BASAL CELL CARCINOMA: REAL-LIFE BURDEN ON HEALTHCARE AND SIMPLIFIED DESTRUCTIVE TREATMENTS

EVA BACKMAN
Department of Dermatology and Venereology
Institute of Clinical sciences
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Illustration front page: Dermoscopic images of a superficial (left) and a nodular(right) basal cell carcinoma

Basal cell carcinoma: real-life burden on healthcare and simplified destructive treatments

eva.johansson.backman@vgregion.se

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MARCUS TULLIUS CICERO

ABSTRACT

Basal cell carcinoma (BCC) is the most common cancer in humans. With steadily increasing incidence rates, there is a constant need to evaluate current diagnostic methods and treatment alternatives to achieve effective care for the patients while considering available healthcare funding. This thesis consists of four original papers and addresses potential changes concerning the burden of BCC but also evaluates whether destructive treatment methods can be further simplified with maintained effectiveness and patient satisfaction.

Paper I compared clinically diagnosed BCCs with histopathologically confirmed BCCs to make an estimation of how well official statistics reflect real-world data. The study indicated that the burden of BCC in Sweden may be up to 70% higher than reported in official statistics and that BCCs with truncal location and superficial subtype were more prevalent than previously reported, especially among males. Papers II to IV are components of a larger research project, with randomized controlled trials, comparing different destructive treatment protocols for various subtypes of low-risk BCCs. **In Paper II,** the effectiveness of curettage alone vs cryosurgery in a single freeze-thaw cycle for superficial BCCs was compared. The 1-year clinical clearance rates were 95.7 vs 100%, respectively (P=0.060). Oozing wounds lasted 0.8 weeks after curettage and 1.6 weeks after cryosurgery (P<0.0001). **Paper III** evaluated the effectiveness of curettage followed by cryosurgery in one or two freeze-thaw cycles for nodular BCCs. The 1-year clearance rates were 99% vs 100%, respectively (P=1). The average duration of oozing wounds was 1.0 week for one cycle and 1.2 weeks for two cycles (P=0.062). **Paper IV** employed a mixed methods design to investigate cosmetic outcomes and patients' preferences when deciding upon BCC treatment. The objective evaluation of cosmetic outcome was not comparable to patients' satisfaction with their scars. For non-facial BCCs, most patients reported little concern about scarring. Their primary consideration was the expected clearance rates of the available treatments.

Taken together, the results indicate that official statistics based on histopathologically confirmed BCCs significantly underestimate the true number of BCCs and that low-risk BCCs are more common than described. These low-risk lesions can be safely treated with simplified destructive treatments and patients seem to value an effective treatment more than an excellent cosmetic outcome.

Keywords: Basal cell carcinoma, cosmetic outcome, cryosurgery, curettage, dermoscopy, epidemiology, randomized controlled trial.

SAMMANFATTNING PÅ SVENSKA

Basalcellscancer (BCC) är den vanligaste cancerformen hos människa och antalet nya fall ökar kraftigt, både i Sverige och internationellt. Under 2021 inrapporterades över 69 000 nya fall till det svenska BCC-registret. Det stora antalet tumörer medför att många personer drabbas och att stora sjukvårdsresurser tas i anspråk för diagnostik och behandling. Det finns därför ett ständigt behov att utvärdera nuvarande metoder för att uppnå effektiv vård för patienterna samtidigt som tillgängliga sjukvårdsresurser beaktas.

BCC växer långsamt och ger nästan aldrig dottertumörer (metastaser) men kan ge lokala besvär i huden, vanligen ett sår som inte läker. Beroende på växtsätt, lokalisation och storlek kan man dela in BCC i lågrisk- och högrisk-BCC. För högrisk-BCC är kirurgi den rekommenderade behandlingsmetoden men för lågrisk-BCC kan andra metoder, såsom krämer, men också destruktiva behandlingar (skrapning, frysning och bränning) användas.

Diagnosen ställs antingen genom att ett vävnadsprov tas från förändringen för en mikroskopisk undersökning, en så kallad histopatologisk bedömning, eller genom läkarens kliniska bedömning. Den kliniska bedömningen har förbättrats de sista 20 åren genom användande av dermatoskopet, ett handhållet instrument som möjliggör bedömning av färger och strukturer i hudförändringar. Detta kan resultera i att fler BCC upptäcks men också att färre skickas för mikroskopisk bekräftelse.

Denna avhandling omfattar fyra arbeten och handlar om möjliga förändringar gällande förekomsten av BCC men utvärderar också om destruktiva behandlingsmetoder kan förenklas ytterligare med bibehållen effekt och patienttillfredsställelse.

Artikel I jämförde kliniskt diagnosticerade BCC med histopatologiskt bekräftade BCC för att göra en uppskattning över hur väl officiell statistik, baserat enbart på histopatologiskt bekräftade tumörer, återspeglar den verkliga situationen. Studien indikerade att en stor andel BCC endast diagnosticeras kliniskt och att ytligt växande BCC på bålen kan vara betydligt vanligare än vad som tidigare beskrivits, särskilt bland män. Mörkertalet av BCC i Sverige beräknades kunna vara upp till 70% högre än vad som rapporteras i officiell statistik.
Artiklarna II-IV ingår i ett större forskningsprojekt med randomiserade kontrollerade studier som jämför olika destruktiva behandlingsprotokoll för olika subtyper av lågrisk-BCC. I artikel II jämfördes skrapning (curettage) med frysning (kryokirurgi) i en omgång för ytliga BCC. Utläkningen efter 1 år var 95,7% för skrapning och 100% för frysning, vilket inte var en signifikant skillnad. Sårläkningen var kortare efter skrapning, med vätskande sår i 0,8 veckor jämfört med 1,6 veckor efter kryokirurgi. Artikel III utvärderade curettage följt av kryokirurgi i en eller två omgångar för nodulära BCC. Utläkningen

efter 1 år var likvärdig, 99% respektive 100%. Det var ingen signifikant skillnad i tid med vätskande sår mellan de två olika behandlingarna, 1,0 respektive 1,2 veckor. I artikel IV undersöktes kosmetiskt resultat och patientnöjdhet efter destruktiva behandlingar liksom patienters preferenser vid val av BCC-behandling. Vi fann att den objektiva bedömningen av det kosmetiska resultatet inte var liktydigt med patienternas tillfredsställelse med sina ärr. För BCC, belägna utanför ansiktet, rapporterade patienterna liten oro för ärrbildning. De värderade den förväntade effektiviteten högst vid val av behandling.

Sammanfattningsvis indikerar resultaten att officiell statistik, baserad på histopatologiskt bekräftade BCC, avsevärt underskattar det verkliga antalet BCC och att lågrisk-BCC är vanligare än beskrivet. Dessa lågrisklesioner kan behandlas säkert med förenklade destruktiva behandlingar och patienter tycks värdera en effektiv behandling högre än det kosmetiska slutresultatet efter behandlingen.

LIST OF PAPERS

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

I. Backman E, Oxelblom M, Gillstedt M, Dahlén Gyllencreutz J, Paoli J.
Basal cell carcinoma: Epidemiological impact of clinical versus histopathological diagnosis.
J Eur Acad Dermatol Venereol 2023; 37(3): 521–527.

II. Backman E J, Polesie S, Berglund S, Gillstedt M, Sjöholm A, Modin M, Paoli J.
Curettage vs. cryosurgery for superficial basal cell carcinoma: a prospective, randomised and controlled trial.
J Eur Acad Dermatol Venereol 2022; 36(10): 1758–1765.

III. Backman E, Polesie S, Gillstedt M, Sjöholm A, Nerwey A, Paoli J.
Curettage plus one or two cycles of cryosurgery for basal cell carcinoma with clinically nodular features - a prospective random-ized controlled trial
J Am Acad Dermatol 2023 Jun 8; Online ahead of print.

IV. Backman E, Heckemann B, Gillstedt M, Polesie S, Paoli J.
Cos-metic outcome following destructive treatments for non-facial basal cell carcinomas and patient treatment preferences – a mixed methods study.
In manuscript.

ABBREVIATIONS

ACO	Assessment of cosmetic outcome
BCC	Basal cell carcinoma
C&C	Curettage plus cryosurgery
C&ED	Curettage plus electrodesiccation
CI	Confidence interval
FU	Follow-up
HH	Hedgehog
iBCC	Infiltrative BCC
laBCC	Locally advanced BCC
mBCC	Metastatic BCC
MMS	Mohs micrographic surgery
nBCC	Nodular BCC
NCCN	National Comprehensive Cancer Network
NMSC	Non-melanoma skin cancer
NRS	Numerical rating scale
PDT	Photodynamic therapy
POSAS	Patient and observer scar assessment scale
PTCH1	Patched 1 gene
RCT	Randomized Controlled Trial
sBCC	Superficial BCC
SCC	Squamous cell carcinoma
SE	Surgical excision
SIR	Standardized incidence ratios
SMO	Smoothened
SNOMED	Systematized Nomenclature of Medicine
SRF	Self-report form
STPC	Scars, treatments, preferences and costs
SUH	Sahlgrenska University Hospital
UVR	Ultraviolet radiation

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INTRODUCTION

1. INTRODUCTION

THE HUMAN SKIN

The human skin is our largest organ and covers the entire body surface. Its primary function is to maintain an internal environment and to protect from environmental risks, including UV radiation (UVR), trauma, chemicals and infections. Other important functions are vitamin D synthesis and interaction with the central nervous system. It is divided in three layers: epidermis, dermis and subcutis (Figure 1).

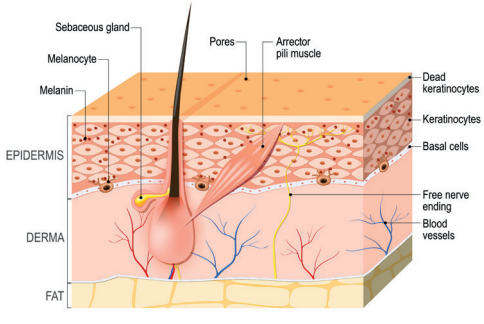

FIGURE 1. Schematic structure of the human skin. © Istock

The outermost layer, the epidermis, is composed mainly of keratinocytes (squamous cells), which produce keratin, that helps to give the skin its strength and waterproofing properties. It also contains melanocytes, which produce the pigment melanin, which is responsible for skin color and protecting the DNA of skin cells against harmful UVR. The third cell type is the Langerhans cell responsible for presenting antigens to the immune system. The basal layer of the epidermis is constituted of the basal cells, also known as basal keratinocytes, essential for the regeneration and renewal of the skin. The epidermis is avascular and receives its nutrients and oxygen through diffusion from the underlying dermal blood vessels.

The dermis is a fibrous structure composed of collagen and elastin, produced by fibroblasts, and other extracellular structures such as blood vessels and nerves. It provides elasticity, structural and nutritional support to the skin and regulates body temperature through sweat production as well as produces sebum for skin moisturization.

The subcutis, also known as the hypodermis, is the deepest layer of the skin. It is primarily composed of fat cells and plays an important role in body contouring, insulation, and protection.[1]

SKIN CANCER

Skin cancer can develop from any cell type present in the skin, leading to a wide range of possible types of cancer. However, the most frequent mutations are caused by UVR exposure to the epidermal cells.[2] Consequently, keratinocyte cancers, *i.e.* squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) comprise the majority of

skin cancers followed by melanoma, which is caused by mutations in melanocytes. Skin cancer is generally categorized in melanoma and non-melanoma skin cancer (NMSC). NMSC includes SCC and BCC, as well as rare forms of skin cancers, such as Merkel cell carcinoma, atypical fiboxanthoma, adnexal carcinomas and various forms of sarcomas.[3] Over 11,300 new cases of NMSC (excluding BCC) were reported in Sweden in 2021, making it the second most common cancer group among both men and women.[4]

BASAL CELL CARCINOMA

BCC accounts for approximately 75-80% of all keratinocyte cancer, making it by far the most common malignant tumor in fair-skinned humans.[5,6] In 2021, over 69,800 new histopathologically confirmed cases were registered in Sweden. The sum of all other primary cancers in Swedish individuals during the same year was approximately 75,300.[4] Due to the large and steadily increasing numbers of new cases, BCC is a public health problem and the diagnosis and treatment consume excessive healthcare resources.[7-9] The increase in incidence is most often explained by an aging population and increased UVR exposure, but other important factors include increased awareness of skin cancer in the general population and among physicians, leading to more full-body screenings. In addition, a shift towards more surgery instead of destructive treatments will result in a larger proportion of BCCs being histopathologically confirmed.[10] Improved sensitivity through dermoscopic diagnostics is another possible factor.

BCCs often present as a slow-growing pinkish nodule or patch in sun-damaged skin in the elderly. According to textbooks and review articles, the most common site is the head and neck area and nodular BCC (nBCC) the most common subtype.[11-16] The diagnosis is uncommon in ages below 40 years, and the highest incidence in Sweden (crude person-based) is found in the age group >84 years.[17] The risk of metastasis is very low, with an estimated risk of less than 1 in 1,000 to 1 in 35,000.[18] Morbidity stems from the ability of BCC to locally invade and destroy surrounding tissue.[19] Therefore, treatment is recommended in order to avoid progress to large and infiltrating tumors.[20]

ETIOLOGY

BCC is named based on the tumor cells' visual similarity to the basal cells found in the epidermis. Nevertheless, the precise cell of origin for BCC remains unidentified.[20] Most BCCs seem to arise from stem cells of the hair follicle,[21,22] but to some extent also from stem cells located in the interfollicular epidermis.[23] It has been suggested that different cell compartments may be targeted depending on the carcinogenic agent involved.[24] The hypothesis of hair follicle-derived stem cells as the most important compartment make sense from a clinical point of view as BCCs are exceedingly rare in palms and soles or in mucosal sites. BCCs also seems to be dependent on local environmental or cellular factors for their growth and therefore have a low potential to spread.[25] The development of BCC involves complex interaction between environmental and host factors, encompassing both phenotypic and genetic factors (Table 1).

TABLE 1. Risk factors for developing basal cell carcinoma.

Environmental	Phenotypic	Genetic mutations (somatic or germline)
· UV-radiation	· Fair skin complexion	· HH signaling pathway PTCH 1 and SMO
· Ionizing radiation	· Poor ability to tan	· TP53
· Immunosuppression	· Multiple moles	· Hippo signaling pathway
· Chemicals - arsenic	· Male sex	· MYCN/FBXW7
· Photosensitizing drugs	· Family history of skin cancer	· TERT
		· NOTCH 1 and 2

ENVIRONMENTAL RISK FACTORS

UVR is the major environmental risk factor. Intense intermittent exposure, especially early in life, has been correlated with an increased risk of developing BCCs.[26,27] The skin's ability to tan modulates this risk. A steady increase of risk is seen in poor tanners whereas people who tan easily develop cancer only after prolonged exposures.[28] UVR exposure encompasses all types of exposure including the sun, tanning beds and medical use of UVR.[29,30]

Two less common but important environmental risk factors are ionizing radiation and systemic immunosuppression. BCCs due to radiation therapy are confined to the area of irradiation and the risk of developing BCC appears to be more pronounced for patients with irradiation early in life.[31] Patients with a chronic use of immunosuppressive medication, especially organ transplant recipients, have an increased risk of keratinocyte cancer, especially SCC and to a lesser extent also BCCs.[32] The increase in risk is partly related to UVR exposure prior to immunosuppression as these drugs alter the cutaneous immune surveillance of already existing UVR-induced mutations. Therefore older age at transplantation, skin susceptible to photodamage as well as time since transplantation are all risk factors for developing keratinocyte cancer including BCCs.[33] Additional environmental risk factors include chemicals such as arsenic and photosensitizing drugs.[34-36]

HOST FACTORS

Fair skin with red/blond hair and blue/green eye color, multiple moles and poor ability to tan are major risk factors for BCC.[37,38] A personal or family history of skin cancer, male sex but also older age are other risk factors.[39] The latter is linked to more years of sun exposure but also the decreased immune surveillance and ability to repair DNA damage with age.[40] Some of the host factors are due to variations in certain genes (e.g. melanocortin 1 receptor), which results in different photoprotective qualities of the melanin produced.[41]

GENETICS

Genetic factors associated with BCC can be divided in somatic mutations seen in sporadic cases and germline mutations, found in genetic syndromes, such as in Gorlin syndrome (basal cell nevus syndrome) but also in xeroderma pigmentosum, Bazex-Dupré-Christol syndrome and oculocutaneous albinism.[42-45] It was discoveries in Gorlin syndrome that gave information about the most important genetic alterations causing BCC, including both syndromic and sporadic cases.[46-48] The key driver mutations are located in the Hedgehog (HH) pathway, most importantly in the *PTCH1* tumor suppressor gene (reported in up to 75% of BCCs) and the *SMO* gene (found in 10-20% of sporadic BCCs).[49] The HH signaling pathway has an important role in embryonic development, cell differentiation and tissue patterning and is normally tightly regulated.[50] In the case of BCC, mutations in *PTCH1* and in *SMO* lead to sustained activation of downstream HH signaling. This promotes uncontrolled cell growth, inhibits cell differentiation and eventually leads to the formation of BCCs.[49,51]

Inactivating mutations of the *TP53* suppressor gene is considered the second most common event in BCC pathogenesis.[52] As an important guardian of the genome, p53 has a crucial role for cell cycle arrests and activation of programmed cell death (apoptosis). The mutational pattern in these genes are consistent with UVR-induced DNA damage, *i.e.* C to T or CC to TT transversions.[53,54] Lower levels of *TP53* mutations have been found in BCCs among sunscreen users compared to non-sunscreen users.[55]

In recent years, new discoveries have been made, due to improved techniques for genomic analyses, describing a more complex genetic background to BCCs than previously thought.[52] These studies have identified different driver mutations, which in part could be explained by differences in BCC subtypes within the studies.[56-58] The discoveries can be keys to understanding why BCCs have different clinical features and behaviors, but also to find new targeted therapies. New discoveries include genes in the Hippo signaling pathway (crucial for organ size control), *MYCN/FBXW7* signaling (effects on downstream events in the HH pathway), *TERT* genes (regulates the telomerase activity), the *DPH3* promoter region (regulatory effects on the genome) and the *NOTCH1* and *NOTCH2* tumor suppressor genes among others. Several of these mutations show UV-signature patterns, supporting the role of UV exposure in the development of BCCs.[52]

CLASSIFICATION

BCCs can be classified in different ways. The traditional classification is according to histopathological subtypes. However, two alternative classifications also exist. These are based on the risk of treatment failure or recurrence (low-risk vs. high-risk) or whether the BCC is easy-to-treat or difficult-to-treat (Table 2). [59-61]

TABLE 2. Summary of different classification systems for basal cell carcinomas.

Histopathological subtype	Low-risk vs high-risk	Easy-to-treat vs difficult-to-treat
· Superficial BCC · Nodular BCC · Micronodular BCC · Infiltrative BCC · Morpheaform BCC · Basosquamous carcinoma · BCC with sarcomatoid differentiation · Fibroepithelial BCC · BCC with adnexal differentiation	*Low-risk* Primary superficial or nodular subtypes with: · Non-facial location · Size <20mm or <10 mm if pretibial *High-risk* · Micronodular, infiltrative, sclerosing and basosquamous subtypes independent of size and location. · Superficial and nodular subtypes if size >20 mm or >10 mm if pretibial · Recurrent lesions · Location on facial area, hands, feet, genitalia or pretibial area · Immunosuppressed patient · Prior radiotherapy in tumor area	*Easy-to-treat* Basal cell carcinomas that can be cured by surgery, destructive or non-invasive treatments. *Difficult-to-treat* Locally advanced or metastatic basal cell carcinomas requiring systemic therapy or radiotherapy.

HISTOPATHOLOGICAL CLASSIFICATION

The most common histopathological subtypes include nodular, superficial, micronodular, infiltrating and sclerosing (morpheaform) BCCs (Figure 2), but rarer subtypes, including fibroepithelial BCC, BCC with adnexal differentiation, basosquamous BCC and BCC with sarcomatoid differentiation also exist. The nodular and superficial subtypes as well as fibroepithelial BCC and BCC with adnexal differentiation have an indolent, low-aggressive growth pattern while the rest are referred to as having a more aggressive growth pattern. Every subtype has distinct histopathological characteristics, but a precise correlation is not always observed between specific histopathological subtypes and clinical characteristics. Further, a mixed pattern (two or more major histopathological patterns) within a single lesion is common and has been described in almost 40% of cases.[62]

Nodular BCC (nBCC) presents as a pinkish nodule with visible telangiectasias or as an ulceration surrounded by characteristic rolled borders. This subtype is particularly prevalent in the head and neck region. Histopathologically, it displays a nodular arrangement of tumor cells with palisading of the cells at the periphery of the nodules. There is often a retraction artefact observed between the tumor nests and the surrounding stroma. Classic dermoscopic findings include arborizing vessels and ulceration as well as blue-grey ovoid nests and multiple blue-grey dots in pigmented nBCCs.

Superficial BCC (sBCC) typically appears as an erythematous scaly patch with erosions and is most frequently found on the trunk. Histopathologically, the tumor nests are superficially attached to the epidermis with minimal penetration into the dermis. In dermoscopy, sBCCs display short fine telangiectasias, multiple small erosions, structureless white-red areas as well as leaf-like, concentric and/or spoke-wheel areas if pigmented.

Micronodular BCC may resemble nBCC clinically and dermoscopically but the tumor nests are smaller, more widely dispersed and extending deeper into the dermis and even the subcutis.

Infiltrative BCC (iBCC) including sclerosing (morpheaform) BCC have a preference for the head and neck area. Clinically, it presents as a pale plaque with a scar-like appearance, and the borders are often indistinct. Histopathologically, this variant is characterized by small, irregularly shaped tumor nests and strands without prominent palisading and retraction. If sclerosing, a dense collagenized stroma infiltrates the tumor strands. These subtypes can exhibit deep infiltration and perineural invasion, leading to higher recurrence rates. Dermoscopic features seen in infiltrative BCCs are thin and more scattered arborizing vessels ("fine arborizing vessels") and often a white or porcelain-like structureless area is present.

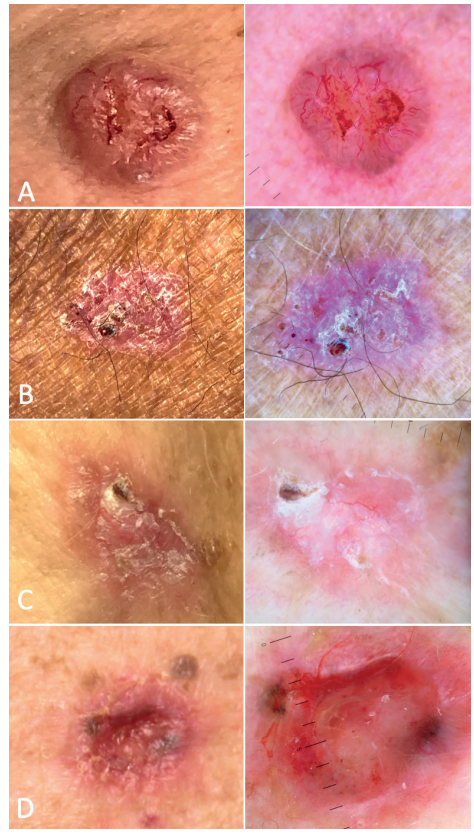

FIGURE 2. Clinical and dermoscopic presentations of (A) nodular, (B) superficial, (C) infiltrative and (D) morpheaform (sclerosing) BCC subtypes.

Basosquamous carcinoma often presents as a facial ulcerated nodule or plaque. Upon dermoscopy overlapping features with SCC is common, such as keratin masses, ulceration with blood spots and peripheral unfocused arborizing vessels.[63] It has the histopathological appearance of both BCC and SCC and is classified as an aggressive subtype with data suggesting a metastatic capacity more similar to SCC than BCC.[64]

In individuals with melanin-rich skin, pigmented BCCs are more commonly seen. The pigmentation is predominately seen in superficial and nodular subtypes.[65]

DIVERSITY IN HISTOPATHOLOGICAL CLASSIFICATIONS

Although a World Health Organization classification for skin cancers including BCCs exists, international histopathological classifications of BCCs are complex and diverse.[66,67] In Sweden, BCCs are categorized into four major subtypes using the Glas (Sabbatsberg) classification system. [68] This classification system which is not utilized elsewhere includes: nBCC (Glas type IA), sBCC (Glas type IB), moderately aggressive iBCC (Glas type II) and highly aggressive iBCC, including sclerosing/morpheaform BCC (Glas type III). In this classification system Glas types II and III are often referred to as aggressive BCCs, encompassing micronodular, infiltrative, and sclerosing/ morpheaform histopathological growth patterns.

The heterogeneity in histopathological classification systems makes it difficult to compare both research and epidemiological data. Therefore, a simplified classification into three main categories (*i.e.* superficial, nodular and infiltrative subtypes) has recently been proposed in order to increase reproducibility and still be practical from a clinical standpoint.[69] This new histopathological classification system would simplify reporting and facilitate comparisons between research publications, but could also impact the treatment recommendations for BCC. For example, current Swedish national guidelines allow for destructive treatments of Glas type II BCCs (moderately aggressive iBCC)[70], but if a less detailed classification system were used, there may be a stronger inclination towards considering only surgery as an accepted treatment option for all iBCCs.

LOW-RISK AND HIGH-RISK BCC

The classification of BCCs into low-risk or high-risk BCCs is based on the risk of treatment failure or recurrence. This classification takes into account not only the histopathological subtype but also size, location, whether the tumor is primary or recurrent or if located in an area of prior radiotherapy or in an individual with immunosuppression. This division into high-risk and low-risk is partly based on outcomes for SCCs rather than BCCs.[59] In addition, this classification varies slightly among different treatment guidelines and has undergone subtle changes over time. [20,59,71,72]

EASY-TO-TREAT AND DIFFICULT-TO-TREAT LESIONS

An alternative classification of BCCs, proposed by the European Academy of Dermato-Oncology is in "easy-to-treat" versus "difficult-to-treat" BCCs.[61] The vast majority (>90%) belongs to the easy-to-treat group, meaning they can be cleared by simple surgical excision, destructive treatments or non-invasive methods such as topical drugs or photodynamic therapy (PDT). Difficult-to-treat BCCs are lesions not reachable through surgery, either being a locally advanced BCC (laBCC) or a

metastatic BCC (mBCC). For difficult-to-treat BCCs , radiotherapy as well as systemic therapies are possible treatment options.

LOCALLY ADVANCED BCC

The term laBCC was introduced with the advent of systemic treatments involving HH inhibitors. While it lacks a precise and universally accepted definition, it typically characterizes a BCC exhibiting the following characteristics: (1) a prolonged history of no treatment, treatment failures, or recurring episodes; (2) substantial tissue damage in the surrounding region; and (3) a condition that has become challenging or unresponsive to surgical intervention or radiotherapy.[73]

METASTATIC BCC

mBCC is rare and is estimated to occur in 0.028-0.55% of all BCCs.[74] Therefore, the TNM classification used for other solid tumors (including skin cancers) does not fit for BCCs as they do not normally follow the three steps of tumor, nodal and distant metastatic disease. Risk factors for metastatic disease and death according to the Brigham Women Hospital staging system include BCCs ≥2cm in diameter with at least 2 of the following 3 criteria: size ≥4 cm, head and neck location or invasion below fat (Stage T2). No additional risk factors were found to be associated with mBCC and death on multivariable analyses and were therefore not included in the staging system design.[75] In a review of 170 metastatic cases the median age at diagnosis was 45 years, which is considerably lower than the median age for BCC diagnosis. In addition, metastatic disease occurred 9 years (median) after diagnosis and the male/female ratio was 2:1. mBCC is an aggressive disease with low response to systemic therapies. Before the era of HH inhibitors and immunologic therapies, the median survival was 8 months.[74]

DIAGNOSIS

The gold standard for BCC diagnosis is histopathology. However, during the last two decades, dermoscopy has enhanced the clinical assessment of skin tumors, including BCCs. By using the dermatoscope's magnifying lens and polarized or non-polarized light, specific structures such as different types of vessels, colors, patterns of pigmentation and/or fibrosis can help the physician distinguish and discriminate different tumor types. In a meta-analysis, a pooled sensitivity of 91% and specificity of 95% could be observed for BCC diagnosis using dermoscopy in combination with on-site clinical assessment of the lesion.[76] Dermoscopy has also shown to be valuable in the evaluation of the histopathological subtype of BCC, particularly in distinguishing superficial BCCs from other subtypes.[77,78] In fact, the updated European guidelines state that a clinical diagnosis confirmed by dermoscopy without histopathological examination is acceptable for small nBCCs on typical locations such as the head/neck or trunk, for multiple BCCs in basal cell nevus syndrome and for sBCCs located on the trunk and extremities. However, histopathological confirmation is mandatory for high-risk lesions and ambiguous cases.[73]

TREATMENT

The purpose of treating BCCs is to eliminate all tumor tissue and avoid recurrences, balanced against the patient's requirements for a satisfactory cosmetic outcome.[79] Recommended treatment methods differ between low-risk and high-risk tumors. Individual patient factors such as preferences, comorbidities and biologically advanced age are also considered. Management guidelines are also, to some extent, influenced by the nation's healthcare system.[20,80,81] The majority of lesions can be successfully treated by surgery, topical treatments or destructive treatments. However, for a small percentage of BCCs, *i.e.* laBCCs or mBCCs, radiotherapy or systemic therapies such as HH inhibitors (Vismodegib and Sonidegib) or immune checkpoint inhibitors (Cemiplimab) are needed to fight the disease.[82]

SURGERY

Surgery is the cornerstone of treatment for BCCs. Standard surgical excision (SE) is performed with a predefined clinical margin, usually between 3 and 5 mm. For facial high-risk lesions, surgery with intraoperative margin control, *e.g.* Mohs micrographic surgery (MMS), is the gold standard.[19,20,80] In MMS, the excised tissue is laid flat, frozen and horizontally sectioned to enable analysis of 100% of both the lateral and deep excision margins. This leads to lower rates of incomplete excisions, lower recurrence rates and tissue preservation compared to SE. An RCT comparing MMS and SE for high-risk facial lesions reported a 10-year probability of recurrence of 4.2% for MMS *vs* 12.2% for SE. [83] Furthermore, two recent meta-analyses on SE and MMS concluded that MMS had improved outcomes for both primary and recurrent BCCs, but due to higher costs should be reserved for high-risk BCCs.[84,85] However, a recent Cochrane review reported only low-certainty evidence of slightly fewer recurrences with MMS over SE for primary facial BCCs (high-risk subtype or located in the 'H-zone' or both).[79] In international guidelines, all iBCCs, independent of location, are classified as high-risk BCCs in which only surgery (including MMS) is recommended.[20,80]

TOPICAL TREATMENTS

Topical drugs such as imiquimod and 5-fluorouracil as well as photodynamic therapy (PDT) are possible treatment options for selected low-risk BCCs, especially sBCC.[86] The clinical clearance rates have varied considerably, especially for PDT due to different treatment protocols used.[87] A large-scale (n=601), non-sponsored RCT resulted in one-year clearance rates of 83.2% for imiquimod, 80.1% for 5-fluorouracil and 72.8% for PDT with the conclusion that imiquimod was superior to and 5-fluorouracil non-inferior to PDT. [86]. A 5-year follow-up of the same study declared the probability of tumor-free survival to be 62.7% for PDT, 80.5% for imiquimod and 70.0% for 5- fluorouracil.[88] A superior cosmetic outcome is often highlighted as an advantage of these treatments compared to cryosurgery and surgery, although the cosmetic outcome for surgery was rated higher by health professionals but not by patients.[89-91]

DESTRUCTIVE TREATMENTS

Destructive treatments include curettage (scraping), electrodesiccation (burning), and cryosurgery (freezing) in various combinations. In recent years, ablative laser treatments with carbon dioxide, erbium-doped yttrium aluminium garnet (Er:YAG) and neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers have been added to the list of destructive treatment methods but their place in the treatment arsenal for BCC is still unclear. [92-94]

The destructive treatments are not standardized, meaning there is no international consensus on the precise technique that should be used to make them as effective and tolerable as possible.[95] Authors also highlight weaknesses of these methods such as the lack of histopathological confirmation of tumor clearance and the methods' dependence on the practitioners' skills.[20,80] Therefore, destructive treatments are generally recommended as second-line alternatives in international guidelines, most suitable for elderly individuals and for those with comorbidities that preclude surgery.[80,96] On the other hand, destructive treatment methods are considered more cost-effective compared to surgery since the treatment is quick and inexpensive to perform and often can be offered at the first visit without the need of operating facilities.

CURETTAGE AND ELECTRODESICCATION

Curettage and electrodesiccation (C&ED) have been used for decades to treat NMSC, including both low-risk and facial BCCs. It is a simple and easily performed procedure. However, there is a lack of RCTs proving its effectiveness compared to other treatments and many studies fail to provide precise descriptions of the treatment protocols used. When performing C&ED, a ring curette is used to scrape away all visible tumor tissue (curettage). The ring curettes can be made out of metal with a semi-sharp cutting edge or disposable plastic curettes with a sharp or semi-sharp edge, depending on what side is used. The curettage should be performed thoroughly including all lateral margins and the base of the lesion until the firmer resistance of uninvolved skin is encountered, a feeling that's accompanied by auditory and visual signs. The relative silence and diffuse bleeding from tumor tissue are replaced by a scratching sound and pinpoint bleeding once normal dermis is encountered. Curettage is followed by electrodesiccation of the tumor surface, as well as a 3-4 mm wide area of surrounding tissue.[97] Electrodesiccation is achieved by an electrosurgical generator set to monopolar mode, operating at high or low voltage, high frequency and low current. The entire procedure is repeated two times or more (Figure 3).

Variations of this protocol include initiating with electrodesiccation before conducting the curettage, as well as substituting electrodesiccation with electrocautery following a single session of curettage or multiple ones.[98-100] Reduced cure rates result from "light handedness" resulting in scratching rather than firmly scraping off the tumor and is regarded as a common failing of the novice.[98,101] Five-year recurrence rates ranging from 1.2-18% have been reported.[100-103] These figures also include facial BCCs in high-risk areas. The group reporting 18% in the late 1950s refined their methods and selection of lesions and reported data separately from 1973-82 showing

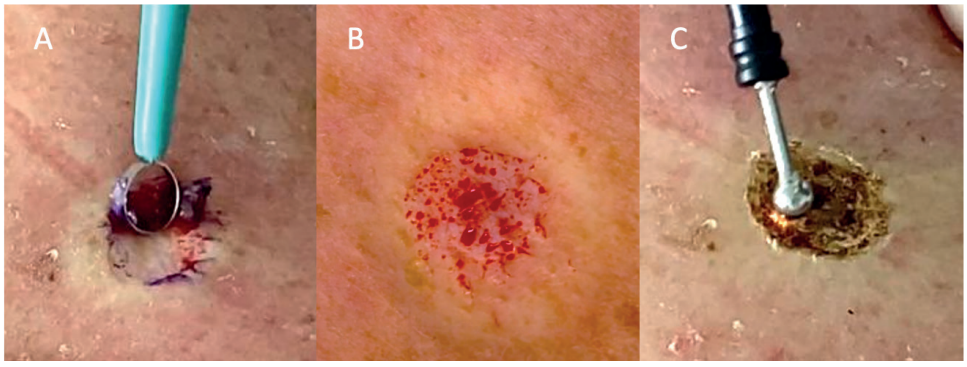

FIGURE 3. (A) Curettage with disposable ring-curette size 7 mm; (B) pinpoint bleeding when dermal surface is free from basal cell carcinoma and (C) electrodesiccation with ball-tipped electrode.

recurrence rates of 3.3% for low-risk areas independent of size, 5.3% in middle-risk sites (scalp, forehead, pre- and post-auricular as well as malar areas) with a diameter <10 mm and 4.5% in high-risk sites (H-zone) and lesions <6 mm.[104] In a later study, Rodriguez-Vigil *et al.* reported a 5-year recurrence rate of 1.2% (*n*=3) on 257 facial high-risk lesions in the best scenario (life-table method), but 20.6% when also counting all 50 dropouts as treatment failures (worst-case scenario). The study excluded fibrosing and recurrent BCCs.[103] Internationally, the use of C&ED appears to be more commonly used and recommended for the treatment of BCC compared to cryosurgery. [59]

CRYOSURGERY

The method of using extreme cold to destroy tissue started by Arnott in England as early as in the mid-1800s with salted ice (-20°C) used to freeze advanced cancers.[105,106] This was followed by the development of better cryogens, *i.e.* liquid air (-182°C) in the late 1800s, followed by carbon dioxide snow (-79°C) in the early 1900s and liquid nitrogen (-196°C) after World War II.[107] Cryoprobes, making it easier to control the procedure, were developed in the beginning of the 1960s by Cooper.[108] Torre and Zacarian, two of the pioneers in cryosurgery within dermatology, presented the first modern spray-guns for liquid nitrogen in 1967-68.[109] Since then, cryosurgery has been a common destructive treatment method for skin cancers.

The importance of correctly performed cryosurgery protocols to reach lethal tissue temperature has been underlined. Initially, thermocouples were used to measure tissue temperature, to ensure that lethal tissue temperatures were attained.[110] However, research performed by Torre in the 1970s simplified the procedure by demonstrating that the lateral spread of freeze correlated with the depth of freeze (Figure 4A).[111] Therefore, by measuring the lateral spread of freeze around the lesion ("halo"), one can estimate the depth of freeze. The tissue destruction varies not only by the lowest temperature reached at the base of the tumor, but also with the rate of temperature fall and the rate of thawing. A fast freeze followed by a slow thaw is desirable (Figure 4B-4C).

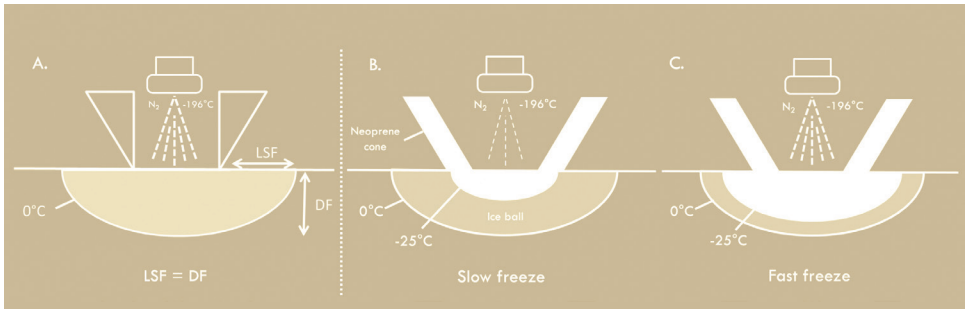

FIGURE 4. (A) Ice-ball proportions in which the lateral spread of freeze (LSF) is equal to the depth of freeze (DF). (B) Position of the -25°C isotherm when cooling rate is slow and (C) fast.

When using an open cone-spray technique, a halo thaw time >60 seconds is recommended.[111] For BCC, the temperature at the base of the lesion is recommended to be -40°C to -50°C, although temperatures around -25°C to -30°C have been suggested as being sufficient for small cutaneous neoplasms.[110,112] Although freezing causes direct lethal effects on the treated cells, there are also delayed effects caused by vascular injuries resulting in ischemia, cell apoptosis as well as introduction of an immune response (Figure 5).[113-116]

The effect of freezing depends on the tissue's properties, specifically its water content, which is necessary for ice formation to occur. Consequently, sclerosing BCCs exhibit greater resistance to cryosurgery and are less suitable for this treatment approach.[117] Tissues with low water content, such as cartilage, bone and vessel walls are resistant to freezing. Therefore, cryosurgery is particularly advantageous for anatomical areas in the face such as the nose, ears and eyelids as these underlying tissues are spared from the effect of freezing.[118-121]

When cryosurgery is conducted, the tumor borders are first delineated with a pen, preferably under dermoscopic guidance. Subsequently, liquid nitrogen is sprayed onto the lesion from a distance of approximately 1 cm, for an average of 10-30 seconds, depending on the lesion diameter, until a frozen halo of at least 4 mm forms around the tumor. The thaw time of the halo is recorded and must be a minimum of 60 seconds. If the thawing occurs quicker, the procedure should be repeated.[70] For nBCC and iBCC, the procedure usually begins with tumor debulking with curettage, followed by cryosurgery in two freeze-thaw cycles. The lesion should be completely thawed before repeating the freeze, which makes the procedure more time-consuming.

In the 1980s, Mallon *et al.* conducted an RCT comparing one *vs* two freeze-thaw cycles of cryosurgery for facial nBCCs. The authors demonstrated a superior clearance rate for two cycles, but cryosurgery was performed without prior curettage.[122] In Sweden, the national treatment guidelines recommend cryosurgery in one freeze-thaw cycle without

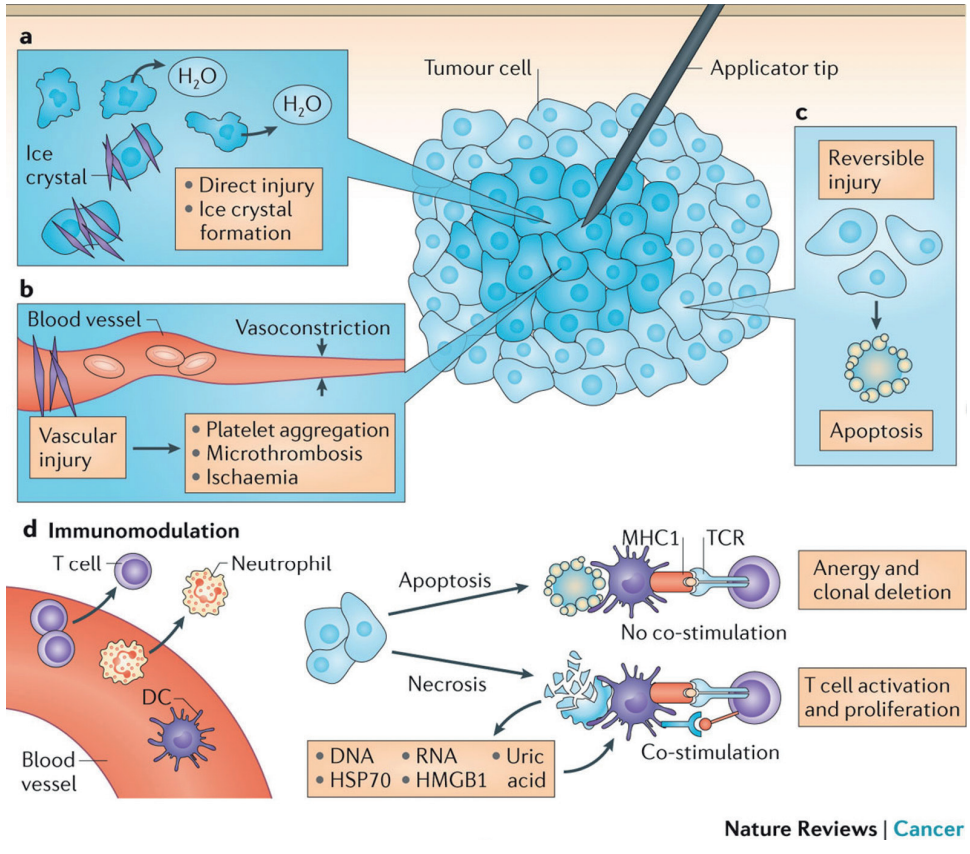

FIGURE 5. Direct and delayed effects of cryosurgery: (a) direct injury to cell, (b). vascular injury leading to ischaemia, (c) apoptosis of injured cells and (d) immunomodulation.

prior curettage for sBCCs and curettage followed by two sessions of cryosurgery for nBCC as well as for BCCs with a moderately aggressive infiltrative subtype[70] (Glas type II according to the Swedish classification system[68]). These recommendations are based on large-scale retrospective and prospective studies, albeit non-randomized, on high-risk facial BCCs conducted by both American and Swedish dermatologists showing high clearance rates (97-99%).[119-121,123,124]

International guidelines underline the lack of evidence for cryosurgery, since few RCTs have been performed.[20,80] Furthermore, cryosurgery lacks standardized treatment protocols.[71] Imprecise descriptions of the treatment protocols used in cryosurgery studies as well as treatment protocols deviating from the original ones described decades ago have resulted in inconsistent clearance rates when comparing older non-RCTs and more recent ones.[89,90,110,111,119,120,124-126] Additional

negative aspects mentioned for cryosurgery are long wound healing times and unsatisfactory cosmetic outcomes.[89,90,126,127]

CURETTAGE ALONE

Few studies have been carried out on curettage alone, *i.e.* not followed by cryosurgery or electrodesiccation, as a possible treatment method for low-risk BCCs. Three retrospective studies, including both facial and non-facial tumors have reported 5-year clearance rates ranging from 89.9% to 96%.[128-130] These studies are difficult to compare as standardized protocols were not used. In some countries, including the USA, a shave biopsy, removing a substantial part of the tumor is performed prior to curettage, while in other countries, including Sweden, curettage is performed directly. At the present time, curettage is not suggested in international guidelines as a possible treatment method for BCCs and further studies are deemed necessary before the technique can be incorporated into clinical practice.[24]

EPIDEMIOLOGY

As mentioned previously, BCC is by far the most common human cancer worldwide and the incidence is increasing.[131] The average life-time risk for fair-skinned individuals to develop BCC is at least 30%.[5] However, reliable epidemiological data are missing from many countries as BCCs are not routinely registered in national cancer registries.[131] If registration is conducted, it sometimes includes only the first-ever BCC for each individual or the first BCC each year for each individual.[27,132] Further, the registers only include histopathologically confirmed BCCs. Therefore, the true incidence is considered to be underestimated and it is also difficult to compare incidence rates between countries.[133] For instance, incidence rates in Europe were reported to range between 24 and 170 per 100,000 person-years during the first decade of the 21st century, based on studies from 14 European countries.[10] Nevertheless, numerous reports from different regions confirm an increasing incidence. The rates are highest in Australia, where over 50% of the inhabitants will be diagnosed with a BCC before the age of 70 years, followed by the USA and Europe. The rates in Europe have increased by 5% annually and in the USA by 2% while in Australia a plateau in incidence rates has been reached with stabilized rates in inhabitants younger than 60 years.[10,131] A recent study from the Netherlands reported a stabilization of the incidence in patients aged <50 years.[134] However, other studies have reported a continuous rise in younger adults, especially in females.[27,135]

Having established a national register in 2003, Sweden is one of few countries that reports all histopathologically confirmed primary BCCs, thus offering relatively reliable data. Between 2004 and 2021, the annual number of new cases has more than doubled, from 31,700 to over 69,800 (Figure 6).[4,136]

The number of new annual cases is slightly higher among males (35,470 in 2021), but varies with age. Under the age of 70 years, the incidence rate is higher among females. In a recent report published by Kappelin *et al.*, the authors concluded that the number of

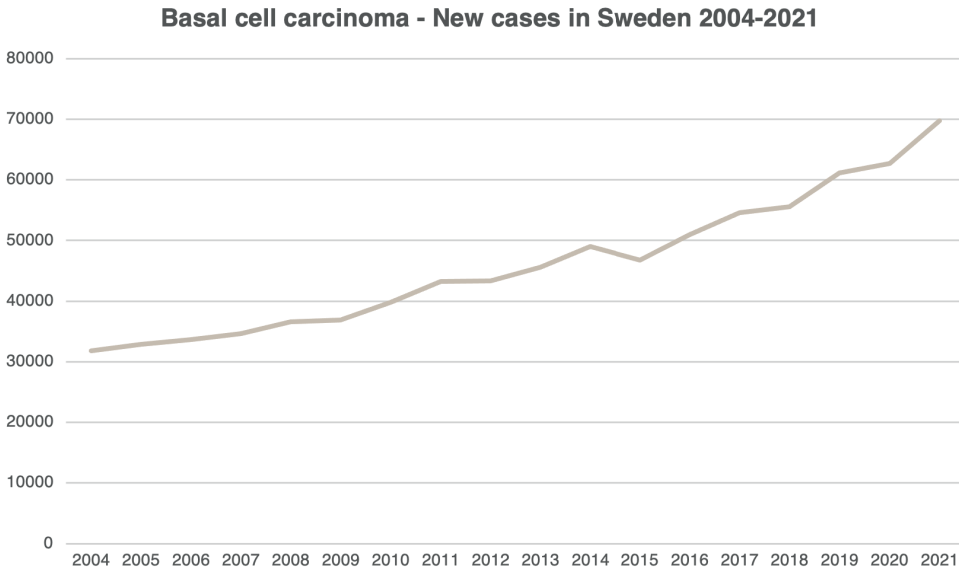

FIGURE 6. Increasing numbers of histopathologically verified basal cell carcinomas in Sweden between 2004 and 2021.

© www.socialstyrelsen.se and Kappelin et al, Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. Br J Dermatol 2022;186:963-9

reported BCCs in Sweden has increased by approximately 3% per year during 2004-2017 with slightly higher increases among women and that the number of aggressive BCCs has increased more than low-risk BCCs. In 2017, the person-based incidence rate was 405 per 100,000 (age-standardized to the 2013 European standard population). The head and neck region was the most common site for BCCs while aggressive BCCs and nBCC were equally common (31% each).[17] These figures are consistent with international reports regarding tumor locations and gender-related differences. However, the high percentages of infiltrative BCCs differ from international comparisons. The authors conclude that one limitation is that many low-risk BCCs are not registered since they are not histopathologically confirmed. In contrast to the reported distribution of subtypes in Sweden, both Ireland and the Netherlands have described an increase in the incidence of sBCCs in clothed areas of the body.[16,27] This has also been reported in a French study measuring real-life cases and not only histopathologically confirmed tumors.[137] The authors were surprised by the high proportion of sBCCs observed (50.7% of all cases). The same group also concluded that different studies have reported varying proportions of sBCCs, ranging from 5% up to 46% of all cases, and that sampling bias most likely contributed to this difference.[12,14,138,139]

In summary, epidemiological data on BCC suffers from incomplete registrations making it very difficult to draw conclusions regarding incidence rates, proportion of subtypes, the most commonly affected anatomical sites as well as possible gender differences.

CRITICAL REVIEW OF CURRENT GUIDELINES

RCTs offer a higher level of evidence compared to prospective or retrospective studies. However, as the destructive treatments for BCCs were developed in the 1950s and 1960s, the original large-scale reports on the destructive treatments, but also several later studies, lack this level of evidence.[102,104,110] This is particularly true for C&ED, where comparative studies are absent.[140] In light of this, non-randomized studies are mentioned as supporting C&ED in the guidelines.[59,103,104] In contrast, smaller RCTs exist for cryosurgery, comparing it with surgery, radiotherapy and PDT.[126,141, 89,90] These RCTs supersede larger non-RCTs performed by experienced cryosurgeons,[119-121,124] which are excluded from the international guidelines.[20,80] Among the most referenced articles are two smaller RCTs, sponsored by PDT-companies, on PDT vs cryotherapy performed in the early 2000s.[89,90] These studies allowed for retreatments of initial treatment failures and the cryo- protocol used, although imprecisely described, deviates from what has been stated as standard for achieving lethal tissue temperatures.[142] Nonetheless, the clearance rates from these two RCTs are considered evidence for cryosurgery being equally as effective (or as ineffective) as PDT.[20,80] The large discrepancies between the clearance rates observed in these studies and earlier non-randomized studies on cryosurgery are not commented on. Moreover, they don't question the deviation from well-described cryosurgery protocols that should be used to achieve lethal temperatures.

Furthermore, the European guidelines prefer the term cryotherapy over cryosurgery, arguing that cryosurgery is the correct term only when temperature probes are used to monitor tissue temperature.[20] This is not accurate, as early cryosurgeons, like Torre in the 1970s, demonstrated that the lateral spread of freeze is related to the depth of freeze, and this method has been widely used since.[111] The term cryotherapy is generally considered a more superficial and less standardized method.[71] Combining studies on both treatment methods within a guideline creates a complex picture of varying treatment success, potentially raising questions about the method's efficacy.

Several aforementioned non-randomized, large-scale studies on destructive treatments have reported high long-term clearance rates also for facial lesions, including infiltrative (but excluding sclerosing) BCCs. However, the European guidelines only refers to the recurrence rates in the worst-case scenario from a C&ED study on facial BCCs conducted by Rodriguez-Vigil *et al.* as support of a high recurrence risk when using C&ED in the head and neck area.[20] In this study 3 recurrences and 47 dropouts out of 257 treated lesions were reported as a recurrence risk of 20% while the actual proportion of established recurrences was 1.2% according to the life-table method.[103] In addition, relatively recent large-scale non-RCTs on cryosurgery for facial lesions are not mentioned.[120,121,143]

A comparison between the 2010 and 2023 NCCN guidelines shows an expansion of the high-risk category. [59,72] Now, all lesions,

independent of their histopathological subtype or size, located in the head and neck area, the pretibial area, on the hands, feet and genitalia are considered high-risk tumors. This classification of low- and high-risk BCC locations are based on the risk of recurrence for BCCs but also on the risk of metastatic disease for SCC but are still applied to BCCs without modifications.[59,75,144] Additionally, the guidelines also include BCCs in immunosuppressed individuals as a high-risk group. Although immunosuppressed patients are known for having an increased risk of recurrence or metastatic SCCs, there is a lack of scientific support for this in immunosuppressed individuals with BCC.[145,146]

In summary, BCC treatment guidelines could be subject to questioning their claims of being based on the best available knowledge. Hopefully, new and stronger evidence can provide more nuanced guidelines in the near future.

Thesis overview

	Paper I	Paper II	Paper III	Paper IV
Design	Retrospective descriptive study	Randomized controlled trial	Randomized controlled trial	Mixed methods study
Objective	Compare frequency of unregistered and registered BCCs.	Compare curettage x1 vs cryosurgery x1 for superficial BCC.	Compare curettage + cryosurgery x1 vs x2 for nodular BCC.	Compare cosmetic outcomes with patient scar satisfaction. Factors of importance for treatment choice.
Results	2,365 BCCs 56% unregistered (62% ♂ vs 47% ♀) Trunk: 46% Superficial BCC: 42% Estimation: 70% higher frequency of BCCs in Sweden.	228 superficial BCCs 1-year clearance rate: Curettage x1= 95.7% Cryosurgery x1=100% Wound healing: Oozing for 0.8 vs 1.6 weeks Healed in 4.3 vs 5.1 weeks	202 nodular BCCs 1-year clearance rate: x1 = 99% x2 =100% Wound healing: Oozing for 1.2 vs 1.6 weeks Healed in 6.3 vs 6.9 weeks	Mean numerical rating scale scores of 1-10: (Low scores are good) Cosmetic outcome 3.6 Patient satisfaction 2.3 Concern about scar 1.7 >96% rated effectiveness of treatment as the most important factor.

FIGURE 7: Overview of the thesis including the design, objectives and main results in Papers I-IV. BCCs, basal cell carcinomas.

2. AIMS

The overall aims of this thesis were to assess how well official statistics on BCC in Sweden, based on histopathologically confirmed tumors, reflect the real-life situation and to investigate if destructive treatments for BCC can be further simplified without decreased effectiveness. The specific aims were:

- To compare clinically diagnosed BCCs with histopathologically confirmed BCCs regarding distribution of subtypes, anatomical locations, sex-related differences and total numbers to make an estimate of how well the official statistics reflect real-life data in Sweden.

- To compare clearance rates after 1 year, wound-healing times and patient satisfaction for curettage *vs* cryosurgery for non-facial BCCs with superficial features located above the knee (Paper II) and for curettage plus cryosurgery with one or two freeze-thaw cycles for non-facial BCCs with nodular features located above the knee (Paper III).

- To evaluate the cosmetic outcome following destructive treatments for non-facial BCCs and to investigate how well an objective scar evaluation correlate to the patients' satisfaction with the scar. Additionally, to investigate patient factors that could influence treatment preferences, such as clearance rates, cosmetic outcome, treatment duration, healing process and cost considerations associated with different treatment options.

METHODOLOGICAL CONSIDERATIONS

3. METHODOLOGICAL CONSIDERATIONS

PAPER I

SUBJECTS

All patients diagnosed with a BCC at the Department of Dermatology and Venereology at Sahlgrenska University Hospital (SUH) and all patients with a histopathologically confirmed BCC at the Department of Pathology, SUH or at Unilabs Clinical Pathology Laboratory in Skövde, Sweden during the period of January 1 to December 31, 2016 were included as subjects in the study.

METHODS

This was a retrospective descriptive study. All primary BCCs diagnosed at the Department of Dermatology and Venereology, SUH were identified using the ICD-10 codes for BCC, *i.e.* C44.0-9, excluding C44.0-9S (squamous cell carcinoma). From the patient records, data on age, sex, number of BCCs, size, location, subtype, clinical or histopathological diagnosis, treatment and the treating physician's specialty were recorded. Information on whether the patient was alive or deceased at the time of data collection (August 18 to October 12, 2020) was also registered. For the second part of the study, all primary BCCs, diagnosed at the two main pathology laboratories in Western Sweden in 2016 were identified using the SNOMED coding system, and the specialty of the treating physician was recorded.

The retrospective design, with identification of patients diagnosed with a BCC through the ICD coding system comes with some limitations. Lesions that were biopsied and treated but for which the exact diagnosis was uncertain may not have been coded and may therefore not have been visualized in this search. In addition, the exact numbers of "multiple BCCs" were sometimes not specified and had to be counted as two lesions. This likely led to an underestimation of the actual numbers. On the other hand, the majority of lesions were only clinically diagnosed and the accuracy of the clinical diagnosis of BCCs as well as their specific subtypes can be questioned. This may have led to a slight overdiagnosis of BCCs and an underestimation of the proportions of more aggressive subtypes, particularly in locations outside the head and neck region.

There were also limitations with the SNOMED reporting system from the pathology laboratories, as they are dependent on information from the clinician regarding if the lesion was a primary or a recurrent BCC. If this information was not provided, recurrent lesions could have erroneously been reported as new primary tumors influencing the data.

When estimating the impact of dermatologists' clinical diagnosis on the total number of BCCs, two assumptions

were made: 1) that only dermatologists rely on clinical diagnosis for BCCs, while other specialists confirm the diagnosis through histopathology and 2) that Swedish dermatologists generally follow a similar approach to diagnosing and treating BCCs.

The validity of the latter assumption may be questioned due to potential variations in treatment traditions among different regions in Sweden and the extent of clinical or dermoscopic diagnosis without histopathological confirmation. A more reliable estimation of the total numbers of clinically diagnosed BCCs would have been possible through a retrospective study conducted at multiple dermatology clinics throughout Sweden and involving pathology laboratories from various regions to ensure consistent distribution among specialties. Unfortunately, this was not feasible at the time. In addition, if the national BCC registry would include information on the specialty of the clinician who submitted the tissue sample, the second part of the study could have been avoided and would have provided us with more reliable data on the proportion of BCCs being handled by dermatologists. This would also have allowed us to compare the proportion of subtypes treated by dermatologists from different regions of Sweden, giving a hint of to what extent dermatologists differ in clinical practice regarding diagnostic and therapeutic traditions.

PAPERS II-III

Papers II and III describe the results obtained so far in two out of three ongoing RCTs comparing simplified versus standard destructive treatment protocols for non-facial BCCs. These studies will continue and involve a planned follow-up (FU) period of 5 years. The third RCT, which focuses on BCCs below the knees, randomized to curettage or C&ED in two cycles, is not addressed in this thesis (Figure 8).

SUBJECTS

The study candidates were recruited from the Department of Dermatology and Venereology at SUH between November 6, 2017 and May 26, 2020 (Paper II) and between November 6, 2017 and October 26, 2020 (Paper III). Patients with clinically or histopathologically confirmed sBCCs (Paper II) or BCCs with clinically or histopathologically confirmed nodular or moderately aggressive iBCCs (Paper III) located between the neck and the knees were informed about the studies and invited to participate.

METHODS

The studies were single-center RCTs with a non-inferiority design to compare the effectiveness of curettage *vs* cryosurgery (Paper II) or curettage plus cryosurgery in one *vs* two freeze-thaw cycles (Paper III). The inclusion criteria were patients ≥18 years with ≥1 primary sBCCs (Paper II) or nBCC/ moderately aggressive iBCC (Paper III) located between the neck and the knees with diameters ranging from 5 to 20 mm. Exclusion criteria were patients with basal cell nevus syndrome or with an expected life expectancy <1 year. Immunosuppression was not an exclusion criterium nor were lesions located on irradiated areas, even

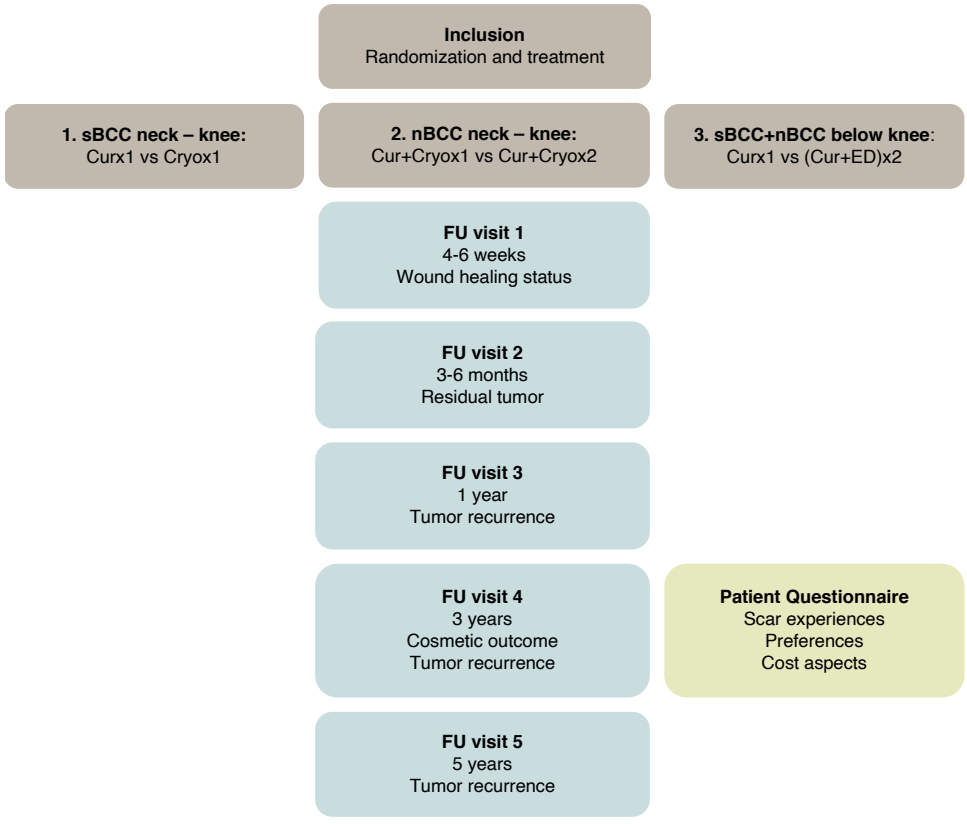

FIGURE 8. Overview of study visits and the performed procedures. sBCC, superficial BCC; cur, curettage; vs, versus; cryo, cryosurgery; nBCC, BCC with nodular features; ED, electrodesiccation; FU, follow-up.

though both these factors, as well as all BCCs with an infiltrative growth pattern (including Swedish Glas type II) are defined as high-risk BCCs according to the NCCN guidelines.[59]

The study included four clinical visits, *i.e.* the inclusion/treatment visit and 3 FU visits. FU visit 1 took place at 4-6 weeks at which time a research nurse evaluated wound healing based on a patient diary and objective findings. At FU visit 2 after 3-6 months, a dermatologist evaluated clinical response determining whether or not there was residual tumor in the treatment area. At 12 months (FU visit 3), a dermatologist evaluated tumor recurrence and carried out an assessment of early cosmetic outcome and patient satisfaction. As the studies are ongoing, results from 3- and 5-year FU visits

will be presented at later stages. At all visits, the lesions/treated areas were documented with both clinical and dermoscopic images, except at FU visit 1 at which only clinical images were taken.

All lesions were confirmed by dermoscopic examination or histopathological analysis, in accordance with our clinical practice, where tissue is obtained from punch biopsy or curettage but not when performing cryosurgery alone. This is also in line with the European guidelines which states that clinically low-risk BCCs can be diagnosed through clinical assessment only.[20] Each included lesion was randomly assigned, using computer-generated block randomization (block size 4) and treated according to a pre-specified protocol by one of five dermatologists employed at our department (four experienced dermatology residents and one board-certified dermatologist).

Interventions

The tumor boundaries were identified through dermoscopic guidance and delineated using a surgical marker. Cryosurgery was conducted using liquid nitrogen administered through a hand-held spray gun, equipped with a B-sized nozzle. An open-cone spray technique was utilized and a neoprene cone with an inner diameter equal to or larger than the tumor size was chosen. The liquid nitrogen was sprayed continuously from a distance of 1 cm from the skin surface until a frozen halo of approximately 4 mm was attained. The halo thaw time was measured, starting from the cessation of freezing and had to be >60 seconds for acceptance. Otherwise, the procedure was repeated after complete thawing of the lesion (Figure 9).

Curettage was performed using disposable ring curettes of sizes 7 mm and 4 mm, starting with the larger size and proceeding to the smaller size until a clean white dermis with pinpoint bleedings was achieved across the entire surface. Older studies have utilized semi-sharp metal curettes, but as they are not so common anymore and not used in daily practice at our department, we chose to use disposable curettes instead.

The equipment used for both curettage and for cryosurgery is presented in figure 10.

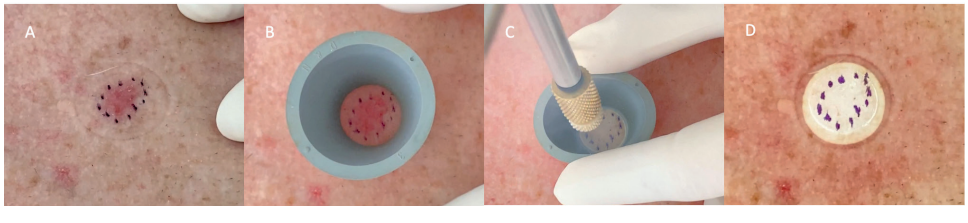

FIGURE 9. Cryosurgery procedure for sBCC. (A) Marked tumor boundaries after dermoscopic guidance, (B) neoprene cone with inner diameter equal to or larger than diameter of tumor, (C) liquid nitrogen sprayed from a distance of 1 cm and (D) frozen halo directly after freezing.

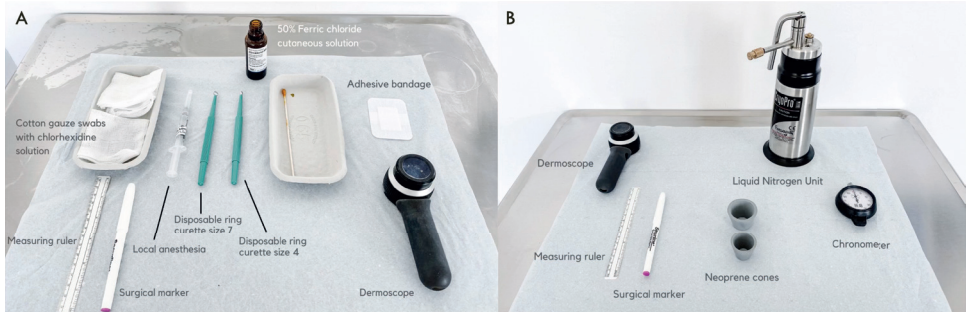

FIGURE 10. Equipment for (A) curettage and (B) cryosurgery

The curettage material was sent for histopathology if the BCC diagnosis had not been previously confirmed. This measure was taken to provide reassurance to ourselves and to future readers of the published study regarding a high specificity for the clinically diagnosed sBCCs randomized to cryosurgery (Paper II).

In Paper III, the only difference in treatments was that curettage was performed with only one size of curette (4 or 7 mm) as the treatment was followed by cryosurgery. For lesions randomized to two freeze-thaw cycles, the second freeze was performed after complete thawing of the lesion. Upon completion of the treatment, the area was covered with a basic adhesive bandage and the patients were instructed to change this as long as the wound was oozing. The patients were also instructed to indicate on a self-report form (SRF) once a week whether the wound was still oozing, covered with crust or had completely healed, and to return this form at the first FU visit. (Figure 11). If, at that time, the wound was still not completely healed, they were asked to continue with the reporting until complete wound healing had occurred.

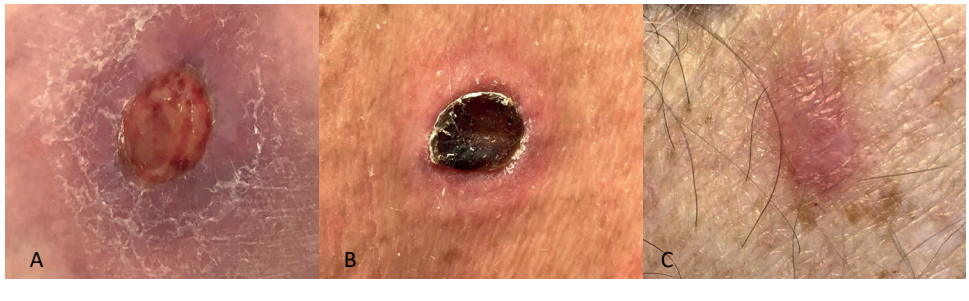

FIGURE 11. Clinical appearance of wounds that are (A) oozing, (B) covered with crust or (C) healed.

In both paper II and III, we decided to include lesions based on either clinical assessment or their histopathologically confirmed subtype. This decision was made as we wanted the research outcome to be trustable and useful in a real-world situation, where the majority of these lesions are treated based on clinical assessment only. By choosing this approach, we could demonstrate that the results are reassuring also for lesions with somewhat infiltrative growth pattern, but clinically judged to be superficial or nodular. Further, taking biopsies from all lesions (measuring 5-20 mm) prior to treatment would change the lesions both in size but also by adding scar tissue compared to the original lesions. Including lesions based on clinical assessment only is not standard when reporting clinical research on treatment outcomes for BCCs today. Current guidelines have, at least historically, made their study selections based mainly on histopathologically confirmed lesions and the Cochrane review from 2018 only included research in which all lesions were histopathologically confirmed.[147]

When reporting clearance rates, we chose the per-protocol analysis instead of the intention-to-treat analysis even though the latter is stricter and often the recommended way of reporting RCTs. However, we claim there is an important difference between RCTs on pharmacological treatments, where therapies often are ongoing, compared to a study where the treatment is given at a single occasion at the beginning of the study and cannot be changed thereafter. With an intention-to-treat analysis, unevenly distributed drop-outs, without relation to the given treatments, could significantly influence the reported clearance rates, especially in the situation where there are few true recurrences.

Recurrences were assessed through dermoscopic evaluation and not routinely biopsied. Biopsies were only obtained in case of clinical suspicion. This study design was selected for various reasons. First of all, the clinical and dermoscopic clues for BCCs, including recurrences, were well-known for the researchers engaged in the study. Secondly, interfering with all lesions at the 1-year FU visit would change the lesions for the following evaluations after 3 and 5 years. Biopsies could affect both the long-term cosmetic outcome and most importantly the risk of recurrences since part of the treated area would have been removed. Lastly, taking biopsies without a clinical suspicion of recurrence also differs from real-life practice.

As the standard treatment protocols provide high clearance rates, our aim with these studies was not to prove that simplified treatments would be equally good or even better, but to be non-inferior. Other positive aspects could be gained from simplifying the methods, such as shortened wound healing times and possibly better cosmetic results. We chose a non-inferiority limit of 8%, which we thought could be accepted from a clinical point of view. Accepting a difference of 8% in clearance rates and still considering the treatment to be non-inferior may seem dubious, but others have accepted a non-inferiority limit of 15%.[126] In retrospect, upon reflection, the non-inferiority limit may actually have been too narrow. We also chose an expected clearance rates of 95% despite older studies from Sweden showing higher clearance rates even after long-term

FU. However, we also took into account other international studies comparing cryosurgery with surgery that reported higher recurrence rates when choosing the 95% expected clearance rates.[126]

Regarding wound healing times, patients tended to forget to fill out the SRF with time passed since treatment. Therefore, the number of incomplete SRFs increased with longer wound healing times, which present a limitation when interpreting the mean and median patient- reported times for complete wound healing. This could potentially have been avoided if a digital-online reporting of wound status had been available coupled with text reminders. However, at that time, we did not utilize an online case report form that provided such technical features.

PAPER IV

SUBJECTS

Patients who had participated in one or more of the three different RCTs on destructive treatments for BCCs described above (including lesions below the knees), and who had completed their 3-year FU by February 13, 2023 were eligible to participate in this study.

METHODS

The study utilized a mixed-method (quantitative and qualitative) design to examine the cosmetic outcome resulting from different destructive treatment protocols and to explore patients' experiences with treatments and scars, as well as their hypothetical treatment preferences for BCCs.[148] Quantitative data formed the primary component, while qualitative data played a supportive role in providing a deeper understanding. We combined a quantitative objective assessment of the scars conducted by both the patient and a dermatologist with a qualitative questionnaire to gain further insights into how patients weighed cosmetic outcomes against treatment effectiveness, time consumption and wound healing. As part of our research, we were also interested in understanding the participants' viewpoints on the extent to which tax-financed healthcare costs should be considered when choosing a treatment method. The qualitative questionnaire was named the "STPC" -questionnaire, which was an abbreviation of scars, treatments, preferences and costs.

It is necessary to provide an explanation for the background and rationale behind the study. One of the secondary objectives of the RCTs was to compare the cosmetic outcomes of the different treatment modalities. We had initially hypothesized that simplified destructive treatments could lead to improved scar cosmesis, which would benefit the patients. Previous research and guidelines emphasize the importance of superior cosmetic outcomes with PDT and imiquimod compared to surgery or destructive treatments.[20,59,80,89,90,127] However, during the evaluation of patients at the one-year FU visit, we were surprised to find that patients expressed overall high satisfaction with their scars regardless of the objective scar cosmesis. As a result, we realized that evaluating whether simplified treatments could result in slightly less visible scars would not be feasible or meaningful. Instead, we discovered that the

patients' satisfaction encompassed a broader perspective beyond objective scar outcomes, which had not been explored or described in earlier research. As a result, we decided to further explore this aspect during the three-year FU visit.

Established and validated scar assessment scales like POSAS and the 4-point scale exist but lack the specific parameters we were interested in studying.[149,150] We therefore developed a new scar assessment scale for both patient and physician ratings. This scar assessment scale was named the "assessment of cosmetic outcome" (ACO) scale and involved a numerical rating scale (NRS) ranging from 1 to 10 with lower NRS values indicating positive scar evaluations. The included parameters in the physician's rating scale were based on conclusions drawn from earlier research on topical treatment for BCCs (vascularity and pigmentation),[150] but we also added a question regarding scar thickness, as this is a known characteristic in scars resulting from electrodesiccation (thicker) and cryosurgery (depressed). The ACO scale has not been externally validated, which is a limitation that should be addressed in future research.

Exploring these questions in a selected group of patients who had willingly participated in a study on destructive treatments can potentially have caused a selection bias. Therefore, the results can be questioned regarding external validity, so the generalizability of the results and conclusions should be interpreted with caution. To partially address this bias, we compared the responses between patients with and without prior treatment experiences to identify possible significant differences in treatment preferences. Such differences were not found, but could be due to insufficient numbers of patients. The total number of lesions (n=372) was considered sufficient for investigating differences, but the number of patients were significantly lower (n=135) since many had multiple lesions included in the study.

In the survey, we opted to use questionnaires instead of conducting interviews as we were also interested in quantifying the responses. However, this comes with the loss of a more profound understanding, which could be criticized from a qualitative research perspective. In other words, the answers may be considered too superficial to allow anything other than manifest content analysis.

STATISTICAL ANALYSES

Paper I was a descriptive study. Data across multiple variables were gathered in order to obtain a comprehensive overview of how well the official statistics reflected real-life data on BCCs. Significant differences between groups were assessed using Wilcoxon's rank-sum test, Kruskal-Wallis test, and Fisher's exact test, and P-values <0.05 were considered significant.

For **Papers II and III**, a power calculation was conducted when planning the study. Based on the assumption that 95% of the included lesions would show complete clinical clearance with the standard treatment, the sample size needed to be 184 lesions (*i.e.* 92 lesions per treatment group) to be able to statistically detect an absolute

difference of 8% with a power of 80% and one-sided α of 5% between the groups. Since we planned for long-term FU and some individuals participated with several lesions each, especially in paper II on sBCCs, we increased the number of lesions with almost 30% in Paper II and with 15% in Paper III to assure enough lesions were included even if a considerable number of patients would drop out.

The non-inferiority hypothesis was tested by calculating the one-sided 95% confidence interval (CI) for the difference in 1-year clearance rates between the two treatments, using Wang's exact method.[151] Fisher's exact test was used to test for significant differences in clearance rates and to compare the proportion of healed lesions at FU visit 1 for each treatment group. Wilcoxon's rank sum test was used to compare the patient-reported wound healing times. A multiple linear regression analysis was performed with wound healing time as the dependent variable and treatment group, lesion diameter, anatomical location, smoking, diabetes, and immunosuppression as independent variables. All tests were two-sided, except when comparing the CI for the non-inferiority analysis. *P*-values <0.05 were considered significant.

In **Paper IV**, statistical analyses were conducted on the quantitative data. In addition to descriptive statistics and tests for significant differences between groups and proportions (Wilcoxon's rank sum test, Kruskal-Wallis test and Fischer's test), Spearman correlation test was utilized to explore correlations between satisfaction with scar, concern for the scar, patient sex and age.

All statistical analyses in this thesis were performed in collaboration with Martin Gillstedt, a statistician and research fellow employed at the Department of Dermatology and Venereology, SUH. R version 3.5.3 or later (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

ETHICAL CONSIDERATIONS

All studies in this thesis were approved by the Swedish Ethical Review Authority (approval number 2020–03260 for Paper I) and by the Regional ethical review board in Gothenburg (approval number 743-17 for Papers II-IV, including an amendment with approval number 2022-06983-02 for Paper IV).

Paper I was a retrospective study, in which the patients were pseudonymized when compiling data. Thus, informed consent from the patients was not considered necessary to obtain. In Papers II-IV, each person received detailed oral and written information before signing an informed consent prior to inclusion. The experimental arms in Papers II and III were simplified treatments compared to the standard destructive treatment used. Therefore, these treatments were not expected to add any extra harm or pain to the research persons but could result in lower clinical clearance rates. This was explained to the patients prior to inclusion.

4. RESULTS

PAPER I

In total 2,365 primary BCCs in 1,171 patients were diagnosed at the Department of Dermatology and Venereology at SUH in 2016. More than 55% of the BCCs were clinically diagnosed, *i.e.* without histopathological confirmation and not visualized in the official statistics. Among all BCCs, the most common location was the trunk (46.3%), the most common BCC subtype was the superficial subtype (41.7%) and the most common management was destructive treatment (60.0%). Almost 40% of the patients were diagnosed with ≥2 BCCs. At the time of data collection, just less than 5 years after diagnosis, almost 20% of patients were deceased.

DIFFERENCES IN BCC CHARACTERISTICS RELATED TO SEX

Even though the sex distribution among patients was even, 49.3% were females, 58,3% of all BCCs were in male patients, indicating that multiple tumors are more common among male patients. Significant sex-related differences was found with only 38% of all BCCs among males being histopathologically confirmed compared to 52% among females. This was related to non-facial sBCCs being almost twice as common in males (64.8%) compared to females. Instead, females had more lesions in the head and neck area (52.9%) and also a higher percentage of infiltrative BCCs (55.8%), resulting in a proportionally greater number of tumors being confirmed through histopathology and visualized in the official statistics.

CHARACTERISTICS OF BCCS CONFIRMED BY HISTOPATHOLOGY

Among the histopathologically confirmed tumors, nBCCs located in the head and neck were the most common subtype and location, which is in agreement with the official BCC epidemiological data, both in Sweden and internationally.

ESTIMATION OF THE UNREPORTED BCCS IMPACT ON THE OFFICIAL STATISTICS

Among all primary BCCs diagnosed by the two pathology laboratories, 55% were managed by dermatologists. The combined results of the percentage of unreported BCCs within the study cohort (55.8%) and the proportion of histopathologically confirmed BCCs treated by dermatologists, resulted in a gross estimate of the official statistics underestimating the actual numbers of new BCCs by approximately 70%.

PAPER II

In this RCT, 228 sBCCs in 97 patients were included in the per protocol analysis.

TUMOR CLEARANCE

No residual tumor was found at FU visit 1 after 3-6 months. After 1 year, 5 recurrences

were detected in patients treated with curettage and none in patients treated with cryosurgery, yielding clinical clearance rates of 95.7% and 100%, respectively (P=0.060). However, the lower limit of the 95% confidence interval for the difference was below the non-inferiority cut-off limit of 8%. Therefore, the non-inferiority analysis was inconclusive.

WOUND HEALING

Both patient-reported mean times to complete wound healing (4.3 *vs* 5.1 weeks) (P<0.001) as well as time with oozing wounds (0.8 *vs* 1.6 weeks) (P<0.001) were shorter for curettage than for cryosurgery.

PATIENT SATISFACTION

Overall, patient satisfaction at one year was high. Among 92 patients with 220 lesions (missing data from 5 patients with 8 lesions), 88 were satisfied, 2 were unsatisfied and 2 found the scars to be irrelevant and were neutral in their opinion.

ADVERSE EVENTS

In total, 83 adverse events were reported, including 5 severe adverse events, but none were related to the study.

PAPER III

The results from Paper III are presented more in detail, as this study was published as a research letter with limited space to report the results.

A total of 202 lesions in 116 patients (34% females) were included (per-protocol analysis). Nine tumors in 3 patients were excluded prior to analysis due to histopathology showing other diagnosis than BCC (n=4), violence to treatment protocol (n=3), withdrawal of consent during FU (n=1) and one case with delayed wound healing leading to excision to exclude residual tumor, but with negative histopathology (n=1).

The median age at inclusion was 72 years. Seventeen patients were immunosuppressed (iatrogenic or due to disease), 12 had diabetes and 3 were smokers. The median lesion diameter was 10 mm. A total of 130 lesions were included based on clinical assessment and 72 based on histopathological diagnosis available at inclusion. However, all lesions were histopathologically confirmed, as tissue samples were sent from the lesions that lacked a histopathological diagnosis at the time of treatment. The distribution of BCC subtypes was 114 nBCCs, 54 iBCCs, 13 sBCCs and 21 BCCs of unspecified subtype, without significant differences between the two treatment groups (P=0.98). Most lesions (n=156) were located on the trunk, followed by the arms (n=23), thigh (n=12) and neck (n=11). There were no significant differences between the two groups during the first freeze-thaw cycle regarding the mean freeze time (18.6 s for a single freeze-thaw cycle *vs* 17.7 s for two freeze-thaw cycles, P=0.087) nor the mean halo thaw time (83.2 s *vs* 84.4 s, P=0.60). Although the mean freeze time during the second cycle was shorter compared to the first cycle (mean difference of 1.4 s, P<0.001) the thaw time was longer (mean difference of 5.9 s, P=0.005) (Figure 12).

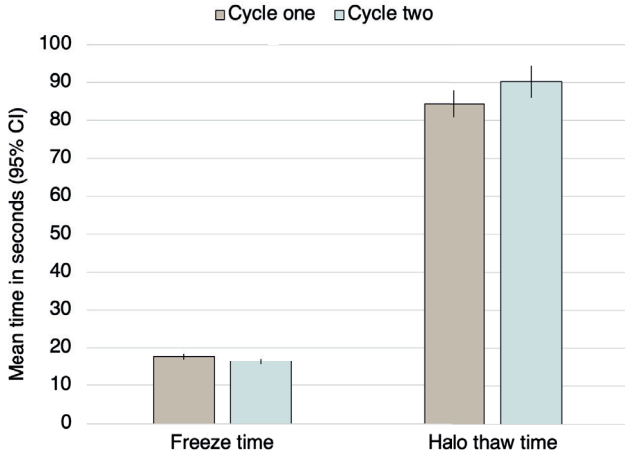

FIGURE 12. Mean freeze times and halo thaw times during the first and second freeze-thaw cycles.

TUMOR CLEARANCE

At FU visit 2, three biopsies were obtained to investigate if any residual tumor remained. All these biopsies were negative. The response rate in another 6 lesions was marked as uncertain and left for re-evaluation at 1 year. At FU visit 3, one recurrence was found in a lesion randomized to a single freeze-thaw cycle resulting in a 1-year clearance rate of 99% *vs* 100%, proving the non-inferiority hypothesis with an absolute difference of less than 8%.

WOUND HEALING

The patient-reported mean time for oozing wounds was 1.0 week for a single freeze-thaw cycle and 1.2 weeks for two freeze-thaw cycles (P=0.062) and the respective complete wound healing times were 6.3 and 6.9 weeks (P=0.075). At FU visit 1, most lesions (71%) had remaining crusts, 13% still had oozing wounds and 11% were completely healed without any significant difference between the two treatment groups. Data was missing for 5% of the lesions. According to linear regression analyses, lesion size was the only significant factor influencing wound healing times, *i.e.* longer times for larger lesions (P<0.001).

PATIENT SATISFACTION

At the 1-year FU visit, 105 patients reported satisfaction with their scars. One patient was dissatisfied and 4 rated their scar cosmesis as neutral (data missing for 6 patients).

ADVERSE EVENTS

In total, 102 adverse events (8 serious adverse events) were reported, of which 9 were related to the treatment: 2 wound infections, 6 excessive oozing or prolonged wound healing and 1 itching from the scar 3 months after treatment.

PAPER IV

In this mixed method survey, 157 patients with 425 scars were included in the quantitative ACO analysis. The qualitative STPC questionnaire was distributed to 155 patients and was responded by 135 patients with 372 scars, resulting in an 87% response

rate. Among the respondents, 49% had prior experience with other treatments for BCCs. Males outnumbered females in the RCTs and were therefore in majority also in this survey, accounting for 70% of scars in the ACO analysis and 59% of patients in the STPC questionnaire analysis.

QUANTITATIVE ASSESSMENT OF COSMETIC OUTCOME (ACO)

Overall satisfaction

The majority of patients rated the scars as being of no (83%) or little (10%) concern. A negligible percentage (0.5%) expressed significant concern regarding the scars. The overall satisfaction with the scars was high (mean NRS score of 2.2). Interestingly, patients evaluated the scars more critically in terms of their objective similarity to normal skin (mean NRS score of 3.6), indicating that objective scar cosmesis evaluations are not necessarily equal to patients' satisfaction with the scars. The dermatologists' ratings of the overall cosmetic outcome aligned with the patients' ratings (mean NRS score of 3.1). Statistically significant differences were not observed in patients' satisfaction with scar cosmesis among the various destructive treatment protocols (P=0.44), nor for different anatomical sites (P=0.081).

Sex differences

Male patients cared slightly less about their scars compared to females (mean NRS scores of 1.5 *vs* 2.1) and were also slightly more satisfied with their scars (mean NRS scores of 2.0 *vs* 2.6). Males in the age group of >70 to ≤80 years, who had the majority of the assessed scars, were more satisfied and also cared less about their scars than the other males and females and the difference was most pronounced in comparison to females in the age group of >50 to ≤60 years.

QUALITATIVE EVALUATION (STPC QUESTIONNAIRE)

Patients experiences with scars

The majority of patients reported they had no concerns or hardly ever thought about their scars in everyday life and for most of them this had not changed over time. Five females were unsatisfied with their scars due to locations on exposed skin areas and 1 male due to itching in a keloid formation (Figure 13).

Factors of importance when choosing a treatment method

Sixty-three percent of all respondents provided complete answers (ranking all 4 factors), while 91% provided either complete or incomplete answers (ranking 1-3 factors). The factors were as follows: 1. expected clearance rate, 2. time required for treatment, 3. time required for wound healing, and 4. cosmetic outcome. Noteworthily, 96% rated expected clearance rate as the most important factor. Among the 63% who ranked all four factors, time required for treatment and wound healing were of intermediate importance, while cosmetic outcome was least important to the patients (Figure 14).

When asked about their preferences for future treatment of sBCC, 92% favored destructive treatment, while 8% preferred PDT or imiquimod to avoid scarring, despite a higher risk of recurrence (15 non-responders). Patient sex (P=0.71) and previous experience with BCC treatments (P=0.094) did not show any significant association with treatment preferences.

Cost aspects for treatments in a tax-funded healthcare system

Regarding the consideration of treatment costs in a tax-funded healthcare system, 50% believed that the patient's own preference should be prioritized over the cost of the treatment, 31% thought the cost should be taken into account to a great extent, and 18% believed that no consideration should be given to costs (26 patients did not respond).

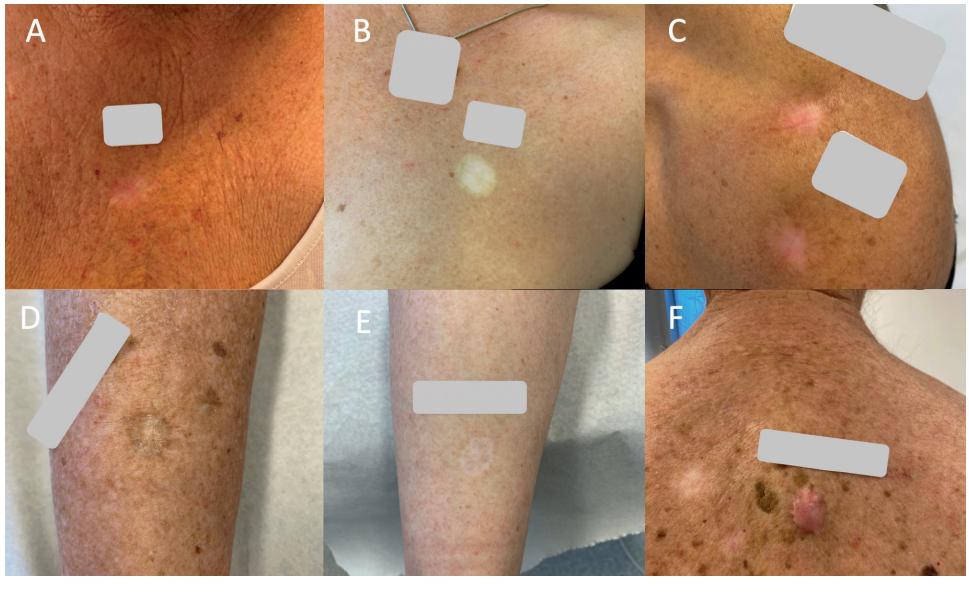

FIGURE 13. Clinical images of scars reported as dissatisfactory by patients. (A) female, chest, 73 years; (B) female, chest, 57 years; (C) female, shoulder, 54 years; (D) female, pretibial, 76 years; (E) female, back lower leg, 73 years; (F) male, back, 89 years.

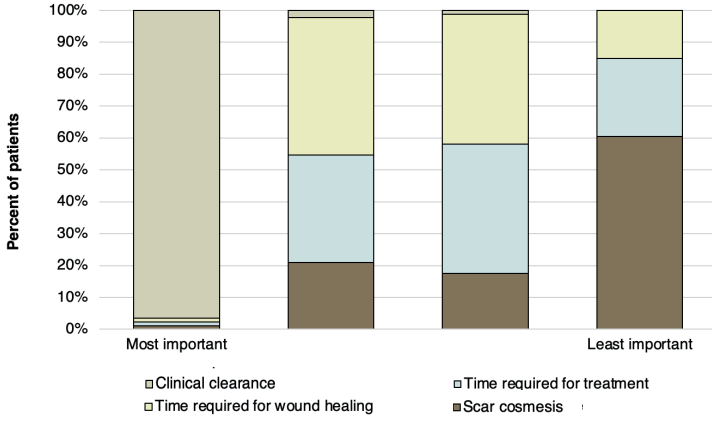

FIGURE 14. How patients rank factors of importance when choosing treatment method for basal cell carcinoma.

5

DISCUSSION

5. DISCUSSION

PAPER I

This study on unregistered and registered BCCs indicates that the true number of primary BCCs diagnosed in Sweden is much higher than what is visualized in the official statistics. Especially the numbers of non-facial low-risk lesions are underestimated. Truncal sBCCs were the most common form and these were much more common in males. On the other hand, females had more infiltrative BCCs in the head and neck area, resulting in a larger proportion of their tumors being visualized in the official statistics.

THE RESULTS IN COMPARISON TO PREVIOUS REPORTS

The large number of unreported low-risk BCCs in males can challenge the conclusions drawn from the Swedish official statistics, as reported by Kappelin *et al.* concluding that BCCs in females have increased more than in males and that infiltrative BCCs have increased more than low-risk lesions.[17] As mentioned in the introduction, some other reports support our results of a changing trend in BCC subtypes and locations, describing an increase of non-facial sBCCs, also in younger age groups, in urban areas and with increasing socioeconomic standards.[16,27,137] Proposed explanations for the increase of BCCs in clothed areas are an increase in intermittent sun exposure with sunburns outside the chronically exposed head and neck area.

POSSIBLE IMPACT ON THE VALIDITY OF OFFICIAL STATISTICS

Our results indicate that the official statistics, based on histopathologically confirmed tumors may no longer be a valid method of estimating the incidence of BCCs, especially not with the enhanced clinical diagnostics by dermoscopy and with an increase of non-surgical treatment options.

WHY IS THIS IMPORTANT?

Without an accurate understanding of the real-world situation, we cannot effectively address the problem, neither in terms of preventive measures nor in managing healthcare resources.[27] Furthermore, when developing guidelines, emphasizing infiltrative BCCs as a more prevalent and increasing subtype can skew the focus of guidelines towards advanced treatment options for these BCCs. As a result, the guidelines might overlook the crucial task of presenting cost-effective approaches for managing a significant proportion of low-risk lesions.

OVERDIAGNOSIS AND OVERTREATMENT

Finally, our results raise the question of the clinical value of diagnosing and treating a large number of low-risk lesions, especially if unknown and asymptomatic to the patients. Almost 20% of the patients were deceased less than 5 years after their diagnosis. These figures are in line with figures from a prospective Dutch cohort study on metachronous BCCs, in which on third of the patients were deceased after a mean follow-up period of 5 years.[152]

The question of overdiagnosis and overtreating indolent lesions, including NMSC, has been raised by others earlier with a prescription for change.[153-155] Recently, a few reports have been published on the outcomes of watchful waiting of BCCs but with limited follow-up times.[156,157,158] However, before evidence-based active surveillance for BCC can be an option, prospective studies have been requested.[159]

PAPERS II AND III

Both curettage alone or cryosurgery in one freeze-thaw cycle without prior curettage for non-facial sBCCs as well as curettage plus cryosurgery with both one or two freeze-thaw cycles for non-facial BCCs with nodular features yielded very high one-year clearance rates. Curettage alone resulted in significantly shorter times with oozing wounds as well as shorter complete wound healing times compared to cryosurgery without prior curettage, while these differences were not significant when one or two freeze-thaw cycles were compared for nBCCs. In addition, the majority of patients were satisfied with their scars following all four different treatment protocols.

CLEARANCE RATES COMPARED TO PREVIOUS STUDIES

Comparisons to previous studies are difficult in general due to different inclusion criteria and the lack of standardized and well-described protocols. Curettage for BCCs has not been evaluated in prospective comparative studies before. Although longer FU is warranted, our results in Paper II are consistent with a retrospective study on curettage for non-aggressive BCCs by Barlow *et al.* showing 96% five-year clearance rates,[130] and a prospective, non-controlled study on curettage for mainly nBCCs by McDaniel *et al.* demonstrating 91% five-year clearance rates.[128]

The clearance rates for cryosurgery have varied considerably between different published studies and few studies have been of a prospective, comparative design. Nevertheless, in comparison to two RCTs comparing PDT and cryotherapy with reported 87% one-year clearance rates and 80% five-year clearance rates, our clearance rates are superior.[89,90] Our results are more aligned with one report by Mallon and Dawber who observed 1 recurrence among 31 clinically diagnosed truncal sBCCs treated with cryosurgery in a single freeze-thaw cycle without prior curettage, with FU ranging from approximately 1 to 7 years.[122] In another prospective, non-randomized study by Peikert *et al.*, a five-year clearance rate of 99% was reported for primarily non-facial sBCCs.[160] However, cryosurgery in a single freeze-thaw cycle was preceded by curettage in this study.

Our results in Paper III align well with several previous investigations performed in Sweden, where two freeze-thaw cycles were also used for facial lesions.[118,119,121] In contrast to the study by Mallon and Dawber, we could not prove any significant difference in clearance rates between one or two freeze-thaw cycles.[122] However, in that study, curettage was not performed prior to cryosurgery and an intermittent freeze

technique was used. In addition, only facial lesions were included making comparisons difficult.

CLEARANCE RATES IN RELATION TO BCC SUBTYPES

In both Papers II and III, the different destructive treatment methods provided high clearance rates even for BCCs with clinically well-defined borders but histopathologically proven to have a moderately aggressive infiltrative growth pattern. This is a difference compared to PDT but also to imiquimod and 5-fluorouracil, which are mainly effective for sBCCs and have lower clinical clearance rates.[86,87,91]

THE DIAGNOSTIC ACCURACY OF DERMOSCOPY

In Paper II, 1 out of 83 clinically diagnosed lesions sent for histopathological confirmation at treatment, was incorrectly diagnosed as a BCC, yielding a specificity of 98.9%. In Paper III, the same figures were 4 out of 134 lesions, yielding a specificity of 97.0%. These results correspond well with earlier studies on diagnostic accuracy of dermcoscopy.[76] In the case of low-risk BCCs, we find this diagnostic certainty to be justifiable, both in relation to the large and increasing number of BCCs as well as the indolent nature of these tumors including common differential diagnoses.

WOUND HEALING TIMES FOLLOWING CRYOSURGERY IN COMPARISON TO SURGERY AND OTHER TREATMENT OPTIONS

The complete wound healing times after cryosurgery were relatively long. While a few patients had prolonged healing processes, the majority experienced oozing wounds for 1-2 weeks. We believe this duration is comparable to the inconvenience and limitations patients face with surgical wounds until sutures are removed. Similarly, a 6-week treatment with imiquimod or undergoing PDT twice with a 1- to 2-week interval also leads to prolonged periods of time with ulcerations and crusts. Consequently, we believe that the frequently mentioned extended wound healing times following cryosurgery could, to some extent, be reconsidered.

PAPER IV

This study revealed that patient satisfaction with scars resulting from non-facial BCCs did not necessarily align with assessments of the cosmetic outcome conducted by dermatologists or patients themselves. Most patients expressed minimal concern about the cosmetic outcome, instead prioritizing the anticipated effectiveness of available treatments. Interestingly, cosmetic outcome was ranked as the least significant factor by the majority of patients.

SATISFACTION IN RELATION TO TREATMENTS OR LOCATIONS

Satisfaction levels did not significantly differ based on the specific type of destructive treatment used. This finding was unexpected, as we initially anticipated that the cosmetic outcome would be less favorable following cryosurgery, since this often results in a hypopigmentation. However, there was a slight tendency (as expressed in the STPC questionnaire) towards lower satisfaction

for lesions located on exposed skin areas, such as the lower legs and chest.

THE RESULTS IN COMPARISON TO PREVIOUS REPORTS

Previous studies have predominantly concentrated on objective assessments of cosmetic outcomes while disregarding the connection to patient satisfaction or their level of concern regarding the aesthetic result.[89-91,127] The absence of this correlation has been noted in previous discussions.[161] However, in one previous publication on imiquimod compared with surgery, researchers commented on the discrepancy between patient and dermatologist evaluations of the cosmetic outcome, with patients expressing more positive ratings.[91]

The majority of earlier studies have either focused on facial lesions or a mix of facial and non-facial lesions. Our study exclusively examines non-facial lesions, which we consider valuable due to the high numbers of sBCCs but also nBCCs occurring outside the head and neck region.

CONCLUSIONS

6. CONCLUSIONS

Based on the studies included in this thesis and the literature reviews conducted, the following conclusions can be drawn:

- Official statistics, relying solely on histopathologically confirmed BCC cases, notably underestimate the incidence of BCCs.

- The vast majority of unregistered BCCs are low-risk, non-facial lesions, which partially challenge the prevailing narrative of the incidence of aggressive BCCs in the head and neck area increasing more than that of the low-risk lesions.

- The RCTs conducted provide stronger evidence supporting the effectiveness of destructive treatments as viable options for a large number of these low-risk BCCs, with 1-year clearance rates ranging from 95.7% to 100%. However, results from long-term follow-up need to be evaluated.

- The objective assessment of the cosmetic outcome does not necessarily align with the patients' satisfaction with their scars. For BCCs located outside the face, patients report minimal concern about scarring and prioritize treatment effectiveness when choosing a treatment option.

7. FUTURE PERSPECTIVES

My doctoral project has raised further questions and generated more ideas at the end of my PhD studies compared to when I embarked on this journey. I therefore hope to be able to continue with research.

The studies within this project have as of today garnered some recognition within the dermatological community, with Papers I and II being referenced in the recently updated European guidelines for managing BCC.[73] Given the absence of standardized protocols for destructive treatment methods, it is crucial to extend efforts to provide practical guidelines for executing these treatments accurately and safely, thereby achieving high cure rates.

ONGOING RCTS

The RCTs on destructive treatments for non-facial BCCs are ongoing. The data on 1-year clearance rates for lesions below the knee have been collected and are ready for statistical analysis. In the end, we anticipate that the 5-year clearance rates for all three studies will contribute to increase the evidence for long-term effectiveness of destructive treatments in the treatment armamentarium for BCCs.

ONGOING WATCHFUL WAITING STUDY

Last year, we obtained ethical approval for a regional multicenter, prospective study on active surveillance instead of treatment for selected BCCs in patients with no symptoms or in patients who decline proposed treatments. The primary objective is to enhance our knowledge on the natural progression of untreated BCCs. As of today, 200 lesions (out of the planned 600 lesions) in 90 patients have been enrolled and will be followed for up to 5 years. The potential results of this study could lead to more informed decision-making for both patients and healthcare providers, including guidance on if and when watchful waiting could be a safe alternative to active treatment.

FUTURE POSSIBLE RCTS

RCTs comparing destructive treatments and medical therapies for low-risk BCCs would be of value, but also on destructive treatments with strict adherence to standardized protocols with surgery, including MMS, for selected non-sclerotic facial BCCs. These studies could also incorporate cost evaluations to comprehensively assess treatment strategies, as these treatment approaches come with different costs.

FUTURE QUALITATIVE STUDIES ON PATIENTS' PERSPECTIVES ON SKIN CANCER TREATMENTS

In this thesis, Paper IV posed the greatest challenge for me due to my background in quantitative research. Therefore, the paper should be considered a 'pilot project' rather than the apex of my work. Nevertheless, I believe the questions raised, with a focus on patient-centered care, are relevant for exploring solutions on how to handle the "skin cancer epidemic" in a wise way. I therefore look forward to future collaborations, also on qualitative studies

related to skin cancer management, including the possible future RCTs above.

INTERNATIONAL STUDY ON UNREPORTED LOW-RISK BCCS

In Paper I, we revealed a significant portion of unregistered non-facial low-risk BCCs, mostly detected during full-body skin examinations for cancer, as recommended by the guidelines. A prior study across European countries showed much lower, but also varying, rates of clinically diagnosed lesions, potentially influenced by examination methods.[162] To address this, an international study involving full-body skin exams during a limited time period could possibly clarify whether discrepancies in numbers are due to examination differences or consequences of varying skin types and sun exposure habits, as partly expressed in the report by Deady et al.[27]

DESCRIPTIVE STUDY ON DERMOSCOPIC FINDINGS IN LOW-RISK BCCS OF THE LOWER LEG

Diagnosing BCCs on the lower leg poses challenges due to dermoscopic disturbances caused by vascular structures and stasis. Large-scale studies on dermoscopic patterns in this area are lacking. Our RCTs have included over 200 BCCs below the knees. Analyzing dermoscopic features and identifying distinctions between lower leg BCCs and other common lesions, such as SCC in situ, eczema, and psoriasis, could improve diagnostic accuracy and reduce unnecessary biopsies.

DESCRIPTIVE STUDY ON DERMOSCOPIC FEATURES RESULTING FROM DESTRUCTIVE TREATMENTS

The ongoing RCTs have generated a substantial collection of clinical and dermoscopic images during FU visits. There is limited research conducted on dermoscopic monitoring of treatment outcomes.

Describing the dermoscopic patterns observed after destructive treatments could be of value, especially vascular patterns can become quite prominent, posing challenges in distinguishing them from vascular structures typically associated with recurrent BCCs (Figure 15).

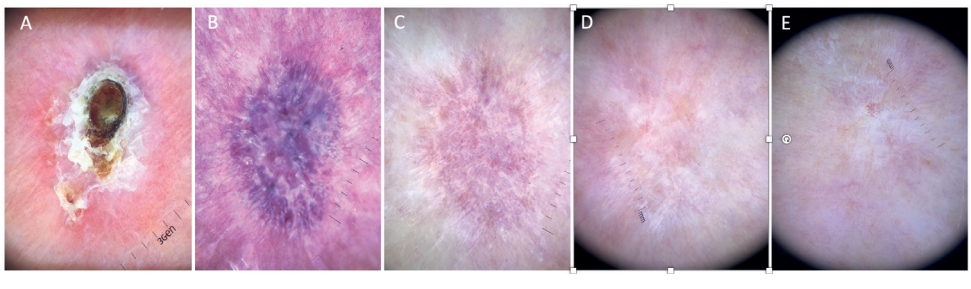

FIGURE 15. Dermoscopic images of a basal cell carcinoma (A) before treatment with curettage, after (B) 3 months, (C) 12 months, (D) 3 years and (E) 5 years without signs of recurrence.

Överläkare Eva Backman visar hur man fryser en basalcellscancertumör på en persons axel. Foto: Helén Palmqvist Novik/Sveriges Radio och Verksamheten för Hud och könssjukvård Sahlgrenska Universitetssjukhuset

CANCER

Effektiva metoden: Hudcancer skrapas bort

1:30 min Min sida Dela

Publicerat fredag 23 juni kl 06.03

- En gammal metod att frysa och skrapa bort hudcancer är både effektiv och billig.
- Det visar en ny studie från Sahlgrenska akademin i Göteborg.
- Nu berättar Eva Backman, överläkare på hudkliniken på Sahlgrenska Universitetssjukhuset, om behandlingen mot världens vanligaste och snabbt ökande hudcancerform.

Helén Palmqvist Novik
helen.palmqvist_novik@sr.se

forskning.se

Skrapa och frysa är säkert och effektivt vid vanligaste hudcancern

19 juni 2023 | Artikel från Göteborgs universitet | Ämne: Hälsa & medicin

Att skrapa och frysa bort tumören är en säker och effektiv behandling vid den vanligaste formen av hudcancer, basalcellscancer, enligt en ny studie.

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