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Hand/Peripheral Nerve

Clinical Outcomes of Symptomatic Neuroma Resection and Reconstruction with Processed Nerve Allograft

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Background: Neuromas causing sensory disturbance can substantially affect nerve function and quality of life. Historically, passive termination of the nerve end and proximal relocation to muscle or bone has been performed after neuroma resection, but this method does not allow for neurologic recovery or prevent recurrent neuromas. The use of processed nerve allografts (PNAs) for intercalary reconstruction of nerve defects following neuroma resection is reasonable for neuroma management, although reported outcomes are limited. The purpose of this study was to assess the outcomes of pain reduction and functional recovery following neuroma resection and intercalary nerve reconstruction using PNA.

Methods: Data on outcomes of PNA use for peripheral nerve reconstruction were collected from a multicenter registry study. The registry database was queried for upper extremity nerve reconstruction with PNA after resection of symptomatic neuroma. Patients completing both pain and quantitative sensory assessments were included in the analysis. Improvement in pain-related symptoms was determined via patient self-reported outcomes and/or the visual analog scale. Meaningful sensory recovery was defined as a score of at least S3 on the Medical Research Council Classification scale.

Results: Twenty-five repairs involving 21 patients were included in this study. The median interval from injury to reconstruction was 386 days, and the average nerve defect length was 31 mm. Pain improved in 80% of repairs. Meaningful sensory recovery was achieved in 88% of repairs.

Conclusion: Neuroma resection and nerve reconstruction using PNA can reduce or eliminate chronic peripheral nerve pain and provide meaningful sensory recovery.
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INTRODUCTION

Neuroma formation caused by peripheral nerve injury is a common and potentially debilitating condition associated with the disorganized growth and generation of hypersensitive nerve tissue.[1] Neuroma-related neuropathic pain may severely affect patient function and quality of life and can require multiple costly surgical interventions[2] due to high recurrence rates.[3] Often, pharmacologic intervention is unsuccessful, as 60%–70% of patients are unresponsive to symptomatic pain management techniques,[4] which supports the role of surgical reconstruction as a salvage treatment. Surgical outcomes may be limited in patients experiencing chronic neuropathic pain due to adverse influences of comorbid conditions such as depression and chronic opioid use.[5,6]

Neuroma resection removes the physical source of neuropathic pain; however, if the nerve end is left untreated after resection, the symptomatic neuroma can reform. Recently, several contemporary surgical techniques have been developed to prevent recurrent neuroma formation, including targeted muscle reinnervation, regenerative peripheral nerve interface,[7] and nerve capping.[8] However, in the setting where both the proximal and distal nerve ends are available for intercalary reconstruction,

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restoration of nerve continuity may provide favorable outcomes.[8,9] Although methods such as targeted muscle reinnervation, regenerative peripheral nerve interface, and nerve capping can be efficacious in reducing neuroma pain, they do not provide potential for restoration of the nerve's original function.[10] Nerve reconstruction promotes physiologic axon regeneration and minimizes growth of abnormal fibrous tissue, thereby minimizing the risk of recurrent neuroma formation while also facilitating potential recovery of somatic and autonomic function and restoring afferent signaling pathways.[11]

At the time of neuroma excision, direct repair is often not a viable option for reconstruction due to excessive tension that would be realized at the potential primary repair site secondary to the anticipated gap following neuroma resection.[10,12] Nerve autograft is an option for reconstruction and has been utilized for this purpose after neuroma excision.[13,14] However, this method creates a new nerve deficit at the donor site that is associated with potential complications and additional comorbidities. Autograft donor sites can cause undesirable sensory symptoms such as cold intolerance and dysesthesias in up to 28.5% of patients,[15] as well as chronic pain, which ironically is most likely due to de novo neuroma formation in up to 22.9%.[16,17] Therefore, the use of an autograft to reconstruct a nerve defect at the time of neuroma excision has the potential to incompletely manage the primary complaint(s) and to add a symptomatic neuroma at a distant site in a patient already exhibiting neuropathic pain sensitization.

An alternative to the reconstruction of a nerve defect using traditional nerve autografts is to use commercially available processed nerve allograft (PNA; Avance Nerve Graft, Axogen, Alachua, Fla.). PNAs are decellularized, pre-degenerated, and sterilized extracellular matrix processed from donated human peripheral nerve tissue. The allograft serves as a scaffold to organize and support the regenerating axons. Clinically, PNAs are advantageous in that they are readily available in multiple diameters and lengths, and the absence of a donor site to acquire autograft nerve tissue for reconstruction minimizes patient morbidity, potentially reduces operative time, and eliminates risk of additional neuroma formation at the potential harvest site.

Extensive clinical data suggest that PNAs are safe and can be used in the reconstruction of nerve gaps of up to 70 mm.[18–23] Several studies have evaluated the outcomes of PNA for reconstruction after neuroma resection. Souza et al demonstrated that neuroma resection and subsequent allograft reconstruction in the foot and ankle contributed to significant decreases in ordinal pain scores as well as the pain behavior and interference scores on the Patient Reported Outcomes Measurement Information System instrument.[24] Unfortunately, this study did not report on sensory recovery. In a separate study, Leckenby et al evaluated both pain reduction and sensory recovery after neuroma resection with allograft reconstruction in a series of 26 patients.[25] They reported improvements in pain-related symptoms for all patients and a reduction in pain medication use after surgery from 65% to 23% of patients. They found that meaningful sensory function [the Medical Research Council Classification (MRCC) scale ≥ S3] was restored in 57% of their patients. These outcomes are in contrast to those described by Taras et al, who evaluated acute digital nerve trauma and showed improvement in pain with neuroma resection and allograft reconstruction in 83% of patients with good or excellent sensory recovery.[26] Therefore, we investigated outcomes of nerve reconstruction using PNA at the time of symptomatic neuroma resection to assess postsurgical pain symptoms and sensory function.

METHODS

The Registry of Avance Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction (RANGER, ClinicalTrials.gov Identifier: NCT01526681) study is a multicenter, IRB-approved registry designed to collect safety, utility, and efficacy data on PNA. RANGER is conducted under institutional review board approval in accordance with good clinical practice standards. As the registry is inclusive of nerve repairs in all regions of the body, specific follow-up time and assessments vary based on the treated nerve and distance of reinnervation. Therefore, treatment, rehabilitation regime, and follow-up were determined by each site's standard of care and the needs of the patient (Medical Research Council).

The RANGER registry database was queried for patients with neuroma resection and subsequent repair with PNA in the upper extremity. To qualify for the present study, patients were required to have reported qualitative or quantitative pre and postoperative pain assessments as well as sensory follow-up assessments at a time-point commensurate with the approximated distance for reinnervation, based on estimated 1–2 mm per day regeneration to the target zone of reinnervation. Patients were excluded from analysis if the PNA repair was not associated with symptomatic neuroma resection; if the neuroma resection and PNA repair was not in the upper extremity; if the subject's information in the registry did not include qualitative or quantitative pre- and postoperative pain and sensory assessments; or if the follow-up time was too soon for the estimated 1–2 mm per day regeneration for their specific nerve gap distance.

Data collected included general subject demographics, details of the nerve injury and neuroma formation, concomitant injury, nerve repair(s) performed, concomitant treatments, adverse events, follow-up evaluations performed, and corresponding outcomes, including meaningful patient recovery and postoperative pain assessments.

Meaningful patient recovery was assessed via the MRCC scale with measurements greater than or equal to S3 designated as meaningful recovery.[1,4,7–10,12,21,23,24,27–30] Alteration in pain symptoms was determined by comparing patient self-reported pain symptoms pre- and post repair. Repairs were assigned a status of either "improvement" or "no improvement" of pain symptoms. Further analysis by status was completed in a subset of patients reporting postoperative VAS pain scores. Safety assessments and additional subgroup analysis of improvement in functional outcomes was completed by nerve type and gap length. The Fisher

exact test was used to evaluate the statistical significance between subgroups and comparisons between the means were assessed via a two tailed *t*-test. A *P* value less than 0.05 was considered significant.

RESULTS

Twenty-five neuromas included in this study were treated in 21 patients by resection and concomitant nerve reconstruction with intercalary PNA. This study included 20 sensory and five mixed sensorimotor nerve reconstructions. All coaptations were performed in a tensionless fashion via epineural suture using size-matched PNA according to product instructions for use (see Fig. 1). The average age of patients in this cohort was 53 years (range: 32–77 years) with a median operative interval from injury to reconstruction of 386 days (range: 49–4748 days). Average nerve gap length following neuroma excision was 31 mm (range: 13–60 mm). Indications for surgery included untreated injuries in nine patients (10 neuromas), failed direct repair in seven patients (eight neuromas), failed conduit and allograft repairs in one patient (one neuroma) each, and unspecified failed repairs in three patients (five neuromas). Summary statistics for the patient cohort are reported in Table 1.

Overall, improvement in pain following surgical reconstruction based on patient subjective reporting was observed in 80% of repairs (Table 2). Twenty percent of repairs were subjectively reported as showing no improvement in pain, including one patient with subjective reporting of worsened pain. Postoperative VAS scores were available for 17 of the 25 repairs. This includes 13 of 20 repairs in the "improvement" group and four of the five repairs in the "no improvement" group. The mean VAS score in patients reporting improvement in pain

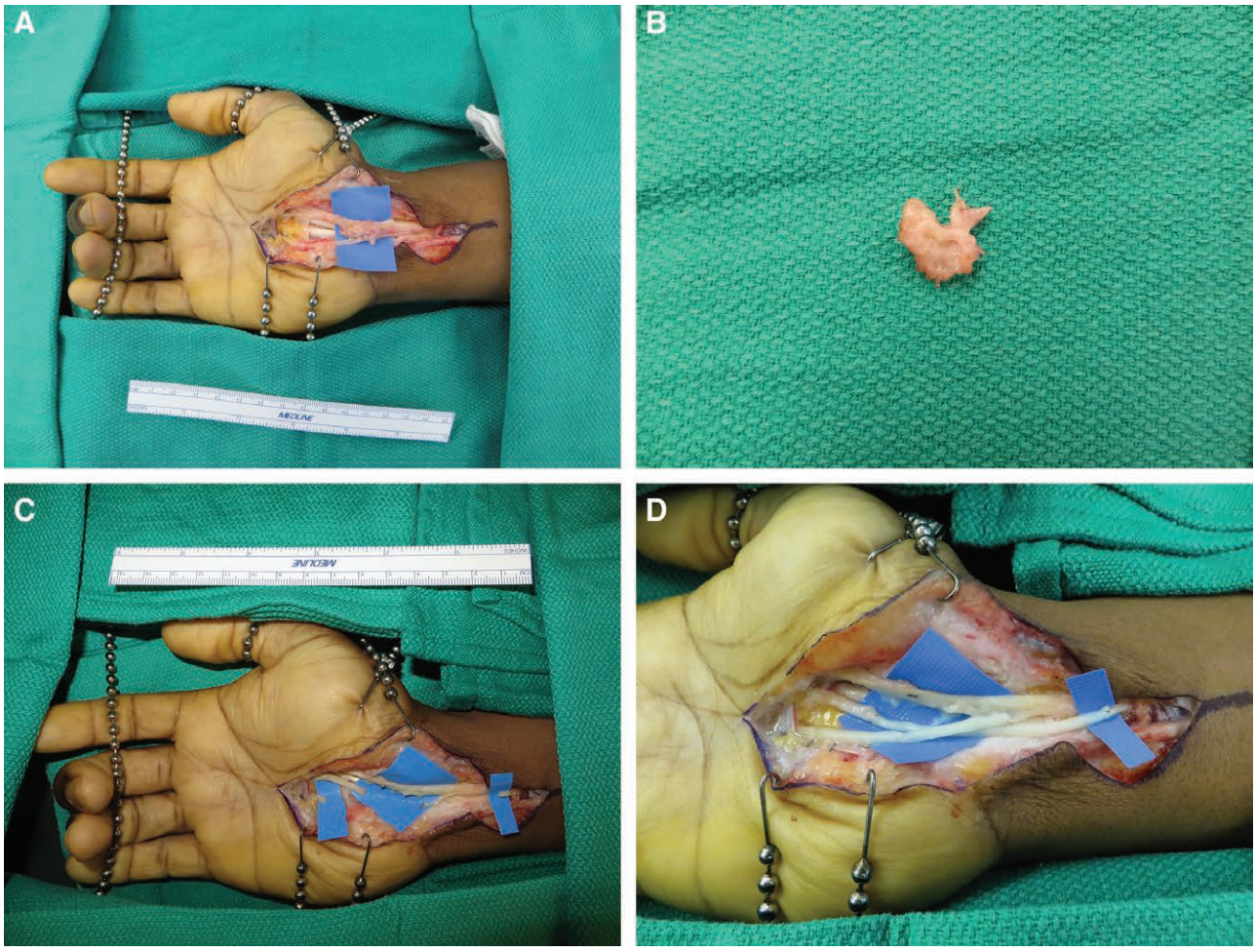

Fig. 1. Neuroma resection and reconstruction with PNA. A, A 45-year-old man with previous nerve repair history of a partial laceration to median nerve sustained during a carpal tunnel release of his right hand. The patient presented 3 years and 5 months post injury with a large painful neuroma in continuity of the median nerve. B, Excised neuroma after internal neurolysis of the median nerve. C, Resection of the neuroma resulted in an approximate 30-mm gap in the nerve to the second webspace and an 80-mm gap in the nerve to the third webspace. D, Nerve transfer with PNA was elected due to the large defect of the third webspace and more distal location of the second webspace nerve defect. This was performed by coapting the proximal sensory fascicles of the second web space digital nerve to the third webspace common digital nerve and vice versa. Reconstruction was performed with two 50 mm × 2–3 mm PNAs, and the proximal and distal coaptations were protected with porcine small intestine submucosa nerve wraps secured with microclips. The patient reported improvement in pain post surgery and return of sensation to S3+.

Table 1. Summary of Patient Demographics and Outcomes

Patient Demographics	
No.	21 with 25 nerve injuries
Average age (y)	53 (32–77)
Median preoperative interval (d)	386 (49–4748)
Average gap length (mm)	31 (13–60)
Reason for surgery	
Untreated injury	10 (40%)
Failed direct repair	8 (32%)
Failed conduit repair	1 (4%)
Failed allograft repair	1 (4%)
Failed repair, method not specified	5 (20%)
% Overall improvement in pain	80
% Overall meaningful recovery (≥MRCC S3)	88

Table 2. Summary of Postsurgical VAS Scores for Patients Reporting either Improvement or No Improvement in Self-reported Postsurgical Pain

Pain Symptoms	No. Repairs/Total Repairs	VAS Score*
Improvement	20/25 (80%)	2.1 ± 1.7 (0–5)
No improvement	5/25 (20%)	7.8 ± 2.3 (4–10)

*$P \leq 0.001$.
Data are mean ± SD.

symptoms was 2.1 ± 1.7 after an average follow-up time of 386 days compared with a mean VAS of 7.8 ± 2.3 after a mean follow-up time of 383 days in patients reporting no improvement. These values were significantly different ($P < 0.001$; Table 2). No related adverse events were reported. Table 3 summarizes demographic data, previous reconstruction status, nerve type, and whether a nerve wrap or sealant was used for patients with and without VAS scores. The majority of repairs involved a digital nerve. The exceptions to this were two median nerve repairs, three ulnar nerve repairs, and one radial nerve repair in the "improvement" group. In the "no improvement group," the only two repairs that were not digital nerves were one repair of the ulnar nerve (which had a VAS score) and one repair of the median nerve (which did not have a VAS score).

In regard to gap length, patients reported a subjective improvement in 12 of 16 repairs less than or equal to 30 mm, and in eight of nine repairs over 30 mm. The Fisher exact test revealed no significant association between gap length (≤30 mm) and subjective pain reporting (improvement or no improvement).

Overall meaningful sensory recovery (≥S3 on the MRCC scale) was 88%. No significant differences in pain status or functional recovery by nerve type and gap length were seen. Meaningful sensory recovery was achieved in 90% of sensory nerves and in 80% of mixed sensorimotor nerves. When considered according to gap length, meaningful sensory recovery was achieved in 88% for both short (10–30 mm) and long (31–60 mm) gap repairs.

DISCUSSION

The RANGER study was designed to create a database of nerve reconstruction outcomes throughout the body, and the goal of this study was to determine if reestablishing nerve continuity with intercalary PNA at the time of neuroma resection would improve pain symptoms and facilitate meaningful sensory recovery. Our study identified that peripheral nerve allograft reconstruction at the time of neuroma resection was safe and led to an overall meaningful sensory recovery rate of 88% and improvements in pain for 80% of nerve reconstruction procedures.

All but one of the patients included in this analysis underwent neuroma resection and PNA reconstruction 150 days or more following their original injury. Interestingly, eight of 25 repairs were performed more than 3 years after injury (two of which were more than 12 years after injury) and all eight obtained meaningful sensory recovery. Our data suggest that successful pain reduction as well as meaningful recovery of sensory function may be attainable despite extended time from injury. Our findings support the concept that if a distal nerve end is available, nerve gap reconstruction with PNA may be a reasonable treatment strategy.

When faced with patients presenting with symptomatic neuroma from very old nerve injuries, a surgeon may understandably opt for passive methods of neuroma treatment such as traction neurectomy or nerve implantation into adjacent muscle or bone.[31] However, traction neurectomy is associated with high rates of neuroma recurrence[31–33] and rates of successful reduction in pain after nerve burial are highly variable with reported success rates of 40%–81% for burial in muscle and 33%–91% for burial in bone.[7,33] The results of this study demonstrate that reconstruction of the nerve, even 3 or more years after the injury, results in improvement in pain that is comparable, if not better than, the rates reported for burial in the muscle or bone while also providing the potential for meaningful functional recovery.

The outcomes of our study compare favorably with historical data in the literature for the surgical treatment of neuromas and reconstruction with PNA in terms of functional recovery[34–36] and reductions in pain.[35] Bi et al presented a clinical case of immediate pain improvement in a patient with intercostal nerve neuroma after neuroma resection and reconstruction with PNA.[33] In a larger study, Jones et al found that neuroma resection and use of nerve allografts for end-to-end reconstruction was effective in relieving pain in traumatic nerve injuries in military veterans, as assessed by the 11 point PI-NRS scale,[36] with 90% and 50% reductions in narcotic use after 6 months in early and late surgical interventions, respectively. In a systematic review, Dickson et al found that digital neuroma excision followed by PNA reconstruction provided an 80% success rate in pain improvement as measured by VAS and patient evaluation measure scores.[34] Additionally, Souza et al found significant decreases in ordinal pain scores as well as in pain behavior and interference scores on the Patient Reported Outcomes Measurement Information System instrument after neuroma resection and allograft repair in the lower extremities.[24] These outcomes support the method of neuroma resection and concomitant nerve reconstruction with PNA as effective in reducing neuropathic pain and for restoring nerve continuity, thereby

Table 3. Summary of Patient and Nerve Repair Characteristics

Pain Symptoms	VAS Score Available	Gap (mm)	Age	Smoking Status (% Current Smoker or if n = 1, Yes or No)	Previous Reconstruction (% or if n = 1, Yes or No)	Repaired Nerve (% Digital Nerves or if n = 1, Yes or No)	Nerve Wrap (% or if n = 1, Yes or No)	Sealant (% or if n = 1, Yes or No)
Improvement	Yes (n = 13)	31.8	52.2	31	46.2	53.8	62	27
	No (n = 7)	33.6	53.6	14	100	100	43	0
No improvement	Yes (n = 4)	20	56.3	0	25	75	50	25
	No (n = 1)	40	44	No	Yes	No	No	No

Mean values are reported for gap length and age.

reducing the risk of neuroma recurrence and potentiating nerve regeneration and restoration of meaningful sensory function.

Determining which patients are candidates for neuroma resection and intercalary PNA reconstruction can be difficult because there have been no validated diagnostic criteria established for differentiating between nociceptive pain and chronic neuropathic pain due to a neuroma. Given the registry-based nature of the study, we were unable to determine the diagnostic methods used for the patients included in this study. However, one recent meta-analysis of 50 articles[37] has identified criteria that may assist in the diagnosis of symptomatic neuroma to help determine which patients may benefit from neuroma surgery. These criteria include a history of nerve injury, with symptoms in a defined anatomical distribution and pain with at least three of the following characteristics: burning, sharp, shooting, electric paresthesias, numbness, and cold intolerance. In addition, it is recommended that the patient also have either a positive Tinel's sign, a positive response to local anesthetic injection, or confirmation of neuroma on ultrasound or MRI.[37] Use of these criteria may be helpful in determining eligibility for patients who may benefit from neuroma resection and intercalary PNA reconstruction to promote pain reduction and to allow for physiologic nerve regeneration.

It is interesting to note that 60% of neuromas in this study formed after a failed repair, emphasizing the critical importance of good technique for minimizing the potential for neuroma formation. Good technique includes resecting back to healthy tissue and avoiding tension at the repair site. Tension can increase the risk for catastrophic failure at the coaptation site and can cause ischemia and poor axonal regeneration, which can lead to misaligned fascicles and subsequent neuroma formation.[38–43] The application of these principles to neuroma resection and concomitant intercalary PNA reconstruction is key to minimizing the potential for neuroma recurrence. Additionally, the use of PNA for reconstruction after neuroma resection may be advantageous, given that preclinical studies have demonstrated that allografts produced using the same Avance process as clinically available Avance nerve allografts reduced neuroma formation and aberrant intrafascicular and extrafascicular axon regeneration.[44,45]

In our study, 10 of 21 patients (48%) were treated for neuromas that resulted from failure to determine and treat nerve damage after injury, whereas 11 of 21 patients were treated for neuromas after nerve repair surgery. Early diagnosis of a nerve injury with prompt appropriate intervention is key to improving outcomes and preventing neuropathic pain. Following injury, sensorimotor dysfunction, loss of sudomotor and vasomotor function, and a positive Tinel's sign are indicative of a nerve injury necessitating repair.

Despite encouraging outcomes, we recognize that our results are limited by the observational design of our study and lack of active controls. We also recognize the inherent limitations of the MRCC scale in defining meaningful outcomes. Another limitation is the binary nature of the improvement in pain symptoms, as preoperative VAS scores were unavailable for the present study, and thus an analysis of changes from the baseline was impossible. However, preoperative neuroma VAS scores have been reported to range from 6.4 to 7.5 in the literature,[24,46,47] which is in line with the average score of 7.8 in patients who did not report postsurgical improvement in pain in this study and indicates that the average score of 2.1 seen in the patients who reported postsurgical improvement in pain likely represents a substantial improvement.

CONCLUSIONS

We demonstrate in this analysis of 25 neuromas in 21 patients that neuroma resection and concomitant intercalary reconstruction with PNA provided meaningful improvements in patient pain scores and effective sensory recovery. PNA reconstruction involves the use of standard microsurgical techniques and an off-the-shelf nerve graft available in a variety of sizes to provide size-matched reconstruction. This reconstruction method may provide advantages when intercalary grafting is feasible, even in very chronic injuries, over current methods of passive traction neurectomy with or without implantation into local muscle or bone by providing more consistent outcomes, reducing the risk of recurrent symptomatic neuroma formation and allowing for the regenerative potential for functional recovery. In considering nerve graft sources for intercalary grafting, compared with nerve autograft harvest, PNA eliminates the need for a second surgical site and a second nerve injury site, and reduces potential operating room time and complication rates associated with nerve autograft harvest. These differences in autograft and PNA reconstructions offer clear benefits for patients. Next steps should include cost–benefit analyses as well as lower extremity cases to accelerate adoption of PNA reconstructions for symptomatic neuromas.

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REFERENCES

1. Ducic I, Yoon J, Eberlin KR. Treatment of neuroma-induced chronic pain and management of nerve defects with processed nerve allografts. *Plast Reconstr Surg Glob Open*. 2019;7:e2467.
2. Gottlieb RW, Westenberg RF, Chen NC, et al. Long-term outcomes after surgical treatment of radial sensory nerve neuromas: Patient-reported outcomes and rate of secondary surgery. *Plast Reconstr Surg*. 2021;147:101–111. .
3. Lu C, Sun X, Wang C, et al. Mechanisms and treatment of painful neuromas. *Rev Neurosci*. 2018;29:557–566.
4. Decrouy-Duruz V, Christen T, Raffoul W. Evaluation of surgical treatment for neuropathic pain from neuroma in patients with injured peripheral nerves. *J Neurosurg*. 2018;128:1235–1240.
5. Belbachir A, Fuzier R, Biau D. Unexplained pain after scheduled limb surgery. *Orthop Traumatol Surg Res*. 2020;106:S13–S18.
6. Zhao S, Chen F, Feng A, et al. Risk factors and prevention strategies for postoperative opioid abuse. *Pain Res Manag*. 2019;2019:7490801.
7. Wu J, Chiu DT. Painful neuromas: a review of treatment modalities. *Ann Plast Surg*. 1999;43:661–667.
8. Eberlin KR, Ducic I. Surgical algorithm for neuroma management: a changing treatment paradigm. *Plast Reconstr Surg Glob Open*. 2018;6:e1952.
9. Guse DM, Moran SL. Outcomes of the surgical treatment of peripheral neuromas of the hand and forearm: a 25-year comparative outcome study. *Ann Plast Surg*. 2013;71:654–658.
10. Challoner T, Nijran A, Power D. The surgical management of traumatic neuromas. *J Musculoskelet Surg Res*. 2019;3:22–29.
11. Hudson TW, Evans GR, Schmidt CE. Engineering strategies for peripheral nerve repair. *Orthop Clin North Am*. 2000;31:485–498.
12. Mauch JT, Bae A, Shubinets V, et al. A systematic review of sensory outcomes of digital nerve gap reconstruction with autograft, allograft, and conduit. *Ann Plast Surg*. 2019;82(4S suppl 3):S247–S255.
13. Verweij JP, van Hof KS, Malessy MJ, et al. Neuropathic pain due to iatrogenic lingual nerve lesion: nerve grafting to reduce otherwise untreatable pain. *J Craniofac Surg*. 2017;28:496–500.
14. Ducic I, Maloney CT Jr, Dellon AL. Reconstruction of the spinal accessory nerve with autograft or neurotube? two case reports. *J Reconstr Microsurg*. 2005;21:29–33.
15. Ducic I, Yoon J, Buncke G. Chronic postoperative complications and donor site morbidity after sural nerve autograft harvest or biopsy. *Microsurgery*. 2020;40:710–716.
16. Graham JB, Xue QS, Neubauer D, et al. A chondroitinase-treated, decellularized nerve allograft compares favorably to the cellular isograft in rat peripheral nerve repair. *J Neurodegen Regen*. 2009;2: 19–29.
17. Whitlock EL, Tuffaha SH, Luciano JP, et al. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. *Muscle Nerve*. 2009;39:787–799.
18. Safa B, Jain S, Desai MJ, et al. Peripheral nerve repair throughout the body with processed nerve allografts: Results from a large multicenter study. *Microsurgery*. 2020;40:527–537.
19. Rinker B, Zoldos J, Weber RV, et al. Use of processed nerve allografts to repair nerve injuries greater than 25 mm in the hand. *Ann Plast Surg*. 2017;78(6S suppl 5):S292–S295.
20. Rinker BD, Ingari JV, Greenberg JA, et al. Outcomes of short-gap sensory nerve injuries reconstructed with processed nerve allografts from a multicenter registry study. *J Reconstr Microsurg*. 2015;31:384–390.
21. Means KR Jr, Rinker BD, Higgins JP, et al. A multicenter, prospective, randomized, pilot study of outcomes for digital nerve repair in the hand using hollow conduit compared with processed allograft nerve. *Hand (N Y)*. 2016;11:144–151.
22. Brooks DN, Weber RV, Chao JD, et al. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. *Microsurgery*. 2012;32:1–14.
23. Isaacs J, Safa B. A preliminary assessment of the utility of large-caliber processed nerve allografts for the repair of upper extremity nerve injuries. *Hand (N Y)*. 2017;12:55–59.
24. Souza JM, Purnell CA, Cheesborough JE, et al. Treatment of foot and ankle neuroma pain with processed nerve allografts. *Foot Ankle Int*. 2016;37:1098–1105.
25. Leckenby JI, Furrer C, Haug L, et al. A retrospective case series reporting the outcomes of avance nerve allografts in the treatment of peripheral nerve injuries. *Plast Reconstr Surg*. 2020;145:368e–381e.
26. Taras JS, Amin N, Patel N, et al. Allograft reconstruction for digital nerve loss. *J Hand Surg Am*. 2013;38:1965–1971.
27. Tang P, Kilic A, Konopka G, et al. Histologic and functional outcomes of nerve defects treated with acellular allograft versus cabled autograft in a rat model. *Microsurgery*. 2013;33:460–467.
28. Safa B, Shores JT, Ingari JV, et al. Recovery of motor function after mixed and motor nerve repair with processed nerve allograft. *Plast Reconstr Surg Glob Open*. 2019;7:e2163.
29. Ives GC, Kung TA, Nghiem BT, et al. Current state of the surgical treatment of terminal neuromas. *Neurosurgery*. 2018;83:354–364.
30. Cho MS, Rinker BD, Weber RV, et al. Functional outcome following nerve repair in the upper extremity using processed nerve allograft. *J Hand Surg Am*. 2012;37:2340–2349.
31. Galeano M, Manasseri B, Risitano G, et al. A free vein graft cap influences neuroma formation after nerve transection. *Microsurgery*. 2009;29:568–572.
32. Yan H, Zhang F, Wang C, et al. The role of an aligned nanofiber conduit in the management of painful neuromas in rat sciatic nerves. *Ann Plast Surg*. 2015;74:454–461.
33. Stokvis A, van der Avoort DJC, van Neck JW, et al. Surgical management of neuroma pain: a prospective follow-up study. *Pain*. 2010;151:862–869.
34. Dickson KE, Jordaan PW, Mohamed D, et al. Nerve allograft reconstruction of digital neuromata. *J Musculoskelet Surg Res*. 2019;3:116–122.
35. Bi A, Park E, Dumanian GA. Treatment of painful nerves in the abdominal wall using processed nerve allografts. *Plast Reconstr Surg Glob Open*. 2018;6:e1670.
36. Jones PE, Meyer RM, Faillace WJ, et al. Combat injury of the sciatic nerve – an institutional experience. *Mil Med*. 2018;183:e434–e441. Erratum in: *Mil Med*. 2018 Sep 1;183(9-10):246.
37. Arnold DMJ, Wilkens SC, Coert JH, et al. Diagnostic criteria for symptomatic neuroma. *Ann Plast Surg*. 2019;82:420–427. Erratum in: *Ann Plast Surg*. 2019 Jul;83(1):120.
38. Yi C, Dahlin LB. Impaired nerve regeneration and Schwann cell activation after repair with tension. *Neuroreport*. 2010;21:958–962.
39. Babu P, Behl A, Chakravarty B, et al. Entubulation techniques in peripheral nerve repair. *The Indian J Neurotrauma*. 2008;5;15–20.
40. Clark WL, Trumble TE, Swiontkowski MF, et al. Nerve tension and blood flow in a rat model of immediate and delayed repairs. *J Hand Surg Am*. 1992;17:677–687.
41. Lundborg G, Rydevik B. Effects of stretching the tibial nerve of the rabbit. A preliminary study of the intraneural circulation and the barrier function of the perineurium. *J Bone Joint Surg Br*. 1973;55:390–401.

42. Schmidhammer R, Zandieh S, Hopf R, et al. Alleviated tension at the repair site enhances functional regeneration: the effect of full range of motion mobilization on the regeneration of peripheral nerves—histologic, electrophysiologic, and functional results in a rat model. *J Trauma*. 2004;56:571–584.
43. Evans PJ, Bain JR, Mackinnon SE, et al. Selective reinnervation: a comparison of recovery following microsuture and conduit nerve repair. *Brain Res*. 1991;559:315–321.
44. Neubauer D, Graham JB, Muir D. Chondroitinase treatment increases the effective length of acellular nerve grafts. *Exp Neurol*. 2007;207:163–170.
45. Graham JB, Neubauer D, Xue QS, et al. Chondroitinase applied to peripheral nerve repair averts retrograde axonal regeneration. *Exp Neurol*. 2007;203:185–195.
46. Dumanian GA, Potter BK, Mioton LM, et al. Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: a randomized clinical trial. *Ann Surg*. 2019;270:238–246.
47. Mioton LM, Dumanian GA, Shah N, et al. Targeted muscle reinnervation improves residual limb pain, phantom limb pain, and limb function: a prospective study of 33 major limb amputees. *Clin Orthop Relat Res*. 2020;478:2161–2167.