MASTER THESIS

Bowen's Disease in Private Practice: Frequency, Diagnosis and Management

Submitted by

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Declaration

I hereby affirm that this work is my own original composition, completed without unauthorized assistance. All sources utilized have been properly cited, and any direct quotations or paraphrased content have been clearly indicated as such.

Bellegem, Belgium July 31th, 2024 *Charlotte Degroote*

1. Introduction

Bowen's disease, initially characterized as a chronic atypical epithelial proliferation, was first described in 1912 by John Templeton Bowen (1,2). Jean Darrier also contributed to the early understanding of this condition, reporting a precancerous dermatosis termed "Bowen dyskeratosis lenticularis et discoides"(1). Bowen's disease (BD), alternatively referred to as cutaneous squamous cell carcinoma in situ (cSCC in situ), manifests as a slowly gradually expanding well-demarcated erythematous or scaly patch on the skin. Often occurring in chronically UV exposed skin of elderly patients. It is most frequent in woman and appears 75% of the cases on the lower legs (2). Left untreated, there is a 3-5% risk of progression to invasive cSCC (3). The primary risk factors to develop cSCC in situ are cumulative exposure to UV radiation, radiotherapy and immunosuppression (2,4). Differential diagnosis of non-pigmented BD includes a wide spectrum of nonpigmented skin tumours and erythemato-squamous skin disorders, f.e. actinic keratosis, basal cell carcinoma, eczema, psoriasis, warts, . . .(2).

There are several synonyms for bowen's disease, the most well-known being cutaneous squamous cell carcinoma in situ (cSCC in situ). For the further course and uniformity of this master's thesis, cSCC in situ will be used further in this text.

The cutaneous squamous cell carcinoma in situ (cSCC in situ) is a precursor lesion of spinocellulair carcinoma and belongs to the group of non-melanocytic skin cancers (NMSC). Non-melanocytic skin cancers are one of the most frequently occurring skin cancers and studies show that their incidence has been increasing sharply in recent years. The SCC has a significant morbidity. Consequently, both SCC and its precursor lesions presents a burgeoning challenge to public healthcare systems, accompanied by escalating economic costs.

In this master's thesis, we want to focus on the frequency, diagnosis and treatment of cSCC in situ in a private dermatological practice. We want to examen in what frequency cSCC in situ is diagnosed and what treatment modalities are currently applied in the private practice.

2. Literature review

2.1 Frequency of Bowen's Disease

2.1.1 Epidemiology of Bowen's disease

There is limited literature available concerning the epidemiology of cutaneous squamous cell carcinoma (cSCC) in situ. Existing studies, often dating back to the previous century, have typically been conducted on small populations and report varying incidence rates. A notable observation is the exclusion of keratinocytic cancers, including cSCC, from cancer registries, due to their high incidence and the challenges associated with recording multiple tumors per patient (3–5). Although global trends indicate a rise in the incidence rates of invasive cSCC, accompanied by corresponding increases in associated costs and healthcare burdens (3,5,6).

In contrast, the Netherlands Cancer Registry (NCR) includes all cases of histopathologically confirmed skin cancers, encompassing keratinocytic cancers such as cSCC in situ (3).

A recent Dutch population-based cohort study, conducted in the Netherlands spanning from 1989 to 2017, showed insights into the trends in incidence rates, revealing increases over time. This cohort study followed 88 754 patients with cSCC in situ and showed that the age-standardized incidence rate increased to 72 cases per 100 000 person-years in women and 68 cases per 100 000 person-years in men. The data also showed that patients with cSCC in situ had a 16-fold higher risk of developing invasive cutaneous squamous cell carcinoma in the year after receiving the diagnosis of cSCC in situ compared with the general population (3). Other studies show that the risk of progression into an invasive SCC ranges from 3%-5% (2,7,8).

Most studies shown a peak incidence in the elderly patient mostly occurring in the seventh decade of life, with a slight female preponderance (2,3,9–11)

The body site-specific incidence rates for cSCC in situ, predominantly manifests on sun-exposed body regions, notably the face and lower limbs in women and the face,scalp and neck in men. This supports the role of cumulative UV radiation exposure in the pathogenesis of cSCC in situ (2).

Geographic location significantly influences incidence rates across various populations. Regions with sunny climates, exhibit higher incidence rates. Conversely, studies based in the UK and Netherlands have indicated a predominant occurrence of cSCC in situ on the lower limbs, suggesting potential variations in sun exposure patterns among countries with lower sunshine rates(2,9,10).

2.1.2 Etiopathogenesis

Various factors influence the prevalence of cSCC in situ in private practice, reflecting its multifactorial etiology. These factors encompass a spectrum of risk elements, including irradiation, immunosuppression, exposure to carcinogens, viral infections, and other determinants.

Irradiation: Both UV radiation and radiotherapy are implicated in elevating the risk of cSCC in situ development. Prolonged exposure to UV light, whether from solar radiation, iatrogenic sources, or sunbeds, induces DNA damage and immunosuppression, thereby facilitating the clonal expansion of p53 mutations (1,2).

Immunosuppression: The use of immunosuppressive medications such as corticosteroids, azathioprine, and cyclosporine is associated with the activation of various pathways that promote the induction and progression of skin malignancies (1,2).

Carcinogens: Exposure to carcinogens, such as arsenic, predisposes individuals to the development of skin malignancies, even in sun-protected areas (1,2).

Viral Infections: Certain subtypes of the human papillomavirus (HPV) have been linked to cSCC in situ. HPV DNA is detected in varying proportions in extragenital cSCC in situ cases, with HPV 16 being the most prevalent subtype, followed by HPV 33. Immunocompromised individuals exhibit a higher detection rate of HPV compared to the general population (1,2).

Other Risk Factors: Additional risk factors for cSCC in situ include Caucasian ethnicity, age over 60 years, fair skin complexion, history of thermal injury, prior PUVA therapy or exposure to ionizing radiation, and increased overall sun exposure, both occupationally and recreationally (1,2).

Patients with compromised immune systems have a higher risk to develop cSSC in situ. The onset of the disease typically occurs at a younger age with multiple lesions manifest, that have a more aggressive behaviour and a higher recurrence rate compared to immunocompetent individuals.

2.2 Diagnosis of Bowen's Disease

2.2.1 Clinical presentation

Typically cSCC in situ presents itself as a well-demarcated, asymptomatic, erythematous, hyperkeratotic plaque with an irregular border. It predominantly is seen on sun-exposed areas of fair-skinned individuals. The pigmented cSCC in situ variant is observed in 1.7% to 5.5% of cases (2). The morphology of Bowen's disease may vary depending on factors such as the age of the lesion, site of origin, and degree of keratinization. Lesions lacking keratinization present as erythematous and velvety, while those with keratinization exhibit scaling that masks the underlying erythema. Bowen's disease lesions are commonly solitary; however, the presence of multiple lesions in a single patient warrants consideration of immunosuppression or exposure to arsenicosis.

Classical Bowen's disease (BD) typically presents as an asymptomatic, slow-growing erythematous patch or plaque, often exhibiting a well-demarcated boundary. Its surface may display scaling, crusting, and occasionally ulceration (1). The scales overlaying the lesion can sometimes resemble those seen in other erythematosquamous diseases, contributing to diagnostic challenges. A broad array of nonpigmented skin tumors and erythematosquamous skin disorders, including amelanotic melanoma, actinic keratosis, basal cell carcinoma, psoriasis, warts and eczema, constitute the differential diagnosis (2). The lesion's size can vary considerably, ranging from millimeters to centimeters, with larger lesions occasionally eliciting pruritic sensations. The full manifestation of the lesion can occur over a prolonged period, spanning from 2 to 40 years, typically characterized by slow growth and lateral spread (1).

Genital BD shows lesions on both mucosal and skin surfaces. Bowen's disease on the skin presents as well-defined, single, dull-red plaques featuring scales, crusting, or pigmentary changes, predominantly localized to the suprapubic area and penile shaft. Conversely, Erythroplasia of Queyrat (EQ) occurs on mucosal surfaces, appearing as painless, well-demarcated, bright-red, velvet lesions with a plaque-like morphology (1). Partners of patients

with EQ should undergo screening due to their heightened risk of developing preinvasive and invasive lesions of the cervix or anus (1).

Perianal BD manifests in various morphological forms, such as nodular, pigmented, verrucous, ulcerated, leukoplakic, and polypoidal, often accompanied by minor symptoms like itching, burning, or bleeding. It predominantly affects women, with a 2%-6% risk of progression to invasive carcinoma (1).

Periungual BD clinically presents as flat, erythematous patches with scaling or crusted verrucoid lesions, often associated with pseudo-fibrokeratoma and melanocytic pigmentation, more commonly observed in men on the first three digits of the left hand (1,12).

Facial BD may present as broad patches of erythema with minimal scales or solar keratosis, exhibiting bright erythema with adherent yellow keratotic scales (12).

Mucosal BD lesions can exhibit erythroplasia-like, nodular, papillomatous, or ulcerative morphology, corresponding to pathological stages dictated by tumor age, infiltration, and degeneration (1).

Pigmented BD typically manifests as well-defined, hyperpigmented, flat, or verrucous plaques with a velvety surface, predominantly observed in genital and interdigital areas. Increased melanocyte hyperplasia and the presence of well-differentiated atypical keratinocytes or tumor cells producing specific cytokines and growth factors contribute to pigmentation (12).

2.2.2 Diagnostic tools and techniques

a. Dermoscopy findings

The dermoscopic features characterizing Bowen's Disease (BD) were initially described in 2004 by Zalaudek et al. Their study, focusing on 21 non-facial BD lesions, with the majority (81%) located on the lower extremities, identified predominant dermoscopic findings including glomerular vessels (90%), scaly plaques (90%), and ulceration (29%) (8). Further investigations, such as a 2018 study by Lallas, showed following dermoscopic features including glomerular and dotted vessels, white and yellow scales, erosions, and brown dots in lines, aiding in the differentiation between BD and superficial basal cell carcinoma (13). Another study conducted by Cameron et al. in 2010 on pigmented BD highlighted notable dermoscopic findings such as glomerular vessels (67.3% of cases), brown/grey dots arranged in lines (21.2% of cases), and dotted/coiled vessels arranged in lines (11.5% of cases) (14).

Notably, the most common dermoscopic findings in non-pigmented BD include dotted/glomerular vessels, keratin (white and/or yellow), and pinkish-white structureless areas, whereas pigmented BD exhibits these findings along with structureless pigmentation and brown/gray/red peripheral dots arranged in lines (8). Dermoscopy of BD typically reveals a predominantly pink or pigmented background, clustered glomerular vessels or dotted vessels, opaque yellow-white scales, and/or erosions. The presence of clustered glomerular vessels serves as a highly accurate discriminator between BD, keratoacanthoma, and cutaneous squamous cell carcinoma (2). Glomerular vessels, resembling the convoluted capillaries of the renal glomerulus, correspond histopathologically to convolutions of grouped, frequently dilated capillaries in the dermal papillae (8). While dotted vessels are observed in various skin conditions, the combination of glomerular vessels and a scaly surface is particularly characteristic of BD, aiding in its distinction from other differential diagnoses (8,15,16).

b. Histopathological examination

Histopathology serves as the gold standard for confirming the diagnosis of Bowen's disease. Common findings include parakeratosis or hyperkeratosis in the stratum corneum and a full-thickness derangement of the epidermis (1,8). Keratinocytes display atypical characteristics throughout all levels of the epidermis, often presenting with a windblown appearance. Additionally, vacuolization, mitoses, individually keratinizing cells, and multinucleated cells populate the epidermis. Pagetoid cells, characterized by large pale keratinocytes with abundant ground-glass cytoplasm, are sporadically distributed throughout the epidermis. Bowen's disease lesions commonly exhibit varying degrees of hyperkeratosis, parakeratosis, and acanthosis, accompanied by a moderate lymphocytic infiltrate in the upper dermis (1,8,17).

The histopathology of mucous membrane BD lesions show fewer dyskeratotic cells and multinucleate cells, with rich plasma cells in the dermis. Pigmented bowen disease shows an increased melanin deposition in the epidermis and melanophages in the superficial dermis on histopathological examination.

Neoplastic cells often cluster around adnexal structures, resembling the histological pattern observed in clonal seborrheic keratosis. However, differentiation is feasible through negative cytokeratin 10 immunohistochemical staining in nests of atypical cells found in seborrheic

keratosis. In Bowen's disease, tumor cells typically stain positive for p53, HPV, and high molecular weight cytokeratin, including cytokeratin 10 (17).

Genetically, Bowen's disease displays increased expression and mutation of TP53, along with reported deletions in the 9q markers (17).

2.3 Management of Bowen's Disease

2.3.1 Treatment options

a. Topical therapies (e.g., imiquimod, 5-fluorouracil)
5-Fluorouracil (5-FU) is a topical cytotoxic agent utilized in the treatment of Bowen's disease. Administration typically entails once or twice daily applications over a span of 3-4 weeks, with the option of repeating the regimen if necessary (1,2). Clinical investigations have demonstrated complete response rates ranging from 48% to 83% among subjects following daily application for 3-4 weeks (18). The effectiveness of 5-FU can be augmented through techniques such as occlusion during application, pre-treatment with laser or iontophoresis, or the incorporation of dinitrochlorobenzene as a medium (19). Common adverse effects include pain, erythema, burning sensations, and ulceration at the site of application (2). In cases where a favorable response is not achieved following this treatment, consideration should be given to conducting a biopsy or initiating alternative treatment modalities once local inflammation has resolved (1).

Indications for 5-Fluorouracil treatment include small lesions (<2 cm) or large lesions situated in low-risk areas, large lesions in poorly healing sites (e.g., lower legs in elderly patients), and in immunosuppressed patients with multiple or recurrent lesions. The standard treatment regimen entails 1-2 times daily application for 3-4 weeks, with potential side effects including local inflammation, ulceration, and the possibility of scarring (2).

Imiquimod 5% functions as an immune response modifier, exerting antitumour activity by stimulating the local production of cytokines (1). Imiquimod represents a viable treatment option for challenging lesions, such as those located on the lower legs, glans penis, and large facial lesions. Numerous studies have reported clinical efficacy rates ranging from 57% to 86% following 6 weeks of application. Commonly encountered side effects include local inflammation, erythema, and pigmentation, with approximately 38% of patients discontinuing

imiquimod prematurely due to side effects. Imiquimod's efficacy in hyperkeratotic lesions appears limited (2,20).

Indications for the use of topical imiquimod 5% include lesions located in low-risk areas where alternative treatments are unavailable or lesions on the lower legs in patients with contraindications to 5-fluorouracil, photodynamic therapy (PDT), laser treatment, curettage, or surgery (2). The standard treatment protocol involves once-daily application, three times per week for 4 to 12 weeks, with potential efficacy reductions in immunocompromised patients. Side effects commonly associated with imiquimod include local inflammation, erythema, and pigmentation (1,2).

b. Surgical interventions (e.g., excision, cryotherapy)
Cryotherapy (Cryosurgery) serves as the primary treatment modality for patients presenting with small lesions (<2cm) of Bowen's disease. However, for larger lesions and those located on the lower extremities, the decision to employ cryotherapy may be contingent upon various patient-specific factors, including age, lesion location, and skin condition. Additionally, cryotherapy can be a viable option for immunocompromised patients. The procedure typically involves either a single prolonged freeze (lasting 20-30 seconds) or two quick successions of freezing (10-20 seconds each), with the commencement of time marked by the formation of a freezing zone. It is noteworthy that in cases of large lesions or those situated in high-risk areas such as the face, a reduction in freezing time may be warranted, albeit potentially compromising treatment efficacy. Commonly reported side effects encompass discomfort, delayed healing, ulceration, and a heightened risk of regrowth compared to curettage (18,19)

Curettage of the lesion may be contemplated when histological confirmation is required, and it remains a consideration even in immunocompromised patients (1).

In instances where diagnostic uncertainty exists, or invasive or recurrent lesions are suspected, surgical intervention should be deliberated. Optimal resolution of the lesion typically necessitates the adoption of a wide excisional margin, with recommendations advocating for margins ranging from 3-5 mm, contingent upon anatomical location. Surgical excision also remains a viable option for immunocompromised patients. Notably, limited studies have explored the efficacy of surgical treatment for in situ squamous cell carcinoma (SCC), and documentation regarding excision margins in the American context for in situ SCC removal remains scarce (21). Moreover, studies have indicated a lack of documented excision margins for in situ SCC removal within the American setting (22).

Moh's Micrographic Surgery represents a technique worthy of consideration for patients with lesions situated in anatomically sensitive areas where tissue preservation is paramount, such as periorbital regions or periungual regions (1).

c. Photodynamic therapy

Photodynamic therapy (PDT) for Bowen's disease entails the local application of methylamino-levulinate (MAL) under occlusion for a duration of three hours, followed by exposure to red light emitted from a narrowband light-emitting diode source. The treatment regimen involves repetition after seven days, with further sessions scheduled three months later if necessary (1). Notably, topical PDT offers a non-invasive, tissue-sparing, and highly effective therapeutic approach, rendering it a favorable option particularly for lesions situated in poorly healing or cosmetically sensitive areas (2,19). Additionally, PDT proves beneficial for patients with multiple or larger lesions. Its efficacy and tolerability in immunocompromised patients are noteworthy, particularly in managing multiple and recurrent lesions. However, evidence supporting the use of daylight PDT remains insufficient (1).

d. Other treatment modalities

Laser treatment emerges as a potential option for addressing in situ squamous cell carcinoma (SCC) when other treatments prove ineffective or unsuitable. Research indicates that ablative CO2 laser therapy surpasses nonablative neodymium:YAG laser therapy in terms of efficacy (2). Particularly, laser treatment may be considered for genital and nail lesion (19). In a comprehensive retrospective study involving 44 patients, CO2 laser treatment resulted in an impressive 86% cure rate after a single session (23). However, due to the sparing of follicular epithelium by CO2 laser, recurrence risk remains high. To mitigate this risk, the final step often involves utilizing a diode laser following three passes with the CO2 laser (2).

Radiotherapy serves as a viable option for recurrent lesions, particularly when surgical intervention is either contraindicated or poses a high risk of morbidity. Brachytherapy, in particular, is suitable for curved surfaces and areas with impaired wound healing, such as the fingers and toes. However, conventional radiotherapy, excluding brachytherapy, is generally avoided on the lower extremities due to prolonged healing times. Moreover, in immunocompromised patients, radiotherapy is reserved for cases of invasive disease, given the elevated risk of malignancy in this population, and its application cannot be repeated at

the same site due to associated risks. Although radiotherapy offers advantages, such as applicability in challenging anatomical regions, drawbacks include high cost, patient discomfort, and impaired wound healing, particularly at lower limb levels (1,2,18,23).

In cases where monotherapy with the treatments mentioned above fails to achieve desired outcomes, combination therapy may be considered. Various combination therapies documented in the literature include cryotherapy paired with imiquimod 5% or 5-fluorouracil 5%, as well as imiquimod paired with CO2 laser or photodynamic therapy (PDT). Additionally, combinations involving laser therapy, PDT, and shaving with PDT have been explored (2).

2.3.2 Factors influencing treatment selection in private practice

In the daily private practice, the decision-making process regarding the initiation of treatment for in situ squamous cell carcinoma (SCC) often commences without preceding biopsy. An array of treatment options is typically considered, with a foundation in various patient-related factors. These factors encompass a multitude of aspects including the patient's age, existing comorbidities, immune status, medication regimen, adherence to treatment protocols, and notably, specific attributes of the lesion itself, such as its size, thickness, and anatomical location (2,19). Furthermore, the patient's personal preferences and the expertise of the clinician exert significant influence over the treatment selection process.

A myriad of treatment options and protocols are available for the management of in situ SCC, with prevalent modalities encompassing surgery, cryotherapy, photodynamic therapy (PDT), and topical chemotherapy (2,7). While surgery remains the cornerstone treatment modality, there exists a burgeoning inclination towards less invasive approaches, owing to the frequent occurrence of multiple cutaneous lesions, often situated in anatomical regions less amenable to surgical intervention. This inclination towards non-invasive modalities is notably accentuated by the prevalent occurrence of in situ SCC among elderly patients, who frequently present with lesions in areas characterized by impaired wound healing (21).

For patients exhibiting compromised immune function and presenting with multiple lesions, especially in high-risk anatomical regions like the lower limbs, a conservative management strategy involving the utilization of urea-based moisturizers, alongside vigilant monitoring and biopsy if invasive lesions are suspected, is frequently recommended (2). In cases where clinical and dermatoscopic examination fail to yield a definitive diagnosis, the consideration

of conducting a punch biopsy or diagnostic excision becomes pertinent. Additionally, follow-up protocols for patients with in situ SCC are ideally tailored to accommodate individual needs (2).

In summation, the factors influencing treatment selection in private practice for in situ SCC encompass a comprehensive array of considerations, including lesion characteristics, patient preferences and comorbidities, as well as deliberations regarding the cost and accessibility of treatment modalities.

2.3.3 Long-term outcomes and recurrence rates

Research into establishing a gold standard treatment for in situ squamous cell carcinoma (SCC) encounters challenges due to the lack of high-quality studies and comprehensive data on various treatment modalities, compounded by the multitude of patient-dependent factors influencing therapeutic decisions (7).

In a Finnish study, surgical intervention demonstrated the lowest recurrence rate at 0.8%. However, consensus remains elusive regarding the optimal excision margin, with the study employing a margin of 2 mm. Instances where excision margins are inadequate and re-excision is not feasible necessitate the consideration of alternative treatment modalities around the scar, coupled with vigilant follow-up (7). Furthermore, the study highlighted comparatively higher recurrence rates following cryotherapy and photodynamic therapy (PDT), standing at 4.7% and 18% respectively, compared to surgical treatment (7).

Randomized clinical studies exploring the efficacy of different treatment modalities for in situ SCC are limited in number. Most of these studies focus on comparing the effectiveness of PDT, cryotherapy, and topical chemotherapy (2,24–26). For instance, one randomized placebo-controlled study examined the efficacy of PDT, cryotherapy, and 5-fluorouracil, revealing recurrence rates of 15%, 21%, and 17% respectively 12 months post-treatment (26). Notably, these studies often feature relatively short follow-up periods ranging from 2 to 4 years. The merits and drawbacks of each treatment modality are best evaluated on a case-by-case basis (7).

Presently, no single treatment method emerges as definitively superior, with the choice of treatment contingent upon factors such as lesion location, size, thickness, and number. Additionally, patient characteristics, practitioner expertise, therapy availability, and institutional experience significantly influence the therapeutic approach.

Thick and chronic ulcerative lesions are best managed through surgical excision due to the likelihood of underlying SCC. While surgery serves as the primary treatment for carcinoma in situ, less invasive approaches are warranted for multiple, extensive carcinomas in situ or lesions in sites prone to poor wound healing post-surgery. In select cases, combined treatment modalities may offer benefits, such as surgical intervention followed by PDT, with the latter often yielding superior cosmetic outcomes compared to surgery alone (7,26).

3. Materials and methods

Our study objective is to investigate the frequency, diagnosis and management of Bowen's disease, also called cutaneous squamous cell carcinoma in situ, in a private dermatology practice over a period of one year. We choose for a retrospective study of cases diagnosed with cSCC in situ at a private dermatology practice in Belgium between January 2023 and December 2023. This is a private practice in a rural area with is equipped with one dermatologist and one general practitioner specialised in dermatology and dermoscopy for the triage of skin lesions.

We selected patients who had a first time diagnosis with cutaneous squamous cell carcinoma in situ between 01/01/2023 and 31/12/2023 and collected the following clinical data for each patient: age, sex, location of the lesion, other skin malignancies, treatment modality, recurrence after first treatment. We also looked at the way a diagnosis was made: clinical, dermoscopy, biopsy or a combination.

Inclusion criteria:

- Patients first time diagnosed with cutaneous squamous cell carcinoma in situ between 01/01/2023 and 31/12/2023.
- Patients of all ages and genders

Exclusion criteria:

- Patients with a prior diagnoses of cutaneous squamous cell carcinoma in situ
- Patients with a prior diagnoses of (invasive) cutaneous squamous cell carcinoma

Key Objectives

1. To determine the **frequency** of cSCC in situ:
   Estimate the annual incidence of cSCC in situ presenting to a private dermatology practice over a one-year period.
2. To evaluate **diagnostic modalities** for cSCC in situ:
   Asses the utilization and effectiveness of various diagnostic techniques (clinical examination, dermoscopy, biopsy) in confirming the diagnosis

3. To investigate **treatment approaches** for cSCC in situ:
   Determine the types of treatment administered for bowen's disease within the private practice and compare the efficacy and recurrence rates associated with different treatment modalities

In addition

- Characterize the demographic profile
    - Identify the age and gender distribution
- Determine recurrence rates
    - Calculate the proportion of patients experiencing recurrence after initial treatment

4. Results

Frequency: Over a 12-month period, we looked at the data from our private dermatological practice. In this period 4.736 patients consulted for a dermatological problem. Of this total patient population, 138 individuals presented with various clinical scenarios related to cSCC in situ, including follow-up treatments and primary diagnoses. This subset represents 2.9% of the total patient population over a one-year period. Further analyse of the data revealed that among the 138 patients with cSCC in situ, 37 cases (26.8%) were newly diagnosed during this period.

Diagnostic Modalities: Over the period of one year, a cohort of 37 patients received the diagnoses of a primary in situ cutaneous squamous cell carcinoma (in situ cSCC). Dermoscopy played a major role in the diagnostic process identificating 19 cases, which constituted 51.35 % of the total sample. Clinical examinations and diagnosis, conducted without the assistance of dermatoscopy or histopathology, led to a diagnosis in 14 cases, representing 37.84%. When clinical and dermoscopic evaluations where inconclusieve, a biopsy was performed, accounting for 4 cases or 10.81 %.

Diagnostic Modality	Frequency	Percentage (%)
Dermoscopy	19	51.35
Clinical	14	37.84
Biopsy	4	10.81

Table 1 – Frequency and Percentage of each diagnostic method used to diagnose cSCC in situ in a private practice.

Treatment Modalities: An analysis of the therapeutic interventions employed for in situ cSCC reveals a diverse array of treatment modalities. The predominant treatment option in our practice was cryotherapy, being utilized in 27 cases, which constitutes 72.97% of the cases. This was followed by the application of 5-fluorouracil (5-FU) in 4 cases (10.81%). The topical chemotherapy agent, Imiquimod and surgical excision wear each used in 2 cases, representing each 5.41 % of the cases. Least frequently utilized were photodynamic therapy (PDT) and biopsy, respectively 2.70 % of the total cases.

Treatment	Frequency	Percentage
cryo	27	72,97%
5FU	4	10.81%
Imiquimod	2	5.41%
Surgery	2	5.41%
PDT	1	2.70%
Biopsy	1	2.70%

Table 2 – Frequency and Percentage of each treatment method used to treat cSCC in situ in a private practice.

Treatment efficacy: Evaluation of the treatment efficacy in this cohort reveals that complete remission was achieved in 59.46% of the cases, while partial remission was achieved in 37.84% of the cases. A minimal proportion, 2.7% of the patients, exhibited no remission.

Treatment efficacy	Percentage
Complete remission	59.46
Partial remission	37.84
No remission	2.7

Table 3 Treatment Efficacy Distribution

Cryotherapy showed notable efficacy with complete remission in 66.67% of the cases where it was used as therapeutic modality. This high success rate underscores its potential as a primary treatment modality for in situ cSCC. Photodynamic therapy (PDT) has a 100% complete remission rate, but fewer cases. Biopsy has a 100 % no remission rate, indicating it's likely used for diagnostic purposes rather than as a treatment modality.

Treatment vs. Recurrence Rate: 59,46 % of patients did not experience recurrence and 40.54% of patients experienced recurrence.

Demographic analysis: This analysis of the patient cohort reveals a predominantly geriatric population affected by in situ cSCC.

Age distribution: The age distribution shows a mean of 72.38 years (SD=9.38), with ages spanning from 52 to 91 years. The distribution appears to be centred around the mean with a moderate degree of dispersion as indicated by the standard deviation, indicating a relatively older patient population.

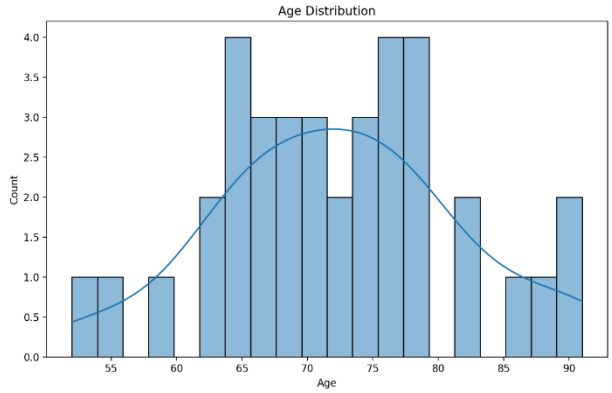

Fig. 1 - Age Distribution

Gender Distribution: The gender distribution shows a marked disparity, with females constituting approximately 73% of the cases and male patients representing the remaining 27%. This indicates a higher prevalence of the condition or a higher rate of seeking treatment among females.

Gender Distribution by Lesion Location: When we look at the gender distribution by lesion location we see that the most common locations for lesions are the face and lower leg, with 10 cases each, followed by the hand with 5 cases. Females have a higher percentage of lesions on the lower leg (33.3%) compared to males (10%). Males have a higher percentage of lesions on the ear (20%) and scalp (20%). Face lesions are common in both genders, but slightly more prevalent in males (30%) than females (25.9%). These findings suggest that there are some gender-specific patterns in the location of lesions, which could be due to various factors.

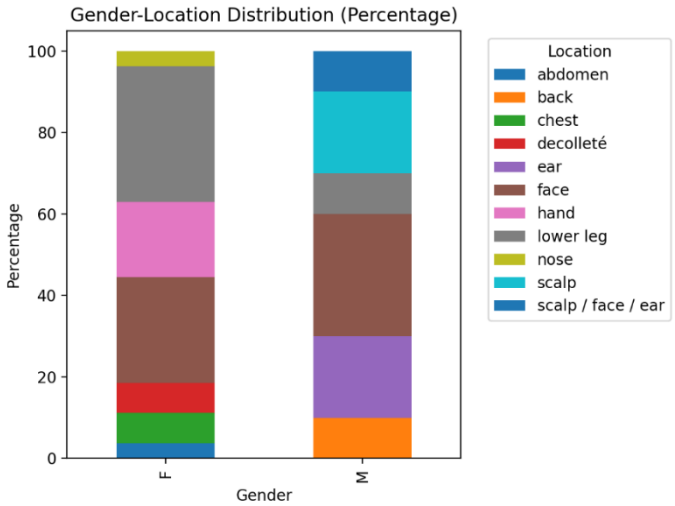

Fig. 2 – Gender – Anatomical Locatin Distribution (Percentage

5. Discussion

Over a 12-month period, we uncovered significant insights into the prevalence and incidence of in situ cSCC in our private practice. Among the total patient population (4736 patients), 138 individuals (2.9%) presented with in situ cSCC related clinical scenarios, including both follow-up treatments and primary diagnoses. This prevalence showes the substantial impact of this condition. Of the 138 in situ cSCC cases, 37 (26.8%) were newly diagnosed during the study period. These new diagnoses highlight the importance of ongoing screening protocols.

Diagnostic Approaches and Limitations:

The predominant diagnostic tool was dermoscopy, followed by clinical examination, with biopsy as least frequently used diagnostic tool. This hierarchy of diagnostic modalities may reflect different factors f.e. patient preference, lesion location, clinical experience, . . . However, it's important to note that we did not confirm our diagnoses with biopsy or surgery, this limiting the ability to assess the effectiveness of each diagnostic modality. This limitation in addition to the small sample size, may restrict the generalizability of our findings.

Treatment Efficacy and Recurrence Rates:

If we analyse the therapeutic options, biopsy showed a 100% no-remission rate. This outcome, however, should be interpreted cautiously. Rather than indicating treatment failure, it likely reflects the primary diagnostic role of biopsy in the management algorithm of cSCC in situ. Biopsy, in this context, serves as a diagnostic tool rather than a therapeutic intervention.

Looking at the other therapeutic options, cryotherapy and PDT showed promising results. But these outcomes should be considered in the context of individual patient factors, tumor characteristics and specific indications for each treatment approach. It would be beneficial to have studies with a larger cohort to validate these findings.

Statistical analysis of treatment versus recurrence rates yielded a Chi-square statistic of approximately 4.85 and a P-value of 0.43, which is greater than the conventional significance level of 0.05. These results suggest that there is no statistically significant association between the type of treatment and the recurrence rates. However, the small sample size (37 cases) and the exclusion of potentially influential factors (e.g., lesion size, patient characteristics, . . .) limit the reliability of these results. Notably, we observed that many patients prescribed 5-FU treatment discontinued the treatment early due to adverse effects.

Demographic Insights:

The age distribution in our sample aligns with the epidemiological patterns of in situ cSCC. We especially see in situ cSCC manifesting in later decades of life. This underlines the importance of targeted screening end preventive strategies for older adults. Furthermore, the age distribution has also implications for treatment choice and management strategies, as comorbidities often correlate with elder age and may influence therapeutic decisions.

Gender-specific patterns emerged in our study, with a preponderance of female patients. These findings could indicate a higher prevalence of in situ cSCC among women in the studied population or reflect gender-specifid differences in seeking healthcare. Moreover, we observed distinct gender-related patterns in lesion distribution. Females showed a higher incidence of lower leg lesions, possibly reflecting gender-specific sun exposure behaviors or clothing choices. In contrast, males exhibited a higher incidence of ear and scalp lesions, potentially associated with hair loss patterns or occupational sun exposure.

6. Conclusion

Bowen’s disease or cutaneous squamous cell carcinoma in situ (cSCC in situ), is a slow growing, well-demarceted erythematous or scaly patch on the skin. It is a precursor lesion of invasive squamous cell carcinoma (SCC). This precursor lesion has a significant morbidity and is a challenge to public healthcare systems due to escalating economic costs for diagnostics and treatments.

In situ cSCC often occurs on chronically UV exposed skin of elderly patients and with a higher prevalence in woman. Anatomically, lesions most frequently appear on women’s legs and men’s face and scalp.

We focused on the frequency, diagnosis and treatment of cSCC in situ in a private dermatological practice. Despite limited literature on the epidemiology of cSCC in situ, with existing studies often dating back to the previous century and conducted on small populations, we found that 2.9% of our consultations over a one-year period were related to cSCC in situ (including both follow-up and primary diagnoses).

While histopathological examination of a biopsy remains the gold standard for confirming cSCC in situ diagnosis, an analysis of data in our practice indicates that most diagnoses are made through dermoscopy.

A wide range of therapeutic modalities exists for treating cSCC in situ. Treatment selection is influenced by clinician expertise, patient preferences, and various patient and lesion factors. These factors include the patient's age, comorbidities, immune status, medication regimen, treatment adherence, as well as lesion size, thickness, and anatomical location. Both literature and our practice demonstrate that cryotherapy is a frequently employed treatment option.

Future research directions should include large-scale population studies and long-term efficacy assessments. Additionally, investigating the percentage of precursor lesions that progress to invasive SCC would be valuable, necessitating a larger study population and extended observation period.

7. References

1. Palaniappan V, Karthikeyan K. Bowen's disease. Indian Dermatol Online J. 2022;13(2):177.

2. Sharma A, Birnie AJ, Bordea C, Cheung ST, Mann J, Morton CA, et al. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma *in situ* (Bowen disease) 2022. Br J Dermatol. 2023 Feb 10;188(2):186–94.

3. Tokez S, Wakkee M, Louwman M, Noels E, Nijsten T, Hollestein L. Assessment of Cutaneous Squamous Cell Carcinoma (cSCC) In situ Incidence and the Risk of Developing Invasive cSCC in Patients With Prior cSCC In situ vs the General Population in the Netherlands, 1989-2017. JAMA Dermatol. 2020 Sep 1;156(9):973–81.

4. Trakatelli M, Ulrich C, del Marmol V, Euvrard S, Stockfleth E, Abeni D. Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. Br J Dermatol. 2007 May;156 Suppl 3:1–7.

5. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012 May;166(5):1069–80.

6. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer Oxf Engl 1990. 2012 Sep;48(13):2046–53.

7. Övermark M, Koskenmies S, Pitkänen S. A Retrospective Study of Treatment of Squamous Cell Carcinoma In situ. Acta Derm Venereol. 2016 Jan;96(1):64–7.

8. Zalaudek I, Argenziano G, Leinweber B, Citarella L, Hofmann-Wellenhof R, Malvehy J, et al. Dermoscopy of Bowen's disease. Br J Dermatol. 2004 Jun;150(6):1112–6.

9. Eedy DJ, Gavin AT. Thirteen-year retrospective study of Bowen's disease in Northern Ireland. Br J Dermatol. 1987 Dec;117(6):715–20.

10. Cox NH. Body site distribution of Bowen's disease. Br J Dermatol. 1994 Jun;130(6):714–6.

11. Hansen JP, Drake AL, Walling HW. Bowen's Disease: a four-year retrospective review of epidemiology and treatment at a university center. Dermatol Surg Off Publ Am Soc Dermatol Surg Al. 2008 Jul;34(7):878–83.

12. Arlette JP, Trotter MJ. Squamous cell carcinoma in situ of the skin: history, presentation, biology and treatment. Australas J Dermatol. 2004 Feb;45(1):1–9; quiz 10.

13. Papageorgiou C, Apalla Z, Variaah G, Matiaki FC, Sotiriou E, Vakirlis E, et al. Accuracy of dermoscopic criteria for the differentiation between superficial basal cell carcinoma and Bowen's disease. J Eur Acad Dermatol Venereol JEADV. 2018 Nov;32(11):1914–9.

14. Cameron A, Rosendahl C, Tschandl P, Riedl E, Kittler H. Dermatoscopy of pigmented Bowen's disease. J Am Acad Dermatol. 2010 Apr;62(4):597–604.

15. Zalaudek I, Kreusch J, Giacomel J, Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part I. Melanocytic skin tumors. J Am Acad Dermatol. 2010 Sep;63(3):361–74; quiz 375–6.

16. Zalaudek I, Kreusch J, Giacomel J, Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part II. Nonmelanocytic skin tumors. J Am Acad Dermatol. 2010 Sep;63(3):377–86; quiz 387–8.

17. Idriss MH, Misri R, Böer-Auer A. Orthokeratotic Bowen disease: a histopathologic, immunohistochemical and molecular study. J Cutan Pathol. 2016 Jan;43(1):24–31.

18. Neagu TP, Ţigliş M, Botezatu D, Enache V, Cobilinschi CO, Vâlcea-Precup MS, et al. Clinical, histological and therapeutic features of Bowen's disease. Romanian J Morphol Embryol Rev Roum Morphol Embryol. 2017;58(1):33–40.

19. Neubert T, Lehmann P. Bowen's disease - a review of newer treatment options. Ther Clin Risk Manag. 2008 Oct;4(5):1085–95.

20. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. J Am Acad Dermatol. 2001 Mar;44(3):462–70.

21. Shimizu I, Cruz A, Chang KH, Dufresne RG. Treatment of squamous cell carcinoma in situ: a review. Dermatol Surg Off Publ Am Soc Dermatol Surg Al. 2011 Oct;37(10):1394–411.

22. Westers-Attema A, van den Heijkant F, Lohman BGPM, Nelemans PJ, Winnepenninckx V, Kelleners-Smeets NWJ, et al. Bowen's disease: A six-year retrospective study of treatment with emphasis on resection margins. Acta Derm Venereol. 2014 Jul;94(4):431–5.

23. Covadonga Martínez-González M, del Pozo J, Paradela S, Fernández-Jorge B, Fernández-Torres R, Fonseca E. Bowen's disease treated by carbon dioxide laser. A series of 44 patients. J Dermatol Treat. 2008;19(5):293–9.

24. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol. 2007 May;156(5):793–801.

25. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol. 2003 Mar;148(3):539–43.

26. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or Fluorouracil for treatment of squamous cell carcinoma in situ: Results of a multicenter randomized trial. Arch Dermatol. 2006 Jun;142(6):729–35.