ON THE DIAGNOSIS AND TREATMENT OF INTRAEPIDERMAL CARCINOMA

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by Julia Fougelberg and John Paoli

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"In the long history of humankind those who learned to collaborate and improvise most effectively have prevailed."

Charles Darwin

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ABSTRACT

Intraepidermal carcinoma (IEC), also referred to as Bowen disease (BD) or squamous cell carcinoma (SCC) in situ, is a precursor to SCC. The incidence of IEC is increasing rapidly in fair-skinned populations with a subsequent increase in patient morbidity. This calls for optimized patient management through improving diagnosis and choosing the most advantageous treatment. A key step is making a correct diagnosis, which is best accomplished using dermoscopy prior to histopathological confirmation. Several treatment options are available for IEC, e.g. photodynamic therapy (PDT), surgical excision and destructive methods like cryosurgery and curettage. The purpose of this thesis was to evaluate the agreement between dermatologists on the dermoscopic findings of IEC as well as the effectiveness of PDT, surgical excisions and a comparison between cryosurgery and curettage.

In Paper I, the interobserver agreement on dermoscopic features in IEC was analysed among eight international dermatologists. The most commonly observed pre-defined dermoscopic features were shown to be: scales (83%), dotted/glomerular vessels (77%), pinkish-white areas (73%), and hemorrhage (46%). The interobserver agreement was poor to moderate overall with scales (0.55) and hemorrhage (0.54) showing the highest Kappa scores. Pinkish-white areas showed the lowest Kappa value (0.015). In Paper II, we assessed the effectiveness, recurrence risk, and factors affecting

the response rate of PDT for IEC. PDT resulted in a clearance rate of 63.4% overall. Larger lesions (>20 mm) and only one PDT session resulted in higher risk for incomplete response or recurrences. In Paper III, we aimed to assess factors affecting incomplete excision of IEC. Surgeons with less experience showed independently higher rates of incomplete surgical excisions using a less strict definition (mild to moderate dysplasia at the resection margin), whereas according to the strict definition (no dysplasia at the resection margin), less experienced surgeons and tumors located on the upper body showed independently higher rates of incomplete excision. In Paper IV, we conducted a randomized controlled trial to compare the effectiveness of cryosurgery and curettage for IEC. The overall clearance rate 1 year after cryosurgery was significantly higher than with curettage (94.6% vs 78.9%). Nevertheless, wound healing times were significantly shorter with curettage.

In conclusion, the interobserver agreement for dermoscopic findings of IEC is poor to moderate. PDT provides clearance in approximately two-thirds of the treated IECs. Risk factors for incomplete excisions of IEC are less experienced surgeons and location on the head and neck area or upper extremities. Cryosurgery and curettage both show high clearance rates, with cryosurgery being significantly more effective and wound healing times being shorter with curettage.

Key words: Intraepidermal carcinoma, Bowen disease, squamous cell carcinoma in situ, dermoscopy, photodynamic therapy, surgical excision, cryotherapy, curettage, destructive treatment.

Sammanfattning på svenska

Intraepidermal cancer (IEC), också kallat skivepitelcancer in situ eller Morbus Bowen (Mb Bowen) är ett förstadium till den näst vanligaste formen av hudcancer, skivepitelcancer. Incidensen i Sverige ökar snabbt och i och med detta ökar även sjukdomslidande och belastning på sjukvården. Det finns flera möjliga behandlingsalternativ. I Sverige är destruktiv behandling med kryokirurgi, alternativt med kyrettage och elektrodesiccation, två av standardmetoderna för behandling av IEC. Internationellt är kirurgisk excision standardmetoden. Andra vanliga behandlingar är fotodynamisk terapi (PDT) och lokalbehandling med 5-fluorouracil kräm. Få jämförande studier av behandlingsmetoder har gjorts och ingen metod har tydligt visats vara överlägsen. Med tanke på den goda prognosen och den ökade förekomsten, är det önskvärt med en effektiv, skonsam och kostnadseffektiv behandlingsmetod vid IEC. Syftet med denna avhandling var att studera dermatoskopiska fynd vid IEC, samstämmigheten mellan dermatologer i bedömning av dessa fynd, samt att beskriva en gemensam terminologi för dessa. Vidare, att ytterligare utvärdera behandlingsalternativ genom att studera effektivitet och riskfaktorer vid behandling med PDT, kirurgiska excisioner och kryokirurgi jämfört med kyrettage.

För att kunna ställa rätt klinisk diagnos på IEC används ett dermatoskop, ett handhållet instrument där strukturer i över- och läderhuden undersöks med hjälp av genomlysning. I studie I undersökte vi frekvensen av dermatoskopiska fynd i en ljushyllt, svensk befolkning, såväl som samstämmigheten mellan dermatologer från olika länder. Vi fann att fjäll (83%), punktata/glomerulära kärl (77%), rosa-vita områden (73%) och blödning (46%) var de vanligaste dermatoskopiska fynden. Samstämmigheten mellan dermatologerna var dålig till måttlig med de högsta Kappa-värdena noterade för fjäll (0.55) och blödning (0.54) och lägst värde för rosa-vita områden (0.015). I studie II utvärderade vi utläkningsgrad samt riskfaktorer för recidiv vid behandling med PDT som visade en total utläkningsgrad på 63%. Stora tumörer (>20 mm) samt en istället för två omgångar med PDT var signifikanta riskfaktorer för återfall. I studie III ville vi utvärdera kliniska och patologiska riskfaktorer för icke-radikala excisioner av IEC. Mindre kirurgisk erfarenhet var associerat med

icke-radikalitet när vi använde en mindre strikt definition (viss dysplasi i operationsmarginalen), medan mindre erfarenhet och tumörer i huvud- och halsområdet eller övre extremiteter var associerade med icke-radikalitet med en strikt definition (ingen dysplasi i operationsmarginalen). Studie IV var en randomiserad kontrollerad studie för att jämföra effektiviteten av kryokirurgi och kyrettage. Båda behandlingsmetoderna visade relativt hög utläkningsgrad efter 1 års uppföljning, dock med signifikant högre utläkningsgrad med kryokirurgi (94.6%) än med kyrettage (78.9%). Kyrettage ledde dock till signifikant kortare sårläkningstid.

Sammanfattningsvis fann vi att samstämmigheten i bedömningen av dermatoskopiska fynd i IEC är dålig till måttlig. Behandling av IEC med PDT ger relativt hög total utläkningsgrad. Riskfaktorer för icke-radikala excisioner av IEC är mindre erfarna kirurger och IEC lokaliserat till huvud- och halsområdet eller övre extremiteter. Kryokirurgi och kyrettage visar båda hög total utläkningsgrad, men det finns en signifikant skillnad mellan metoderna till förmån för kryokirurgi.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Fougelberg J, Luong A, Bowling J, Chamberlain A, Lallas A, Marghoob A, Polesie S, Salerni G, Tanaka M, Zaar O, Zalaudek I, Claeson M, Paoli J. "Dermoscopic findings in intraepidermal carcinoma: an interobserver agreement study". Dermatol Pract Concept. 2023;13(1):e2023114.

II. Zaar O, Fougelberg J, Hermansson A, Gillstedt M, Wennberg-Larkö AM, Paoli J. "Effectiveness of photodynamic therapy in Bowen's disease: a retrospective observational study in 423 lesions". J Eur Acad Dermatol Venereol. 2017;31(8):1289-1294.

III. Fougelberg J, Ek H, Claeson M, Paoli J. "Surgical treatment of Bowen's disease: clinicopathologial factors associated with incomplete excisions". Dermatol Pract Concept. 2021;11(2):e2021046.

IV. Fougelberg J, Backman E, Hasselquist E, Hylén A, Claeson M, Paoli J. "Cryosurgery vs. curettage for intraepidermal carcinoma: a prospective, randomized controlled trial". In manuscript.

Table of Contents

Abbreviations

5-FU	5-Fluorouracil
AK	actinic keratosis
ALA	5-aminolevulinic acid
BCC	basal cell carcinoma
C&ED	curettage & electrodesiccation
CI	confidence interval
CRF	case report form
DL	daylight
FCM	fluorescence confocal microscopy
FTC	freeze-thaw cycle
FU	follow-up
HPV	human papillomavirus
IEC	intraepidermal carcinoma
MAL	methyl aminolevlulinate
NMSC	non-melanoma skin cancer
PDT	photodynamic therapy
SCC	squamous cell carcinoma
SDL	simulated daylight
SUH	Sahlgrenska Univeristy Hospital
UV	ultraviolet
OR	odds ratio

1.

Introduction

1.1 Skin cancer

The steadily increasing incidence of skin cancer is a growing problem in fair-skinned populations worldwide, including the Swedish population. Skin cancer is broadly divided into melanoma and non-melanoma skin cancer (NMSC). Nowadays, NMSC is often referred to as keratinocyte cancer, i.e. squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). However, these terms cannot be used as synonyms since the term NMSC also includes rare skin cancers of non-keratinocytic origin such as Merkel cell carcinoma, pleomorphic dermal sarcoma, atypical fibroxanthoma, dermatofibrosarcoma protuberans, Kaposi sarcoma or angiosarcoma.[1]

In 2021, 5,038 cases of melanoma and 6,484 melanoma in situ were registered in the nationwide Swedish Cancer Registry. In addition, 11,366 cases of NMSCs (mainly SCCs and BCC excluded) were registered. Since 2004, the Swedish Board of Health and Welfare also registers all histopathologically verified cases of BCC. Almost 70,000 new BCCs were diagnosed in Sweden in the year 2021.[2] Along with the increasing number of patients with skin cancer comes a growing cost on society as greater resources are required to diagnose and treat the affected patients.[3, 4] The estimated cost for treating skin cancer in Sweden in 2011 was €177.6 million with NMSC being the most costly diagnosis (€42.8 million in direct healthcare costs alone).[3]

1.2 Non-melanoma skin cancer

In Sweden, NMSC (excluding BCC) is the second most common group of cancers among both women and men after breast and prostate cancer, respectively.[5] In 2021, according to the Swedish Cancer Registry, this group of skin cancers accounted for 96.6 per 100,000 person-years in women and 121.5 per 100,000 person-years in men (age-standardized to the Swedish population in 2000).[2] Over the last decade, the incidence has increased by an average of 4.8% for women and 4.2% for men.[5]

1.3 Squamous cell carcinoma

The number of new cases of SCC diagnosed each year in Sweden today is almost twice as many as 10 years ago.[1] Cutaneous SCC originates from keratinocytes in the epidermal layer of the skin before invading the dermis and eventually deeper structures.[6] Similar to other NMSCs, SCC is more common in fair-skinned individuals, in the elderly, after chronic exposure to ultraviolet (UV) radiation and in immunosuppressed patients.[7, 8] Clinically, SCC can present as a relatively fast-growing nodular lesion with central hyperkeratosis, ulceration or crusting, and it is predominantly located in chronically sun-exposed areas, such as the head and neck area, forearms and back of the hands.[9-11] The risk for primary SCC to metastasize is estimated to be 2-4%. Patients with metastasized SCC carry a poor prognosis.[12] In 2016, 77 people died from SCC in Sweden.[2]

The gold standard for diagnosing SCC is an incisional or excisional biopsy followed by histopathologic evaluation, i.e. when a pathologist uses a microscope to examine the cellular morphology in thin slices of tumor tissue. In addition to histopathology, dermoscopy has become one of the basic diagnostic methods in clinical practice. Dermoscopic signs such as white circles, white structureless areas, concentric hairpin vessels surrounding a hyperkeratotic mass and/or hemorrhage may be present and provide further support for the diagnosis (Figure 1).[13-18]

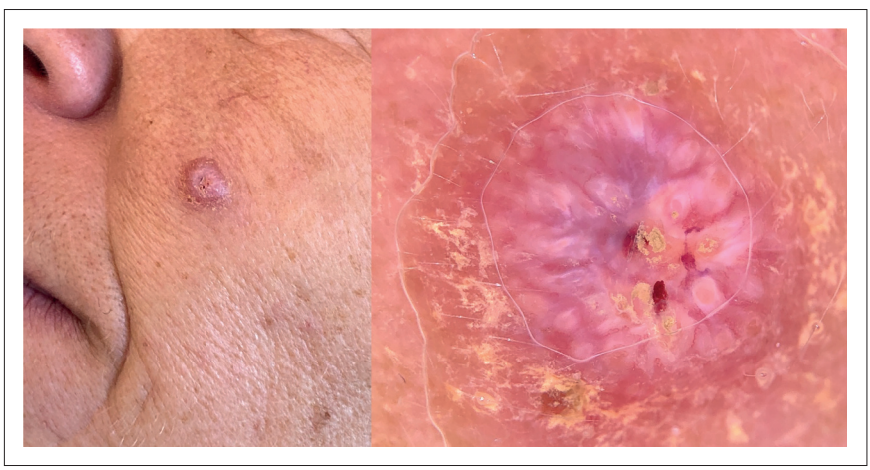
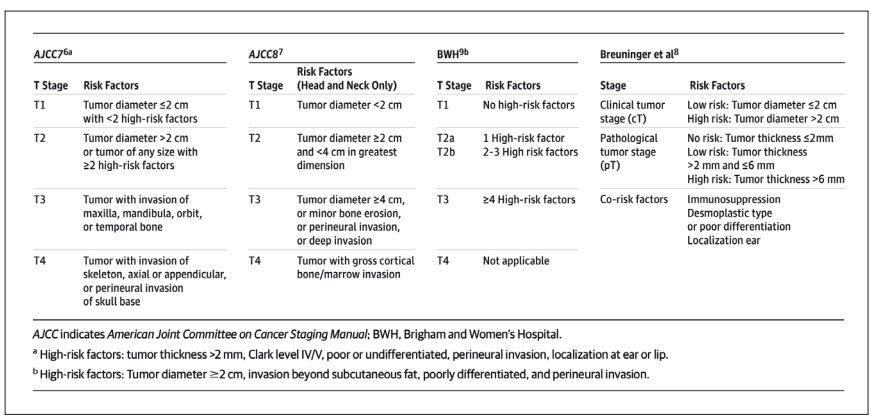


Figure 1. To the left a clinical image of SCC. To the right a dermoscopic image of SCC

SCC can be classified as high-risk and low-risk tumors and affected patients can be considered high-risk and low-risk patients.[19] According to the Swedish national guidelines for managing SCC, high-risk tumors present two or more of the following risk factors according to the Brigham and Women's Hospital staging system: diameter >2 cm, tumor invasion beyond the subcutaneous fat, poor differentiation and perineural invasion in a nerve with a diameter ≥0.1 mm.[19, 20] There are however several other staging systems for SCC apart from Brigham and Women's Hospital BHW used by the Swedish national guidelines for SCC.[20] Other staging systems are American Joint Committee on Cancer staging system 7th edition[21] and 8th edition[22] and the Breuninger system.[23] All systems are based on tumor characteristics and factors related to the risk of metastasis (Figure 2).[24] Organ transplant recipients or patients with other immunosuppression, genetic predisposition or with a history of a large number of previous SCCs are classified as high-risk patients. Such patients have an increased risk of new tumors, of recurrence or metastases. Patients without these risk factors are classified as low-risk patients.[19]



AJCC[6a]

T Stage	Risk Factors
T1	Tumor diameter ≤2 cm with <2 high-risk factors
T2	Tumor diameter >2 cm or tumor of any size with ≥2 high-risk factors
T3	Tumor with invasion of maxilla, mandibula, orbit, or temporal bone
T4	Tumor with invasion of skeleton, axial or appendicular, or perineural invasion of skull base

AJCC[7]

T Stage	Risk Factors (Head and Neck Only)
T1	Tumor diameter <2 cm
T2	Tumor diameter ≥2 cm and <4 cm in greatest dimension
T3	Tumor diameter ≥4 cm, or minor bone erosion, or perineural invasion, or deep invasion
T4	Tumor with gross cortical bone/marrow invasion

BWH[9b]

T Stage	Risk Factors
T1	No high-risk factors
T2a T2b	1 High-risk factor 2-3 High risk factors
T3	≥4 High-risk factors
T4	Not applicable

Breuninger et al[8]

Stage	Risk Factors
Clinical tumor stage (cT)	Low risk: Tumor diameter ≤2 cm High risk: Tumor diameter >2 cm
Pathological tumor stage (pT)	No risk: Tumor thickness ≤2mm Low risk: Tumor thickness >2 mm and ≤6 mm High risk: Tumor thickness >6 mm
Co-risk factors	Immunosuppression Desmoplastic type or poor differentiation Localization ear

AJCC indicates *American Joint Committee on Cancer Staging Manual*; BWH, Brigham and Women's Hospital.

[a] High-risk factors: tumor thickness >2 mm, Clark level IV/V, poor or undifferentiated, perineural invasion, localization at ear or lip.

[b] High-risk factors: Tumor diameter ≥2 cm, invasion beyond subcutaneous fat, poorly differentiated, and perineural invasion.

Figure 2. Figure borrowed with permission from the article "Validating 4 Staging Systems for Cutaneous Squamous Cell Carcinoma Using Population-Based Data: A Nested Case-Control Study"24 showing the risk factors included in different SCC staging systems.

Early detection and surgical removal of SCC improves prognosis.[25, 26] The majority of SCCs are successfully treated with the standard treatment, which is surgical excision.[27, 28] For well- or moderately differentiated low-risk tumors (including keratoacanthoma) <2 cm in diameter, a surgical margin of at least 4 mm is recommended and achieves a complete excision in 95% of cases.[29-32] Second-line treatment options for low-risk tumors are curettage plus cryotherapy or electrodesiccation.[33-35] These methods are only effective in experienced hands and are recommended only in carefully selected cases, i.e. small, well-demarcated, well-differentiated (histopathologically verified) SCC of the trunk or extremities in elderly individuals where surgery is not suitable.[33-35] For high-risk tumors, excision should be performed with 6-10 mm clinical margins to ensure complete excision.[28-31, 36].

In Sweden, most patients with SCC are managed in outpatient care. If major surgery is required or in cases of advanced disease, staging procedures and treatment usually take place within specialist healthcare at larger hospitals in Sweden.[19] For inoperable tumors (e.g. located in areas unsuitable for surgery), radiotherapy can be an option.[37] For advanced or metastasized SCC, systemic treatment options with a curative intent include immunotherapy (cemiplimab), epidermal growth factor receptor inhibitors, chemotherapy and electrochemotherapy.[37]

SCC is part of a spectrum of varying degrees of epithelial dysplasia and has two types of precursor lesions: actinic keratosis (AK) and intraepidermal carcinoma (IEC) (Figure 3). The incidence of SCC precursor lesions has also increased greatly in countries with mainly fair-skinned populations during the past few decades.[38, 39]

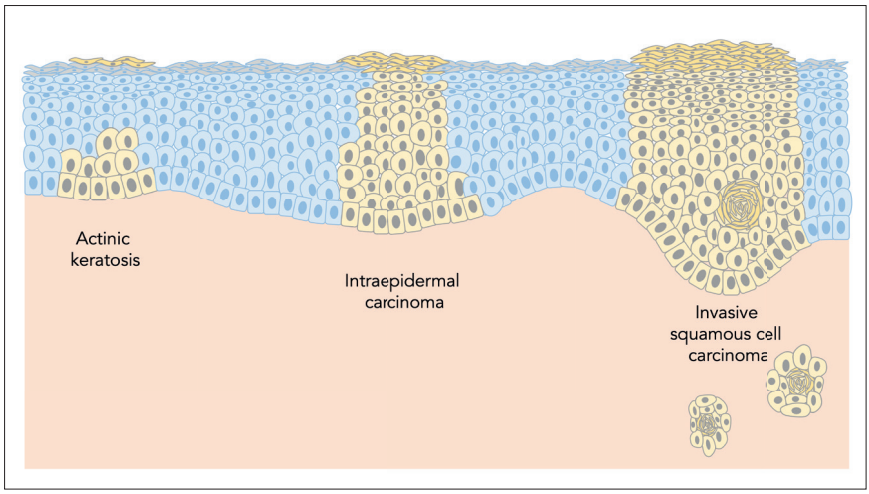


Figure 3. Showing keratinocyte dysplasia. from the left: dysplasia restricted to half or the epidermis (AK). Middle: full thickness epidermal dysplasia (IEC). Right: invasion of dysplasia below basal membrane (SCC).

1.4 Actinic keratosis

Actinic keratosis (AK) is a common diagnosis in dermatological practice and is considered to be a low-risk disease with varying degrees of intraepidermal keratinocyte dysplasia. The estimated overall prevalence of AKs lies between 6% and 26% and, due to an aging population, the incidence is increasing in industrialized countries with mainly fair-skinned populations.[40, 41] Regions with high ambient exposure to UV radiation, present even higher prevalence (40–60%).[42] Although considered a low-risk disease, AKs can progress into invasive SCC, which can subsequently metastasize.[41, 43-45] The risk of progression of AK into SCC ranges between 0.025% and 16% per year.[46] There are clinical and histopathological classification systems for grading AKs.[44, 47] Histopathologically, AKs are classified as grade I with atypical keratinocytes within the lower third of the epidermis, grade II with atypical keratinocytes within the lower two-thirds and grade III or in situ carcinoma with full-thickness epidermal involvement of atypical keratinocytes.[44] The Olsen classification scheme (grades I-III) is a clinical classification based on lesion thickness and degree of hyperkeratosis. The Olsen classification distinguishes between slightly palpable and less hyperkeratotic AK grade I, moderately thick

and hyperkeratotic AK grade II and very thick and hyperkeratotic AK grade III.[47, 48] AKs are usually diagnosed clinically, although two recent studies showed that the the histopathological grade of dysplasia does not match the clinical appearance of AK .[47, 49] Furthermore, the grade of dysplasia within the epidermis was thought to be correlated with the risk of developing invasive carcinoma.[50] However, AK with dysplasia restricted to the lower third of the epidermis (grade I) were shown to be the most common AKs associated with invasive SCC according to a study conducted by Fernández-Figueras et al.[51] This suggests that AK can progress into invasive SCC independently of their histopathological grading and the upward distribution of dysplasia in the epidermis.

1.5 Intraepidermal carcinoma

Intraepidermal carcinoma (IEC) including Bowen disease (BD) and SCC in situ, is named after the American dermatologist Prof. John T. Bowen (Figure 4). In 1912, Bowen described six lesions with red, uneven, crusted and scaling plaques, which he called "precancerous dermatoses" with clinical and histopathological similarities with other precancerous lesions.[52-54] He concluded that the lesions had a potential of being malignant and Darier suggested that the disease be named after Bowen.[52, 55] These lesions are defined as premalignant intraepidermal skin tumors with keratinocyte dysplasia extending throughout the entire epidermis without crossing the basal membrane. [54] Patients may present with single or multiple lesions. There is still an ongoing discussion among dermatologists whether Bowen disease is synonymous to SCC in situ or if they are two different variants of IEC. Bowen disease usually presents as a more well-defined, erythematous patch with scaling surrounded by healthy tissue, whereas SCC in situ normally displays as a poorly defined lesion on sun-damaged skin or as a part of field cancerization. Other clinical presentations of IEC are hyperkeratotic, hyperplastic, pigmented, and partly pigmented variants.

1.5.1 Histopathology

As described above in the section on AK, IEC is similar to AK grade III with keratinocyte dysplasia affecting the full thickness of the epidermis.[44] Histopathologic characteristics include hyperkeratosis, altered

Figure 4. Prof. John T. Bowen (by Nestorek - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=59178473).

maturation of keratinocytes and nuclear atypia with hyperchromasia and multinucleation.[56] There is also a discussion among pathologists whether there is a difference between SCC in situ and BD. In the WHO classification of skin tumors, the terms are described to be synonymous stating that "Bowen's disease and SCC in situ are now used interchangeably to describe epidermal SCC in situ of both sun-damaged and sun-protected skin".[57] However, Elder et al. describe BD histopathologically as containing a greater disorder of the nuclei, clumping of nuclei and dyskeratosis. Furthermore, BD is described as having a thicker layer of dysplasia and are more well-demarcated and without elastosis in contrast to SCC in situ.[58] Examples of these differences are illustrated in Figure 5.

1.5.2 Epidemiology

There are only a few reports available on the incidence of IEC in fair-skinned populations. A Canadian study has shown an annual incidence per

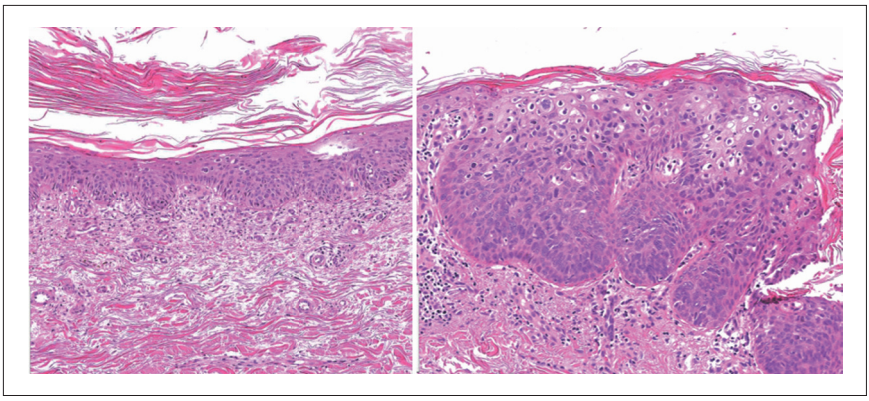


Figure 5. Histopathological images of two IECs with solar elastosis in the example to the left and well-demarcated borders, a thickened layer of dysplasia and without solar elastosis to the right.

100,000 person-years (age-standardized to the 1991 Canadian population) of 22.4 in women and 27.8 in men between 1996 and 2000.[54] A recent single-center study from the Netherlands reported an incidence of 76.8 in women and 59.2 in men per 100,000 person-years (age-standardized to the European standard population in 2013) with incidence increasing significantly between 2003 and 2013.[39] In comparison, the incidence of 115 in women and 174 in men per 100,000 (age-standardized to the 1980 U.S. white population) in the white Hawaiian population between 1983 and 1987 indicated an environmental correlation between UV exposure and higher incidence rates.[59] Thus, these incidence rate estimates are not directly comparable given the different sampling frame and ambient exposure to UV radiation in the study populations. There are no publications describing the change in incidence rate of IEC in Sweden, but the number of new cases per year are available as raw data from the Swedish Cancer Registry.[2] During the 10-year period of 2009 to 2019, the number of new cases per year more than doubled from 6,800 to approximately 13,800. Interestingly, 53% of reported cases in Sweden in 2021 occurred in women.[1]

1.5.3 Risk factors

Risk factors for developing IEC are similar to those of invasive SCC. The most important risk factors are exposure to UV radiation, and

immunosuppression.[54, 60, 61] High age and fair skin, (Fitzpatrick I-III) are also known risk factors.[6, 10] The most common cause of cutaneous SCC and its precursors is considered to be the cumulative effect of UV radiation from sun exposure.[62-64] By producing DNA damage and immunosuppression, UV radiation leads to the development of dysplasia and in situ disease.[65, 66] Another risk factor associated with developing IEC on certain anatomical locations is HPV infection. For example, HPV type 16 has been found in 60% of periungual and palmoplantar lesions of IEC.[67] Further, genital presentations of IEC are often associated with HPV infection and/or lichen sclerosus.[68-70] HPV DNA has also been shown to be present in one-third of extragenital IECs.[71, 72] The risk of developing IEC is much greater in patients with iatrogenic immunosuppression following organ transplantation, in whom SCC occurs 65–250 times more frequently than in the general population.[73-75] Other types of immunosuppressive therapy, such as azathioprine, cyclosporin, and systemic corticosteroids have also been shown to increase the risk of developing cutaneous malignancies.[76, 77] Furthermore, exposure to arsenic (mainly from contaminated water), ionizing radiation, burn wounds and chronic inflammatory skin diseases can also lead to the development of IEC.[78]

The risk of development into invasive SCC has been described to be 3-5% in extragenital IEC.[79] However, a relatively recent study found that 16.3% of 566 cases of IEC diagnosed with a preoperative biopsy were later confirmed as SCC when treated surgically. [80] Furthermore, a retrospective study comparing treatment with 5-fluoruracil (5-FU), PDT and surgical excision showed that 18 of 296 (6.0%) lesions diagnosed as IEC on biopsy were diagnosed as SCCs in the excision specimen and 8 of 287 (2.7%) tumors progressed into a SCC after non-invasive therapies such as PDT and 5-FU.[81] However, IEC lesions treated with surgical excision may represent a group with higher clinical suspicion of SCC, which may explain why physicians choose surgery instead of non-invasive treatments in these cases.[81] Genital IECs, including penile intraepithelial neoplasia (PeIN), vulval intraepithelial neoplasia (VIN) and anal intraepithelial neoplasia (AIN) are in general more difficult to treat and have a higher rate of development into invasive SCC (10%) compared to extragenital IEC.[79, 82] Due to the substantial differences between genital and extragenital IEC, this thesis focuses solely on extragenital IEC.

1.6 Diagnosis and imaging

1.6.1 Clinical diagnosis

For IEC and other skin cancers, the diagnostic approach often combines clinical inspection, the use of dermoscopy, and histopathological examination. The clinical full body examination gives an overall impression of the patient's skin and an overview of the distribution of sun damage and the number of skin cancers, which is important when choosing the right treatment method. IEC usually presents as a well-demarcated, red and hyperkeratotic plaque with slow radial growth. IEC can also be pigmented in some cases.[83-85] The overlying scales are often white or yellowish. Single lesions are most common, but 10-20% of patients with IEC have multiple lesions.[54, 86] However, clinical appearance of IEC differ based on multiple variables such as the degree of keratinization, body site, duration of the of the lesion and skin type.[54]

1.6.2 Dermoscopy

The most commonly used diagnostic device is the dermoscope. Dermoscopy is a non-invasive technique that allows for the visualization of pigmented, fibrous and vascular structures in the epidermis and upper part of the papillary dermis. With the dermoscope, one can study morphological structures, vascular patterns and small pigmentations that are not normally visible to the eye.[87, 88] The instrument consists of a built-in high-quality magnifying lens and a powerful lighting system.[89] The most common types of dermoscopes used today provide a 10x magnification and are hand-held devices. Light sources with polarized and/or non-polarized filtering are used to enhance and visualize the different types of features.

For the diagnosis of NMSC overall, dermoscopy has shown a sensitivity of 87-96% and specificity of 72-92%.[90] Typical dermoscopic features of IEC include the presence of glomerular/dotted blood vessels, yellow-white scales, hemorrhage and pigmented structures.[54, 87, 88, 91-99] A study by Sgouros et al. that only included 9 IECs showed a specificity of 93.6% for the dermoscopic finding of glomerular vessels, 97.9% for clustered vessels, and 87.2% for erosions. Meanwhile, the sensitivity for both glomerular and clustered vessels was 88.9%, whereas erosions had a lower sensitivity of 55.65%. [100] Examples of clinical and dermoscopic images of IEC are shown in Figure 6.

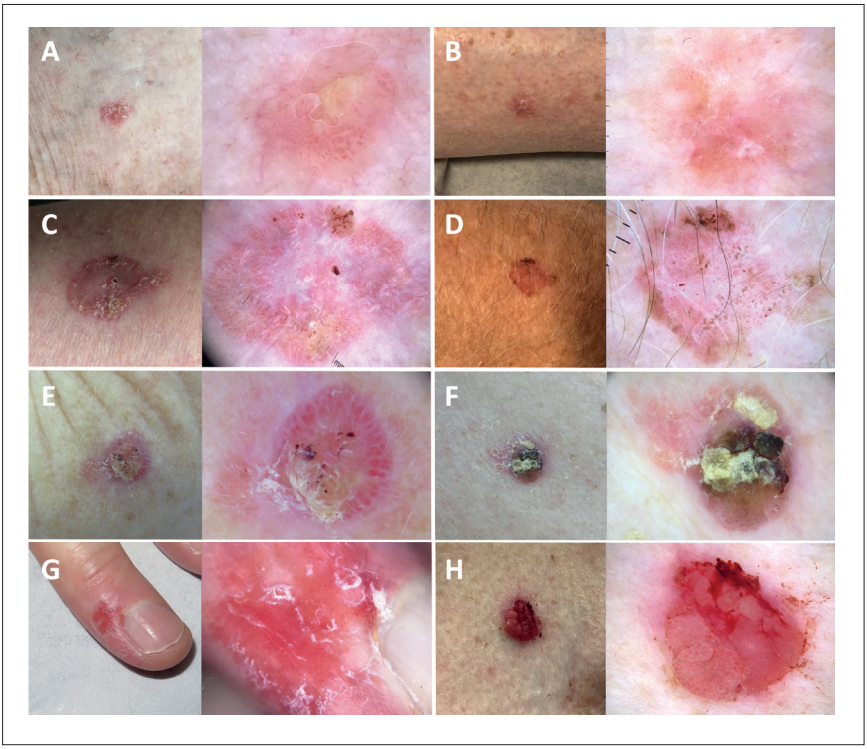


Figure 6. Examples of IEC showing: dermoscopic findings such as (A) & (B) glomerular/dotted blood vessels and yellow-white scales, (C) shiny white structures, (D) pigmented structures and (E) hemorrhage as well as clinical variations including (F) hyperkeratotic IEC, (G) periungual IEC and (H) hyperplastic IEC.

1.6.3 Other diagnostic methods

Although dermoscopy is still the most common non-invasive method used to evaluate skin cancers, other diagnostic methods have also been developed. One of the most promising techniques is in vivo reflectance confocal microscopy (RCM), which is a non-invasive technique that examines the epidermis and papillary dermis with cell level resolution.[101] RCM uses a laser at a wavelength of 830 nm to form a horizontal view of the skin down to a depth of 0.2-0.3 nm.[102] It is generally used as a "second level" of examination after dermoscopy to improve diagnostic accuracy.[103] RCM provides a gray-scale (black and white) horizontal image of the cellular and subcellular structures in the epidermis. A study on

100 tumors of melanocytic and keratinocytic origin showed a sensitivity of 100% and a specificity of 80.0%, for this technique. Sensitivity was higher for experienced RCM users (91%) compared to beginners (85%) while specificity was more similar (80%, for experienced and 78% for beginners).[104] Similarly, Mogensen et al. reported a sensitivity for diagnosing of NMSC between 94-100%.[90]

Confocal microscopy can also be used on excised tissue ex vivo. The ex vivo confocal microscopy uses a fluorescing agent which increases the contrast. The technique is called fluorescence confocal microscopy (FCM). FCM also uses lasers but with two wavelengths (785 nm and 488 nm) for recording both reflectance and fluorescence signals. The technique has been further developed to produce digital staining, i.e. color images mimicking the actual histopathological haematoxylin-eosin stained sections making it easier to interpret the images.[105] Furthermore, FCM has shown potential in assessment of the invasion and grading of SCC.[106]

Although RCM and FCM have proven to be valuable tools for evaluating and diagnosing skin lesions and determining target areas to biopsy or to treat, these techniques are time-consuming and expensive compared to dermoscopy. Also, RCM and FCM require an experienced user before a diagnostic accuracy similar to that of dermsocopy, can be reached. Other non-invasive diagnostic techniques such as optical coherence tomography, high-frequency ultrasound, multiphoton microscopy or terahertz pulsed imaging are not commonly used for the diagnosis of IEC and are therefore not described further in this thesis.[107] .

1.7 Treatment methods

As described above, the prognosis of IEC is good. However, the risk of developing invasive SCC and eventually metastasized SCC, makes it important to treat IEC, preferably at an early stage. The effectiveness and outcome of destructive treatment methods for IEC have been evaluated and reviewed in several studies.[54, 108-112] However, treatment protocols vary greatly and are not always clearly defined. The methods are user-dependent which complicates comparisons and clinical application. To date, no single treatment method has clearly proven to be superior to another.[108-110] Given the relatively benign nature of IEC and the affected

elderly patient population, there is a need to provide an effective yet gentle treatment modality. The economics of the approach are also important given the increased morbidity and social costs.[113] The most common treatment methods used for IEC include: surgical excision, PDT, topical 5-FU and destructive treatment such as cryotherapy, and curettage and electrodessication (C&ED).[110, 114-116] When choosing the optimal treatment method, characteristics of the IEC lesion are considered including its size and location, as well as the patient's general health condition and personal preferences (Table 1).[117]

Table 1. Considerations to be taken when choosing treatment method for IEC.

Patient-related considerations
Age
Comorbidities
Immune status
Previous treatments
Compliance and patient preferences
Cosmetic outcome
Tumor-related considerations
Number of lesions
Anatomical site
Lesion diameter and thickness
Degree of hyperkeratosis
Treatment-related considerations
Availability
Effectiveness
Adverse events
Cost
Physician-related considerations
Skills and experience with different treatment methods
Treatment traditions

1.7.1 Surgical excision

Surgical excision is considered as one of the standard methods for treating IEC. When performing surgical excision on IEC, the tumor is excised with a clinical safety margin added around the lesion. Surgery can be performed with different techniques, elliptic excision being the most common (Figure 7). A punch biopsy excision or shave biopsy excision can also be used in some cases.[118, 89, 119] Recommended excision margins differ from 2-6 mm, but no consensus on excision margins on IEC has been reached.[120, 121] Also, surgical excisions may be complicated on certain locations connected to poor wound healing such as the lower leg.[81, 115] Surgical excision has shown high success rates compared to PDT and 5-FU.[81] However, a relatively large number of incomplete excisions (12.8-23.8%) are observed, especially when smaller safety margins are applied.[119, 120] Furthermore, studies show recurrence rates of 0.8-5.5% upon 5-year follow-up (FU) after surgical excision.

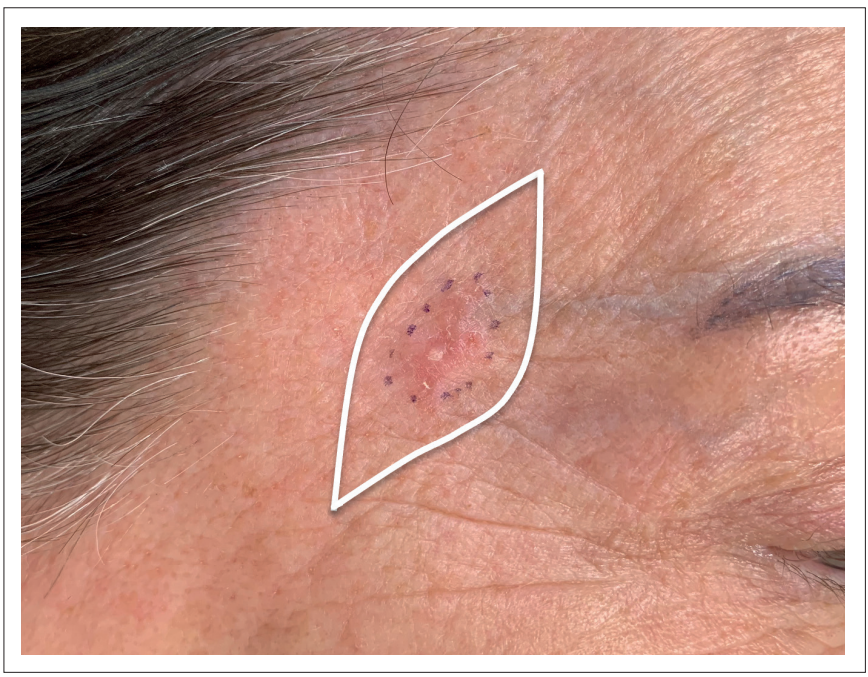


Figure 7. Intraepidermal carcinoma on the temple of a female patient demarcated with a surgical marker (dotted blue line) plus the hypothetical planning of an elliptic excision using a 3-mm clinical margin (white outline).

1.7.2 Photodynamic therapy

Conventional PDT (C-PDT) is performed in two steps. First, gentle curettage is carried out on the IEC to remove any hyperkeratosis. Then, a photosensitizing prodrug, either 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), is applied to the lesion for three hours. Finally, the area is illuminated with red light at 635 nm. The dysplastic keratinocytes in the IEC absorb the ALA/MAL, which is converted to protoporphyrin IX through the heme cycle. During exposure to red light (8-10 min), the photodynamic process generates a production of singlet oxygen and free radicals, which leads to mitochondrial damage and cell destruction.[115] Most commonly, treatment is performed in two sessions with an interval of 1-3 weeks. PDT is frequently used for superficial precancerous and cancerous skin lesions such as AK, superficial BCC and IEC. Response rates after PDT in the treatment of IEC range from 52% to 100% and recurrence rates vary from 0% to 46% but with favorable cosmetic outcomes.[89, 115, 116, 122-131] However, varying treatment protocols, FU periods and number of PDT sessions make comparisons between studies difficult.

C-PDT is known to be painful and expensive compared to other treatment methods.[113, 132] Clinic visits during C-PDT for NMSC with a duration of approximately 4 hours and the discomfort for the patient during therapy as described above can be ameliorated with daylight-mediated PDT (DL-PDT). DL-PDT is considered to be a simpler and more tolerable (less painful) alternative procedure than C-PDT.[133] After lesion preparation and application of a sunscreen, the same sensitizing drug as for C-PDT (MAL or ALA) is applied to the treatment area. Immediately after, patients expose themselves to natural sunlight for 1.5-2.5 hours.[134] Randomized and controlled studies have shown that DL-PDT is an effective, convenient and almost pain-free treatment for AKs.[134-136] However, a study on DL-PDT on IEC, showed low clinical response rates of only 25% (six out of nineteen lesions) (25%) at FU after three months.[137] DL- PDT is especially practical for patients with large areas of field cancerization including grade I or II AKs.[133] Furthermore, in countries with poor weather conditions or where daylight is not enough throughout the year, simulated DL-PDT (SDL-PDT) could be an option. The treatment procedure is similar to DL- PDT but instead of being outside in natural sunlight, the patients stay in a room with artificial illumination simulating daylight. One example is the Lighting System IndoorLUX®, which

can be installed in a regular treatment room indoors, generating the same type of light as a sunny summer day outdoors with standardized light dosing but without the harmful UV rays.[138] Limitations such as restriction to certain times of the year at the Swedish latitudes, rain and cold temperatures can be avoided by using SDL-PDT. As with DL-PDT, SDL-PDT also benefits from being much less painful than C-PDT.[139, 140]

1.7.3 5-Fluorouracil

5-FU is a well-known topical treatment method for IEC. In the 60s, topical 5-FU was identified and proved to be a promising treatment for precancerous lesions such as AK and IEC.[141-143] 5-FU has shown to have minimal effect on normal skin cells and have a selective cytotoxicity for precancerous cells which makes it a treatment option for many dermatologic conditions.[144] There are varying treatment protocols for IEC, but the typical regimen is self-administration of the cream once or twice daily for 3-4 weeks. If necessary, this can be prolonged or repeated.[115] Initial response rates range from 67-83% and clearance rates at 12 months FU are 48-69%.[116, 124] Comparisons between 5-FU and PDT in the treatment of IEC have been assessed in a few reports showing similar or inferior effectiveness with 5-FU.[81, 116, 124, 145] The participation and self-administration can be both an advantage and a disadvantage for the patient. Furthermore, 5-FU can be used in combination with other treatment therapies such as PDT, curettage or cryosurgery, to increase the clearance rates.[146]

1.7.4 Curettage & electrodesiccation

When treating IEC with C&ED, the lesion is scraped with a sharp curette prior to using a high voltage and low current instrument to burn and destroy the remaining tumor tissue.[147] C&ED has shown to be one of the most effective and safest methods for IEC.[111, 147, 148] C&ED is also one of the least expensive treatment modalities.[113] Clearance rates have shown to be 93-98% with FU durations of 2.5-5 years.[148-150] C&ED is preferable to cryotherapy in lesions beneath the knee since treatment with cryotherapy has a higher risk of causing long-term wounds, due to reduced vascular circulation, especially in elderly patients.[111, 114, 115] Other known factors to take into consideration when choosing this treatment method are smoking, diabetes and immunosuppression, which can affect wound healing negatively.[151]

1.7.5 Cryosurgery

Cryosurgery is commonly used in clinical practice worldwide and it is the most common treatment method for IEC above the knee at Sahlgrenska University Hospital (SUH). The lesions are destructed by exposure to liquid nitrogen (-196°C). If the lesion(s) are hyperkeratotic, curettage should be added before cryosurgery. Treatment protocols vary greatly, and different regimens are used by practitioners around the world. In Sweden, standard practice is to spray liquid nitrogen on the lesion until a 4-mm halo is formed around the treatment area. Treatment is considered successful if the thawing time of the 4-mm halo is ≥60 seconds. If not, the freeze-thaw cycle (FTC) must be repeated.[152] A number of factors affect the results of this method including: freeze time, number of FTCs, tumor size and anatomical location[123]. Low recurrence rates have been shown (0–0.8%) at 5-years of FU, with a single FTC freezing for 30 s.[112] Other studies with cryotherapy applied with other protocols showed higher recurrence rates. Övermark et al. showed 4.7% recurrences rate in 64 lesions treated with two FTCs applying a 60-second halo thawing time after a mean FU of 66 months.[89] Furthermore, a study by Cox and Dyson showed that clearance rates were lower after one FTC with a 20-second freeze time (68%) than after a repeated FTC (86%).[153] Prolonged freeze times and repeated FTCs increase clearance rates. However, this also increases complications such as poor healing and hypopigmented scarring, particularly in poorly vascularized areas[153]. In a study comparing cryotherapy to C&ED, a longer median time to complete wound healing was observed with two FTCs of cryotherapy (35 days) compared to C&ED (29days) when treating IEC located on body sites other than the lower legs.[111]

1.7.6 Curettage

Curettage is a treatment regularly used on benign skin lesions such as verruca vulgaris, molluscum contagiosum and seborrheic keratosis.[154, 155] Curettage can be performed using either a disposable sharp curette or a reusable steel curette with a less sharp edge, the latter being more gentle on the surrounding healthy tissue. There are lacking data available on the effectiveness of curettage alone (without combining this with destructive methods such as cryotherapy or electrodesiccation) for treating IEC. A study by Thestrup-Pedersen et al. is, to date, the only study involving

curettage alone as a treatment method for IEC.[92] However, studies have been carried out on curettage alone for BCC demonstrating similar or higher cure rates (91-96% at 1-5 years of FU) compared to other destructive treatment methods and minimal complications.[156-159] Reymann et al. accidently treated 30 IEC with curettage showing a clearance rate of 83% (the real intention of the study was to treat BCC).[158] Furthermore, Yakish et al. studied curettage on SCC and showed a 97% overall clearance rate with a median FU of 6 years.[160] Since curettage is considered to be a less aggressive method compared to other treatment methods for IEC, it is possible that curettage leads to less tissue damage, quicker wound healing and a preferable cosmetic outcome compared to other methods.

2.

Aims

The studies included in this thesis cover diagnostic and treatment methods for IEC. The aims of the investigations were:

- To measure the interobserver agreement between dermatologists for identification of predefined dermoscopic findings in IEC. The secondary aim was to describe the presence of these dermoscopic findings in IEC, in a mainly fair-skinned population, and possibly identify new, previously unknown dermoscopic findings.

- To assess the effectiveness and recurrence risk of PDT in the treatment of IEC. The secondary objectives were to determine what factors affected the response rates and to evaluate the cosmetic result of the treatment.

- To examine what clinicopathological factors affect the rates of incomplete surgical removal of IEC.

- To compare overall clearance rates at 1-year FU for two different destructive treatment methods – cryotherapy and curettage – for IEC located above the knee. The secondary objective was to compare the wound healing times following the respective treatment methods.

3.

Methodological Considerations

3.1 Paper I

Materials

Dermoscopic images of 100 histopathologically verified IEC lesions were collected prospectively from the study cohort in Paper IV.

Methods

This was a descriptive, cross-sectional study carried out at SUH between September 2020 and November 2021. Eight experienced dermoscopists from as many international centers around the world were asked to participate and accepted to analyze the images. Based on previous publications on dermoscopy of IEC, the 11 most common dermoscopic findings within the categories of vascular, keratin-related, pigmented and other structures were preliminarily selected. Prior to performing the image review, the invited dermatologists participated in a consensus meeting to reach agreement concerning the definitions of these dermoscopic findings. During the consensus meeting, approximately 20 images (not included in the study dataset) were assessed and discussed thoroughly. After the consensus meeting, the categories and findings were reorganized to vascular, keratin-related, pigmented and shiny white structures as shown in Table 2. Instead of the terms 'erosions', 'ulceration' and/or 'blood spots', we agreed upon using the collective term 'hemorrhage', and it was organized under the category of vascular structures. Shiny white structures were divided into two different structures and were given new names: stromal structures (shiny white lines, blotches and/or strands) and follicular structures (rosettes or white circles). The images were independently reviewed by the dermatologists, who blindly evaluated the presence or absence of the predefined dermoscopic findings. Lastly, we also asked the dermatologists to specify if further relevant but unlisted dermoscopic findings were identified.

Table 2. Dermoscopic findings before and after the consensus meeting.

Before consensus meeting	After consensus meeting
Vascular structures:	*Vascular structures:*
1) Dotted/glomerular vessels distribution)	1) Dotted/glomerular vessels (clustered or linear distribution)
2) Hairpin vessels	2) Hairpin vessels
3) Short fine telangiectasias	3) Linear vessels
Keratin-related structures:	4) Hemorrhage
4) Scales (white or yellow)	*Keratin-related structures:*
5) Keratin rim	5) Scales (white or yellow)
6) Blood spots on scales	6) Keratin rim
Pigmented structures:	*Pigmented structures:*
7) Structureless brown pigmentation	7) Pinkish-white areas
8) Brown-gray dots	8) Brown pigmented areas
Other structures:	*9) Brown-gray dots*
9) Pinkish-white structureless areas	Shiny white structures:
10) Erosions/ulceration	10) Stromal structures
11) Shiny white structures	11) Follicular structures

Statistics

In this study, we used the Fleiss' kappa method to statistically analyze interobserver agreement. Diagnostic methods, for example dermoscopy, often depend on some degree of subjective interpretation by the observers and when there are more than two observers this can be managed by using Fleiss' kappa. A kappa value of 1 reflects perfect agreement, whereas a kappa of 0 reflects an agreement equivalent to chance.[161] The kappa method is limited by the prevalence of the finding and is therefore less reliable for rare observations.[161, 162] To compare the proportions and distributions of dermoscopic findings we used Fischer's exact test.

Table 3. How to interpret interobserver agreement according to Fleiss' Kappa.

Kappa value	Degree of interobserver agreement
≤0	Poor agreement
>0 - 0.20	Slight agreement
>0.2 - 0.4	Fair agreement
>0.4 - 0.6	Moderate agreement
>0.6 - 0.8	Substantial agreement
>0.8	Almost perfect agreement

3.2 Paper II

Subjects

The subjects of this study were all patients with IEC treated with PDT at the Department of Dermatology and Venerology, SUH between January 1, 2002 and December 31, 2014.

Methods

This research was conducted as a retrospective observational study. Data was extracted from the hospital's electronic health record system. The start date was selected due to the implementation of the current electronic health record system. Data from all patients with IEC treated with PDT were found and retrieved retrospectively through this system with the use of the specific ICD-code for the diagnosis of IEC (D04.9) and the treatment code for PDT (DQ004). A list of 590 patients had matching codes, but only 335 patients with a total of 423 IECs had histopathologically verified IECs that were confirmed to have been treated with PDT and could therefore be included. Each health record for these patients was assessed manually and the following data were analyzed:

- Patient age and sex.
- Tumor location and size.
- Number of PDT sessions, date of treatment, pain assessment with VAS before and after treatment, light source and type of photosensitizer.
- Clinical outcome at first FU and date of any recurrences.
- Cosmetic result.

We defined complete response as no clinical evidence of dysplasia at the first FU visit. Recurrences were defined as any clinical or histopathological evidence of cell dysplasia (including clinically suspected actinic keratosis) during FU. The overall clearance rate was defined as the number of lesions showing complete response and no recurrence during FU divided by the total number of treated lesions.

Statistics

Fischer's exact test was used to analyze different parameters that were considered to have possibly affected the outcome. Patient age and sex, tumor location and size, number of PDT sessions, light source and type of photosensitizer, clinical outcome at first FU and date of any recurrences and cosmetic result were tested.

3.3 Paper III

Subjects

Data were collected on all patients who were treated with surgical excisions for IEC during a two-year period.

Methods

Between January 1, 2014 and December 31, 2015, all consecutive cases of excised and histopathologically verified IEC diagnosed at the Department of Pathology at SUH were collected and reviewed. Data were extracted from electronic health records and each record was assessed manually. Data regarding variables that could hypothetically have a connection to surgical outcome were collected including:

- Patient age and sex.
- Immunosuppression.
- Tumor diameter and body site.
- Specialty of the physician who performed the surgery.
- Experience of the physician who performed the surgery (resident vs. specialist).

- Suspected diagnosis of the lesion prior to surgery.
- Whether a diagnostic punch biopsy was acquired preoperatively or not.
- Excision method.
- Clinical surgical margin used.
- Whether or not complete removal was accomplished.

Inclusion criteria were histopathologically confirmed cases of IEC managed by excisional biopsy and in which data regarding histopathological margin control was available. IEC treated with other methods than surgery, misclassified lesions (e.g., IEC in combination with microinvasive/invasive SCC or IEC found within or connected to other types of skin cancer), inadequate clinicopathological data, lack of data concerning free margins and IEC located in the genital area or on mucous membranes were excluded.

In order to obtain an objective assessment of the information in the health records, a number of guidelines were used:

1) Even very narrow free margins to the tumor were classified as a complete excision.
2) Tumor size measured on the day of surgery was recorded (if it was measured more than once).
3) Whenever tumors were re-excised, only data from the initial excision regarding surgical margins and complete removal were recorded.

We chose to perform two separate analyses of the data given the discussion about whether Bowen disease (often presenting as a more well-defined, erythematous patch with scaling surrounded by healthy tissue) is synonymous to SCC in situ (normally displaying as a poorly defined lesion on sun-damaged skin or as a part of field cancerization) or if they are two different variants of IEC. The first strict definition of a complete excision required the absence of any degree of keratinocytic dysplasia at the resection margin. Contrarily, the second less strict definition of a complete excision allowed for the presence of mild to moderate keratinocyte dysplasia at the resection margins but not severe keratinocyte dysplasia or IEC.

Statistics

Fisher's exact test was used to compare proportions. Wilcoxon's rank sum test was used for two-sample tests. Kruskal-Wallis test was used to compare three or more groups. A multiple logistic regression analysis adjusted for possible confounders.

3.4 Paper IV

Subjects

Study candidates were recruited from the Department of Dermatology and Venerology, SUH between September 2019 and January 2022. Patients visiting the clinic with one or more IECs located on any body site above the knee and suitable for destructive treatment were informed about the study and asked about participation.

Methods

This study was conducted as a randomized and controlled trial using a non-inferiority design to compare the outcome of two different destructive treatment methods for IEC: cryosurgery (the standard treatment method) versus curettage (the experimental method). The study included three FU visits: 1) at 4-6 weeks with a study nurse to assess wound healing; 2) at 3-6 months with a dermatologist to determine clinical response and 3) 1 year after treatment with a dermatologist to evaluate recurrence rates and initial cosmetic results. This study is still ongoing and, in the future, we will be able to present results from 3- and 5-year FU visits.

Inclusion criteria were:

- Patients ≥18 years old with one or more histopathologically confirmed IECs.
- IEC(s) with a diameter of 5-20 mm that were suitable for destructive treatment.
- IEC(s) located above the knee.

Exclusion criteria were:

- Lesions located on mucous membranes or in the genital area.
- Patients with a life expectancy <1 year given their age and/or other medical conditions.

Histopathological verification was performed with a diagnostic biopsy taken either before or during the inclusion visit. In cases where the histopathology report did not confirm the diagnosis, the lesions were excluded and received additional treatment if necessary. The IECs were documented with both clinical and dermoscopic images at inclusion. Images were also taken at all FU visits including the first visit in which wound healing was assessed. All lesions were randomized to treatment with either cryosurgery or curettage using computer-generated block-randomization. A carefully prepared, and well-described treatment protocol was used, and an absolute majority of the lesions were included and treated by the same dermatologist.

Cryosurgery was performed by spraying the lesion with liquid nitrogen using a CryoPro Mini cryosurgery unit (Cortex Technology, Hadsund, Denmark) with a B-sized nozzle until a 4-mm halo of frost had formed around the lesion borders. A neoprene cone (Cortex Technology, Hadsund, Denmark) was used to isolate the lesion and the liquid nitrogen spray. Treatment was only regarded as successful if the thawing time of the 4-mm halo was ≥60 seconds. If not, the FTC was repeated after complete thawing of the entire treatment area. The instrumentation used for cryosurgery is shown in Figure 8.

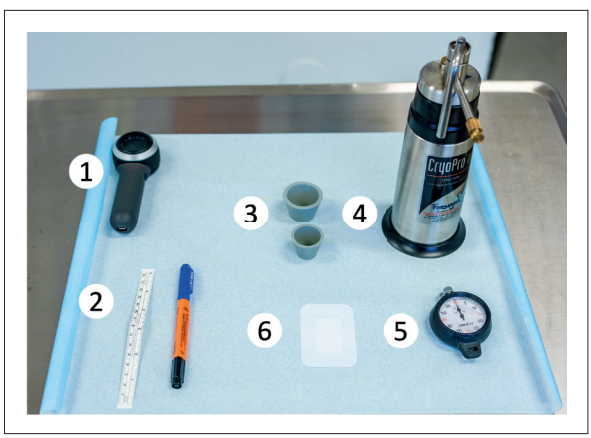


Figure 8. Instruments used for cryosurgery: 1) dermoscope, 2) surgical marker, 3) neoprene cones, 4) liquid nitrogen, 5) timer and 6) dressing.

Curettage was performed with two sharp disposable dermal ring curettes (Kai Medical, Tokyo, Japan) starting with a 7-mm ring curette followed by a 4-mm ring curette. We chose disposable curettes since they are more commonly used today and readily available in everyday practice. Curettage was carried out in at least three different directions until all clinically visible lesion tissue was removed. The instrumentation used for cryosurgery is shown in Figure 9.

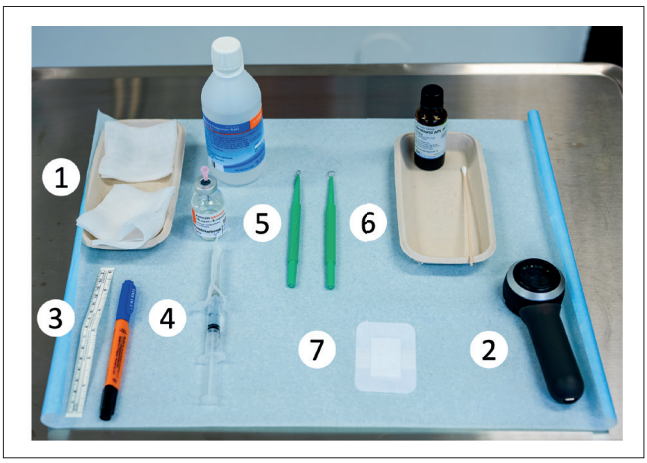


Figure 9. Instruments and materials used for curettage: 1) gauze and chlorhexidine solution for skin sterilization, 2) dermoscope, 3) surgical marker, 4) lidocaine, 5) 4- and 7-mm curettes, F) iron chloride for hemosthasis and 7) dressing.

At the inclusion visit, each patient as well as each included lesion received an identification number. Identification numbers were used to fill in the case report form (CRF) at each visit in order to mask the patient identity. Information about diabetes, smoking habits or immunosuppression was also noted in the CRF. The lesion's maximum diameter (in mm) and exact anatomical location were also recorded. Participants were given a self-report form concerning wound healing status to be filled out once weekly.

The first follow-up visit (FU1) took place 4-6 weeks after treatment. At FU1, a research nurse assessed the wound healing of the treated lesions and clinical images were taken. The wound healing process was divided into three categories: oozing, dry with a crust or healed without a crust.

Assessment of wound healing was documented in the CRF and data from the participants' self-report forms were collected. The patient was instructed to continue filling out the self-report form until the wound was healed without a crust, in case of incomplete wound healing at FU1.

The second follow-up visit (FU2) took place 3-6 months after treatment and the clinical response of the treated lesion was assessed by a dermatologist. Lesions were categorized as having responded clinically or showing signs of remaining tumor. Clinical response was defined as cases in which the treatment area show no remaining tumor tissue visible to the eye or through the dermoscope. If the examining dermatologist suspected remaining tumor tissue, a new biopsy was taken from the lesion for histopathological confirmation. If the pathology report confirmed remaining IEC, FU for that lesion was terminated and it received further treatment as considered appropriate.

The third follow-up visit (FU3) took place one year +/-3 months after treatment. At this visit, clinical recurrence was assessed by a dermatologist. Any suspected recurrence was biopsied to confirm this histopathologically. The patient visits are summarized in Figure 10.

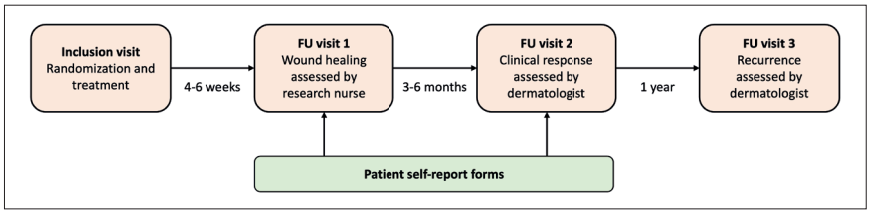


Figure 10. Flowchart of the inclusion and follow-up (FU) visits.

During the course of this study, some data regarding wound healing at 4-6 weeks and clinical response at 3-6 months were lost due to the Covid-19 pandemic. Physical FU visits to assess wound healing at FU1 were in 28 cases replaced by video calls plus clinical images sent by patients for teledermatological assessment as were 8 assessments of clinical response at FU2.

Statistics

Before starting the study, a power calculation was conducted. This suggested that 92 lesions in each group (184 lesions in total) should be included to ensure 80% power with an expected clearance rate of 95% with cryosurgery and a difference in cure rates after five years below 8%. Non-inferiority analysis was conducted with Wang's exact method by testing both one-sided and two-sided 95% confidence intervals for the difference in 1-year clearance rates between the two treatment groups.

Fisher's exact test was used to compare proportions while Wilcoxon's rank sum test was used for two-sample comparisons. A multiple linear regression analysis was performed with non-response/recurrence as the dependent variable and treatment group, lesion diameter, lesion location and patient immunosuppression as independent variables.

3.5 Ethical Considerations

Paper I is part of a larger research project approved by the Regional Ethics Review Board in Gothenburg in 2018 regarding "Artificial intelligence based on clinical, dermatoscopic and histopathological images and hyperspectral analysis for diagnostics of skin diseases" (283-18 plus amendment 2020-01190). Inclusion in this study did not affect care or clinical management of any patients. Only images in which the patient data was anonymized and unidentifiable were used.

In Paper II, ethical approval was granted by the Regional Ethics Review Board in Gothenburg in 2015 before the start of the study (941-15). Patients included in this study were not affected regarding their care since inclusion only involved a retrospective review of information in the electronic health records.

Paper III was also part of a larger project "Comparison and evaluations of excision margins and complete excisions for skin tumors" approved by the Regional Ethics Review Board in Gothenburg in 2016 (430-16 plus amendment 2020-02933).

Paper IV was approved by the Swedish Ethical Review Board of Gothenburg in 2019 (2019-02841). All patients in the study signed a consent form

prior to inclusion. All patient information was de-identified and patient data was stored on a secure server at SUH. Only a few authorized persons have access to this data. Throughout the study, participants were free to withdraw from participation without obligation to state a reason for withdrawal. Patients who were excluded on their own initiative were offered additional treatment and FU if necessary. Furthermore, cryosurgery and curettage are established and safe treatment methods as was also shown in the study in which no adverse events were study-related. Curettage is not as commonly used in the treatment of IEC, but we expected high rates of clinical response and low recurrence rates. Importantly, IEC is a slow-growing condition with a low risk of developing into invasive SCC. Together with the regular and long FU, the safety of the patients was not considered to be compromised.

4.

Results

4.1 Paper I

In this investigation, 100 dermoscopic images of IEC were analyzed by eight dermoscopists. The population consisted of 94 patients of which 46% were females and whose median age was 73 years. The lesions had a median diameter of 13 mm ranging from 5 to 30 mm. Two-thirds of the tumors were located in the head and neck area (43%) or on the upper extremities (24%) while the other one-third were located on the trunk (17%) and lower extremities (16%).

Dermoscopic findings and interobserver agreement

The 11 pre-defined dermoscopic findings arranged from most to least frequently observed in IEC and arranged from highest to lowest interobserver concordance are shown in Figures 11 and 12, respectively.

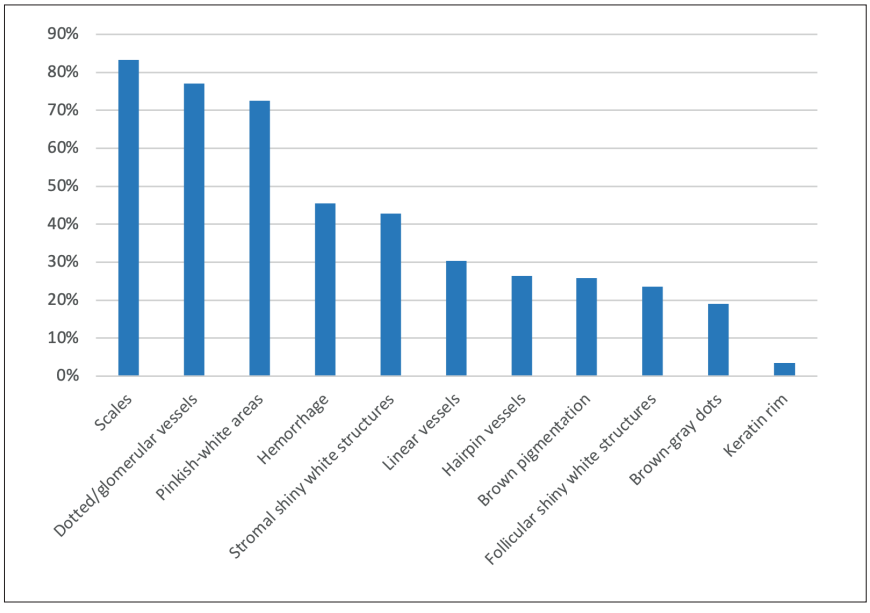


Figure 11. Dermoscopic findings in IEC arranged according to frequency (from highest to lowest).

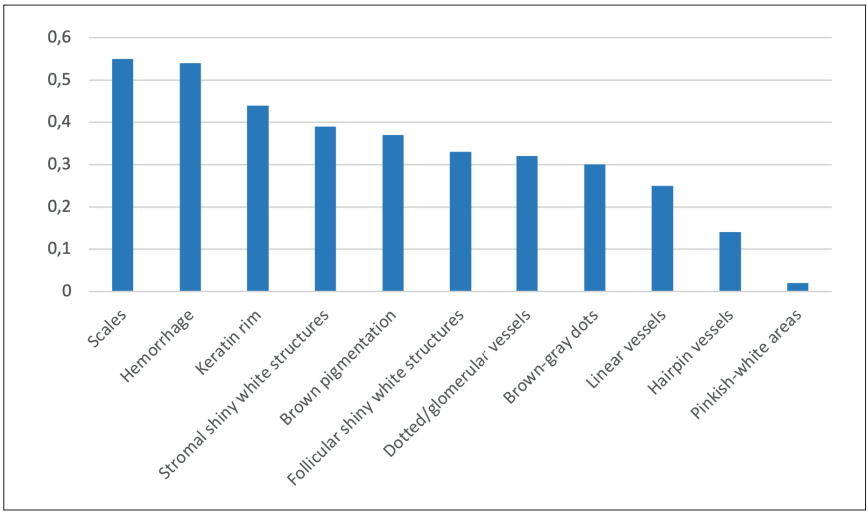


Figure 12. Dermoscopic findings in IEC arranged according to interobserver agreement (from highest to lowest kappa values).

Keratin-related structures

Scales was not only the most frequent dermoscopic finding in the included IECs (83.3%) but also had the highest interobserver agreement with a kappa value of 0.55 (moderate). The most uncommon finding was keratin rim, which was only observed in 3.4% but had moderate interobserver agreement (K=0.44).

Vascular structures

Dotted/glomerular vessels was the second most frequent dermoscopic finding (77.1%), but only showed fair interobserver agreement (K=0.32). Hemorrhage was observed in almost half of the lesions (45.5%) and also had the second highest interobserver agreement (K=0.54). Other vascular structures were less commonly present in the IECs with 30.3% presenting with linear vessels and 26.4% having hairpin vessels. These vessel types also resulted in lower interobserver agreement (K=0.25 and K=0.14, respectively).

Pigmented structures

Pinkish-white areas were the third most frequent dermoscopic finding (72.6%), but had the lowest interobserver agreement (K=0.02, slight).

Brown pigmentation was more common (25.8%) than brown-gray dots (19.1%). The interobserver agreement for both brown pigmented dermoscopic findings was fair (K=0.37 and K=0.30, respectively).

Shiny white structures

Stromal shiny white structures (42.8%) were observed almost twice as often as follicular shiny white structures (23.5%). Both stromal and follicular shiny white structures had fair interobserver agreement (K=0.39 and K=0.33, respectively).

Overall observations

Dotted/glomerular vessels, scales and/or hemorrhage were present in an absolute majority (97%) of all lesions. Furthermore, some form of vascular structure (i.e. vessels and/or hemorrhage) were present in 9 out of 10 IECs. In slightly more than half of the lesions, shiny white structures of either kind were observed. Brown pigmented structures overall (either brown pigmentation and/or brown-gray dots) were observed in one-third of the cases. None of the readers identified any new dermoscopic findings that hadn't previously been described in IEC.

4.2 Paper II

After exclusion, data from 423 IECs in 335 patients were analyzed. The median age of the study population was 79 years (35-96 years) and almost two-thirds were female (65.7%). Half of the lesions were located on the head and neck area (52.2%) followed by lower extremities (28.1%), trunk (11.1%) and upper extremities (8.5%) in terms of frequency. The lower extremities were more commonly treated in female patients (35.6%) than in males (13.8%). All PDT sessions were carried out using MAL as the photosensitizing drug, illumination with an Actilite® lamp (Photocure AS, Norway) as the light source and a standardized total light dose of 37 J/cm^2.

During the study period, no standard time to FU after PDT was utilized at the department. Nevertheless, the mean time to the first FU visit was 3.5 months according to the data extracted from the health records. The mean FU duration in total was 11.2 months but varied greatly from as little as 1 week to as much as 12.5 years.

At the first FU visit, complete response was observed in 328 out of 423 IECs resulting in a response rate of 77.5%. In these 328 responders, 60 recurrences were observed during following FU visits (i.e. a recurrence rate of 18.3% among the IEC lesions that initially responded to treatment). Thus, the overall clearance rate when taking into account both the complete response rate and the non-recurrence rate after FU was 63.4% for all IECs (268 out of 423 lesions).

The only parameters affecting the outcome significantly were: a) whether one or two treatment sessions of PDT were given and b) whether the lesion was smaller or larger than 20 mm in diameter. There were 54 IECs that were only treated with one PDT session and this resulted in an overall clearance rate of 48.1%. In comparison, the 369 IECs that were treated twice showed an overall clearance rate of 65.6%, which was a significantly higher rate (p=0.016). Furthermore, the larger lesions (>20 mm in diameter) had overall clearance rates of 48.7 % in comparison to the smaller lesions (1-20 mm in diameter) in which the rates were 69.1%. Patient sex and age, tumor location, the number of weeks between PDT sessions and the amount of pain felt during PDT were also analyzed as risk factors that could potentially affect the overall clearance rates. However, no significant correlation was found between the success rate of PDT for IEC and any of these parameters.

In almost 60% of the cases, the cosmetic outcome was described in the health records (Table 5). Most cases had no cosmetic complications, but one out of every five cases had some reported degree of scarring, erythema, hypo- or hyperpigmentation.

Table 4. Cosmetic outcome after PDT analyzed in 250 out of 423 cases for which data was available.

Cosmetic outcome after PDT	Cases
No complication	122 (78%)
Scarring	22 (9%)
Erythema	15 (6%)
Hypopigmentation	6 (2%)
Hyperpigmentation	5 (2%)
Combination of above	7 (3%)

4.3 Paper III

In this study, a manual review of medical records and histopathological reports in the pathology register during the study period rendered 463 IECs in 408 patients. The median age of the study population was 78 years and 44% of the patients were males. Approximately half of the lesions were located in the head and neck area (52.7%), while the second most common anatomical location was the trunk (21.6%). The median size of the IECs was 10.0 mm (range 1–55 mm). In 191 cases (41.3%), a preoperative biopsy was secured prior to the surgical excision. Although data regarding immune status was only known in 270 patients, 14% of those had immunosuppression.

The surgical excisions were performed by different physician specialties: dermatologists excised the majority of the IECs (n=202, 43.6%), followed by otorhinolaryngologists (n=78, 16.8%), plastic surgeons (n=70, 15.1%), general surgeons (n=60, 13.0%), general practitioners (n=37, 8.0%), and other specialties (n=16, 3.5%). In the vast majority of the 414 cases in which the physician experience was known, a specialist performed the excision (87%). The surgical margin was reported in less than half of the cases (46.4%). The median diameter of the excised tumors varied between the different physician specialties. Plastic surgeons excised larger lesions than general practitioners and dermatologists ($p<0.001$). In 95% of the cases, the surgeon performing the surgery chose to perform a traditional elliptical excision. Furthermore, the suspected diagnosis was specified in the medical records and/or histopathological reports in nine out of ten cases demonstrating low diagnostic accuracy since IEC was the primary or differential diagnosis in only one-third of the cases.

As described in the method section, the incomplete excision rates were analyzed based on strict and less strict definitions. The strict definition of incomplete excision resulted in a higher overall rate of incomplete excisions (23.8%) compared to the less strict definition of incomplete excision (12.8%). With both definitions, the logistic regression analysis showed that the following factors were associated with higher incomplete clearance rates: 1) less than 3 mm margins when performing surgery, 2) less experienced surgeon and 3) using punch biopsy excision as the surgical method. When applying the strict definition, these three factors

plus anatomical location on either the head and neck area or the upper extremities were also associated with significantly higher rates of incomplete excision. Neither the surgeon's specialty nor the tumor diameter affected the outcome regardless of whether a strict or less strict definition was used.

4.4 Paper IV

In this non-inferiority, randomized and controlled trial, 200 lesions in 163 patients were included and randomized to either cryosurgery (n=93) or curettage (n=90). Initially, a total of 201 lesions in 168 patients were included, but 17 of the lesions in 16 patients were excluded during the study due to misdiagnosis (n=5), patient withdrawal (n=5), breach of protocol (n=3), non-study related deaths (n=3) and patient moving to other part of the country (n=1). Almost half of the patients were women (47%) and the median age of the patients when treated was 75 years (range 39-88 years). The most common anatomical sites of the lesions were the face and upper extremities (both 29.5%), followed by the trunk (20%), thighs (7.7%) and neck (7.1%). There were no statistically significant differences in baseline characteristics between the intervention groups.

Clinical response and recurrence rates

All 183 treated lesions were assessed at FU visit 2, but due to the restrictions related to the Covid 19 pandemic, eight of the lesions were assessed by video calls and images of the treated areas sent in by the patent. At 3-6 months, response rates differed significantly between the groups with 99% responders among those receiving cryosurgery and 90% responders among those receiving curettage (P=0.009).

At FU visit 3 after 1 year, all 173 lesions showing clinical response at the previous FU visit were evaluated again, i.e. 92 in the cryosurgery group and 81 in the curettage group. Recurrences were observed in 4.3% (n=4) of the cryosurgery responders and 12.3% (n=10) of the curettage responders (P=0.09). Thus, a total of 14 recurrences were noted among the initial responders including one microinvasive well-differentiated SCC, 11 IECs and two AKs.

When taking into account both the complete responders and the non-recurrent cases, 88 out of 93 IECs were successfully treated with cryosurgery (94.6%) and 71 out of 90 IECs were successfully treated with curettage (78.9%). The overall clearance rates were significantly higher in the cryosurgery group (P=0.002). However, the non-inferiority analysis was shown to be inconclusive since the lower margin of the 95% confidence interval (CI) for the difference between curettage and cryosurgery was below the cut-off limit of 8%.

When analyzing the potential influence of lesion size, anatomical location, smoking, diabetes and immunosuppression on the overall clearance rates, the only factor showing significant association was lesion size. IECs that were successfully treated had a median diameter of 11 mm, which was significantly smaller than those who were not (16 mm) (P=0.009).

Wound healing

In total, 134 out of 183 self-report forms contained all the data we aimed to collect. The number of healed wounds at 4-6 weeks was significantly lower in the cryosurgery group (57.1%) compared to the curettage group (89.2%) (P=<0.001). Furthermore, the self-reported wound healing times were significantly longer in the cryosurgery group with a mean of 4.8 weeks (95% CI: 4.4–5.2) compared to 3.1 weeks (95% CI: 2.8–3.4) in the curettage group.

Adverse events

Although 82 adverse events including seven serious ones were documented during the study, none of these were related to the applied treatments.

5.

Discussion

5.1 Paper I

Frequency of dermoscopic findings

This study confirmed that scales, dotted/glomerular vessels, pinkish-white areas and hemorrhage were the most frequently found dermoscopic findings in IEC within a predominantly fair-skinned population. These dermoscopic findings were observed at frequencies similar to those described in previous studies performed in non-Nordic populations.[87, 88, 94-97, 99, 163, 164] Vascular structures were observed in the majority of all lesions and the overall frequency of pigmented structures was 32%, which was a higher frequency than expected in a predominantly fair-skinned population.

Interobserver agreement

Furthermore, the interobserver agreement for the respective dermoscopic findings was slight to moderate (poor to moderate when including the 95% CIs). Scales and hemorrhage rendered the highest kappa values. We are unaware of any other study that has examined the interobserver agreement for dermoscopic findings in IEC. Nevertheless, Zaar et al. recently conducted a similar study on the interobserver agreement on dermoscopic findings in porokeratosis, which can display similar features such as dotted/glomerular vessels, blood spots (hemorrhage), shiny white structures and keratin rim. This study showed almost perfect interobserver agreement for these features.[165] The higher interobserver agreement shown may be explained by the fact that only three readers from the same center participated, contrarily to our study which included eight readers from seven different centers.

Terminology

A wide range of terms have previously been used to describe the dermoscopic findings in IEC.[87, 88, 94-97, 99, 163, 164] In recent years, the International Dermoscopy Society has made clear advancements in incorporating standardized terminology for dermoscopic findings for skin

tumors and non-neoplastic dermatoses.[166, 167] However, the list of terms for which consensus has been reached is still incomplete and does not fully cover all dermoscopic findings found in IEC.

In this paper, we suggested that terms like 'erosions', 'ulceration', 'bleeding' or 'blood spots' be grouped and redefined as 'hemorrhage'. Furthermore, terms such as 'structureless pigmentation', 'homogeneous pigmentation', 'clusters of brown pigmentation' and so forth be substituted by 'brown pigmented area'. We also proposed that shiny white 'lines, blotches and/or strands' be considered as 'stromal shiny white structures' since they represent fibrous structures within the dermal stroma. Similarly, 'rosettes' and 'white circles' could be grouped into 'follicular shiny white structures' due to their common histopathologic localization. Other terms like 'scales' and 'keratin rim' had recently been suggested as dermoscopic findings in porokeratosis and were therefore also applied for IEC without changing the terms.[165] We believe that attempts should be made in future dermoscopy studies to include simple, consensus-based and clearly pre-defined terminology while also analyzing interobserver agreement to guarantee that estimations of frequency and diagnostic accuracy are reliable and externally valid.

5.2 Paper II

Clearance rates and risk factors

In comparison with similar studies, our study cohort of 423 IECs in 335 patients treated with PDT over a period of 13 years can be considered relatively large. A clearance rate of 63.4% overall was observed. Treating IEC lesions with a diameter of less than 2 cm improved the results significantly, but only increased the clearance rate to 68.7%. Similarly, two PDT sessions gave significantly better clearance rates than a single PDT session, but only up to 65.6%. Some previous studies on PDT for IEC have also shown that lesion diameter significantly affects the effectiveness[123, 124, 128], whereas other studies did not analyze or find lesion diameter to be a significant risk factor or eluded to analyze this characteristic.[89, 125-127, 129-131] Regarding the number of PDT sessions, many studies have demonstrated, as we did, that two or more sessions are more effective than a single one.[116, 123, 124, 127, 128] Similar to previous studies, PDT resulted in satisfactory cosmetic results in general with almost 80% of the IECs healing without long-term complications.[116, 124, 128-131]

Previous research

As described earlier, varying treatment protocols, FU periods and number of PDT sessions make comparisons between studies difficult. Strict comparisons are also difficult to make since the exact response rates, number of recurrences and overall clearance rates are not consistently outlined in other studies. In a few studies, recurrence rates after 1 year are provided, but not response rates at earlier FU visits.[89, 126, 127] Other studies allowed up to 6 PDT sessions, making it difficult to compare results when using fewer sessions.[124, 128] Lastly, some reports utilize other definitions for complete response, recurrence and overall clearance rates than the ones used in our study.[126, 129]

Limitations

The most relevant limitation of this investigation is the retrospective design. The mean FU time of 11.2 months is also relatively short. Nevertheless, all non-responders and most recurrences could be observed within the first year after treatment. Furthermore, assessment of complete response and recurrences was mainly based on clinical findings which should be taken into consideration when interpreting the results.

5.3 Paper III

Incomplete excision rates

Swedish clinical guidelines for the management of squamous cell carcinoma and basal cell carcinoma state that excision of facial IEC may be preferred to confirm complete removal.[19] Surgical excision is otherwise considered to be one of the standard treatments for IEC and clear margins determine treatment success.[146] For this reason, we found it of importance to evaluate the clinicopathological risk factors for and frequency of incomplete excisions. We conducted a study of IEC in a larger series of lesions (n=463) to evaluate this. Prior to our study, only Westers-Attema et al. had properly investigated the safety margins and risk factors for incomplete excisions of IEC, but only included less than one-fifth of the number of cases.[120] Our investigation showed that IECs were incompletely excised in 23.8% of the cases when applying the strict definition of incomplete excision and 12.8% when applying the less strict definition. In comparison, Westers-Attema et al. showed incomplete excision rates of 17.7% but the definition of incomplete excision was not described.[120]

Risk factors for incomplete excision

The risk factors for incomplete excision also varied depending on which definition of incomplete excision was used. When employing the strict definition, significantly higher incomplete excision rates were observed when surgical margins <3 mm were used, when physicians with less experience performed the surgery, when the IECs were located on the head, neck or upper extremities and when the punch biopsy excision technique was used. With the less strict definition, the same risk factors excluding tumor location showed significant associations with worse outcomes. Following multivariate analysis, surgeons with less experience was the only risk factor that correlated independently with incomplete excisions when applying the less strict definition. When applying the strict definition, both surgeons with less experience and lesions on the head, neck or upper extremities correlated independently with incomplete excisions.

Strict vs less strict definitions

IEC can be localized on areas with extensive sun-damage surrounded by skin with varying degrees of epithelial dysplasia. IEC can also be developed more isolated, on healthy and less sun-damaged skin. Therefore, we decided to analyze our data according to two separate definitions of incomplete excision. The less strict definition accepted mild to moderate dysplasia at the surgical margin taking into account the inherent difficulty of surgically removing an IEC in sun-damaged skin. The strict definition did not allow for any degree of dysplasia to be present at the surgical margin, which would perhaps be most appropriate for isolated IECs in less sun-damaged skin. We find this distinction important since it is unknown how physicians choose to manage pathology reports in which the IEC has been removed completely but signs of mild to moderate dysplasia is still present at the surgical margin. If no further treatment is offered, one could consider the surgery to be successful and vice versa.

The different medical specialties among the physicians performing the excisions did not influence the results significantly in our study. Westers-Attema et al. showed that dermatologists achieved lower incomplete excision rates (8.8%) than GPs (33.3%) and plastic surgeons (54.5%). However, after performing multivariate analysis this difference did not remain significant.[120] Other studies on successful excisions of keratinocyte

cancers, have shown similar trends.[168-171] In our study, plastic surgeons performed surgery more often on lesions located in the face (head and neck area), which may have resulted in unfair comparisons since surgery in this area can be more difficult to carry out.

Surgeon experience influenced outcomes according to our data. Surgical experience was measured based on whether the surgeon was a resident or a specialist, which was the only data available in this regard. It would have been more appropriate to measure experience in number of surgeries performed previously, for example.

Surgical margins

IEC is a precancerous tumor with a relatively low risk of developing into an invasive SCC. Taken this into consideration, it would be preferable to apply the narrowest surgical margins possible. The choice of what should be considered an adequate surgical margin is a delicate decision. Clear margins have to be obtained while also avoiding unnecessarily large scars and postoperative adverse events like bleeding, infections or wound dehiscence. Westers-Attema et al. concluded that a 5-mm clinical margin should be recommended[120], while we conclude that at least 3-mm clinical margins should be used. When excising IECs on the head, neck or upper extremities, where tumors are more often surrounded by sun-damaged skin and incompletely excised when applying the strict definition, the clinical margin could be modified to be 4-5 mm, for example.

5.4 Paper IV

Main results

This trial comparing curettage and cryosurgery as treatment methods for IEC, shows that cryosurgery was significantly more effective than curettage for IEC above the knee, even though the non-inferiority analysis was inconclusive. Both treatment regimens resulted in relatively high overall clearance with cryosurgery (95%) outperforming curettage (78%). On the other hand, complete wound healing rates at 4-6 weeks were significantly higher in the curettage group and self-reported wound healing times were shorter with curettage compared to with cryosurgery.

Cryosurgery

Earlier investigations on the effectiveness of cryosurgery for IEC has shown varying results and a number of factors affecting the outcomes freeze time, number of FTCs, tumor size and anatomical location.[123] As mentioned in section 1.7.4 in this thesis. low recurrence rates below 1% after 5 years of FU have been shown with a single FTC with a freeze time of 30 s.[112] Higher recurrence rates were observed by Övermark et al. (4.7%after >5 years) with two FTCs applying a 60-second halo thawing time as we also used in our study.[89] Lastly, Cox and Dyson showed improved clearance rates with two FTCs (86%) compared to a a single FTC (68%) with 20-second freeze times.[153] In conclusion, prolonged freeze times and repeated FTCs increase clearance rates.

Curettage

To our knowledge, Thestrup-Pedersen et al. is the only group to report an analysis of curettage alone as a treatment method for IEC. This retrospective study from 1988 included 345 IECs, but the treatment protocol on how the curettage was performed or which instruments were used was not described. They reported an overall clearance rate of 81%, which is similar to our results on curettage (78%). One-third of the patients were followed up for <1 year, one-third for 1-4 years, and the last third for >5 years.[92] Furthermore, a study including 89 SCCs treated with curettage analyzed retrospectively by Yakish et al., showed an overall clearance rate of 97% with a median FU time of 6 years.[160] Another interesting result was presented by Reymann, who treated 30 IEC with curettage resulting in a clearance rate of 83%.[158]

Comparisons with other treatment modalities

The effectiveness of cryosurgery and/or curettage compared with other common treatment modalities for IEC such as surgical excision, PDT, 5% 5-FU cream and ablative laser therapy, have been studied before in a few studies.[96, 116, 120, 123, 124] For example, Salim et al. randomized 66 lesions, 33 to PDT and 33 to 5-FU showing a complete clearance after 1 year of 82% for PDT and 48% for 5-FU.[116] Morton et al. randomized 20 lesions to cryosurgery and 20 to PDT showing that cryosurgery only resulted in a clearance rate of 50% after one treatment, whereas PDT resulted in clearance rates of

75% after one treatment and 100% after a second treatment.[123] Another randomized controlled trial by Morton et al. including 229 IECs treated with either PDT, cryosurgery or 5-FU showed that PDT cleared 80% of the lesions at 12 months FU, compared to 67% with cryosurgery and 69% with fluorouracil.[124] Surgical excisions were shown to be completely excised in 82.3% of 96 excised IECs in an investigation by Westers-Attema et al.[120] Regarding ablative CO_2 laser treatment of IEC, a study with 44 cases resulted in clearance rates of 86.3% after one treatment with 7.9% developing recurrences during a mean follow-up of 19 months.[96] Thus, our results show overall clearance rates for both cryosurgery and curettage at 1 year at the similar or higher levels compared to other treatment methods such as PDT, 5-FU, surgery or CO_2 laser.

Wound healing

Secondarily, we intended to investigate whether the time to wound healing differed after treatment with cryosurgery compared to curettage. Lesions treated with curettage had significantly shorter wound healing times according to the self-report forms as well as a significantly larger proportion of completely healed wounds at the 4- to 6-week assessment. These results suggest that curettage is a gentler method with shorter wound healing times which one could bear in mind when choosing treatment method.

The median wound healing time in the cryosurgery group was 4.8 weeks, which interestingly was similar to what Ahmed et al. reported in treatment of IEC with cryosurgery on locations other than the lower legs.[111] Comparable to our results, Ahmed et al. found no significant correlation between lesion location or size and wound healing time when only analyzing IEC lesions above the knee.[111] Another study conducted by Holt, reported wound healing times of 4-6 weeks for NMSC and IEC located on the head and neck after cryosurgery.[112] Cox & Dyson found poor wound healing in 2% of IEC treated with cryotherapy, but wound healing time was not described in this study.[153]

There is no available prior research on wound healing times when treating IEC with curettage. However, wound healing times of 2.0-3.0 weeks after treating superficial BCC with curettage was reported by McDaniel et al.[157] This is comparable to the results in our study, which showed a median

wound healing time of 3.1 weeks in the curettage group. Backman et al. recently reported a median wound healing time of 4.0 weeks after curettage for superficial BCCs, which was slightly longer than the times observed in our study.[159]

Precise treatment protocols

As described previously, treatment protocols for cryosurgery, curettage and other destructive methods have a great variation, which makes fair comparisons between studies difficult. In this randomized controlled trial, we have made an effort to describe the treatment protocol as thoroughly as possible. Furthermore, we filmed the procedures as supplementary material to standardize the methodology and facilitate future comparisons.

6.

Conclusions

Paper I

Assessment of dermoscopic images of IEC resulted in poor to moderate interobserver agreement. The frequency of the most common dermoscopic findings were similar to those observed in previous publications. Brown pigmented structures were seen more often than expected in a fair-skinned population.

Paper II

PDT as a treatment modality for IEC provides successful results after 1 year of FU in approximately two-thirds of the cases. Significant risk factors for non-response and recurrence are larger lesions (>20 mm) and a single PDT session. Patients treated with PDT for IEC should be followed up due to the relatively high risk of either incomplete response or recurrence. At least two PDT sessions should be administered and caution should be taken when treating IECs with a diameter >20 mm. Hopefully, future prospective, randomized and controlled trials can help establish more effective PDT protocols for IEC.

Paper III

This study provides essential insights into factors potentially associated with higher incomplete excision rates for IEC: small surgical margins (<3 mm), punch biopsy excision technique, less experienced surgeon, and tumor location in either the head and neck area or on the upper extremities.

Paper IV

Both cryosurgery and curettage provide clearance rates comparable to those observed with other common treatment methods such as surgery, PDT or 5-FU. Although cryosurgery was more effective than curettage, the non-inferiority analysis was inconclusive. Furthermore, wound healing times were significantly shorter after curettage than after cryosurgery. Although a slightly lower overall clearance rate was observed, curettage may still be considered for IEC in selected cases.

7.

Future Perspectives

This thesis has addressed several clinical questions my co-workers and I have had on how to improve the diagnosis and treatment of IEC. However, many issues still remain to be evaluated. The first step of diagnosing IEC is not easy and needs to be further investigated. As shown in Paper I, interobserver agreement on dermoscopic findings in IEC was poor to moderate and, in Paper III, we showed that IEC wasn't even suspected as a differential diagnosis in two-thirds of the cases planned for excision. Furthermore, there are several ways to manage IEC and many factors to consider when choosing the right treatment method, but still no clear answer to which treatment is the best for each patient and each specific clinical scenario.

Diagnostics

Interobserver agreement in dermoscopy is an insufficiently investigated field and could improve the definitions of common terminology and facilitate educational opportunities. For example, it would be valuable to perform larger studies on the interobserver agreement on dermoscopic findings for several differential diagnoses (i.e. superficial BCC, IEC, AK and SCC) to better understand which terminology is most appropriate for not only IECs, but also clinically and dermoscopically similar lesions. In future studies, readers should ideally use an annotation tool to better demonstrate their visual interpretation of a specific dermoscopic finding.

Another interesting diagnostic method is FCM for bedside preoperative histopathological evaluations. FCM has shown potential in assessment of the invasion and grading of SCC[106] and could theoretically also be useful for IEC. A study could be conducted in which lesions suspected to be IEC or SCC are biopsied and analyzed immediately with FCM for histopathological examination before making the decision on the optimal treatment.

Photodynamic therapy

Within the research field of PDT there is a lack of prospective studies on different treatment protocols. Prospective studies with standardized protocols and long-term FU are required to acquire even better and more reliable data on the effectiveness of PDT for IEC. We know that recurrences sometimes take several years to appear so a long-term FU would be valuable. Furthermore, our research group are currently carrying out a randomized controlled trial comparing C-PDT with SDL-PDT for IEC. Hopefully, the results from this study will give us better knowledge on when and how to use these treatment methods for IEC.

Surgical excision

A common treatment for IEC is surgical excision; and by many considered to be the gold standard treatment. However, only a few studies to date have investigated the safety margins required to achieve the lowest possible percentage of incomplete excisions. Thus, there is still no international consensus on the most appropriate margins. A prospective randomized and controlled trial comparing safety margins of 3 mm vs 5 mm with long-term FU to evaluate recurrence rates, would fill in an important knowledge gap in this field.

Destructive treatment

As for destructive treatments such as curettage, cryosurgery and electrodesiccation, we look forward to analyzing the results of the completed study including 3- and 5-year FU data. Further, we will also have data within the coming year on IEC located below the knee level treated with curettage and electrodesiccation or curettage alone. These results will be important since this anatomical location may be more prone to poor healing and is also more challenging to perform surgery on.

Another interesting, but resource-demanding study, would be a randomized controlled trial comparing destructive treatment methods to topical treatments head-to-head including longer FU periods of at least 3-5 years. It would also be interesting to calculate the economic burden and societal costs of these different treatment methods.

Patient perspectives

Last but not least, it would be useful to assess the patient's perspective on the different treatment modalities for IEC. Our group has ongoing qualitative studies on the patient's experience of destructive treatments for BCC and PDT for AKs, for example, and the same study designs could be applied to IEC with semi-structured interviews and qualitative content analysis. These results could have a great impact on how we choose our preferred treatment methods for individual patients. Today, when patients are increasingly more involved and informed in treatment decisions, their perspective needs to be taken into consideration.

8.

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9.

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