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A retrospective case series reporting the outcomes of Avance nerve allografts in the treatment of peripheral nerve injuries.

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Abstract:

Introduction: Acellular nerve allografts are viable treatment modality for bridging nerve gaps. Several small studies have demonstrated equal results to autologous grafts, however there is lacking information regarding outcomes for wider indications. The aim of this retrospective case series was to evaluate the outcomes of patients treated with a nerve allograft in a variety of clinical situations.

Methods: A retrospective chart analysis was completed between April 2009 – October 2017. The inclusion criteria for this study were: age ≥ 18 years at the time of surgery and be treated with a nerve allograft. Patients were excluded if they had not been followed-up for a minimum of six months. The modified Medical Research Council Classification (MRCC) was used to monitor motor and sensory changes in the post-operative period.

Results: 207 nerve allografts were used in 156 patients; of these 129 patients with 171 nerve allografts fulfilled the inclusion criteria. 77% of patients achieved a sensory outcome score of S3 or above and 36% achieved a motor score of M3 or above. All patients with chronic pain had improvement of their symptoms.

Discussion: Graft length and diameter were negatively correlated with reported outcomes. One patient elected to undergo revisional surgery and the original graft was shown histologically to have extensive central necrosis. Anatomically, allografts used for lower limb reconstruction yielded the poorest results. All chronic patients had a significantly lower post-operative requirement for analgesia and allografts are effective in not only reducing pain, but also restoring a functional level of sensation.

Conclusion: This study supports the wider application of allografts in managing nerve problems however caution must be applied to the use of long grafts with larger diameters.

Introduction:

There is no uniform consensus of the best method to bridge the gap resulting from peripheral nerve injury (1-5); the available options include autologous grafts, synthetic or autologous conduits and allografts. In cases where a tensionless end-to-end neurorrhaphy is not possible, nerve repair with autologous nerve grafts remains the gold standard (5-8). However, harvesting an autologous nerve graft can lead to significant donor site morbidity: sensory loss, neuroma and scar formation have all been reported (9-13). As a consequence, alternatives such as synthetic nerve conduits or acellular nerve grafts have been developed however, these are only recommended nerve gaps up to 3 cm (4). De-cellularized allografts have been processed to remove cellular material from the graft whilst preserving the structural architecture (14). Arguments against the efficacy of allografts cite that beneficial growth factors and supportive cells have been eradicated; this restricts their use to short nerve gaps (<3cm)(15).

Neuropathic pain resulting from a peripheral nerve injury is relatively common in upper and lower extremity injuries being reported in up to a third of patients (16). Despite immediate surgical repair of the nerve lesion it is unpredictable whether a patient will go on to develop neuropathic pain (16-18). Pharmacological treatment with non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants, opioids and topical anaesthesia are the mainstay of treatment (19-23). Surgical intervention is generally advocated after non-operative treatment modalities have failed or where a clear pathological cause is identified (24). Surgery for neuromas is well established and associated with mixed outcomes (25, 26) and an ideal surgical strategy has not been identified. Surgical treatment is targeted at finding an alternative, less problematic, environment for the nerve to regenerate within including muscle, bone, graft and vein. Studies examining the effect of targeting reinnervation of symptomatic neuromas to specific receptors appear to be the most effective way to improve symptoms (27). Therefore, using allografts to help

painful nerves may be considered as an attempt to heal a nerve, rather than to hide it and has been shown to be most beneficial compared to all other types of neuroma treatments (28).

The purpose of the study is to review the outcomes of all nerve injuries that were treated with allografts in a single institution and compare these with existing published reports. If the results of nerve allografts are equal or even superior to alternative techniques it supports their use and avoids secondary complications at the donor site. This series encompasses the repair of sensory and mixed nerves in both the acute and chronic setting thus providing a comprehensive overview of outcomes.

Materials and methods:

Data was collected retrospectively for all patients whom received an Avance® allograft (AxoGen Inc., Alachua, FL) from 1st April 2009 to 31st October 2017 using the electronic patient record. The inclusion criteria were: age ≥ 18 years at the time of surgery and be treated with a nerve allograft. Patients were excluded if they had an alternative nerve repair technique or had not been followed-up for a minimum of six months. Nerve defects were reconstructed by the available length and diameter of nerve allografts that best matched to the defect.

All patients were assessed pre- and post-operatively by either an experienced hand surgeon or therapist. The modified Medical Research Council Classification (MRCC) (29, 30) was used to monitor motor and sensory changes during the post-operative period that included two point discrimination testing (2-PD) and motor recovery; this was chosen as the majority of similar studies use this as an outcome measure (31). Where appropriate, the numeric rating scale (NRS) was used to record subjective pain scores. Further assessment using Semmes Weinstein monofilament (SWMF) testing was used to map the sensory areas affected and to monitor the development during the recovery period (32-34). All patients were operated on by a hand surgeon who had undertaken a specialist hand surgery fellowship. Intra-operatively in all cases, if a tension-free primary neurorrhaphy could not be achieved following debridement, the use of an

interpositional graft was indicated and the surgeon opted to reconstruct the gap with a nerve allograft.

Patients were separated into three categories of nerve injury: acute, delayed and chronic. This classification was determined by the time taken from initial injury to the date of surgery. Patients presenting less than six weeks following injury, were defined as the 'Acute Nerve Injury' group. Patients presenting more than six weeks but less than six months following injury were defined as the 'Delayed Nerve Injury' group. Lastly, patients presenting later than six months following injury were defined as the 'Chronic Nerve Injury' group; these patients presented with either chronic pain or allodynia. Patients with a static mechanical allodynia were tested with allodynography in combination with a rainbow pain scale (35) to map the localization and severity of the hypersensitive territory (Fig. 1). All patients in the chronic nerve injury group had ultrasound guided local anaesthesia injections carried out on at least two separate pre-operative occasions to confirm the diagnosis of a localized neurogenic pain prior to surgical intervention.

Ethical approval for the study was obtained from the regional Ethical Committee and informed consent for all patients was obtained prior to surgical intervention. Statistical analysis using unpaired Student's t-tests was performed using GraphPad Prism (version 7.00 for Windows, GraphPad Software, La Jolla California USA) to compare different groups of the study and linear regression calculations were used to analyse relationships between patient and allograft characteristics and clinical outcomes; significance was attributed to results where $p \leq 0.05$.

Results:

2,499 nerve injuries in 1,475 patients were operated on between 1st April 2009 and 31st October 2017. 1,580 primary neurorrhaphies were completed in 1,188 patients, 207 nerve allografts were used in 156 patients and that 80 patients were treated with a combination of primary repairs and allografts. In total, 129 patients with 171 nerve allografts fulfilled the inclusion criteria. All

primary nerve repairs and 36 nerve grafts in 27 patients were excluded: 8 patients were under the age for licenced use and 19 patients were lost to follow-up, of these 16 were from the acute injuries, 2 from delayed injuries and 1 from a chronic neuroma (Fig. 2). 135 nerve grafts were used in 94 patients to treat acute nerve injuries with at a mean age at surgery of 45 years (range 18 – 82 years) with an average follow-up of 13 months (range 6 – 38 months). The mean length and diameter of the allografts used were 27 mm (range 8 – 100 mm) and 2 mm (range 1 – 5 mm) respectively. 77% of patients achieved a sensory outcome score of S3 or above and 36% achieved a motor score of M3 or above; scores above these levels are deemed to have meaningful recovery (36). A summary of the acute nerve injury results can be seen in Table 1.

Graft length, diameter and anatomical location were the only factors which statistical significance could be attributed to. Patients were allocated to one of four groups according to the length of graft used. The shorter length graft had significantly better outcomes than longer graft groups and grafts used in lower limbs had significantly poorer outcomes than either those used in the hand or upper limb ($p < 0.05$) (Figs. 3&4). Similarly, an increase graft diameter was associated with a significant reduction in outcome ($p<0.05$). Significant differences were seen in the outcomes of the type of sensory nerves reconstructed; pure sensory nerves yielded better sensory outcomes than the sensory component of mixed nerves. The impact of patient age, the mechanism of injury and if individuals with multiple nerve injuries was analysed but no significance was demonstrated (Fig. 4). One patient developed a surgical site infection requiring removal of the allograft; no other complications were noted.

10 allografts were used in 10 patients to treat delayed nerve injuries. The mean age at surgery was 40 years (range 18 – 77 years) with an average time between nerve injury and operation of 3 months (range 2 – 6 months); the mean follow-up was 13 months (6 – 25 months). 70% of patients achieved a sensory outcome score of S3 or above and 100% achieved a motor score of M3 or

above. No significance was demonstrated between outcomes from acute nerve injuries and delayed nerve injuries.

26 allografts were used in 25 patients (19 male, 6 female) with neurogenic pain. The mean age was 44 years (range 19 – 77 years) with an average time between nerve injury and operation of 3 years (range 1 – 16 years); the mean follow-up was 12 months (6 – 49 months). 17 allografts were used to treat upper limb neuropathic pain, of which six were digital nerves. Nine allografts were used for lower limb neuropathic pain. 18 allografts were used to treat injuries resulting from sharp lacerations, six from crush injuries and two from tumour resections. Overall, the mean diameter and length of allografts used was 3 mm (range 1 – 5 mm) and 37 mm (range 8 – 75 mm) respectively. There was no significant difference in lengths of allografts used in upper limb in comparison to lower limb, however the diameter of allografts used in the upper limb was significantly smaller ($p < 0.05$). A summary of this data can be seen in Table 2.

The median pre-operative NRS pain score was 7 (range 3 - 10) in comparison to the post-operative score of 3 (range 0 - 7); t-test statistical analysis revealed this to be a significant reduction in pain score ($p < 0.05$). Prior to surgical intervention 17 out of the 26 patients were taking regular medication for symptoms. Postoperatively this was significantly reduced to six patients ($p < 0.05$) with the category of non-steroidal anti-inflammatory drugs being most affected ($p < 0.05$) (Fig. 5). Similarly, there was a significant improvement in sensation; the pre-operative mean was S1 on the MRCC scale in comparison to S3 post-operatively ($p < 0.05$) and 57% of patients had a meaningful recovery of sensation following surgery.

Ten patients had symptoms of allodynia pre-operatively and all of these reported improvement in their symptoms on the rainbow scale from severe to none (0.03 g to 15 g) and had a significant reduction in the size of the affected area postoperatively ($p < 0.05$) (Fig. 1). Three patients had persistent symptoms of allodynia post operatively however, the area affected was smaller and the

severity had not worsened. A summary of this data can be seen in Table 3. No patients developed a higher level of pain or a diminished level of sensation following surgical intervention.

Discussion:

The purpose of this study was to review a single centre's use of nerve allografts in a variety of nerve injuries. 171 nerve allografts were included in this retrospective case series with patients grouped into acute, delayed and chronic nerve injuries. The inherent limitations of retrospective case series apply to this study as there is no control group, patient variables cannot be controlled and the vulnerability of bias all weaken the strength of any interpretations of these results.

Differences in outcomes based on anatomical distribution:

There is sufficient experimental data in this study to suggest that allografts yield results at least equal to autologous grafts supporting previous published reports (7, 30, 37-40). In an attempt to standardize variables, patients were grouped by age, mechanism of injury and anatomical location. In this series 84% of hand injuries had a meaningful level of recovery; this is comparable to similar studies in the literature (30, 31, 38-44) and re-confirm that allografts are a reliable option for managing digital nerve gaps (31, 42, 45, 46). Analysing outcomes based on anatomical region revealed that allografts used in the lower limb yielded the poorest outcomes. There was no statistical difference in allograft dimensions between the upper limb and lower limb groups, suggesting that allograft use in the lower limb may be independent prognostic factor. There are no published reports directly comparing the outcomes of upper and lower extremity nerve injuries however, the literature reporting lower limb outcomes following nerve grafting range from 14 – 75% with nerve gaps greater than 6 cm having significantly worse outcomes (47-51); the results of this study fall within this range. The literature reports that peripheral nerve lesions in the upper limb are not only more common but also have better outcomes when treated with nerve grafts (39 – 100%) (31). In our series, the mean length of allograft used in the upper limb was 45 mm and in

the hand 22 mm, which are longer than all published reports except one where the mean length was 79 mm (52); these grafts were confined to brachial plexus injuries. From our results, it would appear that more proximal nerve injuries yielded the poorest results possibly as a consequence of the distance the axons have to regenerate. This is well documented in the brachial plexus literature (52) and perhaps accounts for the poorer outcomes associated with lower limb injuries as regeneration must also occur over greater distances. It was interesting to demonstrate a difference in outcomes between pure sensory nerves and the sensory component of mixed nerves; this has not been described in the literature but may be explained by incorrect alignment at a fascicular level when grafting mixed nerves.

Effect of allograft parameters on outcomes:

The most striking results in study were that both an increase in allograft length and diameter yielded a significantly poorer outcome. Analysing the ungrouped data for graft-length demonstrated a significant negative correlation ($p < 0.001$, $r = -0.36$) between allograft length and outcome. When separating graft size into < 30 mm and those > 30 mm, the shorter group had a significantly better outcome ($p = 0.003$). 26 allografts greater than 50 mm in length were used in this study with 54% yielding a meaningful recovery and in one case two 50 mm allografts were combined in series to bridge a 100 mm gap; this result is comparable to the autograft literature reporting between 50 and 84%. A recent publication by Hoben *et al.* (15) postulates that longer grafts show increased accumulation of senescent markers and our findings support this clinically. The results from our study suggest that nerve allografts are not the solution to bridging large nerve gaps, particularly in mixed nerves. The outcome for motor recovery sharply diminished in grafts that were more than 5 cm and for sensory nerves the trend was similar but not as severe. Although the retrospective nature of this study weakens the findings, the number of nerve allografts used in

this study certainly adds weight to draw concerns regarding the efficacy of bridging long mixed nerve gaps.

An increased graft diameter was associated with a significantly poorer outcome. Overall, there was a significant negative correlation between diameter and outcome ($p < 0.0001$, $r = -0.34$) for all the data. Separating the results into those obtaining a meaningful recovery (n = 123) and those not (n= 40), the group with a meaningful recovery had a statistically significant lower mean diameter ($p = 0.003$). Only two of the allograft studies reviewed in this paper commented on the diameter of the graft used and in both the reported diameter was less than 2mm. In our study, allografts with diameters of up to 5 mm were used and the poorest outcomes were seen in larger diameter grafts, with > 3 mm in diameter appearing to be inhibitory to axonal regeneration. Best *et al.* (53) demonstrated that in large diameter nerve grafts, scar formation as a sequelae to central ischaemia develops; this is likely to be the case with our results and has recently been reported in three cases (54). However, in comparison to autologous nerve grafts, the allograft is perhaps more sensitive. The heterogenous nature of the patient population has inherent limitations when attempting to draw a definitive conclusion however the data supports that a long, thick graft is associated with the poorest outcomes (39, 55, 56). In this series one patient failed to have a meaningful recovery at 18 months follow-up and elected to undertake revision surgery. Initially the patient had reconstruction of their median nerve with a 50 mm x 4 mm allograft for chronic painful neuroma. The patient failed to have any improvement in their pain symptoms and at the time of revision the allograft was noted to be small and scarred. Histology confirmed that there was evidence of severe central necrosis with minimal evidence of successful axonal regeneration through the allograft (Fig. 6) supporting the notion of central ischaemia leads to scar formation.

Mixed Nerve Outcomes:

Twenty-five grafts were used to reconstruct mixed nerves. The mean diameter was 3.8 mm (range 1 – 5 mm) and mean length was 41 mm (range 15 – 70 mm). Eleven grafts yielded a meaningful sensory recovery (44%) and nine grafts yielded a meaningful motor recovery (36%). The poorer results demonstrated with increased diameter size is likely a consequence of central ischaemia within the graft, resulting in scar formation (53, 57) blocking the pathway for the axons to regenerate; furthermore, there is additional competition between regenerating motor and sensory axons and the allograft scaffold no longer has sufficient physical channels to permit adequate regeneration. The results suggest that in order to over-come this problem it may be better to use multiple smaller diameter grafts rather than one large diameter graft as this may reduce central ischaemia. Table 4 summarizes the literature cited and allows a succinct comparison between previously published studies.

Chronic Pain Outcomes:

There is currently one data series for the use of allografts for the treatment of chronic neurogenic pain reporting positive results in 26 patients in foot and ankle surgery (43, 58). Although they report a similar reduction in pain symptoms, the unreliable assessment of pre-operative sensation in this patient group meant that the authors were unable to accurately comment on the restoration of sensation. Surgical techniques based on burying or relocating nerve stumps are effective in improving the primary pain symptom (59-61) but there can be no effective recovery of sensation; this is particularly important when considering hand surgery or neuromas associated with amputations. Our study has shown that allografts can not only significantly reduce pain symptoms but also restore meaningful sensation in 57% of cases.

All patients were investigated pre-operatively with ultrasound. Of the 26 patients, 11 were seen to have end-neuromas and 15 had neuromas-in-continuity; these findings were confirmed intra-operatively. In both cases, the neuroma was completely excised and the proximal and distal nerve stumps were debrided so that healthy fascicles were seen in the proximal stump and healthy vascularized nervous tissue was seen in the distal stump. No statistically significant differences were demonstrated between the two groups ($p = 0.43$).

Ten of the patients in this study reported symptoms of allodynia pre-operatively. Although the results are insufficiently powered, every patient had a reduction in their symptoms, with some reporting complete resolution of hypersensitivity (Fig. 2). By treating the cause of neurogenic pain, there was a significant reduction from 65% to 23% of patients requiring pain medication post-operatively. Many of the medications used to treat chronic pain have adverse side effects such as drowsiness, inability to concentrate and the development of tolerance over time (62). The results from this study suggest that by using allografts, patients required lower levels of pain medication; in the long-term this may help to improve their quality of life. This finding cannot be taken in isolation as there are many confounding factors however, the results from this study warrant future prospective investigations into the benefits that allografts have in the management of pain in these patients.

From our experience we find that the most important step in the management chronic pain patients with peripheral nerve lesions is establish the exact pathogenicity. Time is required to precisely localize the source of the neurogenic pain and confirm that symptoms are not part of a diffuse central pain disorder. Therefore, several attempts to stop the pain by local anaesthesia and or change the pain intensity or territory by somatosensory rehabilitation (35) helps predict which patients will benefit from surgical intervention; through mapping it is possible to anticipate the

response to surgery hence it is an important documentation tool in recording surgical outcomes and the incorporation of this into routine practice would be highly recommended (Fig. 7).

Conclusion:

The results of this case series support a wider application of allografts in clinical practice. The outcomes obtained with allografts are comparable to autologous nerve grafts in short defects; the problems encountered with increased graft length and diameter associated with autologous nerve grafts are seen with allografts. This study supports recent literature to suggest that allografts provide a reasonable alternative for short grafts in the clinical setting and can yield similar outcomes without the associated risks of harvesting autologous grafts from a second surgical site. However, caution must be applied when implementing their use in long nerve gaps that require large diameter allografts. A well-designed multi-centre randomized controlled trial is needed to directly compare the outcomes of allografts with other treatment modalities in peripheral nerve injuries.

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Figure Legend:

Figure 1: Improvement of allodynia symptoms in patient CPG08. (Left) Pre-operative illustration of Semmes Weinstein monofilament testing demonstrating how light touch (0.03 g filament) could produce severe (red schematic) allodynia). (Right) Two years post reconstruction demonstrates a drastic reduction in both the area (purple schematic) and the pressure (15 g monofilament) required to produce allodynia symptoms, this remained unchanged at four-year follow-up.

Figure 2: A flow-diagram to demonstrate the inclusion and exclusion criteria of the study, showing the groups the allografts were separated into.

Figure 3: A scatter plot of MRCC outcomes against allograft length. There was a significant negative correlation ($p < 0.05$) associated with increased allograft length and outcome.

Figure 4: A summary of the statistical analysis results of the acute nerve injury group. (* $p < 0.05$, ** $p < 0.001$). No statistical difference was demonstrated between age (Top, left), mechanism of injury (Top, right) and between patients with single versus multiple nerve injuries (Middle, left). Longer graft length groups had significantly pooper outcomes (Middle, right), allografts use in lower limb nerve injuries had poorer outcomes (Bottom, left) and sensory recovery in mixed nerves was significantly worse than pure sensory nerves (Bottom, right).

Figure 5: A bar chart demonstrating the reduction in pain medication used pre- and post-operatively. (** - Significant reduction ($p < 0.05$), NSAID – Non-steroidal anti-inflammatory drug).

Figure 6: A failed allograft with histological findings. (Top, left) A 50 mm x 4 mm allograft was used to reconstruct a median nerve defect resulting from a large painful neuroma. (Top, right) At 18 months follow-up, the patient had no symptomatic improvement and elected to undertake revisional surgery. At the time of the surgery the clinical appearance of the allograft was similar to scarred tissue. (Bottom) Histological examination (H&E staining) demonstrated large areas of central necrosis with little evidence of axonal regeneration through the graft.

Figure 7: Clinical example - restoration of sensory function. (Top, left) A pre-operative photograph of the left medial malleolus. The patient (CPG22) suffered a grade IIIb pilon fracture with secondary osteomyelitis of his tibia 18 months previously. The defect had been covered with an osteocutaneous free scapular flap. The lightning bolt demonstrates the trigger point for neuropathic pain. (Top, right) Intra-operative photography depicting a gap in the tibial nerve after isolating the proximal and distal nerve stumps (red arrows). (Center) An acellular allograft (green arrows) was used to bridge the defect. (d) Semmes Weinstein monofilament testing pre- (bottom, left) and one year post-operatively (bottom, right) showing improved sensation in the distribution of the tibial nerve.

Table 1:A summary of the outcome of acute nerve injuries following treatment with nerve allograft.

Table 2:A summary of the patients and allograft details for all subjects treated in the chronic pain group. (NRS – Numeric Rating Scale, MRCC - Medical Research Council Classification)

Table 3:A summary of the sub-group of patients that exhibited symptoms of allodynia pre-operatively.

Table 4: A comparison table of the cited literature using nerve allografts for the reconstruction of nerve gaps.

Table 1. Outcomes: Acute nerve injuries

				Graft		Location			Nerve Type		Mechanism of Injury				Meaningful Recovery[b]	
Grouped Data	**n (m, f)**	**Age (years)[a]**	**Follow-up (days)[a]**	**Length (mm)[a]**	**Diameter (mm)[a]**	**Hand**	**Upper Limb**	**Lower Limb**	**Sensory**	**Mixed**	**Crush**	**Laceration**	**Avulsion**	**Iatrogenic**	**Sensory**	**Motor**
Age (years)																
18 - 34	40 (30, 10)	23.9 (SD 3.6)	416 (SD 188)	33.5 (SD 20.6)	2.58 (SD 1.34)	26	10	4	30	10	13	21	5	1	70.0%	18.1%
35 - 49	33 (29, 4)	41.9 (SD 6.0)	426 (SD 201)	27.0 (SD 16.6)	2.20 (SD 1.15)	26	3	4	26	7	12	16	5	0	78.8%	42.9%
50 - 64	46 (39, 7)	57.0 (SD 4.4)	402 (SD 219)	21.8 (SD 8.09)	1.99 (SD 0.84)	38	4	4	39	7	15	25	3	3	84.1%	57.1%
65+	16 (16, 0)	73.9 (SD 5.2)	423 (SD 307)	22.5 (SD 13.7)	1.94 (SD 0.93)	15	1	0	15	1	3	11	2	0	68.8%	0%
Gap Length (mm)																
5 - 14	20 (15, 5)	49.1 (SD 19.4)	409 (SD 98.0)	9.95 (SD 0.83)	1.60 (SD 0.50)	20	0	0	20	0	4	15	1	0	90.0%	-
15 - 29	49 (44, 5)	47.5 (SD 15.8)	387 (SD 200)	17.2 (SD 3.07)	2.00 (SD 0.74)	42	2	4	43	5	21	24	1	3	81.3%	66.7%
30 - 49	48 (41, 7)	44.7 (SD 17.7)	362 (SD 190)	30.8 (SD 3.17)	2.09 (SD 1.13)	37	9	1	39	8	11	31	6	0	74.5%	37.5%
50+	18 (12, 6)	34.7 (SD 18.3)	661 (SD 270)	58.8 (SD 14.1)	3.65 (SD 1.27)	5	7	5	7	10	7	3	7	1	52.9%	10.0%
Anatomical Location																
Hand	105 (92, 13)	46.9 (SD 17.6)	384 (SD 207)	22.3 (SD 10.6)	1.74 (SD 0.66)	-	-	-	105	0	30	63	12	0	83.8%	-
Upper Limb	18 (11, 7)	36.9 (SD 16.6)	479 (SD 184)	44.8 (SD 23.8)	4.01 (SD 0.84)	-	-	-	5	12	7	8	3	0	72.2%	25.0%
Lower Limb	12 (11, 1)	41.2 (SD 15.5)	610 (SD 208)	37.5 (SD 18.0)	3.42 (SD 0.99)	-	-	-	0	12	6	2	0	4	25.0%	41.7%
Mechanism of Injury																
Crush	41 (37, 4)	43.6 (SD 16.7)	441 (SD 184)	28.8 (SD 19.1)	2.54 (SD 1.14)	28	7	6	31	10	-	-	-	-	70.7%	30.0%
Laceration	73 (65, 8)	46.6 (SD 18.1)	339 (SD 158)	22.5 (SD 10.9)	1.97 (SD 0.94)	63	8	2	65	8	-	-	-	-	83.7%	25.0%
Avulsion	15 (7, 8)	40.9 (SD 19.1)	643 (SD 287)	42.3 (SD 19.0)	2.27 (SD 1.53)	12	3	0	12	3	-	-	-	-	80.0%	33.3%
Other	4 (3, 1)	55.7 (SD 5.32)	656 (SD 308)	26.3 (SD 16.0)	2.75 (SD 1.50)	0	0	4	0	4	-	-	-	-	0.0%	75.0%
All Acute Data	135 (114, 21)	45.1 (SD 17.6)	417 (SD 214)	26.6 (SD 16.0)	2.19 (SD 1.11)	105	18	12	110	25	43	73	15	4	77.0%	36.0%

[a] *Report in mean ± Standard Deviation (SD)*

[b] *Meaningful Recovery defined as having a score of S3-S4 or M3-M5 according to the modified MRCC outcome*

Patient Details					Pain NRS Score		Sensation Score (MRCC)			Mechanism of Injury			Anatomical Details		
Patient ID	Gender	Age (years)	Follow up (days)	Operative Interval (days)	Preop	Postop	Preop	Postop	Allodynia	Laceration	Crush	Tumour	Causative Nerve	Allograft Diameter (mm)	Allograft Length (mm)
CPG01	M	39	610	195	7	0	S0	S3+		✔			Superficial peroneal n.	3.5	30
CPG02	M	52	354	48	7	5	S1	S2			✔		Superficial radial n.	3	70
CPG03	F	27	382	> 3 yrs	5	0	S3	S4				✔	5th Radial digital n.	1.5	30
CPG04	M	49	525	891	9	3	S0	S3+		✔			Dorsal ulnar n.	3	30
CPG05	M	19	362	826	6	0	S1	S4		✔			Genito-femoral n.	3	30
CPG06	F	48	356	748	8	3	S0	S3	✔	✔			Superficial peroneal n.	2	50
CPG07	M	60	385	242	9	4	S0	S2	✔	✔			Saphenous n.	3	50
CPG08	M	30	1504	2556	10	2	S1	S2	✔		✔		2nd Radial digital n.	3	30
CPG09	M	44	476	973	7	6	S1	S3+	✔		✔		Medial brachial cutaneous n.	3	60
CPG10	M	39	389	161	8	0	S1	S3+		✔			Superficial radial n.	3	15
CPG11	M	40	354	4440	9	4	S0	S2	✔	✔			Superficial ulnar n.	2	40
CPG12	M	42	297	102	3	0	S1	S4		✔			4th Radial digital n.	1.5	8
CPG13	M	46	285	667	9	4	S0	S2	✔		✔		4th Ulnar digital n.	1.5	45
CPG14	M	56	383	5968	6	3	S0	S3		✔			Superficial radial n.	3	20
CPG15	M	77	377	102	5	0	S1	S2		✔			Median n. (sensory)	3	30
CPG16	F	47	300	696	8	7	S0	S3	✔	✔			1st Ulnar digital n.	1.5	15
CPG17	F	47	300	696	8	7	S0	S3	✔	✔			2nd Ulnar digital n.	1.5	15
CPG18	M	47	360	378	5	0	S1	S3		✔			Superficial radial n.	2	50
CPG19	M	36	180	306	5	5	S0	S0		✔			Superficial radial n.	3	40
CPG20	F	51	400	601	9	4	S0	S2	✔	✔			Inferior medial genicular n.	2	15
CPG21	M	48	360	42	5	0	S1	S3		✔			Dorsal ulnar n.	3	15
CPG22	M	37	420	565	5	0	S0	S2			✔		Tibial n.	5	70
CPG23	F	60	355	2896	7	4	S1	S2				✔	Median n. (sensory)	3	75
CPG24	F	18	220	1290	8	2	S1	S3			✔		Tibial n.	4	70
CPG25	M	50	360	330	7	6	S0	S2	✔	✔			1st Radial digital n.	2	25
CPG26	M	27	250	66	5	0	S0	S3+		✔			Tibial n.	4	30

Table 2

Patient Details				Nerve affected	Pre-Operative Assessment		Post-Operative Assessment		Total area reduction (%)
Patient ID	Gender	Age (years)	Follow up (days)		Rainbow Scale	Monofilament Weight (g)	Rainbow Scale	Monofilament Weight (g)	
CPG06	F	48	356	Superficial peroneal n.	Green	1.5	-	-	100
CPG07	M	60	385	Saphenous n.	Blue	3.6	-	-	100
CPG08	M	30	1504	2nd Radial digital n.	Violet	15	Blue	3.5	95
CPG09	M	44	476	Medial brachial cutaneous n.	Violet	15	-	-	100
CPG11	M	40	354	Superficial ulnar n.	Violet	15	-	-	100
CPG13	M	46	285	4th Ulnar digital n.	Violet	15	-	-	100
CPG16	F	47	300	1st Ulnar digital n.	Blue	3.6	-	-	100
CPG17	F	47	300	2nd Ulnar digital n.	Blue	3.6	-	-	100
CPG20	F	51	400	Inferior medial genicular n.	Indigo	8.7	Indigo	8.7	0
CPG25	M	50	360	1st Radial digital n.	Violet	15	Violet	15	20

Table 3

Table 4

				Graft		Location			Nerve Type (n)			Meaningful Recovery[b] (%)		
Reference	**Grafts (n)**	**Age (years)[a]**	**Follow-up (days)[a]**	**Length (mm)[a]**	**Diameter (mm)[a]**	**Hand**	**Upper Limb**	**Lower Limb**	**Sensory**	**Mixed**	**Motor**	**Sensory**	**Mixed**	**Motor**
This study	135	45 ± 18	417 ± 214	27 ± 16	2 ± 1	105	18	12	110	25	-	77		36
Brooks *et al.* (41)	76	41 ± 17	264 ± 152	22 ± 11	-	60	32	3	49	18	9	89	77	86
He *et al.* (55)	72	33 ± 11	180	18 ± 8	1.5 ± 0.5	72	-	-	72	-	-	72	-	-
Cho *et al.* (44)	51	44 ± 16	296 ± 160	23 ± 12	-	35	16	-	35	13	3	86	-	80
Rinker *et al.* (46)	37	43	480	11 ± 3	-	37	-	-	37	-	-	92	-	-
Taras *et al.* (40)	18	39 ± 19	455 ± 138	11 ± 7	-	18	-	-	18	-	-	100	-	-
Safa *et al.* (31)	14	34	360	30	-	-	14	-	-	14	-	-	86	-
Squintani *et al.* (52)	14	33 ± 12	720	79 ± 39	-	-	14	-	-	-	14	-	-	100
Karabekmez *et al.* (39)	10	43 ± 15	255 ± 85	2 ± 1	2 ± 0.5	10	-	-	10	-	-	100	-	-
Ducic *et al.* (45)	8	46 ± 18	130 ± 90	18 ± 8	-	-	8	-	-	-	-	-*	-	-
Guo *et al.* (56)	5	29 ± 8	396 ± 48	23 ± 4	2 ± 0	5	-	-	5	-	-	100	-	-

[a]*Report in mean ± Standard Deviation (SD)*

[b] *Meaningful Recovery defined as having a score of S3-S4 or M3-M5 according to the modified MRCC outcome*

* *Outcome measured according to the QuickDASH score*

Figure 1

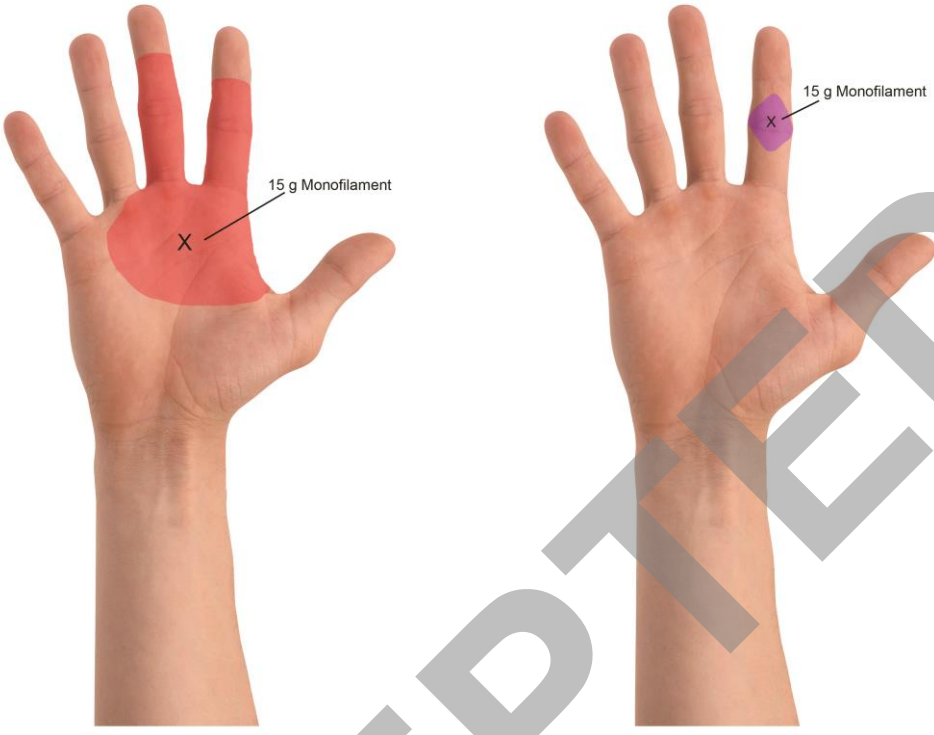

Figure 2

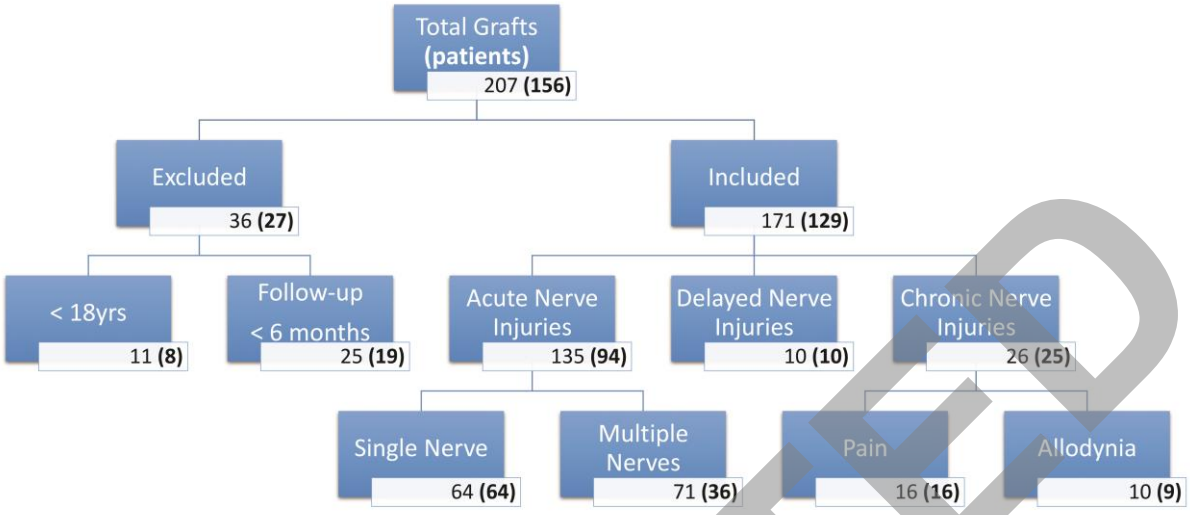

Figure 3

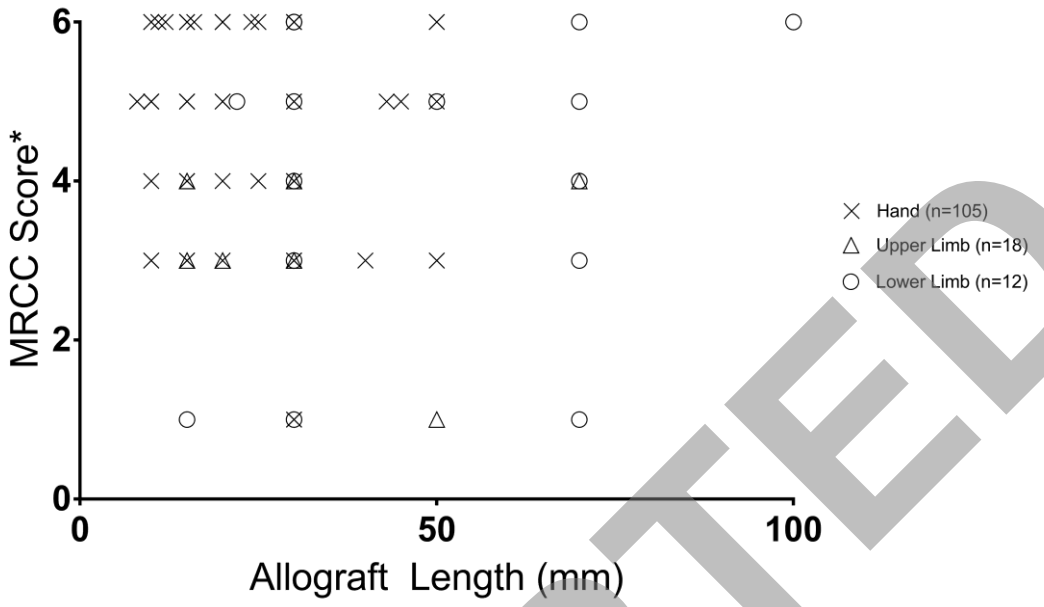

Figure 4

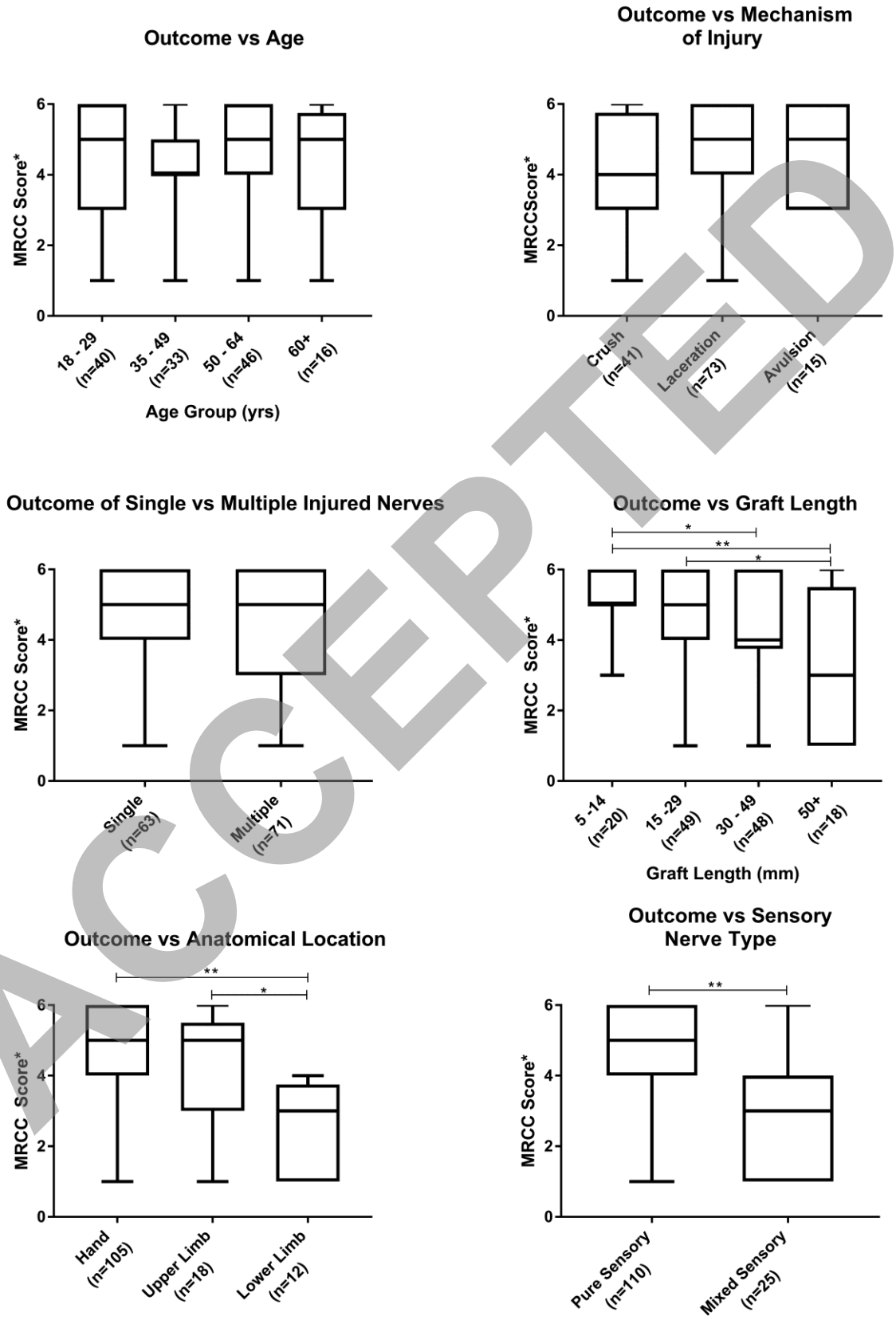

Figure 5

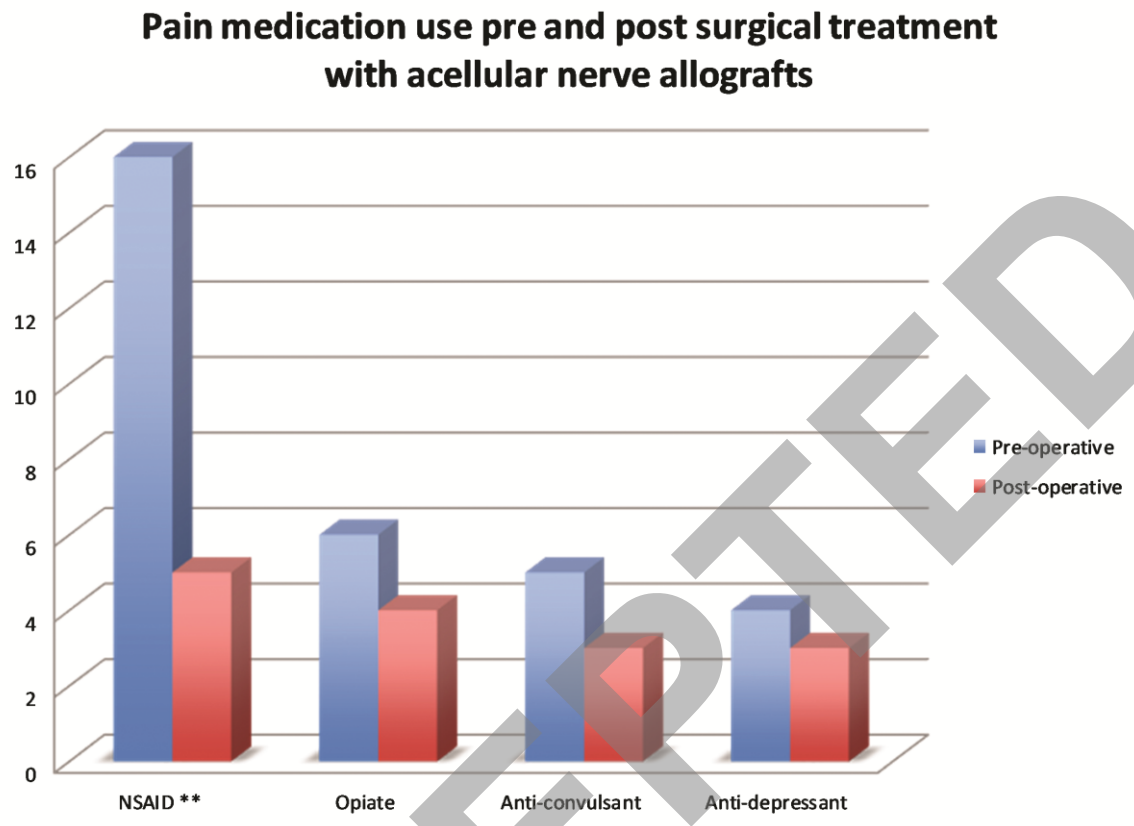

Figure 6

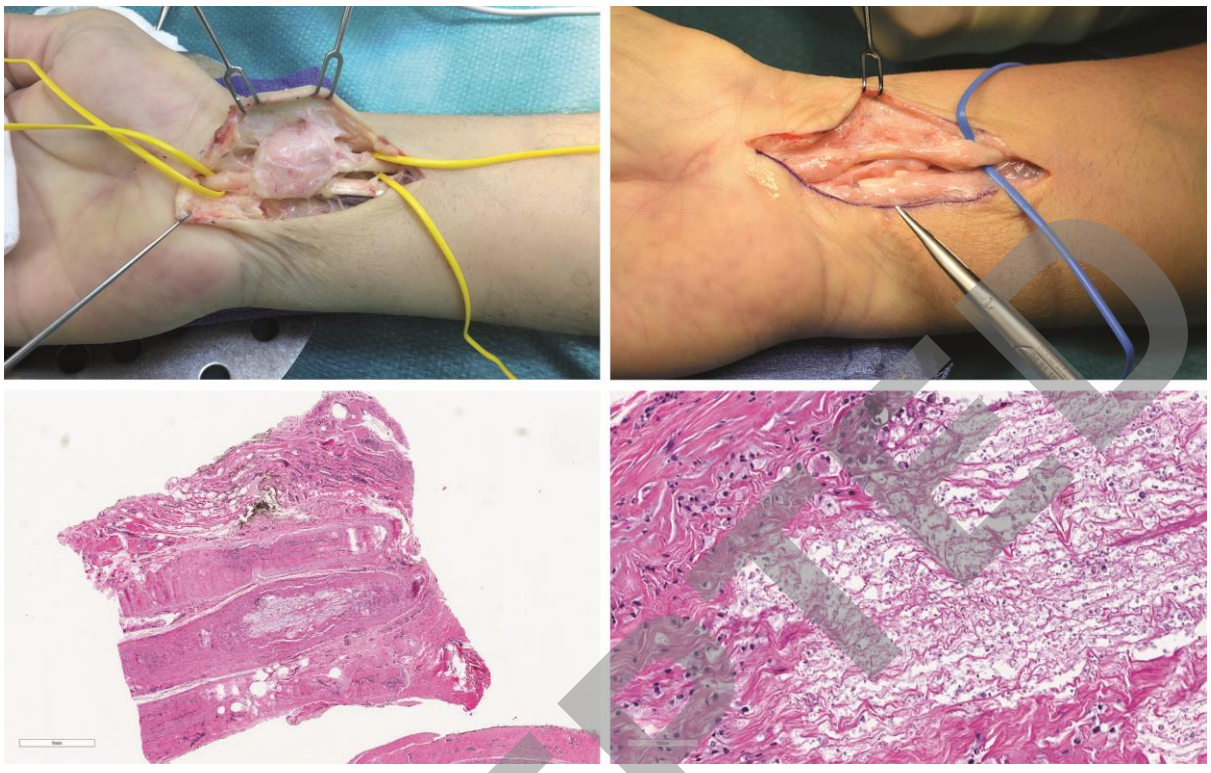

Figure 7