Peripheral Nerve Surgery

Forhad H. Chowdhury, Mainul Haque Sarker, Abul Khair, S. M. Monir Hossain and Mohammod Raziul Haque

Abstract: Surgical conditions involving peripheral nerves are nerve injury, nerve tumor, and nerve entrapment. Injury to the nerves is usually caused by a road traffic accident, cut injury, penetrating injury, or blunt injury. Nerve trauma usually occurs in young people and can be devastating. Decision-making regarding surgical repair of the nerves is critical. In properly indicated cases, early surgical repair can provide the best possible outcome. Various types of peripheral nerve tumors can occur; however, schwannoma, neurofibroma, and malignant neurofibroma are the most common. Nerve tumors need proper evaluation and microsurgical management. Entrapment neuropathies are the other type of pathology that may require surgery. Carpal tunnel syndrome is the commonest type of entrapment. This chapter will discuss surgical diseases of the peripheral nerve. Peripheral nerve injury is discussed in the first part of the chapter and peripheral nerve tumors and entrapment neuropathy are discussed subsequently in brief.

Abbreviations

ATLS	advanced life trauma support	BTT	benign triton tumor
CNS	central nervous system	CT	computed tomography
CTR	carpal tunnel release	CTS	carpal tunnel syndrome
EN	entrapment neuropathy	DTF	desmoid-type fibromatosis
DTR	deep tendon transfer	EMG	electromyogram
FEMT	free functioning muscle transfer	FNA	fine-needle aspiration
LHN	lipofibromatous hamartoma of the nerve	HNST	hybrid nerve sheath tumor
IHO	intraneural heterotopic ossification	IPT	inflammatory pseudotumor
MPNST	malignant peripheral nerve sheath tumor	MRI	magnetic resonance imaging
NCS	nerve conduction study	NCT	nerve conduction test
NF	neurofibromatosis	PET	positron emission tomography
PNS	peripheral nervous system	PNI	peripheral nerve injury
VHL	von Hippel–Lindau		

1. Peripheral Nerve Injury (PNI)

1.1. Introduction and History

Peripheral nerve injury (PNI) causes a major disability in working people. The upper limb is the most common site of peripheral nerve injuries of traumatic etiology (Seddighi et al. 2016; Kouyoumdjian 2006). Some serious PNIs have a calamitous effect on a persons' quality of life. Transected nerve fibers regenerate spontaneously with scaring in the traumatic nerve gap, which produces neuroma (Siemionow and Brzezicki 2009). Sensory symptoms, motor function defects, and sometime the development of intractable neuropathic pain are common symptoms (Siemionow and Brzezicki 2009). The principal target of nerve repair is to foster the re-establishment of neural connections of the innervated organs by allowing regrowth of motor, sensory, and autonomic neuronal axons in the distal part of nerve with very minimal loss of axons at the repaired suture line (Seddighi et al. 2016; Brushart 1991).

Aegineta et al. (626–696 AD) were the first surgeons who reported the repair of traumatized peripheral nerves (Aegineta 1528).

In 1873, Huenter was the first surgeon who demonstrated an epineural nerve repair procedure, which exists in use even today (Millesi 1973). In 1892, Cajal proposed that neurotropic growth factors promote regeneration of axons distally to the target organ (Cajal 1892). Sunderland, in 1945, published the principles of microsurgical repair of peripheral nerves. In 1964, Kurze and Smith converted them into a microsurgical technique (Seddighi et al. 2016; Kurze 1964; Smith 1964; Sunderland 1991).

1.2. Peripheral Nerve Anatomy

Understanding of fundamental anatomy for classification and subsequent treatment of a nerve injury is mandatory for a neurosurgeon. The nervous system's cells differ more than those in any other component of

the body (Grinsell and Keating 2014; Kandel et al. 2000). The peripheral nervous system (PNS) has three types of cells: neuronal cells, stromal cells, and glial cells. The CNS communicates to the rest of the body through peripheral nerves. Different combinations of motor, sensory, and autonomic neurons make up peripheral nerves. Efferent neurons (motor as well as autonomic) receive information and signals from CNS neurons via dendritic connections, primarily using neurotransmitters. Afferent neurons receive signals from specialized cell types (receptors) via their dendritic connections, such as Pacinian corpuscles for fine sensation (Seddighi et al. 2016; Grinsell and Keating 2014). When a spinal reflex activity is required, these signals are delivered to the CNS to send sensory messages to the brain and to interneurons in the spinal cord (Jobe and Martinez 2013). Fascicules are individual bundles that make up a peripheral nerve. Myelin sheaths cover less than half of peripheral nerve fibers. The remaining unmyelinated fibers run along the surface of Schwann cells in deep gutters. The endoneurium, a network of reticular collagenous fibers, muffles each Schwann cell. The perineurium is a connective tissue layer that wraps around each fascicle. The epineurium, a loose vascular tissue tube, surrounds all of the fascicles (which encloses an individual nerve). Although the endoneurium is longitudinal, the perineurium and epineurium are circular (Sunderland 1990). For irrigation of the axons, micro-vessels (vasa nervosa) divide sequentially across the nerve in line with the structural layers. In the endoneurium, microvascular plexuses travel axially through the epineurium and provide transverse branches into the perineurium, producing a vascular network primarily made up of capillaries. These epineural vessels are more vulnerable to harm than nerve core vessels because of their more peripheral placement (Figure 1) (Seddighi et al. 2016; Grinsell and Keating 2014; Rydevik and Lundborg 1977).

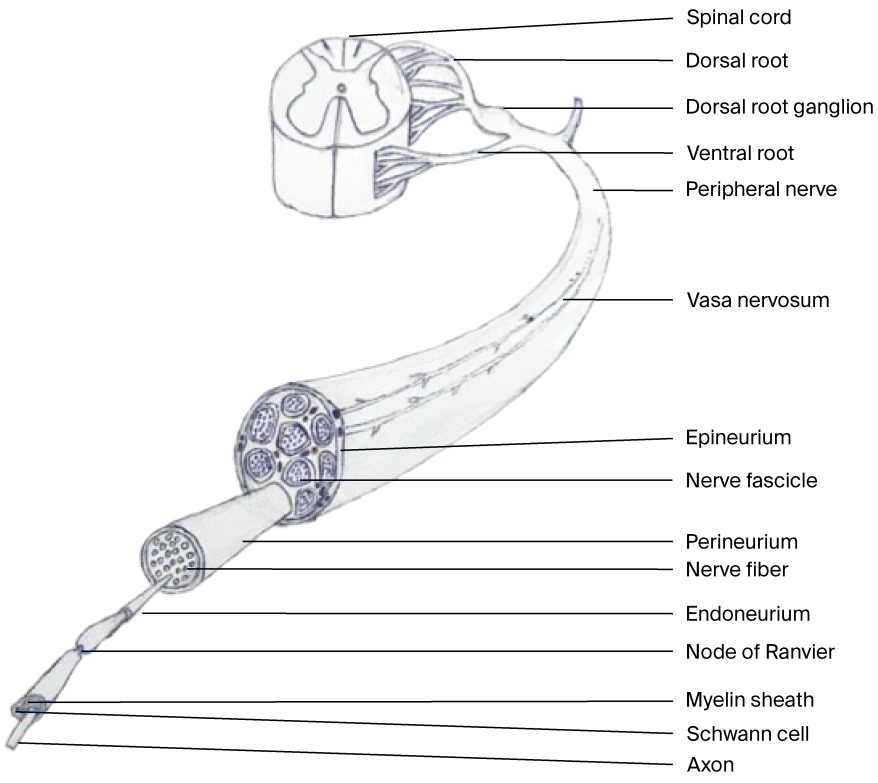

Figure 1. Anatomical organization of a peripheral nerve. Source: Figure by authors.

1.3. Peripheral Nerve Physiology and Trauma Responses

The internal environment of a neuron, like all cells, is diligently controlled. Axoplasmic movement back and forth between the cell body and the axon transports neurotransmitters and structural cell components. Any structural disruption or fault in the axonal or neuronal "lipid bilayer membrane" must be repaired immediately, or an irreversible sequence of apoptosis will begin (Bittner et al. 2000). Axonal degeneration and disintegration occur as a result of a number of events that occur both above and below the traumatic zone. Separated cell bodies and axons (in proximal axon injuries) degenerate through chromatolysis, a type of programmed cell death (apoptosis) (Pfister et al. 2011). From the zone of injury to the sensory or motor receptor, Wallerian degeneration of the distal axonal section of the axon occurs.

Wallerian degeneration takes place 24–48 h following peripheral nerve trauma. Here, both the surrounding myelin and distal axons degenerate (Griffin et al. 2013). The proximal axonal part, likewise, degenerates up to the next neighboring Ranvier node, which is where axonal regeneration occurs. Schwann cells appear as phagocytic cells that phagocytize axonal and myelin debris until there are no more endoneurial tubes. The recruited macrophages release growth factors into the region, stimulating the development of Schwann cells and fibroblasts. Schwann cells form orderly longitudinal columns termed Bungner bands in the empty endoneurial tubes (Pfister et al. 2011). This speed is required for effective axonal regeneration. Axonal regrowth begins at Ranvier's most distal node. A growth cone is formed when 50–100 nodal sprouts mature and elongate distally in response to trophic cues from denervated sensory and motor receptors and local tissue (neurotrophic as well as neurotropic factors) (Lee and Wolfe 2000). In addition, regeneration has motor–axon–motor receptor and sensory–axon–sensory receptor specialization (Grinsell and Keating 2014; Kandel et al. 2000; Brushart 1988). The growth cone also releases protease enzymes to assist axonal regrowth through tissue. Many axonal extensions branch out from the growth cone until they reach a receptor. The surviving neurites are then subjected to axonal pruning. If an endoneurial tube or receptor is not reached, the growth cone branches and grows haphazardly, resulting in a neuroma, which can present as a painful lump (neuroma) (Siemionow and Brzezicki 2009). Studies demonstrate that with severe nerve injury (Pan et al. 2003) axonal regeneration is more disorganized, resulting in fewer axons reaching the distal motor or sensory target due to less optimal axonal regeneration and scarring (Figure 2) (Seddighi et al. 2016; Grinsell and Keating 2014).

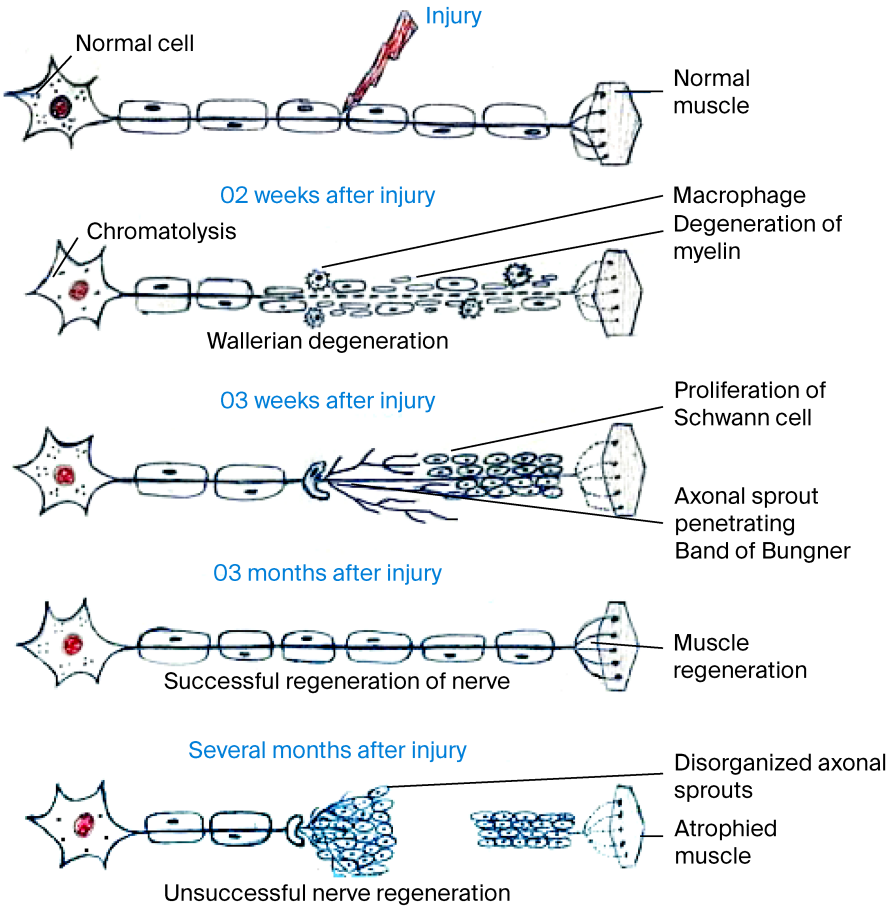

Figure 2. Schematic diagram of degeneration and regeneration of peripheral nerve after injury. Source: Figure by authors.

1.4. Classification of PNI

The Seddon and the Sunderland classifications (Seddighi et al. 2016; Grinsell and Keating 2014; Sunderland 1990; Seddon 1943) are commonly used for PNI, which is shown in Table 1.

Table 1. Classification of PNI.

Seddon Classification		Properties	Sunderland Grade
Neuropraxia		Segmental demyelination	1st degree
Axonotmesis	I	Axon severed but endoneurium intact (ideal condition for regeneration)	2nd degree
	II	Discontinuous axon, discontinuous endoneurial tube, fascicular arrangement, and perineurium preserved	3rd degree
	III	Absence of continuity of endoneurial tubes, axons, perineurium, and fasciculi; intact epineurium (neuroma in continuity)	4th degree
Neurotmesis		Absence of continuity of total nerve trunk	5th degree

Source: Authors' compilation based on data from Seddighi et al. (2016); Grinsell and Keating (2014); Sunderland (1990); Seddon (1943).

1.4.1. Neuropraxia

Neuropraxia (Sunderland grade 1) is the mildest type of PNI, which is a recoverable neuro-conduction interruption that persists for hours to days. Neuropraxia presents with neuro-deficit of the involved nerve. There are minimal or no identifiable histopathologic changes in nerve structure. Early clinical evaluations often demonstrates partial loss of nerve function/s, sparing autonomic function. In patients showing total loss of neuro-function/s, an early single clinical examination cannot differentiate neuropraxia from more serious nerve injuries. PNI grade 1 recovers excellently and spontaneously over days to weeks and seldomly over months (Dumitru et al. 2001; Wilbourn 2002).

1.4.2. Axonotmesis

In axonotmesis-I (Sunderland grade 2) of PNI, the axon is disrupted, but the nerve's connective tissue structures remain relatively unaffected. With low endoneurial edema and fibrosis, the fascicular and endoneurial connective tissue tubes remain intact. Wallerian degeneration takes place in the distal axon following axon division. The proximal axon similarly degenerates for a variable length up to the next Ranvier node. The undamaged endoneurial tube directs the budding terminals of regrowing axons toward the target area. The regrowth rate of a damaged nerve is approximately 1 mm/day or 1 inch/month, which can be utilized for serial clinical assessments of the patient and to estimate the duration to the recovery of function/s. Sunderland grade 2 PNIs normally recover without operation.

Axonotmesis-II (Sunderland grade 3) of PNI occurs when the damage takes place and is confined to endoneurial tubes within the fascicle.

Axonotmesis-III (Sunderland grade 4) of PNI is one where further damage occurs in fascicular tubes and extrafascicular connective tissue. Here, different degrees of interfascicular scaring result in severe obstacles to axonal regeneration, which results in haphazard growth in spite of coarse continuity of the injured nerve. The ultimate traumatic neuroma in injured sites is composed of a connective tissue network entangled with poorly myelinated, fine-caliber axons (Sunderland 1991; Sunderland 1951a; Mackinnon and Dellon 1988).

1.4.3. Neurotmesis (Sunderland Grade 5)

Here, the injured nerve is severed anatomically. It always requires surgical repair, but the timing of surgery is critical. Surgical repair of sharp PNI (e.g., laceration by knife or glass) should be completed within hours to a day or two. A lacerated nerve that has been bluntly wounded should be sutured 3 to 4 weeks following the injury. This time delay permits the longitudinal length of the injury to be completely diagnosed and visible, allowing for nerve clipping to healthy distal and proximal stumps before restoration (Seddighi et al. 2016; Grinsell and Keating 2014; Schmid and Salyapongse 2008; Bittner et al. 2000).

There is no way to tell the differences among the Sunderland grades II and IV without a diagnostic examination. These Sunderland grades are currently solely diagnosed histologically (Pfister et al. 2011).

1.5. Nerve Conduction Studies (NCSs), Electromyograms (EMGs) and MRI

NCSs and EMGs are noninvasive diagnostic procedures that can be used in the case of delayed nerve healing, when muscular fibrillations are present in denervated muscle but not visible right after an injury. As a result, no noninvasive investigative tool can accurately determine the presence or degree (severity) of a PNI in the first few weeks after injury. Clinical examination and/or exploratory surgery are still used to make diagnoses.

NCSs use a voltage stimulator applied to the skin over several locations of the peripheral nerve to be evaluated to examine both sensory and motor function. A surface electrode overlying the muscle bellies supplied by the nerve (motor response) or nerve supply (nervous response) records the evoked response (sensory response).

EMGs are used to assess the electrical activity of resting muscles (the evidence of aberrant spontaneous function such as positive sharp waves and fibrillations) as well as to conduct voluntary motor unit evaluations (Effron and Beasley 2006). Depending on the degree of the injury, fibrillations may not be seen for three to six weeks following PNI (Robinson 2000). NCSs can be performed as a screening test for the absence or presence of conduction blocks, whereas EMGs can provide further data in the form of diminished action potentials (Griffin et al. 2013). So, serial NCSs and EMGs can detect if a PNI is neurapraxic or axonotmetic over time. After three to six months, if there is no spontaneous clinical or NCS/EMG recovery, the nerve must be surgically explored (Grinsell and Keating 2014).

In delayed situations, high-quality MRI imaging (neurograms) in the implicated area/s can reveal the discontinuity of nerves or traumatic neuroma, which can help with surgical decision-making and planning. MRI images are now commonly employed in the treatment of brachial plexus and lumbosacral plexus injuries (Figures 3 and 4).

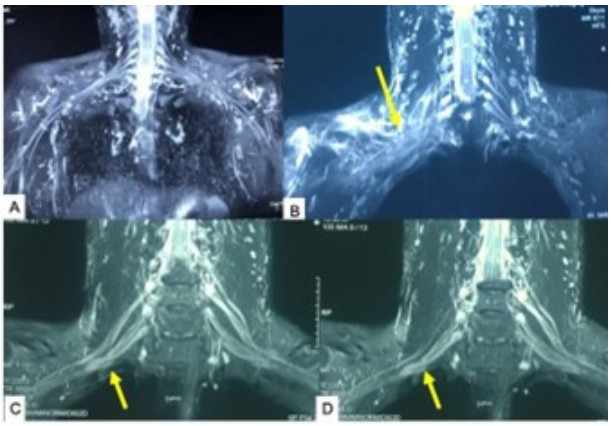

Figure 3. MRI of brachial plexus (BP): (**A**) normal MRI of BP; (**B**) MRI of BP with right-sided pan-brachial plexus injury; and (**C**,**D**) MRI showing right-sided middle and inferior trunks of BP injury. Arrow indicates injury site. Source: Figure by authors.

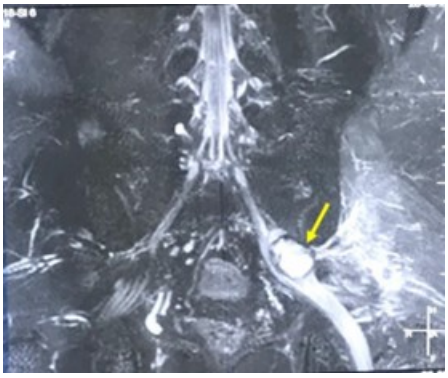

Figure 4. MRI of lumbosacral plexus showing post-stab left lumbosacral trunk injury with neuroma. Arrow indicates injury site. Source: Figure by authors.

1.6. Mechanism of PNI and Neuropathology

PNI increases epineural vascular permeability, which is more sensitive to compression damage than endoneurial arteries, due to its microvascular orientation. Endoneurial arteries are also damaged by sustained and higher pressure levels, as well as more prolonged compression trauma, resulting in intrafascicular edema, which can lead to secondary injury (Hall 2005). PNI can be caused by a variety of traumatic etiologies, including traction, stretch, stab, blow, blunt injury, laceration (transaction), contusion, gunshot wounds, thermal and electrical injuries, compression and ischemia (crush), iatrogenic causes, and injection injuries. Compression damage to nerves is thought to be caused by a variety of causes. Anatomically, restricting a root causes increased tension at that location, compressing blood vessels and causing nerve ischemia, as seen in vasculitis and artherosclorotic disorders (Tapadia et al. 2010; Pham and Gupta 2009).

Crush injuries to the nerve are most commonly caused by compression of the nerve by a blunt item such as a surgical clamp, bat, or another crushing device. Transection injuries (neurotmesis or grade V PNI) are most usually caused by a laceration from a blade, knife, gunshot, or shard of glass (Zochodne and Levy 2005). In actuality, most of these injuries come in a variety of forms (Dellon et al. 1988). Primary exploration and primary microsurgical treatment are the best options for an acute penetrating wound with nerve damage. Most nerve damages from gunshots or high-velocity missile injuries are discovered, contused, or bruised during examination; the contused and divided nerve ends should be sutured to fascial tissue close to each other with a large, non-absorbable suture under moderate distraction (to prevent retraction). Definitive nerve repair should be performed several weeks following the first procedure during secondary exploration (Stanec et al. 1997).

PNI as a result of intramuscular medication injection is a potentially fatal complication. Any nerve can be affected, but the proximal radial nerve and sciatic nerves in the buttocks are the most commonly affected. The needle may cause injury; however, most injuries are due to the toxic effects of the substance delivered into the intraneural region. Traditionally, the needle causes an electric-shock-like sensation down the limb. Severe radiating pain and paresthesia are felt shortly after the medication is injected.

Patients frequently complain afterwards of extreme pain with symptoms such as burning, scalding, and electric-like or numbing discomfort. In a small percentage of instances, delayed onset of neuropathy can develop, with symptoms such as scorching pain, profound discomfort, or annoying paresthesias down the extremity and in the supplying area of the injured nerve. Motor deficiency is generally more common than sensory neuropathic pain when an injury is incomplete (Grinsell and Keating 2014).

1.7. Recovery Time Frame for PNI

Better functional outcomes result from early nerve restoration (Mackinnon 1989). Despite good nerve healing, axonal development is sluggish, averaging only 1–2 mm each day. There is no drug or treatment method for increasing this rate. It takes 12–18 months for muscle reinnervation to achieve functional reinstallation after irreversible motor endplate degeneration (Lee and Wolfe 2000). The sensory renewal process takes longer. For example, ulnar and median nerve lesions at the wrist require axons to regrow over distances of 100 mm (roughly) in order to reach the hand muscles. As a result, functional recovery takes at least one hundred days. More proximal PNIs, such as an upper brachial plexus injury, need nerve regeneration over the gap of up to a meter and take more than 2 to 3 years to reach and reinnervate the arm. Clinically, there may be little or no function restoration in such instances. The target tissue and distal nerve remain denervated during this time because neurons lack target connections (Pfister et al. 2011). Muscle atrophy and fibrosis begin shortly following denervation and reach a halt after 04 months, when 60 to 80% of muscle mass has disappeared (Lee and Wolfe 2000). Although motor endplates develop within the muscle, functional reinnervation is improbable beyond twelve months as a result of fibrosis (Lee and Wolfe 2000). Chronic axotomy of the neurons as well as chronic Schwann cell denervation can cause axon regeneration to fail after PNI (Pfister et al. 2011).

1.8. Treatment Approaches

In the clinical context, the emergency management of a patient with suspected PNI differs dramatically from that of a patient who is in elective or even urgent care. Priority is always given to life-threatening airway, pulmonary, circulatory, and CNS trauma in any acute trauma patient (according to ATLS recommendations) before extremity injuries are handled. Nerve injuries (5%) and brachial plexus injuries (1%) are rather prevalent in

polytrauma patients. In more than 60% of cases, this PNI can be detected during the initial clinical phase (trauma encounter).

An asymmetrical neurological finding, with absence of function restricted to one extremity when associated with loss of DTRs, is frequently related to PNI in trauma patients with an altered level of consciousness (Dahlin 2006; Battiston et al. 2009). Nerve function recovery is mostly determined by the nerve's underlying neuropathologic condition; those with a big neurotmetic element seldom recover; however, those with axonotmetic or neuropraxic pathology, or both, may do so over time. The major justification for surgical investigation is a lack of nerve continuity, either clinically or electrophysiologically (Aguayo et al. 1973; Shokrzadeh et al. 2010). The mechanism of injury helps determine the best time to investigate a continuous nerve injury. More focal injuries, such as those caused by gunshot wounds, stab wounds, iatrogenic causes, lacerations, and fracture-related contusions, should be investigated 2 to 3 months following the initial injury (Thomsen and Dahlin 2007). In grade 3 PNI, clinical outcomes range from no recovery to a full restoration of function. In grade 4 PNI, on the other hand, a neuroma in continuity is the most dangerous pathology. Unless surgical excision and repair are considered, functional recovery is rare (Diao and Vannuyen 2000). PNI caused by injection is treated using the same criteria as any other patient with a continuous nerve lesion. The majority of partial and some complete PNIs regenerate without surgery, with early function recovery seeming to be the most important prognostic indicator in these instances. Patients who do not recover spontaneously after 4 months, and those patients with medically refractory neuropathic pain, may be candidates for surgical intervention, including internal and external neurolysis and nerve repair, based on intraoperative results (Seddighi et al. 2016; Grinsell and Keating 2014)

1.8.1. Nerve Repair

For severe axonotmesis and neurotmesis, epineural microsuturing is the mainstay surgical treatment for traumatic peripheral nerve repair (Figures 5–8). This repair should take place in a tension-free, well-vascularized bed. Gross fascicular alignment and matching should be present, as should correct surface epineural vasa nervosum orientation.

Intra-nerve dissection, direct fascicular matching, and fascicular group suturing are all required for group fascicular repair. Intraneural trauma and scarring can obstruct neural regrowth, and this can happen with a major nerve in the distal limb (Lundborg 2000).

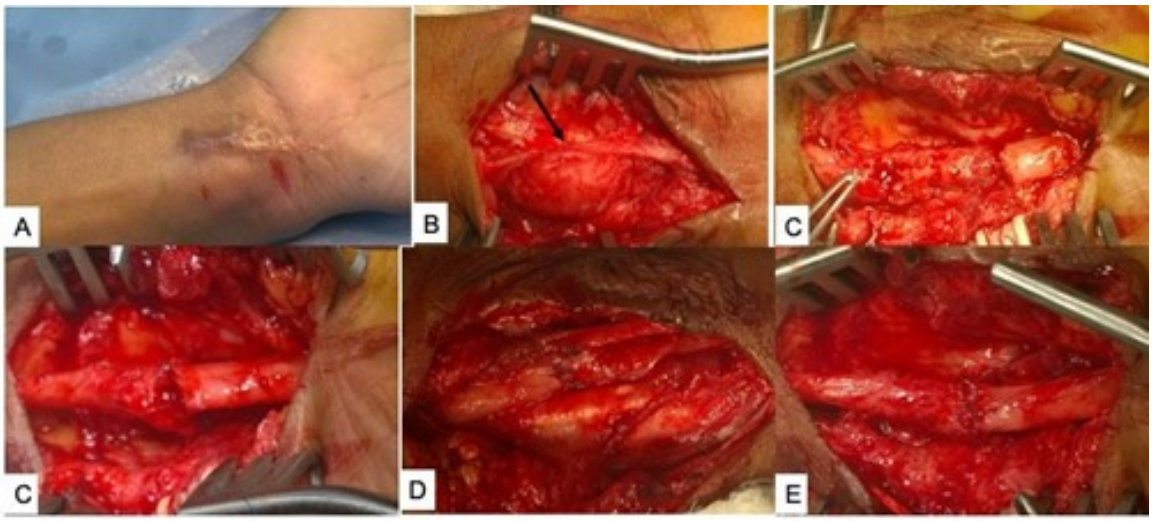

Figure 5. Sequential peroperative images: (**A**) post-traumatic median nerve neuroma at wrist; (**B**) operative exposure of neuroma and nerve; arrow indicating neuroma (**C**) neuroma excision; and (**D**–**F**) epineural repair of nerve without graft. Source: Figure by authors.

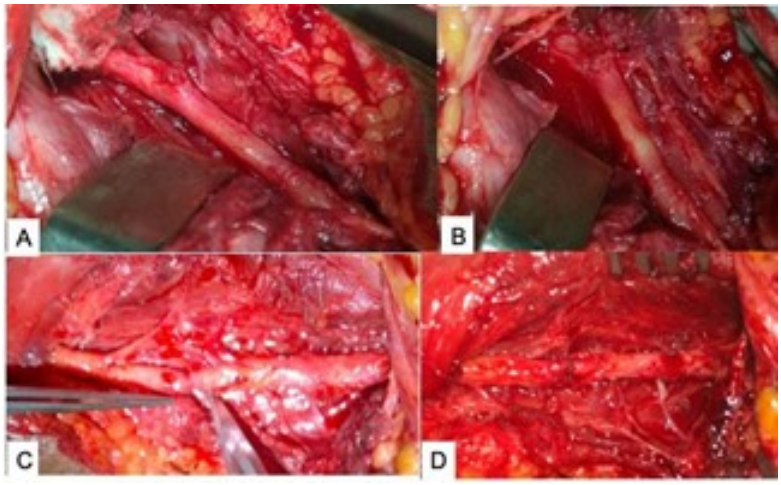

Figure 6. Peroperative sequential images of post-traumatic exposure of radial nerve at midarm (axonotmesis-III). (**A**–**D**) Exposure, identification of pathological part, excision and trimming of scar and neuroma, and direct epineural repair. Source: Figure by authors.

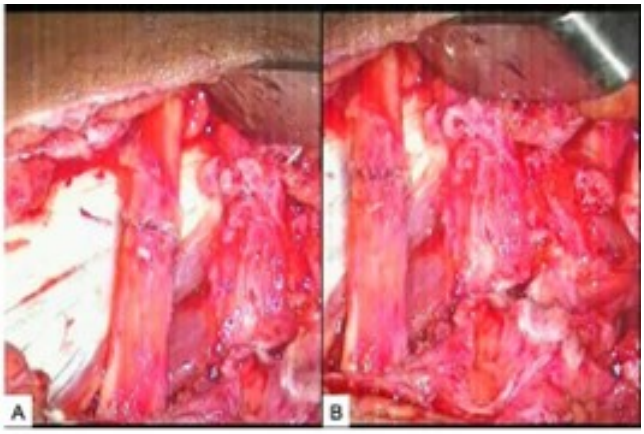

Figure 7. (**A**,**B**) Epineural repair of transected common peroneal nerve at popliteal fossa. Source: Figure by authors.

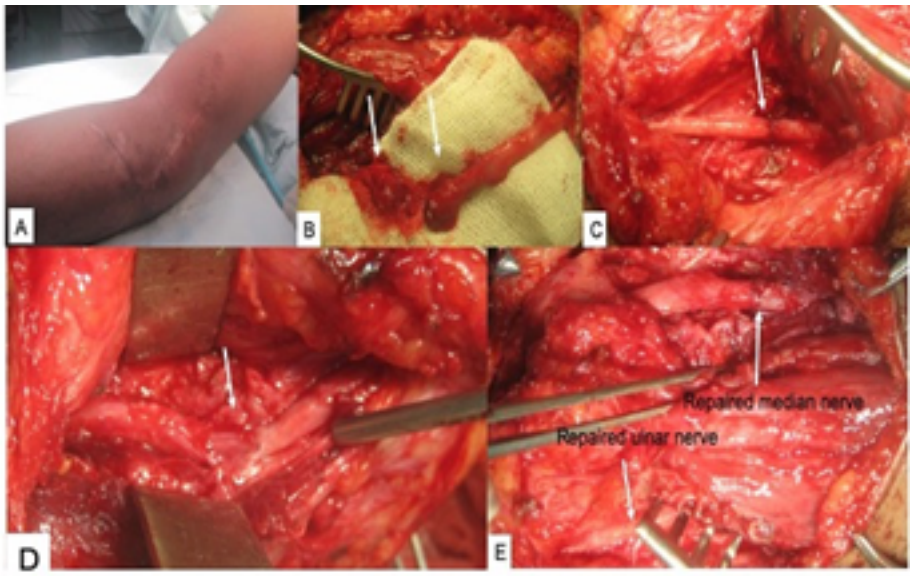

Figure 8. (**A**) Post-RTA injury of both ulnar and median nerve at and around elbow. (**B**) Neurotmesis of ulnar nerve; arrows showing both end of ulnar nerve (**C**) Epineural repair with anterior transposition of ulnar nerve; arrow indicating suture line (**D**,**E**) Exposure of median nerve with the same incision (axonotmesis), excision of scar, and epineural repair. Source: Figure by authors.

When there is an interval between the injured nerve ends, and excessive strain is needed for direct epineural healing, nerve grafting is employed; reversed interposition autologous nerve grafts (such as for the sural nerve) are required (Figures 5–13) (Pfister et al. 2011). Single, cable, trunk, interfascicular, and vascularized autologous nerve cable grafts are available. A single graft connects the nerve interval with a donor nerve segment of a similar width. Cable grafts, which use numerous lengths of a lesser-diameter donor nerve, in order to approximate the diameter of the injured peripheral nerve, are used to bridge gaps between large diameter nerves. Expensive sensory nerves, such as the sural and medial antebrachial nerves, are used as donor nerve grafts and are employed in a reversed orientation (Colen et al. 2009). A damaged recipient tissue bed that will not tolerate a non-vascularized nerve transplant will receive a vascularized nerve graft (Terzis and Kostopoulos 2010).

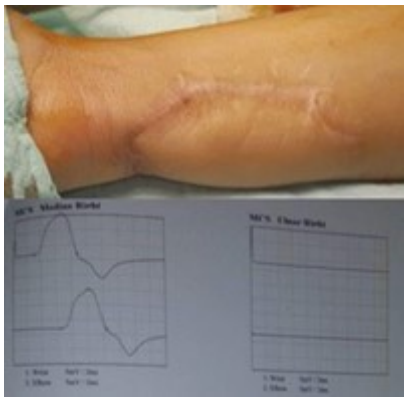

Figure 9. Upper picture showing post-family-violence ulnar nerve injury at wrist and lower forearm. Lower picture showing NCS showing normal activity of median nerve and no activity of ulnar nerve in the same patient of upper picture. Source: Figure by authors.

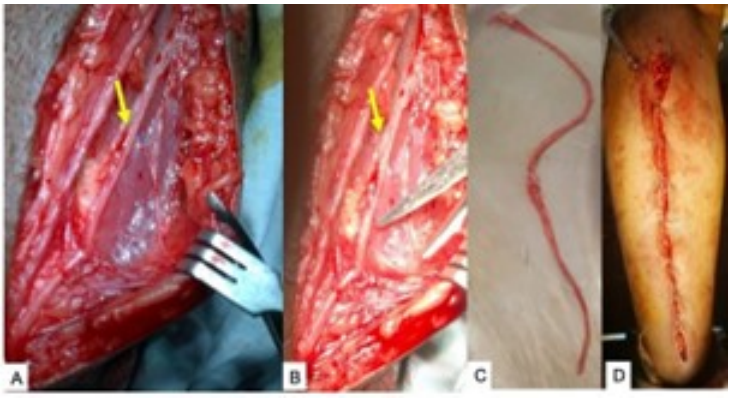

Figure 10. Peroperative pictures of patient of Figure 9: (**A**,**B**) exposure and dissection of sural nerve, arrow indicating sural nerve (**C**) sural nerve after procurement, and (**D**) closure of leg wound after sural nerve procurement. Source: Figure by authors.

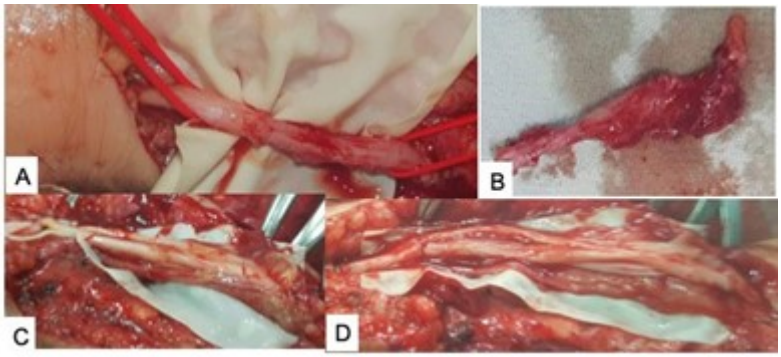

Figure 11. Peroperative pictures of patient of Figure 9. Sequential peroperative images: (**A**) exposure of ulnar nerve, (**B**) excision of neuroma and scar, and (**C**,**D**) "Cables grafting repair" of ulnar nerve by sural nerve graft strands using interfascicular (perineural) sutures. Source: Figure by authors.

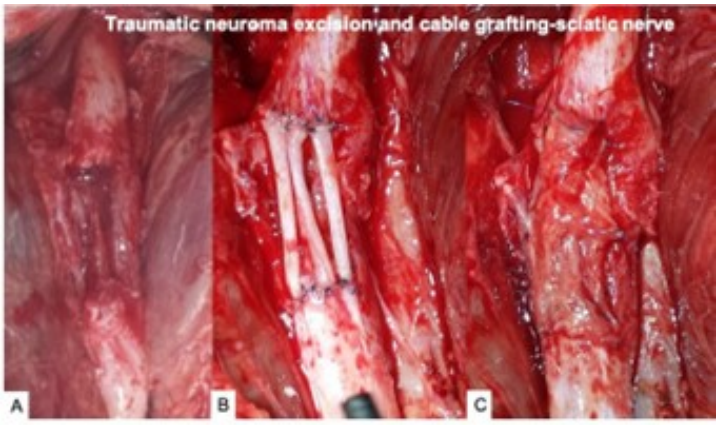

Figure 12. Peroperative pictures of repair of a sciatic nerve (tibial portion injured only) at upper popliteal fossa: (**A**) excision of traumatic neuroma from tibial part of sciatic nerve, (**B**) interfascicular "cable nerve grafting" repair of tibial nerve by sural nerve graft, and (**C**) fascial covering of repaired nerve. Source: Figure by authors.

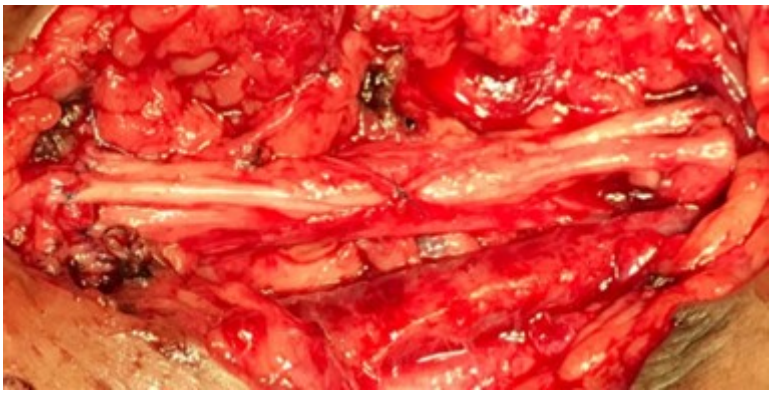

Figure 13. Peroperative picture of interfascicular "cable nerve grafting" repair of sciatic nerve by sural nerve graft at upper thigh. Source: Figure by authors.

The autologous nerve graft passes through Wallerian degeneration, providing only mechanical guidance and a foster structure for axon regeneration (Millesi 1990). Autologous nerve grafts meet the characteristics of an ideal nerve conduit as they elicit a stimulating and permissive environment that includes neurotrophic factors, Schwann cell basal laminae, and adhesion molecules (Siemionow and Brzezicki 2009). Although autografts burn a working nerve (sensory), they are used to replace a more essential wounded nerve (usually motor). At the donor location, there is frequently sensory deficiency and scarring, as well as the possibility of painful neuroma formation (Moore et al. 2009). Fascicle and size mismatch, tissue handling, suture scarring and fibrosis, and the injury itself, as well as any of these factors at the repair site, can all result in poor PNI regeneration. A surgical rule of thumb is that each repair site loses 30–50% of its axons. As a result, roughly 50–70% of the original axons will effectively regrow across the suture line after initial nerve repair. Approximately 25–40% of axons regrow successfully through a nerve transplant with two coaptation sites. Due to persistent axotomy and muscle fibrosis, there will be further axonal loss based on the gap to the sensory/motor target. Numerous conduits and allogenic nerve grafts have been described; however, none of them have proven similar or superior results.

1.8.2. Factors That Dictate the Results of Nerve Repair

Motor axons must be properly attached to motor endplates and axons must land on sensory receptors for functional nerve regeneration. Nerve autografts produce fewer favorable results than original nerve repair. Grafts that extend above the elbow, are longer than 7 cm, are older, and take longer to heal are all bad signs (Lee and Wolfe 2000). The abstract of nerve repair is that early nerve repairs are more result-oriented than late repairs; primary repair is better than the nerve grafts; younger people do better than older people; the distal repair is more effective than the proximal repair; and the short grafts perform better than the long grafts (Sunderland 1990).

1.8.3. Surgical Alternatives to Nerve Repair

Nerve Transfers (Neurotization)

There are alternatives to utilizing healthy donor nerves to treat affected peripheral nerve networks. This is appropriate in injuries to the very proximal nerves and in those who do not have a proximal nerve segment/stump, such as cervical spinal nerve root avulsions. The microsurgical coaptation of a normally functioning nerve donor to an injured nerve is known as nerve transfer/neurotization (Lee and Wolfe 2012). Neurotization is commonly used to regenerate key motor nerves, but it can also be utilized to regenerate critical peripheral sensory nerves. It connects a less-significant limb muscle to a disposable motor donor nerve. The nerve is severed and subsequently attached to the more essential motor nerve's wounded distal end (Seddighi et al. 2016; Grinsell and Keating 2014).

Free Functioning Muscle Transfer

It is a reconstructive treatment for severe and late PNIs, particularly those that have failed after primary surgery, and is a form of free functioning muscle transfer (FFMT) (Siemionow and Brzezicki 2009). A healthy muscle and its neurovascular pedicle are moved to a new site to perform a new function (Carlsen et al. 2009). This could be utilized in a situation when both the nerve and the muscle have been destroyed by a serious acute injury or derangement caused by chronic axotomy as well as muscular fibrosis. Transferring a functioning motor nerve to the FFMT's nerve and restoring the muscle's circulation through microsurgical vascular anastomosis to recipient vessels empowers the muscle. Within a few months, the donor nerve neurotizes the transferred muscle, allowing it to operate independently (Seddighi et al. 2016; Grinsell and Keating 2014).

1.9. Conclusions

In the last half-century, very minor improvements in surgical technique have been made and epineural initial repair remains the gold standard. Microsurgical nerve repair, with end-to-end direct repair or by employing interposition autologous nerve grafts where there is unnecessary strain, is the key to satisfactory results.

2. Peripheral Nerve Tumor Surgery

2.1. Introduction

Peripheral nerve tumors are a diversified group composed of non-neural sheath neoplasms, nerve sheath neoplasms, and sometime non-neoplastic masses (Kokkalis et al. 2019; Seol et al. 2009; Chowdhury et al. 2008b). Nerve tumors of the peripheral nervous system may develop anywhere in the body. Although several cases of malignant peripheral nerve tumors have been reported in the literature (Prudner et al. 2020), the majority of them are benign. Peripheral nerve tumors can take several forms. These tumors could grow within nerves (intraneural tumors) or press against them (extraneural tumors) (Kokkalis et al. 2019; Seol et al. 2009).

2.2. Clinical Presentation and Diagnostic Approach

Swelling or a lump along the course of the peripheral nerve; pain, tingling sensations, or numbness; loss of function in the affected area or weakness; and loss of balance or dizziness are all common clinical symptoms of a peripheral nerve tumor. Depending on the clinical presentation, patients should be thoroughly checked, with particular attention paid to any indicators that may be linked to the presenting symptoms. When a tumor is first noticed, any changes in shape and size, the rate of increasing growth, and any probable B-symptoms that can be attributed to the original diagnosis should be investigated and recorded. It is also worth noting whether there is a family history of tumors. Furthermore, it is important to define whether the symptoms are due to specific events. Following that, a thorough clinical evaluation should be accomplished, beginning with the examination of the tumor and ending with filing of the findings. Regardless of the type of the tumor, regional lymph nodes should be checked on a regular basis. The bulk of clinical symptoms are caused by the tumor mass itself, either through intraneural invasion or involvement of the peripheral nerve, or by the surrounding tissues, primarily due to its size (Kokkalis et al. 2019; Chowdhury et al. 2008b; Mrugala et al. 2005).

2.3. Imaging

The first-choice investigation methods for such tumors are diagnostic ultrasonography (U/S) and MRI. To begin, ultrasound can be utilized to determine the form, integrity, matrix, and size of the mass. More

comprehensive observations and features can be obtained by combining MRI imaging of the mass with a neurogram (Figures 14–18). However, tissue biopsy of the tumor is crucial in the end. When a malignant tumor is suspected in peripheral nerve tumors, biopsy is recommended, and tissue biopsy is required to plan the definitive treatment (Sacks et al. 2013; Hsu et al. 2007; Plate et al. 2006; Mavrogenis et al. 2017). The oncological principles of biopsy should be followed during the procedure (Mavrogenis et al. 2014; Webber 2014). It goes without saying that any oncological case is approached as a collaborative effort by dedicated and experienced treating surgeons. Nerve Conduction Tests (NCTs) performed before surgery are not always accurate, but intraoperative electrophysiological monitoring is critical (Kokkalis et al. 2019; Chowdhury et al. 2011).

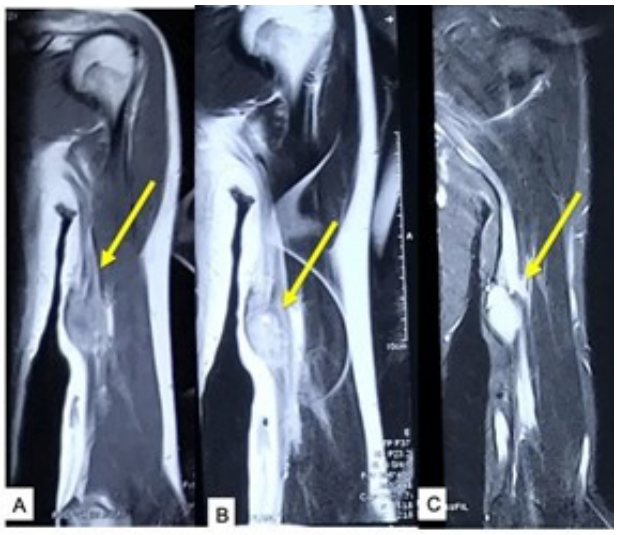

Figure 14. (**A**–**C**) MRI images of arm showing median nerve schwannoma (arrow-marked). Source: Figure by authors.

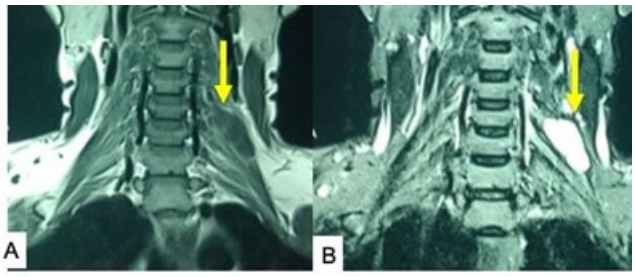

Figure 15. (**A**,**B**) MRI of brachial plexus showing schwannoma(arrow-marked) of left upper trunk. Source: Figure by authors.

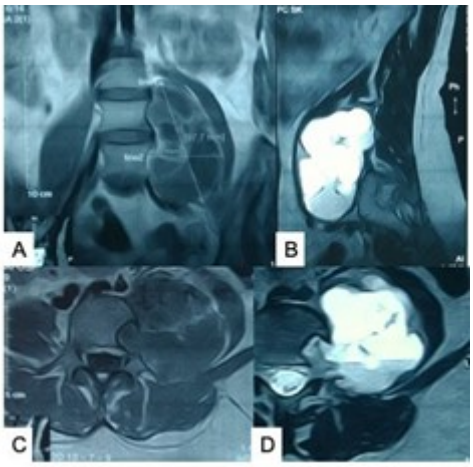

Figure 16. MRI of images: (**A**) coronal, (**B**) sagittal, and (**C**,**D**) axial images showing left lumbar plexus schwannoma. Source: Figure by authors.

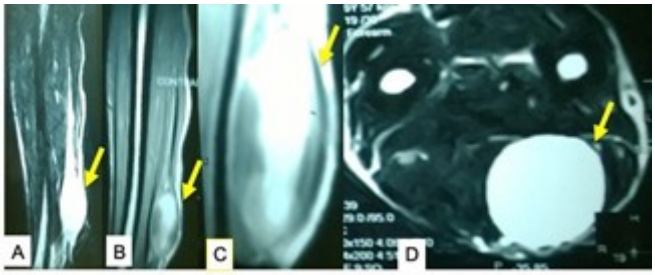

Figure 17. MRI images of thigh: (**A**–**C**) sagittal and (**D**) axial images showing sciatic nerve schwannoma (arrow-marked) at lower thigh. Source: Figure by authors.

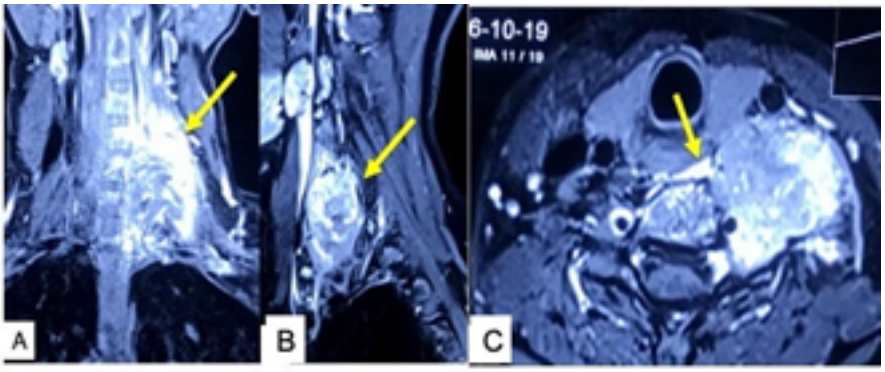

Figure 18. (**A**–**C**) Contrast MRI of brachial plexus (coronal, sagittal and axial view) showing malignant peripheral nerve sheath tumor (MPNST) (histologically proved) of left brachial plexus (arrow-marked). Source: Figure by authors.

2.4. Benign Neoplasms of Nerve Sheaths or Nerve Sheath Tumors

2.4.1. Schwannoma

Schwannomas are slow-growing nerve sheath neoplasms with no known cause, unless they are associated with neurofibromatosis syndrome (Antonescu et al. 2013). They are Schwann cells that have been encapsulated. Antoni A area of highly organized cellular elements and Antoni B area of loose myxoid elements are biphasic sheath tumors with two components. These two areas' component percentages differ. They can strike at any age, although they are commoner in the 4th to 6th decades (Antonescu et al. 2013). About 90% of schwannomas are sporadic, with 3% in cases with neurofibromatosis-2 (NF-2), 2% in cases with schwannomatosis (of which a very small percentage had familial schwannomatosis), and 5% in patients with or without NF-2 in combination with multiple meningiomas (1% with and 4% without) (Antinheimo et al. 2000). Multiple schwannomas can occur in NF-2 syndrome and in Gorlin–Koutlas syndrome (Antonescu et al. 2013; Goldblum et al. 2014). S-100 protein immunohistochemistry contributes to the differentiation from neurofibromas. Schwannomas are usually benign, yet there have been a few reports of malignant alterations (Chowdhury et al. 2010; Rasbridge et al. 1989; Woodruff et al. 1994; McMenamin and Fletcher 2001). Neurofibromatosis is a group of genetically determined disorders (phakomatoses) that is divided into two types: neurofibromatosis-1 (NF-1) and neurofibromatosis-2 (NF-2) (NF-2). A schwannoma is a slow-growing neoplasm that often goes unnoticed for several years before being diagnosed (frequently in peripheral nerves of the subcutaneous tissues and skin of the neck, head, or the flexor surfaces of the limbs) (Chowdhury et al. 2011; Antonescu et al. 2013). Spinal schwannoma is a less common cancer (Zhang et al. 2018). Large tumors cause neurologic symptoms and pain, which are caused by the mass effect. If the neoplasm begins in the nerve sheath, it is encased in a capsule made up of nerve fibers and epineurium (Goldblum et al. 2014). On T1-weighted imaging, schwannomas have a medium signal intensity, while T2-weighted imaging shows a hyperintense signal (Figures 14–17) (Crist et al. 2017). To avoid or reduce neuro-deficits, it is critical to properly detect the incoming and outgoing fascicles, nerve fibers encountered during microsurgery (Kim et al. 2004) (Figures 19–21). Though rare, the occurrence of a schwannoma in the retroperitoneum has been documented (Figure 16) (Khandakar et al. 2014).

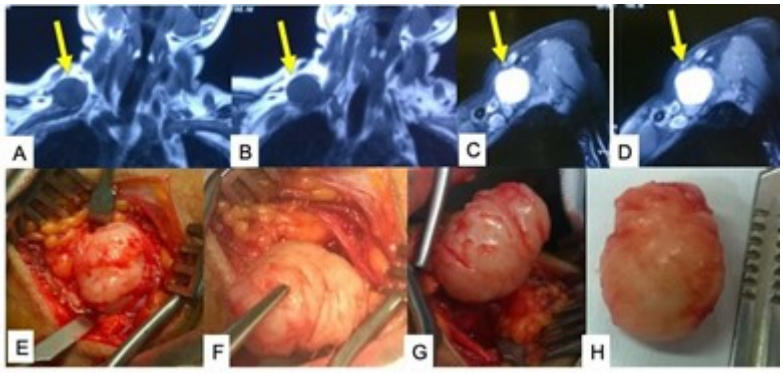

Figure 19. (**A**–**D**) MRI images showing a right brachial plexus schwannoma (arrow-marked). (**E**–**H**) Peroperative pictures of the removal of the schwannoma. Source: Figure by authors.

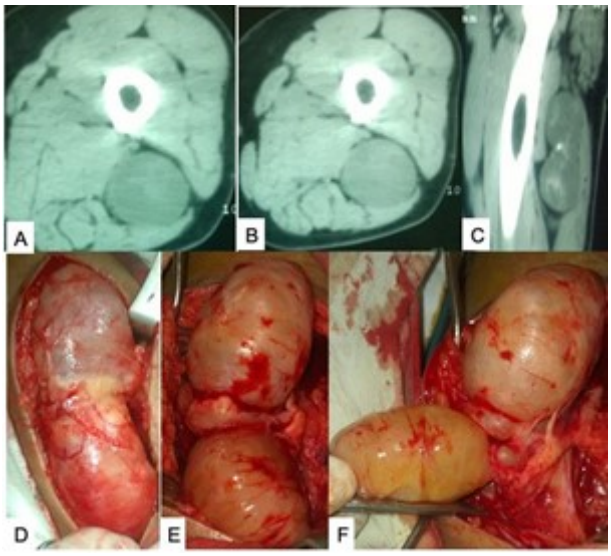

Figure 20. (**A**–**C**) CT scan of thigh showing a dumbbell-shaped femoral nerve schwannoma. (**D**–**F**) Sequential images of the removal of the schwannoma. Source: Figure by authors.

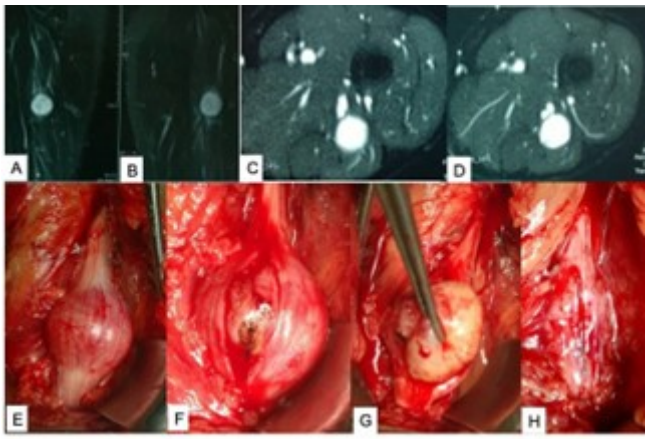

Figure 21. (**A**–**D**) Contrast MRI of thigh showing a sciatic nerve schwannoma. (**E**–**G**) Sequential peroperative images of the removal of the schwannoma. (**H**) After removal of the tumor. Source: Figure by authors.

2.4.2. Cellular Schwannoma

Cellular schwannoma is a type of schwannoma that is distinguished by the absence of Verocay structures in Antoni A tissue. They are found in the paravertebral spaces, retroperitoneum, mediastinum, and pelvis, with about 25% in the limbs (Goldblum et al. 2014). Cellular schwannoma was initially misdiagnosed as a low-grade malignant peripheral nerve sheath tumor (MPNST); however, its benign nature has since been confirmed (White et al. 1990; Casadei et al. 1995; Lodding et al. 1990).

2.4.3. Plexiform Schwannoma

Plexiform schwannomas are extremely rare; however, they can cause brachial plexus involvement. They do not change into a cancerous state (unlike plexiform neurofibromas) (Kokkalis et al. 2019; Chowdhury et al. 2008a).

2.4.4. Melanotic Schwannoma

Melanotic schwannomas can become cancerous (unlike other variants of schwannoma). The tumor, which originates from the sympathetic nervous system, is an adult neoplasm characterized by Schwann cells that produce varying amounts of melanin. Psammoma bodies are spherical, laminated bodies that indicate psammomatous melanotic schwannomas (Antonescu et al. 2013; Goldblum et al. 2014; Millar 1932; Fu et al. 1975; Carney 1990; Keskin et al. 2017).

2.4.5. Neurofibroma

Neurofibromas are the most prevalent PNSTs, and they are made up of perineurial-like cells, Schwann cells, fibroblasts, mast cells, and unmyelinated and myelinated axons entangled in a matrix. The World Health Organization (WHO) classifies neurofibromas into five types. The commonest are "localized subcutaneous", which affects the subcutaneous tissues and dermis, with 90% of cases being sporadic and 10% being linked to NF-1; "diffuse cutaneous", which also affects subcutaneous tissues and the dermis; and "localized intraneural", which affects the spinal, cranial, or autonomic nerves sporadically or in association with NF-1. The remaining two types of tissue are only linked to NF-1: "plexiform" and "massive soft" tissue. The "localized cutaneous" has no malignant potential, while the others are prone to cancer (the plexiform neurofibroma to has the highest risk). Certain clinical criteria have been established for the diagnosis of NF-1 and NF-2 (Pilavaki et al. 2004; Longo et al. 2018; Evans et al. 1992). Neuroimaging can aid in the observation and monitoring of the characteristics and appearance of tumors over the course of treatment. The presence of the so-called "target sign" on T2-weighted imaging, which is a central hypointense area attributed to the fibrous and collagen component, is highly indicative but not pathognomonic of the neurofibroma (Patel and Stacy 2012). Moreover, the "reverse target sign" can be seen on T1W images as a central component enhancement (Patel and Stacy 2012). The function of positron emission tomography (PET) in clinical decision-making and evaluation is critical in circumstances where the neurosurgeon must closely monitor all nodular lesions (Meany et al. 2013). The symptoms as well as the clinical and radiological appearances of the malignancies guide treatment. Surgical resection is the primary option if the patient is symptomatic and the diagnosis is unknown. Systematic therapy can help to stabilize plexiform neurofibromas (Packer et al. 2002; Chowdhury et al. 2008b). The final outcome is heavily dependent on factors such as the tumor's location, extent, and involvement, as well as the nerve functional state prior to surgery. The incidence of malignant transformation is a point of contention because the exact incidence is unknown. Individuals with NF-1 face a lifetime risk of malignant transformation (Kokkalis et al. 2019; Hirbe and Gutmann 2014).

2.4.6. Perineurioma

Perineurioma is a rare nerve sheath neoplasm made up totally of perineural cells that develops in middle age. Only a few occurrences have been documented in the literature (Hornick and Fletcher 2005). As sclerosing and reticular tumors, they are either intraneural or extraneural. Localized hypertrophic neuropathy was the name given to intraneural perineuriomas, although they were recognized as real neoplastic lesions based on the presence of perineural cells in the epithelial membrane antigen (EMA) and S-100 protein immunostaining in cross section imaging (Goldblum et al. 2014; Tsang et al. 1992). Perineurioma intraneural is a benign tumor. Muscle weakness or nerve problems are drawing clinical attention to the presence of malignancies. There have been no definitive guidelines established for their management. Even though both are rare, extraneural (soft tissue) perineurioma is more common than intraneural perineurioma (Hornick and Fletcher 2005). Soft-tissue perineuriomas are typically 4 cm in diameter (Goldblum et al. 2014; Hornick and Fletcher 2005). Treatment is similar to that of an intraneural lesion, with the exception that perineuriomas are benign tumors. Sclerosing perineurioma is a rarer kind of perineurioma that solely affects the hand (Goldblum et al. 2014; Fetsch and Miettinen 1997).

2.4.7. Hybrid Nerve Sheath Tumour

The WHO classification of hybrid nerve sheath tumors (HNSTs) was adopted in 2013 and 2016. HNSTs combine the properties of multiple PNST types. The commonest variety is schwannoma/perineurioma, which

appears on its own, whereas schwannoma/neurofibroma is linked to neurofibromatosis. Hybrid PNSTs are linked to tumoral syndromes, so neurosurgeons should be cautious (25% of cases with NF-2, whereas the percentage is higher in cases with NF-1, which have tumors with hybrid characteristics) (Antonescu et al. 2013; Antonescu et al. 2016; Ud Din et al. 2019; Harder et al. 2012; Kacerovska et al. 2013).

2.4.8. Nerve Sheath Myxomas (NSMs)/Dermal Nerve Sheath Myxomas

NSM was once referred to as a myxoid variety of neurothekeoma, although it is a benign tumor that is not related to neurothekeoma (Antonescu et al. 2013; Fetsch et al. 2005). It is a type of fibrohistiocytic tumor known as neurothekeoma (Sheth et al. 2011). It is mostly found in the dermis and subdermis layers, with the dorsal paravertebral space being a rare exception (Malkoc et al. 2014). NSM is most common in the limbs, with the digits accounting for roughly 35% of all cases (Fetsch et al. 2005). NSMs are small, slowly developing masses that are usually asymptomatic (except diffuse pain in the involved region). According to Fetsch et al., over half of the patients who received surgical resection experienced one or more recurrences but no proof of malignant change was obtained (Fetsch et al. 2005).

2.4.9. Granular Cell Tumor

Granular Cell Tumors are a type of benign nerve sheath tumor that is modest in size, typically found in the skin, neck, soft tissue of the head, and limbs, as well as the viscera. Surgical excision and nerve grafting are used in treatment (if needed). The recurrence rate is almost 8% (Cheng et al. 2016; Smolle et al. 1985; Adeniran et al. 2004; Wadhwa et al. 2014; Davis 2007).

2.4.10. Benign Triton Tumor

Benign triton tumors (BTTs) are tumors of neural and mature skeletal muscle cells that have only a few reported occurrences. They are also known as hamartomatas. They are more likely to affect big peripheral nerves or plexuses, such as the sacral and brachial plexuses. They are more common in childhood or early childhood (Antonescu et al. 2013; Amita et al. 2013). Symptoms of peripheral neuropathy usually led to a diagnosis (Kokkalis et al. 2019).

2.4.11. Nerve Sheath Ganglions/Intraneural Ganglions

Ganglia are more of a degenerative change than a true tumor. Nerve Sheath Ganglia are cystic forms seen in the epineurium of peripheral nerves that contain transparent, jelly-like fluid. The peroneal nerve is the most typical location of involvement; however, there have been reports of other peripheral nerve involvement as well. The cystic formation is associated with a localized expansion of the nerve. Symptoms arise as a result of the cyst's compression impact. Local surgical excision is one approach, while cyst decompression is an appropriate alternative in cases when nerve integrity is at danger (Goldblum et al. 2014; Gillies and Burrows 1991; Ratanshi et al. 2018).

2.4.12. Benign Neoplasms of Non-Nerve-Sheath Origin or Benign Non-Nerve Sheath Tumors (BNNSTs) of Peripheral Nerves

Lipofibromatous Hamartoma of the Nerves

The median nerve and its digital branches are affected by lipofibromatous hamartoma of the nerves (LHN), also known as neural fibrolipoma (Mavrogenis et al. 2017). It has been linked to macrodactyly or macrodystrophia lipomatosa during birth, according to reports. On T1- and T2-weighted MRI images, LHN exhibits a distinct "cable-like" appearance. Excision is rarely recommended since the tumor is "imbedded" inside the nerve fibers. In symptomatic patients, nerve decompression is advised (Antonescu et al. 2013; Chiang et al. 2010; Uchiyama et al. 2016; Mishra et al. 2017; Tahiri et al. 2013).

Desmoid-Type Fibromatosis

Desmoid-type fibromatosis (DTF) in peripheral nerves is a dangerous neoplasm defined by benign fibroblast infiltration. These tumors appear as a firm mass due to the fibrous tissue. In the literature, sporadic occurrences of DTF have been reported (Ferraresi et al. 2001; Siqueira et al. 2012). These are frequently symptomatic, but there

is no consensus on the best therapy; hence, each case should be handled individually based on the symptom(s) (Kokkalis et al. 2019).

Hemangioblastoma

Hemangioblastoma is an uncommon start tumor that affects about 25% of people with von Hippel–Lindau (VHL) syndrome. Even though the majority of cases occur in the CNS, cases from peripheral areas have been documented. Patients with neuro-deficiency symptoms present with increasing neurological symptoms. The standard treatment is surgical removal with clear margins (Doyle and Fletcher 2014; Giannini et al. 1998; Mitchell et al. 2013).

Traumatic Neuromas

Traumatic neuromas are benign tumors that develop after neurotmesis owing to a lack of endoneurium tubes that carry nerve regeneration signals (Figure 5). The important variables in the formation of a traumatic neuroma are axonal regeneration, development, and dissemination. "Traumatic Neuropathic Pain" and dysesthesia are two of the most unpleasant symptoms to deal with. As a mass, a traumatic neuroma appears to be a hard, sometimes painful nodule. Several therapeutic options have been offered, including nerve repair, neuroma excision, neuromodulation, and functional pain surgery, with mixed results (Oliveira et al. 2018; Yao et al. 2017; Kang et al. 2016).

Tumor-like Lesions

Neuritis ossificans or intraneural heterotopic ossification: Intraneural heterotopic ossification has a small number of reports (IHO). A case of neuritis ossificans, or IHO, was reported by Woltman et al. in 1946 and Catalano et al. in 1992 (Woltman and Adson 1946; Catalano et al. 1992). Apposition of fibrovascular tissue along with an intermediate zone of osteoid and a periphery of ossification microscopically characterizes this uncommon lesion. Trauma has been proposed as a risk factor. The clinical evaluation should look for painful mononeuropathy, progressive muscular weakness, focal swelling, and the course of the engaged nerve (Muzaffar et al. 2012; McCarthy and Sundaram 2005; George et al. 2002). When the probability of cancer is doubtful, a biopsy should be performed (as specific varieties of osteoblastic sarcomas exist). IHO is treated symptomatically, and various criteria must be examined in order to avoid iatrogenic nerve injury (Kokkalis et al. 2019).

Inflammatory pseudotumor (IPT) of nerves: IPT is rare and can be mistaken for a variety of malignant and benign neoplasms. IPT was first discovered in the lungs, but it has since been found in practically every anatomic region. It is uncommon in the neck and head, although it most commonly involves the orbit. Pseudotumors of the skull base are uncommon and often act aggressively, resembling a neoplasm (Seol et al. 2009; Chowdhury et al. 2008a).

2.5. Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

2.5.1. Introduction

Sarcomas that arise from peripheral nerves or cells linked to the nerve sheath, such as Schwann cells, fibroblasts, or perineural cells, are known as malignant peripheral nerve sheath tumors (MPNSTs). Because MPNSTs may come from a variety of cell types, the physical appearance can differ greatly from case to case. An MPNST is defined as a sarcoma that originates from a neurofibroma or peripheral nerve. Neurofibrosarcoma, malignant schwannoma, and neurogenic sarcoma are some of the terms that have been used in the past (Prudner et al. 2020; Weiss and Goldblum 2001). When at least one of the following conditions is met, a sarcoma is classified as an MPNST (Prudner et al. 2020):

1. It is caused by a peripheral nerve;
2. It develops from a benign nerve sheath neoplasm that already exists (neurofibroma);
3. On histologic examination, it indicates Schwann cell differentiation.

2.5.2. Epidemiology

MPNSTs are responsible for about 5–10% of all soft-tissue sarcomas. They can exist on their own or in conjunction with NF1. The cause is unknown; however, radiation exposure is a risk factor (Adamson and

Friedman 2004; Amin et al. 2004; Ducatman et al. 1986; Loree et al. 2000). Patients with NF1 account for up to 50% of MPNSTs. NF1 individuals have a 1–2% prevalence of MPNSTs. NF-1 patients have a 10% chance of developing an MPNST in their lifetime. MPNSTs usually strike in adulthood, between the ages of 20 and 50, but they can strike at any age (D'Agostino et al. 1963; King et al. 2000; Huson and Harper 1989; Evans et al. 2002; Ducatman et al. 1984; Ellison et al. 2005).

2.5.3. Clinical Features of MPNSTs

An MPNST usually manifest as a palpable mass that grows in size. The intensity of pain varies. Rapid expansion is more common in the presence of NF1 and should raise concerns about a neurofibroma's malignant change. MPNSTs originating from peripheral nerves can cause radicular discomfort, paresthesias, and motor dysfunction, among other symptoms. The brachial plexus, the sciatic nerve, and the sacral plexus are also examples of major peripheral nerves that grow in tandem with MPNSTs (Prudner et al. 2020).

2.5.4. Imaging

The preferred imaging method is magnetic resonance imaging (MRI). MPNSTs share several imaging features with their benign counterparts. A longitudinal orientation and a fusiform shape in the line of the nerve are two of them. There are, nevertheless, certain distinctions to be made. MPNSTs are more likely to have large tumors (>5 cm), heterogeneity, invasion of fat planes, poorly defined margins, and edema around the lesion (Figure 18) (Friedrich et al. 2005; Pilavaki et al. 2004). The preferred imaging examination for screening for metastases is a chest computed tomography. A bone scan is also recommended to aid in the detection of metastatic bone disease (Prudner et al. 2020). FDG PET assesses the metabolic activity of tumors and metastases (Hruban et al. 1990).

2.5.5. MPNST Staging

Staging identifies the most important aspects of a tumor, allowing for proper planning and therapy. Histologic grade, tumor depth, tumor size, and the absence or presence of metastases all play a role in staging soft-tissue sarcomas (Table 2). The biggest indicators of eventual metastases in the absence of observable metastases are tumor size, histologic grade, and tumor depth (Prudner et al. 2020).

Table 2. The American Joint Committee on Cancer (AJCC) staging system for soft-tissue sarcoma, 6th edition.

Stage	Size	Depth	Grade	Metastases
I	Any	Any	Low	No
II	<5 cm, any depth OR >5 cm	Superficial	High	No
III	>5 cm	Deep	High	No
IV	Any	Any	Any	Yes

Depth is superficial (above the deep fascia) or deep (deep to the deep fascia). Retroperitoneal tumors are regarded as deep. Source: Authors' compilation based on data from Prudner et al. (2020).

A biopsy is an important component of the staging process. It provides a histological tissue diagnosis as well as the ability to detect the lesion's grade. As a result of this data, proper planning of adjuvant therapy, such as chemotherapy or radiation, is possible. It also gives a sense of the prognosis. FNAs, or fine-needle aspirations, are frequently used to determine the existence of malignant cells. However, because it is too small to show the architectural depiction within a neoplasm, it is not commonly used to make an initial diagnosis. FNAs may frequently be successfully utilized to sample tissues of recurrent disease to establish a definitive diagnoses, such as following surgical removal of a neoplasm. True-cut needle biopsy: This sample allows for examination of both individual cells and their architectural layout. This information is frequently needed to make a histopathologic diagnosis. This is frequently performed as a day-case operation in several tertiary care cancer centers under CT guidance. Open biopsy procedure: It is required in some circumstances. An incisional biopsy involves removing a very small piece of tissue from a bigger tumor mass, whereas an excisional biopsy involves removing the tumor mass in its entirety. When a sarcoma is suspected, an incisional biopsy is recommended (Prudner et al. 2020; Mavrogenis et al. 2014; Webber 2014; Ducatman et al. 1986; Ducatman et al. 1984; Hruban et al. 1990).

2.5.6. Surgical Treatment for MPNST

Surgical resection is the principal form of treatment. The purpose of the surgery is to remove the tumor completely and leave tumor-free (broad) margins (Figure 22). This provides the best results in terms of local recurrence as well as distant metastases (Prudner et al. 2020).

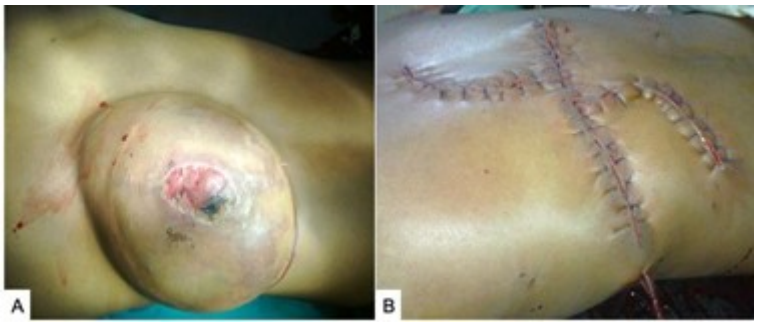

Figure 22. (**A**) Malignant peripheral nerve sheath tumor (MPNST) on back. (**B**) Closure of wound after tumor removal. Source: Figure by authors.

2.5.7. Radiation Therapy

In most soft-tissue sarcomas, radiation treatment is now an integral aspect of local disease control, and it can be used in the preoperative, peroperative, and postoperative periods for MPNST. Radiation therapy, when paired with broad surgical excision, offers local control and overall survival rates comparable to amputation, and the paired-modality treatment typically permits patients to have limb-salvage surgery successfully (Vraa et al. 1998; Yang et al. 1998).

2.5.8. Chemotherapy

Chemotherapy is used to treat systemic diseases that are either too small to detect or too diffuse to be treated locally. Chemotherapy is only used in high-grade cancers where metastatic illness is a possibility. Chemotherapy may be administered both before and after surgery. Chemotherapy's benefits must be evaluated against its side effects, some of which are permanent. As a result, the decision to manage with chemotherapy is influenced by the individual case and their ailment (Prudner et al. 2020).

2.5.9. MPNST Prognosis

MPNST recurrence is described in terms of both local and distant (metastatic) illness. The local recurrence frequency for MPNSTs has been found to be between 40 and 65%, with the distant recurrence frequency being between 40% and 68% (Hruban et al. 1990; Kourea et al. 1998; Wong et al. 1998). The five-year survival rate varies between 16% and 52%. Complete surgical resection, the presence of a low-grade component, and a modest tumor size (less than 5 cm) have all been linked to improved long-term survival (Hruban et al. 1990; Kourea et al. 1998). In recent research, patients managed at a sarcoma facility had an average 84% survival rate (Prudner et al. 2020). This has mostly been ascribed to enhanced imaging, which has resulted in earlier diagnosis, and aggressive therapy with adjuvant and neoadjuvant modalities like chemotherapy and radiation therapy. Patients with metastatic disease at the time of presentation had worse outcomes in this trial (only 33% survival), as one might expect. Patients with NF1 MPNSTs had traditionally been assumed to have a worse prognosis than those with random MPNSTs (Poyhonen et al. 1997). This claim was not supported by a recent report (Kourea et al. 1998; Cashen et al. 2004).

3. Peripheral Nerve Entrapment

3.1. Introduction

"A peripheral nerve lesion occurring without apparent external source and located in one of those anatomical areas where the nerve goes through a limited channel", according to the original definition of entrapment neuropathy (EN) (Wahab et al. 2017; Mumenthaler 1990). These channels are not only very small but they are also often flanked by stiff structures (often a fibro-osseous tunnel or an aperture in fibrous or muscle tissue), which can result in confinement and increased tissue pressures over time (Rempel and Diao 2004). Some ENs are

frequent, while others are uncommon, and some are even debatable, as the word has been applied to different compression syndromes caused by external pressure. EN is also known as compression neuropathy or nerve compression syndrome. The joint is a common site for entrapment neuropathy to develop. If left untreated, the strain on the nerve can cause severe discomfort, nerve damage, and eventually muscular weakening and atrophy. Nerve entrapment can also be caused by other disorders such as bone spurs, cysts, joint swelling, and trauma. EN can also be used to describe nerve root compression caused by a prolapsed disc in the spine (Wahab et al. 2017; Chowdhury et al. 2009).

3.2. Pathological Mechanisms of EN

A fundamental grasp of the basic nerve damage types is required for the integration of EN mechanisms. Stretch-related, compression, and laceration nerve injuries are the three commonest forms. Stretch-related injuries are caused stretching of the peripheral nerve, as observed in brachial plexus avulsion. Knives and other weapons can cause laceration injuries. The third most common type is compression injury. EN is classified as a compression injury. Seddon (Seddon 1942) divided these injuries into three groups: neurapraxia, axonotmesis, and neurotmesis (Stewart 2000). Sunderland later divided them into five categories based on the severity of the injury (Sunderland 1951b). Most entrapment neuropathies fall into the neurapraxia category. Mechanical compression and ischemia are the two main pathogenic pathways engaged in compression injuries (Burnett and Zager 2004).

Mechanical Compression Mechanism

Wallerian degeneration occurs in acute nerve injuries, although the chronic form of nerve compression injuries was linked to some of the degenerative alterations outlined below. These are thought to be signs of nerve compression caused by mechanical forces.

1. Demyelination and remyelination: This process slows down the nerve conduction in EN (Ludwin and Maitland 1984; Berger and Gupta 2006). Myelin plays an important part in the saltatory conduction of action potentials, and this process is responsible for the slower nerve conduction velocity caused by lighter myelin and a shorter internodal distance (Pham and Gupta 2009).
2. Schwann cell proliferation and apoptosis occur simultaneously: Schwann cells proliferate in the compressed axon segment and distal to the site of compression, yet there is no axonal swelling or degeneration; these changes begin before any discernible drop in nerve conduction velocity (Gupta et al. 2012).
3. Downregulation of myelin-associated protein and axonal sprouting: axonal sprouting occurs in the compressed nerve following a decrease in myelin-associated glycoprotein, which usually restricts axonal growth (Gupta et al. 2006).
4. The dorsal root ganglion response: Growth-Associated Protein *43* is upregulated in chronic nerve compression, which is critical for modulating F-actin behavior in response to extracellular inputs. This increase is restricted to calcitonin gene-related, peptide-positive neurons and part of the small-caliber, isolectin-B4-binding protein. This causes a phenotypic alteration in the dorsal root ganglion, as well as an elevation in glial-derived neurotrophic factor close to the compression site (Chao et al. 2008).

Ischemic Mechanism

The peripheral nerves have a well-developed and structured microvascular system, which is important since action potentials are energy-dependent. The compression of this vascular system in EN will lead the nerves affected to dysfunction. Ischemia is caused by thickening of the microvessel walls that occurs in a compressed nerve. All of these things cause thickening, edema, and fibrosis at the compression site (Mackinnon et al. 1984). Common ENs are listed in Table 3 with involved nerves and sites.

Table 3. Involved peripheral nerves and sites in EN.

Nerve	Site
Suprascapular	Spinoglenoid notch
Medial cord or lower trunk of brachial plexus	Neurogenic thoracic outlet syndrome—cervical band or rib at thoracic outlet
Median	Carpal tunnel (at wrist) Pronator teres syndrome—at elbow, in between heads of pronator teres
Ulnar	i. Guyon's canal /ulnar tunnel—at wrist ii. Bicipital groove/cubital tunnel—at elbow
Posterior interosseous	Radial tunnel—arcade of Frohse: at point of entrance into supinator muscle
Lateral femoral cutaneous nerve—meralgia paraesthetica	Inguinal ligament
Obturator	Obturator canal
Posterior tibial	Medial malleolus and flexor retinaculum: tarsal tunnel
Interdigital plantar—Morton's metatarsalgia	Plantar fascia (heads of 3rd and 4th metatarsals)
Supratrochlear and supraorbital nerves	At supraorbital ridge (intractable migraine)
Greater and lesser occipital nerves	Superior nuchal line (intractable basilar migraine)

Source: Authors' compilation based on data from Ropper and Samuels (2009).

3.3. Epidemiology of EN

The most prevalent type of EN is carpal tunnel syndrome (CTS). It is commonest in women over 50. CTS affects women more commonly than men, with a 1.5 per 1000 people yearly incidence compared to 0.5 per 1000 for men (Otoshi et al. 2018).

Cubital tunnel syndrome, on the other hand, is more common in men, with a rate of 24.7 per 100,000 people per annum in the general population. Cubital tunnel syndrome is the second most prevalent EN, with males experiencing it more frequently than women (Otoshi et al. 2018). In the medial elbow overlaying the ulnar coronoid tubercle, men have less fat content than women. In men, the tubercle itself is larger. These anatomical characteristics may explain why men are more likely to develop cubital tunnel syndrome or ulnar neuropathy. Peroneal neuropathy is the most prevalent form of mononeuropathy in the lower limbs and the third most common type of EN. Then, there is tarsal tunnel syndrome, which affects the lower extremities (Dong et al. 2012).

3.4. Causes and Risk Factors of EN

EN is often caused by repetitive injuries. These repetitive injuries may take place in the workplace as a result of repeated movements linked to a patient's profession. Accidental trauma such as sprains and fractures can also result in EN. In addition, certain medical conditions can trigger EN. The risk factors are (Wahab et al. 2017; Chowdhury et al. 2009; Otoshi et al. 2018):

- Diabetes mellitus;
- Autoimmune disorders, such as rheumatoid arthritis;
- Endocrine dysfunctions: thyroid dysfunction, acromegaly, and Cushing syndrome;
- Hypertension;
- Local tumors and cysts;
- Pregnancy or menopause;
- Obesity;
- Congenital (birth) defects (e.g., small carpal tunnel);
- Neural disorders;
- Female sex and middle age.

3.5. Clinical Features of EN

Symptoms and signs of EN vary based on the type and site of the nerve involved. They usually happen near the compression site, but they can also happen in the surrounding tissues and structures. Aches and pains, tingling

or numbness, muscle weakness, diminished flexibility, and trouble with particular activities are all common symptoms (Wahab et al. 2017; Chowdhury et al. 2009; Thomsen et al. 2010; Padua et al. 2016).

3.6. Investigations

Some investigations are used to diagnose EN, especially rarer forms of nerve compression syndrome, and include nerve conduction studies (NCSs), electromyography (EMG), ultrasound, and MRI. Diagnostic testing is not always required for carpal tunnel and cubital tunnel syndrome. They may, however, provide important information indicating the compression's location and intensity (Wahab et al. 2017; Chowdhury et al. 2009; Dong et al. 2012; Thomsen et al. 2010; Padua et al. 2016).

3.7. Treatment Options

Treatment for EN often starts with lifestyle changes and noninvasive therapies. Treating an underlying cause of EN may also relieve symptoms. In severe cases, EN may require surgery.

3.7.1. Lifestyle Changes

Restraining movements that initiate pain, adopting ergonomic strategies at home and at work, or changing job duties may elevate symptoms. When obesity is the etiology, weight reduction can reduce symptoms.

3.7.2. Physiotherapy

Physiotherapy can help to enhance the affected area's flexibility, strength, and range of motion. Physical therapy can also assist with symptoms like numbness and soreness.

3.7.3. Medication

Medication (nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids such as dexamethasone, which are injected directly around the nerve) can aid in relieving symptoms of EN such as inflammation and pain. The type of drug(s) used in EN depends on the severity of symptoms.

3.7.4. Prosthetic Devices

In some cases of EN, a brace or a splint is used to relieve pressure on the nerve.

3.7.5. Surgery

Surgical operations are usually viewed as a last resort in the treatment of these patients. EN does not always necessitate surgery. The type of nerve compression, the degree of compression, and the nerves and structures impacted all influence the surgical treatment. Each technique has its own set of dangers and advantages. Many factors influence the outcome of surgery including the duration and severity of symptoms and underlying general health conditions. Overall, the results of surgery are favorable. If nonsurgical treatment fails to alleviate the pressure on the compressed nerve, surgery may be required. Carpal tunnel release, cubital tunnel release, medial epicondylectomy, ulnar nerve anterior transposition, and tarsal tunnel release are some of the most popular surgical treatments used to treat entrapment neuropathy (Wahab et al. 2017; Chowdhury et al. 2009; Thomsen et al. 2010; Padua et al. 2016).

3.8. Outcomes of EN

The outcomes of EN vary. In very severe, untreated cases, it can result in permanent nerve damage or deficiency of function in the involved area. However, this is relatively rare. When NE is identified and treated early, significant relief can be provided. Many people make a full recovery.

3.9. Carpal Tunnel Syndrome

CTS is caused by compression of the median nerve when it travels through the carpal tunnel (Mumenthaler 1990). It is the most common EN in the world, and it has a substantial effect on the quality of life of those who suffer with it (Thomsen et al. 2010; Padua et al. 2016). However, one of the early signs of CTS is brachialgia paraesthetica nocturna (rising at night due to unpleasant and disturbing sensations in the fingers) (Oyedele et al.

2002). Symptoms of the condition have been found to have a prevalence of 10–20%, whereas definitive CTS has a prevalence of 0.9% to 10% (Al Saleh et al. 2016; de Krom et al. 1992; Ferry et al. 1998; Atroshi et al. 1999; Khedr et al. 2016).

Anatomy and Pathophysiology of CTS

The carpal tunnel (Figures 23 and 24) is an osseo-fibrous tunnel that runs between the carpal bones and the flexor retinaculum.

The nine extrinsic flexor tendons of the thumb and fingers and the median nerve are contained within the tunnel, which is about 2.5 cm distal to its upper limit and densely packed with anatomical components. The pressure within the tunnel varies from 2 to 31 mmHg in healthy people, while it can reach 32–110 mmHg in CTS patients depending on their wrist posture (Werner and Andary 2002). When the wrist is flexed, the pressure within the tunnel is elevated by up to eight times, and if the wrist is extended, by up to ten times (Werner and Andary 2002). The Phalen's test, a clinical test performed in the diagnosis of CTS, has a physiological explanation (Mackinnon 2002). Obesity, diabetes, hypothyroidism/myxedema, acromegaly, ganglion cysts, flexor tenosynovitis, and pregnancy are only a few of the risk factors for CTS. The chance of acquiring CTS increases by 7.4% for every unit increase in body mass index (BMI) (Shiri et al. 2015). It is very common in those who labor with repeated hand movements (England 1999; Violante et al. 2016; van Rijn et al. 2009). It has an idiopathic etiology in up to 50% of cases, mostly in premenopausal women (Dekel et al. 1980).

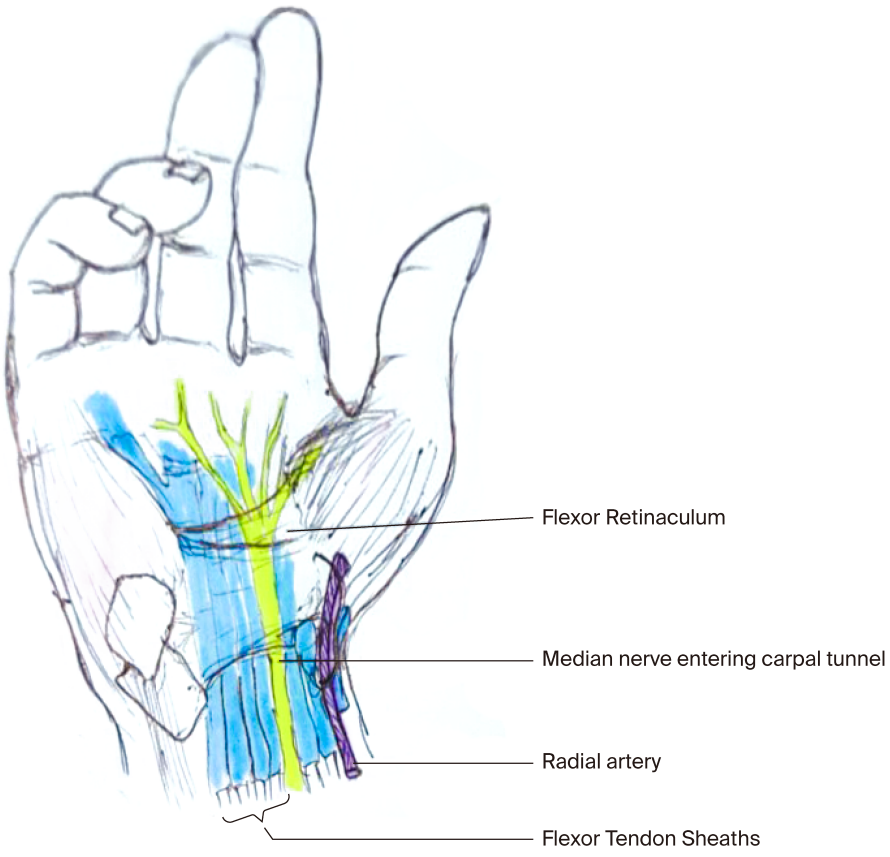

Figure 23. Schematic drawing of carpal tunnel. Source: Figure by authors.

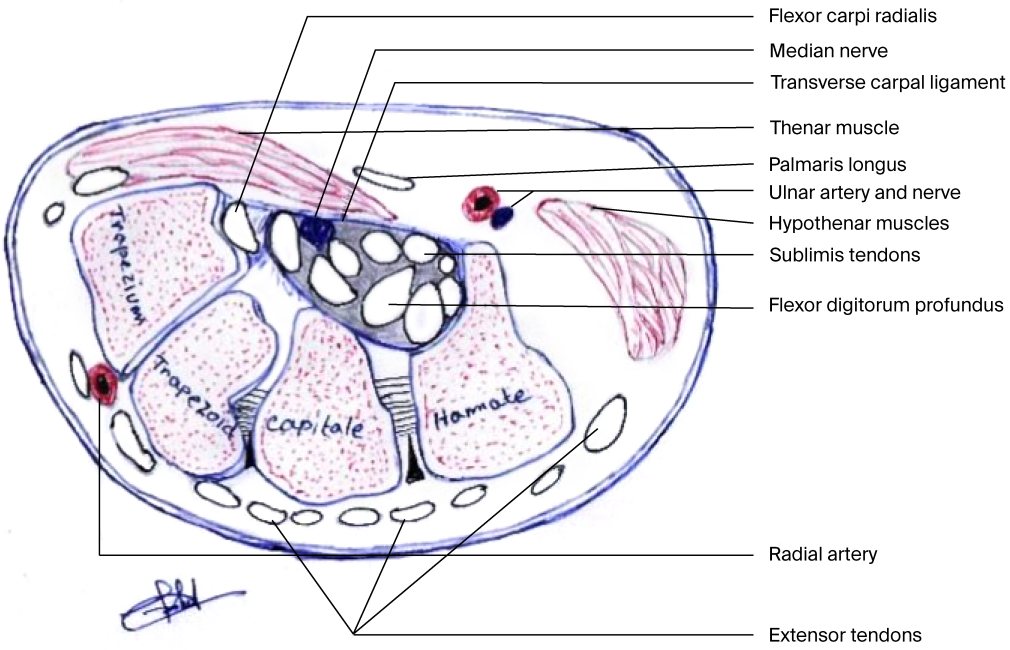

Figure 24. Cross sectional anatomy at wrist showing carpal tunnel and its contents. Source: Figure by authors.

Clinical Presentation of CTS

The thumb and first two and a half fingers are the commonest paresthesias, but some people may experience paresthesias throughout the hand or pain that travels up the arm to the shoulder (Bland 2007). More than 50% of the time, symptoms impact both hands at first, whereas the bulk of the time, symptoms begin on the dominant side. Any one of the symptoms listed below in the median-nerve-supplying zones are highly suggestive of CTS: swelling, dry skin, or color changes in the hand; hand weakness or clumsiness; or hand paresthesias (Bland 2007). Sleep, prolonged arm or hand position, and repetitive wrist/hand movement are the triggers for these symptoms. Changing the hand posture/position or merely shaking the involved hand can bring these sensations to the surface (American Academy of Neurology 1993). Phalen's test, Tinel's signals, and reverse Phalen's test are employed in the clinical examination (Werner et al. 1994). For early CTS diagnosis, a nerve conduction examination is preferred (Fertl et al. 1998).

Confirmation of Diagnosis

Electrophysiological testing in conjunction with clinical testing is a recognized standard method for diagnosis confirmation (Phillips and Juel 1997). The severity of CTS can also be determined via electrophysiology. Although the intensity of nerve conduction studies (NCSs) and symptoms are not strongly correlated, the use of a grading system can aid in the prediction of surgery outcomes. Patients who have moderate-grade NCS abnormalities had a better surgical outcome than those who have very severe or no abnormalities (Stevens 1987; Bland 2001). Other tests include MRI, wrist ultrasonography, and, if necessary, examinations to exclude a systemic disease or underlying cause (Wahab et al. 2017; Dong et al. 2012).

Treatment

Treatment can be conservative or surgical.

Conservative: For situations with milder disease, a conservative approach is used, which includes anti-inflammatory medication (e.g., local steroid injection) and wrist splinting (Wahab et al. 2017; American Academy of Neurology 1993; Peters-Veluthamaningal et al. 2010). A new therapy option is radial extracorporeal shockwaves paired with wrist splinting (Raissi et al. 2017). Another novel therapy option is platelet-rich plasma

injection, which has been demonstrated to be effective in the short term (Padua et al. 2016; Uzun et al. 2017; Malahias et al. 2015).

Surgery: For those patients where conservative management failed or those with severe form of disease, carpal tunnel release (CTR) is advised (Wahab et al. 2017; Chowdhury et al. 2009; Bland 2007; Uzun et al. 2017; Shi and MacDermid 2011). The overall result of CTR is very good. Surgical options:

i. Open surgical CTR (Figure 25);
ii. Percutaneous CTR (mini transverse incision at wrist) (Figure 26);
iii. Endoscopic CTR.

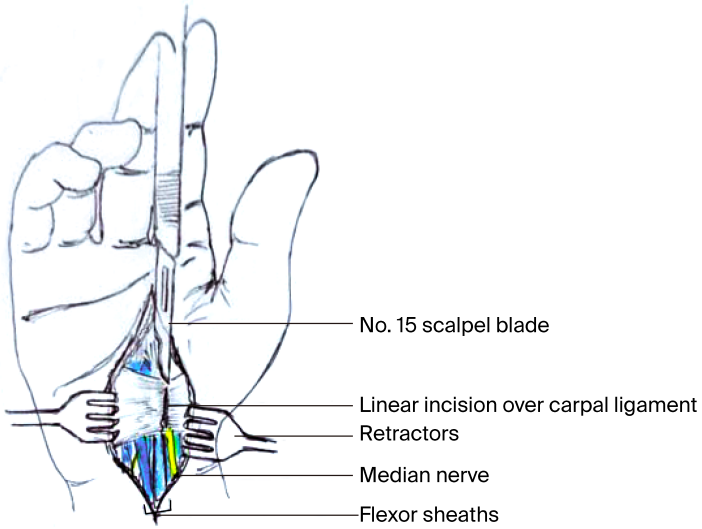

Figure 25. Schematic drawing of open carpal tunnel release. Source: Figure by authors.

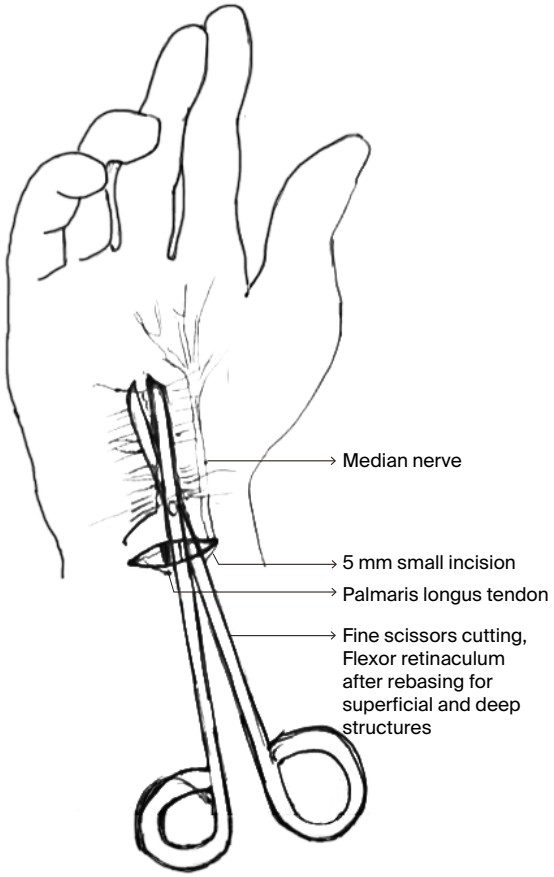

Figure 26. Schematic drawing of percutaneous carpal tunnel release. Source: Figure by authors.

Author Contributions: Conceptualization, methodology, F.H.C. and M.H.S.; validation, formal analysis, investigation, resources, data curation, A.K., S.M.M.H. and F.H.C.; writing—original draft preparation, writing—review and editing, visualization, supervision, F.H.C. and M.R.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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