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**Title:** Non-invasive High Intensity Focused Ultrasound (HIFU) treatment of Cutaneous Neurofibromas (cNF): Protocol and recommendations for treatment of smaller tumors.

**Purpose:** Improve the safety and efficacy of high intensity focused ultrasound (HIFU) for treatment of cutaneous neurofibromas (cNFs).

**Methods:** This study was a continuation (Phase B) of a previous study on HIFU treatment of 147 cNFs in 20 NF1 patients (Peltonen et al 2024, in press). Seven patients from this study were included in Phase B. A single treatment session was performed using a 20 MHz HIFU-device with integrated dermoscopic guidance and a handpiece with a focus depth of 2.3 mm below the skin surface. Dosing was modified from 0.7 J/dose at 250 ms/dose in Phase A to 0.9 J/dose at 500 ms/dose to promote thermal effects over mechanical tissue destruction, and thereby obtain a gentler therapy without superficial skin erosions. Doses, 13-25 per tumor, median 18 were applied with an interval of 1-2 seconds approximately 1 mm between each other to fully cover the tumor including a 1 mm margin. Local anesthesia was not used. Post-treatment effects were evaluated immediately and at follow-up visits.

**Results:** Seven patients and 54 cNFs (diameter 2-5 mm, median  $5.0 \pm 0.85$  mm) were included. The data analysis compared Phase A and B. The immediate and short-term biological responses were local flare and edema. Pain during the treatment was graded by patients between 1 and 8 (median 5) on a 0-10-scale. Mild side effects were reported post-treatment in six cases, and in two cases at the 1-week follow-up, while all other assessments observed no side effects. Pigment changes were observed in some cases and were apparently related to a combination of skin type and the creation of superficial erosions. At the 6-month follow-up, participants rated the treatment as "very satisfying" with no scarring or serious adverse events. The primary safety-endpoints were thus fulfilled.

Visual assessment after six months showed reductions in size for 44% of tumors and 26% were no longer visible or substantially reduced. The efficacy was somewhat lower than that obtained in Phase A with 26% and 49% respectively. The effect was noted to correspond to superficial erosions which in turn may cause dyspigmentation.

**Conclusions:** HIFU presents a rapid, well-tolerated, and precise non-invasive option for cNF treatment. Improvement of tumor appearance can be obtained in 70-76 % of treated tumors, with possibilities to adjust settings to balance efficacy with risks for superficial erosions and dyspigmentation. The method supports repeated treatment and ongoing management of smaller growing tumors.

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