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## Review Article

# Future Considerations in the Diagnosis and Treatment of Compressive Neuropathies of the Upper Extremity



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Compressive neuropathies of the upper extremity are among the most common conditions seen by hand surgeons. The diagnoses of carpal tunnel syndrome and cubital tunnel syndrome have traditionally been made by a combination of history, physical examination, and electrodiagnostic testing. However, findings can be nonspecific and electrodiagnostic testing is invasive for the patient. The diagnosis of compressive neuropathies continues to evolve as technology advances, and newer diagnostic modalities predominantly focus on preoperative diagnostic imaging with ultrasound and magnetic resonance imaging/neurography. With the advent of cheaper, faster, and less invasive imaging, the future may bring a paradigm shift away from electrophysiology as the gold standard for the preoperative diagnosis of compressive neuropathies. Intraoperative imaging of nerve health is an emerging concept that warrants further investigation, whereas postoperative imaging of nerve recovery with ultrasound and magnetic resonance imaging currently has a limited role because of nonspecific findings and potential for misinterpretation. Advances in surgical treatment of compressive neuropathies appear to center around the use of imaging for less invasive neurolysis techniques and other adjunctive treatments with nerve decompression. The management of failed peripheral nerve decompressions and recurrent compressive neuropathies remains challenging.

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Compressive neuropathies such as carpal tunnel syndrome (CTS) and cubital tunnel syndrome (CuTS) are among the most common conditions seen by hand surgeons. The economic impact of CTS alone is estimated to be in excess of \$2 billion annually in the United States.<sup>1</sup> Traditionally, the diagnoses of CTS and CuTS have been made by a combination of history, physical examination, and electrodiagnostic testing. However, history and physical exam findings can be insensitive or nonspecific, as can electrodiagnostic testing, with a sensitivity below 75% for CTS, a surprisingly low number for what many consider the diagnostic gold standard.<sup>2</sup> In addition, electromyography and nerve conduction studies entail greater out-of-pocket and total costs. They are invasive tests that can cause pain and anxiety for some patients, potentially affecting

the quality of the test.<sup>3–6</sup> As such, the diagnosis and treatment of compressive neuropathies of the upper extremity continue to evolve as technology advances. Newer diagnostic modalities predominantly focus on preoperative imaging with ultrasound and magnetic resonance neurography (MRN). Intraoperative imaging of nerve health is an emerging concept, and research in this field thus far has been predominantly in the setting of traumatic nerve injury. Advances in treatment of compressive neuropathies center around adjunctive imaging and less invasive alternatives to surgical decompression. The treatment of failed peripheral nerve decompression procedures remains one of the more challenging aspects of the management of compressive neuropathies.

## Diagnosis of Compressive Neuropathies

### Preoperative diagnostic imaging

#### Ultrasound

Ultrasonography has gained increasing popularity in the diagnosis of compressive neuropathies of the upper extremity. The

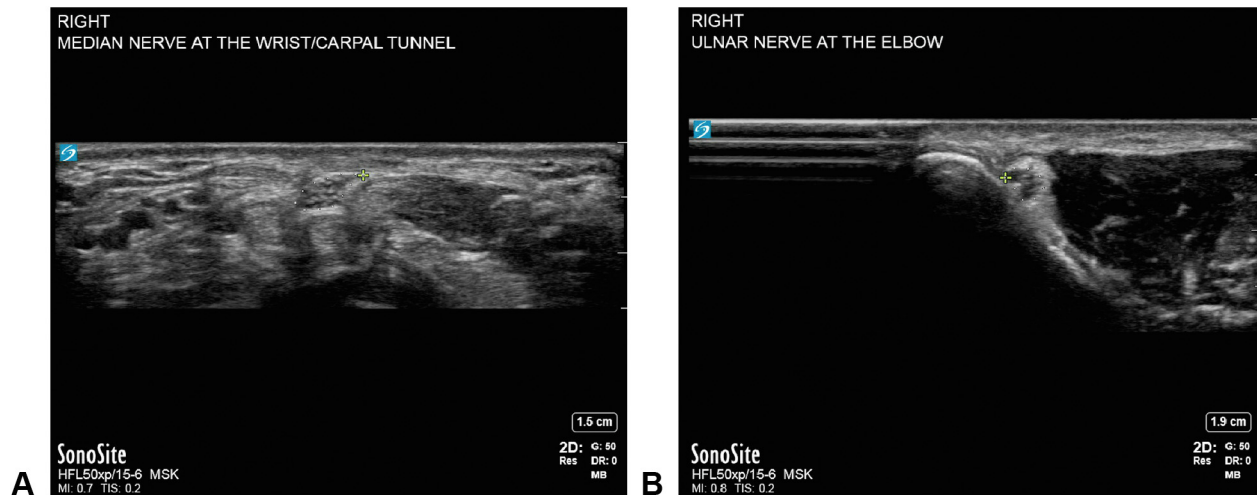
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**Figure 1.** Ultrasound images demonstrating a normal median nerve at the wrist with a CSA of 11 mm<sup>2</sup> (A) and a normal ulnar nerve at the elbow with a CSA of 7 mm<sup>2</sup> (B). Ultrasound images courtesy of and copyright protected by Dale S. Colorado, DO, MPH and David M. Brogan, MD, MSc – used with permission.

primary ultrasound findings seen in CTS include enlargement of the median nerve proximal to the carpal tunnel, flattening of the nerve distally, decreased echogenicity of the nerve, and palmar bowing of the flexor retinaculum.<sup>7,8</sup> Enlargement of the median nerve cross-sectional area (CSA) in the proximal carpal tunnel region (at or proximal to the scaphoid and pisiform) is the most commonly used and validated ultrasound finding. However, the cut-off value and measurement location for CSA to diagnose CTS has been heavily debated in the literature.<sup>9,10</sup> One study by Ratasvuori et al<sup>11</sup> measured the median nerve proximal to the entry into the carpal tunnel and found that a CSA cut-off value of 11.5 mm<sup>2</sup> yielded a sensitivity of 87% and specificity of 91%.

In contrast, another study by Ciloglu et al<sup>12</sup> found that a cut-off value of 11.25 mm<sup>2</sup> yielded a sensitivity of 97.2% and a specificity of 88.0% (Fig. 1).<sup>11</sup> A meta-analysis found that inlet-level measurements of the median nerve CSA were more accurate than those of the outlet-level and noted that CSA cut-off values ranged from 9.0 to 12.6 mm<sup>2</sup>.<sup>13</sup> Similarly, the CSA of the ulnar nerve at the elbow is also a widely utilized ultrasound parameter for the diagnosis of CuTS. Although there is no definite consensus on the CSA of the ulnar nerve that is diagnostic for CuTS, most studies rely on a value of 10 mm<sup>2</sup> (Fig. 2).<sup>14–17</sup>

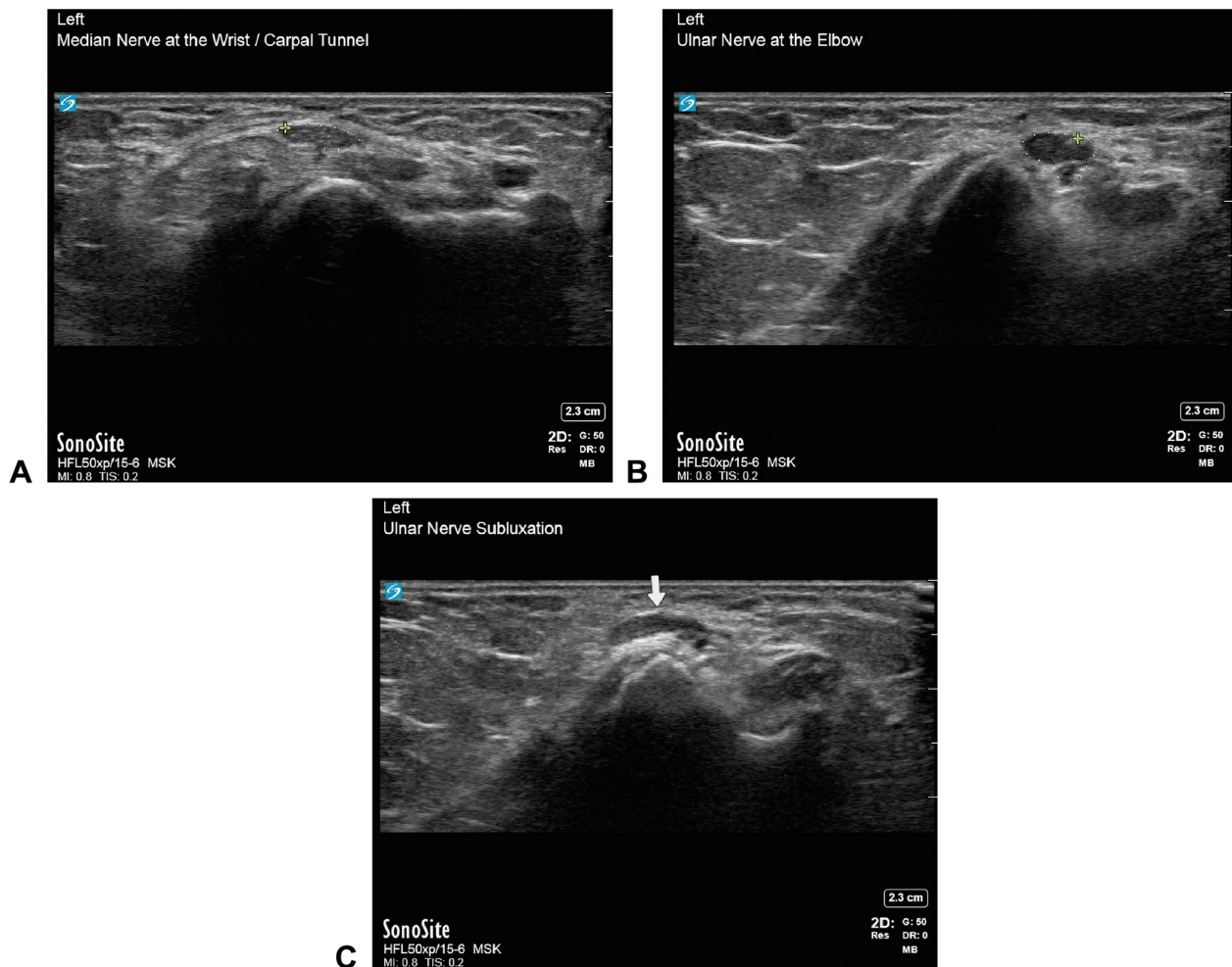
Other ultrasound techniques utilized in the evaluation of compressive neuropathies include elastography, color Doppler or power Doppler ultrasound (PDUS), contrast-enhanced ultrasound, and superb microvascular imaging (SMI). Ultrasound elastography (strain elastography and shear wave elastography) measures the stiffness of tissues using an ultrasound probe to identify underlying pathologic changes, such as the increased stiffness of peripheral nerves in compressive neuropathies because of the replacement of normally compliant myelin with less compliant tissue (Fig. 3).<sup>8,18</sup> Prior studies have demonstrated increased stiffness of the median nerve in CTS compared with control wrists. Some studies have found that the severity of CTS correlates with increasing nerve stiffness.<sup>19–22</sup> Another study found 100% specificity and sensitivity for the diagnosis of CuTS based on ulnar nerve stiffness with shear wave elastography.<sup>23</sup>

Color Doppler ultrasound and PDUS are ultrasound techniques used to quantify blood flow in nerves. Increased intraneural blood flow seen in CTS can be evaluated with PDUS, which detects changes in the low flow states present intraneurally (Fig. 4).<sup>8,24,25</sup> A systematic review by Landau et al<sup>26</sup> found that PDUS is unreliable as a screening test but increases the diagnostic accuracy of

ultrasound in compressive neuropathies. The analysis of PDUS waveforms provides a surrogate for intraneural blood flow by assessing the velocity of flow. However, the utility of PDUS to evaluate intraneural vascularity is limited by the detection thresholds of flow velocity.<sup>8</sup> High-resolution contrast-enhanced ultrasound is a recently developed technique to quantify low-volume intraneural blood flow.<sup>27–29</sup> Studies on contrast-enhanced ultrasound have been limited to date because of Food and Drug Administration restrictions on the use of their contrast agents, despite satisfactory safety profiles in prior studies.<sup>30</sup> Its use may be supplanted by SMI, a new ultrasound technique that allows visualization of lower-velocity blood flow and smaller vessels without contrast.<sup>31,32</sup> Early comparisons of SMI and PDUS have shown improved sensitivity of SMI over PDUS.<sup>31,33</sup>

#### Magnetic resonance neurography

Advances in MRI equipment and the development of sequences with higher structural resolution have established the technique of MRN for peripheral nerve evaluation (Fig. 5).<sup>34,35</sup> A study comparing high-resolution ultrasound and MRN found greater diagnostic accuracy with MRN (93.89% vs 80%).<sup>36</sup> There is high intraobserver and interobserver agreement for the measurement of carpal tunnel MRI parameters.<sup>37</sup> MRI findings in patients with CTS are similar to ultrasound findings. They include increased median nerve CSA, increased flattening ratio, increased T2 signal intensity of the median nerve, and palmar retinacular bowing (Fig. 6, Table 1).<sup>38</sup> A median nerve CSA of >15 mm<sup>2</sup> is used as the cut-off value for the diagnosis of CTS on MRI, achieving a sensitivity of 100% and specificity of 94% for CTS.<sup>38–40</sup> A cross-sectional study by Park et al<sup>40</sup> compared MRI findings for patients with CTS with a control group and found that the mean, median nerve CSA at the pisiform was 18.8 mm<sup>2</sup> in the CTS patients and 12.1 mm<sup>2</sup> in the control group. There is a discrepancy in median nerve CSA measurements obtained by MRI and ultrasound, with MRI having a higher CSA threshold than ultrasound. MRI has advantages over ultrasound, including being less operator-dependent, allowing clearer delineation of carpal tunnel contents, and enabling the entire median nerve to be measured using only 2 standard axial sequences.<sup>39</sup> One study compared median nerve CSA measurements at the wrist obtained with ultrasound and MRI compared with cadaveric measurements and found that median nerve CSA measurements by MRI were larger than ultrasound measurements and correlated better with cadaveric measurements.<sup>41</sup>



**Figure 2.** Ultrasound images demonstrating examples of pathologic peripheral nerves. **A** shows an enlarged median nerve at the wrist with a CSA of 13 mm<sup>2</sup>. **B** shows an enlarged ulnar nerve at the elbow with a CSA of 19 mm<sup>2</sup>. **C** demonstrates ulnar nerve subluxation at the cubital tunnel. Ultrasound images courtesy of and copyright protected by Dale S. Colorado, DO, MPH, and David M. Brogan, MD – used with permission.

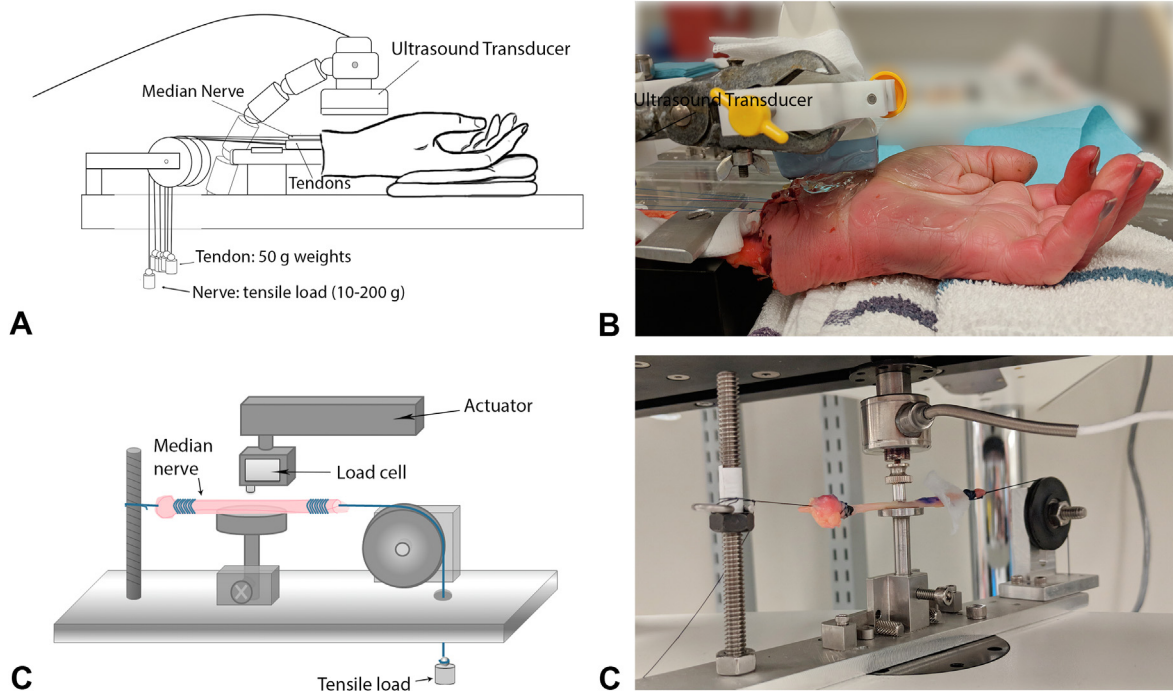
Newer techniques, including diffusion-weighted imaging, diffusion tensor imaging, and tractography, provide more functional and quantitative information about peripheral nerves than conventional MRN.<sup>42,43</sup> Diffusion tensor imaging characterizes tissue microstructure and generates reproducible proxy measures of nerve health sensitive to microstructural changes in myelination, axon diameter, and fiber density and organization.<sup>44–46</sup> A meta-analysis by Rojoa et al<sup>44</sup> summarized normal and pathologic diffusion tensor imaging values of the median nerve and found that patients with CTS have significantly lower fractional anisotropy (mean difference 0.12 [95% CI 0.09, 0.16]) and higher mean diffusivity (mean difference  $0.16 \times 10^{-3}$  mm<sup>2</sup>/s [95% CI 0.05, 0.27]) than controls.

#### *Intraoperative imaging of nerve health*

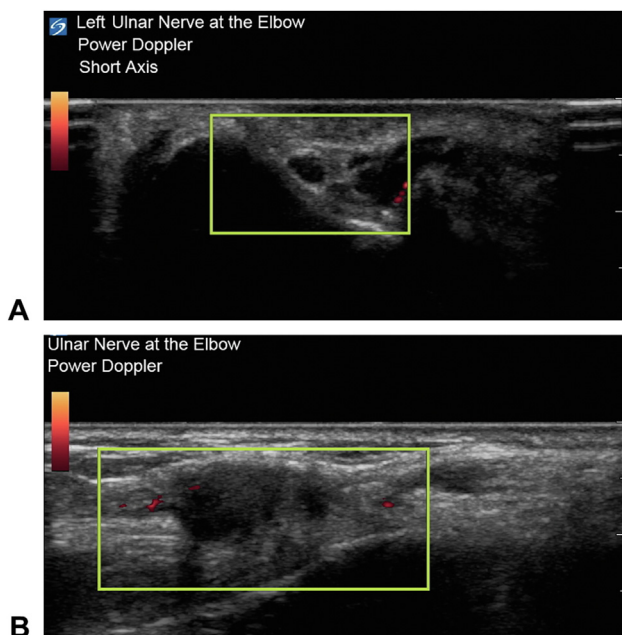
Although much has been written about preoperative imaging techniques, studies on intraoperative nerve evaluation are relatively sparse. Second Harmonic Generation (SHG) microscopy is a form of nondestructive multiphoton microscopy that can be used for imaging of neural collagen and can detect signs of structural damage within the nerve without causing further harm to the nerve. Gluck et al<sup>47</sup> created an *in vivo* peripheral nerve stretch model in rats and then utilized SHG microscopy to detect collagen

continuity and damage in the nerve after acute stretch injury. Based on the findings of the study, the authors proposed that the *in vivo* application of SHG microscopy should be further investigated as a method of real-time intraoperative assessment of nerve damage that may help guide diagnostic decisions.<sup>47,48</sup>

An alternative imaging technique is optical coherence tomography (OCT), which utilizes the light-backscattering properties of various tissue types to generate an image. It has traditionally been used in ophthalmology but more recently has shown promise in peripheral nerve imaging.<sup>49,50</sup> The microstructure of a peripheral nerve is beyond the resolution of imaging modalities such as ultrasound and MRI. Optical coherence tomography is able to resolve a nerve's structure down to the level of myelinated axons. With its micrometer resolution, OCT can provide new information about the microanatomy of peripheral nerves, including their fascicles, perineural barrier, vascularization, and the processes of nerve degeneration and regeneration.<sup>49</sup> Carolus et al<sup>49</sup> performed a feasibility study of *in vivo* human peripheral nerve assessment using OCT. They found the intraoperative use of OCT to be easy and intuitive. However, limitations included the small image window generated and the fact that the imaging quality depends on the location and depth of the nerve.<sup>49</sup> Use of an OCT system integrated into a surgical microscope is a promising concept that requires further development.



**Figure 3.** Representation of an experimental setup during shear wave elastography testing. **A, B** demonstrate the schematic version of the total setup. The median nerve was attached to increasing tensile loads, and the 5 flexor tendons in the closest approximation to the nerve were attached to 50 g weights. A surplus of ultrasound gel was used to prevent excessive pressure. **C, D** demonstrate the setup during indentation testing on an ex vivo nerve. Figures reproduced with permission.<sup>18</sup>



**Figure 4.** **A, B.** Examples of power Doppler ultrasound of the ulnar nerve at the elbow in 2 separate patients with advanced CuTS. Note the evidence of a positive Doppler signal within the ulnar nerve, suggesting increased intraneural vascularity. Ultrasound images courtesy of and copyright protected by Dale S. Colorado, DO, MPH, and David M. Brogan, MD, MSc – used with permission.

### Postoperative imaging of nerve recovery

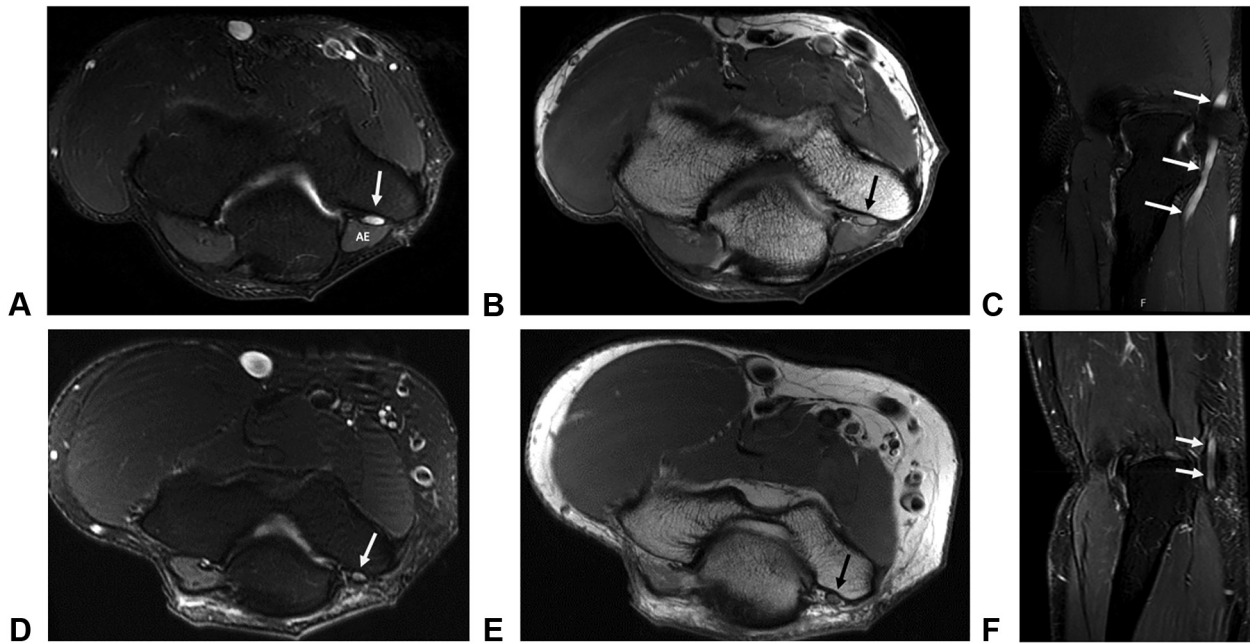
#### Ultrasound

Although both ultrasound and MRI have been extensively studied for the preoperative diagnosis of compressive

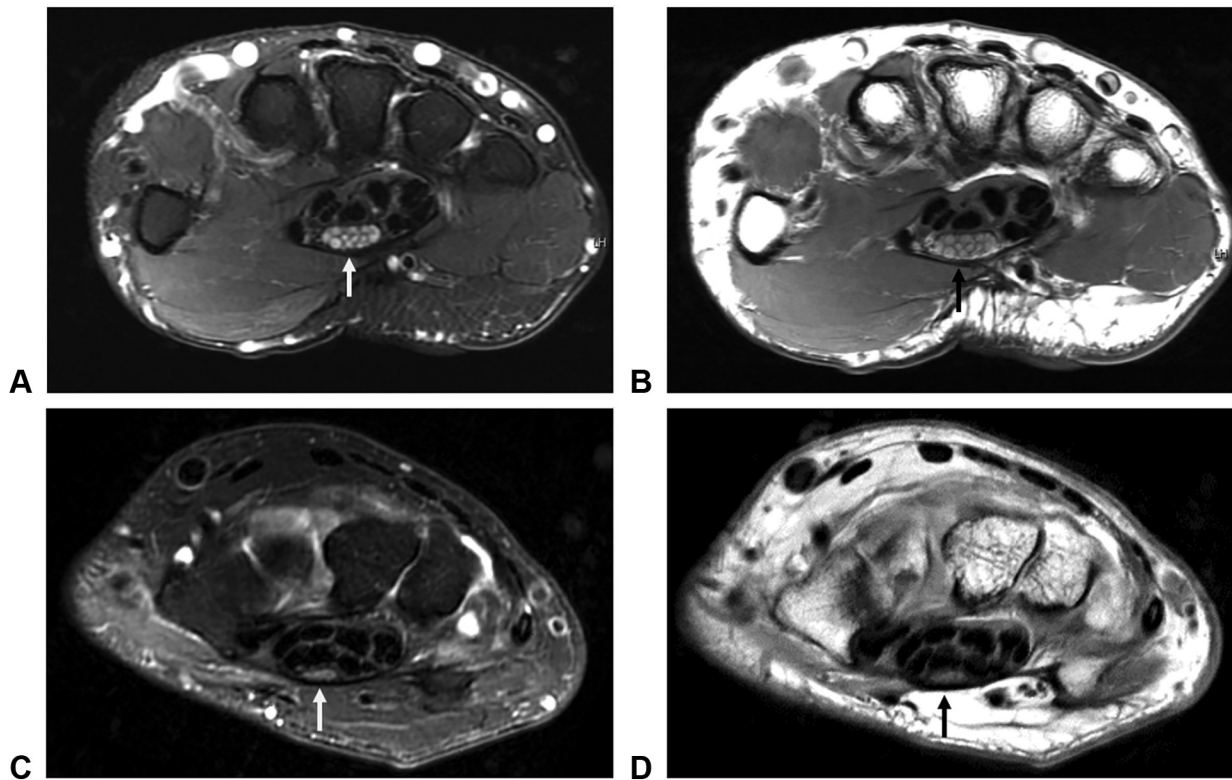
neuropathies, these imaging modalities have also been utilized to a lesser extent to monitor nerve recovery. Multiple studies have reported the morphologic changes in the median and ulnar nerves that can be seen on ultrasound after a carpal tunnel release (CTR) or cubital tunnel decompression. After surgery, most studies reported reductions in the median nerve CSA, which is believed to be a result of decreased intraneural edema after transverse carpal ligament (TCL) release. The reductions in CSA were found to be similar in patients treated with open and endoscopic CTR.<sup>51–57</sup> Despite the improvement in median nerve CSA after CTR, permanent morphologic changes within the nerve may result in persistently increased diameter.<sup>9</sup> The relationship between postoperative CSA changes and clinical symptoms has been debated. However, recent studies have shown no notable correlation between postoperative nerve CSA changes and clinical outcomes after CTR and cubital tunnel release.<sup>53,57–59</sup> Kim et al<sup>53</sup> found that clinical symptoms resolve rapidly after CTR. However, median nerve swelling takes several months to improve, and changes in postoperative median nerve CSA were not considerably correlated with postoperative changes in Boston Carpal Tunnel Questionnaire scores. However, a recent cadaver study found that ultrasound can be utilized to rapidly diagnose the incomplete release of the TCL after CTR, which supports the use of bedside ultrasound as an initial screening modality for failed CTR (Fig. 7).<sup>60</sup> Electrodiagnostic testing is limited in its ability to elucidate residual median nerve compression after CTR as nerve dysfunction may persist on electrodiagnostic testing because of chronic neuropathy even in the setting of an adequately released nerve and symptomatic clinical improvement.

#### Magnetic resonance imaging

The ability of MRI to image intraneural swelling, increased signal intensity, perineural scarring, completeness of retinacular resection, and carpal tunnel size make it an appealing study to



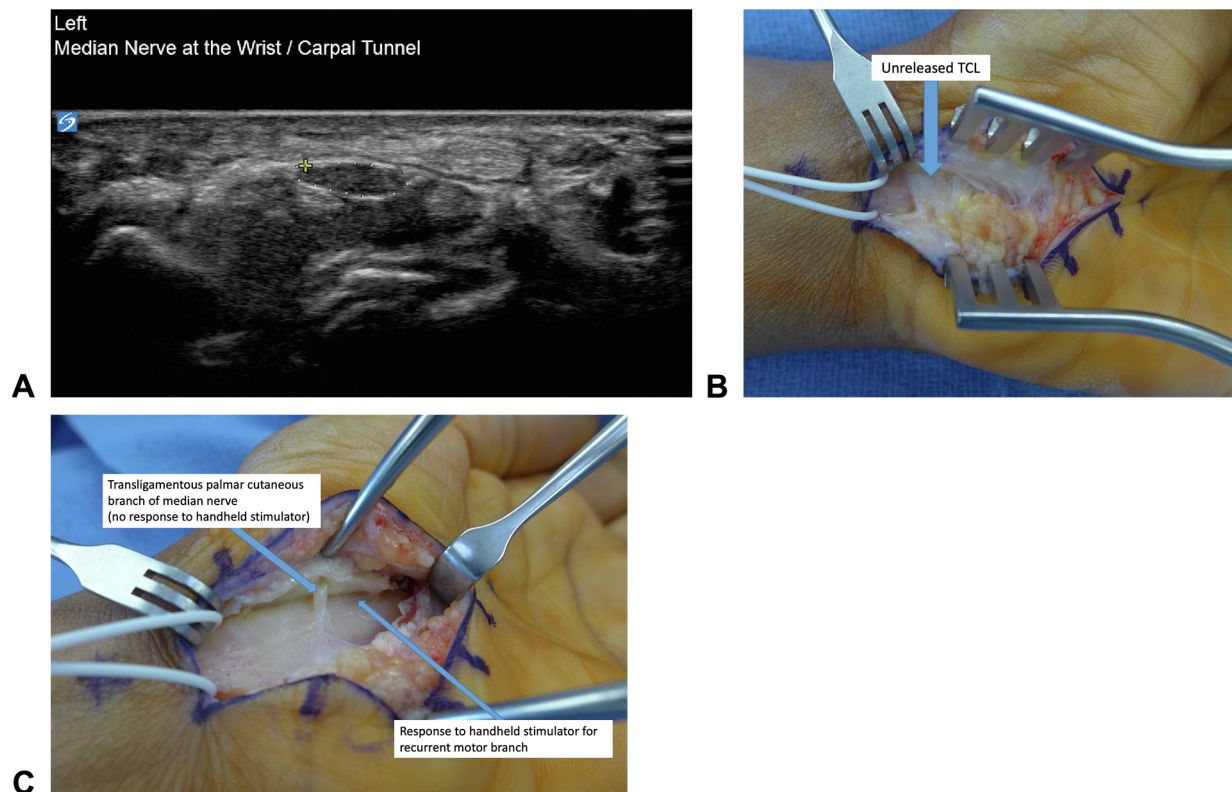
**Figure 5.** MR images of the ulnar nerve at the elbow. **A–C** Top row: A 28-year-old male with ulnar nerve distribution numbness and weakness for one year, worsening over the past month. **A** Axial 2-point Dixon water and **B** proton density MR images through the retrocondylar sulcus of the cubital tunnel demonstrate flattening and signal hyperintensity of the ulnar nerve (arrows) in the setting of an accessory anconeus epitrochlearis (AE) muscle. **C** Curved multiplanar reformatted image from a 2-point Dixon water sequence demonstrates prominent signal hyperintensity of the ulnar nerve (arrows) as it courses through the cubital tunnel. **D–F** Bottom row: By comparison, MR images in a 54-year-old man with no ulnar nerve symptoms demonstrate a normal appearance of the ulnar nerve (arrows). Images courtesy of and copyright protected by Darryl B. Sneag, MD – used with permission.



**Figure 6.** MR images of the median nerve at the wrist. **A, B** Top row: 47-year-old woman with numbness of the thumb, index finger, and middle finger for 3 months. **A** Axial 2-point Dixon water and **B** proton density MR images through the carpal tunnel demonstrated prominent enlargement and signal hyperintensity of the median nerve (arrows). **C, D** Bottom row: By comparison, MR images in a 58-year-old man with paresthesia in the right hand demonstrate normal appearance of the median nerve (arrows). Images courtesy of and copyright protected by Darryl B. Sneag, MD – used with permission.

**Table 1**  
Summary of Ultrasound and MRN Findings Seen in CTS Preoperatively

Ultrasound Findings in CTS	MRI Findings in CTS
Standard ultrasound: <ul style="list-style-type: none"> <li>• Enlargement (increased CSA) of median nerve proximal to TCL</li> <li>• Flattening of median nerve distal to TCL</li> <li>• Decreased echogenicity of median nerve</li> <li>• Palmar bowing of flexor retinaculum</li> </ul> Ultrasound elastography: <ul style="list-style-type: none"> <li>• Increased stiffness of median nerve</li> </ul> Power Doppler ultrasound: <ul style="list-style-type: none"> <li>• Increased intraneural blood flow</li> </ul>	<ul style="list-style-type: none"> <li>• Increased median nerve CSA at the carpal tunnel</li> <li>• Increased flattening ratio of median nerve</li> <li>• Increased T2 signal intensity within median nerve</li> <li>• Palmar bowing of flexor retinaculum</li> </ul>



**Figure 7.** A–C Ultrasound images and clinical photos of a patient that presented 7 months after an open carpal tunnel release with recurrent symptoms. The ultrasound shows the median nerve at the wrist with an increased maximum CSA of 18 mm<sup>2</sup> (normal CSA is ≤11 mm<sup>2</sup>). Clinical photographs demonstrate an incompletely released TCL with a transligamentous palmar cutaneous branch of the median nerve. Ultrasound images courtesy of and copyright protected by Dale S. Colorado, DO, MPH – used with permission. Clinical photographs courtesy of and copyright protected by Christopher J. Dy, MD – used with permission.

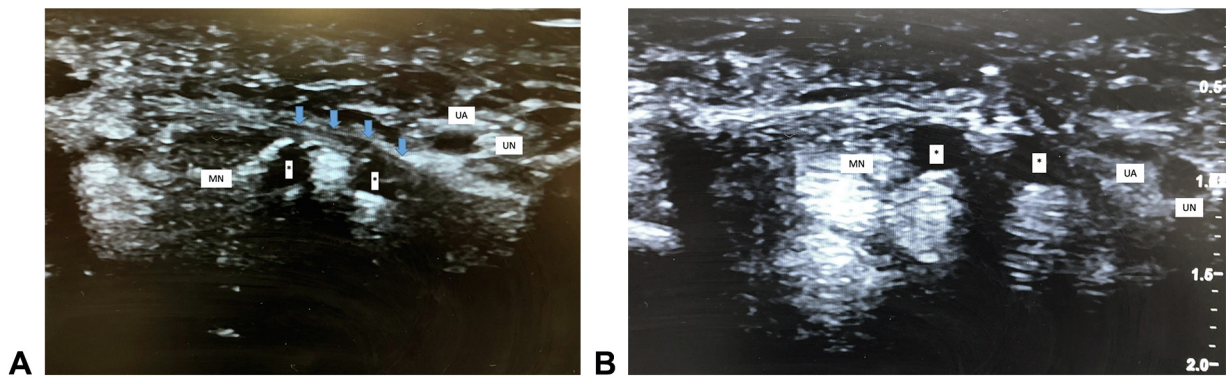
use in postoperative evaluation after CTR.<sup>37,61–64</sup> However, MRI may be misinterpreted after surgery and is of limited clinical utility in the work-up of persistent or recurrent CTS. One study examining MRI findings after successful endoscopic carpal tunnel release found that although median nerve swelling decreased proximally, the nerve remained swollen (>15 mm<sup>2</sup>) and flattened in all areas as long as 12 months after surgery, even in patients with clinical improvement.<sup>37</sup> In addition, the gap in the transected flexor retinaculum closes in most wrists by 12 months after endoscopic carpal tunnel release but maintains a more elongated, bowed configuration which increases the carpal tunnel volume.<sup>37,38</sup> Therefore, it is suggested that the use of MRI after CTR should be confined to instances where masses, tumors, or space-occupying lesions are on the differential for recurrent or persistent CTS.<sup>65,66</sup>

## Treatment of Compressive Neuropathies

### New techniques for nerve decompression

#### Ultrasound-guided carpal tunnel release

Over the years, there has been a trend to reduce the incision size in CTR to minimize surgical morbidity, expedite return to activity, and improve patient outcomes.<sup>67</sup> Ultrasound-guided CTR is performed through a <1 cm incision proximal to the wrist crease, made under ultrasound guidance using a custom blade, and is typically done under local anesthesia (Fig. 8). Several different techniques have been described.<sup>68</sup> A single-use disposable device has recently become available that uses expandable protective balloons to allow for a consistent carpal tunnel transverse safe zone while a retractable microknife cuts the TCL.<sup>69</sup> Leiby et al<sup>70</sup> reported on the



**Figure 8.** Ultrasound examination of the carpal tunnel and distal ulnar tunnel in the short axis during an ultrasound-guided CTR. **A** The blue arrows demonstrate the TCL prior to release. The asterisks demonstrate the inflated balloons for the ultrasound-guided CTR device, which expand the interval between the median nerve and ulnar artery. **B** An ultrasound image immediately after release of the TCL. Note the volar translation of the device relative to the prior image. MN = median nerve, UA = ulnar artery, UN = ulnar nerve. Images courtesy of and copyright protected by Christopher J. Dy, MD – used with permission.

1-year follow-up for patients who underwent ultrasound-guided CTR and found statistically and clinically significant improvements in Boston Carpal Tunnel Questionnaire symptom severity and functional status scores as well as Quick Disabilities of the Arm, Shoulder, and Hand scores, with high patient satisfaction and no documented complications or recurrent symptoms. This study also reported a large proportion of patients who underwent simultaneous bilateral ultrasound-guided CTR, noting that a potential advantage of this technique is the increased feasibility of bilateral CTR. However, it should be noted that the authors of this study had financial interests in the company that developed the microknife device, so further studies without industry relationships are needed to compare ultrasound-guided CTR with other CTR methods.

#### Thread carpal and cubital tunnel release

A new incision-less approach for CTR has been developed that combines ultrasound guidance with cannulated needles and a thread to divide the TCL. Guo et al<sup>71</sup> developed and described the ultrasound-guided thread carpal tunnel release (TCTR) in 2015, using an abrasive thread looped percutaneously around the TCL and pulling sequentially on the free ends of the threads to cut through the TCL. In a follow-up clinical study using a modified technique with distal-to-proximal hydrodissection, Guo et al<sup>71</sup> found improved patient-reported clinical outcomes compared with open and endoscopic CTR with a faster return to work. However, the senior author disclosed a financial interest in the TCTR device.<sup>72</sup> A more recent controlled trial by authors with no connection to the TCTR device development evaluated the safety and effectiveness of TCTR and found high patient satisfaction with no reported complications.<sup>73</sup> Schrier et al<sup>74</sup> provided a detailed description of the TCTR technique and emphasized the prerequisite of a thorough knowledge of the anatomic landmarks and experience with musculoskeletal ultrasound. The ultrasound-guided thread technique has also been investigated for percutaneous cubital tunnel decompression in a cadaveric study and found that complete release of Osborne's ligament and deep fascia was achieved without neurovascular injury. However, the authors did not address the release of the more proximal compressive structures, such as the arcade of Struthers and the medial intermuscular septum.<sup>75</sup>

#### Endoscopic cubital tunnel release

The endoscopic approach to in situ decompression of the ulnar nerve was first described by Tsai et al<sup>76</sup> in 1995, with the refinement of the surgical technique by Hoffman and Siemonow.<sup>77,78</sup>

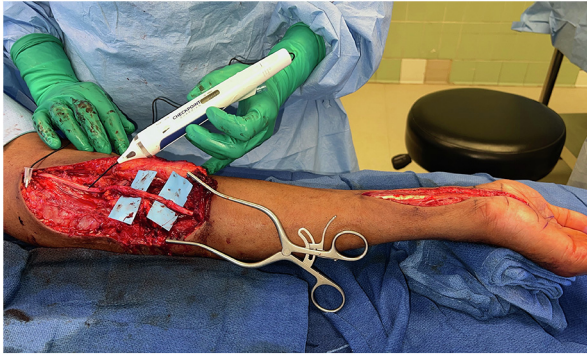
Reported advantages include the extensive release of the ulnar nerve proximally and distally with a smaller incision than open procedures. This approach can also be applied to anterior transposition by creating an additional volar portal.<sup>79–81</sup> A meta-analysis in 2018 comparing endoscopic cubital tunnel release to open cubital tunnel release found equivalent clinical improvement in terms of Bishop score and visual analog scale score reduction.<sup>82</sup> Endoscopic cubital tunnel release has an overall low rate of complications, the most common of which is hematoma formation.<sup>81,83</sup> Robotic endoscopic ulnar nerve decompression has recently been described, with proposed advantages of movement accuracy, high-resolution imaging, gas infusion rather than saline, movement scaling, and hands-free camera manipulation. However, it is hindered by a higher cost, lack of tactile feedback, and limited use in patients with a poor tissue envelope.<sup>84</sup>

#### Adjunctive treatments with nerve decompression

##### Electrical stimulation

Low-frequency electrical stimulation (ES) is a promising adjunctive therapy to peripheral nerve surgery. Prior animal studies using acute nerve injury models have shown that ES results in accelerated axonal outgrowth, remyelination of regenerating axons, and improved target organ reinnervation, likely by increasing intraneuronal cyclic AMP.<sup>85–87</sup> More recent clinical trials have investigated the use of ES in the perioperative setting for both acute nerve injuries and compressive neuropathies. Intraoperative and immediate postoperative ES is a clinically feasible adjunctive treatment. However, it does require the surgery to be performed under general anesthesia (Fig. 9). Wong et al<sup>88</sup> reported on the use of implanted electrodes to deliver 1 hour of continuous ES after a digital nerve repair for complete nerve transection and found improved temperature and tactile sensation compared with digital nerve repair alone. Power et al<sup>89</sup> performed a randomized, double-blind, placebo-controlled trial in which patients with severe CuTS underwent cubital tunnel surgery and then a single 1-hour session of postsurgical ES and were compared with a control group that underwent sham stimulation. ES after cubital tunnel surgery was found to enhance muscle reinnervation as measured by motor unit number estimation and improve functional recovery as measured by key pinch, grip strength, and McGowen-Goldberg grades.<sup>88–90</sup> Transcutaneous electrical nerve stimulation has also been widely used in the setting of chronic pain. However, a 2017 Cochrane Review was unable to make a definitive conclusion on the effectiveness of transcutaneous electrical nerve stimulation in the





**Figure 9.** Image demonstrating the intraoperative use of electrical stimulation on the median nerve. Image courtesy of and copyright protected by Amy M. Moore, MD – used with permission.

treatment of neuropathic pain because of the very low quality of evidence in the literature.<sup>91</sup>

#### Acetyl-L-carnitine

In severe nerve compression injuries in which there is significant axonal loss, there is a role for adjuvant therapies can help enhance axonal regeneration after nerve decompression. Acetyl-L-carnitine is a naturally occurring molecule that plays a role in lipid metabolism and has been shown to have neuroprotective effects on the nervous system.<sup>92–94</sup> It has been used in the treatment of polyneuropathies caused by human immunodeficiency virus, diabetes, and chemotherapy but has not yet been well studied in the treatment of compressive neuropathies.<sup>95</sup> Curran et al<sup>92</sup> performed a randomized, double-blind, placebo-controlled trial to investigate the effect of acetyl-L-carnitine in promoting nerve regeneration and improving functional recovery in patients with severe CTS. However, they found no significant differences in patients who received the acetyl-L-carnitine versus placebo.<sup>92</sup> Further studies utilizing chronic nerve compression models are needed to improve the understanding of the effects of acetyl-L-carnitine and its potential use in the adjuvant treatment of compressive neuropathies.

#### Immunophilin ligand drugs

Prior studies have demonstrated the neuroprotective and neurotropic effects of immunophilin ligands or immunosuppressive drugs, such as tacrolimus (FK506), cyclosporine, and rapamycin, for acute compressive or traumatic nerve injuries.<sup>96–99</sup> More recently, there has been an interest in studying the use of these drugs in the treatment of chronic nerve compression. A study in 2021 used a rat chronic nerve compression model to test the effects of systemic administration of tacrolimus, cyclosporin, and rapamycin on axonal regeneration. All 3 drugs demonstrated improved axonal regeneration in vitro and neuromuscular regeneration in vivo, independent of their immunosuppressive effects.<sup>100</sup> Given concern for the potential systemic side effects of immunosuppressive agents, other studies have investigated the local delivery of these agents. Daeschler et al<sup>101</sup> developed a biodegradable tacrolimus nerve wrap to promote axonal regeneration and functional recovery with minimal systemic drug exposure. This has the potential to be used intraoperatively during nerve decompression surgeries as an adjuvant for nerve recovery.

#### Alternative techniques to nerve decompression

##### Hydrodissection

Hydrodissection is a minimally invasive procedure that involves injecting fluid into anatomic spaces to facilitate

adhesiolysis and dissection during surgery.<sup>102</sup> Ultrasound-guided steroid injections with nerve hydrodissection have been described in the treatment of both CTS and CuTS.<sup>103–105</sup> However, additional studies have shown that nerve hydrodissection alone may be an effective treatment independent of a steroid injection. The proposed mechanism of action of hydrodissection is the separation of the compressed nerve from soft tissues to decrease the risk of adhesion and chronic constriction. Wu et al<sup>102</sup> investigated saline hydrodissection in the treatment of mild-to-moderate CTS and found improved patient-reported outcomes and cross-sectional areas of the median nerve compared with controls. A randomized controlled trial compared hydrodissection with a hyalase and saline solution versus a saline-only solution. They found that patients in the hyalase group had improved visual analog scale and functional disability scores in addition to improved nerve conduction study parameters.<sup>106</sup> Further studies are needed to compare hydrodissection with traditional nonoperative treatment modalities and assess its utility in the treatment of postoperative adhesions after peripheral nerve decompression surgeries.

##### Low-level laser therapy

Several studies have reported on the efficacy of low-level laser therapy (LLLT) in treating mild-to-moderate CTS with a focus on improvements in hand grip strength and electrodiagnostic parameters compared with placebo or the use of wrist splints.<sup>107–110</sup> More recent literature has examined the effects of LLLT on ultrasound parameters in the treatment of CTS. Nalbant et al<sup>111</sup> performed a randomized sham-controlled study of LLLT and found significant improvements in CSA, flattening ratio, and vascularity of the median nerve as determined by PDUS. Another study by Tezcan et al<sup>112</sup> utilized strain elastography and found that mean values of the strain ratio and CSA of the median nerve decreased after LLLT. The decrease in median nerve CSA and stiffness supports the proposed mechanism of LLLT in reducing nerve inflammation and improving the vascular supply. Future studies will need to examine the long-term treatment outcomes of LLLT.

##### Future of revision of failed nerve decompressions

The evaluation of recurrent compressive neuropathies and revision of failed peripheral nerve decompressions remain among the more challenging aspects of compressive neuropathy management. Reasons for persistent or recurrent symptoms after CTR include incomplete TCL release, failure to identify a secondary site of nerve compression, incorrect preoperative diagnosis, scar formation, and iatrogenic nerve injury.<sup>113,114</sup> As previously discussed, it can be difficult to interpret an ultrasound or MRI after a CTR. However, in the setting of recurrent or persistent CTS after CTR, ultrasound may detect an incomplete TCL release, while MRI may rule out a space-occupying lesion. Electrodiagnostic testing is limited in its ability to elucidate residual median nerve compression after CTR, as nerve dysfunction may persist in electrodiagnostic studies even in an adequately released median nerve. However, it can be compared with preoperative electrodiagnostic testing to evaluate for new or worsening findings. Revision CTR is typically performed with a more extensive open approach to identify the normal median nerve proximal to the carpal tunnel, and external neurolysis of the nerve may prove beneficial. Reasons for persistent or recurrent CuTS include incomplete decompression, persistent traction on the ulnar nerve, scar formation, new areas of compression, iatrogenic injury to the ulnar nerve or medial antebrachial cutaneous nerve, incorrect preoperative diagnosis, and recalcitrant advanced disease.<sup>115</sup> Most surgeons recommend submuscular transposition for revision

ulnar nerve decompression, and adjunctive procedures such as distal Guyon canal release may also be considered if there is evidence of intrinsic muscle denervation. In both revision carpal tunnel release and revision cubital tunnel surgery, it is critically important to counsel patients that complete resolution of symptoms after revision surgery may not be achieved.<sup>115,116</sup>

In conclusion, compressive neuropathies such as CTS and CuTS have traditionally been diagnosed by a combination of history, clinical examinations, and electrodiagnostic testing. Ultrasound and MR neurography demonstrate promise in the diagnosis of peripheral nerve entrapment. Ultrasound has been established as a helpful adjunct with defined morphologic parameters consistent with compressive neuropathies, although less is understood currently regarding the importance of vascularity as measured on ultrasound. MRI is a sensitive but nonspecific modality for detecting peripheral nerve pathology. MR neurography has the potential for better identification of physiologic and internal structural changes of peripheral nerves secondary to compression. However, further work is needed to establish optimal imaging methods and sequences as well as normative values for calculated parameters of MRI. With the advent of cheaper, faster, and less invasive imaging, the future may bring a paradigm shift away from electrodiagnostic testing as the gold standard for the diagnosis of compressive neuropathies. Traditional surgical treatment for CTS and CuTS has been open surgical release, with recent innovations trending toward less invasive techniques, such as mini-open, endoscopic, and ultrasound-guided releases. Advances in the surgical treatment of compressive neuropathies appear to center around adjunctive imaging for less invasive neurolysis techniques. The management of failed peripheral nerve decompressions and recurrent compressive neuropathies remains challenging.

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