

Effectiveness and tolerability of treatment for isolated actinic keratoses: A retrospective comparison between cryotherapy, CO₂ laser and 5-fluorouracil 0.5%/salicylic acid 10%

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Abstract

Actinic keratoses (AK) have been described as either intraepithelial keratinocytic dysplasia that can evolve into invasive squamous cell carcinoma (SCC) or as in situ SCC that can progress into an invasive form. A retrospective study was conducted to compare outcomes of three different topical therapies for patients with single AK (<4): cryotherapy, CO₂ laser and 5-fluorouracil 0.5%/salicylic acid 10%. We included 72 patients who presented at the Dermatology Clinic of Maggiore Hospital of Trieste between 1 November 2019 and 31 January 2020 for the treatment of AKs. All treatments led to a significant reduction in the average diameter of AK. Pain felt by patients was significantly lower after 5-FU 0.5%/SA 10%. Side effects appeared similarly distributed among the three groups, with erythema and crusts being the most frequent. Aesthetic outcomes were highest in the 5-FU 5%/SA 10% group, as evaluated by both the patient and the operator. Cryotherapy, CO₂ laser and 5-FU 5%/SA 10% were all effective, with no significant efficacy differences among them. Additionally, 5-FU 5%/SA 10% was proved to have the best aesthetic result and to cause the least pain, while necessitating long-term administration. This should be taken into account for patients with low pain tolerance and low treatment adherence. Cryotherapy and CO₂ laser have the advantage of requiring a single session, which might be more suitable for uncooperative patients.

KEYWORDS

5-fluorouracil, actinic keratoses, CO₂ laser, cryotherapy, salicylic acid, treatment

1 | INTRODUCTION

Actinic keratoses (AK) have been described as either intraepithelial keratinocytic dysplasia that can evolve into invasive squamous cell carcinomas (SCC) or as in situ SCC that might progress to an invasive stage.^{1,2} Rates of malignization vary between 0.025% and 16% and the risk of progression to SCC is greater in patients with multiple AKs.³⁻⁵

AKs rarely develop as a single lesion; there are usually several AKs affecting an entire area of photodamaged skin.^{6,7} They can appear as rough, scaly papules, plaques or patches on an erythematous basis,⁸ varying from a few millimeters to more than 2 cm.⁹ The Olsen clinical classification system is based on the thickness of AKs: grade 1 lesions are slightly palpable, grade 2 are moderately thick and grade 3 are very thick, hyperkeratotic lesions.¹⁰

The relationship between AK and SCC is supported by common histological and genetic pathomechanisms. Additionally, more than

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half of the SCCs develop in the vicinity of AKs and it has been documented that 80% of the SCCs evolved from previous AKs.^{11,12} Two progression pathways have been hypothesized: either from type I AK, to types II, III and then to SCC, or directly from type I AK to SCC. However, there is still no consensus on the actual pathomechanism.^{7,13}

Diagnosis can be made based on clinical presentation, patient history and assessment of risk factors.⁸ Additionally, dermatoscopic examination improves diagnosis accuracy,^{14,15} with a 98% sensitivity and 95% specificity.¹⁶

Therapies for AKs are divided into therapies against isolated AKs (<4) or against the field of cancerization.¹⁷ The former, represented by cryotherapy, surgical therapy and CO₂ laser, are based on the physical removal of AK, but do not act against subclinical lesions, which link them to a greater recurrence rate.¹⁸ The latter are used for patients with numerous AKs (>4), can be applied on areas of around 25 cm² and they treat both clinical and subclinical lesions, also known as “cancerization field”. This reduces the likelihood of SCC development and they include 5-Fluorouracil (5-FU), diclofenac, imiquimod, photodynamic therapy (PDT), chemical peeling, metubate ingenol and retinoids.^{8,12,18}

2 | MATERIALS AND METHODS

A retrospective study was performed with the aim of comparing the outcomes of three different topical therapies which have been used to treat patients with single AK (<4): cryotherapy, CO₂ laser and 5-Fluorouracil 0.5% /Salicylic Acid 10% (5-FU 5%/SA 10%).

The aim of this study was to retrospectively analyze whether there were differences in terms of clinical efficacy, side effects, treatment compliance and pain, among the three common therapies mentioned above (cryotherapy—CO₂ Laser—5-FU 5%/SA 10%).

We included patients who had previously underwent PDT or laser therapy in a 90-day period, from 1 November 2019 to 31 January 2020, at the Dermatology Clinic of Maggiore Hospital of Trieste. No limits on sex, age and phototype were imposed. Immunocompromised patients, as well as patients whose medical records were incomplete were excluded.

The diagnosis of actinic keratoses was performed by dermatoscopic examination; in doubtful cases, a skin biopsy with histological confirmation was performed.

Only records of patients who had given informed consent for the acquisition of photographic images and medical data were included. Relevant data were selected: age, sex, phototype, clinical and dermatoscopic images, lesion diameter measurements, local treatment, VAS pain scales, adverse effects, satisfaction with the aesthetic result. Photographs of all lesions were taken during the first visit and at follow-ups. Aesthetic improvement was assessed by both the patient and the operator. Clinical images were captured using Canon EOS 90D (Japan) camera and dermatoscopic images, as well as lesion diameter measurements were obtained using Dermlite 3Gen, x20 (California, USA).

A total of 27 patients were treated with 5-FU 5%/SA 10%, 21 patients with cryotherapy and 24 patients with CO₂ laser. Primary outcomes were: average lesion diameter at 30 days and at 12 weeks follow-up; treatment response interpreted as either complete (100%), partial (>75%) or non-existent; secondary outcomes were: VAS pain scales, satisfaction with aesthetic results interpreted by both the patient and the operator, the presence of adverse effects, in the form of erythema, skin maceration, vesicles, crusts, hypo- or hyper-pigmented areas, burning or itching sensation were noted. Satisfaction with aesthetic results evaluations were expressed as either excellent, good, moderate or poor.

The results were expressed as mean and SD in case of continuous numerical variables and as frequency of values in case of categorical variables. Comparisons between treatment groups were carried out using Student t test for continuous numerical variables and chi square test for categorical variables. The predetermined significance level ($P < .05$) was redetermined by applying Bonferroni correction for multiple statistical tests, for which P values of less than .00079 were considered significant.

3 | RESULTS

Seventy-two patients (55 male, 17 female) were enrolled: 27 treated with 5-FU 5%/SA 10%, 24 with CO₂ laser and 21 with cryotherapy. Tables 1-3 and Figures 1-3 show patient characteristics, treatment outcomes and statistical significance levels. The three groups were homogeneous in male: female ratio, phototype and lesion diameter measurements, while the average age in the laser group was significantly lower than in the cryotherapy ($P = .0003$) and 5-FU 5%/SA 10% groups ($P = .002$).

All treatments were effective (Table 2) at inducing significant diameter reduction at the 30-day follow-up visit, as compared to baseline, with P values less than .00079 (P -value compared to baseline: 1.2×10^{-9} for lasers, 1.2×10^{-7} for cryotherapy, 1.1×10^{-8} for 5-fluorouracil). Additionally, significant diameter reduction was observed at the 12-week follow-up visit, as compared to baseline and compared to the 30-day follow-up visit: P values for CO₂ laser were

TABLE 1 Characteristics of patients in the three treatment groups studied

	Laser	Cryotherapy	5-FU/SA
No. of patients	24	21	27
Sex			
M	17	17	21
F	7	4	6
Mean age (years)	64.2 ± 9.8	75.3 ± 9.1	74.3 ± 12.2
Phototype			
I	0	3	3
II	16	13	16
III	8	5	8

TABLE 2 Treatment response and side effects

	Laser (n = 24)	Cryotherapy (n = 21)	5-FU/SA (n = 27)
Average lesion diameter (mm) before treatment	7.3 ± 4.0	8.9 ± 3.1	10.4 ± 9.0
At 30 days follow-up	2.8 ± 3.1	5.4 ± 3.6	7.8 ± 8.4
At 12 weeks follow-up	1.1 ± 1.7	3.6 ± 3.8	3.2 ± 7.8
VAS after therapy	5.1 ± 1.8	4.9 ± 2.2	1.7 ± 1.6
Treatment duration (days)	1	1	72.9 ± 20.0
Side effects			
Erythema	24	20	27
Crusts	24	18	19
Heartburn	5	8	11
Itch	13	6	5
Maceration	0	5	7
Vesicles	0	1	2
Hypopigmentation	4	2	2
Hyperpigmentation	5	4	2
Treatment response			
Complete	15	7	17
Partial (> 75%)	9	6	7
Nonexistent	0	8	3
Aesthetic result (operator judgment)			
Excellent	5	7	15
Good	17	11	9
Moderate	1	2	4
Poor	1	1	0
Aesthetic result (patient judgment)			
Excellent	2	1	20
Good	20	16	5
Moderate	1	5	1
Poor	1	0	1

9.4×10^{-10} and .00081, respectively; for cryotherapy they were 10^{-8} and .0003, for 5-fluorouracil 7.8×10^{-11} and 6.5×10^{-8} . The exception here is in the case of CO₂ laser, for which the *P* value at the second follow-up visit, of .00081 was marginally not statistically significant. However, CO₂ laser and 5-FU 5%/SA 10% seemed to give the best results: a complete response (CR) was obtained in 62.5% of the patients treated with the CO₂ laser, 62.9% of the patients treated with 5-FU 5%/SA 10% and only in 33.3% of the patients treated with cryotherapy. In the cryotherapy group there were eight null responses, against three null responses obtained with 5-FU 5%/SA 10% and 0 with CO₂ laser.

The comparison between the therapies showed no significant differences in efficacy (Table 3). However, the results obtained with CO₂ laser were better at the first follow-up visit and, to a lesser extent, at the second follow-up visit, as compared to cryotherapy (*P* = .013 and *P* = .0011, respectively) and 5-FU 5%/SA 10% (*P* = .007 and *P* = .19, respectively).

5-FU 5%/SA 10% was also associated with the least pain, as measured using VAS pain scales. Patients indicated an average value of

1.7 ± 1.6 after treatment. Otherwise the pain reported in the CO₂ laser, as well as in the cryotherapy group was 5.1 ± 1.8 and 4.9 ± 2.2 , respectively. This difference, which was significant during the statistical analysis of drug comparison, with a *P* value less than .00079 in both comparisons (*P* = 3.7×10^{-9} and *P* = 2×10^{-6} , respectively), was directly linked to the method of application. 5-FU 5%/SA 10% was applied daily for 72 days on average, while cryotherapy and CO₂ laser therapy were performed in a single session.

Side effects appeared similarly distributed among the three groups, both qualitatively and quantitatively (Table 2). Erythema and crusts were the most frequent (Figures 1 and 3), followed to a much lesser extent by itching or burning sensation.

A statistically significant difference regarding the aesthetic outcome was obtained: in the evaluation carried out by the patient, 5-FU 5%/SA 10% reported an excellent result in 20 of 27 cases, against 1 of 21 in the cryotherapy group and 2 of 24 in the CO₂ laser group, with *P*-values $<10^{-300}$ in both comparisons. Similar results were obtained through operator evaluation, reporting 15 excellent results in the 5-FU 5%/SA 10% group, 7 in the cryotherapy group and 5 in

	Cryotherapy vs Laser	Cryotherapy vs 5-FU	Laser vs 5-FU/SA
Sex	0.40	0.86	0.64
Age	0.0003	0.75	0.002
Phototype	0.18	0.84	0.35
Average diameter before treatment	0.14	0.42	0.11
At 30 days follow-up	0.013	0.19	0.007
At 12 weeks follow-up	0.0011	0.82	0.19
VAS after therapy	0.71	2×10^{-6}	3.7×10^{-9}
Side effects			
Erythema	0.23	0.22	0.5
Crusts	0.047	0.30	0.005
Heartburn	0.26	0.89	0.11
Itch	0.10	0.40	0.006
Maceration	0.008	0.87	0.007
Vesicles	0.23	0.79	0.35
Hypopigmentation	0.53	0.81	0.30
Hyperpigmentation	0.86	0.30	0.17
Response to treatment	0.002	0.006	0.28
Aesthetic result			
Operator judgment	0.63	0.23	0.007
Patient judgment	0.23	0	0

TABLE 3 Significance of differences between the three treatment groups studied

Note: Significant values after Bonferroni correction are shown in bold.

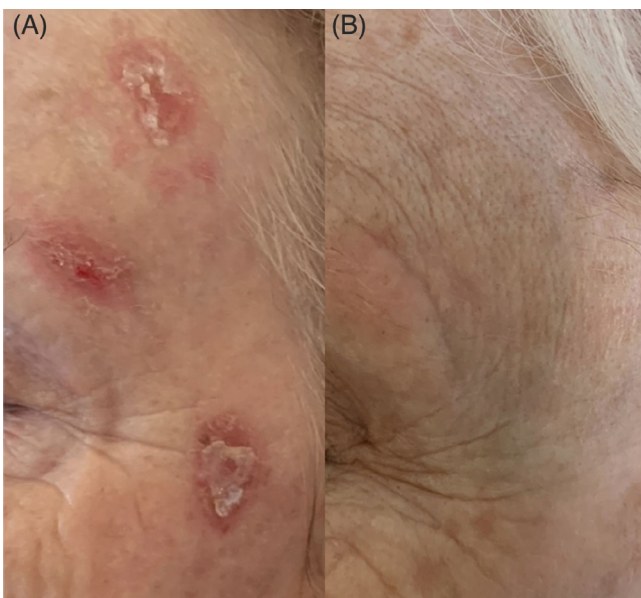


FIGURE 1 A and B, Before and after treatment with 5-FU 5%/SA 10% therapy, showing an excellent result achieved with the topical treatment

the CO₂ laser group, even though not statistically significant. Thus, 5-FU 5%/SA 10% generated the most satisfying aesthetic outcomes, as evaluated by both the patient and the operator.

4 | DISCUSSION

AK are common lesions caused by cumulative sun exposure and they appear on sun-damaged skin,¹⁹⁻²¹ with a 2-3 times higher risk of developing AK in people working outdoors.^{22,23} Numerous risk factors influence the development of AK: sex, age, skin type, particularly Fitzpatrick skin types 1 and 2,²⁴⁻²⁷ genetic disorders^{28,29} previous history of NMSCs^{22,26} and immunosuppression.³⁰ Dermatoscopically, they every so often exhibit the well-known “strawberry pattern”.^{7,31} Vascular pattern analysis can aid in the differentiation between AKs and seborrheic keratoses, Bowen's disease and non-pigmented BCCs.^{32,33} Additionally, it can identify the first signs of invasive SCC, typified by the presence of dotted vessels around hair follicles, as well as in situ SCC, in which dotted/coiled vessels evolve into glomerular vessels and the follicular openings miniaturize and finally disappear.^{34,35}

In doubtful cases, histopathological evaluation or reflectance confocal microscopy (RCM) may be useful. RCM presents good accuracy in AK diagnosis and it has been used both in monitoring AK treatment and in the evaluation of the field of cancerization. In fact, the in vivo examination allows the observation of stratum corneum, in which typical features of AK, like the disruption of the stratum corneum, presence of isolated keratinocytes, polygonal cells, or a honeycomb arrangement can be seen.³⁶

In our study, all therapeutic modalities have proven to be effective in the treatment of isolated actinic keratoses. Statistical analysis

FIGURE 2 AK before (A and B), during (C and D) and after (E and F) cryotherapy and its dermatoscopic patterns

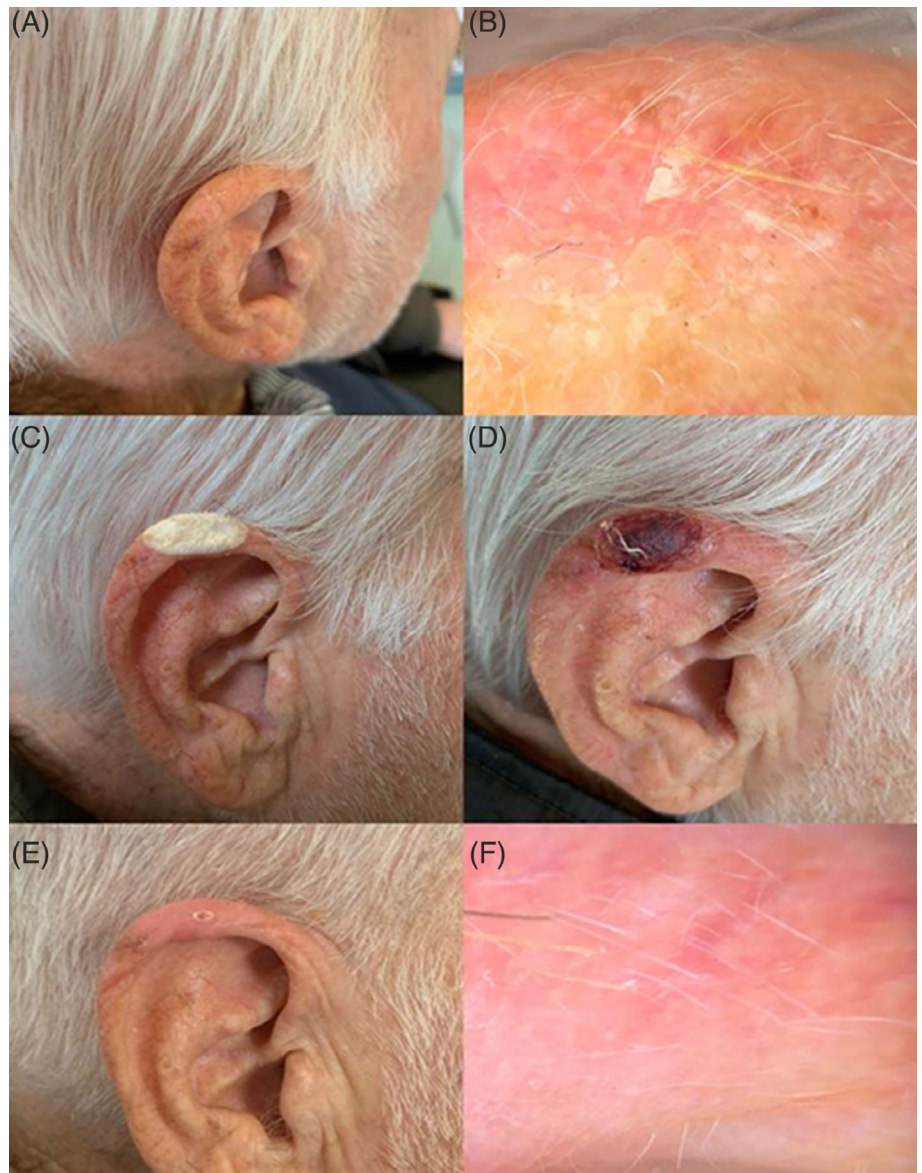


FIGURE 3 Side effects developed during 5-FU 5%/SA 10% therapy



did not find significant differences in treatment effectiveness: all therapies led to a significant reduction in the average lesion diameter at 30 days follow-up and these results further improved at 12 weeks follow-up. However, CO₂ laser and 5-FU 5%/SA 10% seemed to give the best results, quantified by measurement of complete response rates. These results contrast with those of a similar study carried out at the dermatological clinic of the University of Brescia, which reported better CR rates for cryotherapy rather than for CO₂ laser: 78.2% vs 72.4%.³⁷ It should be noted, however, that laser technology has been improved since the Brescia study was carried out, which might explain our results. Additionally, taking into account that both CO₂ laser and cryotherapy are operator-dependent techniques, a larger variability of clinical results is expected.

Pain felt by patients was significantly lower after 5-FU 5%/SA 10% treatment as compared to CO₂ laser and cryotherapy. The onset of side effects appeared to be superimposable both in frequency and in clinical manifestation: in all three groups erythema and excoriations were the most frequent, while burning and itching sensations were occasional. 5-FU 5%/SA 10% was significantly superior to CO₂ laser and cryotherapy in terms of patient satisfaction with the aesthetic results.

5 | CONCLUSIONS

Actinic keratoses (AKs) are among the most frequent keratinocytic tumors requiring treatment even in the early stages, given the likelihood of progression to squamous cell carcinoma (SCC). The therapeutic goal is to eradicate clinically visible lesions, reduce the number of recurrences and to prevent SCC transformation. Among the available treatments, we distinguish between treatments directed *at the lesion* and treatments directed *at the field of cancerization*. The most frequent topical therapies include laser therapy, cryotherapy, curettage, diclofenac 3% gel, 5-fluorouracil, chemical peels, imiquimod and photodynamic therapy.³⁸

In our study, we compared cryotherapy, CO₂ laser and 5-FU 5%/SA 10%; they were all effective, with no significant efficacy differences among them. Additionally, 5-FU 5%/SA 10% was proved to have the best aesthetic result and to cause the least pain, while necessitating long-term administration. This should be taken into account for patients with low pain tolerance and low treatment adherence. Cryotherapy and CO₂ laser have the advantage of requiring a single session, which might be more suitable for uncooperative patients.

Further comparative investigations of the therapy outcomes and trend analysis (complete response to therapy, lesion diameter reduction and aesthetic evaluation) should be conducted through prospective studies and larger statistical samples.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Claudio Conforti: Writing, original draft preparation. **Roberta Giuffrida:** Writing, original draft preparation. **Caterina Dianzani:** Investigation. **Fabrizio Guarneri:** Resources. **Giovanni Francesco Marangi:** Methodology. **Neagu Nicoleta:** Visualization. **Paolo Persichetti:** Supervision. **Iris Zalaudek:** Conceptualization. **Nicola di Meo:** Writing, review and editing.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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