultrasound regarding the outcome of CTS patients has rarely been studied and the results are contradictory, our research confirms findings of previous studies, but also stands in contrast to others, which either could not verify CSA as a significant predictor, or found that a smaller baseline CSA predicts a worse outcome. This inconsistency might be explained by the fact that the studies which presented opposite results measured the CSA at different anatomic levels and that the study which could not establish significance had a too small number of patients with poor outcomes for the CSA to result to be a significant predictor. (59–61) Our study is different from these prior investigations regarding three major aspects: (1) The time period to follow-up visit in these studies did not exceed 3-6 months; our research, however, focused on a long-term follow-up of more than 2 years after baseline. (2) All previous studies focused on the outcome of CTS patients that underwent CTR, whereas our research included operated patients, as well as patients that did not undergo surgery. Therefore we focused on a long-term functional outcome, independent of invasive or conservative treatment, while the previous investigations concentrated on a short-term postoperative outcome, defined by surgical success. (3) Lastly, only one method of CSA-measurement was chosen previously, whereas we evaluated the predictive value of CSAs of different anatomic levels.

Concerning the predictive value of hypervascularisation of the median nerve, which has not been investigated in other studies so far, we found that PD examination has no predictive value, regarding the long-term functional outcome of CTS patients.

The limitations of our study are the single-centre design and the low number of patients. All patients that attended baseline visit were contacted by phone and

asked whether they are willing to return for follow-up. Some patients, however, declined because their symptoms have improved. Therefore, we cannot exclude the possibility that this loss to follow-up influenced our results; even though patients that underwent all three follow-up visits did not show significant differences in major clinical characteristics compared to patients that did not attend follow-up (as described in 3.1). The reproducibility of ultrasound findings in multicentre trials with a more substantial number of patients has to be addressed by future studies.

In conclusion, we showed that a higher CSA at baseline predicts a worse clinical long-term outcome of CTS patients as determined by VAS and DASH. PD examination has no predictive value regarding CTS outcome.

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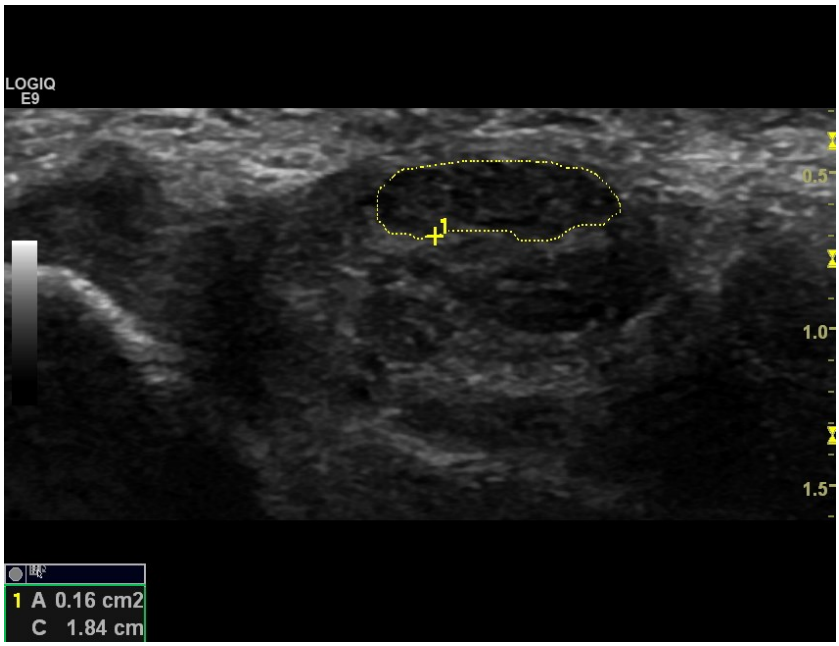
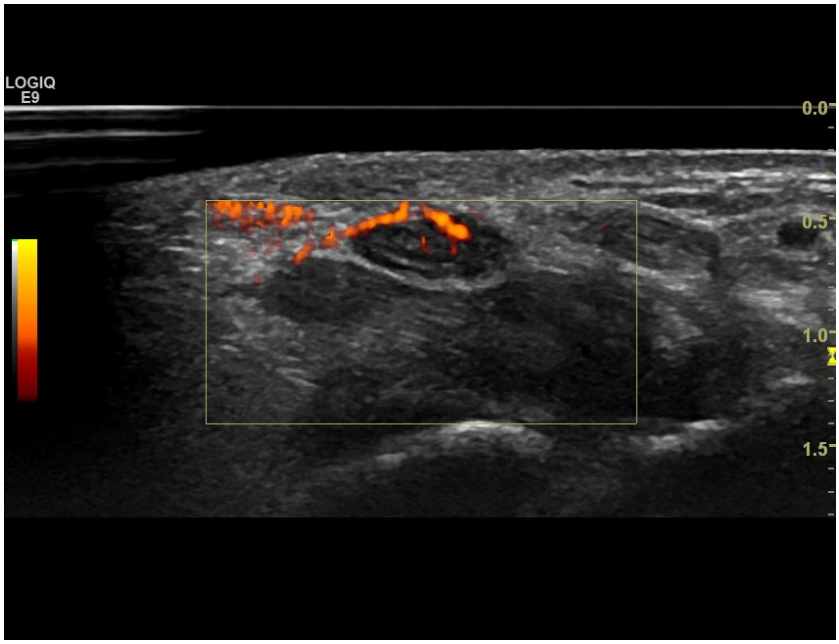
6 Appendix – Figures

Figure 1



Example for CSA measurement at the Anatomic level of the carpal canal; level of the Scaphoid tubercle and pisiform bone (CsS).

Figure 2



Example for Power Doppler assessment of intraneural hypervascularisation.