Surgical Management of Peripheral Nerve Tumors in NF2 Patients—A Review of the Literature and an Operative Case

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Abstract

This study reviews the latest literature relating to the surgical treatment of peripheral nerve sheath tumors (PNSTs) in patients with neurofibromatosis 2 (NF2). Up to 40% of patients carrying a diagnosis of NF2 present with a symptomatic PNST. Here we review and report on current literature regarding the history and diagnosis of NF2, the current guidelines and surgical approach to schwannoma excision, as well as postoperative outcomes, including sensory and motor nerve function. We also present a case of one of our NF2 patients who underwent surgical excision of multiple peripheral nerve tumors in the right upper extremity.

Keywords
- neurofibromatosis 2
- schwannoma
- surgical management
- peripheral nerve

Introduction

The neurofibromatoses are a group of genetic disorders featuring lesions of the skin and nervous system. An estimated 100,000 people in the United States have been diagnosed with one of the three subtypes: neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis (SWN).[1]

The three subtypes have varying incidences. NF1 is the most common subtype with an incidence of 1 in 3,000 live births, followed by NF2 with an incidence of 1 in 25,000 live births.[2,3] The third subtype, SWN, is rarer with an incidence that is unknown, although estimates in several populations have ranged from 1 in 40,000 to 1 in 1.7 million people.[4-6]

In patients with NF2, peripheral nerve sheath tumors (PNSTs), histologically characterized as schwannomas, are a common manifestation that occur in over 40% of patients.[7] Although schwannomas are benign in nature, as they increase in size, patients often present with focal neurological deficits due to nerve compression. As a result, patients may experience debilitating symptoms such as pain, weakness, and paresthesia, which consequently reduces their functional abilities and substantially decreases their quality of life. Current treatment guidelines are focused on managing symptoms such as pain and neurological deficits. However, there are no current surgical guidelines for the management of PNSTs in NF2 patients, which poses a unique challenge for peripheral nerve surgeons.

In this article, we report on the current available literature regarding the surgical management of peripheral schwannomas in patients with NF2. Additionally, we described the clinical course of one of our own patients who underwent surgical excision at our institution. Lastly, we reviewed and summarized guidelines for the surgical management and follow-up of PNSTs in patients with NF2.

History and Diagnosis of Neurofibromatosis

The description of neurofibromatosis dates back to the 13th century. The first description of neurofibromatosis in the medical literature was by Friedrich von Recklinghausen in

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1882 and the disease was then called von Recklinghausen's disease (VRD) which is now synonymous with NF1. NF2 was first described by Wishart in 1822 in a deaf patient with tumors in the skull, dura mater, and brain. Inheritance of NF2 was first described in 1920 through the description of three generations of a family with vestibular schwannomas, and autosomal dominant inheritance was demonstrated through following five generations of a family with NF2. NF1 and NF2 were often intertwined until separate locations of the genes for NF1 and NF2 were identified in 1987 allowing for a more formal distinction of the neurofibromatoses. The third genetically distinct type of neurofibromatosis, SWN, was then linked with a mutation in the *SMARCB1* tumor-suppressor gene located on chromosome 22q11 and the *LZTR1* gene.

Neurofibromatoses are genetically distinct and as a result they have different clinical presentations. NF1 is characterized by multiple cafe-au-lait maculae, cutaneous and subcutaneous neurofibromas, Lisch nodules, optic gliomas, and bony manifestations. NF2 is characterized by bilateral vestibular schwannomas; however, schwannomas may develop on other nerves, and other nervous system tumors also occur in NF2 such as meningiomas and ependymomas. SWN is characterized by multiple noncutaneous schwannomas in the absence of vestibular schwannomas.The diagnosis of the neurofibromatoses, thus, differs and is summarized in ►**Table 1**.

The diagnosis of NF2 is based on clinical criteria and the presence of the NF2 mutation is not a determining factor in the current diagnostic criteria. The most widely used criteria for diagnosis of NF2 is the Manchester diagnostic criteria (►**Table 1**). Family history of the disease and bilateral vestibular schwannoma are not required to diagnose NF2, making this criteria both sensitive and specific as 50 to 60% of patients have no family history of NF2.

NF2 typically presents in early adulthood with the average age of symptom onset being 20 years. The most distinctive feature of NF2 is bilateral vestibular schwannomas which are identified in 90 to 95% of patients. Although these bilateral vestibular schwannomas are typically benign, the location causes hearing loss and tinnitus, which are common presenting symptoms in NF2 in 60% of adults and 30% of children. The second most common tumor type in NF2 is intracranial meningiomas which most commonly present with headaches. These tumors can cause other symptoms depending on location due to compression of the optic nerve and cranial nerves. NF2 often leads to the growth of schwannomas in the vestibular nerve as previously mentioned but also can lead to schwannomas in other cranial nerves, spinal nerves, and peripheral nerves. Up to 51% of patients develop schwannomas in nerves other than the vestibular nerve. Peripheral neuropathy is, thus, a common symptom in NF2 and occurs in up to 66% of patients with NF2. Additionally, spinal compression by these tumors can cause paresthesia, muscle weakness, and pain. Vision impairment is common in NF2 and lens opacities can also serve as marker of NF2 as cataracts affect up to 80% of patients. Vision disturbances can also be caused by optic nerve meningiomas and retinal hamartomas. Skin lesions are present in 70% of patients with NF2; however these patients typically present with fewer lesions as compared to those presenting with NF1. Schwannomas that develop in the dermis can create plaque-like lesions, whereas subcutaneous schwannomas that develop along peripheral nerves and can be palpated or seen as large nodular swellings, may result in pain and paresthesia, and may also impact daily life activities depending on the location of the tumor.

Table 1 Manchester criteria for clinical diagnosis of neurofibromatosis type 2 (NF2)

Additional findings required for diagnosis of NF2	
Bilateral vestibular schwannomas	None
First-degree family relative with NF2	Unilateral vestibular schwannoma or any of the two NF2-assocaited lesions: meningioma, glioma, neurofibroma, schwannoma, or cataract
Unilateral vestibular schwannoma	Two NF2-associated lesions: meningioma, glioma, neurofibroma, schwannoma, or cataract
Multiple meningiomas (two or more)	Unilateral vestibular schwannoma or two other NF2-associated lesions: glioma, neurofibroma, schwannoma, or cataract

Source: Table for NF2 diagnosis: Adapted from Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, Lonser RR. Neurofibromatosis type 2. Lancet 2009; 373(9679):1974-1986.

Peripheral Schwannomas in NF2 Patients

PNSTs that occur in the neurofibromatoses include neurofibromas and schwannomas. These tumors are characterized by neoplastic proliferations in the Schwann cells. Neurofibromas are typically found in NF1, whereas schwannomas are found in NF2 and SWN. In neurofibromas, the Schwann cell is the primary neoplastic cell component; however, neurofibromas are also composed of other peripheral nerve components such as axons, perineural cells, fibroblasts, blood vessels, and mast cells. Schwannomas are composed of a more homogenous neoplastic proliferation of mature Schwann cells. In terms of surgical management of neurofibromas and schwannomas, the distinction is of value because schwannomas can be resected while preserving the nerve, whereas in most neurofibromas, the nerve is incorporated in the mass and surgery may require subsequent nerve grafting.

Neurofibromas are benign nerve sheath tumors. Pathological features of neurofibromas are a tan-white appearance grossly. Cytologically Schwann cells in neurofibromas have wavy nuclear contours and S-100 protein expression. They commonly occur in superficial cutaneous sites presenting as pedunculated growths. There are several

variants of neurofibromas based on growth patterns including localized, diffuse, and plexiform. The localized cutaneous neurofibroma is the most common. The plexiformneurofibromas are extensive soft tissue neurofibromas of varying sizes that are usually localized to major nerve trunks and involves numerous adjacent nerve fascicles. Plexiformneurofibromas are often closely monitored as malignant PNSTs (MPNST), an aggressive sarcomatous lesion, may arise from plexiform neurofibromas. Around 10% of patients with NF1 will develop MPNSTs from plexiform neurofibromas.

Schwannomas are benign PNSTs. Pathologically their gross appearance is in the form of a well circumscribed mass and a well-formed collagenous capsule is often seen. Cytologically Schwann cells have S-100 protein expression and there is abundant expression of pericellular collagen type IV. Unlike plexiformneurofibromas, cellular schwannomas lack malignant potential.

Patients with NF1, NF2, and SWN have a reduced quality of life. Pain shows a clear relationship to tumor burden in neurofibromatoses. However, the relationship of schwannomas to quality of life has not been formally studied, and as schwannomas can often be resected while preserving the nerve due to their origin and location, it would be of value to know if resection improves quality of life for these patients. This remains an area of ongoing research at our institution.

Management of Peripheral Schwannomas in NF2

Presently, there is no effective form of medical management for these lesions reported in the literature. Additionally, there are no evidence-based guidelines for the surgical management of benign nerve sheath tumors in this cohort of patients.

Historically, indications for treatment have been largely focused on the management of presenting symptoms and volume progression. As previously mentioned, patients can present with a palpable mass, pain, or focal neurologic deficits such as paresthesia, weakness, or atrophy. These symptoms often result in reduced daily life activities, and at times may result in social isolation. Patients who undergo lesion resection often report improvement in or resolution of their symptoms; however, the effectiveness of this treatment option in improving overall quality of life in this cohort of patients has not been formally studied.

Surgical management consists of direct lesion excision, which may be followed by nerve repair depending on the degree of neural involvement. Several studies suggest the use of intraoperative nerve stimulation with electromyography recording for all procedures involving motor nerves. Unlike neurofibromas, schwannomas do not infiltrate the surrounding tissues and are usually amenable to complete surgical resection.[1] The involved nerve is carefully dissected away from the surrounding soft tissue both proximal and distal to the lesion. A microsurgical approach is then used to isolate the tumor. Once the tumor is isolated and dissected, fascicles adherent to the tumor are carefully dissected. If there is lack of electrophysiological activity in the fascicles that pass through the tumor, these fascicles are sacrificed and the tumor is removed en bloc. For larger tumors, surgical technique consists of enucleation via intracapsular dissection, followed by removal of the capsule if it does not adhere to the surrounding fascicles. Once the mass is excised completely, the wound is copiously irrigated, hemostasis is established, and layered closure is performed.

NF2 patients who have undergone peripheral schwannoma excision have reported improvement in neurologic symptoms. Prior studies have reported improved motor function in up to 89% of surgically excised schwannomas. Although surgical management has been shown to successfully improve symptoms in some patients, the procedure is not without its associated risks. In a larger series conducted by Levi et al, transient postoperative motor deficits was reported in 8% of schwannoma excisions. Smaller series have reported permanent postoperative sensorimotor deficits in 11 to 36.7% of schwannoma patients. Lastly, as with any procedure, patients should be counseled on risk of localized wound complications such as hematoma, seroma, and infection.

Following surgical resection, regular surveillance is highly encouraged. Although the recurrence rate for previously excised benign PNSTs ranges from 1.3 to 35.9% in the literature, patients with NF2 also remain at high risk for the development of new schwannomas. Patients should be educated about their condition in order to help them recognize the early signs and symptoms of a symptomatic schwannoma.

Illustrative Case

The patient is a 46-year-old woman with a history of NF2 and multiple resections of intracranial lesions, who presented with multiple palpable masses in her right upper extremity that she reported to be painful for a duration of 6 months. Additionally, she reported poor sensibility in all of her digits but denied motor concerns as she was still able to use all fingers for her daily life activities. Her neurological exam was notable for weakness in both upper extremities, with her right arm noted to be weaker than the left and with mildly increased tone. Physical exam of the right upper extremity revealed several palpable subcutaneous masses: a 6-cm mass in the axilla, a 3-cm mass left distal forearm, a 1-cm mass in the carpal tunnel area, a 5-mm mass over the proximal transverse wrist crease, and a small 2-mm nodule in second web space. Magnetic resonance imaging (MRI) of the right upper extremity and wrist were performed which demonstrated numerous circumscribed lesions in the axilla, forearm, and wrist. The dominant lesion in the axilla was located along the course of the brachial plexus interposed between the biceps brachii and pectoralis major muscle and measured 10 cm × 4.7 cm × 4.6 cm (►**Fig. 1**). Additionally, there were more lesions in the right distal forearm, wrist, and visualized portions of the hand, with the largest lesion in this region measuring 2.5 cm × 2.2 cm × 2.4 cm, along the course of the ulnar nerve within the distal forearm, causing mass effect on the flexor tendons.

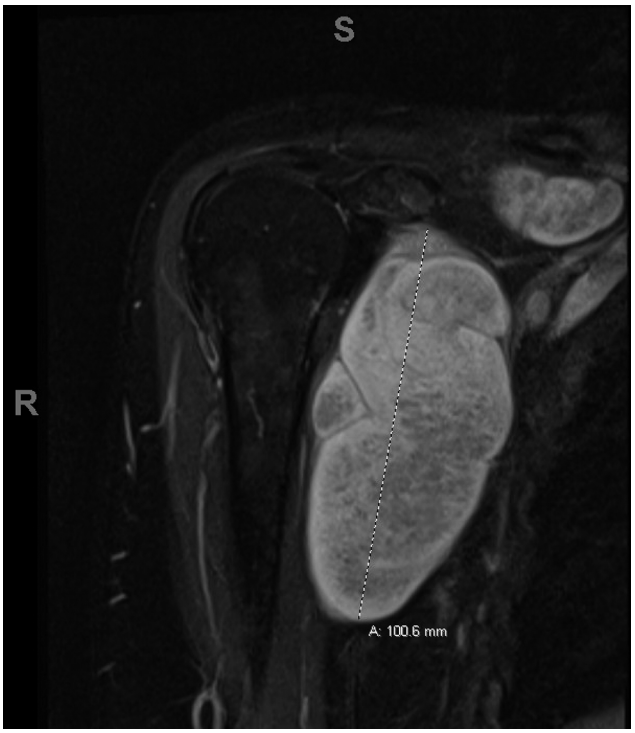

Fig. 1 MRI of an axilary Schwannoma located along the course of the brachial plexus interposed between the biceps brachii and pectoralis major muscle and measuring 10 cm X 4.7 cm x 4.6 cm.

Given her ongoing symptoms in addition to the MRI findings on imaging, the decision was made to excise the lesions in an effort to provide relief to her pain symptoms and improve her sensory and motor neuropathies. As a result she underwent excision of schwannomas involving the right brachial plexus, posterior upper arm, ulnar nerve in the forearm, median nerve proximal to the carpal tunnel, index finger radial digital nerve at the palm, and the common digital nerve of the index/middle finger in the hand.

Operative Report

On the day of the surgery, the lesions on the right upper extremity were marked. The right upper extremity was prepped and draped in the usual sterile manner. Intraoperative monitoring electrodes were placed in the deltoid, biceps, triceps, flexor carpi ulnaris (FCU), adductor digitiminimi (ADM), and abductor pollicisbrevis muscles (►**Fig. 2**).

The right brachial plexus tumor was first addressed. A sinuous incision was drawn in the right axilla. Local anesthesia was administered using 1% lidocaine with epinephrine. The skin incision was made and the skin flaps were retracted. The pectoralis muscle was retracted and the large primary tumor, estimated to be 11 cm × 5 cm, was found between the coracobrachialis and the pectoralis muscle, intimately adherent to the musculocutaneous nerve and the ulnar nerve, which was confirmed via intraoperative nerve stimulation (►**Fig. 3**). The nerves were isolated from the tumor and the tumor capsule was opened revealing a multilobulated schwannoma.

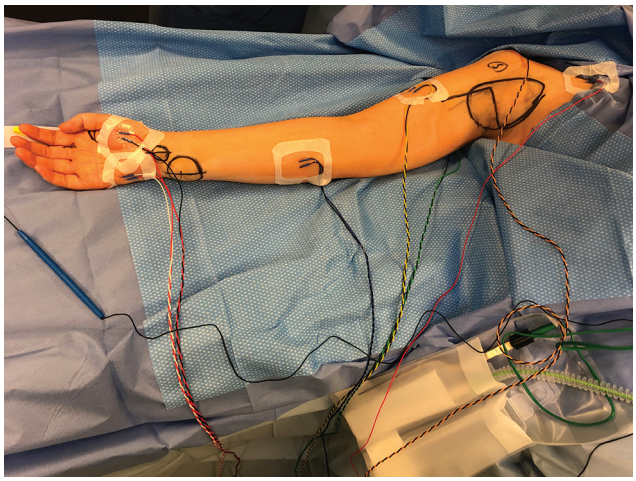

Fig. 2 Intraoperative monitoring electrodes placed on the deltoid, biceps, triceps, flexor carpi ulnaris (FCU), adductor digitiminimi (ADM), and abductor pollicisbrevis muscles.

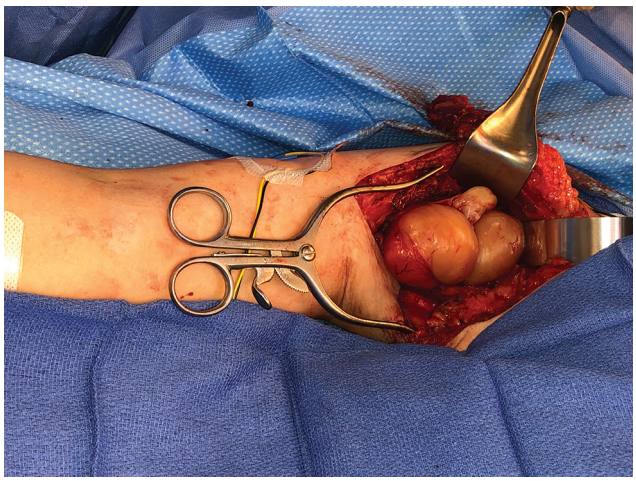

Fig. 3 Large primary tumor in the axilla found between the coracobrachialis and the pectoralis muscles.

The capsule was carefully dissected and incised. There was extension of the tumor into the axilla, where it was traced and noted to be intimately adherent to the axillary artery, axillary vein, and the brachial plexus. The brachial plexus was found to be intact and intraoperative nerve stimulation was carried out to confirm this after tumor excision. The tumor was excised and sent for histopathological analysis. After hemostasis was achieved, fibrin sealant was placed into the wound. A size 10 JP drain was placed. Layered closure of the axillary incision was carried out after approximating the fascia with Vicryl sutures.

The right posterior arm tumor was then approached. The arm was abducted and externally and internally rotated and a longitudinal marking was drawn directly over the 5-cm tumor. Local anesthetic was infiltrated, a longitudinal incision was made, skin retractors were placed, and the tumor was found deep to the triceps muscle. The triceps muscle was then was separated, revealing a schwannoma arising from a branch of the radial nerve. This was excised by an intracapsular dissection and the entire tumor was removed and sent for

histopathology. Hemostasis was achieved, wound cavity was irrigated, and layered closure was performed.

Attention was then directed to the ulnar nerve tumor which was located at the distal forearm just proximal to the Guyon's canal. A longitudinal incision was drawn directly over the tumor and a sterile tourniquet was applied. Additionally, another longitudinal incision was drawn directly over the carpal tunnel in preparation for the excision of the tumor involving the median nerve. These were infiltrated with 1% lidocaine with epinephrine, and the arm was elevated, and the tourniquet was raised. The ulnar nerve tumor was first approached. The FCU muscle was retracted out of the field and the ulnar neurovascular bundle was identified. Vessel loops were placed on the ulnar nerve and intracapsular dissection was carried out and the schwannoma was excised, taking care to preserve the ulnar nerve. The capsule of the schwannoma was then repaired and layered closure was carried out. The median nerve schwannoma was then addressed. The median nerve was exposed in the carpal tunnel. An intracapsular dissection was carried out and the tumor was excised in total and sent for histopathology (►**Fig. 4**). This incision was also closed in layers.

Next, the right digital nerve schwannoma was then addressed. A transverse incision was made in the proximal transverse crease of the wrist in line with the index finger. Skin retractors were placed, and the schwannoma arising from the radial digital nerve to the index finger was isolated, intracapsular dissection was carried out, and the tumor was excised.

Lastly, the tumor in the second web space was approached. A Brunner-type incision was made. Skin retractors were placed and a 5-mm schwannoma was isolated from the radial digital nerve of the right index finger. An intracapsular dissection performed and the tumor excised in total keeping the nerve intact. At this point, the tourniquet was released, hemostasis was achieved, and layered closure was performed. All digits were noted to be well vascularized at the end of the procedure. All the incisions in the forearm and hand were wrapped with fluffs, Webril is made by Covidien Kendall; Coban by 3M.

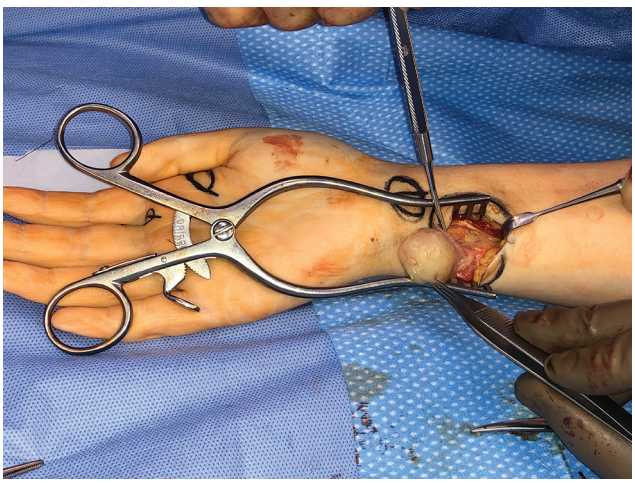

Fig. 4 Median nerve schwannoma exposed in the carpal tunnel.

The patient was then reversed from anesthesia, extubated, and discharged to the recovery room in a stable condition.

The patient was discharged home on the same day. At a 6-month follow-up visit, the patient demonstrated well-healing incisions with improvement in her baseline strength and sensation. She denied pain symptoms and no postoperative neurological deficits were noted on physical exam.

Summary and Conclusion

Although NF2 is a relatively rare disease, benign PNSTs are extremely prevalent and burdensome for these patients. The goals of treatment are to reduce pain symptoms as well as interference with daily life activities. Unfortunately, there is a paucity of literature describing standardized guidelines and techniques for excision of these tumors. We have presented our review of the existing literature and demonstrated an illustrative case, highlighting important concepts in the surgical management of schwannomas in this demographic of patients.

Indications for treatment of benign schwannomas in patients with NF2 should be evaluated on a case-by-case basis. Patients may present with a painful mass and associated sensory abnormalities or, less commonly, with motor deficits. Although guidelines for management of these lesions do not presently exist, options are limited as surgical excision remains the mainstay of treatment if location permits. Common and accepted indications for surgical excision include a painful or debilitating mass that may affect the patient's daily life activities or rapidly enlarging mass resulting in focal neurologic deficits. If an existing and asymptomatic lesion is present, sequential MRI can be performed to monitor the size of the lesion. MRI sequences and MR neurography clearly display the appearance of PNSTs. In particular, contrast-enhanced 3D STIR-SPACE imaging also shows important information about the tumor's nerve origin, involvement extent, and the relationship with the adjacent nerve, which is of great clinical value for aiding early diagnoses and guiding the surgical treatment of PNSTs.

If the patient meets criteria for surgical excision, consideration may be given to performing the excision(s) as an outpatient procedure. As we have demonstrated in our illustrative case, it is important to note that patients with NF2 and multiple symptomatic schwannomas can safely undergo multiple simultaneous surgical excisions. Additionally, intraoperative nerve monitoring is strongly encouraged for neural tumors involving major motor nerves. Following surgical excision, we recommend patients to receive follow-up at 2 weeks for evaluation of surgical wounds. Additionally, patients are often assessed between week 6 and week 12 to assess for any postoperative neurologic deficits. Given their hereditary predisposition, patients with NF2 should be monitored regularly for recurrence and emergence of new symptomatic schwannomas.

Lastly, although there are currently no available studies that have assessed the impact of surgical excision of these lesions on patient reported quality of life, surgical resection

has been shown to be effective and relatively safe, with low rates of postoperative complications, in this patient population. Ultimately, specific patient factors and preferences as well as available surgical expertise should guide the management of benign PNSTs in patients with NF2.

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Conflict of Interest
None declared.

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Note: References 8-42 are available online.

