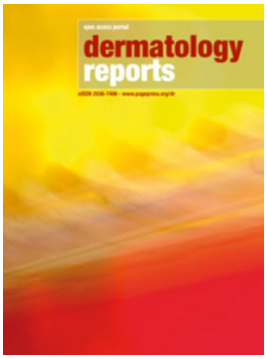

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Could an intra-procedural dermoscopic approach be necessary for obtaining radical treatment of actinic keratosis cancerization field if combined with ablative CO_2 laser?

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Contributions: Pietro Pasquale Cozza: conceptualization, methodology, validation, visualization, investigation, writing – original draft, writing – review & editing; Luigi Bennardo: validation, data curation, conceptualization, writing – review & editing; Steven Paul Nisticò, Antonella Tammaro, Elena Zappia: validation, formal analysis; Antonino De Caridi: investigation, resources, visualization, supervision; Marco Marcasciano: methodology, validation, writing – review & editing; Valeria Falcomatà: writing – review & editing, supervision, validation, methodology, conceptualization, project administration, investigation. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: the study protocol was drawn up in accordance with the Good Clinical Practice Standards provided for by Italian legislation and the current revision of the Declaration of Helsinki. All participants were carefully informed about the purpose of the study and the planned procedures and signed an informed consent to participate.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abstract

Actinic keratosis (AK) is a common skin disorder resulting from chronic sun exposure, which can be treated with various treatment modalities, including ablative CO_2 laser. Dermoscopic evaluation is fundamental in diagnosis and post-procedural follow-up. This study aimed to achieve radical clearance of AK cancerization fields through a combined approach using an ablative CO_2 laser and intra-procedural dermoscopy, rather than a pre- and post-procedural approach only. Twenty patients with 25 AKs were included in the study. Treatment with ablative CO_2 laser through a dermoscopic intraprocedural approach was performed for every patient with Olsen grade I or II AK. The results of this study showed that 100% of patients treated with this method achieved clinical clearance at follow-up, and 92% had no clinical recurrence after 2 months. The intra-procedural dermoscopic approach demonstrated to be useful to extend laser ablation to the AK cancerization field. According to the results of our study and after a comprehensive literature review, we conclude that intra-procedural dermatoscopy combined with ablative CO_2 laser therapy can be considered a valid alternative to CO_2 laser therapy alone.

Introduction

Actinic keratosis (AK) is a pre-cancerous skin lesion caused by prolonged exposure to solar UV rays during life. AK manifests itself clinically with the presence of an erythematous macule with or without fine overlying desquamation, rough to the touch. In some cases, it may appear in the pigmented variant, which enters into the differential diagnosis with lentigo maligna melanoma. Olsen *et al.*[1] classified AKs clinically into grade I mild (slight palpability, with AKs felt better than seen), grade II moderate (moderately thick AKs that are easily seen and felt), and grade III severe (very thick and/or obvious AKs) which correlate positively with the total area involved, with the degree of hyperkeratosis increasing respectively in the 3 grades mentioned, and with the percentage of area histologically damaged by sun exposure (I: <25%, II: 25-75%; III: >75%) in the determination of the Actinic Keratosis – Field Assessment Scale (AK-FAS) score.[2,3] The diagnosis of AK also includes dermoscopic examination with the characteristic "strawberry pattern", characterized by an intense erythematous punctate pattern, surrounded by normal skin, and possibly overlaid by small hyperkeratotic areas. The pigmented variant is characterized by a fine brown-grey granulation with a peri-follicular distribution, followed by rhomboid structures, and with an annular-granular pattern of pigment distribution.[4,5] Incisional or excisional biopsy may represent the definitive diagnosis, through intra-lesional punch sampling or through total excision of the keratosis itself and histological examination.[6,7] AKs sometimes may undergo spontaneous regression. However, in most cases, therapy is required.[8-11] Irradiation with a sufficiently high CO_2 power produces the vaporization of

the tissue,[12] due to the evaporation of the water contained in the tissue itself, limiting the depth of penetration of the laser to just 50 micrometers.[13] This characteristic, in combination with correct management of the pulses, allows for an extremely precise AK treatment, obtaining after several steps the desired clinical end-point, the vaporization of the dermatological lesion, until reaching the most superficial dermis (papillary), limiting the thermal damage. The achievement of the established endpoint is identifiable by minimal "point-like" blood dripping. The minimal thermal damage is obtained by high-power and very short-duration pulses, ensuring that vaporization occurs in a time shorter than the tissue thermal relaxation time.

Materials and Methods

The study was conducted at the Dermatology Department of Reggio Calabria Hospital, Italy. The protocol was drawn up in accordance with the Good Clinical Practice Standards provided for by Italian legislation and the current revision of the Declaration of Helsinki. When selecting patients to be enrolled in our study, some inclusion and exclusion criteria were established.

Inclusion criteria were: both male and female patients without age limits, AKs with Olsen grade I and II, new-onset AKs. Exclusion criteria included: AKs with Olsen grade III, patients treated with topical creams/lotions, the presence of active infections, patients with coagulation diseases, phototype V-VI, a history of cheloids or hypertrophic scars, and hypersensitivity to light. The study participants were carefully informed about the purpose of the study and the planned procedures and signed an informed consent. The subjects with AK were enrolled at the Dermatology Department of Reggio Calabria Hospital on the basis of the selection criteria previously described, after an appropriate dermatological general visit and a clinical and instrumental new diagnosis of AK through dermatoscopic or bioptical examination. Patients were provided with a pre-procedure preparation form that instructed them to: discontinue the use of exfoliating or retinol-containing products at least 7 days before the procedure; avoid prolonged sun exposure in the days preceding the treatment unless using an SPF50+ sunscreen; ensure that the skin was thoroughly cleansed without applying creams, make-up, or other topical substances on the day of the procedure; inform the treating clinician of any previous history of herpes simplex virus infection to allow appropriate antiviral prophylaxis, if indicated; and disclose all chronic medications to enable proper patient assessment, particularly in cases of anticoagulant or antiplatelet therapy, allowing appropriate management before the procedure. After the procedure, the recommendations included: using an SPF50+ sunscreen throughout the year; applying moisturizers and gauze dressings impregnated with a 15% aqueous extract of Triticum vulgare to the treated area to promote wound healing for at least 15-20 days; and avoiding applying make-up for 72 hours after the treatment.

The procedure was performed in supine position on a surgical table, with the application of protective glasses capable of shielding the electromagnetic laser radiation for both the patient and the operators present in the room. The patients were appropriately informed about home management of the lesions and underwent fortnightly check-ups (starting from 14 days after the treatment). The laser delivery mode selected was based on patients' phototype and on the AK to be treated (Olsen grade).

A constant CO_2 laser output of 0.5 W at a wavelength of 10,600 nm was preferred, as it produced uniform ablation areas while allowing real-time operator control. This setting was used particularly in patients with Olsen grade II AKs and a light skin phototype (I-II). For patients with Olsen grade I AKs and darker skin phototypes (III-IV), the pulsed mode (H-pulse) was preferred. In this mode, the laser emitted a sequence of discrete pulses with a power setting of 0.1 W, a repetition frequency of 10 Hz, and an energy output of 10 mJ per pulse; this pulsed delivery allowed for higher peak power during each emission, enhancing the ablative efficiency while reducing overall thermal diffusion to adjacent tissues. The Smart-Pulse technology was also designed to optimize the balance between ablation and coagulation by modulating the pulse shape and duration. This resulted in precise microablative effects suitable for targeted removal of AKs, with improved healing profiles and a reduced risk of post-procedural erythema or scarring, also reducing the risk of residual hyperpigmentation. Dermoscopic examination of the treated patients was performed in manual mode in the pre-procedural context (Figures 1-3) and during the execution of the procedure itself (Figures 4A, 5A, and 6A), to allow radicalization of the lesion by extending the vaporization to the margins of the lesion itself (Figures 4B, 5B, and 6B). We then proceeded with the mechanical removal of the laser outcome on AKs (Figures 5C and 6C) until clinical and dermoscopic resolution of AKs (Figures 7 and 8) by 14-day evaluation. Clinical photographs of AKs were taken using standardized conditions and assessed according to the AK-FAS, which evaluates the number of lesions, the degree of erythema, and the overall field damage on a 0-4 scale per item (total score range: 0-12). Images were captured under uniform lighting with a fixed distance and a neutral background, including a color calibration chart and size reference to ensure reproducibility and comparability. Clinical response to CO_2 laser treatment was assessed using a 5-point clinical response scale (CRS), ranging from (0 = *no response*) to (4 = *complete clearance*) of visible lesions. Standardized digital photographs were taken at each follow-up to document the extent of improvement and assist in blinded clinical evaluation.

Patients with AKs treated with the CO_2 laser were compared to a control group, whose patients were matched for age and clinical characteristics of the AKs (based on the Olsen grade). Patients in the control group were treated during the same post-laser follow-up period with photoprotection SPF50+.

Results

Twenty patients were enrolled for a total of 25 AKs treated, of which 10 (40%) were Olsen grade I and 15 (60%) were Olsen grade II; of the 10 AKs of Olsen grade I, three were in the pigmented variant (12%). All patients were evaluated clinically and dermoscopically during the first visit (pre-procedural), the laser procedure (intra-procedural), and at 14-day follow-up (post-procedural). Patients with Olsen grade I were treated with CO_2 laser according to the superpulse mode (pulsed, not continuous) at an average power of 0.1-0.2 W, while patients with Olsen grade II were treated according to the continuous-wave mode with an average power of 0.5 W. The achievement of the established end-point was identifiable by minimal "point-like" blood dripping, confirming reaching the most superficial dermis (papillary), limiting the thermal damage.

All patients (100%) affected by AKs, both Olsen grade I and Olsen grade II, treated with CO_2 laser therapy under dermatoscopic guidance showed, at the 14-day follow-up, complete clinical and dermatoscopic resolution of the keratoses and their cancerization fields, so as to demonstrate the radicality of each single lesion. The AK-FAS scale evaluation started from 1.25 in terms of the number of lesions for patients, 3.1 for erythema, and 4 for the overall field; the first parameter (number of lesions) decreased from 1.25 to 0 ($p<0.01$) over a period of 14 days and from 1.25 to 0.1 over 2 months ($p<0.01$); the second parameter (erythema) decreased from 3.1 to 1.25 ($p<0.01$) over 14 days and from 3.1 to 0.75 over 2 months ($p<0.01$); the third parameter (overall field assessment) decreased from 4 to 0 over 14 days ($p<0.01$) and from 4 to 0.1 over 2 months ($p<0.01$). The changes in AK-FAS parameters (number of lesions, erythema, and overall field assessment) between baseline and follow-up visits were analyzed using the Wilcoxon signed-rank test for paired samples, as this non-parametric test is appropriate for small sample sizes and ordinal/semiquantitative clinical data. All patients were recommended a preventive treatment based on SPF50+ sunscreen and topical antioxidants with the aim of avoiding the onset of new lesions and preventing residual hyperpigmentation in the treated areas.

The CRS showed a mean score of 3.9 at the follow-up evaluation. CRS values were calculated using an ordinal 4-point clinical response scale, with complete clearance corresponding to the highest score. Statistical analysis of CRS changes over time was performed using the Wilcoxon signed-rank test for paired samples.

We also compared the cohort of 25 patients with AKs treated with CO_2 laser ablation (and subsequent preventive treatment) to a control group of 25 patients under active surveillance who used only high-SPF sunscreen. At the 2-month follow-up from baseline, 92% of the laser-treated group showed complete lesion clearance and maintenance of clinical resolution, compared with only 30% in the control group. This difference was statistically significant (χ^2 test, $p<0.0001$).

Discussion

Laser therapy is a viable option for the management of widespread AKs and extensive photodamaged skin. De Vries *et al.* (2015) utilized both ablative lasers (CO_2 and Er:YAG) and non-ablative fractional systems.[12] Ablative laser systems remove superficial layers of skin, including epidermal and superficial dermal actinic damage, thus promoting re-epithelialization from adjacent healthy skin and follicular keratinocytes. CO_2 ablative laser also provides cosmetic benefits *via* removal and tightening of photodamaged collagen in the superficial dermis. The main risks of ablative treatment include scarring and dys-pigmentation, which could be reduced by fractional techniques that create micro-columns of ablation or coagulation while sparing surrounding tissue. In our study, no patients developed hypertrophic scarring or post-procedural pigmentary alterations, owing to optimal surgical scar management as described in the *Materials and Methods* section. Both ablative laser resurfacing and fractional non-ablative laser showed effectiveness in reducing AKs and photodamage; clinical experience and comparative studies are favorable. Ablative laser resurfacing also retained a role in field therapy for the treatment of widespread AKs and extensive photodamage. Dermatoscopy can therefore be fundamental in achieving the radicalization of AKs, helping to fully recognize the cancerization field.

As demonstrated by Tai *et al.* (2021), fully ablative laser resurfacing (with CO_2 or Er:YAG lasers) demonstrated superior efficacy compared to fractional ablative techniques in the treatment of AKs. The treatment response rate was approximately 90%, with a recurrence rate of 10-15% at 6 months. Some studies suggested that laser resurfacing monotherapy was less efficacious than photodynamic therapy (PDT), however, it is considered equally effective as topical 5-fluorouracil and 30% trichloroacetic acid (30%).[13]

A prospective study by Micali *et al.* involved 10 patients presenting with a single clinically visible AKs. Patients were treated with imiquimod 3.75% cream, applied once daily to the lesion and to a surrounding 5×5 cm field, administered in two 2-week cycles, separated by a 2-week off-treatment interval, after clinical, dermoscopic, and reflectance confocal microscopy evaluations to detect subclinical lesions. At the end of the intervention, subclinical AKs were detected in 8 out of 10 patients (80%), indicating that field cancerization may be present even when only one AK is clinically evident. The authors therefore suggested that the concept of field cancerization may also apply to solitary clinical AKs, supporting the use of field-directed therapy rather than only lesion-targeted interventions, as performed with CO_2 lasers in our study, where the treatment field was extended to include the peri-lesional erythema.[14]

A study by Yang *et al.*[15] (2018) highlighted the importance of dermoscopic monitoring in assessing treatment response and follow-up of PDT. In confirmation of this, in our clinical study involving 25 AKs treated with CO_2 ablative laser under dermatoscopic guidance, dermoscopy played an even more pivotal role. This is because the extent of CO_2 laser ablation is highly operator-dependent, and only real-time dermoscopic monitoring allows for greater treatment radicality by identifying subclinical margins that are not visible to the naked eye.[15]

In Yang *et al.*'s study, only 2.85% of AKs treated with PDT recurred during follow-up, indicating high therapeutic efficacy under dermatoscopic guidance. This is also confirmed in our study by the minimal rate of recurrence (8%) at 2 months from treatment, with a smaller sample size (25 *vs.* 75 lesions).

In contrast to our dermoscopy-guided CO_2 laser study, in which subclinical margins are precisely ablated, resulting in a remarkably low 8% recurrence rate at 2 months, previous studies such as the randomized trial by Miller & Padilla (2020), which evaluated CO_2 ablative fractional resurfacing without real-time dermoscopic guidance, observed lower treatment radicality and a higher likelihood of persistent lesions. Furthermore, our study achieved a mean CRS score of 3.9, indicating near-complete lesion clearance. This is significantly higher than the outcomes reported in CO_2 laser protocols without dermoscopic support, underlining the critical role of dermoscopy in enhancing efficacy, especially in operator-dependent procedures such as laser ablation.[16]

The identification of the cancerization field in AK is fundamental for effective treatment planning and long-term disease control without any recurrence. Recent evidence from a large prospective study demonstrated that dermoscopy significantly improves the detection of the cancerization field compared with clinical examination alone, with a diagnostic concordance of 96.7% *vs.* 58.1%, with $p<0.001$.[17] This statistically significant improvement highlights dermoscopy as an indispensable tool for delineating subclinical disease margins. Our study, which employs real-time dermoscopic guidance during CO_2 laser ablation, builds upon this principle by enabling precise visualization of subclinical lesions and ensuring maximal treatment radicality. These findings collectively emphasize the critical role of dermoscopy not only in diagnosis but also in guiding operator-dependent therapies to optimize patient outcomes.

Conclusions

We can conclude by underlining how this procedure can be applied for the treatment of Olsen grade I and II AKs, particularly in patients who are not highly compliant with topical therapies based on creams, lotions, or gels, and in those with a limited number of lesions, and therefore with a restricted cancerization field confined to the treated and treatable area, depending on the operator's experience.

CO_2 laser treatment thus proves to be effective in the management of AKs, particularly when performed under dermoscopic guidance, facilitating complete eradication by targeting the entire field of cancerization. When performed by experienced laser specialists, CO_2 laser therapy may help reduce adverse effects associated with topical creams and lotions currently available for the treatment of AKs, especially when combined with appropriate at-home lesion care by the patient. A split-face study could be useful to compare the efficacy of AK treatment under dermoscopic guidance with its counterpart performed without dermoscopy, as well as with topical treatments using creams and lotions, assessing the impact on the field of cancerization and the long-term clinical recurrence rate.

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Figure 1. Video-dermoscopic appearance of an AK of the scalp vertex before the removal procedure using pulsed CO_2 laser (lesion grade: Olsen I).

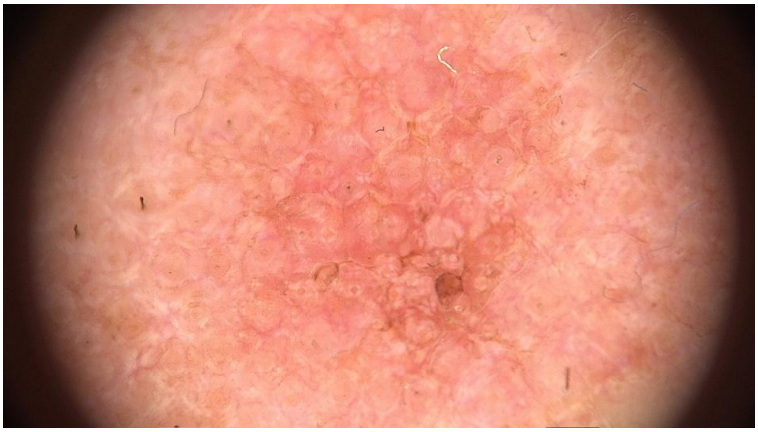

Figure 2. Dermoscopic appearance of an AK of the scalp vertex before CO_2 laser procedure (Olsen grade: II).

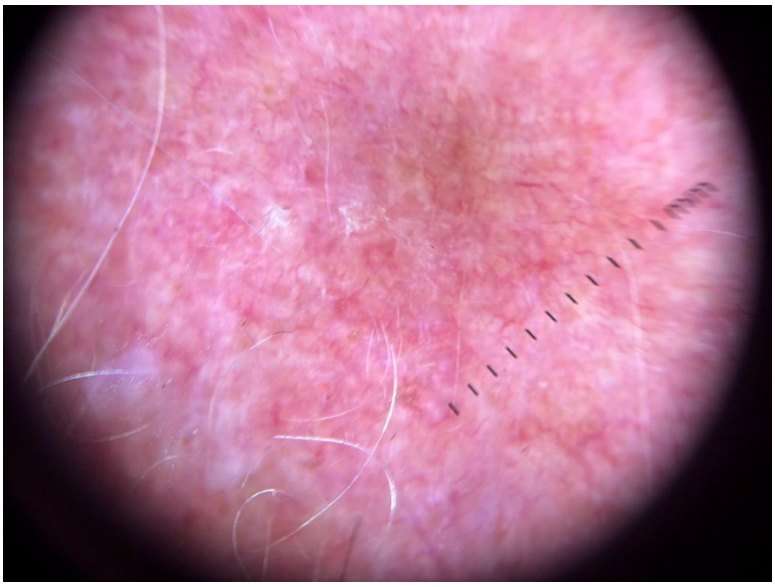

Figure 3. Dermoscopic appearance of an AK of the scalp vertex before CO_2 laser procedure (Olsen grade: II).

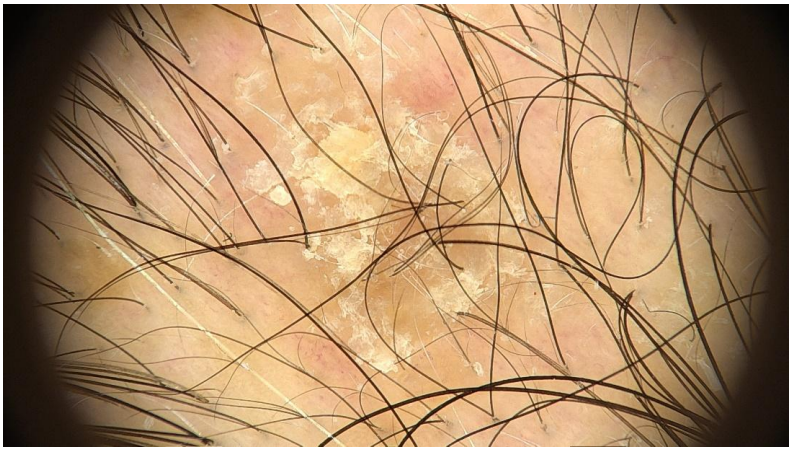

Figure 4. A) Dermoscopic appearance of an AK in the treatment phase (intra-procedural), which shows the lack of complete involvement of the lesion within the laser range (residual erythema on the upper left, compared to the "frost" effect created by the laser on the lesion, a sign of vaporization that has occurred); **B**) dermoscopic appearance of an AK during treatment (intra-procedural), from which the expansion of the laser field of action is evident, compared to the previous image and on the same lesion, allowing the to treat the cancerization field completely, with radical excision of the lesion itself, by subsequent rubbing with sterile gauze.

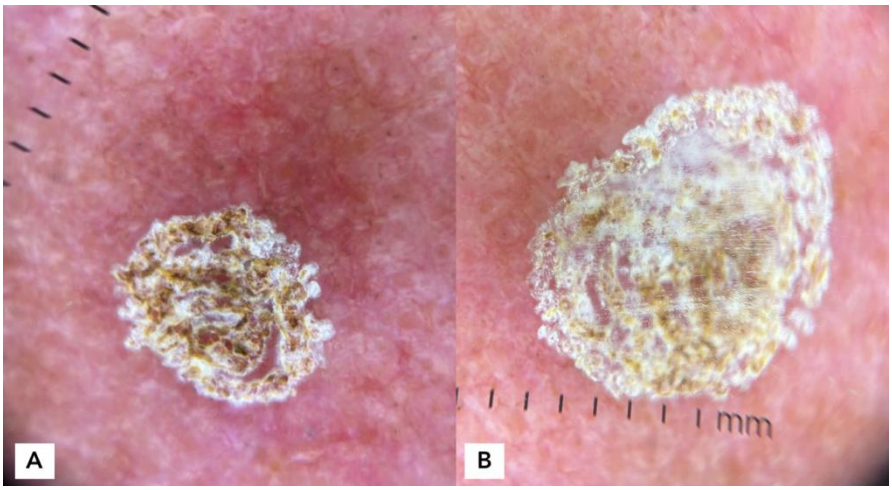

Figure 5. A) Dermoscopic appearance of an AK in the treatment phase (intra-procedural), showing the lack of complete involvement of the lesion within the laser range; **B**) dermoscopic aspect of an AK during treatment (intra-procedural), from which the expansion of the laser field of action is evident, compared to the previous image and on the same lesion; **C**) intra-procedural aspect of the lesion after application of CO_2 laser therapy all over the AK.

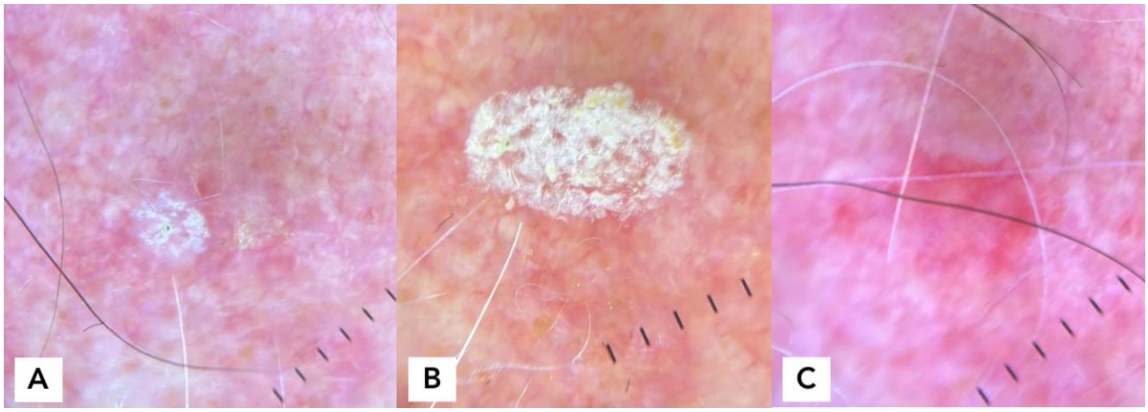

Figure 6. A) Dermoscopic appearance of an AK in the treatment phase (intra-procedural), which shows the lack of complete involvement of the lesion within the laser range; **B**) dermoscopic aspect of an AK during treatment (intra-procedural), from which the expansion of the laser field of action is evident; **C**) intra-procedural aspect of the lesion after application of CO_2 laser therapy all over the AK.

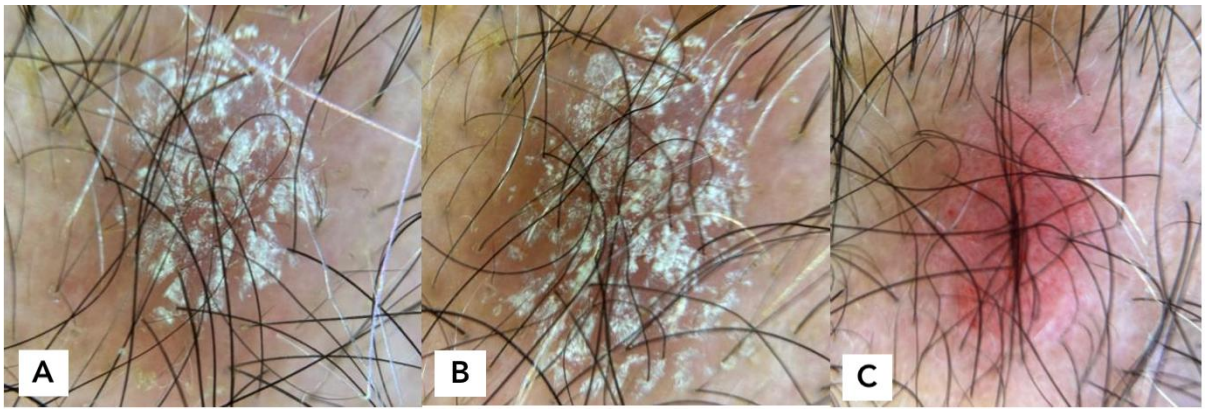

Figure 7. Dermoscopic appearance of the scalp vertex at the fortnightly check-up, showing complete clinical resolution of the AK previously treated with CO_2 laser, under intraprocedural dermoscopic guidance.

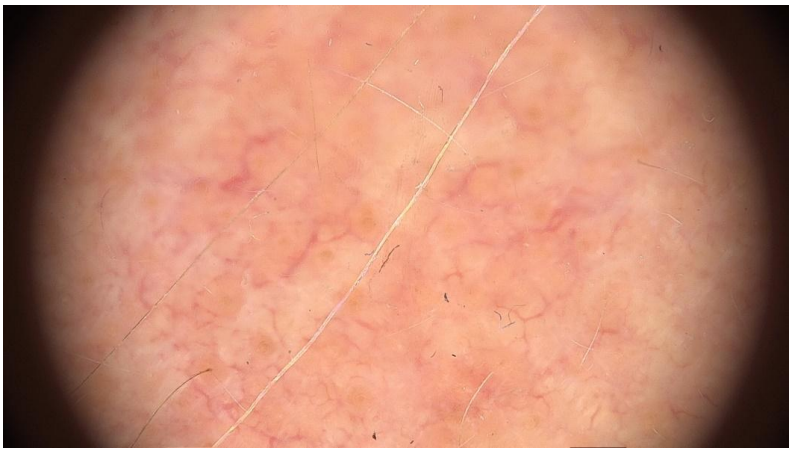

Figure 8. Post-procedural follow-up 2 weeks after application of CO_2 laser therapy on AK of the scalp.