

Enhancing the Management of High-Risk Basal Cell Carcinoma

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Histopathological image of a high-risk basal cell carcinoma sectioned during Mohs micrographic surgery.

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*If you take
shortcuts, you
get cut short.*

Gary Busey

Abstract

Basal cell carcinoma (BCC) is the most common skin cancer, with over 71,000 new cases in Sweden in 2023. High-risk facial BCCs are most appropriately treated with Mohs micrographic surgery (MMS), which is considered the gold standard. However, MMS is rarely performed in Sweden due to resource constraints leading to high rates of incomplete excisions and recurrences. The four papers in this thesis address key topics related to high-risk BCCs including risk factors associated with incomplete excisions, differences in outcomes following MMS for primary and previously treated high-risk BCCs, their dermatoscopic features and the feasibility of hyperspectral imaging for tumor delineation prior to MMS.

In Study I, clinical and histopathological risk factors for incomplete excision of high-risk BCCs were evaluated. In our cohort, the overall incomplete excision rate was 20.6%. BCCs located on the nose, ear, scalp, and periorbital areas as well as BCCs with high-risk histopathological subtypes exhibited the highest proportions of incomplete excisions. In study II, we found that primary facial high-risk BCCs required fewer MMS stages and had smaller wound areas after complete surgical removal compared to BCCs that had been treated previously. In Study III, we investigated which clinical and dermoscopic findings characterize high-risk BCCs. A bumpy surface, poorly defined borders, the dermoscopic presence of 'white porcelain area' and/or 'vessels within ulceration' were indicative of high-risk BCCs. An algorithm was developed for predicting high-risk BCCs preoperatively with a sensitivity of 81.4% and a specificity of 53.3%. Study IV was a prospective pilot study assessing the feasibility of hyperspectral imaging using supervised learning of a convolutional neural network to preoperatively delineate the lateral margins of high-risk BCCs prior to MMS. Hyperspectral imaging

achieved a pixel-wise classification accuracy of 0.76, a sensitivity of 0.75, a specificity of 0.78, and an area under the receiver operating characteristic curve of 0.84.

In conclusion, the results of this thesis contribute to an expanded understanding of the factors affecting treatment outcomes for high-risk BCCs. Better preoperative diagnostics, such as clinical and dermatoscopic findings, are needed to correctly identify high-risk BCC candidates for MMS instead of undergoing incomplete excisions due to traditional surgery. This knowledge ensures that patients receive the most effective treatment from the start. Pre-operative margin delineation using hyperspectral imaging could potentially decrease the number of MMS stages required and, in situations where MMS is not an option, it may help reduce the need for additional surgeries in traditional surgery.

Keywords: Basal cell carcinoma, dermoscopy, interobserver agreement, Mohs micrographic surgery, algorithm, incomplete excision, non-melanoma skin cancer, risk factors, hyperspectral imaging.

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Sammanfattning på svenska

Basalcellscancer (BCC) är den vanligaste typen av hudcancer, med över 71 000 nya fall i Sverige 2023. Beroende på växtsätt, lokalisering och storlek och om/hur den har behandlats tidigare delas BCC in i lågrisk- respektive högrisk-BCC. Valet av behandling styrs av tumörens subtyp där den rekommenderade behandlingen för högrisk-BCC är kirurgi. Risken för icke-radikala excisioner och/eller recidiv är dessutom betydligt vanligare för dessa BCC. I Sverige anses Mohs kirurgi (*eng.* Mohs micrographic surgery, MMS) vara förstahandsvalet vid behandling av högrisk-BCC i ansiktet, men erbjuds sällan på grund av resursbrist. Detta leder till att dessa tumörer ofta behandlas med mindre effektiva metoder.

Denna avhandling omfattar fyra delarbeten vilka berör ämnen relaterade till högrisk-BCC. Studierna berör riskfaktorer förknippade med ofullständig excision, skillnader i behandlingsresultat efter MMS för primära och tidigare behandlade högrisk-BCC, kliniska och dermatoskopiska egenskaper hos högrisk-BCC samt genomförbarheten av hyperspektral avbildning (HI) för tumöravgränsning preoperativt.

I delarbete I utvärderades kliniska och histopatologiska riskfaktorer för icke-radikala excisioner av högrisk-BCC. Andelen patienter där det fanns kvar tumör efter excision var 20,6%. Tumörens lokalisering samt hur aggressiv den var påverkade om all tumörvävnad kunde avlägsnas. Högst andel icke-radikalitet sågs vid tumörer på näsa, öra, skalp och runt ögonen samt tumörer med medel- till högaggressivt växtsätt.

I delarbete II jämfördes primära och tidigare behandlade högrisk-BCC i ansiktet som exciderades med MMS avseende antal omgångar som krävdes för att avlägsna tumören och slutlig defektstorlek. Antalet omgångar var signifikant lägre och slutlig defektstorlek var signifikant mindre för primära BCC.

Diagnostik av BCC kan ske kliniskt med hjälp av ett dermatoskop, ett handhållet instrument med ljuskälla och förstoringsglas som möjliggör undersökning av strukturer i över- samt läderhuden. I delarbete III undersöktes vilka kliniska och dermatoskopiska fynd som kännetecknar högrisk-BCC i ansiktet. Förekomst av en knölig yta, dåligt definierade gränser, förekomst av 'vita porslinsområden' och 'blodkärl inom ulceration' pekade på att tumören var ett högrisk-BCC. Dessa fynd användes som grund för utvecklingen av en klinisk algoritm som förutsåg högrisk-BCC med en sensitivitet på 81,4% och en specificitet på 53,3%.

Delarbete IV var en prospektiv pilotstudie som utvärderade genomförbarheten av hyperspektrala bilder med hjälp av ett konvolutionellt neuralt nätverk för att preoperativt avgränsa de laterala marginalerna av hög-risk BCC jämfört med de histopatologiskt verifierade tumörkanterna som observerades under MMS. Hyperspektral avbildning uppnådde en noggrannhet på 0,76, en sensitivitet på 0,75, en specificitet på 0,78 och en area under ROC-kurvan på 0,84.

Sammanfattningsvis bidrar resultaten av denna avhandling till en utökad förståelse av faktorerna som påverkar behandlingsresultaten för högrisk-BCC. Bättre preoperativ diagnostik, såsom kliniska och dermatoskopiska fynd, behövs för att korrekt identifiera högrisk-BCC-kandidater för MMS istället för att genomgå ofullständiga excisioner med traditionell kirurgi. Denna kunskap säkerställer att patienter får den mest effektiva behandlingen från början. Preoperativ avgränsning av marginaler med hjälp av hyper-

spektral avbildning kan potentiellt minska antalet MMS-steg som krävs, och i situationer där MMS inte är ett alternativ kan det bidra till att minska behovet av ytterligare operationer vid traditionell kirurgi.

List of papers

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

- I. Clinicopathological factors associated with incomplete excision of high-risk basal cell carcinomas.
Hannah Ceder, Annie Ekström, Lajla Hadzic, John Paoli
ACTA DERM VENEREOL. 2021 JUL 13;101(7):ADV00496. DOI:10.2340/00015555-3856.
- II. Mohs micrographic surgery for primary versus recurrent or incompletely excised basal cell carcinomas.
Hannah Ceder, Malin Grönberg, Martin Gillstedt, John Paoli
ACTA DERM VENEREOL. 2021 FEB 2;101(2):ADV00381. DOI: 10.2340/00015555-3698
- III. Importance of both clinical and dermoscopic findings in predicting high-risk histopathological subtype in facial basal cell carcinomas.
Hannah Ceder, Eva Backman, Ashfaq Marghoob, Cristián Navarrete-Dechent, Sam Polesie, Ofer Reiter, John Paoli.
DERMATOL PRACT CONCEPT. 2024 JUL;14(3):E2024212.DOI:10.5826/DPC.1403A212.
- IV. Hyperspectral imaging for lateral tumor demarcation of high-risk basal cell carcinomas during Mohs micrographic surgery.
Hannah Ceder, John Paoli, Ilkka Pölonen, Mari Salmivuori, Noora Neittaanmäki.
IN MANUSCRIPT.

Contents

| | |
|---|-------------|
| Abstract | III |
| Sammanfattning på Svenska | VII |
| List of papers | XI |
| Abbreviations | XVII |
| 1 Introduction | 1 |
| THE HUMAN SKIN | 1 |
| SKIN CANCER | 2 |
| SQUAMOUS CELL CARCINOMA | 3 |
| MELANOMA | 4 |
| BASAL CELL CARCINOMA | 4 |
| EPIDEMIOLOGY | 4 |
| PATHOGENESIS | 7 |
| CLASSIFICATION | 8 |
| DIAGNOSIS | 13 |
| <i>Clinical diagnosis</i> | 13 |
| <i>Non-invasive imaging</i> | 16 |
| Dermoscopy | 16 |
| Reflectance Confocal Microscopy | 19 |
| Optical Coherence Tomography | 20 |
| Line-field Confocal Optical Coherence Tomography | 22 |
| High frequency ultrasound | 23 |
| Hyperspectral imaging | 23 |
| Artificial intelligence | 24 |
| Non-invasive imaging and detection of subclinical extension in BCCs | 24 |
| <i>Histopathological diagnosis</i> | 26 |
| TREATMENT | 26 |
| <i>Surgical treatments</i> | 27 |
| Mohs micrographic surgery | 29 |
| <i>Destructive treatments</i> | 32 |
| <i>Non-surgical treatments</i> | 32 |
| Topical medications | 32 |
| Photodynamic Therapy | 32 |
| Radiation therapy | 33 |

| | | |
|-----------|--------------------------------------|------------|
| 2 | Aims | 35 |
| <hr/> | | |
| 3 | Methodological considerations | 37 |
| <hr/> | | |
| | PAPER I | 37 |
| | PAPER II | 39 |
| | PAPER III | 40 |
| | PAPER IV | 45 |
| | STATISTICAL ANALYSES | 48 |
| | ETHICAL COMMENTARY AND REFLECTIONS | 50 |
| 4 | Results | 53 |
| <hr/> | | |
| | PAPER I | 53 |
| | PAPER II | 55 |
| | PAPER III | 56 |
| | PAPER IV | 59 |
| 5 | Discussion | 61 |
| <hr/> | | |
| | PAPER I | 61 |
| | PAPER II | 64 |
| | PAPER III | 67 |
| | PAPER IV | 71 |
| 6 | Conclusions | 75 |
| <hr/> | | |
| 7 | Future perspectives | 77 |
| <hr/> | | |
| 8 | Acknowledgements | 83 |
| <hr/> | | |
| 9 | References | 87 |
| <hr/> | | |
| 10 | Papers | 105 |
| <hr/> | | |

Abbreviations

| | |
|---------------|---|
| AI | Artificial intelligence |
| BCC | Basal cell carcinoma |
| IBCC | Infiltrative basal cell carcinoma |
| IER | Incomplete excision rate |
| IE-BCC | Incomplete excised basal cell carcinoma |
| HFUS | High-frequency ultrasound |
| HI | Hyperspectral imaging |
| MS | Micrographic surgery |
| MMS | Mohs micrographic surgery |
| NBCC | Nodular basal cell carcinoma |
| NMSC | Non-melanoma skin cancer |
| OCT | Optical coherence tomography |
| P-BCC | Primary basal cell carcinoma |
| PDT | Photodynamic therapy |
| PTCH1 | Patched 1 |
| R-BCC | Recurrent basal cell carcinoma |
| RCM | Reflectance confocal microscopy |
| SBCC | Superficial basal cell carcinoma |
| SCC | Squamous cell carcinoma |
| SE | Surgical excision |
| UVR | Ultraviolet radiation |

Introduction

The Human skin

The human skin serves as a vital barrier that protects us from external harm. Comprising three layers—the epidermis, dermis, and subcutaneous tissue—it plays an important role in managing body temperature, preventing fluid loss, and shielding against pathogens, ultraviolet radiation (UVR), and physical injuries. It also controls sensory perception via various receptors and synthesis of vitamin D when exposed to sunlight (**Figure 1**).

The outermost layer, the epidermis, is composed primarily of keratinocytes. This layer provides waterproofing and immune defense. It also contains melanocytes that produce melanin, the pigment that determines skin color and protects against harmful UVR.

Below the epidermis is the dermis, a thicker layer in which we find blood vessels, pilosebaceous units, sweat glands and nerves, which contribute to sensation and thermoregulation. Furthermore, it is responsible for skin's strength and elasticity.

The deepest layer, the subcutaneous tissue, is composed of fat and connective tissue providing energy storage, offering insulation and cushioning for the body's muscles and bones.

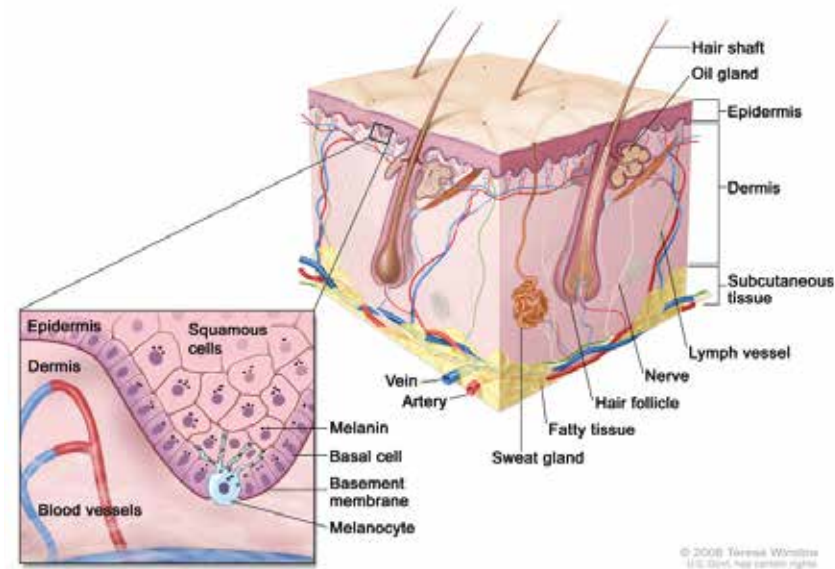


FIGURE 1. Anatomy of the skin.

© 2008 Terese Winslow LLC Created for the National Cancer Institute.

Skin Cancer

Skin cancers are one of the most common types of cancer globally, affecting millions of patients each year⁽¹⁾. They can develop from various cell types in the skin, leading to a wide range of potential cancer types. It is generally categorized into two main groups: non-melanoma skin cancer (NMSC) and melanoma. NMSC primarily refers to keratinocyte cancers such as basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), which together make up the majority of skin cancer cases. These tumors typically result from UVR exposure affecting the basal epidermal cells. Melanoma, which is caused by mutations in melanocytes, is the next most frequent type of skin cancer. NMSC also encompasses other rare skin cancers of non-keratinocytic origin, such as Merkel cell carcinoma, atypical fibroxanthoma, adnexal carcinomas and sarcomas⁽¹⁾. In 2023, over 13,000 cases of NMSCs were registered (BCCs excluded) in Sweden⁽²⁻⁴⁾ and this group of

skin cancers make up the second most common type of cancer in both sexes, following prostate cancer in men and breast cancer in women⁽²⁾.

Several factors have been shown to increase the likelihood of developing skin cancer. Prolonged exposure to UVR from the sun or tanning beds is the most important risk factor^(5,6).

- Fair skin: People with blond hair, blue/green eyes and fair skin are more prone due to lower levels of melanin (Fitzpatrick skin types I and II)^(7,8).
- Family history: A genetic predisposition to skin cancer can increase an person's risk⁽⁸⁾.
- Age: The likelihood of developing skin cancer rises with age as the cumulative UVR-exposure adds up over time^(5,6,8).
- Immunosuppression (e.g., organ transplant recipients, HIV/AIDS)^(9,10) and ionizing radiation⁽¹¹⁾.
- Genetic predisposition (e.g., Gorlin syndrome, xeroderma pigmentosum)⁽¹²⁻¹⁴⁾.

Squamous cell carcinoma

cSCC is less common than BCC but more serious. Compared to melanoma, however, the mortality is much lower. In 2021, 88 people died in Sweden because of cSCC^(2,15). cSCC originates from keratinocytes in the epidermal layer of the skin and can invade the dermis and deeper structures. The tumor typically develops from dysplastic epithelium. Most cSCCs are attributed to excessive UVR exposure, resulting in a higher prevalence on body parts frequently exposed to sunlight, such as the neck, face, arms and hands⁽⁴⁾. Immunosuppression is a significant risk factor for cSCC develop-

ment. Lesions on the lips and ears more often exhibit an aggressive growth pattern with a higher risk for metastasis ⁽¹⁶⁾.

Melanoma

In 2023, over 5,700 people were diagnosed with cutaneous melanoma (hereinafter referred to as melanoma) in Sweden and the median patient age was 68 years ⁽¹⁷⁾. This is more than double the number from 20 years ago, even when considering population growth. Melanoma arises from the malignant transformation of melanocytes predominantly located in the basal layer of the epidermis. The risk factors underlying melanoma are both genetic and environmental, with UVR being responsible for approximately 90% of cases ⁽¹⁷⁾. Melanoma tumors exhibit a high number of mutations, particularly in those that develop on sun-exposed skin. As the number of acquired mutations increases, more cellular signaling pathways become activated, potentially leading to melanoma formation ⁽¹⁸⁾.

Basal cell carcinoma

EPIDEMIOLOGY

BCC was first described as a distinct entity in the early 19th century, though it took some time for the full characterization and naming of the condition. In 1827, Arthur Jacob, an Irish ophthalmologist, provided one of the earliest descriptions of what we now know as BCC. He termed it “ulcus rodens” (rodent ulcer) due to its destructive nature. He noted its slow progression, peculiar appearance, and lack of lymphatic spread. In 1900, Edmund Krompecher made a significant contribution to the understanding of this skin cancer. His description of “Carcinoma epitheliale adenoides” as a malignant, locally invasive, and destructive cancer was a significant step in understanding BCC. In 1903, Krompecher further refined his description and coined the term “Basalzellenkrebs” (basal cell cancer), signifying that the tumor

developed in either the basal layer of the epidermis or in the epithelium of a hair follicle ^(19,20). Before Jacob’s description, there were earlier mentions of skin tumors that might have been BCCs. For instance, Aulus Cornelius Celsus described tumors in the 1st century AD that could have been BCCs. The term “basal cell carcinoma” has been retained in the WHO classification since 1974 ⁽²¹⁾.

Each year, around 70,000 BCCs are histopathologically confirmed in Sweden ⁽²⁾. Compared to other skin cancers in Sweden, BCC is approximately seven times as common as cSCC and thirteen times as common as melanoma. However, since many countries do not register BCCs routinely in national cancer registries, the epidemiological data are not completely reliable ⁽¹⁾. Sweden, on the other hand, established a national register in the autumn of 2003 and since then reports all histopathologically confirmed primary BCCs. During the past decades, a steady increase in incidence has been observed in Sweden. In 2004, 31,770 histopathologically verified BCCs were registered, and the corresponding figure in 2023 was 71,854 (**Figure 2**), an increase observed not only in Sweden but worldwide ⁽²²⁻²⁴⁾. The incidence of BCC has traditionally been higher in men. However, recent trends show a significant increase in cases among young women in Europe and the United States. This shift has resulted in women becoming the predominant group affected by BCC in this particular age group. Experts suggest that this change may be linked to the rising popularity of indoor tanning services and a greater consciousness about skin health issues among young women ⁽²⁵⁾. A recent study by Kappelin *et al.* showed that the probability of developing an additional BCC progressively increases in individuals with multiple previous BCCs ⁽²⁶⁾. Currently, the average age at diagnosis is 69 years for women and 70 years for men. The risk of developing BCC in Sweden before the age of 74 has been estimated at just over 15% ⁽²⁷⁾ and fair-skinned individuals have an average lifetime risk of at least 30% for developing BCC ⁽²⁸⁾. In another report by Kappelin *et al.*, the authors showed that the incidence of aggressive BCCs has been more prominent than that of low-risk BCCs ⁽²⁹⁾.

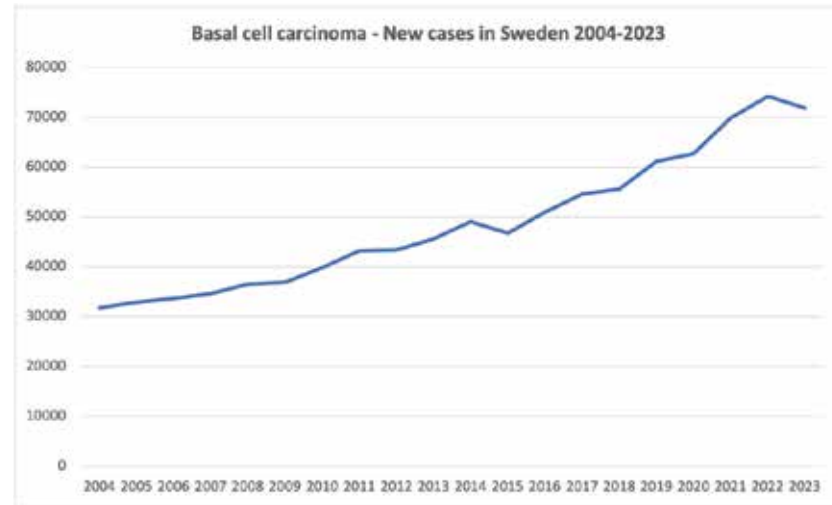


FIGURE 2. Increasing numbers of histopathologically verified basal cell carcinomas in Sweden between 2004 and 2023.

© John Paoli, created with data from the Swedish National Board of Health and Welfare provided by and used for Kappelin et al. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. *Br J Dermatol* 2022;186:963-9

The tumor's growth pattern can vary, either spreading superficially within the papillary dermis or invading more deeply into the deep dermis, subcutaneous tissue, and occasionally extending beyond the skin to affect skeletal muscle and other internal organs. While traditionally considered slow-growing, recent studies have revealed varying growth rates. A meta-analysis found a mean growth rate of 0.71 mm/month for the longer axis of BCCs but can differ depending on BCC subtypes⁽³⁰⁾. Other studies have similar results, with an estimated tumor diameter increase of 4.46 mm/year for infiltrative/micronodular BCCs versus 1.06 mm/year for nodular and superficial subtypes⁽³¹⁾. Kokkinos *et al.* presented an increase of 1.41 ± 0.42 times during 3-11 months waiting time for MMS⁽³²⁾. Superficial types have been reported to be more slow-growing, with a growth rate of 0.07 mm/month for the longitudinal axis⁽³³⁾. Periocular BCCs showed faster growth, with a mean rate of 1.46 mm in length every 30 days⁽³⁴⁾. This gradual development can lead to delayed diagnosis and treatment. On the other hand, a

prospective study reported that the size of BCCs awaiting MMS for an average of six months do not double but instead remain almost stable. Moreover, they found that it can be challenging to predict the impact of longer delays since the growth is not linear^(25, 35).

In addition to histopathologically confirmed cases, many BCC diagnoses are established clinically without confirming them histopathologically. A study conducted at our department estimated that 55% of BCCs are diagnosed solely based on clinical examination, meaning that true number of new cases diagnosed in Sweden each year is probably over 100,000⁽²³⁾.

Fortunately, mortality is low. However, the large number of tumors, the morbidity and associated costs to society are significant. Moreover, the high incidence and morbidity caused by BCC in the general population make it a significant global health concern⁽³⁶⁾. Recent significant advancements in understanding the genetic background of BCC have enabled the development of targeted therapies⁽³⁷⁾. However, clinical presentation and histopathology are still considered the gold standard for predicting prognosis and determining optimal individualized treatment^(38, 39).

PATHOGENESIS

BCC is believed to develop from keratinocytes located in the dermo-epidermal junction zone and the basal layer. Nevertheless, the precise cell of origin for BCC remains unidentified^(20, 38). The majority of BCCs seem to originate from stem cells found in the hair follicle^(40, 41), but to some extent also from stem cells located in the interfollicular epidermis⁽⁴²⁾. The hypothesis that hair follicle-derived stem cells are the most important source makes sense, given that BCCs are extremely rare on palms and soles. Unlike cSCC, which also develops from keratinocytes, BCC emerges with-

out prior precursor lesions⁽⁴²⁾. The pathogenesis of BCC is strongly associated with UVR, which induces DNA damage in skin cells. The main genetic alterations associated with BCC are found in the PTCH1 gene, which is part of the hedgehog signaling pathway. Mutations in PTCH1 result in uncontrolled cell growth and inhibits cell differentiation. Other genetic factors, such as mutations in **SMO** (Smoothed) and **SUFU** (Suppressor of Fused), also contribute to the development of BCC⁽⁴³⁻⁴⁷⁾. Finally, rare genetic syndromes significantly predispose affected individuals to skin cancer formation, including BCC, such as albinism, xeroderma pigmentosum and Gorlin syndrome⁽¹²⁻¹⁴⁾.

CLASSIFICATION

BCCs can be categorized in various ways. The conventional method of classification is based on histopathological subtypes. The other types 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^(3, 48-50). Although a WHO classification for BCCs exists, international histopathological classifications of BCCs are intricate and varied^(21, 51).

The WHO's classification includes nodular BCC (nBCC), superficial BCC (sBCC), infiltrative BCC (iBCC), morpheaform/sclerosing BCC, micronodular BCC and basosquamous carcinoma (metatypical BCC)⁽²¹⁾ (**Table 1**).

TABLE 1. Histopathological classification of basal cell carcinoma based on the recurrence risk, according to WHO 2023.

| | Low-risk | High-risk |
|-------------------------------|---|---|
| Histopathological type | <ul style="list-style-type: none"> • Superficial • Nodular (including pigmented and keratotic subtypes) • Infundibulocystic (variant of BCC with adnexal differentiation) • Fibroepithelial BCC | <ul style="list-style-type: none"> • Micronodular • Infiltrating • Sclerosing/morpheic • Basosquamous • BCC with sarcomatoid differentiation • Perineural |
| Perineural invasion | Absent | Present |

In Sweden, BCCs are categorized into four major subtypes according to the “Sabbatsberg model” (**Table 2, Figures 3 and 4**). The model comprises 3 risk categories: (i) “low-risk” Glas type Ia (nodular) and Glas type Ib (superficial), (ii) “medium-risk” Glas type II (less aggressive infiltrative or micronodular) and (iii) “high-risk” Glas type III (more aggressive infiltrative or micronodular, morpheaform and basosquamous) subtypes. The distinction between the types is determined by four histopathological factors: growth pattern, depth of invasion, tumor border definition and the dimensions of the tumor aggregates. In type I (a and b) the growth pattern is either nodular or superficial in the dermis. nBCCs and sBCCs often have a retraction artefact observed between the tumor nests and the surrounding tissue. Type II BCCs demonstrate tumor islands of varying size within the dermis, with either infiltrative or micronodular growth pattern and well-defined borders. Various growth patterns are seen in type III BCCs presenting with infiltrative, micronodular, morpheaform, or basosquamous characteristics. The invasion reaches the deep dermis or even subcutis, muscle, bone, or cartilage, with irregular, poorly defined borders and tumor cell band 1-2 cells thick.^(52, 53)

TABLE 2. Histopathological classification of BCC based on the risk of recurrence, according to Sabbatsberg/Glas classification from 1988.

| | IA/Less aggressive | IB/Less aggressive | II/Moderately aggressive | III/Highly aggressive |
|----------------------------|--|--|---|---|
| Growth pattern | Nodular | Superficial | Infiltrative or micronodular | Infiltrative, micronodular, morpheaform or basosquamous |
| Invasion front | Well-defined, rounded, and distinct border | Well-defined | Clearly demarcated, uneven | Irregular, without any clear demarcation |
| Depth of invasion | Dermis | Papillary dermis or in association with adnexal structures | Dermis, more seldom subcutis, cartilage and skeletal muscle | Dermis, more seldom subcutis, cartilage and skeletal muscle |
| Perineural invasion | Never | Never | Never | Sometimes |

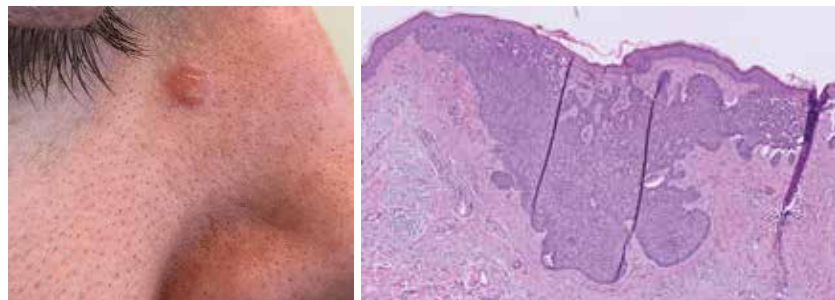


FIGURE 3A. Clinical and histopathological images of nodular basal cell carcinoma, type 1a.
(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital, Histopathological photo: Jan Siarov)

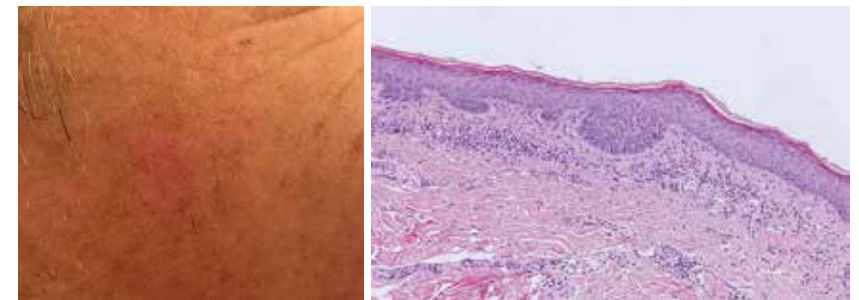


FIGURE 3B. Clinical and histopathological images of superficial basal cell carcinoma, type 1b.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospita, Histopathological photo: Jan Siarov)

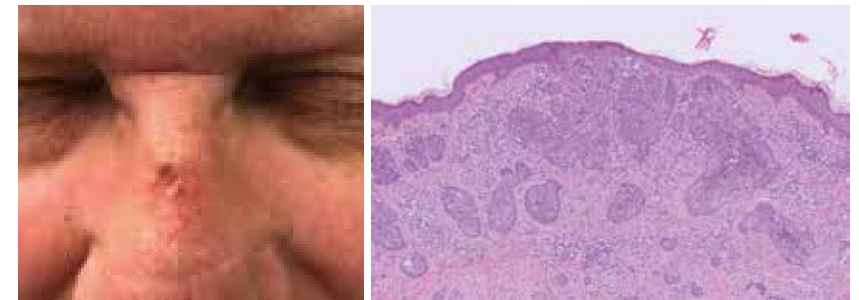


FIGURE 3C. Clinical and histopathological images of moderate aggressive infiltrative basal cell carcinoma, type II.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital, Histopathological photo: Jan Siarov)

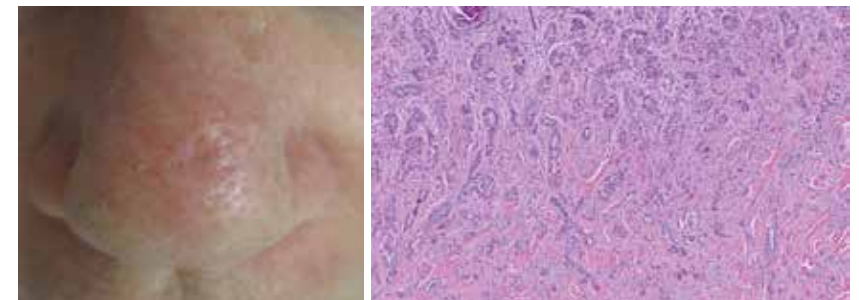


FIGURE 3D. Clinical and histopathological images of morpheaform basal cell carcinoma, type III.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital, Histopathological photo: Jan Siarov)

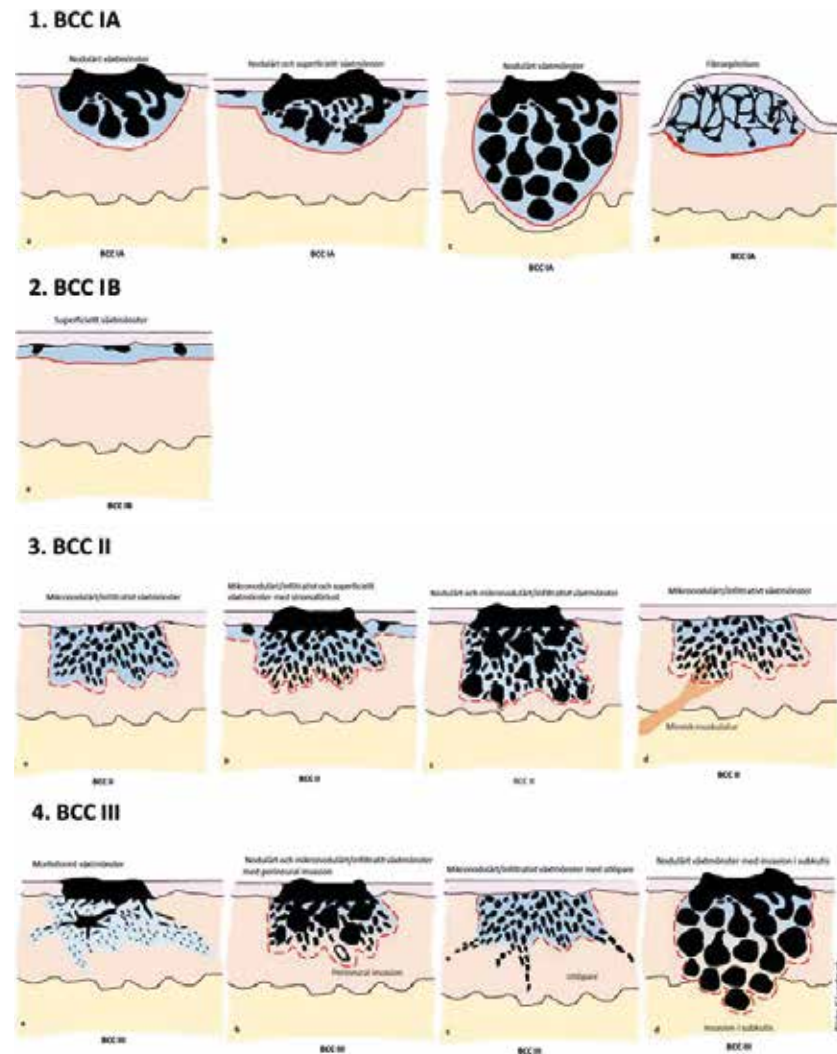


FIG 4. Schematic illustration of the basal cell carcinoma subtypes based on the risk of recurrence according to the updated Sabbatsberg model or Glas classification. <https://svf.se/media/p1apf4cf/hud-kvast-basalcellscancer-2024.pdf>

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In 2013, a study from the USA revealed substantial interobserver agreement among dermatopathologists regarding subtyping BCCs (κ -value of 0.699) ⁽⁵⁴⁾ proposing to group all infiltrating subtypes together as one category. A 2016 Australian study showed only 50% agreement in histopathological diagnoses and recommended classifying BCCs into low-risk and high-risk categories to increase consistency in results ⁽⁵⁵⁾. This heterogeneity in subtype interpretation may be due to the vast array of BCC appearances, with 66 variants identified so far ⁽⁵⁴⁾, and the lack of comprehensive histopathological criteria for the primary subtypes. The diverse range of histopathologic phenotypes, inconsistent terminology, unclear definitions, the presence of multiple subtypes within a single tumor and partial sampling can contribute to the difficulty of subtyping. Achieving uniformity in the histopathological subtyping of BCC is crucial for providing optimal patient treatment. A simplified classification into three primary categories (superficial, nodular, and infiltrative subtypes) has been suggested to enhance reproducibility while remaining practical for clinical use ⁽⁵⁶⁾. This new histopathological classification system would facilitate reporting and enable easier comparisons between research publications.

DIAGNOSIS

Diagnosing BCC involves a combination of clinical examination (**Figure 5**), dermoscopy, and histopathological analysis.

Clinical diagnosis

Nodular BCC

nBCC is the most common subtype, accounting for 50-80% of all histopathologically verified cases. It typically presents as a pearly, flesh-colored or pink bump, often with visible telangiectasias. They are especially seen in the face and neck, *i.e.*, areas with a lot of sun

exposure. This type grows slowly but can eventually ulcerate and bleed, which may lead patients to seek medical attention.

Superficial BCC

sBCC is the second most common subtype, comprising about 15% of histopathologically verified cases. It is characterized by thin, pink patches or plaques and found on the trunk, shoulders, or extremities. This type can be mistaken for eczema or psoriasis due to its appearance.

Infiltrative and morpheaform BCC

iBCC and morpheaform BCCs are aggressive subtypes with a preference for the head and neck area. Clinically, they present as a whitish, scar-like plaque with ill-defined borders. They tend to invade deeply and can be more challenging to treat due to their tendency to spread beyond visible margins.

Micronodular BCC

Micronodular BCC is considered to be an aggressive subtype of BCC. It may resemble infiltrative BCCs clinically but the tumor nests in micronodular BCC are typically smaller. These tumors tend to occur more frequently on the face, particularly in high-risk areas such as around the eyes, nose, and ears.

Basosquamous BCC

Basosquamous BCC (metatypical BCC) is a rare and aggressive variant of BCC that exhibits features of both BCC and cSCC. They present clinically as an ulcerated nodule or plaque with keratin masses most often in the head and neck area. It has a higher risk of metastasis more similar to cSCC^(57,58).

There are many clinical differential diagnoses for BCC including malignant tumors such as cSCC, microcystic adnexal carcinoma, atypical fibroxanthoma, pleomorphic dermal sarcoma, merkel cell

carcinoma, melanoma (especially for pigmented BCC) and sebaceous gland carcinoma. Also, benign lesions like intradermal nevus, trichoepithelioma/trichoblastoma, fibrous papule, actinic keratosis, epidermal cyst and sebaceous gland hyperplasia can mimic BCC.



FIGURE 5. Clinical images of basal cell carcinomas showing the variation in clinical appearance.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

Non-invasive imaging

Non-invasive imaging technologies have become integral to dermatology, offering clinicians advanced tools for diagnosing and managing skin conditions without the need for invasive procedures (**Table 3**)⁽⁵⁹⁻⁶³⁾.

Dermoscopy

Histopathology is the gold standard for diagnosing BCCs, but since the 2000s, dermoscopy has become an increasingly important tool for diagnosing skin cancers⁽⁶⁴⁾. This handheld device, combining a light source and magnifying lens, uses polarized and non-polarized light to visualize structures in the epidermis and papillary dermis at 10-fold magnification (**Figure 6**).



FIGURE 6. Dermoscopes and dermoscopic photography.

(Photo by Paul Björkman)

Originally developed for melanocytic lesion evaluation, dermoscopy use has expanded to include BCCs and other skin lesions^(63, 65). Today, it is the most used diagnostic technique in addition to the traditional naked eye examination for early detection of skin cancer improving the sensitivity and specificity for BCCs⁽⁶⁶⁻⁶⁸⁾. Dermoscopy used in combination with clinical assessment for BCC diagnosis has demonstrated a pooled sensitivity of 91% and a specificity of 95% according to a recent meta-analysis. It also increased sensitivity by 14% over visual inspection alone⁽⁶⁶⁾.

A precise correlation is not always observed between histopathological subtypes and clinical and dermoscopic characteristics. Additionally, a mixed subtype within a single lesion has been described in almost 40% of the cases⁽⁶⁹⁾. The dermoscopic features of sBCCs and nBCCs are well-described in multiple studies^(65, 66, 70-72). However, dermoscopic features of high-risk facial BCCs have been less commonly investigated⁽⁷³⁻⁷⁵⁾ (**Figure 7**).

Nodular BCC presents dermoscopically arborizing vessels, ulceration, shiny white blotches and strands and, if pigmented, blue-gray dots and globules and large blue-gray ovoid nests.

Superficial BCC displays short fine telangiectasias, multiple small erosions, structureless white-red areas and, if pigmented, leaf-like, concentric and spoke-wheel areas.

Infiltrative BCC (including morpheiform BCC) is characterized by white or porcelain-like structureless areas. The vessels are usually arborizing, but the caliber of the vessels may be smaller than in nBCC. Pigmentation is less common.

Micronodular BCC imitates nBCC dermoscopically.

Basosquamous BCC shares attributes with cSCC such as keratin masses, peripheral unfocused arborizing vessels and ulceration with blood spots⁽⁷⁶⁾.

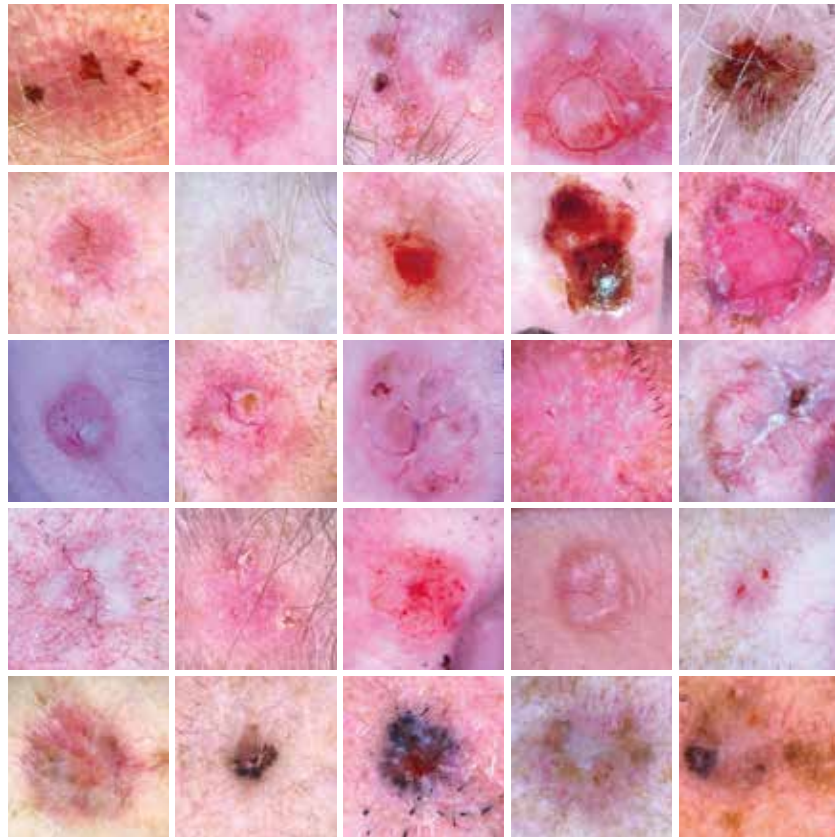


FIGURE 7. Dermoscopic images of basal cell carcinomas.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

For detecting lateral tumor margins, dermoscopy is the most commonly used method in clinical practice. However, its preoperative use to reduce the number of stages in Mohs micrographic surgery (MMS) has been a subject of debate^(60, 77). Additionally, the data on the interobserver agreement among dermatologists concerning the dermoscopic features of BCCs is limited^(73, 74).

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) (**Fig 8**) is often referred to as an "optical biopsy". The image depth is 250–300 μm , ranging from the stratum corneum to the superficial papillary dermis. It offers high-resolution, cellular-level images of skin lesions, aligned with the skin surface. It is particularly useful for diagnosing melanoma and other skin cancers, as well as monitoring treatment responses^(78, 79). By using a laser light source at a near-infrared wavelength, RCM captures high-resolution images that reveal the skin's microscopic features, such as melanin and keratin, which appear as white structures on a dark background due to their reflective properties. A systematic review showed a sensitivity of 97% and a specificity of 93% for BCC diagnosis using RCM⁽⁸⁰⁾. A recent prospective, randomized multicenter study demonstrated that using *in vivo* RCM for diagnosing and categorizing BCC is as effective as standard care. In this study, RCM was compared to the conventional method in which the surgical plan is determined by the histopathological diagnosis obtained from a punch biopsy⁽⁸¹⁾. Despite its advantages, the widespread adoption of RCM in clinical practice is limited due to its elevated cost as well as the training needed to interpret the grayscale images accurately.



FIGURE 8. Reflectance Confocal Microscopy.

(Photo Rahime Inci)

Optical Coherence Tomography

Optical coherence tomography (OCT) (**Fig 9**) is increasingly being utilized in dermatology as a non-invasive imaging tool that provides detailed insights into the surface layers of the skin, to a depth of 1 to 2 mm with a resolution ranging from 3 to 15 μm .

OCT applies infrared light to generate high-resolution images of the skin's architecture and offers a unique balance between resolution and depth penetration. In dermatology, OCT is particularly valuable for evaluating skin lesions, including NMSC⁽⁸²⁻⁸⁴⁾. OCT has a sensitivity of around 86% for detecting BCC and a specificity of approximately 75%⁽⁸⁵⁾. In combination with MMS, OCT has been studied for margin assessment of BCCs⁽⁸⁶⁻⁸⁸⁾. The number of excision stages in MMS of BCCs have been demonstrated to decrease if using *in vivo* RCM and OCT preoperatively^(60, 86). It provides real-time, *in situ* images without the need for tissue removal.

A variant of OCT is Dynamic OCT (D-OCT). It enhances the evaluation by providing functional information about the microvasculature within skin lesions. This is particularly useful for assessing blood vessel distribution and can be applied to a variety of skin diseases, including melanoma⁽⁸²⁾.

High-resolution Optical Coherence Tomography (HR-OCT) is also a variant of OCT. One of the primary advantages of HR-OCT is its ability to capture high-resolution images quickly, with greater penetration depth and a larger field of view compared to other imaging modalities like RCM. This technique utilizes near-infrared light to capture high-resolution cross-sectional images of the skin, allowing clinicians to examine the microarchitecture of skin lesions *in vivo*. It is an effective tool for distinguishing between different types of skin lesions, such as differentiating melanocytic nevi from cutaneous melanoma. HR-OCT can identify architectural patterns and cytologic features of pigmented cells in various layers of the skin, including the epidermis and dermis, which aids in the diagnosis and management of skin conditions⁽⁸⁴⁾. Despite its promise, further research and technological advancements are needed to enhance its clinical utility and integration into routine dermatological practice.

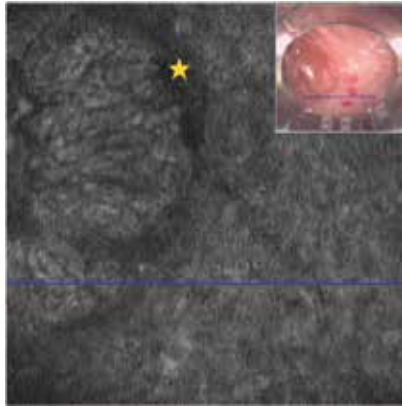


FIGURE 9. Optical coherence tomography image of a nodular basal cell carcinoma.

Reprinted with permission from David M. Ozog MD Department of Dermatology, Henry Ford Medical Center, Detroit

Line-field Confocal Optical Coherence Tomography

Both of the aforementioned methods are integrated in line-field confocal optical coherence tomography (LC-OCT) (**Fig 10**). The resolution is better compared to OCT but the penetration is more superficial. It creates both vertical and horizontal images in real time, in contrast to only horizontal images in RCM, with a similar resolution on the cellular level⁽⁸⁹⁻⁹¹⁾.



FIGURE 10. Line-field Confocal Optical Coherence Tomography.

Reprinted with permission from Arnaud Dubois Laboratoire Charles Fabry, Centre National de la Recherche Scientifique, Institut d'Optique Graduate School, Université Paris-Saclay, France.

High frequency ultrasound

High frequency ultrasound (HFUS) (**Fig 11**) is used for diagnosing and monitoring skin diseases, including skin cancers such as BCC and cSCC. It allows for the precise measurement of tumor depth, lateral extension, and vascularity, which are critical for preoperative planning and early detection⁽⁹²⁾. Optically guided HFUS has demonstrated high sensitivity (82.4%) and specificity (91.3%) in differentiating aggressive from low-risk BCC subtypes⁽⁹³⁾. In assessing the margins of BCCs and cSCCs before MMS, it has a sensitivity of 32% and a specificity of 88%⁽⁹²⁾. Despite its advantages, HFUS requires specialized training to interpret the images accurately, which can be a barrier for widespread use among general practitioners and dermatologists.

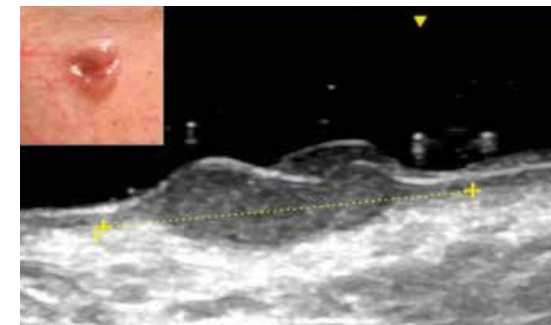


FIGURE 11. High frequency ultrasound image of a nodular basal cell carcinoma.

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Hyperspectral imaging

Hyperspectral imaging (HI) is a non-invasive technique that captures spectral data from an image. Unlike regular cameras that use three broad color bands (red, green, blue), HI employs dozens of continuous narrow wavebands, including subtle wavelength differences and wavelengths outside the human visible range 460-830 nm. The resulting hyperspectral cube contains two spatial dimensions and a third dimension with the spectral data for each pixel, creating a unique spectral graph for different biological tissues⁽⁹⁴⁾.

The spectra can be presented as abundance maps showing the localization and demarcation of tumors ⁽⁹⁵⁻⁹⁸⁾. The extensive field of view and fast imaging procedure are major benefits of HI. Only one study has used HI to delineate the lateral margins of BCCs preoperatively ⁽⁹⁹⁾ but HI has shown potential in preoperatively delineating lentigo maligna ⁽⁹⁶⁾ and detecting field cancerization in skin ⁽⁹⁷⁾.

Artificial intelligence

Artificial intelligence (AI) has shown promising results in detecting and classifying BCCs using various imaging modalities. In dermoscopy, AI algorithms demonstrated high accuracy, sensitivity, and specificity for BCC detection, averaging 90%, 87%, and 91%, respectively but the generalizability was limited by lack of external validation and data diversity ⁽¹⁰⁰⁾. A systematic review of articles from the last 10 years indicated that AI technology can be used to detect and classify BCC in dermoscopic, OCT, and RCM images ⁽¹⁰¹⁾. AI combined with dermoscopy also shows promising potential for improving melanoma detection and diagnosis ⁽¹⁰²⁻¹⁰⁵⁾. However, challenges remain in generalizing these algorithms across diverse populations and skin types, standardizing image processing methods as well as demonstrating ability to predict BCC subtypes. Additional research is crucial to overcome current limitations and guarantee that AI-driven methods are effective and reliable in a clinical settings ⁽¹⁰⁶⁾.

Non-invasive imaging and detection of subclinical extension in BCCs

In the preoperative evaluation of aggressive BCCs, dermoscopy has not shown effectiveness in reducing the number of MMS stages required ⁽⁶⁰⁾. RCM, when used for preoperative BCC delineation, has revealed subclinical extensions beyond the dermoscopically visible margins in 30% of cases ⁽⁷⁸⁾. Optical coherence tomography (OCT) has demonstrated promising results in margin assessment. For BCCs requiring only one MMS stage, OCT typically delineates margins that are 1.4 ± 1.3 mm smaller than those determined by

clinical assessment. More importantly, OCT successfully identified subclinical extensions in all cases where multiple MMS stages were necessary ⁽⁸⁷⁾. When comparing the LC-OCT group to the control group, which relied solely on dermoscopy, LC-OCT showed a significantly lower average number of MMS stages. Also, through preoperative mapping of the BCC tumor margins LC-OCT significantly reduced the risk of undergoing > I MMS stage ⁽⁹⁰⁾.

These findings suggest that advanced imaging techniques, like OCT and RCM, offer improved accuracy in preoperative BCC margin assessment. Their ability to detect subclinical extensions, particularly in cases requiring multiple MMS stages, highlights their potential value in surgical planning and potentially reducing the number of stages required in MM. These techniques are though costly and not readily available.

TABLE 3. Characteristics of non-invasive devices for diagnosing and delineating BCCs.

| Imaging Technique | Sensitivity | Specificity | Field of View | Resolution | Image depth |
|---|---|--|--------------------------|------------|---------------------------|
| Dermoscopy | 91% | 95% | Several cm ² | - | 0.5 mm (papillary dermis) |
| Optical Coherence Tomography | 95%, compared to visual inspection of 80% | 77% compared to visual inspection of 37% | 6x6 mm ² | 1-15 | 1-2 mm |
| Reflectance Confocal Microscopy | 94% vs 85% for dermoscopy | 95% vs 92% for dermoscopy | 1x1mm ² | 1 um | 200 um |
| Multispectral imaging | 98.3% for Melafind 80% for SiaScope | 9.9% Melafind 76% Siascope | 12 cm ² | 20 um | 2 mm |
| Line-field Confocal Optical Coherence Tomography | 87% | 91% | 1.2 mm x 0.5 mm x 0.5 mm | 1-15 um | 500 um |

Histopathological diagnosis

Histopathological examination of the skin involves analyzing an incisional (partial) or excisional biopsy sample. For incisional biopsies, a pathologist reviews the tissue under a microscope to confirm the diagnosis and identify the BCC subtype. However, histopathology based on the incisional biopsy may not correlate with the definitive BCC subtype in the subsequent excisional biopsy. Inconsistencies are seen between preoperative and postoperative pathology reports, with discrepancies observed in 20-62 % of cases⁽¹⁰⁷⁻¹⁰⁹⁾. The diagnostic concordance rates in the subtyping of BCC also vary between different dermatopathologists. Maher *et al.* showed substantial interobserver agreement for sBCC ($\kappa = 0.64$), but moderate interobserver agreement for nBCC ($\kappa = 0.45$), morpheaform/sclerosing BCC ($\kappa = 0.45$), iBCC ($\kappa = 0.49$) and micronodular BCC ($\kappa = 0.57$)⁽¹¹⁰⁾. Another study also resulted in higher reproducibility for nodular BCCs ($\kappa = 0.87$) than for morpheaform BCCs ($\kappa = 0.61$)⁽¹¹¹⁾. Similar results have been illustrated by Popadic *et al.* with κ -values of 0.85 for sBCCs and 0.62 for nBCCs, but only 0.13 for aggressive BCCs⁽¹¹²⁾. Basing treatment decisions on BCC subtype classification exclusively on histopathological examination of the preoperative biopsy can therefore be problematic.

Once diagnosed, the BCC is evaluated for risk factors that may influence treatment decisions. Factors that increase the risk of tumor recurrence include the tumor's location in central facial areas, larger tumor size, aggressive growth characteristics, ill-defined borders, perineural or perivascular tumor growth, incomplete removal of the tumor, and a history of prior recurrence^(3, 29, 113-117).

TREATMENT

Effective treatment is crucial to prevent BCCs from spreading and recurring. The recommended treatments depend on various

factors, including tumor size, location, and subtype, as well as the patient's overall health and preferences. The guidelines are also dependent of the nation's healthcare system^(38, 118, 119). Most BCCs can be effectively treated with surgery, topical therapies, or destructive methods⁽¹²⁰⁾. For advanced or metastatic BCCs, targeted therapies inhibiting the Hedgehog signaling pathway like Vismodegib and Sonidegib or novel immunotherapy drugs such as cemiplimab are also available⁽¹²¹⁾.

Surgical treatments

For many BCCs, surgery is the recommended treatment^(3, 38, 118, 122). Based on the tumor's clinical and histopathological risk factors, guidelines suggest conventional surgical excision (SE) with clinical margins ranging from 3 to 10 mm^(3, 38, 118). Regarding high-risk subtypes, the recommendation is to use larger margins (5-15 mm) or MMS^(22, 113, 118, 122, 123). The conventional method for histopathological examination of tissue samples is known as "bread-loafing" or serial sectioning (**Figure 12**). This technique, however, has limitations in its coverage, typically allowing only 0.1-2 % of the actual margins to be checked histopathologically⁽¹²⁴⁻¹²⁸⁾, compared to 100% of the margins with MMS^(113, 115, 129-133) (**Figure 13**). In serial sectioning, the tissue is usually cut into sections measuring 1-5 mm in length, while the thickness of each slice is maintained at just a few micrometers⁽¹²⁸⁾. A technique that examines 100% of the tumor margins is significantly more effective at detecting subclinical extensions (*i.e.*, tumor growths invisible to the naked eye during clinical examination) compared to traditional serial sectioning methods. The importance of identifying these hidden extensions is underscored by the relationship between surgical margin size and BCC recurrence rates. For instance, the risk of recurrence is ten times higher when a 2-mm surgical margin is used compared to a 5-mm margin⁽¹³⁴⁾.

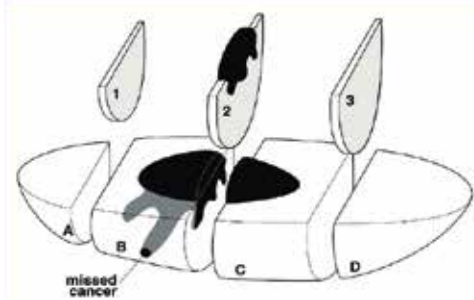


FIGURE 12. Bread-loaf technique or serial sectioning.

Reprinted with permission from Dr. Stephen Snow, Mohs Micrographic Surgery, 2nd Edition, The University of Wisconsin Press, 2004

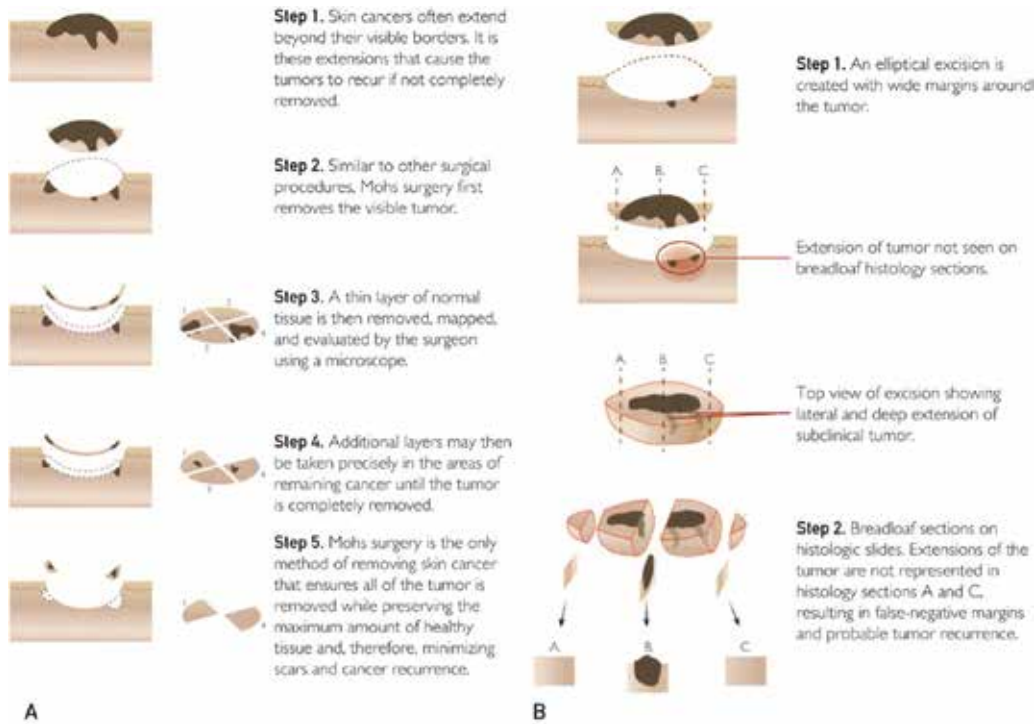


FIGURE 13. A, Mohs micrographic surgery technique. B, Surgical excision for wide local excision with breadloaf histopathology.

Reprinted with permission from Stanislav N. Tolkachjov (Understanding Mohs Micrographic Surgery - A Review and Practical Guide for the Nondermatologist).

An aggressive growth pattern is associated with higher rates of incomplete excisions, the need for re-excisions and a high risk of recurrence. These tumors often have clinically ill-defined tumor borders with subclinical extension. They are also often located in cosmetically sensitive anatomic areas in the face such as the nose, eyelids or ears⁽³⁸⁾.

Mohs micrographic surgery

Dr. Frederic E. Mohs (**Figure 14**) developed the MMS technique in the early 1930s. He discovered that the microscopic structure of cancer tissues was preserved following application of a 20% zinc chloride solution⁽¹³⁵⁾. Thus, the removed cancerous tissue could be analyzed microscopically intraoperatively during MMS. Originally, the approach was called chemosurgery since the use of zinc chloride paste for tissue fixation was more innovative than the microscopic monitoring.

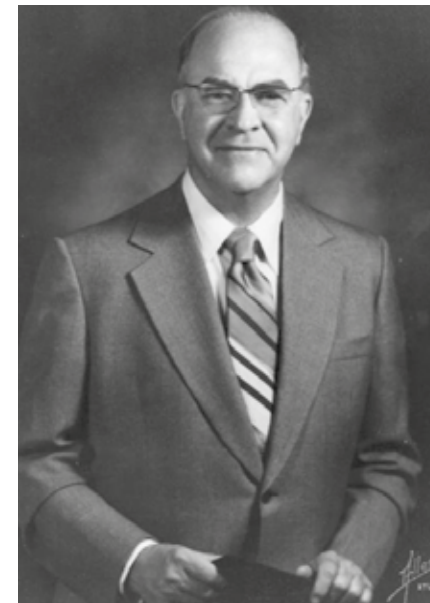


FIGURE 14. Portrait of Frederic. E. Mohs.

Dr. Frederic Mohs. UW Archives Image S06369.

The introduction of the fresh-tissue technique in 1953 eliminated the need for zinc chloride fixation and the procedure was refined over the subsequent decades. After European dermatosurgeons learned the technique in the USA, they began applying it in their home countries and the technique began to spread in the 1970s and 1980s. In Germany, other micrographic surgery techniques such as the Tübingen torte, the Muffin technique or the Munich method were introduced ⁽¹²²⁾.

Micrographic surgery, particularly classic MMS, is widely recognized for achieving the most effective treatment with the most favorable cosmetic outcomes for multiple skin cancer types. Since it is a resource-heavy procedure, it's preferable to use it for tumors that are challenging to remove completely and/or have high recurrence rates. One of the most common examples of this would be an infiltrative BCC with ill-defined borders in the facial area.

In areas where larger defects could cause functional or aesthetic issues, MMS is especially beneficial ⁽¹³⁵⁾. While MMS practically ensures the complete removal of the tumor, traditional SE may lead to incomplete excisions ^(29, 136). Several studies show that high-risk BCCs are incompletely excised in 25-50% of cases when regular SE is performed ^(29, 136-139). A randomized controlled trial comparing MMS and SE for high-risk facial lesions reported incomplete excisions of 18% with SE ⁽¹⁴⁰⁾ and 10-year recurrence rates of 4.4% and 3.9% for MMS versus 12.2% and 13.5% for SE for primary and recurrent tumors, respectively ⁽¹³³⁾. Additionally, two recent meta-analyses on SE and MMS concluded that MMS had better outcomes for both primary and recurrent BCCs but should be reserved for high-risk BCCs due to higher costs ^(126, 141). However, a recent Cochrane review found only low-certainty evidence suggesting that MMS results in slightly fewer recurrences compared to SE for primary facial BCCs ⁽¹⁴²⁾ and in a systematic review and meta-analysis low to moderate evidence that MMS is superior to

SE in reducing recurrences of BCCs ⁽¹⁴³⁾. Notably, most studies only focus on recurrences and not on incomplete excisions, the need for repeated surgeries or morbidity.

When performing MMS (**Figure 15**), local anesthesia is administered to the skin area around the tumor. The surgeon uses small incisions ('nicks') or sutures in order to ensure correct orientation and for tissue mapping. The clinically visible tumor is removed in the first stage adding a small margin in the surrounding healthy skin. Then the surgeon or a histotechnician precisely inks the nicked edges in the laboratory. The histotechnician then flattens the tissue so that the superficial and the deep margins align within the same plane. The sections obtained in the cryostat will then allow for circumferential histopathologic margin evaluation under the microscope by the surgeon with or without the assistance of a pathologist. If the margins aren't clear, additional tissue samples are removed from the corresponding mapped areas until there is no tumor left. The entire procedure typically takes a few hours. ^(122, 130)

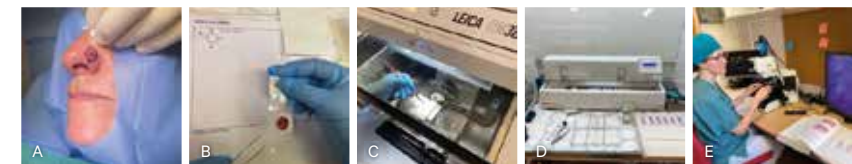


FIGURE 15. MMS-procedure. A) The tumor drawn with adding a narrow margin and 'nicks' at 3, 6 and 9 o'clock. B) The removed tumor specimen including the corresponding detailed map are sent to lab. The nicked edges are inked. C) Sections obtained in the cryostat and D) stained with HE staining, E) histopathological margin evaluation under the microscope.

The resulting wound is usually closed on the same day. Depending on its characteristics, the wound can be managed with secondary intention healing, primary closure, grafts and/or local or staged flaps.

Destructive Treatments

Destructive treatments involve curettage, electrodesiccation and cryosurgery in different combinations. These methods involve scraping the BCC with a curette (a sharp, spoon-shaped instrument or a ring currete), using electrodesiccation, (an electrosurgical generator set to monopolar mode) and freezing the BCC with liquid nitrogen. Destructive treatments have not been standardized in the past, meaning there has not been an international consensus on the precise techniques to make these treatments as effective and tolerable as possible ⁽¹⁴⁴⁾. The weaknesses of these methods is lacking confirmation of the tumor clearance and the dependence of the practitioner's skills ^(38, 145). Therefore, these treatments are generally recommended as second-line alternatives, preferably used in the elderly and for those with comorbidities that make surgery impossible ⁽¹⁴⁵⁾. However, a recently published randomized controlled trial of curettage vs cryosurgery for sBCCs from our department showed clearance rates of 95.7% for curettage and 100% for cryosurgery after 1 year ⁽¹⁴⁶⁾. The same group also conducted a prospective randomized controlled trial for nBCCs comparing one or two cycles resulting in 1-year clearance rates of 99% versus 100% ⁽¹⁴⁷⁾.

Non-Surgical Treatments

Topical Medications

Topical treatments for sBCC include imiquimod (an immune response modifier) and 5-fluorouracil (5-FU, a chemotherapy agent). These treatments are used over several weeks and are non-invasive.

Photodynamic Therapy

Photodynamic therapy (PDT) uses a photosensitizing prodrug applied to the skin, which results in accumulation of light-sensitive protoporphyrin IX through the enzymatic processes involved in the heme cycle. Subsequent exposure to light with a specific wavelength activates reactive oxygen species, which then destroy

the cancer cells. This method is effective for sBCCs and offers good cosmetic outcomes.

Radiation Therapy

For patients who are not suitable for surgery or when the BCC is located in an area where surgery might be difficult, radiation therapy can be considered instead. It involves using targeted radiation to destroy the cancer cells over several sessions.

Thesis Overview

| | Paper I | Paper II | Paper III | Paper IV |
|------------------|---|---|--|---|
| Design | Retrospective descriptive study | Retrospective descriptive study | Retrospective descriptive study | Prospective pilot study |
| Objective | To examine which factors affect the incomplete excision rates of high-risk BCCs. | Differences of defect size and stages between primary and treated facial high-risk BCCs undergoing MMS. | To describe clinical and dermoscopic features of facial high-risk BCCs and their interobserver agreement. | To test the feasibility of hyperspectral imaging to demarcate the lateral margins of high-risk BCCs prior to MMS. |
| Results | <p>987 BCCs</p> <p>Overall incomplete excision rate 20.6%. The nose, ear, scalp, and periorbital areas as well as high-risk subtypes revealed the highest proportions of incomplete excisions.</p> | <p>913 BCCs</p> <p>Fewer MMS stages were required and smaller wound areas were obtained for primary facial high-risk BCCs compared to BCCs that had been treated previously.</p> | <p>307 BCCs</p> <p>A bumpy surface, poorly defined borders, dermoscopic presence of 'white porcelain area' and/or 'vessels within ulceration' were indicative of high-risk BCCs. An algorithm demonstrated a sensitivity of 81.4% and a specificity of 53.3%.</p> | <p>30 BCCs</p> <p>Overall accuracy of pixel-wise classification was 0.76. The sensitivity was 0.75 and the specificity was 0.78. The AUC was 0.84.</p> |

FIGURE 16. Overview of the thesis including the design, objectives and main results in Paper 1-IV. BCCs, basal cell carcinoma

Aims

The overall objectives of this thesis were to expand our knowledge on high-risk BCCs, aiming to investigate risk factors associated with incomplete excisions, identify and characterize their distinctive clinical and dermoscopic features and determine optimal treatment strategies to maximize the likelihood of successful initial treatment.

The specific aims were:

- Study I: To examine which factors affect the incomplete excision rates (IERs) of high-risk BCCs.
- Study II: To measure differences between primary, incompletely excised and recurrent facial high-risk BCCs undergoing MMS regarding number of stages and final defect sizes.
- Study III: To describe clinical and dermoscopic features of facial high-risk BCCs and their interobserver agreement.
- Study IV: To test the feasibility of HI to preoperatively demarcate the lateral margins of high-risk BCCs planned to be treated with MMS.

Methodological considerations

Paper I

Subjects

The study included all Glas type II-III BCCs treated with traditional SE and analyzed histopathologically at the Department of Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden during the period of November 2018 to May 2020. Dermatopathologists analyzed all cases but no slides were reviewed by separate pathologists. Inclusion criteria were BCCs excised with the intent of complete tumor removal. BCCs removed using a shave excision technique, curettage, or with a partial punch biopsy were excluded since these procedures are used for diagnostic purposes rather than definitive for definitive treatment.

Methods

This retrospective study used electronic patient records and histopathological reports to collect the following information (**Table 4**).

TABLE 4. Data variables included in the study.

| Category | Details |
|-----------------------------|--|
| Patient demographics | <ul style="list-style-type: none"> • Age • Sex |
| Tumor characteristics | <ul style="list-style-type: none"> • Location • Size (maximum diameter on day of surgery) • Histopathological subtype |
| Preoperative details | <ul style="list-style-type: none"> • Partial biopsy (yes/no) |
| Physician information | <ul style="list-style-type: none"> • Specialty • Experience level (resident or specialist, according to electronic patient records) |
| Surgical details | <ul style="list-style-type: none"> • Excision type (elliptical, circular, or punch) • Clinical margins (smallest margin recorded when ambiguous) |
| Outcome measures | <ul style="list-style-type: none"> • Incomplete excision (histopathologically verified positive surgical margin) |
| Specific margin involvement | <ul style="list-style-type: none"> • Lateral, deep, or both |

Limitations

The comprehensive collection of consecutive cases strengthens the statistical reliability and reduces selection bias. Further analysis of potential confounding factors was performed, minimizing the risk of drawing incorrect conclusions. The retrospective nature of the study caused challenges in obtaining all relevant clinicopathological data from the electronic patient records and histopathology reports. Also, since Sweden uses the Sabbatsberg classification for BCCs, comparisons with studies that use the WHO classification system becomes more difficult ^(14,8). Additionally, more uncommonly observed BCC subtypes such as the morpheaform, micronodular or basosquamous types, made it harder to make definitive conclusions about such variants. Furthermore, the presence of perineural invasion was inconsistently reported in the histopathological records. Finally, the comparison between residents and specialists was used as an indirect measure or indicator of experience level.

Paper II

Subjects

The study retrospectively reviewed all consecutive patients who underwent MMS for BCC at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden, between 2012 and 2019 (based on the power calculation outlined in the statistical analyses). If the treated tumor was not a BCC, if the BCC had recurred following MMS or if important data regarding stages, defect size, or treatments before MMS were unavailable the patients were excluded.

Methods

In this retrospective observational study three different tumor categories were examined; primary BCCs (P-BCC), incompletely excised BCCs (IE-BCC) and recurrent BCCs (R-BCC). The following information was gathered:

- 1) Patient demographics:
 - Age
 - Sex
- 2) Tumor characteristics:
 - Location and diameter
 - Histopathological subtype
 - Previous treatments
- 3) Clinical timeline:
 - Date of diagnosis
 - Date of surgery
- 4) Medical professionals involved:
 - Specialty of pre-MMS treating physician
 - Specialty of referring physician

5) Surgical details:

- Number of MMS stages
- Final defect dimensions (largest and smallest diameters)
- Reconstructive technique used

Surgical defect areas were calculated using the formula: $\text{area} = \Pi \times (\text{major axis}/2) \times (\text{minor axis}/2)$.

Limitations

The study's primary strength lies in its comprehensive data collection, encompassing all consecutive cases from our department's local register of MMS procedures during an 8-year period. However, the study was conducted at only one institution, potentially limiting its generalizability. The lack of randomization may introduce selection bias and the study's retrospective design may lead to inherent biases and limitations in data quality. For R-BCC and IE-BCC, scarring from previous treatments may have affected the accuracy of lesion size estimates prior to MMS.

Paper III

Subjects

A retrospective analysis was conducted on primary facial BCCs diagnosed at the Department of Dermatology, Sahlgrenska University Hospital, from January 2019 to December 2022. The study included high-quality clinical and dermoscopic images of histopathological confirmed BCCs. The sample distribution mirrored the most frequently excised facial BCC subtypes as reported in the Swedish registry: 40% nBCCs, 10% sBCCs, and 50% high-risk BCCs.

To be eligible for inclusion, cases had to meet two criteria: the BCC must be located on the face and have a specific histopathological subtype (cases with mixed subtypes were excluded). Basosquamous

carcinomas were not included in the study. Dermatopathologists at the Department of Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, carried out all histopathological examinations.

Methods

Data collection included demographics such as sex and age at diagnosis, lesion characteristics such as size (in mm), anatomical location and histopathological classification. Six independent experts with over 10 years of dermoscopy experience, three Swedish readers and three international readers (from Chile, Israel, and the United States) evaluated the images. The task was to evaluate paired clinical and dermoscopic images which were acquired using an iPhone 8 smartphone (Apple, Cupertino, California, USA) coupled with a DermLite DL4 dermatoscope (DermLite LLC, Capistrano, California, USA) using polarized light.

Prior to commencing the study, all readers participated in a consensus meeting. During this meeting, they collectively examined and discussed 40 clinical and dermoscopic images of BCCs representing various histopathological subtypes. These images were compiled separately from the study dataset. The purpose of this meeting was to establish agreement on a predefined list of features that could be observed clinically and/or dermoscopically. The readers discussed appearance (flat, raised and/or depressed), borders (well/ill-defined), ulceration (number of areas with ulceration/erosion), vessels (predominately focused arborizing vessels or unfocused short fine telangiectasias), as well as the presence or absence of a whitish background ("white porcelain area"), shiny white structures and brown-gray (leaf-like, spoke-wheel or concentric areas) or gray-blue (dots/globules or ovoid nests) pigmented structures.

Following this consensus-building exercise, the readers were given access to the study's image dataset for independent evaluation. To ensure unbiased assessment, the readers were not informed of the

histopathologic diagnoses. Their task was to independently score the presence or absence of the predefined criteria for each image pair .

The evaluation process consisted of several steps:

1) Clinical image assessment (**Fig 17**):

Readers first examined the clinical image to classify each tumor’s surface topography as raised, flat, depressed, or any combination thereof. For data analysis purposes, any mixed topography (i.e., not exclusively flat or raised) was categorized as ‘bumpy’.

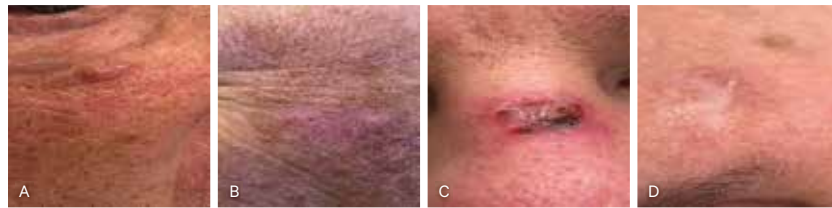


FIGURE 17. a) Raised basal cell carcinoma (BCC) b) flat BCC c) “bumpy” , (i.e. not exclusively flat or raised) BCC and d) depressed BCC.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

2) Tumor border classification (**Fig 18**):

Using both clinical and dermoscopic images, readers categorized tumor borders as either well-defined or ill-defined.



FIGURE 18. a) Clinical image well-defined BCC, b) Clinical image ill-defined BCC, c) Dermoscopic image, well-defined BCC and d) Dermoscopic image, ill-defined BCC.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

3) Dermoscopic feature evaluation. Readers then assessed the dermoscopic images for presence or absence of the following features (**Fig 19**):

- a) Ulceration/erosion
- b) Predominance of focused (arborizing) or unfocused vessels
- c) White porcelain area
- d) Shiny white blotches and/or strands
- e) Classic pigmented structures
- f) Vessels within ulceration

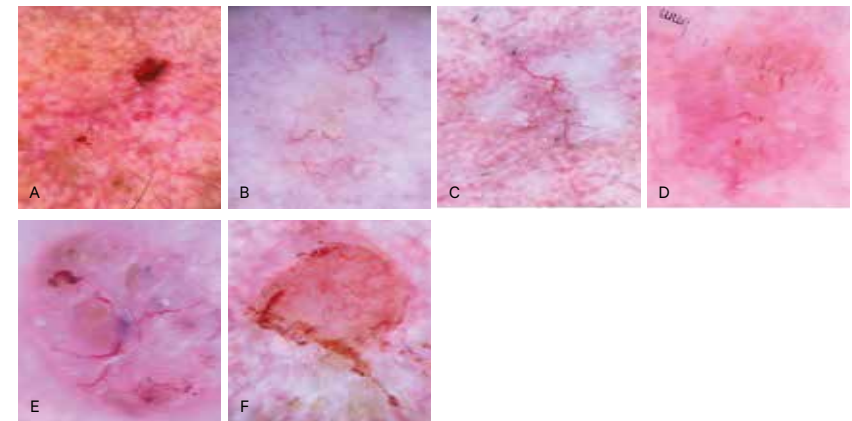


FIGURE 19. Showing dermoscopic features of, a) ulcerations, b) focused arborizing vessels, c) white porcelain area, d) shiny white blotches and strands, e) pigmented structures including blue-gray ovoid nests, f) vessels within ulceration.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

4) Histopathological subtype prediction:

Finally, based on their observations, readers were asked to predict the histopathological subtype of each tumor (i.e., nodular, superficial or high-risk) (**Fig 20**).



FIGURE 20. Histopathological subtype of a) nodular BCC, b) superficial BCC and c) high-risk BCC.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

Limitations

Although the study focused exclusively on facial BCCs, which is a limitation, BCCs located on other body sites are seldom as challenging when it comes to incomplete excisions and recurrence risks. The images were retrospectively collected from a single-center and this design may limit the generalizability of the findings. The study depended on the Swedish Glas type classification for BCCs, which lacks international acceptance. Also, histopathological reports were only analyzed by one pathologist without independent review of the cases. Most BCCs occurred in patients with Fitzpatrick phototypes I-II but patient skin phototype was not recorded, potentially limiting the applicability of findings to diverse populations. It was also known that the tumors being analyzed were all BCCs and were provided with a predefined set of criteria which may have influenced the readers' assessments, leading to reading bias. A clear limitation is the lack of a study that validates the created algorithm. Finally, the study focused solely on BCCs. A greater number and other frequency of dermoscopic features would likely have been seen if other keratinocyte cancers had been included. These limitations highlight the need for further research, including multicenter studies with independent histopathological reviews of all included cases, and a more diverse patient population to validate and expand upon our findings.

Paper IV

Subjects

Patients awaiting treatment for high-risk BCC with MMS at the Department of Dermatology at Sahlgrenska University Hospital in Gothenburg, Sweden were invited to participate. The recruitment process was conducted prospectively from January 2022 to January 2023 to include around the 30 patients intended to be included. Given the pilot nature of this study, a precise calculation of the required sample size was not performed. All patients received verbal and written study information and written consent was secured before surgery.

Inclusion criteria:

- Facial primary BCCs scheduled for MMS
- Lesions located on flat facial surfaces (*i.e.*, not ears or eyelids for example)

Exclusion criteria:

- Patients unable to provide informed consent

Methods

Initial evaluation of all lesions was conducted both clinically and dermoscopically using a Dermlite® DL200 Hybrid device (3Gen, CA, USA). Photographic clinical and dermoscopic documentation was performed for each lesion prior to and after the dermoscopically observed tumor borders were marked on the skin using a marking pen. The Cutica® hyperspectral imaging (HI) system (Revenio Group Oyj, Vantaa, Finland) (**Figure 21**) was employed to capture hyperspectral images of the lesion and surrounding healthy skin without border markings and the same area with dermoscopic lesion borders marked on the skin. The hyperspectral data cube was captured within seconds.

The BCCs were then excised following the standard MMS protocol adding a superficial incision along the demarcation line to facilitate comparison between dermoscopically visible tumor borders and histopathological findings (see Figure 1 in the Paper IV). The borders observed in hyperspectral images were then compared with the true demarcation confirmed by histopathology.



FIGURE 21. The hyperspectral imaging system used.

Photo by Hannah Ceder.

The HI system incorporates a diffuse light system and a hyperspectral imager⁽¹⁴⁹⁾. It captures 120 wavebands within seconds using visible and near-infrared light (460–830 nm) reflected from the skin. The system's spatial resolution is 6,400 pixels/cm and covers a large field of view (12 cm²). Based on the wavelength, the imaging depths range from 0.5 to 5.0 mm⁽¹⁵⁰⁾.

The camera used has a resolution of 1,920×1,200 pixels, corresponding to a spatial resolution of approximately 15 μm/pixel. It features an adjustable filter that selects specific wavelength bands, capturing images sequentially. These images are then combined into a three-dimensional image cube, containing both spatial and spectral information (see Figure 2 in Paper IV). The image cube is input into a deep neural network model with two branches: one branch analyzes spatial features, while the other examines spectral features.

In addition to the spectral data cube, the HI system also produces standard RGB images of the scanned area. Further details can be found in previous studies^(95, 96, 151). Supervised learning was used for data analysis, utilizing annotated images as the ground truth. These annotations were based on histopathologically verified lesion borders marked on RGB images. Tumor areas seen with dermoscopy were marked in red and the subclinical extension based on histopathology were marked in yellow (see Figure 3 in Paper IV.) Using these annotations, the machine learning models were trained.

The developed AI model was a convolutional neural network (CNN), modeled after approaches previously reported in the literature⁽¹⁵¹⁾. It had two parts: one that looked at images (a 2D CNN)⁽¹⁵²⁾ and another that analyzed light wavelengths (a 1D CNN). These two sets of information were combined for the final AI model.

Due to the limited number of lesions, the network training procedure involved vertically splitting the lesion images at their center⁽⁹⁸⁾. One side was used for learning, and the other for testing accuracy. The testing was done on the unannotated right side lesion halves and the annotations served as the ground truth. The model training was performed using individual pixels from the image with each pixel on the left half of the lesion considered a separate sample, with the class designated for each pixel independently. The training process included flipping and rotating images to help the model recognize patterns better. The model was built using PyTorch, optimized with Optuna, and trained on a powerful NVIDIA RTX A4000 graphics card.

Limitations

The modified deep neural network used for data analysis still requires further development. Another limitation is the pilot nature of the study, that the sample size was small and only allocating half of the available images for training the CNN. Ideally, CNN training

and classification would be done with separate datasets, but given our constraints, that wasn't possible. Even so, the pixel-by-pixel analysis helped minimize bias and strengthened the credibility of our results.

Statistical analyses

Paper I

The study utilized R version 3.5.3 for statistical computations. Fisher's exact test was utilized for proportion comparisons. Wilcoxon rank-sum test and Kruskal-Wallis test were used for two-group and multi-group comparisons, respectively. All tests were two-tailed and statistical significance was defined as a p-value of less than 0.05.

Paper II

Based on previous data, a power calculation was conducted when planning the study. An estimated ratio of P-BCCs to R-BCCs: 3.75:1, with a desired power of 80%, α -error: 0.05 required a sample size for achieving differences in number of stages of 656 P-BCCs and 175 R-BCCs. For differences in final defect size 480 P-BCCs and 128 R-BCCs were required. The study utilized R version 3.0.3 for statistical computations. For two-group comparisons and for comparison of three or more groups Wilcoxon rank sum test respectively Kruskal-Wallis test were used. Fisher's exact test was used for comparison of proportions. Two-tailed tests were used and $p < 0.05$ was established for statistical significance.

Paper III

In this study, we used Fisher's exact to compare frequencies of the features used. Odds ratios were calculated to determine the associations between clinical and dermoscopic features and the confirmed histopathological BCC subtype. For predicting high-risk subtypes, the outcomes were employed to create a potential diagnostic al-

gorithm. For interobserver agreement between multiple readers, we used Fleiss' kappa (**Table 5**) which can be used when there are more than two observers. A κ -value of 1 reflects perfect agreement, whereas a κ -value of 0 reflects an agreement level corresponding to chance ⁽¹⁵³⁾.

TABLE 5. How to interpret interobserver agreement according to Fleiss' kappa.

| Fleiss' Kappa Value (κ) | Agreement Level |
|----------------------------------|--------------------------|
| < 0 | Poor agreement |
| 0.01 – 0.20 | Slight agreement |
| 0.21 – 0.40 | Fair agreement |
| 0.41 – 0.60 | Moderate agreement |
| 0.61 – 0.80 | Substantial agreement |
| 0.81 – 1.00 | Almost perfect agreement |

All analyses were conducted using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria) and statistical significance was defined as a p-value below 0.05.

Paper IV

The area under the receiver operating characteristic curve (AUC) was used to assess the model's performance, *i.e.*, the model's overall ability to differentiate between classes. Furthermore, sensitivity as well as specificity were calculated.

Ethical commentary and reflections

Paper I acquired approval by the Regional Ethical Review Board in Gothenburg (approval 430-16) and an amendment approved by the Swedish Ethical Review Authority (approval 2020-02933).

Paper II was accepted by the Regional Ethical Review Board in Gothenburg (approval 412-10) and an amendment granted by the Swedish Ethical Review Authority (approval 2019-05972)

In Paper III, the Regional Ethical Review Board in Gothenburg (approval 283-18) and the Swedish Ethical Review Authority (amendment approval 2020-01190) sanctioned the study.

In paper IV, approval was given by the Swedish Ethical Review Authority (approval 2021-04753).

Most of the studies included in this thesis are of retrospective design and the collected data were de-identified. We collected data from registers and medical records, which are all on a secure electronic server at the Department of Dermatology and Venereology at Sahlgrenska University Hospital. Only relevant information was collected and analyzed following confidentiality rules and regulations.

In the retrospective studies, informed consent was not considered to be required. The dermoscopic images used in Paper III were taken in a way in which the patients couldn't be identified. The images were also de-identified removing personal data. The prospective study IV adhered to Good Clinical Practice as described in the Declaration of Helsinki (last revised in 2013 at the time of the study). Oral and written forms were given to the patients before the surgery and patients not wishing to give informed consent did not participate in the study. The participants could withdraw their consent and stop participation at any time, without affecting the results of their treatment.

Overall, the benefits outweighed the risks, which are minimal, in this project. Hopefully, these studies will lead to better knowledge about high-risk BCCs, allowing for better resource utilization and less suffering for the patient. The benefits, however, will mainly apply for future patients with high-risk BCCs and not necessarily for the research subjects in these studies.

Results

Paper I

During the research period, a total of 987 type II–III BCCs were surgically removed. These tumors were excised from 894 patients, comprising 469 men (52.5%) and 425 women. The patient cohort had a median age of 75 years, ranging from 31 to 101 years.

Regarding tumor features, the median tumor diameter of the BCCs was 10 mm (range 2–200 mm). Histopathologically, 68.1% of the BCCs were classified as Glas type II, and 31.9% as type III. Among these, 82.5% were highly aggressive infiltrative tumors while the remaining lesions were of the morpheaform, micronodular, or basosquamous subtypes. A total of 203 cases were incompletely excised (20.6%) and the lateral margin was most commonly involved (52.7% of incomplete excisions). Both the lateral and deep margins were involved in 16.3%. Comparing type III BCCs versus type II BCCs, incomplete excisions were significantly more frequent in type III BCCs (27.0% vs. 17.6%, $p < 0.001$). The highest IERs varied from 28.0% to 37.0% and these were seen on the nose, ear, scalp, and periorbital region (**Figure 22**).

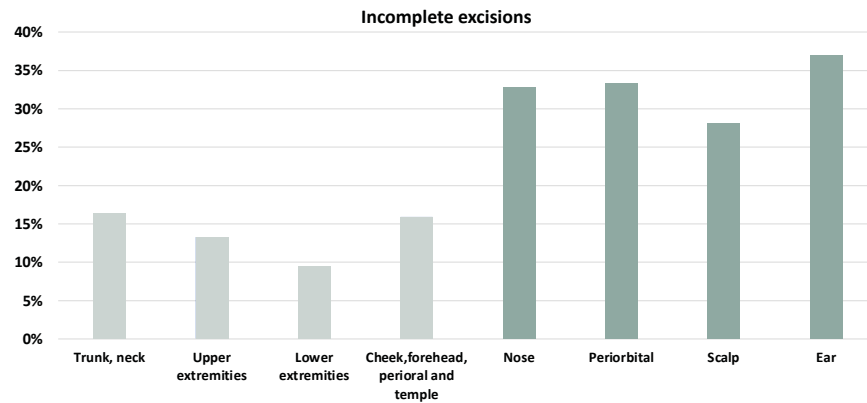


FIGURE 22. Overall proportions of incomplete excisions on different locations.

When comparing BCCs removed with a clinical margin of ≤ 5 mm versus clinical margins > 5 mm, no significant effect on IERs was observed ($p=0.44$). Tumor size did not appear to affect the IERs significantly either. Elliptical excisions produced lower IERs compared to circular and punch excisions ($p<0.001$). BCCs diagnosed preoperatively with a punch biopsy were not significantly excised incompletely more often ($p=0.12$). Interestingly, among the lesions biopsied prior to SE, the preoperatively diagnosed histopathological subtype did not correspond to the postoperative one in 38.5% of the cases.

Incomplete excisions were seen in 41.0% of the cases removed by general practitioners, who had the highest IERs. Nevertheless, most of the BCCs were excised by dermatologists, otorhinolaryngologists and plastic surgeons (85.2%). When these three specialties excised lesions on the face and scalp, the IERs did not differ significantly ($p=0.12$). Furthermore, no statistically significant differences in IERs were observed between specialists and residents ($p=0.39$). Type III BCCs located on the nose had the highest IERs (55.0%). This was the only anatomical site that showed a significant difference in IERs between type II and type III BCCs ($p<0.001$).

Paper II

After exclusion, data from 903 tumors in 813 patients were analyzed. The majority of patients were women, accounting for 59%. In terms of the tumor types, 70.1% were P-BCCs, 10.4% were IE-BCCs, and 19.5% were R-BCCs

Significant variations in the mean number of stages were observed among P-BCCs, IE-BCCs, and R-BCCs ($p=0.013$) (**Table 6**). R-BCCs demonstrated a significantly higher mean number of stages (2.11) compared to both P-BCCs (1.89, $p=0.03$) and IE-BCCs (1.82, $p=0.007$). However, the difference in the number of stages between P-BCCs and IE-BCCs did not reach statistical significance ($p=0.09$).

TABLE 6. Number of stages used during Mohs micrographic surgery (mean, 95 % CI) for primary, incompletely excised and recurrent basal cell carcinomas. ***P-BCC**, primary basal cell carcinoma; **IE-BCC**, incompletely excised basal cell carcinoma; **R-BCC** recurrent basal cell carcinoma; CI, confidence interval.

| | Total | P-BCC | IE-BCC | R-BCC |
|------------------|-------|-------|--------|-------|
| Number of stages | 1.9 | 1.89 | 1.82 | 2.11 |
| Upper 95% CI | 1.98 | 1.94 | 2.00 | 2.27 |
| Lower 95% CI | 1.87 | 1.84 | 1.64 | 1.96 |

P-BCCs had significantly smaller final defect areas compared to IE-BCCs ($p=0.003$) and R-BCCs ($p<0.0001$). Between IE-BCCs and R-BCCs, no statistically significant differences were seen in terms of final defect size ($p=0.54$) (**Table 7**). The post-MMS defect size exceeded the pre-MMS clinical tumor size more significantly in R-BCCs ($p<0.001$) and incompletely IE-BCCs ($p=0.015$) compared to P-BCCs.

TABLE 7. Final defect size in cm² for P-BCC, IE-BCC and R-BCC. ***P-BCC**, primary basal cell carcinoma; **IE-BCC**, incompletely excised basal cell carcinoma; **R-BCC** recurrent basal cell carcinoma.

| | Total | P-BCC | IE-BCC | R-BCC |
|--------------------------------------|-------|-------|--------|-------|
| Final defect size (cm ²) | 4.4 | 3.55 | 5.10 | 6.34 |

Primary closure was the most commonly used reconstructive technique for all tumors, applied in over half of the cases (50.8%). This was followed by various types of flaps (22.4%) and grafts (16.3%). Secondary intention healing as well as cases requiring a combination of techniques were used in a lower percentage of cases. In one case, reconstruction was done by a plastic surgeon.

In P-BCCs and R-BCCs, dermatologists were responsible for the referral for MMS in more than 90% of cases. Otorhinolaryngologists as well as plastic surgeons were responsible for about one-third of MMS referrals for IE-BCCs.

Patients with R-BCCs had undergone unsuccessful treatments a mean of 1.8 times while IE-BCCs had failed SE 1.5 times on average (range 1-6 treatments for both R-BCCs and IE-BCCs) before finally undergoing MMS. In both cases, dermatologists had performed most of the unsuccessful treatments.

Paper III

This study included images of 297 BCCs, after excluding 10 cases due to poor image quality. The included lesions consisted of high-risk BCCs (57.6%), nBCCs (33.0%) and sBCCs (9.4%). The cheek was the most common anatomical location (24.6%) followed by the nose (21.5%), forehead (18.2%), temple (13.5%) and the periorbital area (29.9%). The median patient age was 75 years (range 24-96 years), and 52.2% of patients were female. The study identified

several clinical and dermoscopic features that were commonly associated with different BCC subtypes.

Clinical features:

- Solely flat surface topography was strongly associated with sBCCs (OR 10.0).
- Solely raised surface topography was associated with nBCCs (OR 6.1)
- 'Bumpy' surface topography was associated with high-risk BCCs (OR 3.8).

Clinical and dermoscopic features

- Ill-defined borders were seen more frequently in superficial and high-risk BCCs (OR 2.4 and 3.4, respectively).
- Well-defined borders were more common in nBCCs (OR 5.4).

Dermoscopic features:

- Predominantly focused arborizing vessels suggested the BCC was not superficial.
- White porcelain areas and the novel finding of 'vessels within ulceration' (**Figure 23**) were associated with high-risk BCCs (OR 3.5 and 3.1, respectively).
- Blue pigmented structures were more frequently observed in nBCCs (OR 2.5).
- >4 erosions were associated with sBCCs (OR 2.7).

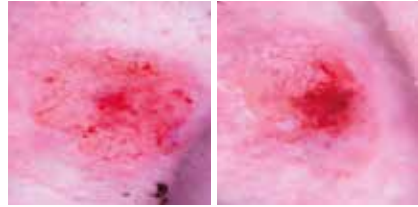


FIGURE 23. Examples of vessels within ulceration.

(Photo: Department of Dermatology and Venereology, Sahlgrenska University Hospital)

To identify which facial BCCs may need a preoperative biopsy to exclude a high-risk histopathological subtype, a diagnostic algorithm was created combining the positive criteria for high-risk subtypes with the negative criteria for low-risk subtypes. The algorithm demonstrated a sensitivity of 81.4% and a specificity of 53.3% for predicting high-risk subtype. When only surface topography was used, the corresponding sensitivity and specificity was 57.3% and 74.1%, respectively.

Regarding interobserver agreement, the highest κ -values were seen for areas with ulceration/erosion ($\kappa=0.72$) followed by presence of classic pigmented features ($\kappa=0.59$). Moderate agreement was seen regarding presence of white porcelain areas ($\kappa=0.54$), predicted histopathological subtype ($\kappa=0.53$), presence of vessels within ulceration ($\kappa=0.51$) and borders, if they were well or ill-defined ($\kappa=0.51$). Features with fair interobserver agreement included clinical surface topography ($\kappa=0.36$) and whether vessels were predominantly focused or unfocused ($\kappa=0.38$) (**Figure 24**).

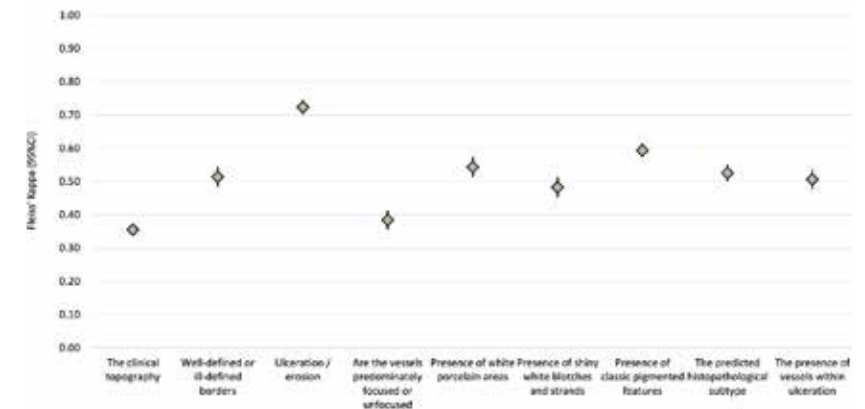


FIGURE 24. Interobserver agreement for the clinical and dermoscopic findings assessed by the readers.

Paper IV

A total of 36 lesions meeting the inclusion criteria were imaged. One lesion was excluded due to being a recurrent BCC, and five others were excluded due to poor image quality or missing images. Consequently, 30 lesions from 30 patients (11 men and 19 women) were included. The median age of the patients was 69 years (range 38–86 years). The imaged lesions were located on the nose (n=8), cheek (n=8), perioral area (upper, lower lip) (n=5), temporal area/forehead (n=5) and peri-orbital area (medial cantus, eyebrow) (n=4). The median diameter of the tumours was 13 mm, varying between 5 and 21 mm. All lesions fit within the field of view and were successfully imaged in a single session.

A total of 19 lesions exhibited histopathologically verified subclinical lateral tumor extension beyond the tumor border identified through dermoscopy. In all cases, the lateral margin was affected, and in one instance, the deep margin was also involved.

The overall accuracy of the pixel-wise classification of hyperspectral images was 0.76, the sensitivity was 0.75 and the specificity was 0.78. The AUC was 0.84.

Discussion

Together, these studies emphasize a multifaceted approach to managing high-risk BCCs. The results highlight the importance of knowing which risk factors exist to avoid failed treatments in combination with accurate preoperative assessments using clinical and dermoscopic findings. Each study underscores the importance of tailored strategies for high-risk BCCs to reduce treatment failure and recurrence. MMS has demonstrated superior efficacy in treating both primary and recurrent BCCs, particularly those located in high-risk facial areas. In contrast to SE, MMS capability to assess 100% of the surgical margins is crucial for securing high cure rates and low recurrence rates. These studies are also intended to optimize resource utilization and ensure that more people receive the right treatment from the start.

Paper I

This study confirmed that factors associated with higher IERs are: type III BCC subtype, tumor location on the face/scalp, certain physician specialties (higher rates for general practitioners) and excision technique (higher rates with circular and punch excisions). Tumor diameter, surgeon experience, clinical margins applied and the use of a preoperative biopsy were statistically not associated with IERs.

Incomplete excisions more commonly involved the lateral margin compared to the deep margin with both margins involved even less frequently. Other studies that included both high-risk and low-risk BCC subtypes have also observed similarly frequent involvement of the lateral margins (52–82%) the deep ones (14–36%) or both

(2–16%)^(137, 154-158). The higher IERs, particularly involving the lateral margins, highlight the technical challenges in completely removing high-risk BCC subtypes, even with specialized surgical techniques. Careful preoperative planning and intraoperative margin assessment are crucial to minimize incomplete excisions and subsequent tumor recurrence.

No significant difference in IERs was found between type II and III BCCs beside for tumors located on the nose, where type III BCCs had higher IERs. Previously, MMS has mainly been recommended for type III BCCs but these findings suggest that it should also be offered to patients with type II BCCs in functionally critical anatomical regions.^(122, 132, 133, 159-161) This has also been partially addressed in the new Swedish national clinical guidelines for BCC⁽³⁾.

Previous studies reported IERs of 9.5-50.0% for aggressive BCC subtypes^(29, 116, 137-139, 155, 156, 162-164) For type III BCCs (27.3%) our study aligned well with the largest prior study by Kappelin *et al.* (27%)⁽²⁹⁾. However, the current study found a higher IER for type II BCCs (17.6%) compared to Kappelin *et al.* (7.5%). This may be due to differences in tumor locations, as only half of their type II BCCs were found on the face or scalp. The current study also showed that BCCs on the face and scalp had positive margins more often than tumors on the body with IERs of 22.4% versus 14.7%, respectively. Additionally, other research examining all subtypes of BCC also suggests that the tumor's anatomical location impacts the IERs with higher rates for nose, ear and periorbital areas^(116, 137, 138, 154, 155, 157, 165-168).

The effect of physician specialty on IERs for aggressive BCC subtypes on the face and scalp is probably minimal or insignificant. Other studies have shown similar results with no statistically significant differences^(169, 170). A limited number of studies suggest though that dermatologists have lower IERs compared to other

medical specialties^(137, 163), However, this relationship is probably highly influenced by confounding variables.

Whether the treating physician was a specialist or a resident did not affect the IERs. Regarding case complexity, both groups excised a similar proportion of type III BCCs and tumors with comparable mean diameters, although specialists removed a significantly higher percentage of tumors located on the face and scalp. Similar results regarding the physician's level of experience, were seen in two studies covering all BCC subtypes^(139, 155). In another study, specialists had higher IERs, probably due to managing more difficult-to-treat BCCs⁽¹⁵⁷⁾. In another one, higher IERs were reported for residents in training⁽¹⁶²⁾.

Our study as well as research in the field generally suggest that using traditional SE for aggressive BCCs on the face and scalp results in suboptimal IERs. Therefore, due to its precision and tissue-sparing properties, MMS should be considered a more appropriate treatment for aggressive BCCs in cosmetically and functionally critical areas, particularly the face and scalp.

In our study, a partial biopsy before surgery did not impact the IERs. Studies contradicting as well as confirming these findings have been reported in the literature^(116, 167). We showed that 38.5% of preoperative biopsies did not match postoperative findings and 92.2% of these mismatches involved upgrading from type II to more aggressive type III BCCs. Previous research has also documented inconsistencies between preoperative and postoperative pathology reports, with discrepancies observed in 20-62% of cases⁽¹⁰⁷⁻¹⁰⁹⁾. Relying solely on preoperative partial biopsies for BCC subtype classification and treatment planning may lead to suboptimal surgical approaches, potentially compromising patient outcomes.

Higher IERs were, as expected, seen for circular and punch excisions. Due to this it may be inadvisable to immediately cover the resulting defects with a graft before confirming a complete excision. Furthermore, flap reconstructions should be particularly avoided following circular excisions for aggressive BCCs without histopathological confirmation of free margins.

These findings highlight the challenges in completely excising high-risk BCC subtypes, especially in cosmetically sensitive facial regions with traditional SE. Careful preoperative assessment and appropriate surgical technique is necessary to optimize outcomes and minimize incomplete excisions.

Paper II

Regarding the number of MMS stages, P-BCCs required significantly fewer than R-BCCs, but significant differences were not observed when comparing P-BCCs to IE-BCCs. Comparable reports demonstrating this can be found in the literature^(132, 160, 171). A prior study by our research group found that P-BCCs required 0.2 fewer stages than R-BCCs, although IE-BCCs were not considered as a separate group in that analysis⁽¹³²⁾. Leibovitch *et al.* and Santos-Arroyo *et al.* demonstrated that fewer MMS stages (0.23 and 0.61 less, respectively) were needed for P-BCCs than for R-BCCs^(160, 171). In our study, the disparity in the number of MMS stages was relatively minor, with an average difference of 0.22 stages per procedure. However, this seemingly small difference suggests that if MMS had been the initial treatment for R-BCCs, it could potentially eliminate one surgical stage for every five cases.

Both Leibovitch *et al.* and Santos-Arroyo *et al.* as well as our study demonstrate a substantial difference in defect sizes between P-BCCs and R-BCCs, with P-BCCs being more likely to result in

smaller defects^(160, 171). In a previous study by our group, the median defect area following MMS for P-BCC was 1.03 cm² smaller than for R-BCCs⁽¹³²⁾. The consistent findings across studies suggest that R-BCCs generally require more extensive excisions compared to P-BCCs potentially leading to larger surgical defects and more complex reconstructions.

Regarding reconstruction, primary closure was utilized most, while flaps and grafts were used more infrequently. We observed a trend where P-BCC defects were more often suited for primary closure compared to R-BCC defects. Closing a surgical wound with a primary closure is widely regarded as a straightforward, quick, and dependable technique with less complications⁽¹⁷²⁻¹⁷⁴⁾. Although no studies have directly demonstrated it, primary closures are also considered to be less time-consuming. Therefore, more frequent use of primary closures thanks to more frequent use of MMS as first-line treatment for P-BCCs when indicated could potentially save time and reduce postoperative complications.

Analyzing the difference between pre-MMS lesion size and final defect size, we saw an average difference of 13.4 mm for R-BCCs and 12.0 mm for IE-BCCs implying that average clinical margins of around 6.7 mm and 6.0 mm, respectively, are needed. These findings suggest that the standard 5-mm clinical margins often used for high-risk R-BCCs and IE-BCCs in SE are frequently insufficient. This would explain the high IERs observed when using SE for these tumor types^(137, 138, 162).

There are many challenges in optimal BCC management. Misidentification of high-risk BCCs across medical specialties, knowledge gaps regarding MMS indications and benefits as well as long waiting times for MMS leads to suboptimal treatment choices. We have also seen that unreliable preoperative biopsies can misguide treatment decisions^(109, 175, 176). To improve this, we need to enhance

preoperative diagnostic techniques, improving diagnostic accuracy through dermoscopy and clearer indications for when and how to perform preoperative biopsies to improve treatment decision. Also, broader education on MMS indications across medical specialties will hopefully lead to referrals of P-BCCs rather than previously treated tumors.

Sweden and many other Nordic countries have historically viewed MMS as a last resort, limiting its adoption. However, our department's shift to prioritizing MMS for P-BCCs has yielded significant improvements compared with the previously studied time between 1993-2003⁽¹³²⁾.

- MMS for P-BCC increased from 56% to 70.1% of all surgeries.
- The number of daily MMS procedures doubled since fewer stages were required.
- Average stages per tumor decreased from 2.4 to 1.9
- Median defect size reduced from 3.9 cm² to 2.7 cm²
- Primary closures increased from 16.2% to 51.0%

R-BCCs have been shown to be a risk factor for needing ≥ 4 stages of MMS more frequently⁽¹⁷⁷⁾. Recurrence rates after MMS are also higher for R-BCCs reducing its effectiveness^(133, 159, 160, 178). These results demonstrate that embracing MMS as a primary treatment when indicated rather than a rescue method when less effective methods have failed enhances patient outcomes.

Paper III

This retrospective analysis of facial BCCs explored the clinical and dermoscopic characteristics that can predict histopathological subtypes. The study found moderate agreement among observers and highlighted the importance of combining clinical features with dermoscopy for accurate diagnosis. A 'bumpy' topography and poorly defined tumor borders, *i.e.*, clinical features, were notably two of the criteria most strongly linked to high-risk BCCs. This underscores the importance of considering both clinical and dermoscopic features in the assessment of BCCs, particularly when attempting to predict the histopathological subtype and associated risk level.

High-risk BCCs have been characterized as having a more complex surface topography, described as a plaque with areas that may be depressed, raised, and/or resemble scars^(38, 74, 75, 179). Previous research has shown that 71.4-100% of sBCCs exhibit flat surface topography, 75.0-92.5% of nBCCs show an 'elevated'/'infiltrated' or nodular surface topography, and 53.7-100% of high-risk BCCs have either a flat or 'elevated'/'infiltrated' surface topography⁽¹⁸⁰⁻¹⁸³⁾.

Our study revealed that nBCCs were characterized by well-defined clinical and dermoscopic borders, a finding consistent with several earlier publications. For instance, Conforti *et al.* noted it in 77.8% of nBCCs⁽¹⁸⁴⁾. Our results show that ill-defined clinical and/or dermoscopic borders are linked to high-risk BCCs. This partially aligns with seen in Conforti *et al.*'s observations of sclerodermiform BCCs observed to have ill-defined edges in 82.5% of cases compared to 30.5% of sBCCs⁽¹⁸⁴⁾. On the contrary in our study, both in high-risk BCCs and sBCCs ill-defined borders were seen. A recent study by Kamimura *et al.* demonstrated high consistency in border assessment among medical professionals. They reported an 86% interobserver agreement when evaluating whether the clinical borders of BCCs were well-defined or ill-defined.

In 39% of the high-risk BCCs in our study we found the presence of white porcelain areas. This aligns with recent research, where white porcelain areas were described in 30.4% of >100 high-risk BCCs, including micronodular and morpheaform subtypes⁽¹⁸⁵⁾. This percentage is slightly lower than our findings but still indicates a significant presence of this feature in high-risk BCCs. In a related study, pink-white areas' (analogous to white porcelain areas) were observed in 84.5% of sclerodermiform BCCs⁽¹⁸⁴⁾. The higher prevalence in that study may be attributed to its focus on sclerodermiform BCCs, a particularly aggressive subtype.

Vessel morphology in BCCs is complex due to the large number of different terms used. In our study as well as in others, focused or arborizing vessels have been shown to be more common in high-risk BCCs as well as in nBCCs (75-86% and 50-76% respectively) than in sBCCs (7-21%). Conversely, unfocused vessels (also called 'short fine telangiectasias') were only seen in 3-18% of nBCCs, 20-46% of high-risk BCCs but in 60-75% of sBCCs^(74, 183, 186). Conforti *et al.* used a different classification for vessel morphology but found that only 2.1% of 95 sBCCs exhibited 'classical' arborizing vessels⁽¹⁸⁴⁾. This differentiation between vessel types is crucial for accurately diagnosing and categorizing BCC subtypes.

Lesions that show raised topography and well-defined borders are likely to be diagnosed as a nBCC. Though only identified in 27.5%, we identified 'vessels within ulceration' as a novel sign that could serve as a key clue in identifying BCCs with high-risk histopathological subtypes despite a raised surface topography or having well-defined tumor borders for example.

sBCCs were associated with the presence of ≥ 4 erosions, although this was a relatively rare finding occurring in only 7% of the cases. Previous studies have reported 'multiple small erosions' in 38.6-47.1% of sBCCs^(181-183, 186).

Additionally, the presence of any blue pigment was linked to nBCCs, with this feature observed in 17% of such tumors. Other researches, included patients from, among others, Spain, Italy, USA, Germany, the Netherlands, and Austria have identified blue-gray ovoid nests in 27-55%, of nBCCs, compared to 9-21% of sBCCs and 5-21% of high-risk BCCs^(182, 183, 186). Our cohort as well as in Ahnlides *et al.* study was from the Swedish fair-skinned population which may explain the difference.

Understanding the degree of interobserver agreement is crucial for enhancing the core teaching methodologies used to identify high-risk facial BCCs⁽¹⁸⁷⁾. In our study, the overall interobserver agreement for clinical and dermoscopic findings ranged from fair to substantial. For comparison, Di Meo *et al.*'s study using four observers assessing small BCCs reported κ -values between 0.27 and 0.55⁽¹⁸⁸⁾. Similarly, Peris *et al.*'s study with five observers assessing pigmented BCCs found κ -values between 0.26 and 0.85⁽¹⁸⁹⁾.

When it comes to predicting the histopathological subtype of BCCs, our study demonstrated a higher level of interobserver agreement compared to some previous research. We observed a κ -value of 0.53, which indicates moderate agreement among observers. In contrast, Nedved *et al.* reported lower interobserver agreement ($\kappa=0.30$) when six observers participated⁽⁵⁴⁾. Popadic *et al.* reported a lower κ -value for iBCCs (0.13) than for sBCCs, (0.85) and nBCCs (0.62) in a study involving two observers⁽¹¹²⁾. These findings highlight the variability in agreement levels across different BCC subtypes and underscore the challenges in consistently predicting histopathological subtypes based on clinical and dermoscopic features.

Prior to commencing the study, a consensus meeting was conducted. The potential advantages with a consensus meeting are the standardization of the definitions of the assessed features,

which may improve data quality and an increased interobserver agreement. A consensus meeting could also allow for education and skill alignment as well as identification of ambiguities so that they could be addressed during the meeting and reduce the need for clarification or revisions later. The disadvantages with a consensus meeting include the time consumption, the logistical challenge due to varying time zones and reduced observer independence. Furthermore, in clinical practice, it is the individual dermatologist and not a consensus among multiple readers that determines the diagnostic process and management decision.

Finally, we developed a diagnostic algorithm aimed at identifying high-risk subtypes of BCCs. This algorithm demonstrated promising results, achieving relatively high levels of both sensitivity and specificity. We observed a significant increase in sensitivity when dermoscopic features were incorporated alongside clinical topography assessment and despite the increase in sensitivity, the algorithm maintained a relatively high level of specificity. During the algorithm's development, we employed an innovative "inverse approach" strategy to exclude (rather than identify) superficial and nodular subtypes, even when the surface topography suggested their presence. These findings suggest that integrating multiple significant clinical and dermoscopic features can improve the preoperative prediction of high-risk BCC subtypes, which is crucial for guiding the need for a preoperative biopsy and optimizing surgical planning. The proposed diagnostic algorithm shows promise as a tool to identify facial BCCs that may warrant further evaluation and perhaps the need for MMS.

Paper IV

Based on our understanding, this pilot study represents the first attempt to integrate MMS with *in vivo* HI for preoperative delineation of the lateral margins of high-risk facial BCCs. Using a CNN with pixel-wise classification, the model achieved relatively high sensitivity and specificity in detecting subclinical lateral tumor extensions.

Several non-invasive imaging techniques are available for assessing the lateral margins of BCCs, including dermoscopy, RCM, OCT, and LC-OCT. Among these, dermoscopy is the most widely used in clinical practice for detecting lateral BCC margins. However, its effectiveness in reducing the number of excision stages during MMS remains debated, with limited evidence supporting its accuracy^(60, 61). Yeom *et al.* suggest that dermoscopic evaluation can help reduce the final number of MMS stages and defect size, particularly in BCC patients⁽⁷⁷⁾. However, the diagnostic accuracy of dermoscopy is highly user-dependent⁽⁶⁶⁾.

In contrast, preoperative use of RCM and OCT has shown promise in minimizing the number of excision stages required during MMS for BCCs⁽⁶⁰⁾. These advanced imaging techniques, along with LC-OCT, may provide more precise margin delineation compared to dermoscopy, potentially improving surgical outcomes and efficiency.

Paradise *et al.* demonstrated considerably lower numbers of MMS stages and lowered likelihood of patients undergoing more than one MMS stage by preoperatively mapping BCC tumor margins with LC-OCT⁽⁹⁰⁾. Similarly, Micheli *et al.* demonstrated an overall sensitivity of 100% and a specificity of 96.3% on margin evaluation⁽⁹¹⁾. On the other hand, a study by Adan *et al.* reported a sensitivity of 63.0% and a specificity of 53% for assessing BCC resection margins

with OCT before MMS⁽⁸⁸⁾. Comparatively, Venturini *et al.* found that RCM detected subclinical extensions in only 3 of 10 cases in contrast to margins evaluated dermoscopically before excision⁽⁷⁸⁾. Another study reported a sensitivity of 37.5% and a specificity of 95.2% for primary lateral margin detection using RCM⁽¹⁹⁰⁾.

HI offers key advantages for preoperative margin assessment, including a large field of view, rapid image acquisition, and greater imaging depth. It can capture up to 12 cm² in 5–10 seconds, whereas RCM covers only 1 cm² in 2 minutes⁽¹⁹¹⁾ and OCT scans 0.36 cm² in 40 seconds⁽⁸⁴⁾. HI provides an imaging depth of ~2 mm, surpassing RCM (200 μm)⁽⁶⁰⁾ and LC-OCT (500 μm⁽⁸⁹⁾), while OCT ranges from 0.2–2.5 mm.⁽⁸⁴⁾ LC-OCT enables real-time imaging in multiple mode⁽⁸⁹⁾ while ultrasound techniques offer deeper scanning (3.8–15 mm), making them more suitable for tumor depth assessment^(61, 192).

In this study's cohort, dermoscopy frequently led to incorrect detection of lateral margins. Similar findings have been reported in studies on incomplete excisions, where lateral margins were the most affected, followed by deep and both margins^(137, 139, 154-157, 193). However, most previous studies did not specify margin involvement by BCC subtype. This highlights the need for continued development of non-invasive imaging techniques to improve the accuracy of lateral tumor extension detection, particularly for high-risk BCCs.

This study demonstrates that HI is effective in detecting BCC lateral borders with relatively high sensitivity, specificity and overall accuracy. However, limitations include a small sample size and the use of the same dataset for CNN training and classification. To overcome this last limitation, a pixelwise approach was chosen. Moreover, the study was not designed to assess deep margins and the use for HI for this task needs further development. Additionally, lesions on highly

irregular surfaces were excluded due to technical challenges. This has previously posed a problem with HI and has led to exclusions, so further adjustments are warranted⁽¹⁹⁴⁾.

Despite these limitations, HI shows potential in reducing MMS stages by accurately defining lateral margins preoperatively and may help minimize re-excisions in conventional surgery when MMS is unavailable.

Conclusions

Based on the studies included in this thesis the following conclusions can be drawn:

- The results indicate that a large proportion of high-risk facial BCCs become incompletely excised using traditional SE. For high-risk BCCs, the tumor's histopathological subtype and anatomic location are more important risk factors for incomplete SE than factors like resection margins, tumor size or surgeon experience.
- Starting with MMS as the primary treatment for Glas type II-III BCCs leads to fewer stages and smaller final defects. By using MMS more often for P-BCCs when indicated instead of limiting its use to being a rescue option for IE-BCCs and R-BCCs, we can improve the utilization of our resources as well as reduce patient suffering.
- Accurate assessment of facial BCCs requires a comprehensive approach that combines both clinical and dermoscopic evaluations. This integrated method enhances subtype prediction and helps determine when a preoperative biopsy is warranted. Our newly developed algorithm for clinical and dermoscopic findings has shown promising results in identifying high-risk BCC cases, but needs to be validated in a prospective setting.
- Using HI for tumor demarcation in high-risk BCCs demonstrated relatively high sensitivity, specificity, and overall accuracy. These findings provide a foundation for future research.

Future perspectives

My doctoral project has made me even more confident in believing that MMS is an underutilized method for high-risk facial BCCs in Sweden. I therefore hope to be able to continue with research and convince decision-makers that more resources should be allocated for this treatment, enabling better resource utilization and less suffering for the patients.

Study I in this project contributed to changing our indications for MMS, from the beginning only including highly aggressive facial BCCs (type III according to the Swedish classification) to even include infiltrative (type II) BCCs in sensitive anatomical areas of the face. I believe this is important to avoid unnecessary incomplete excisions, which we have observed occur frequently with these tumors.

An aspect that always comes up when discussing MMS is the cost. It is a more resource-intensive and expensive method compared to SE, which leads to short-term thinking rather than considering the long-term benefits of receiving correct treatment immediately, even if it involves higher initial costs. Studies have shown that incompletely excised BCCs or recurrent BCCs can be associated with increased healthcare costs and poorer outcomes for patients^(195, 196), especially when multiple surgeries are required, and MMS is ultimately used as a “rescue technique” when conventional SE or other methods have failed. A study by Seidler et al. included BCCs and SCCs in evaluating MMS and SE in terms of effects and costs. The authors concluded that MMS was more cost-effective and associated with a gained QALY⁽¹⁹⁷⁾.

However, the literature is lacking relating to cost-effectiveness of MMS compared to traditional SE. MMS can save costs compared to SE according to a few studies, while other studies show the opposite^(141, 195, 198). These differences may depend on the healthcare context. Many of the cost-effectiveness studies conducted have evaluated the real cost of MMS with a potential cost for SE without assumptions about recurrence or incomplete excisions, which may lead to an underestimation of the total cost for SE⁽¹⁴¹⁾.

There is currently a lack of studies examining actual healthcare utilization and costs associated with each surgical method for the treatment of primary facial BCC, both nationally and internationally. Taking into account that skin cancer has one of the fastest-growing incidence rates, demands need to be placed on effective treatment to reduce both patient suffering and societal impact. To utilize limited healthcare resources as efficiently as possible, it is desirable to provide the right treatment to the right patient from the start. This can help fill knowledge gaps, reduce suffering for the patient group, and improve the efficient use of healthcare resources.

To investigate this, I have started with a retrospective registry study that can examine healthcare consumption and cost data in detail for each treatment method and enable a longer time perspective. The main purpose of this upcoming retrospective registry study is to map, study, and compare resource utilization and associated costs within healthcare for the patient group with high-risk BCCs where MMS could have been relevant as a primary treatment method, of which only a proportion of patients underwent this procedure.

Regarding study III and testing the algorithm on consecutive cases will help assess its performance in a real-world clinical setting, gather new data rather than relying solely on retrospective data. By testing the algorithm across different centers, we can evaluate its generalizability and robustness across varied clinical settings and

patient populations. This future work will be crucial in confirming the algorithm's clinical utility and potentially refining it for broader application in diagnosing high-risk BCC subtypes.

Another study I hope to conduct is a qualitative investigation using patient-reported outcome measures (PROMs) to assess patients' perceptions of their illness and treatment. This project is similar to one being implemented by colleagues in the Netherlands. Given our long waiting times for MMS and the fact that many patients have undergone inappropriate traditional SE before reaching us, it would be valuable to conduct such a qualitative study in our specific setting. This research could provide insights into patient experiences and potentially inform improvements in our care delivery process.

Mentioned in press



"Låt oss få göra rätt behandling direkt"
Sahlgrenska, 26 april 2021



Digitalt stöd kan hitta allvarlig hudcancer
GU, 2 juli 2024



Fler med högrisk-basalcellscancer i ansiktet bör erbjudas Mohs kirurgi
Läkartidningen, 24 mars 2022



Komplex kirurgi kan vara enklaste lösning vid basalcellscancer
Läkartidningen, 12 april 2021



Här är nya algoritmen som upptäcker hudcancer lättare
SVT, 8 juli 2024



Kliniska och dermatoskopiska fynd för att förutsäga högrisk BCC
Onkologi i Sverige, 10 sept 2024



Forskaren varnar för vanliga cancerformen – som går att bota
GP



Dr Hannah Ceder och Dr Eva Backman besöker Hudläkarpodden
Hudläkarpodden, 11 juli 2023

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