Appendix A

Baseline characteristics, page 1

Description of the surgical intervention, pages 2-5

Baseline characteristics

Characteristic	n = 10
Age [year]	50.1 ± 12.6
Female sex, n (%)	4 (40%)
Body mass index [kg/m^2]	29.2 ± 2.2
Height [meters]	1.71 ± 0.1
Weight [kg]	86.5 ± 15.0
Dominant hand, right side, n (%)	10 (100%)
Right hand included in study, n (%)	8 (80%)
Bilateral CTS, n (%)	7 (70%)
Duration of symptoms [years]	6.0 ± 4.9
Median (range)	5.5 (1.0 – 15.5)
Severity of NCS (1–3)	2.2 ± 0.8
Smoking currently, n (%)	3 (30%)
Previous treatments	
Wrist splint, n (%)	1 (10%)
Glucocorticoid injection, n (%)	5 (50%)

Values are mean ± Standard Deviation unless specified otherwise. n = number of participants. NCS: Nerve Conduction Study. NCS evaluated as mild (1), moderate (2), or severe (3).

Ultra-minimally invasive ultrasonographic-guided carpal tunnel release (UMIU-CTR) - description of the surgical intervention.

The intervention is described according to the Template for Intervention description and replication (TIDIerR) guidelines [1]. The following description of the UMIU-CTR procedure is based on the studies by Rojo-Manaute et al. [2, 3].

The procedure was performed in a standard outpatient room at the Dept. of XXX (Figure 1D). Sterile procedure included that the patient washed their hands with soap, and the skin was disinfected three times with chlorhexidine alcohol in the area from the fingers to just proximal to the elbow. The procedure followed the recommendation for safe office-based surgery [4]. A sterile

cover was used for the US probe and cord. Chlorhexidine alcohol was used as the liquid needed to secure contact between the US probe cover and the skin. The physician used sterile gloves, mouth protection, and a hair cover. A nurse was present in the room for assistance. The patient was positioned in a supine position with the arm abducted to 90 degrees resting on an operating table with the wrist supinated in a neutral position.

US-guided local anesthetic (lidocaine with adrenaline 2 ml) was injected subcutaneously at approximately 2 cm proximal from the pisiform (normally coinciding with the second antebrachial skin crease) between the median nerve and the canal of Guyon. Then approximately 3–4 ml lidocaine was injected under US guidance between the TCL and the palmar aponeurosis, entering at the level of the first antebrachial skin crease and continuously injecting all the way down to the distal edge of the TCL. The palmar aponeurosis is at the level of the carpal tunnel, referred to as a reinforced antebrachial fascia by some authors [5].

To create a point of entry, the skin was punctured at the level of the second antebrachial skin crease between the median nerve and the canal of Guyon with the use of a peripheral venous catheter (Abbocath X1G) angled at 45 degrees proximal to distal orientation. Once the tip of the Abbocath was under the skin surface, the antebrachial fascia was perforated with multiple punctures in the antebrachial fascia, creating a defect allowing for entrance of the hook knife, Acufex 3.0-mm hook knife (010600; Smith & Nephew PLC, London, UK), shown in Figure 1C. The hook knife was inserted with a semicircular movement, allowing for the knife to enter through the 1 mm point of entry (Figure 1C).

Once below the antebrachial fascia, the hook knife was positioned flat, with the hook blade facing the canal of Guyon (to protect the median nerve) and on top of the flexor tendons. From here, the hook knife was advanced through the carpal tunnel ulnar to the median nerve (in the Nakamichi's safe zone, Figure 2A) [6] just below the TCL and on top of the flexor tendons. The advancement of the hook knife continued until the distal cutting point, which was distal to the TCL's distal edge (named the "duck's beak", Figure 2B) and at least 2 to 3 mm proximal from the superficial palmar arch. Before reaching the duck's beak, the wrist was placed in light dorsal flexion to allow the hook knife to move superficially to a fatty area where the ulnar-median nerve anastomosis is located (Barretini branch) and prone to iatrogenic injury [7, 8].

As the hook knife reached the distal cutting point, with the wrist in a neutral position, the hook knife was rotated 90 degrees and the hook blade pressed volarly to catch the distal edge of the TCL, thus sparring the deepest part of the palmar aponeurosis (Figure 2C). From this position, the hook knife was pulled retrogradely and the TCL was released until 1 cm proximal to the level of the pisiform bone because the exact point of transition between TCL and antebrachial fascia was not easily identifiable on US. The exit of the hook knife was performed with a semi-circular motion in a reverse direction to its insertion.

The procedure left a skin wound of approximately 1 mm or less that was covered with an adhesive bandage. Hence the term ultra-minimally invasive in this technique covered both that the skin entrance was very small and that only the TCL was released, leaving the richly innervated superficial structures intact (Figure 2B) [5, 9, 10].

The entire procedure was guided under US to assure:

- The correct point of entry for the skin portal.
- That the hook knife was below the antebrachial fascia and located between the median nerve and the canal of Guyon (Nakamichi's safe zone).
- That as the hook knife was advanced under the TCL, after a correct intra-tunnel real-time position of the hardware had been confirmed, until the position of the distal cutting point was reached at the duck's beak (Figures 2B-C).
- That the hook of the hook knife only caught the TCL at the duck's beak, leaving the richly innervated structures of the overlying antebrachial fascia intact (Figures 2B-C).

Proper US guidance was confirmed in two planes. By switching between the longitudinal and transverse positions of the US probe, the correct position of the hook knife was confirmed. Before the retrograde release was initiated, the correct hook knife position was checked again to ensure that no structures were in the way of the retrograde release path. US was not continuously performed during the retrograde release because the operator needed both hands for the procedure, one hand for fixating the patient hand and one hand for pulling the hook knife.

Postoperative care. Patients were asked to remain in the waiting room for 30 minutes before leaving the hospital. They were advised to refrain from demanding hand activities for the rest of the day, but light activities were allowed. A description of a home rehabilitation program was handed out,

advising continuous stretching and active motion of the wrist, hand, and fingers. Patients were informed that from day 1 they were allowed to perform daily activities that did not elicit pain. They were allowed to resume work when they felt ready but advised that they could not count on resuming work for the first week. They were also informed that most patients will not be able to lift heavy weights until after the sixth postoperative week and that mild pain could be present for 2–3 months when doing strenuous exercises like push-ups.

Appendix B

Detailed description of the patient rated outcome measures, pages 1-2

Details of the three patients that did not answer "no symptoms" at the 12-month follow-up. Their individual courses are specified below:

Patient no. 4: male, hard manual work, disease duration 3 years, mild NCS changes. MRI showed incomplete release in the proximal part of the TCL. At 12-month follow-up, he reported mild symptoms at night but none during the day. He was pleased with the results of the operation and had no wish for additional surgery.

Patient no. 5: male, retired, disease duration 1 year, severe NCS changes. No MRI sign of incomplete release. At 12-month follow-up, he reported mild symptoms at night and during the day. He was pleased with the results of the operation and had no wish for additional surgery.

Patient no. 6: female, hard manual work, disease duration 3 years, moderate NCS changes. No MRI sign of incomplete release. At 12-month follow-up, she reported mild symptoms at night and moderate during the day. This participant was partially dissatisfied but not to a degree that she wished further surgery.

Appendix C

Details of the 3 patients with some degree of persistent symptoms, page 1

Details of the three patients that did not answer "no symptoms" at the 12-month follow-up. Their individual courses are specified below:

Patient no. 4: male, hard manual work, disease duration 3 years, mild NCS changes. MRI showed incomplete release in the proximal part of the TCL. At 12-month follow-up, he reported mild symptoms at night but none during the day. He was pleased with the results of the operation and had no wish for additional surgery.

Patient no. 5: male, retired, disease duration 1 year, severe NCS changes. No MRI sign of incomplete release. At 12-month follow-up, he reported mild symptoms at night and during the day. He was pleased with the results of the operation and had no wish for additional surgery.

Patient no. 6: female, hard manual work, disease duration 3 years, moderate NCS changes. No MRI sign of incomplete release. At 12-month follow-up, she reported mild symptoms at night and moderate during the day. This participant was partially dissatisfied but not to a degree that she wished further surgery.

Appendix D

MRI sequence parameters, page 1
MRI figures 3 & 4, pages 2-3
Imaging discussion, pages 4-7

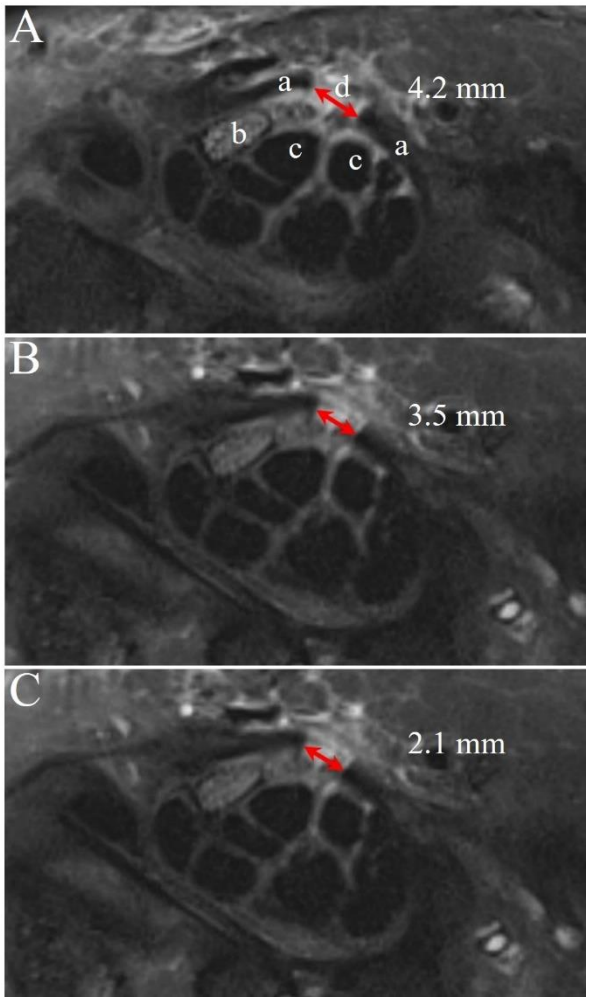
Supplementary TABLE

MRI sequence parameters

Parameter	PD-weighted TSE	T1-weighted IR TSE
Repetition Time (TR) [ms]	5050	3540
Echo Time (TE) [ms]	46	23
Field of View (FOV) [mm]	90 x 90	120 x 120
In-plane resolution [mm]	0.3 x 0.3	0.5 x 0.5
Slice Thickness [mm]	2.2	3.0
Matrix size	320 x 320	256 x 256
Bandwidth [Hz/Pixel]	260	241
Number of Signal Averages	2	3
Flip Angle [°]	150	150
Echo Train Length	50	13
Turbo Factor	9	8
Fat Saturation Technique	SPAIR	None
GRAPPA factor	none	2
Acquisition Time [min:sec]	8:37	2:23

MRI = Magnetic Resonance Imaging, PD = Proton Density, TSE = Turbo Spin Echo, IR = Inversion Recovery, GRAPPA = GeneRalized Autocalibrating Partial Parallel Acquisition.
Images were acquired using two transversal imaging series: a proton density weighted Turbo Spin Echo (TSE) sequence with Fat Saturation and a T1-weighted Inversion Recovery TSE sequence. MRI images were evaluated using a standard clinical PACS system (Agfa IMPAX version 6.5 Agfa Healthcare NV, Mortsel, Belgium).

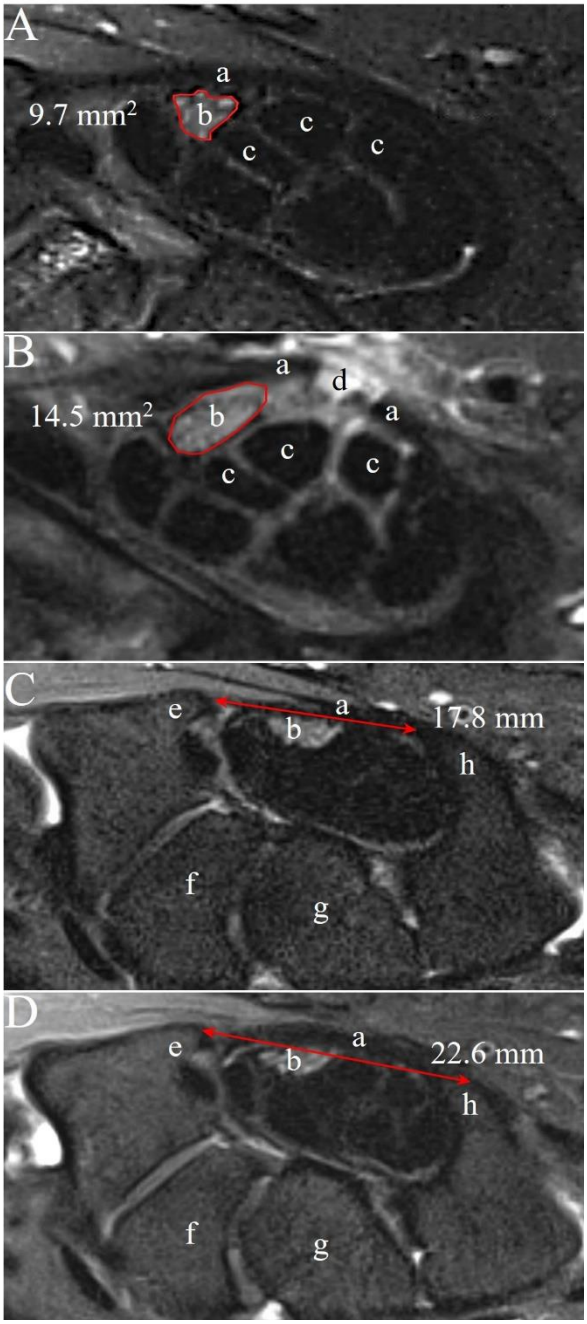
Figure 3



MRI T2 weighted axial view of the carpal tunnel illustrating the gap width in the transverse carpal ligament at 3 locations (**A**) proximally, (**B**) centrally, and (**C**) distally in the carpal tunnel, 1 month after ultra-minimally invasive US-guided CTR.

The red double-sided arrow marks the borders of the sectioned transverse carpal ligament with a gap width notation in millimeters (mm). a: transverse carpal ligament, b: median nerve, c: flexor tendons, d: gap in the transverse carpal ligament.

Figure 4



MRI T2 weighted axial view of the carpal tunnel. A-B Cross-sectional area of the median nerve (encircled in red) at the level of hook of hamate. A. Pre-operative. B. Post-operative (enlarged median nerve). C-D. Distance from hook of hamate to the trapezium tubercle (red double-sided arrow). C. Pre-operative. D. Post-operative. a: transverse carpal ligament, b: median nerve, c: flexor tendons, d: gap in the transverse carpal ligament, e: trapezium tubercle, f: trapezoid bone, g: capitate bone, h: hook of hamate.

MRI Imaging Discussion.

MRI was primarily included to document the release of the TCL. Secondarily, it was performed to assess post-surgical structural changes in the TCL, median nerve, and the carpal tunnel after 1 month and 12 months.

Gap width. To visualize and document the release of the TCL, we measured the gap width in the TCL after 1 month at three locations in the carpal tunnel, proximal, central, and distal and found average values of 4.7 mm, 4.4 mm, and 3.1 mm, respectively (Figures 3A-C in Appendix D). Petrover et al. followed 129 patients after ultra–minimally invasive US-guided CTR for 6 months including MRI at baseline and after 1 month [1]. They measured an average gap width of 5.1 mm and a complete section in 100% of the patients. In all our gap width measurements, there was 1 case evaluated as an incomplete release with an incomplete diastasis in the proximal part of the TCL. Despite MRI signs of only partial release, the CTS-6 score in this patient improved from 3.3 at baseline to 1.7 at final follow-up but with a mild recurrence of CTS symptoms. However, the patient was pleased with the result and had no wish for any additional treatment.

Ng et al. investigated how long a visible gap in the TCL could be observed on MRI following arthroscopic release [2]. They found that the gap in the TCL was still visible in 94% of the TCLs after 3 months and in 17% after 12 months [2]. In our study, the gap was still visible in 11% of the TCLs at the final 12-month follow-up.

Release length. Petrover et al. described the advantages of US when used to guide the hook knife during the retrograde release of the TCL. In our study, we measured the TCL release length and found an average length of 27.7 mm (median 26.4 mm, range 20.5 to 37.1 mm). In a similar surgical procedure, termed “looped thread carpal tunnel release”, Burnham et al. investigated the release length on 13 cadavers [3]. They dissected the carpal tunnel after the release and measured the length of the TCL and compared the length of the TCL to the release length. In their study, the median TCL length was 22.3 mm (range 14.4 to 30.8 mm). These two studies are not directly comparable, but they show that the length of TCL has a great natural variation, and therefore the release length in each US-guided CTR procedure should be expected to vary.

Carpal tunnel cross-sectional area. The rationale behind TCL release is to increase the space in the carpal tunnel, leaving more room for the median nerve. To assess and verify dimensional changes of the carpal tunnel, we measured by MRI the CSA of the carpal tunnel at baseline and after 1 and 12 months. We observed that after releasing the TCL, the CSA increased an average of 25.4 mm^2 (10.8%) after 1 month and that this increase was observed throughout the study (29.5 mm^2 (12.3%) after 12 months). This indicates, as expected, that the procedure does leave more room for the structures inside the carpal tunnel including the median nerve. In theory, once the TCL was released, one could assume that the observed increase in CSA was solely related to an expansion of the carpal tunnel in the palmar direction. This is supported by studies showing that the TCL bulges outward (palmar bowing) in patients with CTS [4]. However, this might be only a part of the explanation for the increased CSA. We measured the distance between the hook of hamate and the trapezium tubercle, (Figures 4C-D in Appendix D) and found the distance had increased by 1.7 mm (7.7%) after 1 month and 2.7 mm (11.6%) at final follow-up after 12 months. This indicates that the bone structures of the carpal tunnel also change their anatomical position and that it is not only the soft tissue that is affected by the release of the TCL. Our findings are supported by Somay et al., who found that the diameter of the carpal tunnel increased significantly by 3.7 mm at the level of the hamate bone 8 weeks after open CTS surgery [5].

Median nerve cross-sectional area. The median nerve becomes compressed and flattens underneath the TCL in chronic CTS. Outside the compressive area, however, the nerve tends to thicken both proximally and distally to the TCL. This nerve compression gives an hourglass configuration of the nerve on longitudinal US and MRI [6]. After TCL release, the hourglass configuration changes, nerve thickness being reduced just outside the carpal tunnel. The opposite happens inside the carpal tunnel, where the nerve that was previously under pressure underneath the now released TCL increases in thickness [2]. In the literature, increase in median nerve thickness (the CSA) at the inlet to the carpal tunnel in both MRI and US scans has been validated to diagnose CTS compared to NCS [6-8]. The average CSA of the median nerve in our study at the inlet was 18.2 mm^2 at baseline. In one study, >15 mm^2 was recommended as a diagnostic cut-off value for CTS on MRI [6]. Ninety percent of the participants in our study had a CSA > 15 mm^2, thereby fulfilling the diagnostic MRI criteria for CTS. Most studies are based on US. The US cut-off criteria cannot be

applied directly to MRI because median nerve CSA measurements obtained by MRI are larger than US measurements [8].

The median nerve CSA was 12.5 mm^2 inside the carpal tunnel, measured at the level of the hook of hamate (Figures 4A-B in Appendix D) compared to 18.2 mm^2 at the inlet where there was no compression/confined space. No statistically significant CSA change in the median nerve was observed at the inlet to the carpal tunnel at 1 month or after 12 months. This was unlike the study by Chappel et al., where the median nerve decreased in CSA at both 2-4- and 6-10- week follow-up after US-guided CTR on 37 wrists [9]. Across most studies, the tendency has been the same, that the median nerve thickness at the inlet is reduced after surgery, but it remains enlarged and does not reach normal thickness in the follow-up period, which in several trials has been up to 1 year [2, 10, 11]. The value of measuring the CSA has been related to its diagnostic properties, whereas in the follow-up assessment after surgery, there has been no relationship between improvement in symptoms and changes in CSA [2, 11]. There could be several reasons why we did not reach a statistically significant decrease in nerve thickness. The most likely reason could be related to the imaging evaluation technique/choice of MRI measuring landmark at the inlet. Other explanations could be the duration of injury in the patient population (risk of irreversible neural structural changes) or the release procedure itself. With a sample size of only nine this is speculative. The median nerve CSA did increase in our study inside the carpal tunnel following surgery, at both 1 month and after 12 months. This was also demonstrated after endoscopic CTR by Ng et al. [2].

Reactive changes. We assessed reactive changes within the carpal tunnel in regard to the soft tissue (fat tissue and connective tissue) on MRI. The MRI definition for reactive changes was high signal changes on T1 STIR and PDfs. Preoperatively, the reactive changes could represent part of the underlying CTS pathology, whereas postoperatively, the reactive changes at 1 month were primarily edema following tissue damage. This was observed in five of nine patients (missing data in one patient) before the surgery and in all 10 patients at 1-month follow-up due, as expected, to the tissue damage following the procedure. After12 months, the postoperative edema had resolved in eight of nine patients (missing data in one patient). We believe this to be a sign of tissue healing after the procedure and speculate that the inflammatory changes that initially were observed and were part of the carpal tunnel syndrome had resolved due to the release of the TCL. Without a control group, this remains a hypothesis.

Litterature

(1) Petrover D, Silvera J, De BT, et al. Percutaneous Ultrasound-Guided Carpal Tunnel Release: Study Upon Clinical Efficacy and Safety. Cardiovasc Intervent Radiol. 2017;40(4):568-75.

(2) Ng AWH, Griffith JF, Tsai CSC, et al. MRI of the Carpal Tunnel 3 and 12 Months After Endoscopic Carpal Tunnel Release. AJR Am J Roentgenol. 2021;216(2):464-70.

(3) Burnham R, Playfair L, Loh E, et al. Evaluation of the Effectiveness and Safety of Ultrasound-Guided Percutaneous Carpal Tunnel Release: A Cadaveric Study. Am J Phys Med Rehabil. 2017;96(7):457-63.

(4) Kim MK, Jeon HJ, Park SH, et al. Value of ultrasonography in the diagnosis of carpal tunnel syndrome: correlation with electrophysiological abnormalities and clinical severity. J Korean Neurosurg Soc. 2014;55(2):78-82.

(5) Somay G, Somay H, Cevik D, et al. The pressure angle of the median nerve as a new magnetic resonance imaging parameter for the evaluation of carpal tunnel. Clin Neurol Neurosurg. 2009;111(1):28-33. Epub 2008/10/14.

(6) Ng AWH, Griffith JF, Tong CSL, et al. MRI criteria for diagnosis and predicting severity of carpal tunnel syndrome. Skeletal Radiol. 2020;49(3):397-405.

(7) Bagga B, Sinha A, Khandelwal N, et al. Comparison of Magnetic Resonance Imaging and Ultrasonography in Diagnosing and Grading Carpal Tunnel Syndrome: A Prospective Study. Curr Probl Diagn Radiol. 2020;49(2):102-15.

(8) Lee S, Cho HR, Yoo JS, Kim YU. The prognostic value of median nerve thickness in diagnosing carpal tunnel syndrome using magnetic resonance imaging: a pilot study. Korean J Pain. 2020;33(1):54-9.

(9) Chappell CD, Beckman JP, Baird BC, Takke AV. Ultrasound (US) Changes in the Median Nerve Cross-Sectional Area After Microinvasive US-Guided Carpal Tunnel Release. J Ultrasound Med. 2020;39(4):693-702

(10) Abicalaf CA, de Barros N, Sernik RA, et al. Ultrasound evaluation of patients with carpal tunnel syndrome before and after endoscopic release of the transverse carpal ligament. Clin Radiol. 2007;62(9):891-4; discussion 5-6. Epub 2007/07/31.

(11) Kim JK, Koh YD, Kim JO, Choi SW. Changes in Clinical Symptoms, Functions, and the Median Nerve Cross-Sectional Area at the Carpal Tunnel Inlet after Open Carpal Tunnel Release. Clin Orthop Surg. 2016;8(3):298-302. Epub 2016/09/02.