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Treatment of cutaneous neurofibromas with carbon dioxide laser: Technique and patient experience

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ABSTRACT

Cutaneous neurofibromas (cNF) are one of the hallmarks of neurofibromatosis 1 (NF1). The number of cNFs varies between individuals from a few to hundreds or even thousands and increases throughout adult life. cNFs cause a significant disease burden to adult patients and constitute an unmet need for therapy, since they may cause itch and pain and, being conspicuous and unsightly, stigmatize the patient. There is a lack of reports on how the outcome of various treatment options are perceived by the patients. Here we describe a technique for cNF removal using CO_2 laser, and report how patients experience the procedure. Questionnaires were sent to patients who had had CO_2 laser surgery in the French Referral Center for Neurofibromatoses, and in the Turku University Hospital, Finland, to retrospectively evaluate the patients' global satisfaction of the procedure, treatment indications, and reasons for withdrawal from treatment, if this was the case. The number of returned questionnaires was 233/473 in France and 23/27 in Finland. The results showed that the most important indications for cNF removal were esthetic, and pain and itch caused by the tumors. In general, the procedure was well tolerated, and the degree of satisfaction was 8–10 on a scale from 0 to 10. For those 30% who discontinued the tumor removal program, the main reasons were organizational constraints, a non-satisfactory esthetic result, too many cNFs to treat, or problems with healing. Thus, the CO_2 laser method is well tolerated but does not fully answer to the needs of the patients. Since medical treatment is not yet available, we encourage the use of laser removal of cNFs as a feasible method to decrease the tumor burden of the patients.

1. Introduction

Neurofibromatosis type 1 (NF1; Mendelian Inheritance in Man, 162200) is a cancer predisposition syndrome with a prevalence of 1:2000–1:3000. NF1 is dominantly inherited, and in about 50% of patients, the syndrome is caused by a *de novo* mutation in the *NF1* gene located on chromosome 17. The *NF1* gene encodes neurofibromin tumor suppressor protein which functions as a Ras-GTPase activating protein (RasGAP). Pathological variants of the *NF1* gene lead to over-activation of the Ras signaling pathway and, further, to tumor development (Gutmann et al., 2017).

Cutaneous neurofibromas (cNFs) are the most characteristic findings of NF1. About 90% of individuals with NF1 develop multiple cNFs during adulthood, and the number of tumors varies between less than ten to hundreds or even thousands (Duong et al., 2011). Some cNFs may be present in childhood, but new tumors typically emerge during puberty and become more numerous throughout life (Duong et al., 2011). Although cutaneous NFs lack the potential for malignant transformation and are thus not life threatening, they are the main NF1-associated health problem for most adult patients. cNFs cause a significant disease burden and affect the daily life of patients due to their prevalence and disfigurement (Wolkenstein et al., 2001; Page et al., 2006; Kodra et al., 2009; Guiraud et al., 2019). Since cNFs are so conspicuous, they have a major negative impact on quality of life of patients (Wolkenstein

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at al., 2001; Guiraud et al., 2019). Cutaneous NFs may also be tender or itch chronically, and their number may increase during pregnancy.

Histologically, cutaneous NFs are composed of elements of peripheral nerve: Schwann cells, fibroblasts, perineurial cells, abundant collagenous connective tissue, and immune cells, such as mast cells (Peltonen et al., 1988; Ortonne et al., 2018). cNFs are located within the dermis and, hence, the skin does not slide over the tumor on palpation, but the tumor moves with the skin. cNFs can be classified into various descriptive forms according to their growth pattern and protrusion; there is a continuum from flat to sessile and further to globular and pedunculated cNFs (Fig. 1). The diameter rarely exceeds 3 cm.

To date, there are no medical treatments available for cNFs. The options include surgical removal, various laser treatments, electrosurgical excision (Levine et al., 2008) and radiofrequency ablation (for review, see Chamseddin and Le 2019). Treatment with CO_2 laser (Becker 1991; Katalinic 1992; Moreno et al., 2001; Algermissen et al., 2001; Chiang et al., 2012) and neodymium:yttrium aluminum garnet (Nd:YAG) laser (Elwakil et al., 2008; Kriechbaumer et al., 2012, 2014) has proven to yield good results and patient satisfaction. The most recent studies indicate that (Nd:YAG) laser treatment results in a better cosmetic outcome and less hypopigmentation than CO_2 laser (Kriechbaumer et al., 2012, 2014). The newest method is radiofrequency

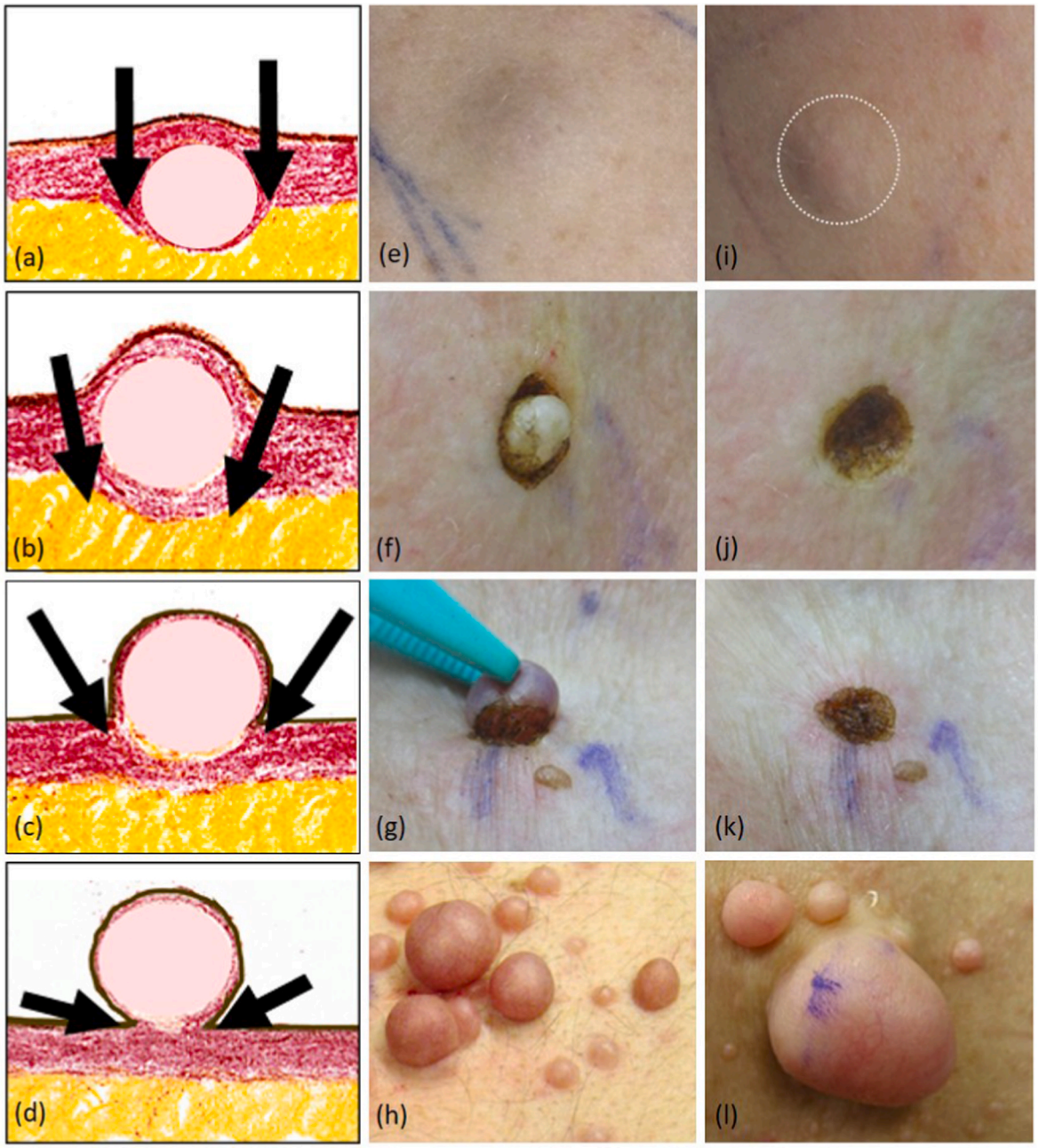

Fig. 1. Schematic drawing and clinical images showing the structure of various cNFs and their treatment with CO_2 laser. (a–d) Schematic drawings of cNFs showing various growth patterns. (a) flat, (b) sessile, (c) globular, (d) pedunculated. The arrows indicate the cutting directions with laser. (e–k) Clinical images or cNFs with growth patterns corresponding to the drawing. (f–k) Laser removal of tumors with various growth patterns. (i) White line indicates the tumor borders and the line for penetration of the epidermis and dermis with laser. (f) A "buttonhole" is cut around the top of a sessile neurofibroma. (g) Protrusion of the tumor is promoted by pulling with forceps and by cutting with laser around the tumor. Tumor protrusion can also be facilitated by pressing digitally the surrounding skin while cutting. (j, k) Removal of a sessile tumor results in a deeper wound than removal of a globular tumor.

ablation and excision, which may be an alternative treatment for patients with large numbers of cNFs, when the equipment is available (Kim et al., 2013). Speed of the treatment process is the most important advantage of all ablative methods over blade surgery: 10–20 tumors can be removed in local anesthesia in one session, and even hundreds of small tumors during general anesthesia.

Here we report how patients experience CO_2 laser treatment of cNFs in two European centers, Créteil, France and Turku, Finland. We also provide detailed instructions on a technique for tumor removal, which is based on the understanding of the structure and growth patterns of cNFs. This study was also driven by two circumstances: CO_2 laser is commonly available in dermatological clinics and patients would benefit from a wider practice of removal of cNFs. Ultimately, we wanted to examine if there are grounds to encourage the wider use of CO_2 therapy for removing cNFs.

2. Patients

Patients with NF1, aged 22–75 years, who fulfilled the NIH criteria for NF1, and who had been operated on for cNFs in the NF1 clinic in the Turku University Hospital, Turku, Finland, during the previous 2–12 months were invited to participate in the survey. Patients with NF1 who underwent laser surgery for cNF in the French Referral Center for Neurofibromatoses (Dept. of Dermatology, Henri-Mondor Hospital Créteil, France) between 2005 and 2018 were invited to answer a questionnaire on their retrospective experience of the procedure.

3. Methods

3.1. Patient survey

3.1.1. Center of Turku, Finland

The survey was carried out in the Turku University Hospital, Turku, Finland, and the images of the tumors were taken with the consent of the patients. A 9-question survey was used to evaluate the patient's experience of the previous laser treatment. The questions included the number and body area of cNFs treated, reasons for treatment, peri- and postoperative, convalescence, satisfaction with the outcome and choice of treatment method in the future. The questionnaire, plus a return envelope with the postage paid, was sent to the home address of 27 patients.

3.1.2. French Referral Center

A questionnaire with 10 questions was designed for retrospective evaluation of satisfaction, comments, criticisms, and expectations of patients who had had CO2 laser surgery. The questions concerned overall satisfaction with the procedure, subjective feeling about the visibility of the disease, total number of cNFs, reasons for treatment, number of treated lesions, and reasons for withdrawal from treatment, if this was the case. The last question was important since it reflected the patient's expectations for future treatments. The questionnaire, plus a return envelope with the postage paid, was sent to the home address of 499 patients.

3.1.3. Laser treatment of cNFs

Selection of the tumors for laser treatment in Turku, Finland: The initiative for tumor removal came from the patients and the operations were carried out as a part of routine patient care. Only solitary tumors which were located within dermis (Fig. 1) were operated. To ensure the correct diagnosis of cNF, the tumors were palpated to make sure that the tumor moved with the skin. Subcutaneous tumors, i.e., nodules located deeper than where the skin slides over the tumor were not removed with laser. The tumors most suitable for laser removal were the globular and pedunculated tumors because the postoperative wound was not as deep as when removing flat or sessile tumors. Tumors ranging in size from 1 mm to approximately 30 mm would be suitable targets for the treatment, but removal of flat or sessile tumors more than 1–2 cm in diameter results in a larger wound, which heals slowly, in up to five weeks.

Preoperative patient information: The patients were informed at the time of booking the appointment and again before the operation. The information covered the following: healing time of the wounds, risk of discharge from the wounds during the first to second postoperative weeks, importance of daily shower, and avoidance of swimming and sauna until wounds have healed. Slight cognitive impairment was not a contraindication for the treatment.

Anesthesia: To ensure sufficient analgesia, the skin was anesthetized with a local anesthetic around and under the tumor. General anesthesia enables removal of dozens or even hundreds of small tumors during the same session.

Equipment: We have used various CO_2 lasers, the most recent SmartXide (DEKA, Florence, Italy). Various laser settings with continuous or pulsed wave were used depending on the size of the cNF and thickness of skin in the area, e.g., pulsed wave with a frequency of 20 Hz and a power level between 1.3 and 1.8 W was used. The room was equipped with smoke evacuation.

Technique: Removal of cNFs must be complete to avoid regrowth. On the other hand, minimal margins avoid damage to healthy skin and results in a smaller scar. Neurofibromas with a diameter less than 2–5 mm were vaporized. For sessile and flat tumors, a circular hole was cut through the epidermis and dermis at the edge of the tumor (Fig. 1a–j). The tumor was pushed from the side with fingers or pulled with forceps simultaneously as the side and bottom of the tumor was cut to deliver it (Fig. 1g). Pedunculated tumors (Fig. 1d–i) were well-suited for the laser procedure since they can be removed by cutting the base of the tumor. Neurofibroma tissue is slightly paler than the dermis. This property was exploited to examine that the tumor had been removed intact. When laser cutting reached the subcutaneous fat and all tumor tissue and dermis had been removed, the dermis around the wound was lasered with less energy to facilitate shrinkage of the wound. Bleeding during the operation was no major problem and most cNFs with a diameter of 1–2 cm were removed with minimal or no bleeding.

Postoperative treatment: Removal of the cNF left a wound bed which healed from the bottom in 1–5 weeks depending on the diameter and depth of the wound. Wound beds deeper than 1–2 mm usually secreted tissue fluid for 1–2 weeks, but the patients did not report pain. They were instructed to shower the wound daily with clean, lukewarm tap water to prevent precipitation of the exudate onto the wound. To prevent infection, daily application of ointment containing fucidic acid was recommended before application of wound dressings.

4. Results

4.1. Outcomes of the procedure

Altogether, about 380 cNFs were removed in the Turku study center from patients who returned the questionnaire. All patients were operated in local anesthesia. Removal of the tumors left a wound bed which healed by secondary intention from the bottom (Fig. 2a) and the skin epithelialized in 1–5 weeks, depending on the diameter and depth of the wound. The result was a white, flat scar of the same size as the original tumor (Fig. 2c–e). Some patients developed slightly elevated scars on arms or upper chest (Fig. 2f), but there were no hypertrophic scars or keloids. The wounds in the face area healed very well (Fig. 2b and c).

Of all tumors removed, 2/380 (0.5%) led to complications: One postoperative wound on the shoulder of a young male resulted in overgrowth of granulation tissue; this was treated by laser removal and healed completely. One patient was prescribed a course of oral antibiotics by the general practitioner for a suspected postoperative wound infection, but the condition could not be verified by us.

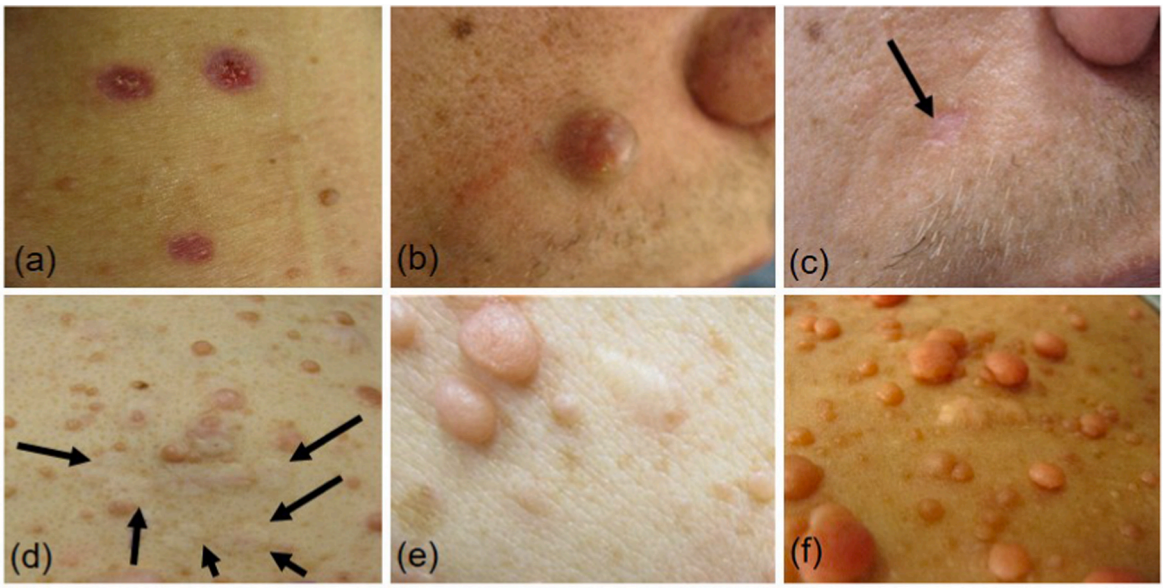

Fig. 2. Outcome of laser operations. (a) Healing wounds of over 1 cm in diameter two weeks after the operation. The wound bed is partially epithelialized. (b–c) Laser removal of a cNF from the face resulted in an acceptable scar (arrow) in only one month after the operation. (d–f) Typical scars after laser operation of cNFs on the trunk of three patients.

4.2. Patient survey

4.2.1. Center of Turku

Twenty-three out of 27 (85%) surveys were returned. Of all tumors removed, 48% were from the trunk, 25% from the head and neck, and 27% from the extremities. Fourteen patients had been treated more than once (2–5 times). The two equally most common reasons for operating were pain (35%) and esthetic reasons (35%). Itch was the main reason for two (9%) patients. The average per-operative pain experienced was 1.46 in a visual scale from 1 to 5. Only one patient preferred traditional surgery over laser.

4.2.2. French Referral Center for Neurofibromatoses

Between 2005 and 2018, 499 patients had at least one procedure, and 37 patients were treated in general anesthesia. 26 of the patients did not live at the address available, 233 (49%) completed the questionnaire. There were 153 females and 79 males (1 gender not recorded), and the mean age was 50.4 (±11.9) years.

The indication for laser surgery was mainly esthetical, 92.7% (216/233), and symptom of pruritus or pain, 51.9% (121/233). Laser surgery was performed on visible areas, 82% (191/233), and more than 50 cNFs were laser treated or removed in 41.6% (97/233) of the patients.

The patients' overall satisfaction was high and was at a median of 8 on a numerical scale from 0 to 10. Nevertheless, 29.6% (69/233) discontinued treatment. The reasons were organizational constraints for 66.7% (46/69), unesthetic or insufficient result for 46.4% (32/69), too many cNFs to treat for 37.7% (26/69), poor tolerance or problems of healing for 34.8% (24/69) (tolerance of the procedure 8.7% (6/69), healing 26.1% (18/69)). More than half or 55.8% (130/233) of the patients would have preferred medical treatment with average efficiency but good tolerance rather than very efficient treatment with numerous side effects.

5. Discussion

Laser excision of cNFs requires that the clinical diagnosis is correct. Cutaneous NFs are situated in the dermis, are not associated with larger nerve branches or other vital structures and are thus safely removed with laser. On the other hand, solitary neurofibromas may be situated subcutaneously and the skin slides over the tumor upon palpation. These tumors may be associated with a nerve branch and are best removed surgically. Nor is the laser technique suitable for diffuse dermal neurofibromas since they have irregular borders (Ortonne et al., 2018). Cutaneous NFs do not become malignant and hence it is not necessary to have a histological diagnosis of typical cNFs, if numerous tumors are removed, and small tumors can thus be vaporized entirely. The cNFs most suitable for CO_2 laser treatment are the globular and pedunculated types, since the postoperative wounds will be smaller in diameter and in depth and heal thus quicker than the postoperative wounds after removal of flat or sessile tumors. Globular and pedunculated tumors are also the types that patients most often wish to have removed. For the best postoperative patient satisfaction, we recommend, in connection with the patient's first visit, removal of a few cNFs $\leq$1 cm in diameter to evaluate the healing response and the patient's experience. In general, were recommend application of CO_2 laser mainly to cNFs around 1 cm in diameter or to globular or pedunculated cNFs with a maximum stalk diameter of about 1 cm.

Because cNFs are not life threatening, the impact of the condition may be overlooked during patient follow-up. However, cosmetic factors are important when patients self-grade the severity of their disease (Wolkenstein et al., 2001). Visible neurofibromas are stigmatizing and are the major cause of impaired quality of life of adult patients with NF1 (Wolkenstein et al., 2001; Page et al., 2006; Kodra et al., 2009).

Based on the results of the present study, we find that the esthetic condition of the patient is an equally important indication for removal of cNFs as any other. The esthetic condition was the most important indication for tumor removal in the present study, in addition to pain and itch. Actively growing csNFs may itch and be painful. Although the molecular basis for itch and pain is not known, the presence of many mast cells in neurofibromas may imply that interactions between mast cells and local neural factors contribute to the pain and itch so typical for cNFs.

Cutaneous tumors usually emerge grow during adolescence years, and it is possible to remove the most disturbing tumors before adulthood, if the adolescent is mature enough to understand and accept the healing process which results in scarring and accepts that all tumors which will grow in the future cannot be removed. Most adult patients with NF1 have adapted to the fact that the number of cNFs in their skin is too high for complete removal. Nevertheless, patients will often point to a few cNFs that are the most disturbing ones due to cosmesis, itch and

pain. Although an excessive number of tumors was the reason for discontinuing treatment for the 37.7% of 69/233of the patients who discontinued treatment, it is important for the patient to have the most disturbing tumors removed. For example, removal of the largest and most bulging tumors on the trunk or arms may increase the clothing alternatives for the patient. Indeed, discomfort is the primary indication for treatment, and considerations of the esthetic impact are unique to each individual.

The operation results in scarring, the final appearance of which depends on the skin area and the personal properties of the patient. Of the patients who discontinued treatment, 46.4% did so because they considered the operative outcome unesthetic or insufficient. Wound healing in patients with NF1 is not different from wound healing in non-NF1 subjects (Koivunen et al., 2005), nor have previous studies on laser treatment reported wound healing problems (Algermissen et al., 2001; Kriechbaumer et al., 2014). In general, the skin of the upper chest and shoulders may be prone to develop more prominent scar than other skin areas. CO_2 laser surgery typically results in hypopigmented scars, which may be disturbing on visible skin areas, especially in dark skin. However, it is not uncommon that patients still prefer having a scar instead of a cNF on visible areas. Nd:YAG laser results in less hypopigmentation and a better esthetic outcome, and would probably be a better alternative if generally available (Kriechbaumer et al., 2014). To date, there are no comparison studies available on the esthetic results of other destructive treatment modalities.

Complications after the procedure are very rare, if the postoperative follow-up by patient is adequate. Regrowth of cNFs in the same location from which they have been removed does not occur if tumor removal has been complete. However, if the patient has a tendency to develop numerous cNFs, new tumors may grow in the skin next to the scar. In the series of Finnish patients, two complications were reported in 23 patients who had some 380 tumors removed. Among the French patients, problems in healing were mentioned as a reason for stopping the treatment by 18 out of 69 patients.

Satisfaction among the French patients in the present series was high with a median value of 8 on a numerical scale from 0 to 10 and of the Finnish patients all but one out of 22 preferred laser over traditional operation. Nevertheless, laser surgery has its limitations. Even if the patients were generally satisfied, a third discontinued their program of tumor removal. The hope of medical treatment is clearly on the wish list of patients and professionals. Patients prefer medical treatment but fear side effects. Meanwhile, since there is no medical treatment available, CO_2 laser to remove cNFs should be kept in mind as an option in dermatological centers which have the equipment available.

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Author statement

Sirkku Peltonen: Conceptualization, Data curation, Investigation, Methodology. Formal analysis, Visualization, Writing - original draft, review & editing. Pierre Wolkenstein: Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Writing - original draft, review & editing. Arnaud Jannic: Data curation, Investigation, Methodology, Formal analysis, Writing - review & editing.

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