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The use of in vivo reflectance confocal microscopy and dermoscopy in the diagnosis of actinic keratosis, squamous cell carcinoma in situ, and invasive squamous cell carcinoma and its variants

PhD THESIS SUMMARY

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Content

1. Introduction

Actinic keratoses and cutaneous squamous cell carcinoma represent major entities within keratinocyte-derived pathology induced by chronic photoexposure, and are regarded as distinct stages within the same continuum of cutaneous carcinogenesis. Actinic keratosis is a premalignant intraepidermal lesion characterized by atypical keratinocyte proliferation and by a variable potential for progression to invasive squamous cell carcinoma. Its clinical relevance derives from its high prevalence in the elderly population, particularly among individuals with fair skin phototypes and cumulative ultraviolet exposure, as well as from its role as a marker of cutaneous field cancerization.

Cutaneous squamous cell carcinoma is one of the most common non-melanoma skin cancers and frequently develops in the setting of pre-existing actinic lesions. Although the prognosis is favorable in cases diagnosed at an early stage, certain forms may display biological aggressiveness, characterized by deep invasion, recurrence, perineural or lymphovascular invasion and, less frequently, metastatic dissemination. Risk assessment is based on parameters such as tumor diameter and thickness, degree of differentiation, anatomical site, depth of invasion and immunological status.

Chronic exposure to ultraviolet radiation, particularly UVB radiation, induces the accumulation of molecular alterations in keratinocyte DNA, thereby disrupting the mechanisms involved in cellular proliferation, differentiation and apoptosis. The diagnosis of actinic keratoses is predominantly clinical, supplemented by dermoscopy and, in selected cases, by in vivo reflectance confocal microscopy. In cutaneous squamous cell carcinoma, histopathological examination remains essential for diagnostic confirmation and prognostic stratification.

In this context, the present thesis aims to analyze the clinicopathological characteristics of actinic keratoses and cutaneous squamous cell carcinomas, as well as to evaluate the role of dermoscopy and reflectance confocal microscopy in early diagnosis, identification of high-risk lesions and personalization of therapeutic management.

2. Hypothesis and general objectives

The present study aims to provide an integrated evaluation of keratinocyte-derived proliferations, including keratoacanthoma, squamous cell carcinoma in situ, invasive cutaneous squamous cell carcinoma, and their main variants. These entities represent a significant diagnostic

challenge, largely due to the frequent overlap of their clinical and dermoscopic features. In this context, establishing an early and accurate differential diagnosis is essential for the prompt initiation of appropriate therapeutic management, with a direct impact on patients' quality of life and prognosis.

Although the literature describes dermoscopic criteria suggestive of keratoacanthoma and cutaneous squamous cell carcinoma, their diagnostic accuracy remains limited when used in isolation. In this setting, in vivo reflectance confocal microscopy emerges as a non-invasive imaging technique with superior diagnostic potential, capable of providing additional information regarding lesion architecture and cytological features. The integration of this method may contribute to reducing the number of biopsies and excisions performed solely for diagnostic purposes, thereby decreasing the morbidity associated with invasive procedures and facilitating the selection of optimal treatment.

The rationale for this research is supported by the high prevalence and increasing incidence of proliferations originating from keratinocytes of the spinous layer, the socio-economic burden of cutaneous squamous cell carcinoma, and the absence of systematic national databases. Furthermore, the lack of large-scale studies integrating confocal microscopy into the assessment of these lesions has generated a knowledge gap regarding the relationship between confocal, dermoscopic, and histopathological features.

The general objectives of the research included the analysis of demographic and clinical characteristics of the study cohorts, the identification of risk factors involved in the pathogenesis of keratoacanthoma and squamous cell carcinoma, the detailed assessment of histopathological features relevant to disease evolution and prognosis, and the characterization of findings detectable by in vivo reflectance confocal microscopy. The study also aimed to correlate dermoscopic and confocal features in order to assess the complementarity of these methods and to develop severity criteria with practical clinical utility.

The research was structured into three main directions: a retrospective epidemiological study designed to define the clinico-histological profile of patients with keratoacanthoma in Romania; a similar retrospective study focused on the characterization of cutaneous squamous cell carcinoma; and a prospective study dedicated to the clinical, dermoscopic, and confocal evaluation

of keratoacanthoma, with the aim of developing a severity score applicable in routine dermatological practice.

3. General research methodology

The subjects included in the research were recruited from among patients evaluated and treated within the Department of Oncologic Dermatology, Allergology and Clinical Immunology and the Department of Plastic Surgery and Reconstructive Microsurgery of Elias University Emergency Hospital, Bucharest. The epidemiological studies included histopathologically confirmed cases of keratoacanthoma and cutaneous squamous cell carcinoma diagnosed between January 2018 and May 2025. The research was conducted in accordance with the principles of the Declaration of Helsinki and with national and international regulations concerning patients' rights and good medical practice. The study was approved by the Department of Dermato-Oncology and by the Ethics Committee of Elias University Emergency Hospital, decision no. 1179/25.02.2025. Eligible patients were included only after informed consent had been obtained.

The first study aimed to define the clinico-epidemiological and histopathological profile of patients with keratoacanthoma in Romania. A descriptive retrospective analysis was performed on histopathologically confirmed cases admitted and treated between January 2018 and December 2023. Inclusion criteria comprised age over 18 years and the availability of sufficient clinical, epidemiological and histopathological data. Cases with incomplete information, incomplete excision, punch biopsy without full lesion characterization or uncertain histopathological diagnosis were excluded. The collected clinical variables included age, sex, residence environment, anatomical site, comorbidities and the presence of ulceration. The histopathological parameters assessed included lesion size, histological subtype, KIN grade, cyto-nuclear pleomorphism, characteristics of the peritumoral inflammatory infiltrate and the severity of perilesional solar elastosis.

The second study focused on defining the clinico-histological profile of patients with cutaneous squamous cell carcinoma. It was designed as a retrospective descriptive analysis based on medical records and electronic files of patients with histopathologically confirmed diagnoses treated during the same period. Inclusion required age over 18 years, a definite histopathological diagnosis of cutaneous squamous cell carcinoma and complete relevant data. Cases with incomplete excision, incisional biopsies insufficient for assessment of tumor architecture,

incomplete clinical data or uncertain diagnosis were excluded. Clinical variables included demographic data, residence environment, lesion site, comorbidities, smoking status and ulceration. Histopathological assessment included tumor subtype, diameter, degree of differentiation, depth of invasion, lymphovascular and perineural invasion, cyto-nuclear pleomorphism, inflammatory infiltrate and perilesional tissue changes, including solar elastosis and adjacent actinic keratoses.

The third study was designed as a cross-sectional observational study, aiming to evaluate keratoacanthoma clinically, dermoscopically and by in vivo reflectance confocal microscopy, as well as to develop severity scores. Adult patients with clinical, dermoscopic and confocal diagnosis of keratoacanthoma, evaluated between July 2021 and June 2025, were included. Exclusion criteria comprised recent local treatment, uncertain diagnosis, incomplete data or refusal to provide informed consent. Clinical assessment included demographic data, lesion site and Olsen grade. Dermoscopy was performed using a Dermlite DL4 device and the dermoscopic module of the confocal microscope. Linear wavy vessels, microerosions, the "strawberry" pattern, scales and diffuse erythema were evaluated, each parameter being scored from 0 to 3, with a total score ranging from 0 to 15. In vivo reflectance confocal microscopy, performed with the Vivascope 1500 system, assessed atypical honeycomb architecture, inflammatory infiltrate, superficial dermal solar elastosis, nuclear atypia and central dark areas of parakeratosis, using the same severity scale.

Statistical analysis was performed using SPSS Statistics for Mac, version 30.0. Variables were analyzed according to their nominal, ordinal or quantitative nature, using appropriate tests, including Chi-square, Fisher's exact test, Mann–Whitney U test and uni- or multivariate logistic regression models. Results were expressed as mean ± standard deviation, median and range, with statistical significance set at $p < 0.05$. Data were summarized in tables and graphs, facilitating comparison with the literature and supporting the scientific validity of the conclusions.

4. Results

4.1. First study – Clinico-histological profile of the patient with AK in Romania

The analyzed cohort included 58 cases of keratoacanthoma, with a relatively balanced sex distribution, although a slight male predominance was observed: 32 male patients, representing

55.2%, and 26 female patients, accounting for 44.8%. Patient age ranged from 55 to 90 years, with an overall mean age at diagnosis of 76.36 ± 7.84 years. This demographic profile supports the association between keratoacanthoma and advanced age and, implicitly, cumulative ultraviolet exposure, a central factor in the pathogenesis of actinic lesions. Female patients had a slightly higher mean age at diagnosis compared with male patients, 77.58 ± 7.5 years versus 75.38 ± 8.08 years, respectively. Most cases were diagnosed in patients over 70 years of age, underscoring the need for periodic dermatological surveillance in elderly populations, particularly in individuals with a significant history of occupational or recreational photoexposure.

From a clinical perspective, only 17 of the 58 cases, representing 29.31%, were initially classified as suspected keratoacanthoma at admission. This relatively low proportion reflects the difficulty of clinical diagnosis, largely due to the overlap between the clinical appearance of keratoacanthoma and that of other cutaneous lesions, including entities with malignant potential. Therefore, histopathological confirmation remains essential in persistent, hyperkeratotic, ulcerated, rapidly evolving lesions or in those with atypical clinical features.

With regard to lesion size, small lesions predominated: 31 cases, corresponding to 53.45%, had a diameter below 1 cm. Lesions measuring between 1 and 2 cm were identified in 18 patients, representing 31.03%, while lesions between 2 and 3 cm were observed in 9 patients, accounting for 15.52%. The predominance of subcentimetric lesions may suggest diagnosis at a relatively early stage, although clinical size does not always reflect the severity of histopathological changes. Anatomical distribution confirmed the predilection of keratoacanthoma for photoexposed areas, with the head and neck region involved in 51 cases, representing 87.9%. The limbs were affected in 6 cases, whereas the trunk was involved in a single case. This distribution reinforces the role of ultraviolet radiation and highlights the importance of careful examination of the face, scalp, auricle, lips and neck in elderly patients.

Histopathological analysis revealed a predominance of the hypertrophic form of keratoacanthoma, identified in 35 cases, corresponding to 60.3%. This was followed by the atrophic form, present in 16 cases, the bowenoid variant in 4 cases and the lichenoid variant in 3 cases. The predominance of the hypertrophic subtype is clinically relevant, as these lesions, due to marked hyperkeratosis, may pose diagnostic difficulties in relation to early forms of cutaneous squamous cell carcinoma.

The severity of dysplasia was assessed using the Keratinocyte Intraepidermal Neoplasia system. In the studied cohort, KIN II was the most frequent grade, identified in 24 cases (41.38%). KIN I was present in 20 patients, while KIN III was observed in 14 patients. Thus, nearly two thirds of the lesions exhibited moderate or severe dysplasia, supporting the importance of early diagnosis and appropriate treatment in preventing progression to cutaneous squamous cell carcinoma.

Solar elastosis was present in all cases, confirming the close relationship between keratoacanthoma and chronic photoexposure. Severe elastosis was observed in 28 lesions, moderate elastosis in 22 cases and mild elastosis in 8 cases. These data indicate that most lesions developed on a cutaneous background with significant ultraviolet-induced dermal damage. Cyto-nuclear pleomorphism was predominantly mild or moderate: 24 lesions showed mild pleomorphism, 28 showed moderate pleomorphism and 6 showed severe pleomorphism, suggesting that most cases were identified during early or intermediate stages of dysplastic transformation.

The peritumoral inflammatory infiltrate was mainly of moderate intensity, observed in 33 cases, followed by marked infiltrate in 17 cases and mild infiltrate in 8 cases. Most lesions did not exhibit ulceration, with 40 of the 58 cases showing an intact surface epithelium. The absence of ulceration supports the non-invasive character of most lesions, whereas its presence should be interpreted with caution, as it may suggest biological aggressiveness, secondary trauma or malignant transformation.

The analysis of comorbidities included smoking, cardiovascular disease, diabetes mellitus and oncological history. Smoking was documented in 8 patients, although this proportion may be underestimated due to incomplete recording of smoking status. The association between smoking and labial localization was notable: 4 of the 8 smokers had lesions located on the lips, and among the 6 labial cases, 4 were associated with smoking. Cardiovascular comorbidities were present in 35 patients, most likely related to the advanced age of the cohort. Diabetes mellitus was identified in 8 patients, while a history of malignancy was recorded in 11 patients, possibly reflecting both the increased susceptibility of oncological patients and the profile of the medical institution.

Correlation of KIN grade with clinico-histological parameters revealed significant associations. KIN I and KIN III predominated in men, whereas KIN II was more frequent in

women, the difference being statistically significant. The relationship between KIN grade and pleomorphism was strong: KIN I was almost constantly associated with mild pleomorphism, whereas KIN II and KIN III were predominantly correlated with moderate pleomorphism. Moreover, the severity of solar elastosis increased with the degree of dysplasia, with all KIN III lesions showing severe elastosis. The inflammatory infiltrate was predominantly lymphoplasmacytic; however, its severity increased progressively with KIN grade, suggesting amplification of the local immune response as epithelial atypia became more pronounced.

Overall, the results define keratoacanthoma as a lesion predominantly occurring in elderly patients, mainly localized on photoexposed areas, frequently associated with marked solar elastosis and moderate dysplastic changes. The correlations identified between KIN grade, pleomorphism, elastosis and inflammatory infiltrate support the role of chronic photoexposure in the histological progression of these lesions and emphasize the utility of rigorous histopathological assessment for risk stratification and therapeutic decision-making.

4.2. Second study – Clinico-histological profile of the patient with SCC in Romania

The analyzed cohort included 148 patients diagnosed with cutaneous squamous cell carcinoma, with a male predominance: 90 men (60.8%) and 58 women (39.2%). Patient age ranged from 23 to 97 years, with a mean age of 74.72 years. Although these data confirm the predominantly geriatric profile of cutaneous squamous cell carcinoma, the main relevance of the study lies in the analysis of associations between clinical and histopathological parameters and factors with potential prognostic value.

Anatomically, lesions were predominantly located in the head and neck region, which accounted for 121 of the 148 tumors (81.8%), followed by the limbs (10.8%) and trunk (7.4%). This distribution supports the role of cumulative photoexposure in the etiopathogenesis of cutaneous squamous cell carcinoma, an assumption further reinforced by the presence of solar elastosis in all analyzed cases. However, the association between anatomical site and histological subtype did not reach statistical significance ($p = 0.366$), suggesting that the predilection for

photoexposed areas was shared by most histological variants, without significant topographical differences between subtypes.

In contrast, histological subtype was significantly associated with tumor size ($\chi^2 = 13.406$; $p = 0.037$; Cramér's V = 0.213; Phi = 0.301), with a weak to moderate effect size. Conventional squamous cell carcinoma, NOS, and the keratoacanthoma-like variant were more frequently encountered in pT1 and pT2 categories, whereas the acantholytic subtype tended to be associated with larger tumors, corresponding to pT3. This finding may indicate a more aggressive biological profile of the acantholytic variant, although the limited number of cases requires cautious interpretation.

A statistically significant association was also identified between histological subtype and tumor differentiation grade ($\chi^2 = 18.936$; $p = 0.004$; Cramér's V = 0.253; Phi = 0.358). Keratoacanthoma-like lesions were predominantly well differentiated, while NOS tumors showed a more balanced distribution across G1, G2 and G3 categories. This correlation supports the existence of distinct morphological patterns among histological subtypes and suggests that subtype classification may contribute to risk stratification, particularly when interpreted alongside tumor size and depth of invasion.

Tumor differentiation grade correlated significantly with cyto-nuclear pleomorphism ($\chi^2 = 18.178$; $p = 0.001$; Cramér's V = 0.248; Phi = 0.350), confirming the relationship between loss of differentiation and increasing cytological atypia. Tumor grade was also significantly associated with tumor size ($\chi^2 = 13.691$; $p = 0.008$; Cramér's V = 0.215; Phi = 0.304), suggesting that larger tumors tend to exhibit a higher degree of dedifferentiation and a more aggressive morphological profile.

Tumor thickness represented another parameter of major prognostic relevance. It ranged from 0.5 to 43 mm, with a mean value of 8.31 mm. Mean tumor thickness increased progressively with depth of invasion, from 3.11 mm in tumors limited to the superficial dermis to 6.71 mm in those invading the deep dermis, 9.82 mm in tumors extending into the hypodermis and 14.03 mm in cases with striated muscle invasion. The Kruskal–Wallis test demonstrated statistically significant differences between groups defined by invasion depth ($p < 0.001$). Pairwise comparisons confirmed significant differences between superficial dermal invasion and all deeper levels, as well as between deep dermal invasion and hypodermal or muscular invasion ($p < 0.001$),

while the difference between hypodermal and muscular invasion was not statistically significant ($p = 0.488$). These findings indicate that tumor thickness accurately reflects local deep extension and may be considered a robust histopathological marker of local aggressiveness.

Lymphovascular invasion was present in 21 patients (14.2%) and was significantly associated with tumor thickness, the mean value being almost twice as high in positive cases compared with tumors without lymphovascular invasion (13.52 mm versus 7.45 mm; $p < 0.001$). Furthermore, the frequency of lymphovascular invasion increased progressively with tumor diameter, from 2.94% in pT1 tumors to 11.11% in pT2 and 66.67% in pT3 tumors, with a statistically significant association ($\chi^2 = 26.566$; $p < 0.001$; Cramér's V = 0.424; Phi = 0.424). This result supports the relationship between increased tumor volume, local extension and the likelihood of vascular or lymphatic structure invasion.

Perineural invasion was identified in 31 patients (20.9%) and showed multiple significant associations with parameters of tumor aggressiveness. Most notably, perineural invasion strongly correlated with lymphovascular invasion ($\chi^2 = 71.450$; $p < 0.001$; Cramér's V = 0.695; Phi = 0.695), with 19 of the 31 cases showing both features. This strong association suggests the existence of a biologically aggressive tumor subset characterized by increased capacity for invasion of deep anatomical structures. In addition, mean tumor thickness was significantly higher in cases with perineural invasion than in those without it (13.66 mm versus 6.89 mm; $p < 0.001$). Tumor diameter was also significantly associated with perineural invasion ($\chi^2 = 45.824$; $p < 0.001$; Cramér's V = 0.556; Phi = 0.556), as was tumor grade ($\chi^2 = 10.055$; $p = 0.007$; Cramér's V = 0.261; Phi = 0.261). These findings confirm that perineural invasion is more frequently encountered in larger, thicker and less differentiated tumors.

Solar elastosis, present in all lesions, was predominantly severe or moderate. Its severity was significantly associated with tumor diameter ($\chi^2 = 21.358$; $p < 0.001$; Cramér's V = 0.269; Phi = 0.380), adjacent actinic keratoses ($\chi^2 = 6.801$; $p = 0.033$; Cramér's V = 0.214; Phi = 0.214), histological subtype ($\chi^2 = 12.962$; $p = 0.044$; Cramér's V = 0.209; Phi = 0.296), cyto-nuclear pleomorphism ($\chi^2 = 35.498$; $p < 0.001$; Cramér's V = 0.346; Phi = 0.346) and depth of invasion ($\chi^2 = 18.908$; $p = 0.004$; Cramér's V = 0.253; Phi = 0.357). Tumors invading the hypodermis or striated muscle more frequently showed severe elastosis, suggesting that marked dermal

photodamage may represent an indirect marker of a cutaneous field predisposed to more invasive tumors.

The peritumoral inflammatory infiltrate also demonstrated relevant associations. The type of infiltrate correlated significantly with its severity ($\chi^2 = 13.983$; $p < 0.001$; Cramér's V = 0.307; Phi = 0.307), with polymorphous infiltrates being more frequently severe. Infiltrate severity was associated with tumor diameter ($p = 0.003$), cyto-nuclear pleomorphism ($p < 0.001$) and depth of tissue invasion ($p < 0.001$), being more intense in pT2–pT3 tumors and in deeply invasive lesions. Polymorphous inflammatory infiltrate was also correlated with adjacent actinic keratoses ($p < 0.001$), macroscopic ulceration ($p < 0.001$), histological subtype ($p = 0.033$) and marked pleomorphism ($p < 0.001$). These correlations suggest that severe and polymorphous peritumoral inflammation may reflect a complex interaction between tumor aggressiveness, surface necrosis or ulceration and the local immune response.

Overall, the findings indicate that the parameters with the greatest prognostic relevance in the analyzed cohort were tumor size, tumor thickness, depth of invasion, differentiation grade, cyto-nuclear pleomorphism, lymphovascular invasion and perineural invasion. The statistically significant associations between these variables support the existence of a histopathological profile of tumor aggressiveness characterized by large, thick, deeply invasive and poorly differentiated tumors, frequently associated with vascular or neural invasion. At the same time, the correlations between solar elastosis, inflammatory infiltrate and invasiveness parameters further support the role of chronic photoexposure and the tumor microenvironment in the progression of cutaneous squamous cell carcinoma.

4.3. Third study – Clinical, dermoscopic and *in vivo* RCM evaluation of AK

The analyzed cohort included 50 AK lesions from 50 patients, with a male predominance, comprising 72% men and 28% women. The mean age was 69.76 years, with a range between 57 and 86 years, confirming the epidemiological profile of keratoacanthoma as a condition associated with cumulative sun exposure and advanced age. Regarding skin phototype, 62% of patients had Fitzpatrick phototype III and 38% had phototype II, a distribution consistent with the increased susceptibility of fair skin to actinic lesions. Clinical severity was assessed using the Olsen score,

on a scale from 1 to 3, and the results were correlated with dermoscopic parameters and those identified by reflectance confocal microscopy.

Dermoscopic analysis focused on the main features associated with AK: linear wavy vessels, microerosions, the “strawberry” pattern, scales and diffuse erythema. Among these, linear wavy vessels were not significantly associated with the Olsen score ($p = 0.566$), suggesting that the dermoscopically visible vascular architecture does not accurately reflect the clinical severity of the lesions. In contrast, microerosions were significantly correlated with the clinical score ($p = 0.002$), with a moderate strength of association, indicating that focal loss of epidermal integrity becomes more frequent as keratoacanthoma progresses clinically.

The dermoscopic “strawberry” pattern showed a significant association with clinical severity, although the relationship was moderate and not strictly linear ($p = 0.038$). This pattern may therefore be regarded as a useful indicator in the clinical assessment of AK, but not as a sufficient standalone marker of severity. Diffuse erythema emerged as the most robust dermoscopic parameter correlated with the Olsen score ($p < 0.001$), showing a strong association and a clear linear trend: higher clinical scores were accompanied by increased erythema intensity. The degree of scaling was also significantly associated with clinical severity ($p = 0.012$), reflecting the contribution of hyperkeratosis and impaired epidermal maturation to the clinical appearance of advanced lesions.

The total dermoscopic score was strongly associated with the Olsen score ($p < 0.001$), supporting the value of dermoscopy as a complementary method to clinical assessment. Increasing clinical severity was accompanied by progressive accumulation of dermoscopic signs, demonstrating that an integrated interpretation of surface changes provides a more accurate estimation of lesion severity than the isolated analysis of a single criterion.

Correlations between clinical severity and RCM parameters were particularly relevant. The atypical honeycomb pattern showed the strongest association with the Olsen score ($p < 0.001$), suggesting that disruption of epidermal architecture represents one of the most important confocal markers of AK severity. As the clinical score increased, alteration of the normal epidermal pattern became more pronounced ($p < 0.001$), confirming that RCM can detect deeper structural changes corresponding to dysplastic progression.

Nuclear atypia identified by RCM was significantly associated with the Olsen score ($p = 0.011$). Its frequency increased with clinical severity ($p = 0.004$), supporting the role of nuclear

atypia as a marker of dysplastic transformation and cellular instability. The inflammatory infiltrate observed by RCM was also correlated with clinical severity ($p = 0.005$), suggesting intensification of the local immune response in more advanced lesions ($p = 0.001$). Solar elastosis and parakeratosis showed significant relationships with the Olsen score ($p = 0.001$ and $p = 0.004$, respectively), indicating that chronic ultraviolet-induced damage and keratinization disorders progressively increase in parallel with clinical severity ($p < 0.001$).

The total RCM score was strongly associated with the clinical Olsen score ($p < 0.001$), with a large effect size, highlighting the value of RCM in the non-invasive stratification of AK. This relationship confirms that clinically observed changes are supported by objective microscopic alterations, and that RCM can complement clinical evaluation by identifying signs of dysplasia, inflammation and actinic remodeling that are not always evident on direct examination.

The relationship between the total dermoscopic score and the total RCM score was also strong ($p < 0.001$), with a significant association and a very large effect size. Lesions with higher dermoscopic scores consistently showed a more severe confocal classification, demonstrating concordance between visible surface changes and microscopic epidermal and dermal alterations. This concordance supports the combined use of dermoscopy and RCM for a more accurate assessment of AK severity.

Analysis of RCM features in relation to dermoscopic severity showed that the atypical honeycomb pattern strongly correlated with the total dermoscopic score ($p < 0.001$). As dermoscopic signs accumulated, the epidermal architecture observed confocally became increasingly disorganized. Nuclear atypia ($p = 0.012$), inflammatory infiltrate ($p < 0.001$), solar elastosis ($p < 0.001$) and parakeratosis ($p < 0.001$) were also significantly associated with higher dermoscopic scores. Among these parameters, parakeratosis and the atypical honeycomb pattern demonstrated the strongest relationships with dermoscopic severity, supporting their role as important confocal biomarkers of AK progression.

Conversely, analysis of dermoscopic features in relation to the total RCM score showed that erythema, scales and microerosions were the most relevant dermoscopic predictors of confocal severity. Erythema was strongly associated with the total RCM score ($p < 0.001$), suggesting that clinically visible inflammation reflects advanced microscopic changes. Scales correlated significantly with confocal severity ($p < 0.001$), probably through their relationship with hyperkeratosis and parakeratosis. Microerosions indicated compromised epidermal integrity and

were associated with more advanced confocal alterations ($p < 0.001$). By contrast, linear wavy vessels ($p = 0.296$) and the "strawberry" pattern ($p = 0.132$) did not reliably predict overall confocal severity.

5. Discussions

5.1. First study - Clinico-histological profile of the patient with AK in Romania

5.1.1. Epidemiologic aspects of the AK study group

The study findings confirm the epidemiological profile of AK reported in the literature, with a predominance among elderly patients, a median age of 76.36 years and peak incidence in the seventh and eighth decades of life. This age distribution supports the role of cumulative ultraviolet exposure in the pathogenesis of AK [1].

A male predominance was observed in the analyzed cohort, in line with existing epidemiological data. This may be explained by greater cumulative sun exposure, occupational or recreational outdoor activities, lower adherence to photoprotection, as well as androgenetic alopecia and shorter hair length, which reduce the natural protection of the scalp and face. The slightly younger age at clinical detection among men may reflect these behavioral and biological differences, whereas more consistent use of photoprotective measures among women may delay the clinical manifestation of lesions [2].

Most AK's were diagnosed at small sizes; however, a relevant proportion presented as larger lesions, possibly due to delayed presentation, variable growth rates or unequal access to dermatological care. Large lesions are clinically important because of their increased risk of progression to invasive cutaneous SCC. Although small lesions were more frequent in men, the distribution of larger lesions was relatively balanced between sexes, supporting the need for periodic dermatological screening in both groups.

The predominance of patients from urban areas should be interpreted with caution, as it may reflect better access to medical services, rural-to-urban migration and the administrative

expansion of metropolitan areas, rather than a true difference in incidence according to residence environment.

The identified comorbidities support the profile of an elderly population, with a high frequency of cardiovascular disease and a relevant proportion of patients with a history of malignancy (19%). These findings are clinically meaningful given the association between immunosuppression, oncological history and increased risk of AK and non-melanoma skin cancers. Smoking, although probably underreported, was associated with labial localization, a region particularly vulnerable to the combined effects of ultraviolet radiation and tobacco exposure [3].

Anatomical distribution showed a clear predominance of photoexposed areas, especially the head and neck region, where 87.9% of cases were located. This finding supports the direct relationship between AK and chronic ultraviolet exposure. The limited involvement of the trunk and limbs may be explained by lower cumulative sun exposure, but also by reduced detection or reporting of lesions in these anatomical sites [4].

The statistically significant associations between AK subtypes and lesion size ($p < 0.05$), as well as anatomical localization ($p = 0.008$), highlight the importance of integrating morphological patterns with the clinical context. This integrated approach may inform both prognostic assessment and therapeutic planning, particularly in distinguishing high-risk lesions requiring excision from lesions that may be managed through field-directed therapies.

5.1.2. Histopathological aspects of the AK study group

Histopathologically, the presence of solar elastosis in all cases confirms the central role of chronic photoaging in the pathogenesis of AK. The significant association between the severity of elastosis and advanced KIN grades ($p < 0.001$) supports its value as an indirect marker of cumulative ultraviolet-induced damage and lesion progression.

The hypertrophic subtype was the most frequently identified, in accordance with the literature, where it is described as one of the most common forms of AK. Differences in distribution according to anatomical site and lesion size suggest that the histological subtypes may

represent distinct morphological expressions of the same ultraviolet-driven etiopathogenic process.

Assessment of dysplasia using the KIN system showed a predominance of KIN II lesions, followed by KIN I and KIN III. Higher KIN grades correlated with more pronounced cyto-nuclear pleomorphism, marked solar elastosis and intense peritumoral inflammatory infiltrate. These parameters may be regarded as histological indicators of potential progression toward invasive cutaneous SCC.

The peritumoral inflammatory infiltrate was predominantly lymphoplasmacytic, consistent with a local immune response to ultraviolet-damaged keratinocytes. The increase in its intensity with the severity of dysplasia suggests amplification of the immune reaction in more advanced lesions, with possible prognostic implications.

Ulceration was present in a limited proportion of cases (31%), while most lesions retained a superficial, intraepidermal character. Nevertheless, the identification of ulceration requires careful interpretation, as it may raise suspicion of early transformation toward cutaneous SCC.

5.2. Second study - Clinico-histological profile of the patient with SCC in Romania

5.2.1. Epidemiologic aspects of the SCC study group

The findings of this study confirm the predominance of cutaneous SCC in male patients, with a male-to-female ratio of 1.81:1, higher than that observed in the AK cohort, where the ratio was 1.23:1, while maintaining the same overall trend. This distribution supports the role of cumulative ultraviolet exposure, as well as the influence of behavioral and biological differences between sexes. The higher mean age observed in women, 77.43 years compared with 72.97 years in men, may suggest a later clinical onset, potentially explained by lower cumulative sun exposure, more consistent photoprotection, or hormonal factors [5].

The peak incidence in the 80–89 and 70–79 age groups confirms cutaneous SCC as a disease predominantly associated with advanced age, primarily driven by the cumulative effects

of ultraviolet radiation. The more frequent involvement of men under 60 years of age suggests earlier and more intense actinic exposure in this subgroup. The predominant localization in the head and neck region, identified in 81.8% of cases, further supports the direct relationship between cutaneous SCC and chronic photoexposure [6].

The frequent comorbidities, particularly cardiovascular disease and diabetes mellitus, reflect the profile of an elderly population, without necessarily indicating a direct correlation with tumor severity. The relatively balanced urban–rural distribution suggests that residence environment did not substantially influence case distribution within this cohort.

Overall, these results support the concept of cutaneous SCC as a pathology of advanced age, with biological behavior influenced by cumulative factors such as ultraviolet exposure, age and sex. Tumor diameter, thickness and histopathological features, including lymphovascular and perineural invasion and cyto-nuclear pleomorphism, represent essential parameters for oncological risk assessment. Furthermore, the strong association with solar elastosis emphasizes the need for prevention and education programs focused on photoprotection [7].

5.2.2. Histopathological aspects of the SCC study group

Only 28.37% of cases were initially clinically suspected to represent cutaneous SCC, with lesions more frequently being misinterpreted as other entities, such as BCCC or AK. This finding highlights the essential role of histopathological examination in establishing a definitive diagnosis, particularly in lesions with nonspecific clinical features.

The NOS subtype was predominant, accounting for 82.4% of cases, reflecting the absence of distinctive morphological features in most tumors. Nevertheless, the acantholytic, verrucous and keratoacanthoma-like subtypes displayed relevant particularities, with the acantholytic variant being associated with larger lesions and potentially more aggressive behavior, whereas keratoacanthoma-like lesions were predominantly well-defined tumors [8].

Tumor size, thickness and depth of invasion were important parameters of aggressiveness. Lesions larger than 2 cm accounted for more than half of the cases and were associated with lymphovascular and perineural invasion. Furthermore, increasing tumor thickness correlated with

invasion of deeper structures, confirming the value of these parameters in oncological risk assessment [8].

Tumor differentiation grade was associated with histological subtype and local extension, with poorly differentiated tumors tending to show more advanced invasion. Thus, histological grading remains essential for assessing biological behavior and for prognostic stratification [9].

Lymphovascular and perineural invasion were correlated with each other, as well as with tumor size and thickness, representing important markers of aggressiveness and of the risk of recurrence or metastasis. These findings support the need for rigorous microscopic evaluation and accurate staging [10].

Solar elastosis, present in all cases, confirms the role of chronic ultraviolet exposure in cutaneous squamous cell carcinogenesis. Its severity was associated with tumor size, depth of invasion, adjacent actinic keratosis, cellular pleomorphism and inflammatory infiltrate, suggesting the involvement of the photoaltered dermal microenvironment in tumor progression [11].

The inflammatory infiltrate was predominantly lymphoplasmacytic; however, its severity increased with tumor size, thickness and depth of invasion. Polymorphous infiltrates were more frequently associated with marked pleomorphism, ulceration and adjacent actinic keratosis, indicating a more active inflammatory response in advanced lesions or in tumors with tissue destruction [12].

In conclusion, the aggressiveness of cutaneous SCC is determined by the integration of multiple clinico-histological parameters, including tumor size, thickness, differentiation grade, depth of invasion, lymphovascular and perineural invasion, pleomorphism, solar elastosis and inflammatory infiltrate. Correlating these elements is essential for risk stratification, prognostic assessment and individualized therapeutic management.

5.3. Third study - Clinical, dermoscopic and *in vivo* RCM evaluation of AK

Statistical analyses revealed several key findings. First, a strong and significant association was observed between increasing clinical severity and multiple dermoscopic features, particularly erythema, scales and erosions, all of which demonstrated robust ordered trends. Diffuse erythema emerged as the most reliable surrogate for clinical severity, reflecting the complex interaction

between neoangiogenesis and chronic inflammation in ultraviolet-damaged skin. Microerosions, indicative of stratum corneum fragility, also increased in parallel with higher Olsen scores. By contrast, traditionally emphasized signs, such as fine wavy vessels and the "strawberry" pattern, although diagnostically useful, did not independently predict severity. This finding underscores the importance of weighting individual features rather than merely counting them within dermoscopic algorithms. These surface-visible features were further validated by their significant correlations with RCM-derived parameters, including parakeratosis, nuclear atypia, inflammatory infiltrate and the atypical honeycomb pattern—features indicative of epithelial dysplasia and chronic ultraviolet-induced damage [13–15]. The total dermoscopic score correlated strongly with both clinical and confocal scores, supporting its utility as a semi-quantitative, non-invasive marker of disease progression.

The high degree of concordance between total dermoscopic and confocal classifications (Cramér's $V = 0.806$, $p < 0.001$) highlights the interoperability of these imaging modalities. This correlation suggests that dermoscopy and RCM assess complementary layers of the same pathogenic spectrum: dermoscopy excels in depicting surface architecture and vascular tone, whereas RCM reveals cellular disarray that may precede invasive transformation. When used together, these methods provide a holistic, layer-by-layer assessment of risk, potentially reducing the need for routine punch biopsies in areas of extensive field cancerization. This convergence supports the integration of structured dermoscopic and confocal scoring systems into a multimodal diagnostic framework. From a translational perspective, this synergy improves the non-invasive grading of AK and provides a reproducible basis for lesion stratification, monitoring and treatment selection.

Biologically, the results confirm that surface-visible features, when assessed systematically, may serve as proxies for deeper epidermal and dermal pathology. This reinforces the concept of AK as a continuum of keratinocytic atypia and architectural disorder, beginning with subtle histological alterations and potentially progressing toward invasive transformation. The integration of dermoscopy and RCM facilitates the early identification of high-risk lesions, offering the possibility of preventive intervention before malignant progression occurs [16,17].

From a practical standpoint, our data support the incorporation of structured dermoscopic and confocal scores into outpatient clinical workflows. Lesions with high erythema scores or elevated composite confocal scores could be prioritized for field-directed therapies, such as topical

5-fluorouracil, photodynamic therapy or ablative laser resurfacing, thereby reducing the therapeutic delay that may precede progression to cutaneous SCC. Conversely, lesions with low scores could be actively monitored, minimizing overtreatment in elderly patients or in those with multiple comorbidities. Structured scores also provide an objective framework for monitoring treatment response and comparing outcomes across clinical studies.

By demonstrating robust and statistically significant links between clinical appearance, dermoscopic patterns and confocal microarchitecture, this study lays the foundation for a unified imaging-based severity index for AK. Such an index could harmonize eligibility criteria in interventional trials, facilitate personalized therapeutic algorithms and serve as an early indicator for chemopreventive strategies targeting field cancerization. Integration with artificial intelligence-assisted image analysis could further enhance reproducibility and extend access to advanced diagnostics beyond tertiary referral centers.

Diffuse dermoscopic erythema and key RCM features—disrupted honeycomb architecture, parakeratosis, nuclear atypia, inflammation and solar elastosis—represent high-impact non-invasive biomarkers that correlate with the Olsen grading system. Their combined use may refine risk stratification, optimize therapeutic timing and, most importantly, help prevent the evolution of apparently indolent keratinocytic dysplasia into potentially life-threatening cutaneous SCC. The present study represents a substantial step in this direction.

This cross-sectional study provides one of the most comprehensive demonstrations to date that the macroscopic, dermoscopic and cellular landscapes of AK describe a single, measurable continuum of disease severity. By prospectively correlating clinical Olsen grades with structured dermoscopic and RCM scores, we showed that non-invasive imaging not only reflects direct clinical inspection, but often provides a more nuanced perspective on early malignant potential. This approach supports the longstanding clinical concept of AK as a field disease, in which apparently heterogeneous lesions share a common biological trajectory toward cutaneous SCC.

In conclusion, this study supports the validity of combining clinical, dermoscopic and confocal assessments for grading AKs. By identifying statistically significant and biologically coherent associations between these modalities, the study contributes to the development of a unified, non-invasive and clinically applicable severity classification system. Such a framework has the potential to standardize lesion assessment, improve patient stratification and ultimately

guide therapeutic decision-making in the management of AK and early keratinocyte-derived neoplasia.

6. CONCLUSIONS

6.1. First study - Clinico-histological profile of the patient with AKs in Romania

1. AKs were diagnosed predominantly in elderly patients, with ages ranging from 55 to 90 years, a mean age of 76.36 ± 7.84 years, and a median age of 77 years. The most frequently affected age group was 70–79 years, accounting for 41.4% of cases.
2. AKs were diagnosed predominantly in elderly patients, with ages ranging from 55 to 90 years, a mean age of 76.36 ± 7.84 years, and a median age of 77 years. The most frequently affected age group was 70–79 years, accounting for 41.4% of cases.
3. Most AK lesions were small, with more than half of the patients presenting lesions measuring less than 1 cm in diameter. This finding suggests that AKs were frequently identified at relatively limited clinical stages.
4. The head and neck region represented the predominant anatomical site of AK, being involved in 87.9% of cases. This distribution supports the role of chronic ultraviolet radiation exposure in the development of these lesions.
5. From a histopathological perspective, moderate dysplasia, corresponding to KIN II, was the most frequent finding, identified in 41.38% of cases. This indicates a predominance of lesions with intermediate-grade keratinocytic atypia within the studied cohort.
6. KIN grade showed relevant associations with patient age and sex. KIN I and KIN III lesions were more frequent in the 70–79-year age group, whereas KIN II predominated among patients aged 80–89 years and among female patients, the latter association being statistically significant ($p = 0.042$).
7. The severity of keratinocytic dysplasia correlated significantly with the intensity of cyto-nuclear pleomorphism ($p < 0.001$), confirming that higher KIN grades are associated with more pronounced cellular atypia.
8. The association between KIN grade and the severity of solar elastosis was statistically significant ($p < 0.001$), highlighting the relationship between keratinocytic atypia and the extent of ultraviolet-induced dermal damage.

9. Histological subtypes displayed distinct clinicopathological features. Most lesions were located in the head and neck region, with a statistically significant association ($p = 0.008$). Hypertrophic and lichenoid lesions were more frequently associated with diameters below 1 cm, whereas atrophic and bowenoid forms were more commonly associated with lesion sizes between 1 and 2 cm.

6.2. Second study - Clinico-histological profile of the patient with SCC in Romania

1. Cutaneous SCCs were diagnosed predominantly in male patients, with a male-to-female ratio of 1.8:1. This ratio was higher than that observed in the AK cohort, while maintaining the same overall trend of male predominance.

2. The frequency of cutaneous SCC increased progressively with age, with the highest number of cases observed in the 80–89-year age group. This finding supports the relationship between cutaneous aging, cumulative photoexposure and the development of cutaneous SCC.

3. The head and neck region represented the main anatomical site of cutaneous SCC, being involved in 81.8% of cases. Within this region, the most frequent locations were the lower lip (28/121 cases; 23.14%), nasal region (21/121 cases; 17.35%) and auricular region (20/121 cases; 16.53%), all corresponding to chronically photoexposed areas.

4. Tumor size was relatively evenly distributed between lesions smaller than 2 cm and those larger than 2 cm, with a slight predominance of tumors exceeding 2 cm. Macroscopic ulceration was present in most cases, particularly among male patients.

5. The predominant histological subtype was conventional cutaneous SCC, NOS, accounting for 82.4% of all cases. This was followed by keratoacanthoma-like lesions (8.8%), verrucous squamous cell carcinoma (5.4%) and acantholytic squamous cell carcinoma (3.4%). Most NOS lesions were located in the head and neck region (82.78%), while the acantholytic subtype was identified exclusively in this anatomical area.

6. Histological subtypes showed distinct patterns of tumor extension. Most NOS and keratoacanthoma-like SCCs were classified as pT1–pT2, whereas the acantholytic subtype was more frequently associated with larger tumors, corresponding to pT3.

7. Tumor thickness and depth of invasion highlighted the infiltrative behavior of cutaneous SCC. Tumor thickness ranged from 0.5 to 43 mm, with a mean value of 8.31 mm, and nearly half of the tumors invaded the deep dermis.

8. Lymphovascular and perineural invasion were associated with parameters of tumor aggressiveness, being more frequent in tumors with larger diameter and greater thickness. Mean tumor thickness was almost twice as high in cases with lymphovascular invasion compared with those without it (13.52 mm versus 7.45 mm). Moreover, the correlations between perineural invasion, lymphovascular invasion and tumor thickness were statistically significant ($p < 0.001$).

9. Solar elastosis was frequently associated with cutaneous SCC, particularly with the NOS subtype, in which most cases showed either moderate (39.34%) or severe (50.82%) solar elastosis. The severity of elastosis increased with the depth of tumor invasion, supporting the role of chronic ultraviolet exposure in cutaneous carcinogenesis.

10. The peritumoral inflammatory response showed relevant associations with lesion aggressiveness. The intensity of the inflammatory infiltrate increased in parallel with the severity of solar elastosis and cyto-nuclear pleomorphism. Non-ulcerated lesions predominantly showed a lymphoplasmacytic infiltrate, whereas ulcerated lesions more frequently exhibited a polymorphous inflammatory infiltrate, which was particularly predominant in the acantholytic subtype.

11. Assessment of comorbidities among the 148 patients with cutaneous SCC revealed the following distribution: cardiovascular disease was present in 72 patients (48.6%), while 76 patients (51.4%) had no recent cardiovascular history; diabetes mellitus was identified in 20 patients (13.5%), whereas 128 patients (86.5%) did not present this comorbidity; a non-cutaneous SCC oncological history was recorded in 8 patients (5.4%), while the majority, 140 patients (94.6%), had no other malignancies; psoriasis was documented in only 2 patients (1.4%), compared with 146 patients (98.6%) without this dermatological condition.

6.3. Third study - Clinical, dermoscopic and *in vivo* RCM evaluation of AKs

1. The clinical Olsen score showed a statistically significant correlation with dermoscopic features suggestive of AK severity, particularly erythema, scaling, erosions, and the

“strawberry” pattern, confirming the utility of clinical assessment in estimating the degree of lesional involvement.

2. Erythema represented one of the strongest dermoscopic correlates of clinical severity. The significant and strong association between the Olsen score and the degree of erythema indicates that erythema intensity may reflect the clinical progression of AK.

3. The dermoscopic “strawberry” pattern was significantly associated with the Olsen score, suggesting that this feature may serve as a relevant dermoscopic marker for assessing clinical severity, although the observed relationship was not strictly linear.

4. The total dermoscopic score increased proportionally with the Olsen score. The significant and strong association between these two scores demonstrates concordance between clinical severity and composite dermoscopic changes.

5. The Olsen score correlated significantly with RCM findings, including nuclear atypia, inflammatory infiltrate, parakeratosis and solar elastosis, indicating that clinical severity also reflects progressive microscopic alterations.

6. Nuclear atypia detected by RCM became more frequent with increasing Olsen and dermoscopic scores, supporting the role of non-invasive imaging in assessing cellular changes associated with AK progression.

7. Inflammation detected by RCM intensified with increasing clinical and dermoscopic severity, suggesting a biological relationship between surface-visible lesional changes and the epidermal or dermal inflammatory response.

8. Solar elastosis assessed by RCM was associated with higher Olsen and dermoscopic scores, confirming the link between AK severity and chronic ultraviolet-induced cutaneous damage to the dermal extracellular matrix, particularly degradation and accumulation of abnormal elastic fibers.

9. The total dermoscopic score correlated significantly and strongly with the total RCM score. Higher dermoscopic scores were associated with progressive loss of the normal honeycomb pattern, nuclear atypia, inflammation and more severe solar elastosis.

10. Not all dermoscopic criteria had predictive value for confocal severity. Vascular patterns did not reliably correlate with the RCM score, whereas erosions showed a strong association with the total confocal score, reflecting more advanced microscopic structural damage.

7. Original elements and future prospects

The completion of this thesis fulfilled the proposed objectives, allowing the delineation of a complex clinicopathological profile of patients diagnosed with actinic keratoses and cutaneous squamous cell carcinoma in Romania. At the same time, the thesis assessed the utility of integrating clinical examination, dermoscopy and in vivo reflectance confocal microscopy in evaluating the severity of actinic keratoses.

The originality of the research derives from its broad and integrative character, through the inclusion of a relevant number of patients and the detailed analysis of clinical, epidemiological and histopathological parameters. In addition to describing the anatomo-clinical features of the lesions, the study incorporated variables such as associated comorbidities and residence environment, thereby contributing to a more nuanced understanding of the context in which chronic photoexposure-induced cutaneous lesions arise and evolve.

A major distinctive element is represented by the prospective study dedicated to correlating clinical, dermoscopic and confocal assessments in the grading of actinic keratoses. To our knowledge, this represents the first study of this type conducted on a Romanian patient cohort. The results support the role of in vivo reflectance confocal microscopy as a complementary, non-invasive method with the potential to increase diagnostic accuracy and reduce the need for biopsies in selected situations, particularly in patients with multiple lesions or lesions requiring additional evaluation before therapeutic decision-making.

However, the interpretation of the results must take into account several methodological limitations, including the relatively small sample size of the prospective study, single-center recruitment, exclusion of immunocompromised patients and histopathological confirmation limited mainly to atypical or treatment-refractory lesions. These aspects restrict the generalizability of the conclusions and limit direct lesion-by-lesion comparison between confocal findings and the histopathological depth of invasion.

Future perspectives include the development of larger multicenter prospective studies, with systematic histopathological validation and longitudinal follow-up. Such studies could enable the definition of more precise imaging criteria, the establishment of severity thresholds and the assessment of the predictive value of clinical, dermoscopic and confocal parameters for progression, recurrence and therapeutic response. Thus, the present thesis may provide a

foundation for the development of personalized, efficient and minimally invasive diagnostic and monitoring algorithms.

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