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SPECIAL TOPIC

Regenerative Peripheral Nerve Interface Surgery: Anatomic and Technical Guide

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Summary: Regenerative peripheral nerve interface (RPNI) surgery has been demonstrated to be an effective tool as an interface for neuroprosthetics. Additionally, it has been shown to be a reproducible and reliable strategy for the active treatment and for prevention of neuromas. The purpose of this article is to provide a comprehensive review of RPNI surgery to demonstrate its simplicity and empower reconstructive surgeons to add this to their armamentarium. This article discusses the basic science of neuroma formation and prevention, as well as the theory of RPNI. An anatomic review and discussion of surgical technique for each level of amputation and considerations for other etiologies of traumatic neuromas are included. Lastly, the authors discuss the future of RPNI surgery and compare this with other active techniques for the treatment of neuromas. *(Plast Reconstr Surg Glob Open 2023; 11:e5127; doi: 10.1097/GOX.0000000000005127; Published online 17 July 2023.)*

INTRODUCTION

Nearly 200,000 major amputations are performed in the United States each year, with many of these patients developing chronic postamputation pain.[1,2] Postamputation pain comprises residual limb pain and phantom limb pain.[2] Residual limb pain is pain at the site of amputation and can have multiple etiologies, including inflammation, infection, heterotopic ossification, and neuroma pain.[3] Neuroma pain is caused by instances in which regenerating nerves cannot reinnervate an end target and develop into a neuroma bulb consisting of aberrant free axons, fibrotic tissue, and blood vessels.[4,5] When peripheral nerves are divided and undergo Wallerian degeneration, the active cell body in the spinal cord directs axonal regeneration through a series of well-established physiological pathways.[6,7] Small, unmyelinated nociceptive free nerve endings in the neuroma bulb have a lower threshold for activation, resulting in increased neuronal activity and hypersensitivity.[8–10] Neuromas of mixed and motor nerves have also been demonstrated to be sources of significant neuropathic pain.[11] Neuromas release inflammatory cytokines that have been attributed to changes in processing of pain in the somatosensory cortex and subsequent centralization of pain that in turn contributes to amplification and perpetuation of the pain response.[12]

Phantom limb pain is the sensation of pain in the perceived missing limb and occurs in up to 95% of amputees.[2,13–15] Although the exact pathogenesis of phantom pain is not fully understood, it is believed to be multifactorial with contributions from the peripheral and central nervous systems.[14] From a peripheral standpoint, the abnormal, spontaneous axonal activity, and inflammatory cytokines from neuromas are known to contribute to phantom limb pain.[16] Additionally, ectopic activity in the dorsal root ganglia amplifies the effects of residual limb neuromas and may additionally produce cross reactivity with neighboring axons, resulting in symptomatic pain. Spinal and supraspinal changes have been well described in the literature and clearly play significant roles in this process.[17,18] These key roles include spinal cord sensitization, and reorganization of the somatosensory cortex and thalamus, which are dictated by peripheral feedback. Moreover, psychological components potentiate and exacerbate phantom limb pain by contributing to the aforementioned thalamic reorganization.[17,19] Psychosocial well-being, depression,

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and anxiety are predictive factors for pain and distress and contribute to this negative neuropsychological feedback loop.[17,19,20]

Numerous treatments have been proposed to treat or prevent postamputation neuromas.[21–26] Neuroma management can be broadly categorized into passive and active interventions.[22] Passive interventions excise the diseased nerve end but do not address the subsequent regeneration. Active interventions aim to address healthy, physiologic regeneration after neuroma excision. Some examples of active methods for neuroma prevention include burying the transected nerve end into adjacent muscle, proximal crushing, or burning the distal nerve end. Burying nerve ends into adjacent muscle, bone, or vein is one of the most popular techniques for neuroma.[27] This technique does not prevent formation of neuroma because the regenerating axons are buried into neighboring muscle that is already innervated, where each muscle fiber is already in physiologic contact with a nerve fiber.[22] Due to the low rate of success with these traditional approaches, novel new approaches have been developed to improve outcomes by actively guiding axonal regeneration into denervated tissues. The two most notable active approaches to control axonal sprouting and elongation are regenerative peripheral nerve interfaces (RPNIs) and targeted muscle reinnervation (TMR).[28] RPNI is the placement of free nerve ends into free, devascularized muscle or dermal grafts. TMR includes excision of the terminal neuroma, and then the fresh end of the nerve is coapted to a nearby, expendable motor nerve.[29] Both have demonstrated great results with the treatment and prevention of neuroma and phantom limb pain.[24,30,31,49–53] The authors' preference is to use RPNI surgery, which has been demonstrated to yield favorable results in the literature and in our own practices.[32] The purpose of this article is to provide a step-by-step technical guide for the use of RPNIs in different anatomical regions.

THE RATIONALE FOR RPNI

RPNI was originally designed as an interface for advanced neural control of prosthetic devices and to overcome the limitations of current control strategies.[33–44] RPNI surgery was developed in response to the limitations of existing peripheral nerve electrodes that directly interface with fascicles but yield well-documented adverse sequelae.[35,45,46] Similarly, the use of surface electromyographic signals to drive a prosthetic limb has been associated with poor prosthetic performance. In contrast, electrodes placed in muscle have greater reliability, less impedance, and improved resistance to fibrosis/longevity.[35] Capitalizing on this feature, the regenerative peripheral nerve interface was designed to create an interface composed of peripheral nerve fascicles reinnervating free skeletal muscle grafts, that can then be interrogated by electrodes. RPNIs have been demonstrated to exhibit greater amplification, specificity, and reliability of EMG signals for advanced prosthetics and have been shown to decrease neuroma formation and reduce postamputation pain.[32,46,47]

Takeaways

Question: How do reconstructive surgeons unfamiliar with regenerative peripheral nerve interfaces use them in their practice?

Findings: A step-by-step technique and anatomical guide, background of the method, and future direction have been outlined to aid surgeons in addressing neuroma pain and preventing neuroma formation during nerve transection.

Meaning: Regenerative peripheral nerve interface surgery is safe, straightforward, reproducible, reliable, effective, and scalable to many surgical specialties. It allows reconstructive surgeons of all types to treat and prevent traumatic nerve pain.

The goal of physiologic surgery for neuroma-related pain is to provide neuromuscular targets for regenerating axons of transected nerves.[31,48–55] Currently, the autologous free muscle or dermal grafts utilized in RPNI surgery are designed to be small enough to revascularize and provide living motor end plates or dermal appendages suitable for reinnervation within 1–3 months.[13,24,47,56,57] As long as these grafts are appropriately sized and placed within well-vascularized tissue, they theoretically incorporate via imbibition, inosculation, and revascularization. It is believed that the grafts receive support from the surrounding soft tissues they are embedded within and from the vasa nervorum itself.

TECHNICAL GUIDE

RPNI surgery can be performed any time peripheral nerves are transected and direct nerve repair cannot reapproximate these axons back to their native targets. In immediate RPNI surgery, major peripheral nerves are isolated, marked, and sharply transected during the amputation. Traction neurectomy is not performed to purposefully avoid proximal retraction of the nerve end. Free skeletal muscle grafts are the most common form of RPNI and may be harvested from a healthy area within the amputated limb or from an alternative donor site. In cases of amputation for oncologic reasons, the muscle grafts should be harvested far from the tumor. Proximal muscle may also need to be harvested in cases of delayed presentation or in mangled extremities without suitable donor muscle in the amputated extremity. Because the technique relies on free muscle grafts, one should be careful when performing this technique on patients with acutely traumatized limbs, patients with poorly controlled diabetes, smokers, or patients with vascular disease. However, there are no absolute contraindications to RPNI surgery. If adequate vascular supply to the wound bed is demonstrated, RPNI surgery can be effectively performed.

The ideal choice for muscle is one that is long and broad; in the lower extremity, the choice includes the vastus lateralis, gracilis, sartorius, or soleus muscles. The

muscle grafts should be harvested along the axis of the muscle fibers to minimize disruption of individual muscle fibers and to optimize regeneration.[13] Grafts that are too thick will undergo central necrosis. Thus, for larger caliber nerves such as the sciatic nerve, fascicular dissection is performed to enable multiple fascicular RPNIs rather than creating a single large RPNI. Doing so also improves the ratio of denervated muscle fibers to regenerating axons to maximize reinnervation.[58] Each graft should be trimmed of connective tissue to minimize obstruction to revascularization. Theoretically, grafts revascularize not only from the surrounding tissue but also from the nerve itself with its intrinsic supply (vasa nervorum). The ideal size of muscle graft varies with the caliber of the peripheral nerve being treated. For most peripheral nerves (diameter: 5–10 mm), each muscle graft should be approximately 3 cm long, 2 cm wide, and about 0.5 cm thick.[57,59] This can be reduced depending on the caliber of the nerve but should allow a complete wrapping of the nerve at least 1 cm proximal to its end and be able to cover the nerve circumference without tension, while still being thin enough to revascularize. The transected nerve is then placed within the central portion of the muscle graft. The epineurium of the nerve is then secured to the muscle graft distally and 1 cm proximally with interrupted sutures of either 5-0 Monocryl or 6-0 nonabsorbable monofilament on a small cutting needle. The muscle graft is then wrapped around the nerve end circumferentially, and additional sutures are placed in the ends of the muscle graft to tubularize and secure it around the nerve. Accordingly, the dimensions of the graft may be made smaller to accommodate smaller nerves, such as digital nerves (Fig. 1).

In cases of sensory nerves, such as the dorsal radial sensory nerve, sural nerve, or digital nerves, an RPNI can be performed utilizing either a muscle graft or a dermal graft. In clinical practice, both demonstrate efficacy in treating neuroma pain. Denervated muscle tissue contains sensory targets that associate with regenerating sensory axons during reinnervation.[60–62] Alternatively, a de-epithelialized dermal graft may be used for sensory nerve RPNI surgery.[63] Dermal grafts contain a large number of sensory organs that will serve to make functional connections with regenerating sensory afferents.[35] Successful reinnervation of dermal grafts have been demonstrated with RPNIs, and stimulation of the dermal graft can result in meaningful compound sensory nerve action potentials, which can be measured from the proximal nerve.[35] For most sensory nerves (diameter: 2–5 mm), a single dermal graft for each RPNI is harvested by de-epithelializing a 2.0 × 1.0 × 0.5 cm piece of full-thickness skin graft and then completely removing the underlying adipose tissue[35,56] (Fig. 2).

Upper Extremity

Digital

If selecting a muscle graft, options include the brachioradialis due to its expendable nature and broad, long muscle belly. The graft should be about 1.0 × 1.0 × 0.3 cm and can simply be placed in an adjacent subcutaneous pocket. In cases of digital neuromas, the patient is placed in a soft dressing and allowed to resume gentle use of the affected hand at 3 days postoperatively.[56] (**See table, Supplemental Digital Content 1,** which displays the guide for upper extremity RPNI, including anatomical considerations and recommendations for graft size and placement. **http://links.lww.com/PRSGO/C665**.)

Transradial

The brachioradialis is a good donor site for muscle graft. It has a broad, long muscle belly with adequate tissue for graft harvest. This muscle inserts into the distal

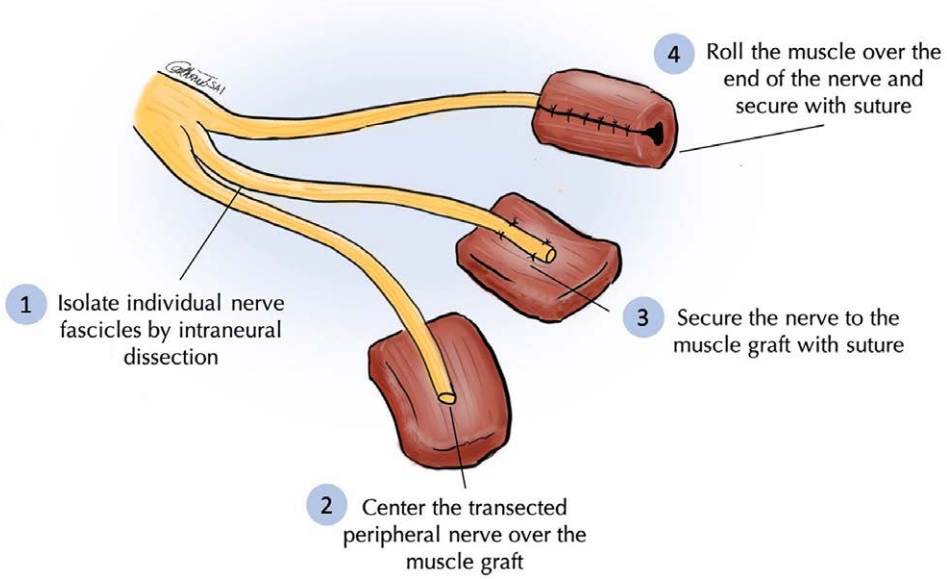

Fig. 1. Diagram illustrating the steps of RPNI procedure: (1) intraneural dissection to isolate individual nerve fascicles, (2) placing the nerve in the muscle graft, (3) securing nerve to muscle graft with monofilament suture, and finally, (4) securing RPNI with rolling muscle graft upon itself. Figure credit: Catherine Tsai, MD.

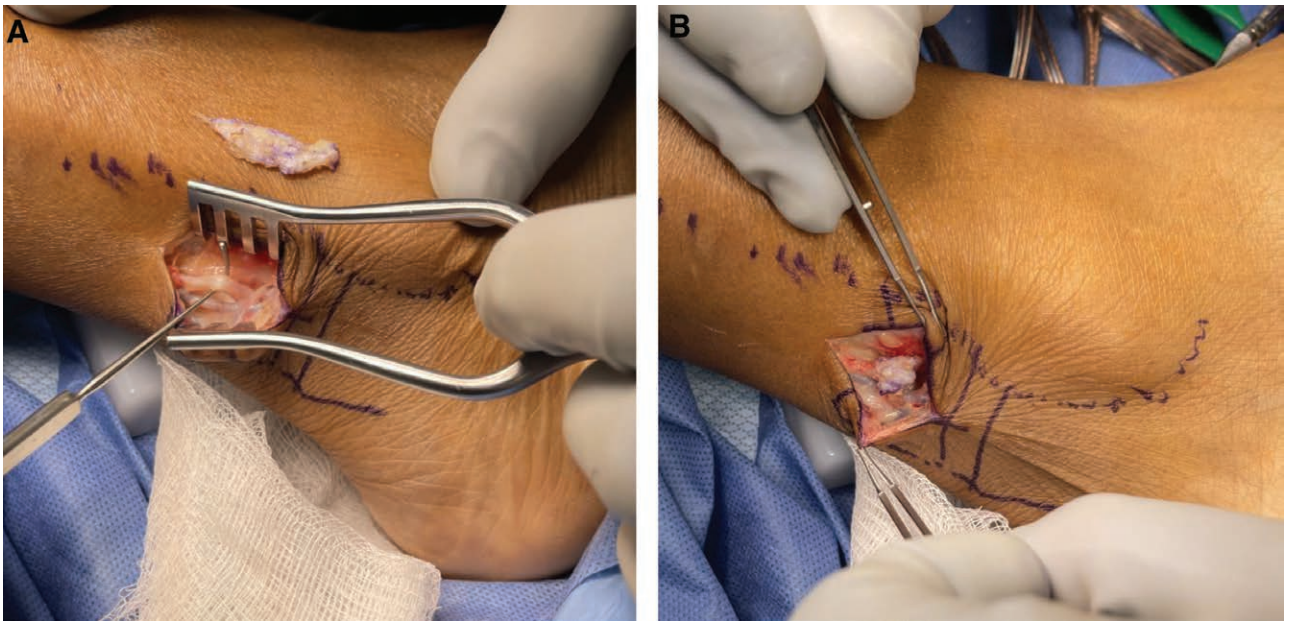

Fig. 2. RPNI surgery performed via dermal graft for a patient with neuroma after sural nerve biopsy. A, Demonstrating the exposure. B, Demonstrating creation of the regenerative peripheral nerve interface with the dermal graft.

radius and thus is not a functional muscle after transradial amputations. If more muscle for grafting is needed, local muscles may be suitable, or a distant muscle like the vastus lateralis may need to be used.

Thus far, the median and ulnar nerves have been the principal targets for RPNI in transradial amputations. We strongly recommend performing RPNIs on the radial nerve branches as well, including the dorsal radial sensory nerve and the posterior interosseous nerve. Consider performing RPNI surgery on the anterior interosseous nerve. Also, consider performing a fascicular dissection to make multiple RPNIs on the median, ulnar, and radial nerves if large in caliber[36] (**See table, Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/C665**).

Transhumeral

In the upper arm, the long head of the triceps offers a long, broad muscle for graft harvest. Amputations above the elbow render the triceps muscles nonfunctional, further making them a great option for muscle graft harvest.

The principal nerves to address are the median, ulnar, radial, and musculocutaneous. Particularly in the median and ulnar nerves, the more proximal that these nerves are discovered, the stronger the indication for interfascicular dissection and creation of multiple RPNIs (**See table, Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/C665** and Fig. 3).

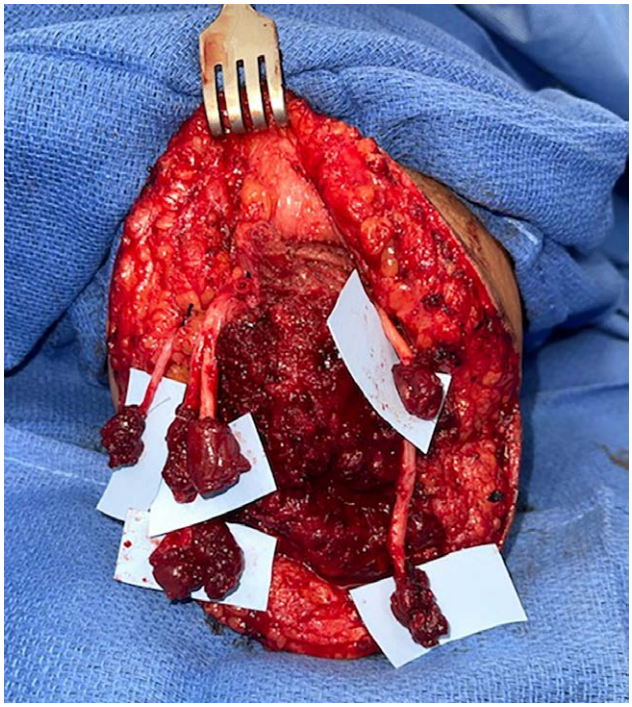

Fig. 3. RPNI surgery performed at the time of transhumeral amputation. Nerves identified and receiving RPNIs included ulnar, radial, median, medial antebrachial cutaneous, and musculocutaneous.

Shoulder Disarticulation

The anatomy encountered in shoulder disarticulation is rather variable. The axillary neurovasculature frequently migrates after removal of the humeral head. Any part of the amputated limb is a good choice for graft selection, particularly the aforementioned muscle groups, as long as the muscle chosen is out of the zone of traumatic injury or located an oncologically safe distance from the tumor. These grafts may then be buried in this space (**See table, Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/C665**).

Nonamputation Indications

Upper extremity neuromas may be encountered secondary to traumatic laceration or iatrogenic injury (ie, distal radius exposure). In these cases, the site can be identified via Tinel's test or confirmed with injection of local anesthetic. The neuroma should be accessed through the previous cutaneous scar and should be excised. The proximal nerve stump is wrapped in a dermal (our practice's preference) or muscle graft. Common nerves are discussed in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/C665**). These sensory nerves may be encountered during amputation and should be addressed as well if encountered.

Lower Extremity

Below Knee

Grafts can be harvested from the ipsilateral proximal thigh, typically the vastus lateralis. The amputated limb offers reasonable options to avoid a separate incision by harvesting from the anterior or deep posterior compartments. We advocate not harvesting muscle grafts from the soleus or gastrocnemius, as these will be used for the myodesis and padding of the BKA residual limb. During initial amputation planning, if there is some redundant posterior compartment musculature, then it is a suitable RPNI donor. RPNIs should be performed on the tibial, peroneal, sural, and saphenous nerves at the time of BKA.

RPNIs to the peroneal nerves may be performed through a separate incision at the level of the common peroneal nerve, as it crosses the lateral head of the fibula. During below-knee amputation surgery, the fibular head is easily palpable, and a curvilinear incision is designed over the course of the common peroneal nerve, as it exits the popliteal fossa and travels laterally in a superficial plane. Care is taken to maintain enough width between this incision and the below-knee amputation incision to preserve skin viability. Dissection is performed into the investing fascia around the common peroneal nerve, and the nerve is exposed circumferentially. At the level of the fibular neck, the separation between superficial and deep peroneal nerves is visible. The two nerves are divided with a knife as distally as possible, and intraneural dissection is performed proximally to sharply separate the superficial and deep peroneal nerves within the common peroneal nerve for about 4 cm. Two free muscle grafts are then used to create two separate RPNIs in the subcutaneous plane. Compared with the previous method of finding the two main branches of the peroneal within the muscular compartments of the lower leg, this technique requires no intermuscular dissection but does result in more denervation of the residual lateral and anterior compartment muscles. However, this additional denervation does not seem to be clinically meaningful (Figs. 2 and 4). (**See table, Supplemental Digital Content 2**, which displays the guide for lower extremity RPNI, including anatomical considerations and recommendations for graft size and placement. **http://links.lww.com/PRSGO/C666**.)

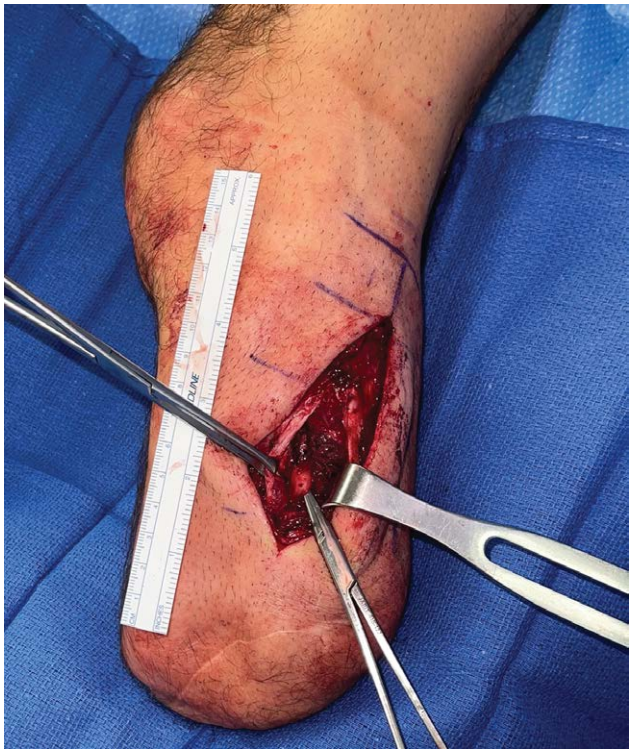

Fig. 4. Photograph showing RPNI surgery performed on the common peroneal nerve. Please note the access via a separate incision at the level of the common peroneal nerve, as it crosses the fibula.

Above Knee

The vastus lateralis is a large muscle with expendable mass for graft harvest. The sartorius and gracilis muscles are suitable donors.

When the sciatic nerve is identified, component fascicles of the tibial and common peroneal nerves can very often be seen through the epineurium. An epineural incision is made, and crossing nerve branches are sharply divided. The tibial and common peroneal nerves can be further divided into components for a total of three or four individual fascicles available to make RPNIs (**See table, Supplemental Digital Content 2**, **http://links.lww.com/PRSGO/C666** and Fig. 5).

Hip Disarticulation

Like the shoulder disarticulation, the anatomy of residual transected peripheral nerves after a hip disarticulation is much more variable. However, the vastus lateralis is still an excellent graft choice for the nerves at this level.

Nerves reliably encountered included the femoral, anterior, and posterior obturator, and sciatic nerves. The femoral and sciatic nerves should receive further fascicular dissection into components. Each of these should receive individual RPNIs (**See table, Supplemental Digital Content 2**, **http://links.lww.com/PRSGO/C666** and Fig. 6).

Nonamputation Indications

The lower extremity frequently has indications for RPNI beyond amputation. Patients who have experienced an iatrogenic or traumatic nerve injury, which cannot be repaired or was not repaired, should undergo an RPNI on the proximal

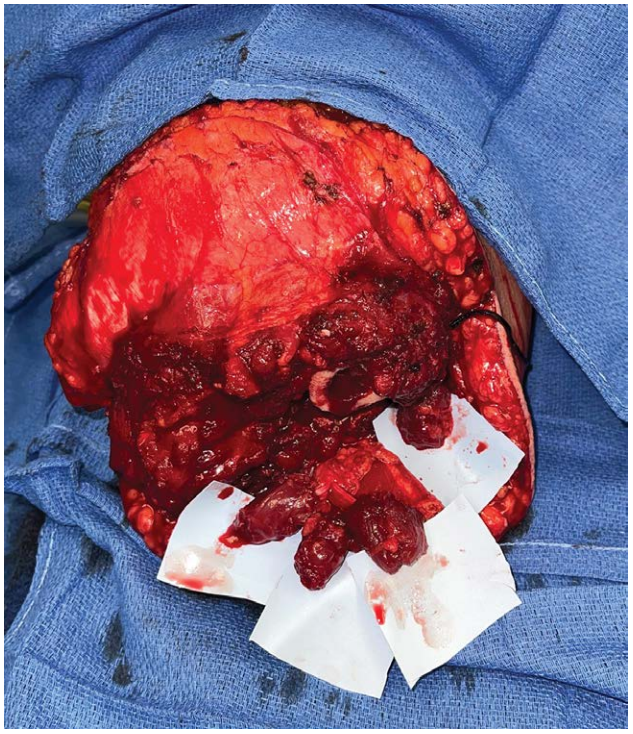

Fig. 5. Photograph showing RPNI surgery in total on below-knee amputation. Note the intraneural dissection to isolate the individual fascicles of the sciatic nerve.

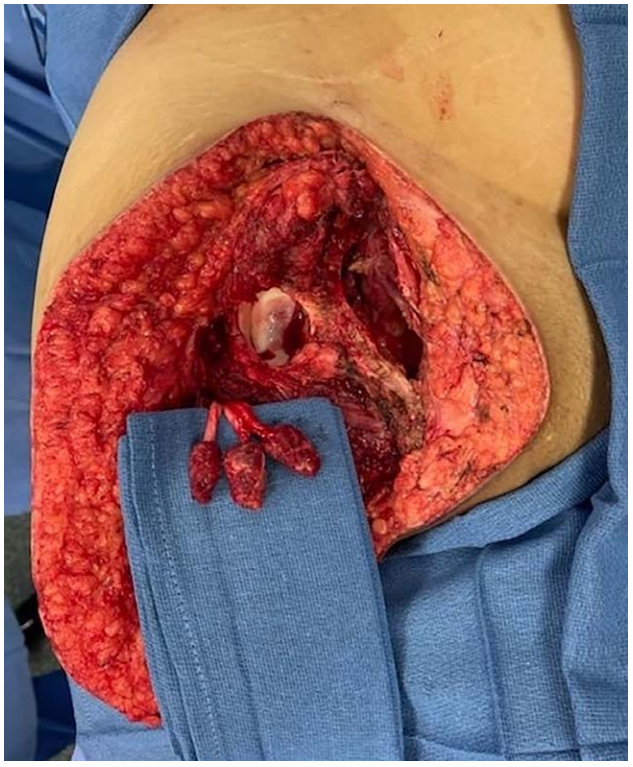

Fig. 6. RPNI surgery in a case of hip disarticulation.

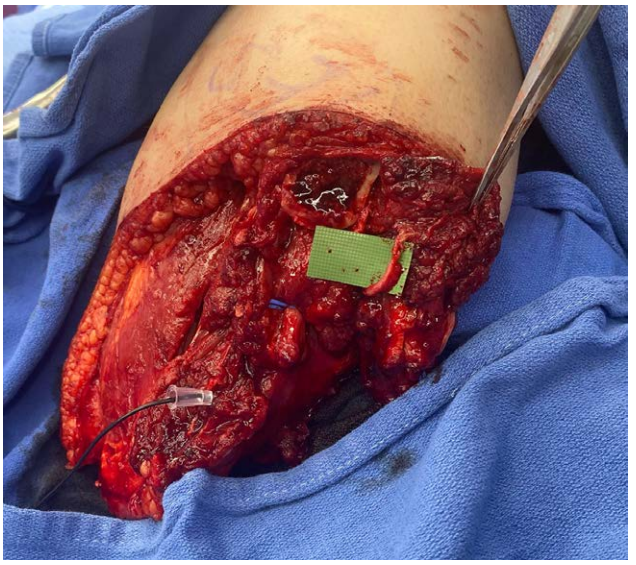

Fig. 7. TMR surgery demonstrating the size mismatch of nerve coaptation.

aspect of the divided nerve. In addition, patients should also undergo RPNI to treat the proximal end of a sural nerve after nerve graft harvest (**See table, Supplemental Digital Content 2**, **http://links.lww.com/PRSGO/C666**).

In these cases, the previous incision can be opened and explored to identify the neuroma, which should be excised if possible. The nerve can then be wrapped in a muscle or dermal graft. We prefer the vastus lateralis for this indication. The RPNI can then be left in the subcutaneous pocket. Additionally, we advocate for prophylactic RPNI at the time of biopsy to avoid subsequent neuroma formation (**See table, Supplemental Digital Content 2**, **http://links.lww.com/PRSGO/C666**).

Other Indications

Treatment of thoracic neuromas in cases of postmastectomy neuroma or abdominal neuromas after hernia repair may also be necessary, and these are discussed in Table 1.

DISCUSSION

RPNI surgery has demonstrated its reliability and durability in harnessing neural signals for neuroprosthetic control.[35–44] Additionally, RPNI surgery is effective for treatment and prevention of postamputation pain, including both symptomatic neuroma pain and phantom limb pain.[59,64–68] In the authors' practice, RPNI surgery has also been successful in management of neuromas of superficial sensory nerves particularly in cases of nerve autograft harvest.

This procedure is simple, requires no specialized training or equipment, and adds only a modest amount of time to the operation. RPNIs effectively and actively guide axonal regeneration into denervated targets.[37] This theory has been supported in the literature, as the RPNI

Table 1. Guide and Technique Recommendations for Addressing Thoracic and Abdominal Neuromas

Thoracic nerves (intercostal nerves)	There is increasing awareness of postmastectomy pain syndrome stemming from injury to the intercostal nerves resulting in neuromas. Injury to the lateral intercostal nerves along the midaxillary line is most common, but anterior branches may be transected just lateral to the sternum. Again, these neuromas can be identified via patient history and confirmed with physical examination and local block. Incisions are made over the intercostal space with dissection through the external intercostal muscle. The nerves are dissected proximally to healthy ends, and dermal graft is applied.
Abdominal nerves (intercostal/subcosta/ilioinguinal)	Neuroma pain due to mesh placement during hernia repair or injury during placement of laparoscopic ports is a common etiology of chronic abdominal pain. History and physical examination including interoffice nerve block can readily identify these neuromas. By marking the area of pain, an incision is made from this area curving toward the superiolateral flank (toward the anterior superior iliac spine in cases of inguinal neuromas). The external oblique fascia is divided. The neuroma is identified and excised back to healthy fascicles, which are wrapped in a dermal graft.

data demonstrate significant reduction in neuroma pain and phantom limb pain, and improved prosthetic experience and psychosocial well-being.[13,24,32] As previously mentioned, peripheral pain has an impact on centrally-mediated pain via cortical and thalamic remodeling. This plays a significant role in the development of chronic pain. Treating all other etiologies of peripheral nerve pain (ie, migraine headache and carpal tunnel syndrome) can also help reduce centrally-mediated pain[69–73] This proposes a future direction of RPNI surgery in that the treatment of peripherally-mediated pain associated with neuromas may have a role in mitigating centrally-mediated pain. In other words, RPNI may have benefit in treating amputation patients with phantom limb pain, even if there is no severe neuroma pain in the residual limb. However, this will require further investigation.[74,75]

Like RPNI surgery, TMR surgery involves denervation of muscle and reinnervation of this denervated target with regeneration axons. We prefer RPNI in our practices for several reasons. Particularly in cases of amputation, TMR is more technically demanding regarding identification and dissection, and prolongs operative time. We believe the donor morbidity of a muscle graft harvest is less than the morbidity of compromising a motor branch in the residual limb. However, the authors' primary preference for RPNI over TMR is the size discrepancy of the donor to recipient nerves.[76] The mismatch in nerve calibers is potentially a source for axonal escape. This can result in a symptomatic neuroma-in-continuity at the site of the nerve coaptation or may lead to loss of reinnervation[76–79] (Fig. 7). The proximal end of the lost motor nerve could form a symptomatic terminal end neuroma.[80] In theory, either could contribute to peripheral or central sensitization, thereby contributing to and worsening chronic pain experienced by these patients.[81–85]

One proposed solution to address this nerve-size mismatch and corresponding axonal escape is to place a denervated piece of muscle around the TMR coaptation site. The free denervated skeletal muscle graft to address the escaping axons from the TMR makes this similar to RPNI alone.[76] One reason for the size mismatch is that in the TMR method, large caliber peripheral nerves cannot be divided into multiple smaller component fascicles because there are not enough expendable motor branches in the vicinity to perform a multitude of nerve transfers (eg, >10). RPNI surgery does not rely on the limited availability of expendable local motor branches but instead is based on the freedom to harvest many free muscle grafts. This allows for a much greater ability to divide peripheral nerves into smaller component fascicles, each with its own free muscle graft. This distinct feature of RPNI surgery to harness discrete motor and sensory signals through reinnervation of multiple individual RPNIs is advantageous when using it as an interface for advanced prosthetic limb rehabilitation.[38–47,86]

There are some limitations with RPNI. Long-term follow-up is still pending. Initial follow-up data has only been reported out of a few centers. As previously noted, the success of neuroprosthetics mediated via RPNI and ultrasound studies support RPNI survival.[87] Imaging studies at that time were conducted in a small sample, and further studies will need to confirm these findings. Additionally, the basic science regarding graft survival and reinnervation has been performed on animal models, thus far necessitating further investigation for confirmation in humans.[88]

An initial study in a rat model demonstrated that smaller grafts perform better.[89] Larger grafts lose muscle mass in a process consistent with our theory that the portion of the graft receiving plasma imbibition and inosculation will vascularize, with the rest simply sloughing off. Again, this too will need further investigation.

The last limitation of RPNI is the need for a second donor site in cases of treating a neuroma in a delayed fashion. However, we believe this morbidity is minimal, as there is ample redundant muscle for donor, and, in cases of pure sensory nerves, dermal grafts have displayed excellent promise.[90]

CONCLUSIONS

RPNI surgery is safe, straightforward, reproducible, reliable, effective, and scalable to many surgical specialties. It allows reconstructive surgeons of all types to treat and prevent traumatic nerve pain. Moreover, it is a powerful tool for enabling the use of advance neuroprosthetics and, more recently, sensory feedback.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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