Robust surgical approach for cutaneous neurofibroma in neurofibromatosis type 1

Bahir H. Chamseddin, …, Juan Vega, Lu Q. Le


**BACKGROUND.** Cutaneous neurofibromas (cNF) are physically disfiguring, painful, and cause extensive psychologic harm in patients with neurofibromatosis type 1 (NF1). There is currently no effective medical treatment and surgical procedures are inaccessible to most NF1 patients globally.

**OBJECTIVE.** While research is underway to find an effective medical treatment for cNF, there is an urgent need to develop surgical approach that is accessible to all NF1 patients in the world with the skill set and equipment found in most general medical office settings. Here, we present a robust surgical approach to remove cNF that does not require sterile surgical field, utilizes accessible clinical equipment, and can be performed by any health care providers including family practitioners, and physician assistants.

**METHODS.** In a prospective case-series, patients with NF1 underwent this surgical procedure which removes multiple cutaneous neurofibromas. The Dermatology Life Quality Index was given to subjects before and after the procedure as surrogate for patient satisfaction.

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Robust Surgical Approach for Cutaneous Neurofibroma in Neurofibromatosis Type 1

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Abstract

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Results: 83 tumors were removed throughout the body from twelve individuals. Examination at follow-up visits revealed well-healed scars without infection or adverse events including aberrant scarring. Patient satisfaction with the procedure was high with significant improvements in symptoms, daily activities, leisure, personal relationships, and treatment experience (p=0.00062).

Conclusion: This study demonstrates a robust surgical approach to management cutaneous neurofibromas which can be accessed world-wide to individuals with NF1 and performed by a wide-variety of medical specialists with high clinical efficacy and patient satisfaction.
Introduction

Neurofibromatosis Type 1 (NF1) is one of the most common autosomal dominant genetic disorders affecting 1 in 3000 live births and is found worldwide independent of gender, race, or geographic location (1). It results from loss of the NF1 tumor suppressor gene in Schwann cell lineage leading to extensive tumor formation throughout the body and a hallmark of the disorder is multiple dermal or cutaneous neurofibromas (cNF) (2). About 30% of NF1 individuals also develop plexiform neurofibroma, a Schwann cell tumor along the internal nerve plexuses that has around 10% lifetime risk for malignant transformation (1). On the other hand, the cNF are present in virtually all patients with NF1. They are exclusively located in the cutaneous dermis layer and are not prone to malignancy. Despite their benign physiology, patients with NF1 attribute the cNF as their greatest medical burden due to their physical disfigurement (3). NF1 patients can develop thousands of cNF that are 2mm-3cm in size, soft, skin-colored nodules covering the face, trunk, and extremities. cNF are the primary source of chronic physical symptoms such as pain and itching and emotional distress given a greater burden of cNF strongly correlates to negative quality of life and self-image (4).

The cNF compose diverse cellular components including Schwann cells, fibroblasts, macrophages, mast cells, and blood vessels in a collagenous matrix within the dermis (5-7). Although their pathophysiology is unknown, cNF are affected by genetic variation of NF1, the skin microenvironment, and hormones and may grow in evolving stages (Figure 1) (8, 9). They are classified by stage according to appearance: the nascent stage detected only through ultrasound or other forms of imaging, the flat stage depicted by thinning or hyperpigmentation at the surface of the skin, the sessile stage with a raised papule, the globular stage with a 20-30mm
base with comparable height, and the pedunculated stage which extrudes its dermal contents through a visible stalk connecting the portions above and below the skin (9, 10). In all stages, considerable mass is located within the deeper dermis layer whereas typical shaving or electrodessication treatments which target only the visible projection may lead to tumor regrowth and collagen scar formation (Figure 1) (11, 12). Currently, there is no available medical treatment for cNF. Physical removal remains the mainstay of treatment, primarily focused around surgical excision with primary closure by dermatologists or general and plastic surgeons (13, 14). Unfortunately, this method may be inaccessible to a majority of the global population due to the requirement of surgical expertise, sterile field, and general anesthesia. CO₂ lasers have been developed since the 1980’s to remove hundreds of tumors at one time but contain high risk of hypopigmented or hypertrophic scarring (Figure 1) and continues to remain largely inaccessible to the NF1 population due to lack of specialized training and equipment (15, 16).

Due to the dearth of accessibility to treatment for patients with NF1 worldwide, we offer a robust surgical approach for management of cutaneous neurofibromas that can be performed in an outpatient setting with equipment available to most general medical clinics and can be performed by almost all medical providers including family practitioners, physician assistants, and nurse practitioners. In this study, we recognize all adverse events associated with the procedure and quantify patient satisfaction.

**Results**

Twelve patients with NF1 were consented and underwent the surgical procedure (Figure 2). The average age of the subjects was 46.6 (standard deviation (SD), 17), 10 (80%) of the
subjects were female, and 11 (92%) were Caucasian with one African American. In the entire study, 83 cNF were removed and were an average size of 1cm (SD, 0.35). An average of 6.9 (range: 1-10) cNF were removed each operation. Thirty-one (37.3%) of cNF removed were located on the upper extremity, 29 (35%) from the trunk, 11 (13.3%) from the head & neck, 10 (12%) from the abdomen, and 2 (2.4%) from the lower extremity. This surgical technique is based on the biology and anatomy of the cutaneous neurofibroma where a large portion of the tumor is in the dermis. Therefore, a critical component to this procedure is further removal of the mass within the deeper dermis. This is accomplished after shaving off the outer projection of the neurofibroma by grasping the remaining mass with forceps, lifting the mass outwards, and using the dermablade (or razor blade) to remove the pale, collagenous tumor. The open lesion is then closed by one or two interrupted stitches depending on its size. The whole procedure can be done in less than 2 minutes per tumor. There were no complications during the operations including excessive pain or problems with local anesthesia. Initial follow-up was 14 days and extended follow-up averaged 5 months. Representative photographs of the tumors before and after the procedure are depicted in Figure 3. Examination at the extended follow-up revealed one site with hypertrophic scar formation (1.2%) (Supplemental Figure 1) and 10 sites with post-inflammatory hyperpigmentation (12%) (Supplemental Figure 2), but no other complications were noted including skin infection, tumor regrowth, hypopigmentation, or keloid formation (Table 1).

The Dermatology Life Quality Index (17) was administered to all twelve patients prior to the surgical procedure and after the extended follow-up visit. Every question was answered to completion and the ten-question survey took a maximum of five minutes to complete for each
The initial DLQI average and total scores were 9.83 and 118, respectively, which improved significantly at the extended follow-up visit to 1.83 and 22, respectively (p=0.00062). The individual DLQI dimensions prior to and after the surgical procedure are displayed in Table 2 and Supplemental Figure 3. The index of symptoms and feelings dropped from 3.1 (SD, 1.1) to 1.1 (SD, 0.9) (p<0.0001), daily activities from 2.8 (SD, 1.2) to 0.5 (SD, 0.4) (p<0.0001), leisure activities from 1.7 (SD, 1.1) to 0.3 (SD, 0.3) (p<0.0001). Personal relationships and treatment efficacy dropped from average scores of 1.1 (SD, 0.8) and 0.6 (SD, 0.8) to zero, respectively. Although work and school functioning improved from 0.6 (SD, 1.2) to zero, the results were not significant.

**Discussion**

The goal of the present report is to propose a novel technique of removing cutaneous neurofibromas that is accessible to the global NF1 population. The procedure described herein is considered accessible by using inexpensive medical equipment present in most outpatient general clinical settings, employing a non-sterile technique, and following a low-risk procedure which can be performed by most health care providers. The procedure yields favorable cosmetic results and improves quality of life in NF1 patients.

Definitive treatment for cNF is a major obstacle for NF1 patients. NF1 patients are often affected with other medical problems including bony deformities, malignant neoplasms, and learning disability which could impact their access to treatment (18). Additionally, the type and size of cNF, location of the tumor, and patient demographics must be considered for different treatment modalities. Excisional operations performed by general and plastic surgeons have the
capability of removing extremely large cNF or hundreds of cNF in one operation with exceptional reconstructive results (13, 14, 19). Unfortunately, this method mandates trained surgical specialists, requires a sterile surgical field, runs a high-risk side effect profile with use of general anesthesia, higher costs, and potential requirement of post-operative hospitalization (13, 14). Dermatologists typically will conduct excisional removal using local anesthesia to manage cNF in an outpatient setting. It has a lower risk profile and cost to the NF1 patients than operative surgery, yet the necessity for a longer excision to remove the cNF limits post-operative cosmetic outcome (20). In addition, this traditional excision can only remove a few tumors per session due to the time constraints. The procedure herein targets cNF anatomy by selectively removing the dermal component which will prevent tumor regrowth and ultimately yields more favorable post-procedural cosmetic outcomes for the patients by shortening the excision length. Local anesthesia with Lidocaine 1% with epinephrine 1:100,000 is the agent of choice for skin surgery and is generally safe to use with maximum dose of 40cc (mL) per session or 7mg/kg total (21, 22). Cautionary use is advised when using epinephrine to the fingers, toes, nose, or penis to avoid a theoretical complication of vasoconstriction and digital gangrene despite evidence largely in support of its safety in the digits (23, 24). Rare, systemic toxicity from lidocaine may include hypotension, bradycardia, or systemic allergic reaction (22). For wound closure, the use of surgical glue or staples could replace sutures to expedite the removal process of cNF and in addition to minimize the resultant skin tension from sutures after removal of clustered cNF. Staples could be considered for larger neurofibroma in areas of less cosmetic concern (i.e. non exposed skin) with benefits of quicker operational time and lesser infection risks but are prone to greater post-operative pain than traditional sutures (25). Surgical glue should only be implemented on small lesions under no tension post-operatively. This modality
may offer less scarring but additionally risk of allergic reaction to adhesives, and should not be
used in high moisture areas such as the axillae and perineum or highly mobile areas including
hands, feet, and joints (26).

The CO₂ laser is commonly employed tool for treating cNF by rapidly heating and
vaporizing the intra-cellular water which leads to destruction of tissue (15). The advantage of
this technique includes the ability to treat hundreds of tumors at close proximity to one another
and can be performed in both the operating room or outpatient clinical setting with high patient
satisfaction (15, 27, 28). The CO₂ laser technology is, however, unavailable to most global
clinical settings and specialized training is required to operate the machinery. Local infection
rate has been reported up to 15% and scarring is a frequently observed side effect (15, 27-29).
Minimally invasive photocoagulation including Er:YAG or Nd:YAG lasers have been
successfully implicated as recent treatment options for small to medium sized cNF with
complications such as post-inflammatory hyperpigmentation occurring in 4% of tumors yet the
access is limited to large academic centers (30, 31). Other destructive methods including
electrodeessication and radiofrequency ablation have shown high patient satisfaction outcomes six
months post-procedure but should be considered as second-line therapies due to the high risks of
aberrant scarring and hypopigmentation associated with the techniques (10, 31, 32).

This study provides a robust, accessible method to remove multiple cNFs per visit that
can have a strongly positive impact on quality of life for NF1 patients. The DLQI survey was
specifically chosen due its ability to assess cNF removal impact directly on physical and
psychosocial factors related to the skin, while the Impact of NF1 on Quality of Life survey, an
important tool to assess quality of life for NF1 patients, assesses non-dermatologic features of the disease including vision problem, gait abnormalities, and mental status changes that will not reflect the outcomes of this procedure (4, 33). Symptoms of itchiness, soreness, or pain and feelings of self-consciousness were among the highest reasons for poor quality of life pre-operatively; however, the described procedure significantly diminished the magnitude of these dimensions and most others based on the DLQI. Removal of cNF with this technique could be implemented as a low-risk therapy for both symptomatic and aesthetically troublesome neurofibromas in patients with a limited number of cNF. It is important to assess the potential risks of complications including hypertrophic scarring, keloid formation and post-inflammatory pigmentation. Keloids, abnormal collagen scarring formation, may occur in higher frequencies in African-American patients or patients with a history of keloid formation (34). Thus clinicians should warn such individuals about these risks when performing any surgical procedure in this context. Post-inflammatory hyperpigmentation (PIH) more commonly occurs in people with Fitzpatrick Skin Type IV-VI and Asian descent due to activation of melanocytes after trauma and dermal procedures (35). Patients with PIH should be reassured for the benign nature of the conditions and spontaneous resolution occurs after months, or potentially years (35). If PIH is an issue, it can be managed post-operatively with UV protection, topical steroids, or retinoids and lightening cream hydroquinone (36). Future studies should stratify treatment strategies based on these risks, skin types, and location of cNF (31).

Physicians of different subspecialty training background and advanced practitioners can utilize this simple technique to remove cNFs for their NF1 patients, but caution should be used to ensure safety. cNF must be accurately identified from other potential differentiating soft tissue
masses including plexiform neurofibromas, dermatofibroma protuberans, or dermatofibromas. Due to the superficial nature of this operation and low-risk for complications, the procedure is deemed “low-risk” thus may be performed by practitioners licensed in the United States with credentialing for performing these operations. We provide the Supplemental Movie showing step by step of the whole procedure for additional training. Patients on anticoagulation or at risk of bleeding should continue to undergo the procedure given the low-risk of the operation. Additionally, cost of the operation would be comparable to a tangential biopsy (Billing Code: 11102 for the first lesion and 11103 for additional lesions). There is a need for more accurate billing codes for cNF resection as a priority for future work given the physical disfigurement and psychological harm of the lesions.

There are a several of limitations to this study to address. The procedure was performed at a single-institution with relatively small sample size thus impacts generalizability. Selection bias may have influenced the quality of life improvements given the individuals who were most unhappy with their skin elected to undergo the surgery. The majority of subjects were of Caucasian descent and post-procedural outcomes including post-inflammatory hyperpigmentation may not accurately reflect outcomes for the entire population affected by NF1.

**Materials and Methods**

Patients over the age of 18 with a diagnosis of NF1 established by the Neurofibromatosis NIH Guidelines were recruited at the Neurofibromatosis Clinic at UT Southwestern Medical Center, Dallas, Texas between February 01, 2018 to June 30, 2018 in a prospective clinical case
series (18). The procedure, risks and benefits, and importance of post-operative care were described to the patients prior to consent. Preoperative assessment included a skin examination and the collection of sociodemographic characteristics.

Materials

The surgical procedure requires isopropyl alcohol (70%) pads, local anesthetic (1% Lidocaine Hydrochloride & Epinephrine 1:100,000), dermablade or razor blade, forceps, sutures, needle driver, curved/straight Mayo scissors, non-sterile gloves, band aid and petrolatum ointment. Required materials are depicted in Figure 4. Surgical glue or stapler may replace suturing supplies for an expedient technique on smaller cNF.

Procedure

First, we disinfected the cNF with alcohol wipes and applied local anesthesia with 1% Lidocaine/Epinephrine 1/100,000 to the neurofibroma and surrounding skin. After several minutes to allow effects of anesthesia, a dermablade (or razor blade) was used to shave off the outer projection of the neurofibroma level to the surrounding skin. Of note, the tumor within the deeper dermis may naturally project out due to surrounding tension from the skin. A critical component to this procedure is further excision or removal of the mass within the deeper dermis. This is accomplished by grasping the remaining mass with forceps, lifting the mass outwards, and using the dermablade (or razor blade) to remove the pale, collagenous tumor. The open lesion is then closed by one or two interrupted stitches depending on its size. The closed wounds are covered with white petroleum and a band aid. The subjects are educated to continue application of petroleum ointment every day until the two-week follow-up for suture removal.
No antibiotics, oral nor topical, were given prior or after the procedure and clean, non-sterile gloves were used throughout the procedure. The procedure can be viewed in Supplemental Movie 1 and it takes less than two minutes to remove each tumor.

Demographic features of the subjects such as age, gender, ethnicity and the tumor properties including size and location were recorded on the day of the procedure. The patients had up to ten cNF removed per session with follow up in the clinic for suture removal in 2 weeks and wound check. The subjects returned for an extended follow-up visit of at least 4 months from the procedure date to analyze the following outcomes; infections, scar assessment, keloid formation, hypo/hyperpigmentation, and other adverse events.

The Dermatology Life Quality Index (DLQI) (17), a survey which assesses patient satisfaction with their skin, was administered to each patient before the procedure and at the extended follow-up. The DLQI is a questionnaire containing ten questions, each with a response of “not at all”, “a little”, “a lot”, or “very much” with corresponding scores of 0, 1, 2, and 3, respectively (33). Higher scores are indicative of worsening quality of life. Question 1 and 2 are representative of the patient’s symptoms and feelings, question 3 and 4 examines daily activities, question 5 and 6 indicate impact on leisure activities, question 7 analyzes problems with work and school, question 8 and 9 indicate personal relationships, and question 10 examines treatment efficacy.

Statistics
Statistical analysis includes continuous data presented as means with standard deviations and categorical data as counts with percentages. A two-tailed paired T-Test was used to compare the outcomes of the DLQI. P≤.05 was considered significant.

Study Approval

The UT Southwestern Institutional Review Board approved this study and all patients provided signed IRB consent and HIPPA privacy form for inclusion into the study. Written informed consent was provided for pictures appearing in the manuscript.

Author Contributions

BHC: Acquiring data, analyzing data, drafting the manuscript

LH: acquiring data

DS: acquiring data

JV: acquiring data

LQL: Designing research study, acquiring data, analyzing data, draft and review manuscript

Acknowledgments

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References


## Tables

**Table 1. Demographics and Operation Outcomes of Patients who underwent Cutaneous Neurofibroma Removal**

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<th>Age</th>
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**Abbreviations:** M, male; F, female; AA, African American; C, Caucasian.
Table 2: Dermatology Life Quality Index averages among patients who removed cutaneous neurofibromas

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Pre-Op (mean, SD)</th>
<th>Post-Op (mean, SD)</th>
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<td>Symptoms &amp; Feelings (Maximum: 6)</td>
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<td>1.1 (0.9)</td>
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<td>Daily Activities (Maximum: 6)</td>
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<td>0.5 (0.4)</td>
<td>&lt;0.0001</td>
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<td>Leisure (Maximum: 6)</td>
<td>1.7 (1.1)</td>
<td>0.3 (0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Personal Relationships (Maximum: 6)</td>
<td>1.1 (0.8)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Work &amp; School (Maximum: 3)</td>
<td>0.6 (1.2)</td>
<td>0 (0)</td>
<td>0.0967</td>
</tr>
<tr>
<td>Treatment (Maximum: 3)</td>
<td>0.6 (0.8)</td>
<td>0 (0)</td>
<td>0.0183</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation. n = 12 patients
Statistical Test: Two-tailed, paired T Test
Figure 1: Clinical Stages/Evolution of Cutaneous Neurofibromas and Treatment

A) Nascent, a dormant stage undetectable without instrumentation. B) Flat, thinning or hyperpigmentation at the surface of the skin. C) Sessile, tumor raised with an apex. D) Globular, 20-30mm base with comparable height and globular shape. E) Peduncular, a stalk connects the portions above and below the skin. F) Scars from CO$_2$ laser treatment in its final stage (permanent).
Figure 2

Enrollment

Assessed for eligibility (n= 12 patients)

Excluded (n= 0)

Procedure

Time: 0 weeks (n=12 patients with 83 tumors)
• Patient consented
• Dermatology Life Quality Index
• Physical Examination
• Photographs taken
• Operation conducted

Follow-up: 2 weeks

Time: 2 weeks (n=12 patients with 83 tumors)
• Physical Examination
• Suture Removal
• Photographs taken
• Instructions to follow up given at 5 months

Follow-up: 5 months

Time: 5 months (n=12 patients with 83 tumors)
• Physical Exam
• Photographs Taken
• Dermatology Life Quality Index
Figure 2: Flow Diagram for Operation
Figure 3. Cosmetic Outcomes of Cutaneous Neurofibromas Removal Using Described Procedure at 5 months

Representative photos of before (left panel) and after (right panel) tumor removal at the A) Right shoulder, B) Chest, C) Left nipple, D) Posterior auricular, E) Posterior neck, and F) Back.
Figure 4: Materials and Visual Procedure Sequences