# The knife cuts one way

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## non-invasive diagnosis and surgical treatment of basal cell carcinoma

Eva van Loo

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# THE KNIFE CUTS ONE WAY:

## NON-INVASIVE DIAGNOSIS AND SURGICAL TREATMENT OF BASAL CELL CARCINOMA

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**Promotores**
Prof. dr. P.M. Steijlen (Universiteit Maastricht/Maastricht UMC+)
Prof. dr. K. Mosterd (Universiteit Maastricht/Maastricht UMC+)

**Copromotor**
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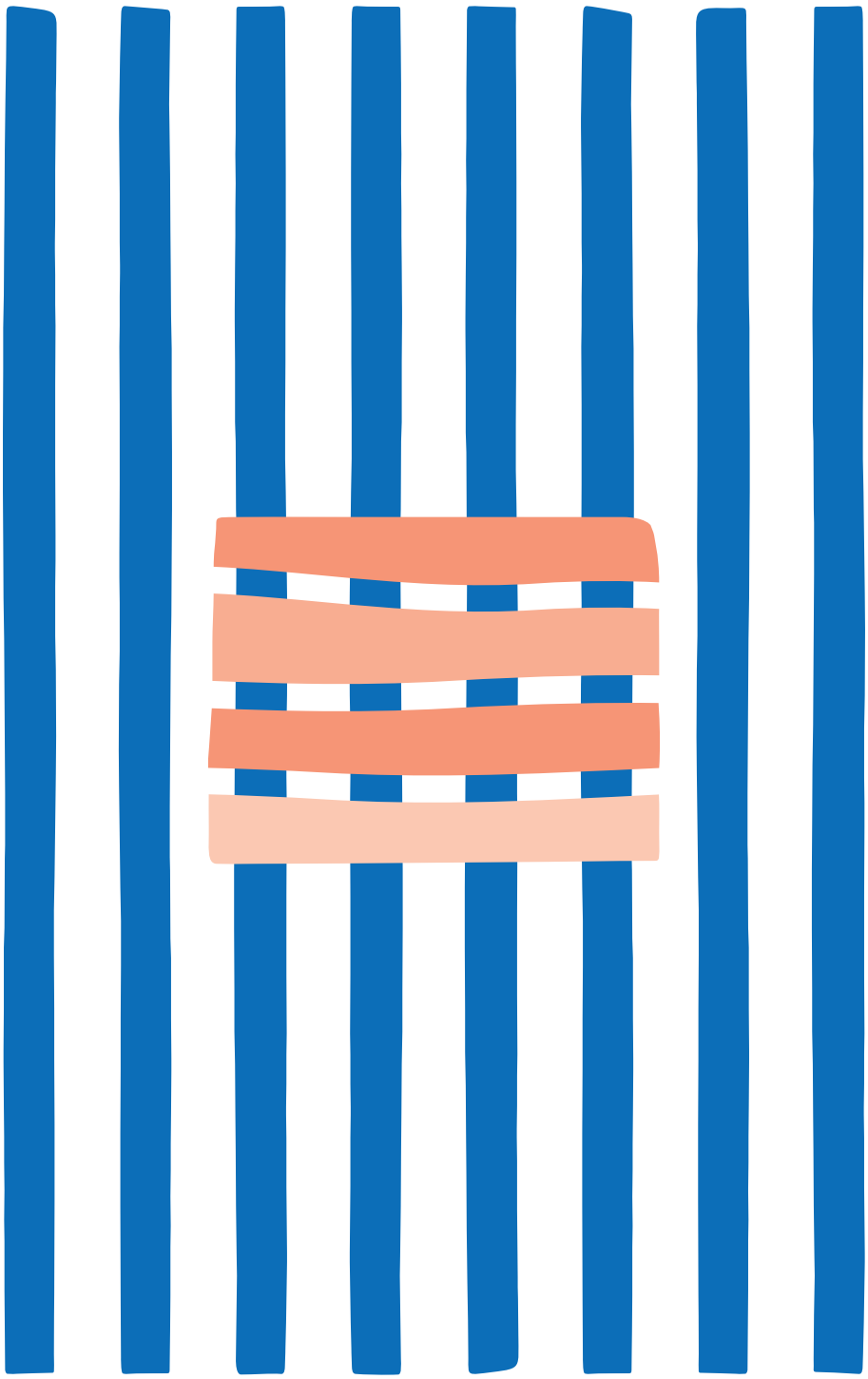

# GENERAL INTRODUCTION

# Introduction

If the world-wide skin cancer epidemic was to be a movie, it would be a blockbuster with basal cell carcinoma (BCC) starring in the lead role. With almost six million new cases worldwide yearly and 48 000 per year in the Netherlands, BCC is the most common cancer among Caucasians, exceeding the incidence of breast cancer, lung cancer, colorectal cancer and prostate cancer combined.[1,2] The lifetime risk of developing a BCC in the Netherlands is 1 in 5 for men and 1 in 6 for women.[3] Incidence of BCC has risen by 2-5% annually in Europe and the US over the last decades and is still rising.[4,5] Furthermore, after a first diagnosis of BCC, a patient has a 1 in 3 risk of developing one or more subsequent BCCs.[6] Due to the massive prevalence numbers, diagnosing, treating and follow-up of BCC poses a great burden to health care costs and has a significant societal impact.[7-9] Globally, the percentage of total disability-adjusted life-years due to keratinocyte carcinomas increased from 0.03% in 1990 to 0.05% in 2017.[2] In the Netherlands, disability-adjusted life-years increased by 107% between 1989 to 2008 due to a first BCC.[7]

Besides its consequences for society, BCC diagnosis and treatment also greatly influences the individual patient. Being diagnosed with skin cancer frequently causes emotional distress in patients.[10] Several studies have demonstrated that the diagnosis of a non-melanoma skin cancer negatively impacts quality of life, especially before treatment has taken place.[11-13] The waiting time from the biopsy till the final diagnosis can be stressful and the biopsy can be complicated by an infection or bleeding.[14] The treatment itself can also cause morbidity such as disfiguring scarring, pain, bleeding and complications such as wound infections. Anxiety levels among patients that undergo dermatologic procedures are significantly higher than in patients seeking general regular dermatologic care.[15] A BCC rarely metastasizes or causes mortality but can lead to significant morbidity. Worries about the appearance of the surgical scar are common and interfere with the patient's social life.[16,17] The fact that BCCs are mostly located in cosmetically and functionally sensitive areas such as the head and neck area may add to these concerns.

The burden of BCC diagnosis and treatment on societal as well as patient level, together with its ever-rising incidence, stresses why it is of paramount importance to diagnose and treat BCC in an effective, efficient and patient-friendly way. This was the starting point of the research presented in this thesis.

## Aetiology

Skin cancer can be roughly divided in melanocytic and non-melanocytic skin cancer. Melanocytic skin cancer comprises melanoma. Of the non-melanocytic skin cancers, keratinocyte neoplasms are most common and consist of squamous cell carcinoma and basal cell carcinoma. BCC arises from epidermal cells, though different hypotheses exist on its precise cell of origin. Most research has suggested that BCC arise from follicular stem cells [18,19], but in other studies evidence was observed for the origin of BCC from interfollicular and infundibular stem cells and progenitor cells.[20,21]

Risk factors for developing BCC are UV-exposure, a fair skin type, age, use of immunosuppressive medication, genetic predisposition and a history of burn wounds or radiation. It is more common in men than in women.[3] UV-exposure is the most important risk factor and has shown to cause genomic mutations in keratinocytes leading to uninhibited cell proliferation.[22] On molecular level, the Hedgehog signalling pathway is recognized as the main pathway involved in BCC development. In basal cell nevus syndrome, a genetic condition in which BCCs develop from an early age on, mutations in the PTCH gene of the Hedgehog pathway, located on chromosome 9q22.3, are the most common cause.[23] A 'two-hit' mechanism is involved. Patients with basal cell nevus syndrome have a germline mutation in one of their two copies of the responsible gene (typically the PTCH tumour suppressor gene). In order for carcinogenesis to occur, a second somatic mutation (second 'hit') is necessary, e.g. by means of UV-radiation, causing loss of function of their other copy of the PTCH-gene. In sporadic BCC, 70-75% are estimated to have a mutation in the PTCH gene as well, while 10-20% carry activating mutations of SMO.[22,23] PTCH and SMO are both transmembrane proteins. The oncogene SMO is normally inhibited by the tumour suppressor gene PTCH. In case of loss of inhibition, due to a loss-of-function mutation of PTCH or an activating SMO mutation, the Hedgehog signalling pathway is in a constant active state, leading to transcription of genes stimulating cell proliferation, ultimately leading to the development of BCC in the skin.[24]

## Diagnosing basal cell carcinoma

*Clinical features*

BCC presents as a slow growing, translucent or pearly skin coloured or erythematous papule, nodule or patch, often with ulceration, mostly located on sun exposed body sites such as the head and neck area (Figure 1.1: A1-D1). Typical dermoscopic features for BCC include arborizing blood vessels, shiny white streaks and, in pigmented BCC,

spoke wheel-like pigment or ovoid globules/nests. Clinical differential diagnosis mostly includes other (pre)malignancies such as actinic keratosis, morbus Bowen, squamous cell carcinoma, adnexal tumours, clear cell acanthoma, (amelanotic) melanoma, but also benign tumours such as dermal nevi, sebaceous hyperplasia, and in the case of superficial BCC, inflammatory skin disorders such as eczema or psoriasis.

*Histopathology*

The gold standard for diagnosing BCC is histopathology and in case of clinical suspicion of BCC a biopsy is taken to confirm the diagnosis in common practice.[25] In selected cases a dermatologist can refrain from a biopsy, for example in case of an obvious clinical diagnosis in a patient with a history of BCCs and a tumour on a low-risk location that will be treated surgically.[25] In the Netherlands, 63-90% of BCCs are diagnosed by biopsy.[6,26] Besides confirming BCC diagnosis, histopathological analysis can also identify the tumour's histopathological growth pattern. This is an important factor in determining the most appropriate treatment, which will be discussed later.

Under the microscope, BCC has a basaloid appearance with peripheral nuclear palisading. Tumour nests are surrounded by a variable fibromyxoid stroma which retracts around the tumour, forming clefts, one of the characteristic microscopic features of BCC.[27]

Different histopathological growth patterns of BCC can be distinguished (Figure 1.1: A2-D2):

- *Superficial:* In superficial BCC, or BCC in situ, tumour nests are contained within or stay in contact with the epidermis. Clinically, it typically presents as an erythematous patch with scaling and/or ulceration. This type of BCC is the least aggressive subtype and comprises 20-30% of all BCC.[28,29]
- *Nodular:* In nodular BCC, tumour nests grow in relatively large, sharply demarcated solid nodules located in the dermis. Clinically it presents as a well-defined papule or nodule. This is the most common subtype as it comprises 40-60% of all BCCs.[28, 29]
- *Infiltrating:* This type of BCC contains small strands of tumour cells invading in a sclerotic stroma. Delineation with healthy tissue can be vague, histopathologically as well as clinically. Other terms used are 'morpheaform' and sclerosing'. Clinically this type of BCC can resemble a scar. Infiltrating BCC is considered an aggressive type of BCC as it often invades surrounding tissue more extensively and deeper, often sub-clinically.

- *Micronodular:* In this type of BCC, tumour nests are rounded, but much smaller than in nodular BCC and the tumour nests are not grouped. This is also considered an aggressive type of BCC.

Apart from histological growth patterns, BCC can also show various types of differentiation such as cystic, adnexal or squamous differentiation. The latter shows features of eosinophilic keratinizing tumour cells, but predominantly basaloid features or cell markers typical for BCC. This is also an aggressive subtype of BCC along with infiltrating and micronodular BCC.[30] Around 15-30% of all BCC are of an aggressive histologic subtype.[28,29] Mixed pathological subtypes are common, occurring in 74% of cases.[31]

*Non-invasive diagnostic techniques*

Although most dermatologists would probably deem themselves capable of diagnosing a BCC clinically, literature on this matter is more ambiguous. In a Cochrane review on diagnostic accuracy of clinical diagnosis of keratinocyte skin tumours, the observed sensitivity greatly varied between studies and ranged from 20-100%, increasing with a higher prevalence of BCC in the study populations and the use of dermoscopy.[32] Subtyping abilities of clinical diagnosis are limited with an observed sensitivity of 89.0% in distinguishing superficial versus nodular and aggressive BCC and 56.3% for aggressive versus nodular BCC.[33] Cons of skin biopsies are potential complications such as bleeding or infections and patient discomfort due to pain, wound healing and a delay between the moment of biopsy and final diagnosis which might add to a patient's anxiety.[14] Also, an additional appointment is needed to discuss biopsy results and start therapy as necessary. Therefore, it is no surprise that interest for non-invasive diagnostic techniques has grown in last decades. One of these techniques that will be highlighted in this thesis is optical coherence tomography (OCT). OCT was introduced in 1991 and since then has become the standard for imaging of retinal disease in ophthalmology and has evolved for intravascular imaging in cardiology.[34,35] OCT was first described for skin imaging in 1997.[36] The physics are comparable to ultrasound, but light waves are used instead of sound waves. It relies on low coherence interferometry to measure backscattering of light (optical beams) in tissue in vivo. The OCT device emits a light beam towards the tissue and the resulting light reflections interfere with a reference beam, which creates an interference signal.[35] This signal is transduced to create a grey-scaled image of a transection of the skin. One commercially available OCT system used in the studies presented in this thesis is the VivoSight® OCT scanner of Michelsons Diagnostics Ltd, which uses multiple beam technology (Figure 1.2).[37] It is a mobile device consisting of a class 1 eye-safe laser (centre wavelength 1305 nm), a handheld

probe and a screen. The camera on the probe aids in precisely locating the skin area to be scanned. A scan takes about 15-30 seconds and the image directly appears on the device's screen. An area of 6x6 mm can be scanned in one take. Vertical and horizontal images can be constructed. The vertical images provide a cross section of the skin, comparable with vertical histopathology slides, only in black and white. The scanning depth is about 1-2 mm and the resolution is <10 µm.[37] Figure 1.1 shows examples of clinical, OCT and histological images of BCCs.

Another non-invasive optical imaging technique used for diagnosing skin cancer is reflective confocal microscopy (RCM). It also relies on a low-power laser (wavelength 830 nm) and can obtain a high lateral resolution of around 1 µm by only allowing light reflection from a desired focal point in the skin.[38] This allows the generation of high-resolution, grey-scaled images comparable with high magnification in histology. The imaging depth is limited to about 200 µm (epidermis and papillary dermis). It is available in a larger device with a wide probe and in a handheld device with a view of 1x1 mm.[38] There are several advantages of OCT over RCM which led us to focus on OCT research at our centre, with the ultimate goal to test its use in expediency studies. RCM creates horizontal images in bird view, which makes it difficult to interpret the images and requires a long learning curve. In contrast, OCT generates images in the vertical plane which resemble histological slides that dermatologists are already familiar with. Diagnostic criteria for BCC on OCT were already defined and also showed high similarities with histopathology (Figure 1.1: A2-D2 and A3-D3).[39] Taking this into account, a relatively short learning curve was expected for recognizing BCC on OCT. For RCM, no generalized criteria were available at the time in regular care to facilitate its interpretation. Also, the higher scanning depth of OCT is more suitable than RCM for the imaging of dermally located pathologies such as BCC, as the average depth of a nodular BCC is around 1300 µm.[40,41] Furthermore, the high frequency of BCC diagnosis in daily practice facilitates the conduction of high-powered trials for which large numbers of cases are required.

A newer technique is line-field confocal optical coherence tomography (LC-OCT), which combines the technical advantages of RCM and OCT. LC-OCT was not available yet for skin imaging at the time the research presented in this thesis was conducted, but has promising prospects with a penetration depth higher than RCM (around 500 µm, which is still lower than OCT) and a resolution higher than OCT (around 1 µm).[42]

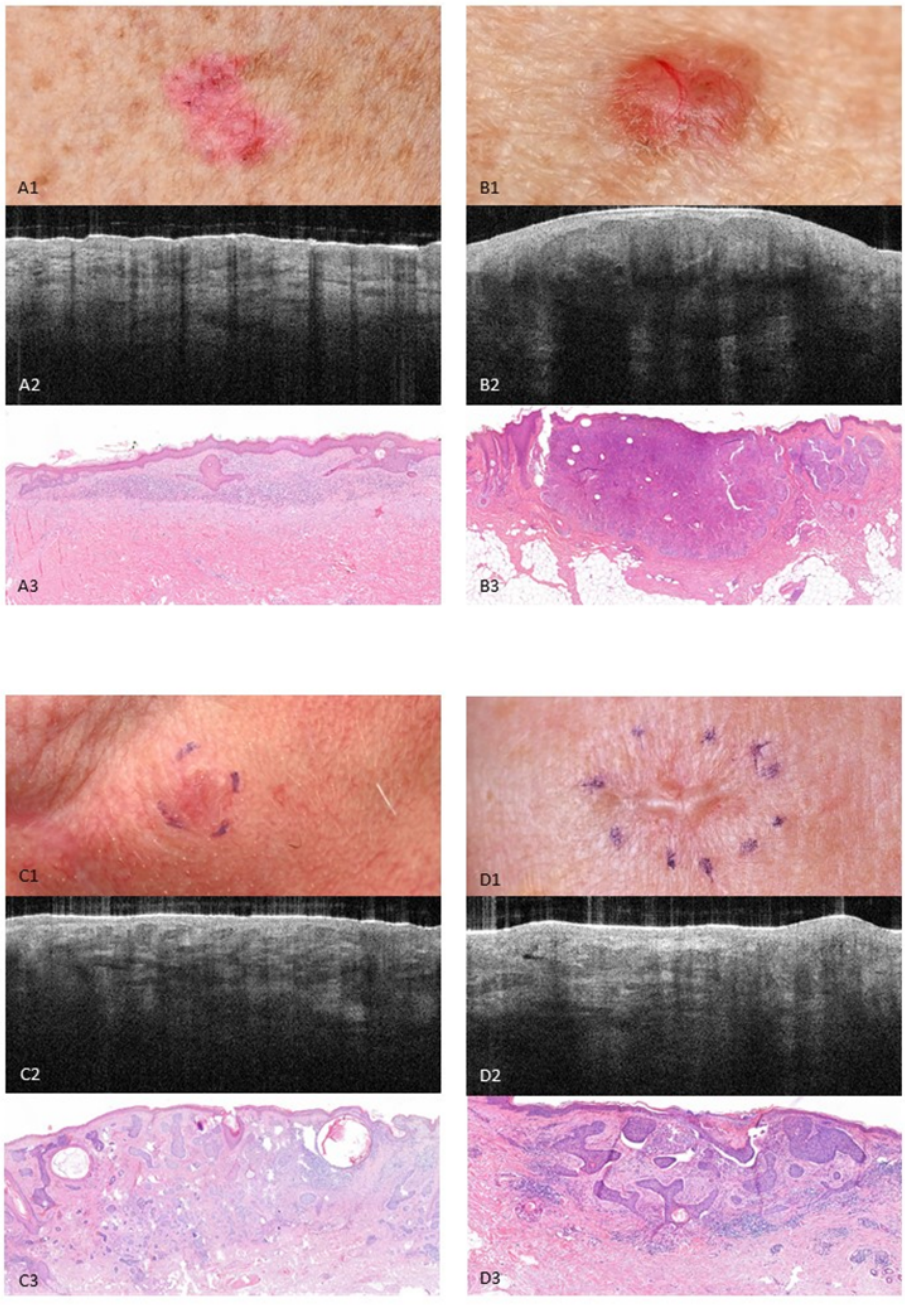


**Figure 1.1**: Clinical (1), OCT (2) and histopathological (3) presentation of a superficial (A), nodular (B), micronodular (C) and infiltrative (D) basal cell carcinoma.

**Figure 1.2**: VivoSight OCT system (left) and the performance of an OCT scan on a patient's lesion in clinical practice (right).

## Classification of BCC

BCCs can be classified in low-risk or high-risk tumours according to their biological behaviour, i.e. their risk of subclinical tumour spread and risk of recurrence after treatment. This classification serves as the foundation for choosing the most appropriate treatment for a BCC. Several tumour-related clinical and histological factors are used in this classification.

*Previous treatment*

A cohort of 2016 BCC demonstrated that previously treated BCC showed a higher degree of subclinical tumour spread that primary BCC, requiring a margin for complete removal of nearly twice that for primary BCC.[43] In another large cohort of 5755 BCC, primary lesions treated by curettage-electrodessication, surgical excision or X-ray therapy were shown to have a 5-year recurrence risk of 10.6%, compared to 15.4% in previously treated BCCs.[44]

*Anatomic location*

BCC is mostly located on sun exposed body sites such as the head and neck.[44] BCC located in the head and neck area have a higher risk of recurrence after treatment with surgical excision compared to BCC located on other body sites, as shown in a cohort of 588 BCC in which the 5-year recurrence risk was 0.7% compared to 6.6%, respectively.[45] A special site in the central face is called the H-zone and is comprised of the nose, peri-oral and peri-orbital areas, temples and the ears. The H-zone overlaps with sites of embryological fusion planes. BCCs are more likely to occur in an embryonic fusion plane than in other mid-face regions which suggests a possible embryologic role in the pathogenesis of BCC.[46] Also, BCC in these areas show higher rates of incomplete excision and recurrence and invade more deeply, possibly due to loose collagen tissue in the fusion planes.[46-48] Infiltrating BCC occurs more frequent in the H-zone than on other body sites.[43]

*Histological subtype*

Subclinical tumour spread is more common in infiltrating BCC than in nodular or superficial BCC.[43] In addition, BCC with an aggressive histologic subtype poses a higher risk of recurrence after treatment.[49,50]

*Tumour size*

Tumours larger than 2 cm in diameter have a significantly higher risk of subclinical tumour spread than smaller tumours.[43]

In the Dutch guideline BCC are subdivided in low-risk and high-risk tumours, as shown in Table 1.1.

**Table 1.1**: Classification of basal cell carcinoma in high-risk and low-risk tumours.[25]

| Characteristic | Low-risk | High-risk |
|---|---|---|
| **Previous treatment** | Primary tumour | Recurrence after previous treatment |
| **Histological subtype** | Non-aggressive (superficial, nodular) | Aggressive (micronodular, infiltrating) |
| **Size** | <2 cm | >2 cm |
| **Anatomical location** | Trunk | H-zone |

## Treatment of BCC

A wide variety of therapies for BCC are available, ranging from non-invasive treatment to surgery and from treatment at home to treatment in a hospital setting. Some

treatments can be initiated by the general practitioner (first line) while other require guidance of a dermatologist or other medical specialist in the hospital (Table 1.2). Which treatment is the most appropriate depends on tumour characteristics as well as patient related factors and availability.

**Table 1.2**: First line and second line treatments for BCC.

| |
|---|
| **First line treatments for BCC** |
| Conventional surgical excision |
| 5-Fluoro-uracil cream |
| Imiquimod cream |
| **Second line therapies for BCC** |
| Mohs surgery |
| Photodynamic therapy |
| Radiotherapy |
| Systemic treatment |

## Non-invasive treatments

Non-invasive therapies used today are imiquimod, 5-fluorouracil and photodynamic therapy.

*Imiquimod*

Imiquimod is an immune response modifier which triggers a local immune reaction when applied cutaneously. Dendritic cells are the primary responsive cells and a tumour-directed cellular immune response follows.[51] The biologic effect of imiquimod primarily comes about through an agonistic activity on TLR-7 and TLR-8.[52] In the signalling cascade that follows, activation of nuclear-factor kappa B leads to transcription of inflammatory mediators such as cytokines including interferon-alpha and gamma, TNF alpha, and interleukins.[51] It is probable that imiquimod's anti-tumour activity comes about via the generated immune response and by inducing apoptosis (via CD95 receptor) in BCC.[53,54] Imiquimod is approved for the treatment of superficial BCCs in immunocompetent adults, applied five times per week during six consecutive weeks.[55] Side effects include local skin reactions on the application site (but occasionally extending beyond) such as erythema, scaling, erosion and oedema. Also, systemic reactions may occur such as flu-like symptoms and malaise.[53] Imiquimod proved to be superior to photodynamic therapy and 5-fluorouracil cream in a randomised controlled trial in terms of efficacy in the treatment of superficial BCC, with a 5-year cure rate of 80.5%.[56]

*5-Fluorouracil*

5-Fluorouracil is an antimetabolite and interacts with DNA synthesis by inhibition of the enzyme thymidylate synthase.[57,58] This results in reduction of DNA synthesis and cell proliferation and the induction of cell death. It especially targets fast dividing cells.[57] It is approved for treatment of superficial BCCs and is applied in a 5% cream twice daily for four weeks.[55] Treatment leads to local skin reactions such as erythema, vesicles, erosion, ulceration and necrosis.[57,58] Its 5-year probability of recurrence free survival is 70%.[56]

*Photodynamic therapy*

In photodynamic therapy (PDT), a light source is combined with a photosensitizer and oxygen to generate a photochemical reaction in the skin. A photosensitizer is a chromophore that transfers energy and induces a local reaction after exposure to light of specific wavelengths. In PDT, a cream is applied to the skin as photosensitizer. Most commonly used are 5-aminolevulinic acid (5-ALA) and methyl aminolevulinate (MAL) - containing creams. 5-ALA and MAL are both natural compounds in the heme biosynthetic pathway of human cells. These prodrugs are converted in the skin to protoporphyrin IX and after external application of ALA or MAL to the skin, intercellular accumulation of protoporphyrin IX occurs, which can generate singlet oxygen after activation by light of the appropriate wavelength. Due to a high cellular metabolism and local factors such as enhanced perfusion, accumulation of the photosensitizer occurs in higher concentrations within tumour cells compared to normal tissue. The singlet oxygen reacts with various cellular components and causes tumour destruction via direct cellular damage, vascular shutdown and induction of an immune response.[59] In clinical practice, the photosensitising 5-ALA or MAL cream is applied to the skin and illumination is performed at the outpatient clinic after three hours by a LED light source with a wavelength of 570-670 nm. The procedure is then repeated after one week. Side effects include local redness, erosion, crust formation and a burning pain sensation during illumination.[60] PDT is mainly used for superficial BCC in the Netherlands, though the European guideline also mentions it as an option for thin nodular BCC.[25,55] Its 5-year probability of recurrence-free survival for superficial BCC is 63-76.5%.[56,61] Trials including superficial and nodular BCC observed 3-year recurrence-free survival rates of 81.1% and even 95.5% after curettage and 2-3 PDT-sessions.[62,63]

## Invasive therapies for BCC

The most common invasive therapies for BCC are surgical excision and Mohs surgery, which are also the focus of this thesis and will be discussed further below. Alternative

invasive treatments such as curettage and electrodessication and cryosurgery are applied far less frequently in the Netherlands, have inferior results and are only recommended for small, low-risk BCC.[30] These will not be further discussed.

*Conventional surgical excision*

The gold standard treatment of all subtypes of BCC is surgical excision due to the ability of histological margin control and high efficacy.[60] This procedure is usually performed under local anaesthesia. For primary nodular or superficial BCC smaller than 2 cm in diameter, the Dutch guideline advises a surgical margin of 3 mm of surrounding healthy-looking tissue to account for subclinical tumour growth and ensure complete resection.[25] For recurrent BCC or BCC of an aggressive histological subtype, a margin of 5 mm is recommended.[25] Surgical excision is usually performed in an elliptical shape, with an incision perpendicular to the skin surface, and the excision specimen is sent for histopathological assessment to check if the margins are clear. In conventional histological assessment, vertical slides are taken from the centre of the specimen as well as from the pointy ends.[64] With this 'bread loaf' technique, less than 0.5% of the total excision margin surface is checked for residual BCC and small tumour strands extending into the margin may be missed (Figure 1.3).[65] The most common adverse events and complications of surgical treatment are scar formation, bleeding, wound infections, wound dehiscence and pain.[14,66-68] Pain experience during dermatologic surgery will be further explored in this thesis.

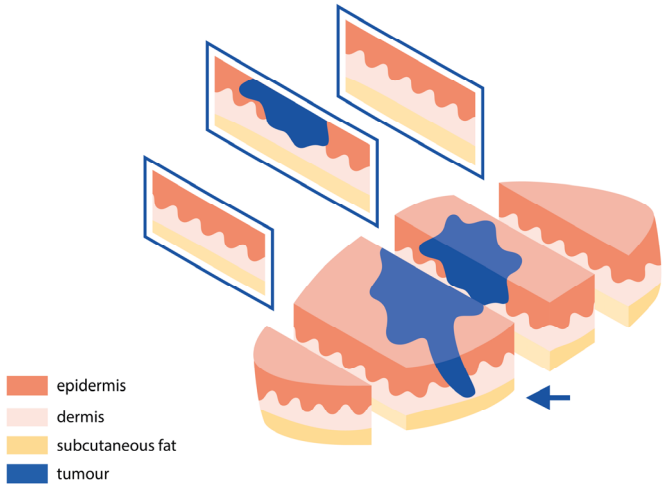


**Figure 1.3**: Bread loaf technique in histological assessment of an elliptical skin excision. Extension of tumour beyond the surgical margins may be missed (arrow).

*Mohs micrographic surgery*

Mohs micrographic surgery (MMS) is a specialized technique first described by the American surgeon Dr. Frederic Mohs as 'chemosurgery' in 1941.[69] His original method involved applying zinc chloride to the tissue in situ, which fixed the tissue and allowed for horizontal tumour removal. Furthermore, he introduced tissue mapping: drawing a map on paper and on the tissue in order to precisely locate any areas of residual tumour in the skin. His technique has two major advantages over conventional surgery and the histopathological bread loaf technique: 100% of the excision margin can be evaluated microscopically and, in case residual tumour is seen, a re-excision can be performed specifically only in the area where residual tumour is located. This is especially advantageous in functional and cosmetic sensitive areas such as peri-ocular, the nose, around the lips and ears. His technique was refined in the following years. Nowadays, it is performed under local anaesthesia and the tissue is not fixed in vivo anymore. The tissue is not shaved off horizontally but excised under a 45-degree angle. The round, fresh excision specimen is then divided into quarts and each piece is flattened and mounted in a cryostat. Then horizontal frozen sections are made and examined microscopically, which still allows for 100% of the resection margins to be examined (Figure 1.4). The use of frozen sections means that rapid histological assessment is possible and a reconstruction of the defect can be performed on the same day, which is another major advantage over the conventional histopathological evaluation of paraffin-embedded slides. The combination of microscopic control and graphical tissue mapping in this technique has led to the current name 'micrographic surgery'. MMS should theoretically lead to fewer recurrences with maximal sparing of surrounding healthy tissue.[70] Complications are comparable to regular surgical treatment, but patients experience higher anxiety levels and may consider the waiting time between treatment rounds as a disadvantage.[15,66,71]

Treatment efficacy of conventional excision and Mohs surgery will be further discussed in this thesis.

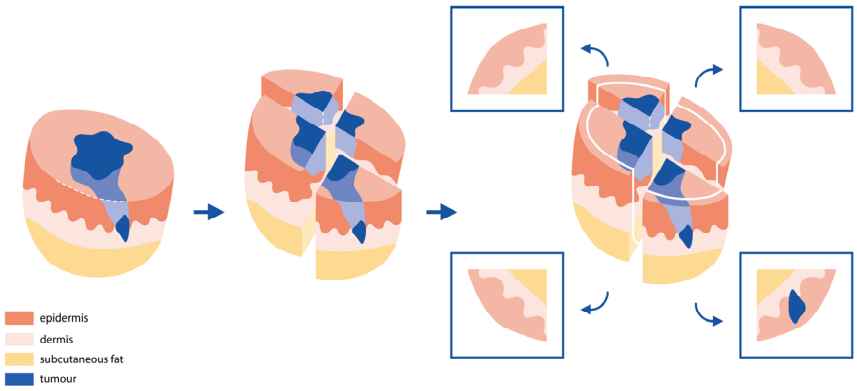


**Figure 1.4**: Histological assessment in Mohs micrographic surgery. 100% Of the excision margin can be evaluated. The blue mass on the bottom right histological slide represents residual tumour.

## Other non-surgical treatments

Other non-surgical treatments are radiotherapy and systemic treatment.

*Radiotherapy*

Radiotherapy is reserved for more complex cases of BCC in which curative surgery is not possible or for patients that refuse surgery. The general principle of radiotherapy is destruction of malignant cells by delivering energy in the form of ionizing radiation. The damage to cellular DNA causes cellular death. Healthy tissue is also affected by the radiation, but malignant cells are more sensitive to its effects because they lack the molecular mechanisms needed for detection and repairing DNA damage that are present in healthy tissue. Many different modalities are available, such as external beam radiation therapy with photons or electrons, or proton therapy. BCC is a radiosensitive tumour and radiotherapy results in 2-year cure rates of over 93% and 4-year cure rates of over 86%.[72,73] Radiotherapy has the advantage over surgery of maintaining contours (e.g. of the nose or ear) but development of dyspigmentations and telangiectasia in the years post treatment deteriorates cosmetic results on the long term.[72,74] Other long-term complications include alopecia, fibrosis, atrophy, dry eyes and soft tissue or bone necrosis.[73] Acute radiation effects include erythema, crust formation, erosion and desquamation.

*Systemic therapies*

Oral hedgehog pathway inhibitors, including vismodegib and sonidegib, are registered for locally advanced BCC that are not eligible for conventional therapy with surgery or radiotherapy. Vismodegib is also registered for the treatment of metastasized BCC. The indication for oral hedghehog inhibitors should be determined multidisciplinary.[25] Overall response rates and adverse events between vismodegib and sonidegib seem comparable, but comparative studies are not yet available.[75-77] In patients with locally advanced BCC, the overall response rate following vismodegib treatment is 60-66% after six months.[78-80] The median duration of response is about 10 months and many patients experience adverse events such as alopecia, muscle cramps, fatigue, ageusia and weight loss.[78-80] Vismodegib can induce radio-sensitization of the BCC and aggravates radiation-induced DNA damage.[81] In advanced cases, combination therapy of vismodegib and radiation can therefore be considered.

## Aims and outline of this thesis

The continuing increase in the prevalence of BCC poses a great burden on health care. Even more so, on an individual level, diagnosis and treatment of BCC has an impact on the patient. The aim of this thesis was to help in optimizing the diagnostic and therapeutic process in terms of efficacy, efficiency and patient-friendliness.

This thesis aimed to answer the following questions:

- Is OCT a reliable technique for diagnosing and subtyping BCC? (chapter 2.1)
- What is the learning curve for novel OCT assessors for diagnosing BCC? (chapter 2.2)
- How can we optimize OCT image quality? (chapter 2.3)
- What is the most optimal surgical margin of conventional excision for high-risk and low-risk BCC? (chapter 3)
- Is Mohs surgery superior in terms of efficacy to conventional excision for certain high-risk BCC after long-term follow-up? (chapter 4)
- Which patients experience high pain scores during surgery? (chapter 5)

This thesis is dived in two parts. Part one focuses on BCC diagnosis using non-invasive optical coherence tomography. This is a relatively new technique for which a learning curve in diagnosing BCC was not yet described. In **chapter 2.1**, we present the results of a prospective study on the diagnostic value of OCT in diagnosing and subtyping BCC. We also illustrate how cumulative sum charts can be used to determine how many optical coherence tomography scans novice assessors should evaluate in order to

obtain competence in diagnosing basal cell carcinoma (**chapter 2.2**). **Chapter 2.3** contains the results of a prospective study on optimizing the evaluability of OCT images by applying glycerol to the skin surface.

Part two of this thesis is focused on the surgical treatment of BCC. In **chapter 3.1**, the results of a retrospective single centre study on excision margins of BCC are presented. **Chapter 3.2** contains the results of a systematic review of excision margins of BCC.

**Chapter 4** is focused on Mohs surgery of BCC and describes the results of a 10-year follow-up study of a randomized controlled trial comparing Mohs surgery with conventional excision for high-risk BCC in the head and neck area.

**Chapter 5** considers patient experience around dermatologic surgery and describes the results of a prospective trial on experienced pain during dermatologic surgery.

**Chapter 6** contains a discussion of all study results and implications for future practice.

**Chapter 7** contains a summary of the thesis and **chapter 8** the impact paragraph.

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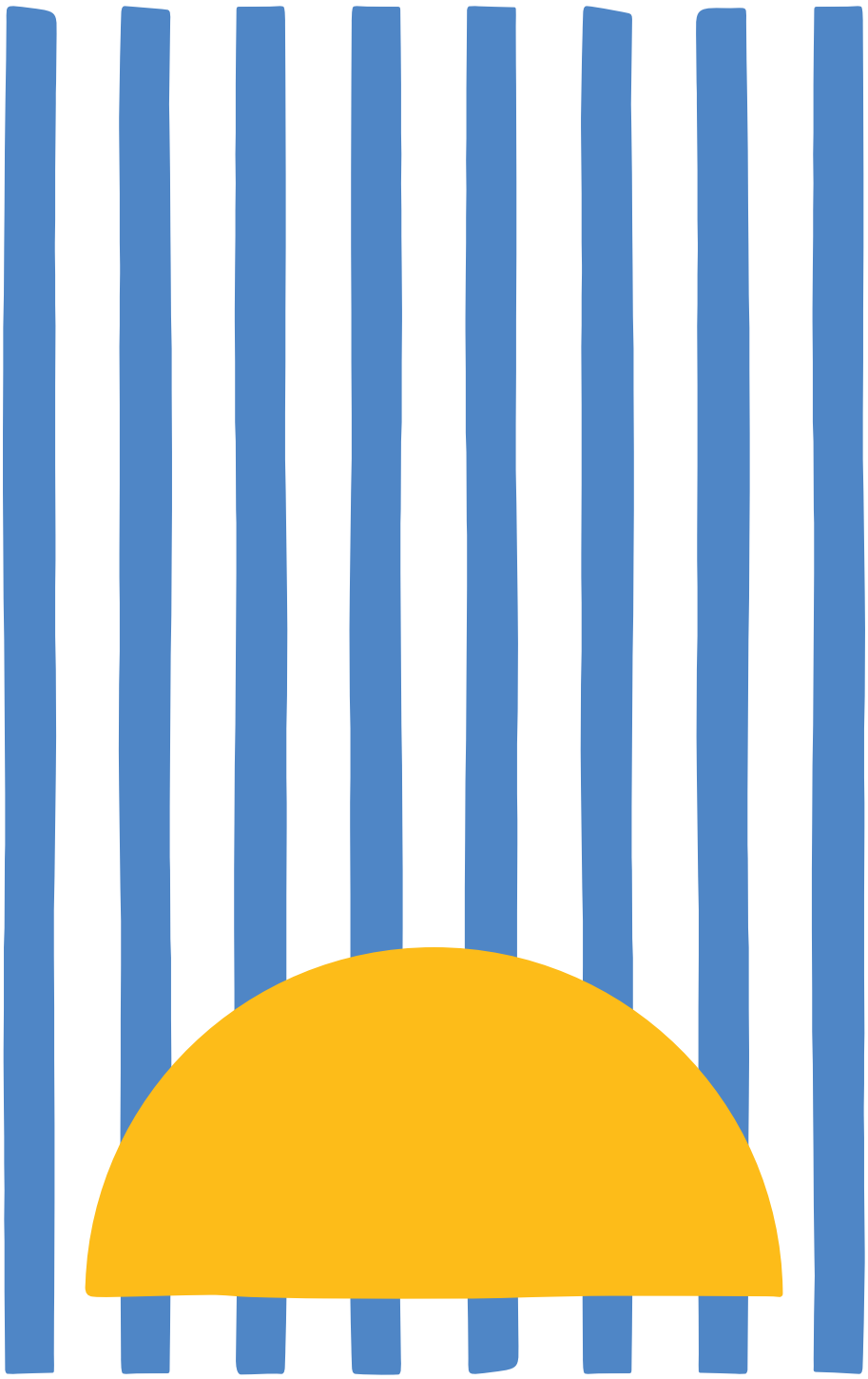
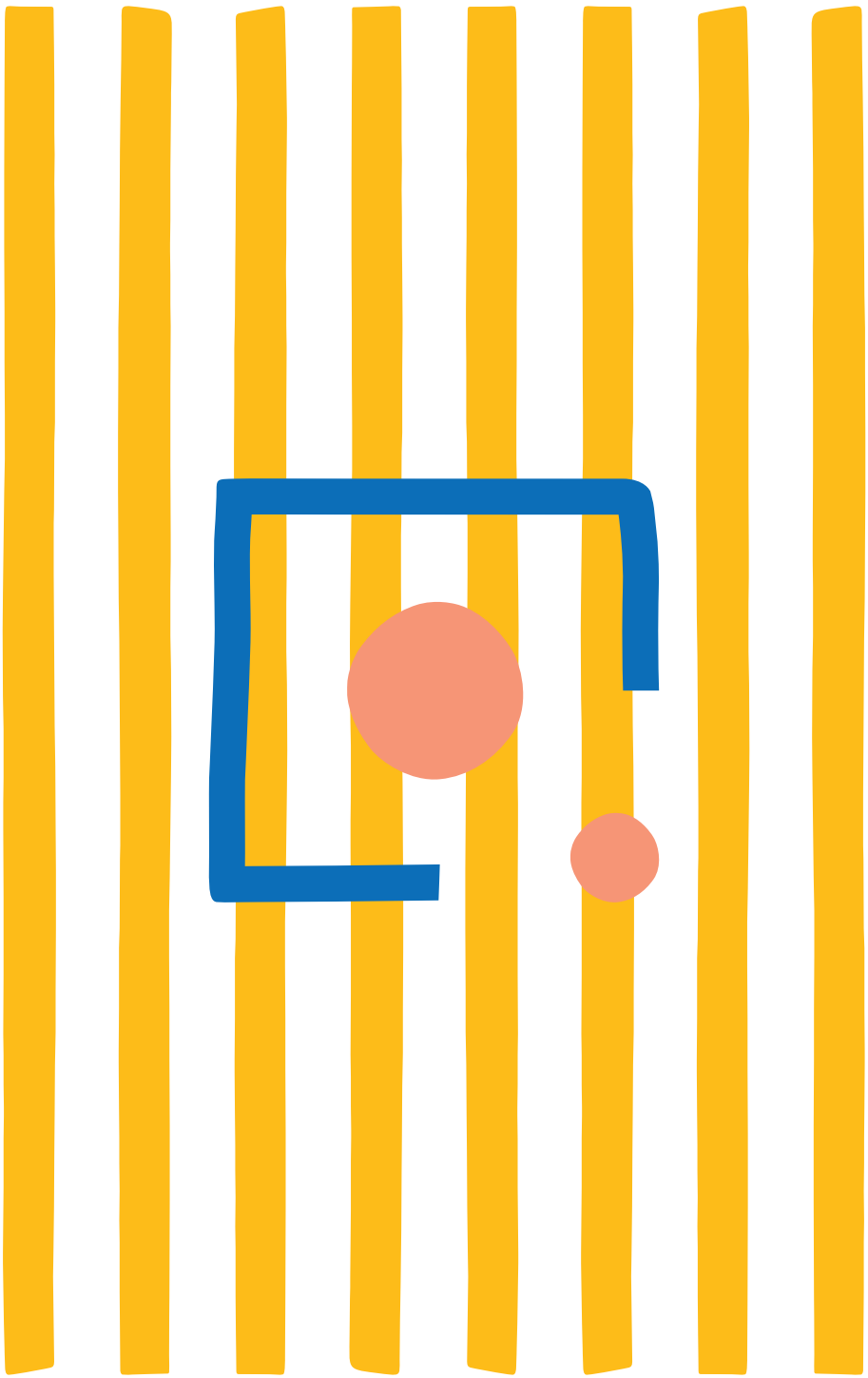


# PART ONE

## Non-invasive diagnosis of basal cell carcinoma with optical coherence tomography



# CHAPTER 2.1

## Optical coherence tomography for non-invasive diagnosis and subtyping of basal cell carcinoma, a prospective cohort study

Kelly A.E. Sinx[1] · Eva van Loo[1] · Erwin H.J. Tonk · Nicole W.J. Kelleners-Smeets · Veronique J.L. Winnepenninckx · Patty J. Nelemans[2] · Klara Mosterd[2]

[1] Authors contributed equally to this work

[2] Authors share senior authorship

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# Abstract

Non-invasive diagnostic strategies such as optical coherence tomography (OCT) enable detailed examination of skin tissue architecture and have potential for identification and subtyping of basal cell carcinoma (BCC). To evaluate the additional diagnostic value of OCT, a prospective cohort study was performed in 182 patient with 250 lesions suspected for non-melanoma skin (pre)malignancies requiring a biopsy. Accuracy of BCC diagnosis and subtype based on clinical examination (CE) of patients was compared with that on the basis of OCT scans in conjunction with clinical images of lesions (cOCT). Confidence levels were recorded on a 5-point scale, where score 0 indicated absence of BCC and scores 1-4 indicated increasing suspicion of BCC. Diagnostic performance parameters were compared using histopathological diagnosis as gold standard.

The patient-based area under the receiver operating characteristic curve (AUC) increased from 85.6% for CE to 91.2% for cOCT ($p$=0.061) and the lesion-based AUC from 82.7% to 91.3% ($p$<0.001). When confidence scores 1-4 were defined as positive, patient-based specificity increased from 47.5% (CE alone) to 76.8% (cOCT) at similar sensitivity (97.6% and 95.2%, respectively). cOCT slightly improved the ability to discriminate between superficial and non-superficial BCC subtypes and seemed to be a valuable addition to CE alone in the diagnosis and subtyping of BCC.

# Introduction

Skin cancer incidence is rising worldwide. The most common type of skin cancer is basal cell carcinoma (BCC). The general population has a lifetime risk of 16-20% to develop a BCC.[1] A punch biopsy is required to discriminate BCC from alternative diagnoses and to determine the histopathological subtype.[2,3] Knowledge of the histopathological subtype is especially relevant in determining the optimal treatment. In case of superficial BCC, treatment with a topical therapy may be prescribed. In non-superficial BCCs information of the subtype helps to determine the width of resection margins or to set an indication for Mohs micrographic surgery. A punch biopsy is an invasive procedure that may be painful and carries a small risk of complications such as bleeding, scarring and infection. Moreover, awaiting histological assessment (approximately 1 week), causes treatment delay and can be stressful for patients. With the high volume of BCCs and potential drawbacks of invasive diagnostics, interest in non-invasive diagnostic methods is increasing. Optical coherence tomography (OCT) is an imaging technique that generates real-time in vivo cross-section images of tissue microarchitecture with a depth of 1.5-2 mm.[4] OCT is based on light interferometry; the interference of two optical beams reflected by the tissue produces distinguishable shades in the black and white spectrum. Morphologic characteristics of BCC that may be distinguished on OCT images have been established in recent years.[5] Small studies coordinated by the OCT producers with selected patient populations have reported promising results with the use of OCT in diagnosing BCC and subtyping of superficial BCC.[6-8] A recent Cochrane Diagnostic Test Accuracy review on the accuracy of OCT for diagnosis of BCC stated that the small number of studies and varying methodological quality make it impossible to guide practice.[9] This prospective cohort study was initiated to investigate the ability of OCT in conjunction with clinical images (cOCT) to discriminate between (i) BCC and other diagnoses and (ii) between superficial and non-superficial (nodular and aggressive) subtypes of BCC. An additional objective was to evaluate how often cOCT imaging enabled making a diagnosis of BCC with high confidence and how many lesions would be misclassified if the punch biopsy would have been omitted in these cases.

| Differential diagnosis: |
| --- |
| Level of confidence<br>○ 0. This is not a BCC<br>○ 1. Suspicion of BCC is low, I would biopsy to exclude BCC<br>○ 2. Suspicion of BCC is high, but I still consider other diagnosis<br>○ 3. Surely BCC, but I want a biopsy to determine the BCC subsype<br>○ 4. Surely BCC and sure about the BCC subtype, I would omit the biopsy and start treatment |
| If BCC is suspected, which subtype?<br>○ 1. Nodular<br>○ 2. Superficial<br>○ 3. Aggressive<br>○ 4. Not applicable |

**Figure 2.1.1**: Classification of diagnosis according to level of confidence in BCC diagnosis and BCC subtype.
BCC: basal cell carcinoma.

## Methods and materials

A prospective cohort study was conducted at the Dermatology outpatient clinic of the Maastricht University Medical Center, Maastricht, The Netherlands. Adult patients (18 years or older) receiving a skin biopsy of a lesion clinically suspected for a non-melanoma skin cancer or premalignancy were included in this study. Patients who were incompetent to sign informed consent were excluded.

Clinical examination (CE) consisted of macroscopic/visual examination and dermoscopic evaluation (Heine Delta 20T) by the treating physicians. The level of confidence in the diagnosis was documented using a 5-point Likert-scale ranging from 0 to 4 by the treating physician (Figure 2.1.1). If there was any suspicion of BCC on the basis of clinical characteristics (such as shiny border, telangiectasia, ulceration) and dermoscopic findings (such as telangiectasia or ovoid nests), the most likely BCC subtype (superficial, nodular or aggressive) was recorded by the physician. The physician marked the biopsy area of the clinically most aggressive part and a photograph was taken by a medical photographer (Nikon D750). A dermoscopic image was only taken if indicated by the physician. In the same patient consultation, the marked biopsy area was scanned with OCT without any preparations of the skin in advance (Vivosight Multi-beam Swept-Source Frequency Domain OCT, Michelson Diagnostics, Maidstone, Kent, United Kingdom; specifications: class 1 eye safe, resolution <7.5 µm lateral, <5 µm axial, depth of focus = 1.0 mm, scan area = 6 x 6 mm).

During the same consultation and following the OCT scan, a 3-mm punch biopsy was taken according to regular care. The histopathologic outcome served as the gold standard and was diagnosed by independent specialized dermato-pathologist with over 10 years of experience, blinded to the OCT images. BCC subtypes were classified as either superficial, nodular or aggressive BCC. In case of mixed subtypes, the most aggressive subtype was used for analysis.

OCT images were coded and saved anonymously. These OCT images in conjunction with clinical photographs (cOCT) were assessed by two researchers who had received training and had previous experience with OCT. Diagnosis was based on criteria for OCT assessment, as previously described by Hussain et al..[4] The two researchers documented the level of confidence in the ultimate diagnosis that was reached by consensus using the 5-point Likert-scale. When BCC was suspected, BCC subtype was also recorded (Figure 2.1.1). The assessors were blinded for the results of histopathologic examination. This study was approved by the local independent Ethics Committee. All patients provided written informed consent.

## Statistical analysis

This study was based on data from 182 patients with a total of 250 lesions. The data were part of a dataset of 400 lesions in 289 consecutive patients between February 2017 and May 2017. The first 150 lesions were used for training purposes. Before this study, it was assumed that the prevalence of BCC in our study population of patients suspected for non-melanoma skin cancer or pre-malignancy was about 45% (based on retrospective unpublished data of our department). The goal was to evaluate whether the use of cOCT will result in an increase in specificity when compared with CE alone at similar sensitivity. On the basis of the literature, sensitivity and specificity of CE were estimated at 95% and 45%, respectively.[7,8] Thus, 100 patients without BCC (55% of 182) were expected to be available for evaluation of specificity. This number enables detection of an increase of specificity by 20% or more (from 45% to 65%) with a power of 80% (two-sided alpha=5%).

The primary analysis was performed on the level of patients, where only one lesion per patient was included to ensure independence of observations. A secondary analysis was performed on the level of lesions. The diagnostic performance of CE alone and OCT images in cOCT was expressed by sensitivity, specificity, positive predictive value,

negative predictive value, and the area under the receiver operating characteristic curve (AUC) with corresponding 95% confidence intervals.

Receiver operating characteristic curves were constructed, where each point on the receiver operating characteristic curve represented a sensitivity and specificity pair corresponding to different thresholds for a positive test result. Receiver operating characteristic curves visualized the trade-off between sensitivity and specificity and the AUC was used as a measure of global diagnostic performance.[10]

With respect to the ability of cOCT to distinguish between BCC subtypes, we focused on the ability to discriminate between superficial BCC and nodular and/or aggressive BCC. This distinction was relevant to decide whether excision was required or not. For BCC subtyping, sensitivity was defined as the proportion of patients with histologically verified non-superficial BCC (requiring excision) that were detected. Specificity was defined as the proportion of patients with histologically verified superficial BCC (not requiring excision) that were identified as superficial BCC.

Differences in diagnostic performance parameters between CE alone and cOCT were tested for statistical significance using the McNemar test for paired proportions. For the paired comparison between the AUC of CE and cOCT, an algorithm developed by Delong et al. was used.[11]

SPSS (version 23) and STATA (version 13.1, StataCorp LLC, College Station, TX) were used for statistical analyses. Two-sided *p*-values of 5% were considered to indicate statistical significance.

### Data availability statement

Datasets related to this article can be found at https://dataverse.nl/dataset.xhtml?persistentId=hdl:10411/XOULRC, hosted at Datahubmaastricht (OCT in BCC diagnosis).

## Results

A total of 182 patients with 250 lesions clinically suspicious for non-melanoma skin cancer or premalignancy were included in this study. All lesions were scanned by OCT and histopathologically verified by either punch biopsy or excision biopsy. If patients

had multiple lesions, the first scanned lesion was selected for the analysis on patient level. The patient-based analysis therefore consisted of 182 lesions of which 83 were BCCs and 99 were non-BCCs, corresponding with a BCC prevalence of 45.4%. Of those 83 BCCs, 26 (31.3%) were superficial BCCs, 36 (43.4%) nodular BCCs and 21 (25.3%) aggressive BCCs. Patient and lesion characteristics are summarized in Table 2.1.1.

**Table 2.1.1**: Baseline characteristics of the patient-based and lesion-based analyses.

| Characteristic | Patient-based | Lesion-based |
|---|---|---|
| **Mean age (SD)** | 66.8 (13.0) | 67.4 (13.5) |
| **Sex, n (%)** | | |
| Male | 93 (51.1) | |
| Female | 83 (45.6) | |
| **Localization, n (%)** | | |
| Head/neck | 96 (52.7) | 123 (49.2) |
| Trunk | 51 (18.0) | 72 (28.8) |
| Extremities | 35 (19.2) | 55 (22.0) |
| **Number of lesions (%)** | | |
| 1 | 134 (73.7) | |
| 2 | 37 (20.3) | |
| 3 | 7 (3.8) | |
| 4 | 2 (1.1) | |
| 6 | 2 (1.1) | |
| **Histological diagnosis, n (%)** | | |
| BCC | 83 (45.6) | 116 (46.4) |
| No BCC | 99 (54.4) | 134 (53.6) |
| **BCC subtypes, n (%)** | | |
| Superficial BCC | 26 (31.3) | 34 (29.3) |
| Nodular BCC | 36 (43.4) | 56 (48.3) |
| Aggressive BCC | 21 (25.3) | 26 (22.4) |
| **Other diagnoses (non-BCC), n (%)** | | |
| Benign* | 48 (48.4) | 62 (46.3) |
| SCC | 19 (19.2) | 23 (17.2) |
| AK | 17 (17.2) | 24 (17.9) |
| Bowen's disease | 13 (13.1) | 23 (17.2) |
| Atypical fibroxanthoma | 1 (1.0) | 1 (0.7) |
| CD30 proliferation | 1 (1.0) | 1 (0.7) |

* Including: sebaceous gland hyperplasia and/or adenoma, dermatofibroma, folliculitis, dermal nevus, seborrhoic keratosis, scar, pseudolymphoma, interface dermatitis, benign lichenoid keratosis. BCC: basal cell carcinoma; SCC: squamous cell carcinoma.

## Ability to distinguish basal cell carcinoma from non-basal cell carcinoma

The AUC was 85.6% (95% confidence interval = 80.2%-89.0%) for CE alone and 91.2% (95% confidence interval=86.7%-95.8%) for cOCT improvement in diagnostic performance ($p$=0.061). (Figure 2.1.2).

The trade-off between sensitivity and specificity at different thresholds (on the basis of level of confidence) for a positive test result are shown for CE and cOCT in Table 2.1.2. When confidence scores 1-4 were considered as test positives and a confidence score of 0 as test negative, sensitivity was 97.6% for CE and 95.2% for cOCT ($p$=0.687). Specificity increased from 47.5% for CE to 76.8% for cOCT ($p$<0.001). Positive predictive values were 60.9% for CE and 77.5% for cOCT, and negative predictive values were 95.9% and 95.0%, respectively.

When only a confidence score of 4 was considered as test positive and confidence scores 0-3 as test negatives, higher specificity was observed for CE (100%) than for cOCT (93.9%) ($p$=0.0313). Sensitivity of CE (10.8%) was significantly lower than of cOCT (59.0%) ($p$<0.001). The positive predictive values increased to 100% for CE and 89.1% for cOCT, whereas negative predictive values decreased to 57.2% for CE and 73.2% for cOCT.

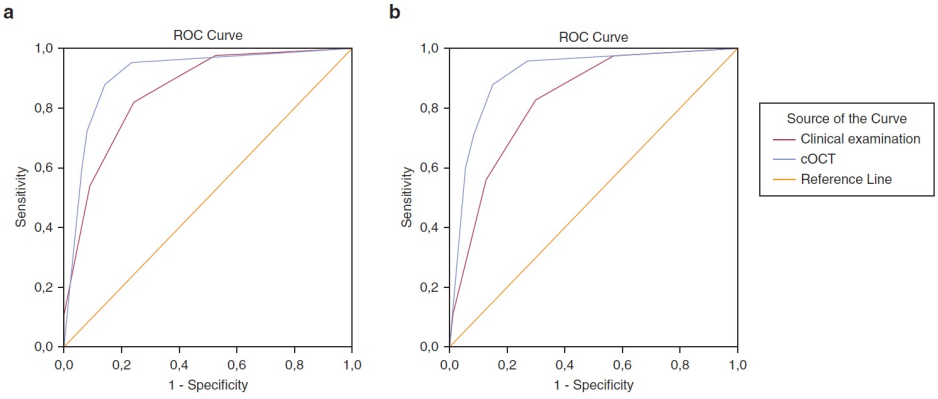


**Figure 2.1.2**: Receiver operating characteristic (ROC) curves for clinical examination and cOCT, for the patient-based analysis (a) and lesion-based analysis (b). cOCT, optical coherence tomography in conjunction with clinical images; ROC, receiver operating characteristic.

**Table 2.1.2**: Diagnostic performance of clinical examination (CE) and OCT in conjunction with clinical images (cOCT) from patient-based (182) and lesion-based (250) analyses. Sensitivity and specificity are given for various cut-off values of the confidence score.

| | Patient-based CE, % (CI) | Patient-based cOCT, % (CI) | Lesion-based CE, % (CI) | Lesion-based cOCT, % (CI) |
|---|---|---|---|---|
| **Cut-off 1234 vs 0** | | | | |
| Sensitivity | 97.6 (90.8-99.6) | 95.2 (87.5-98.4) | 97.4 (92.1-99.3) | 95.7 (89.7-98.4) |
| Specificity | 47.5 (37.4-57.7) | 76.8 (67.0-84.4) | 43.3 (34.8-52.1) | 73.1 (64.7-80.2) |
| PPV | 60.9 (52.0-69.1) | 77.5 (67.9- 84.9) | 59.8 (52.4-66.8) | 75.5 (67.6-82.1) |
| NPV | 95.9 (84.7-99.2) | 95.0 (87.0-98.4) | 95.1 (85.4-98.7) | 95.1 (88.5-98.2) |
| **Cut-off 234 vs 01** | | | | |
| Sensitivity | 81.9 (71.6-89.2) | 88.0 (78.5-93.8) | 82.8 (74.4-88.9) | 87.9 (80.3-93.0) |
| Specificity | 75.8 (65.9-83.6) | 85.9 (77.1-91.8) | 70.1 (61.5-77.6) | 85.1 (77.6-90.4) |
| PPV | 73.9 (63.5-82.3) | 83.9 (74.1-90.6) | 70.6 (62.1-77.9) | 83.6 (75.6-89.5) |
| NPV | 83.3 (73.7-90.1) | 89.5 (81.1-94.6) | 82.5 (73.9-88.7) | 89.1 (82.0-93.7) |
| **Cut-off 34 vs 012** | | | | |
| Sensitivity | 54.2 (43.0-65.1) | 72.3 (61.2-81.3) | 56.0 (4.5-65.1) | 70.7 (61.4-78.6) |
| Specificity | 90.9 (83.0-95.5) | 91.9 (84.2-96.2) | 87.3 (80.1-92.2) | 91.8 (85.4-95.6) |
| PPV | 83.3 (70.2-91.6) | 88.2 (77.6-94.4) | 79.3 (68.6-87.1) | 88.2 (79.4-93.7) |
| NPV | 70.3 (61.5-78.0) | 79.8 (71.1-86.5) | 69.6 (62.0-76.4) | 78.3 (70.9-84.3) |
| **Cut-off 4 vs 0123** | | | | |
| Sensitivity | 10.8 (5.4-20.1) | 59.0 (47.7-69.5) | 12.1 (6.9-19.7) | 58.6 (49.1-67.6) |
| Specificity | 100 (95.3-100.0) | 93.9 (86.8-97.5) | 98.5 (94.2-99.7) | 94.8 (89.1-97.7) |
| PPV | 100 (62.8-100.0) | 89.1 (77.1-95.5) | 87.5 (60.4-97.8) | 90.7 (81.1-95.8) |
| NPV | 57.2 (49.5-64.6) | 73.2 (64.5-80.5) | 56.4 (49.8-62.8) | 72.6 (65.2-78.9) |

CE, Clinical Examination; CI, confidence interval; cOCT, OCT in conjunction with clinical images; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value.

## Ability to distinguish between subtypes of basal cell carcinoma

Accurate subtyping of BCCs is important to decide whether an excision is indicated (non-superficial BCC) or whether the BCC can be treated non-invasively (superficial BCC). There were 83 histologically confirmed BCCs in the database, 57 non-superficial BCCs and 26 superficial BCCs.

Of the 83 histologically verified BCCs, CE detected 81 BCCs and cOCT identified 79 BCCs. There was overlap in 77 BCCs (54 non-superficial BCCs and 23 superficial BCCs), which were used for the paired comparison of subtyping ability of CE and cOCT (Table 2.1.3). Sensitivity to detect nodular and/or aggressive BCC was 87.0% for CE and 88.9% for

cOCT ($p$=1). Specificity to detect superficial BCC significantly increased from 47.8% with CE to 78.3% with cOCT ($p$=0.031)

**Table 2.1.3**: Ability to distinguish between superficial and non-superficial BCC of clinical examination (CE) and OCT in conjunction with clinical images (cOCT).

| | Patient-based CE | Patient-based cOCT | *p*-value (McNemar test) | Lesion-based CE | Lesion-based cOCT | *p*-value (McNemar test) |
|---|---|---|---|---|---|---|
| **All BCCs that were identified both by CE and cOCT; 54 non-sBCC and 23 sBCC** | | | | | | |
| Sensitivity | 87.0 (47/54) | 88.9 (48/54) | 1.00 | 85.9 (67/78) | 83.3 (65/78) | 0.727 |
| Specificity | 47.8 (11/23) | 78.3 (18/23) | 0.031 | 60.0 (18/30) | 80.0 (24/30) | 0.031 |
| PPV | 79.7 (47/59) | 90.6 (48/53) | 0.178 | 84.8 (67/79) | 91.5 (65/71) | 0.311 |
| NPV | 61.1 (11/18) | 75.0 (18/24) | 0.530 | 62.1 (18/29) | 64.9 (24/37) | 0.981 |
| **BCCs that were identified by cOCT with high confidence (level 4); 34 non-sBCC and 15 sBCC** | | | | | | |
| Sensitivity | 91.1 (31/34) | 94.1 (32/34) | 1.00 | 89.6 (43/48) | 85.4 (41/48) | 0.625 |
| Specificity | 53.3 (8/15) | 86.7 (13/15) | 0.063 | 65.0 (13/20) | 90.0 (18/20) | 0.063 |
| PPV | 81.6 (31/38) | 94.1 (32/34) | 0.209 | 86.0 (43/50) | 95.3 (41/43) | 0.243 |
| NPV | 72.7 (8/11) | 86.7 (13/15) | 0.691 | 72.2 (13/18) | 72.0 (18/25) | 0.743 |

BCC; basal cell carcinoma; CI, confidence interval; CE, clinical examination; cOCT, OCT in conjunction with clinical images; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; sBCC, superficial basal cell carcinoma.
Sensitivity was defined as the proportion of patients with histologically verified non-superficial BCC (requiring excision) that were detected. Specificity was defined as the proportion of patients with histologically verified superficial BCC (not requiring excision) that were identified as superficial BCC.

## Optical coherence tomography in conjunction with clinical images diagnosis of basal cell carcinoma made with high confidence (level 4)

In a clinical scenario, high confidence in the presence of BCC according to cOCT diagnosis could lead to a treatment decision without the need for verification of the histopathological diagnosis by punch biopsy. To evaluate the outcome of this potential scenario, the ability to predict BCC and subtype was evaluated within the group of cases in which BCC was diagnosed by cOCT with a confidence score of 4. Certainty about presence of BCC and subtype according to cOCT was observed in 55 of 182 patients (30%) (Table 2.1.4) According to histopathology, 49 of those 55 lesions were BCCs (positive predictive value=89.1%). The other six diagnoses were one actinic keratosis, one sebaceous gland adenoma, one Bowen's disease, two interface dermatitis, and one benign lichenoid keratosis.

According to histological subtyping, those 49 BCCs consisted of 15 superficial BCCs and 34 non-superficial BCCs. With respect to subtyping, sensitivity to detect non-superficial BCCs was 94.1% (32 of 34) for cOCT compared to 91.1% (31 of 34) for CE ($p$=1). Specificity for cOCT was 86.7% (13 of 15) and higher than that for CE at 53.3% (8 of 15) ($p$=0.063) (Table 2.1.3).

Table 2.1.4 shows that, in total, 18 BCCs were classified as superficial BCC by cOCT, but five of these lesions were misclassified. Of those, two were non-superficial BCC (nodular BCC) and three lesions turned out to be two interface dermatitis and one benign lichenoid keratosis. A total of 37 lesions were classified as non-superficial BCC by cOCT. Of those, 32 were indeed non-superficial BCC. A total of two lesions were actually superficial BCC and three lesions turned out to be one Bowen's disease, one actinic keratosis and one sebaceous gland adenoma.

**Table 2.1.4**: BCC diagnosis and subtyping by cOCT correlated to histopathologic diagnosis for patient-based (55) and lesion-based (75) based analysis diagnosed with high confidence (score 4).

| | Histopathology Patient-based | | | | Histopathology Lesion-based | | | |
|---|---|---|---|---|---|---|---|---|
| | **No BCC** | **Superficial** | **Non-superficial** | **Total** | **No BCC** | **Superficial** | **Non-superficial** | **Total** |
| **cOCT** | | | | | | | | |
| Superficial | 3 | 13 | 2 | 18 | 3 | 18 | 7 | 28 |
| Non-superficial | 3 | 2 | 32 | 37 | 4 | 2 | 41 | 47 |
| **Total** | 6 | 15 | 34 | 55 | 7 | 20 | 48 | 75 |

BCC, basal cell carcinoma; cOCT, OCT in conjunction with clinical images; OCT, optical coherence tomography.

## Lesion-based analysis

The 182 patients, who were included in this study, had a total of 250 lesions. The number of patients with one or more lesions are described in Table 2.1.1. The 250 lesions consisted of 116 BCCs and 134 non-BCCs, corresponding with a BCC prevalence of 46%. Of the 116 BCCs, 34 (29.3%) were superficial BCCs, 56 (48.3%) nodular BCCs, and 26 (22.4%) aggressive BCCs. The results from lesion-based analyses are also presented, enabling comparison with the results from patient-based analyses. There were small differences in the estimates for diagnostic parameters, and a statistically significant increase from 82.7% to 91.3% in AUC was observed ($p$<0.001).

## Discussion

This study shows that the use of OCT in conjunction with clinical pictures demonstrates a better ability to differentiate BCC from other diagnoses compared to CE alone. In both analyses, the AUC indicated better diagnostic performance for cOCT than for CE. When confidence scores 1-4 were considered as test positive (versus score 0 as test negative), addition of cOCT was associated with a significant increase in specificity from 47.5% to 76.8% without compromising sensitivity. Previous studies also found increase in specificity without affecting sensitivity.[6-8]

This study showed that the ability of cOCT to discriminate between superficial and non-superficial BCCs (nodular BCC and aggressive BCC) was slightly better compared with that of CE. With cOCT, a larger proportion of histologically verified superficial BCC was detected than with CE, meaning higher specificity of cOCT compared with CE alone. Sensitivity to detect non-superficial BCCs (nodular BCC and aggressive BCC) increased only slightly. An explanation for this finding may be that sensitivity of CE alone is already high (87.0%). Nodular BCCs are clinically well recognizable, having characteristic features such as elevation, a pearly translucent margin, and telangiectasia. The typical shiny appearance of a nodular BCC is even better seen when a light beam is moved over the tumour. Owing to the design of the study, the assessors of cOCT had to do with photographs in which elevation and shiny appearance are obviously less clear. Recognition of nodular BCC might improve when cOCT is used directly during CE of a patient.

In this study, we performed both a patient-based and a lesion-based analysis. The patient-based analysis using only one lesion per patient ensures independence of observations and provides information on the proportion of patients who are diagnosed correctly. However, in the patient-based analysis, there is a risk of missing an OCT diagnosis of BCC if a patient with multiple lesions has a BCC or other malignancy in a lesion that is not included for analysis. This occurred in one patient. The lesion-based analysis gives information on the proportion of lesions with a correct diagnosis and is also relevant, because generally treatments are chosen per lesion. Treatments of BCC lesions are usually not systemic and the decision to treat one lesion and leave one untreated can be taken at once. Although there were small differences in the estimates of diagnostic parameters, both analyses lead to similar conclusions. A significant difference in AUC between cOCT and CE was found in the lesion-based analysis, but significance was not reached in the patient-based analysis owing to a limited power.

The idea has been put forward that non-invasive diagnostic techniques, such as OCT, may make it possible to omit punch biopsy in part of the patients for whom the OCT diagnosis of BCC can be made with high confidence.[6,7] In this way, the delay caused by the necessity for a punch biopsy could be avoided. For this reason, this study evaluated whether the predictive value in case of high confidence in the cOCT diagnoses was high enough to guarantee that the prognosis of patients was not compromised and that over- or undertreatment could be avoided. In this study, high confidence (level 4) in BCC diagnosis with cOCT was observed in 30% (55/182) of patients.

Within the subgroup of 55 lesions in which BCC was diagnosed with high confidence by cOCT, 6 lesions turned out not to be BCC after histological verification. In one case, Bowen's disease was diagnosed by cOCT as nodular BCC with high certainty (score 4). If treatment would have been started on the basis of the cOCT diagnosis, the treatment would have been surgery, which is an adequate treatment for Bowen's disease. In one patient with two lesions, the second lesion (not included in the patient-based analysis) was a histologically verified SCC that by cOCT was diagnosed as nodular BCC. Treatment would have been surgery, but misclassification of invasive tumours like SCC or melanoma as BCC is always undesirable.

For subtyping of BCC, two of the 55 lesions diagnosed as BCC with high confidence were histologically nodular BCC that were misdiagnosed as superficial BCC. Consequently, these lesions would have been treated with non-invasive therapy instead of surgical excision. Treatment of nodular BCC with imiquimod is inferior to surgical excision, but results of the SINS trial showed a 5-year sustained clearance of 81% and recurrences are detected early and can easily be retreated with excision.[12] Unnecessary surgery could have occurred in the patients with actinic keratosis and sebaceous gland adenoma, both misdiagnosed as nodular BCC. The patients with interface dermatitis and benign lichenoid keratosis that were diagnosed as superficial BCC by cOCT would probably have been over treated with non-invasive therapy. The risk of over- or undertreatment must be weighed against the advantage of treatment without diagnostic delay and less invasive procedures. More importantly, the scenario above is a hypothetic scenario and whether OCT-guided diagnosis and treatment compromises effectiveness in terms of remaining free from recurrences at the long term cannot be concluded from this diagnostic study and needs to be verified in a randomized trial comparing the long-term effect of an OCT-guided strategy with standard care.

Instead of retrospectively looking at the scans, real-time scanning could benefit the outcome of the OCT-guided strategy as it provides the opportunity to obtain a second scan of a different area within the tumour in case of doubt of the diagnosis. As with all diagnostic procedures, increased training yields better results. In this study, we excluded the first 150 scans for training purposes. Therefore, the diagnostic performance of OCT is likely to improve after more training.

## Conclusion

This study shows that use of cOCT improves ability to distinguish between BCC and other diagnoses in patients with lesions clinically suspect for a non-melanoma skin cancer or premalignancy. Ability to distinguish between BCC subtypes needs further improvement. This may be realized with more training and under optimal conditions using OCT directly during CE of a patient. If treatment would be guided by OCT diagnosis, a punch biopsy could be omitted in about 30% of patients. This strategy harbors a small risk of misclassifications.

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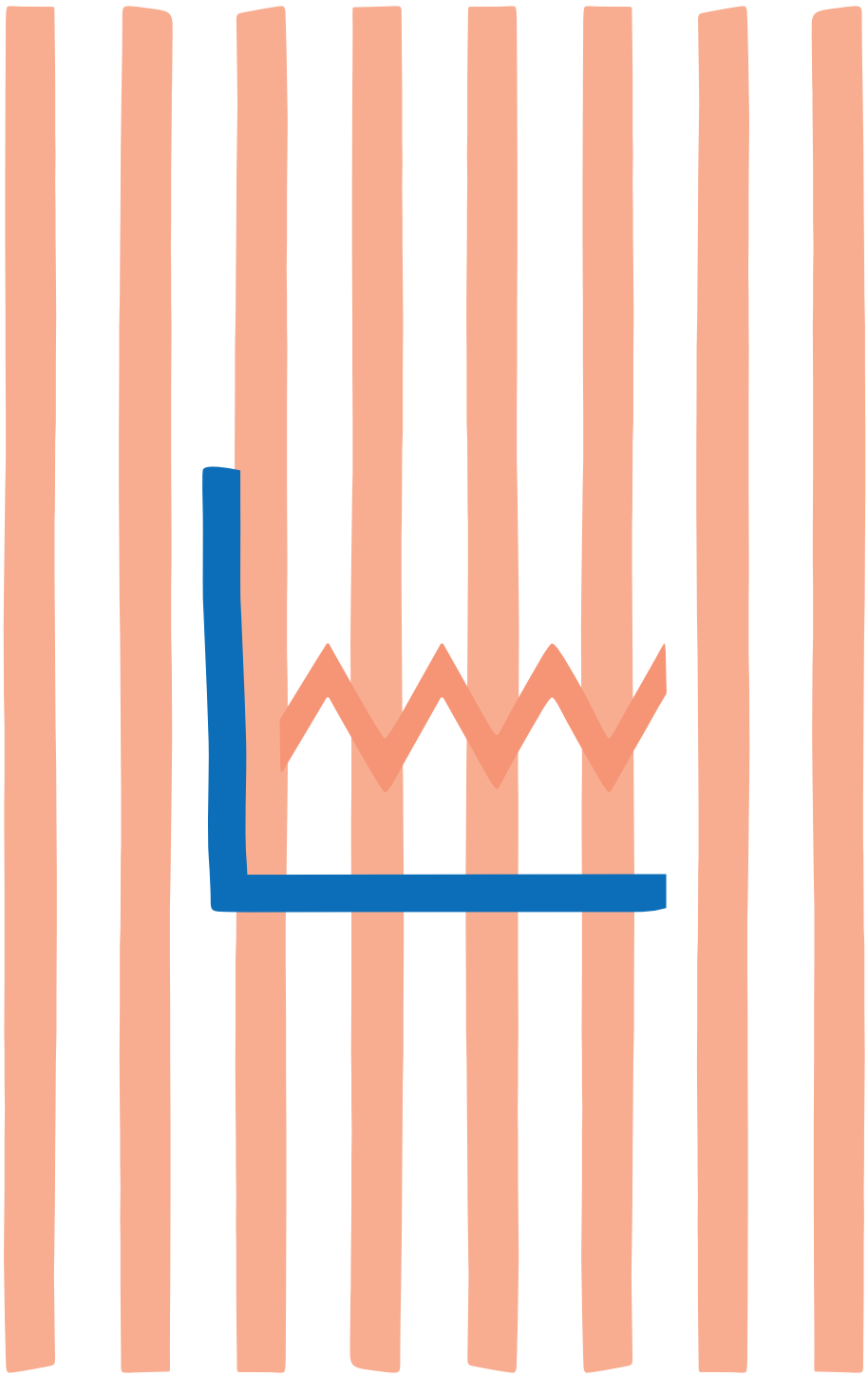

# CHAPTER 2.2

## Cumulative sum analysis for the learning curve of optical coherence tomography-assisted diagnosis of basal cell carcinoma

Eva van Loo[1] · Kelly A.E. Sinx[1] · Julia Welzel · Sandra Schuh · Nicole W.J Kelleners-Smeets · Klara Mosterd[2] · Patty J. Nelemans[2]

[1] Authors contributed equally to this work

[2] Authors share senior authorship

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## Abstract

The amount of training needed to correctly interpret optical coherence tomography (OCT) scans of the skin is undefined. The aim of this study was to illustrate how cumulative sum (CUSUM) charts can be used to determine how many OCT scans novice assessors should evaluate in order to obtain competence in diagnosing basal cell carcinoma. Four hundred lesions suspected for non-melanoma skin cancer were evaluated by OCT in combination with clinical photographs, using a 5-point confidence scale. The diagnostic error rate (sum of false-negative and false-positive OCT results / total number of cases) was used to evaluate performance, with histopathologic diagnosis as the reference standard. Acceptable and unacceptable error rates were set at 16% and 25%, respectively. Adequate performance was reached after assessing 183-311 scans, dependent on the cut-off for a positive test result. In conclusion, CUSUM analysis is useful to monitor progress of OCT trainees. The caseload necessary for training is substantial.

# Introduction

The incidence of keratinocyte carcinoma has increased over the past decades, with basal cell carcinoma (BCC) being the most prevalent cancer in the Caucasian population worldwide.[1-3] Diagnosis of BCC is often confirmed histopathologically by a biopsy, which also allows BCC subtyping and accommodates choice of the most appropriate treatment.[4] Biopsies are invasive, may be painful, and can be complicated by, for example, bleeding.[5] Moreover, histological assessment takes time and treatment may only be started following a second consultation. In recent years, non-invasive diagnostic techniques have improved and interest in their application for skin cancer is comprehensively growing. Optical coherence tomography (OCT) was first described as a potential imaging method for dermatology in 1997.[6] It relies on the reflection of light to obtain cross-sectional images of tissue, with an axial resolution of about 15 µm and a detection depth of approximately 1.5 mm.[7] Real-time, in vivo images of tissue microarchitecture are provided. For BCC, morphological features on OCT have been defined that show high concordance with regular histopathology slides.[8-11] Several studies have explored the diagnostic value of OCT for discrimination between BCC and other diagnoses, and have reported high sensitivity (≥ 80%), with specificity ranging from 75% to 96%.[12-15] Higher diagnostic accuracy has been described for more experienced observers.[12, 16] However, data on learning curves for OCT interpretation is not available, whilst this is valuable information for physicians who are considering working with OCT. The learning curve for OCT-assisted diagnosis of BCC was studied using cumulative sum (CUSUM) analysis. The aim of this study was to illustrate how CUSUM charts can be used to determine how many OCT scans have to be evaluated by novice assessors in order to achieve an adequate level of competence in distinguishing BCC from other diagnoses.

# Materials and methods

The research database of a prospective observational cohort study, initiated at the outpatient clinic of the Dermatology Department of Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands, was used.[17] The study was approved by the Medical Ethical Committee of MUMC+.

Patients, age 18 years or older, receiving a skin biopsy of a lesion clinically suspect for a keratinocyte carcinoma or premalignancy, were included between 15 February and 29 June 2017. Written informed consent was obtained. Exclusion criteria were: patients

who were unable to sign informed consent. The physician marked the area for biopsy and clinical and (if ordered by the physician) dermoscopic pictures were taken by a medical photographer. The marked biopsy area was scanned with OCT (VivoSight OCT, Michelson Diagnostics, Maidstone, UK) and consecutively a 3-mm punch biopsy was taken. Histopathology was assessed by independent pathologists, who were unaware of the OCT diagnosis.

OCT images were coded and saved anonymously. OCT assessment was performed by 2 researchers who evaluated the clinical (and if available, dermoscopic) pictures in conjunction with the OCT images. Assessment of the OCT images on presence of BCC was based on the criteria described by Hussain et al. and the VivoSight online atlas (http://www.vivosightatlas.com/) (Table 2.2.1).[8, 18] Level of confidence in the diagnosis of BCC was documented using a 5-point Likert-scale (range 0-4, Table 2.2.2).

The OCT assessors reached consensus on each OCT scan and were unaware of the histopathological results before making a final diagnosis. In order to accommodate the learning process, the assessors received immediate feedback of the histopathological outcome after each scan for the first 100 scans. For the remaining cases in the database, feedback on histopathological outcome was given after every 10-15 scans.

The diagnostic error rate, defined as the sum of false-negative and false-positive OCT results as a proportion of the total number of cases, was used as the criterion to assess diagnostic performance in this study, with histopathological diagnosis as reference standard.

**Table 2.2.1**: Criteria used for assessing optical coherence tomography (OCT) images on presence and subtyping of basal cell carcinoma.*

| **Presence of basal cell carcinoma** |
|---|
| • Disruption of layering |
| • Hyporeflective ovoid structures |
| • Dark areas surrounded by a hyperreflective halo |
| • Peritumoural white/ refractile stroma |
| • Palisading at margin |
| • Necrosis |
| • Widened epidermis |

*Adapted from Hussain et al.[8] and https://www.vivosightatlas.com/category/basal-cell-carcinoma/.

**Table 2.2.2**: Level of confidence in diagnosis of basal cell carcinoma (BCC) on optical coherence tomography (OCT) and definition of positive and negative OCT test results according to 2 different cut-off values of the confidence score.

| | | Cut-off value of confidence score for a positive test result | |
|---|---|---|---|
| **Level of confidence** | | **Cut-off ≥2** | **Cut-off ≥3** |
| 0: | certainly no BCC | No BCC (negative test result) | No BCC (negative test result) |
| 1: | low suspicion of BCC | No BCC (negative test result) | No BCC (negative test result) |
| 2: | high suspicion of BCC, other diagnosis may be possible | BCC (positive test result) | No BCC (negative test result) |
| 3: | certain of BCC diagnosis, unsure of subtype | BCC (positive test result) | BCC (positive test result) |
| 4: | certain of BCC diagnosis and subtype | BCC (positive test result) | BCC (positive test result) |

## Training prior to the study

Before the start of the study, the OCT assessors received instructions on BCC diagnosing and subtyping with OCT by a representative from the manufacturer. Also they studied literature on OCT in dermatology and attended a convention on OCT.[19] Approximately 20 OCT scans were assessed purely for educational purposes and to become familiar with the OCT device (scans not included in this study).

One of the OCT assessors had several years of clinical experience with diagnosis and treatment of BCC (including Mohs surgery) as a dermatology resident, and one had two years of experience in clinical dermato-oncology as a research fellow.

## Learning curve analysis

A cumulative sum (CUSUM) chart was used to track performance over time and was constructed using an Excel spreadsheet.[20] CUSUM is an analysis technique typically used for sequential monitoring of cumulative performance and detection of change in performance over time. CUSUM charts were originally developed for industrial process monitoring and are based on the classification of a product's quality into 1 of 2 categories: 'defective' or 'non-defective'.[21] The purpose is to detect changes in the proportion ($p$) of items in the 'defective' category. It is necessary to pre-specify an acceptable failure rate ($p_0$) and an unacceptable failure rate ($p_1$). In the same manner, a CUSUM chart can be applied to evaluate the learning process in medical interventional and diagnostic techniques.[20,22-25] The outcome of the diagnostic technique (in this case OCT) has to be classified into 'success' or 'failure'. For construction of the CUSUM chart, the cumulative sum after each case is plotted against the index number of that case.

For each failure, a certain score (*S*, see formula in Appendix 2.2.1) is added and for each success, a score (1 - *S*) is subtracted. The CUSUM is the running sum of a mixture of increments (with each failure) and decrements (with each success). A continuing descending curve indicates that successes occur more frequently than failures.

When the running sum exceeds a certain threshold boundary, this signals a critical change. The upper and lower limits represent the boundary above which performance becomes unacceptable ($h_0$) or below which performance becomes acceptable ($h_1$), respectively. These boundaries depend on the setting of $p_0$ and $p_1$, but also on the setting of the false positive or type I error (α, risk of falsely concluding that a trainee's performance is unacceptable when it is not) and the false-negative or type II error (β, the risk of falsely concluding that a trainee's performance is acceptable when it is not). The type I and type II error are conventionally set at 0.1, making $h_0$ and $h_1$ equal.[22] For a detailed explanation see Appendix 2.2.1.

The primary endpoint in this study was the number of OCT assessments after which an adequate level of competence was achieved. A cut-off value of the confidence score in the OCT diagnosis has to be chosen to define positive and negative test results. CUSUM curves were made using two alternative cut-off values; ≥2 and ≥3 on the Likert scale (Table 2.2.2). All diagnoses were compared with the histopathological diagnosis.

The acceptable diagnostic error rate was set at 16% and the unacceptable error rate at 25%.

## Results

A total of 400 OCT scans with corresponding clinical images of 400 lesions in 289 patients were included. All lesions were clinically suspicious for keratinocyte carcinoma or pre-malignancy. Of all 289 patients, 208 patients had 1 lesion, 63 patients had 2 lesions, 10 patients had 3 lesions, 6 patients had 4 lesions and 2 patients had 6 lesions. Lesion characteristics are presented in Table 2.2.3. Histopathology results revealed a total of 192 BCCs and 208 other diagnoses.

**Table 2.2.3**: Characteristics of the 400 lesions included in the study.

| | N=400 | % |
|---|---|---|
| **Location** | | |
| Head and neck area | 186 | 46.5 |
| Trunk | 123 | 30.8 |
| Extremities | 91 | 22.8 |
| **Diagnosis** | | |
| Basal cell carcinoma | 192 | 48.0 |
| Actinic keratosis | 42 | 10.5 |
| Morbus Bowen | 24 | 6.0 |
| Squamous cell carcinoma | 29 | 7.3 |
| Melanoma or lentigo maligna | 2 | 0.5 |
| Other malignant | 6 | 1.5 |
| Benign naevoid | 13 | 3.3 |
| Other benign tumours | 34 | 8.5 |
| Inflammatory | 36 | 9.0 |
| Inconclusive diagnosis | 6 | 1.5 |
| Other | 16 | 4.0 |

When using a cut-off value ≥2, high suspicion of BCC (score 2) as well as certainty of the presence of BCC (scores 3 and 4) are defined as a test-positive result of OCT. There were 23 false-negative diagnoses and 40 false-positive diagnoses corresponding with an overall error rate of 15.8% (63/400). The CUSUM curve is presented in Figure 2.2.1. From case 55 onwards the curve starts declining, and definitively crosses the acceptable boundary ($h_1$) from above at case number 183. This crossing signals that the hypothesis, that acceptable performance at the pre-set error rate of 16% has been reached, can be accepted (with α=0.1 and β=0.1). The CUSUM curve keeps declining indicating that performance remains acceptable.

When using a cut-off value ≥3, only certainty of BCC presence on OCT is defined as a positive test result. There were 48 false-negative and 26 false-positive OCT diagnoses corresponding with an overall error rate of 18.5% (74/400). The curve initially courses around and above the x-axis, indicating a 'trial and error' state until case 52 (Figure 2.2.1). It first crosses the acceptable boundary ($h_1$) from above at case 202, but subsequently fluctuates around the critical *h*-line giving it an overall horizontal course to definitely cross it from above at case 311. At this point, the hypothesis that the diagnostic error rate reached 16%, can be accepted.

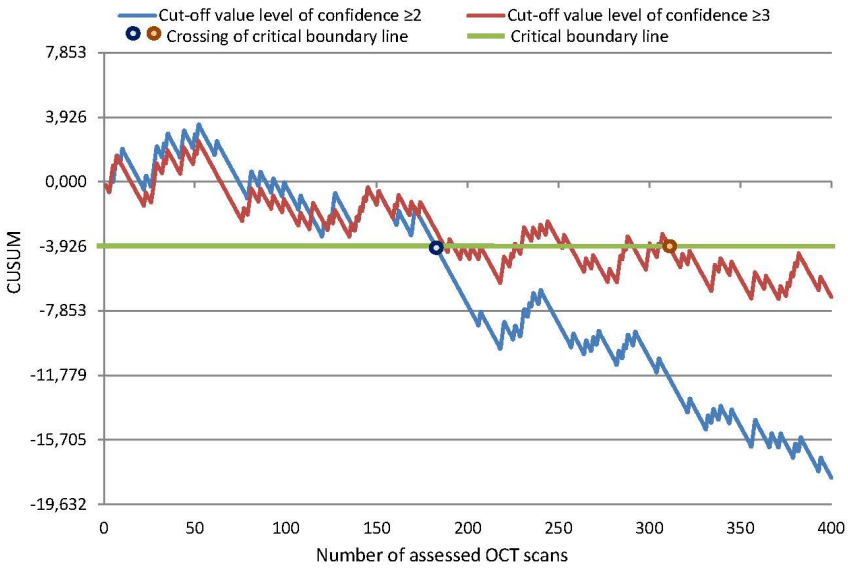


**Figure 2.2.1**: Cumulative sum (CUSUM) curves for optical coherence tomography (OCT) assisted diagnosis of basal cell carcinoma (n=400), with $p_0$ = 16% and $p_1$ = 25% for cut-off value level of confidence ≥2 (blue line) and ≥3 (red line).

## Discussion

This study illustrates how the CUSUM method can be used to create learning curves and estimate after how many OCT scans diagnostic performance meets pre-specified standards.

Learning curves graphically show the relationship between learning effort and achievement. The benefit of CUSUM is that it continuously assesses individual performance and progress in mastering a new technique.[20] It also serves as a rapid detector of change and allows for early intervention, such as retraining or continued observation, which is especially useful in its application in trainee programmes.[26,27] It has become an accepted method for monitoring performance in medical therapeutic and diagnostic procedures.[20,24,28,29] The diagnostic error rate can be used as a measure for overall diagnostic performance in learning curves.[20] This rate does not distinguish between sensitivity and specificity, which are discussed in another paper.[17]

The OCT-trainees reported their diagnosis on a 5-point confidence scale, which enabled us to monitor performance for different thresholds for a positive test result for OCT. Since a score of 3 or more on the Likert scale reflected the assessor being certain of the diagnosis BCC, we considered this as the most appropriate threshold. However, in a scenario in which the aim is not to miss a BCC, one may opt for a confidence level ≥2 as the cut-off point for a positive test result. For the latter, the number of cases (183) that need to be evaluated before reaching acceptable performance was lower than the 311 required scans when the more strict threshold ≥3 was used. A possible explanation is that less experienced OCT users tend to exercise more caution in their judgement, represented by lower confidence scores, which is penalized when using a high confidence score as the cut-off value.

When the ultimate goal of OCT is to be able to omit punch biopsy, it becomes important to monitor the ability to make both accurate and confident diagnoses. However, such ability requires more and longer training.

The number of cases required to achieve acceptable performance depends strongly on the choice of the acceptable and unacceptable failure rates ($p_0$ and $p_1$). These parameters set the target that one wants to achieve and may differ between centres. However, the setting of realistic targets for our centre, where OCT has not yet been implemented in clinical practice, was challenging. Diagnostic error rates of 12% have been reported by 2 (industry-initiated) studies on diagnostic performance of OCT.[13,14] However, the prevalence of BCC was higher than in the current study, and thus the study populations may represent a different case mix. Moreover, the level of confidence in the OCT diagnosis used to define a positive test result of OCT was not explicitly reported in these studies.[13,14] Therefore, efforts were made to obtain an estimate of the failure rate of a competent, experienced operator. For this purpose, 2 OCT users with 23 and 8 years of experience (JW and SS) assessed a randomly chosen subset of 100 scans from our database. The error rates of these OCT users were 16%. The setting of the unacceptable error rate at 25% was more straightforward, since this was the error rate accomplished by clinical examination in this study and, in order to be of added value, we considered that OCT-assisted diagnosis should not exceed this rate.[17]

This study gives an indication of the number of cases that given our clinical, histopathological and OCT experience, need to be assessed with OCT before being able to discriminate BCC from other diagnoses. However, these results cannot be universally applied to other centres, because previous experience with OCT may differ, as well as

targets considered feasible or acceptable. In former studies, OCT training programmes (if described) consisted of a 30-min instruction with 50 OCT images or a 20-min lecture on OCT.[12,16] In the current study, training was more extensive. We consider that a basic level of background knowledge is necessary in order to understand the structures visible on the scans and a similar 2-day course, consisting of general lectures and hands-on training by experienced users, is minimally required before starting to train with OCT in clinical practice.

## Conclusion

Currently, no recommendations or guidelines on training in OCT exist. This study illustrates our experience with how a learning curve can help to establish the number of cases that are required to achieve an adequate level of performance. At an acceptable and unacceptable diagnostic error rate of 16% and 25%, adequate performance in diagnosing BCC was reached after 183-311 scans. In conclusion, a substantial number of scans need to be evaluated to achieve adequate competence in diagnosing BCC with OCT.

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# Appendix 2.2.1

Formulas used in the construction of the CUSUM chart [20]
General CUSUM formula:

$$S_n = \sum (X_i - s)$$

$S_n = \text{CUSUM}$, $X_i = 1$ for failure

$s$ is a score calculated from the probabilities of 'success' ($p_0$) and probabilities of failure ($p_1$):

$$s = \frac{\ln((1-p_0)/(1-p_1))}{\ln(\frac{1-p_0}{1-p_1}) + \ln(\frac{p_1}{p_0})}$$

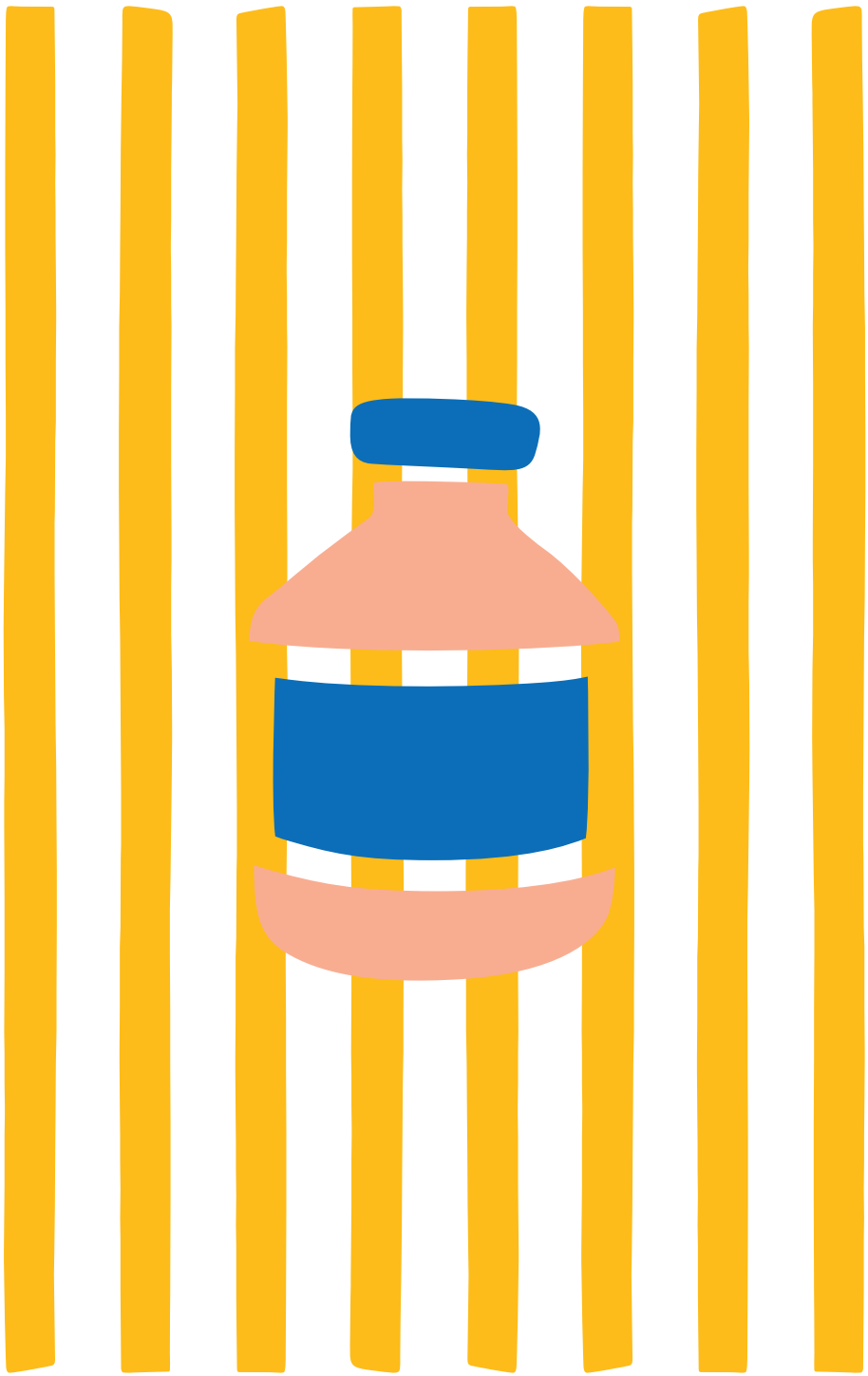
Decision limits ($h_1$) and ($h_0$) are graphical boundaries which determine if a process is in or out of control and are calculated based on the risk of:

α: risk of type I error

β: risk of type II error

$$h_1 = \frac{\ln\frac{1-\beta}{\alpha}}{\ln\left(\frac{1-p_0}{1-p_1}\right) + \ln\left(\frac{p_1}{p_0}\right)}$$

$$h_0 = \frac{\ln\frac{(1-\alpha)}{\beta}}{\ln(\frac{1-p_0}{1-p_1}) + \ln(\frac{p_1}{p_0})}$$



# CHAPTER 2.3

## Topical application of glycerol increases penetration depth of optical coherence tomography in diagnosis of basal cell carcinoma

Fieke Adan · Ellen M.M. Oyen · Robert J. Holtackers · Eva van Loo · Gert-Jan Dermont · Nicole W.J. Kelleners-Smeets · Patty J. Nelemans · Klara Mosterd

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# Abstract

Optical coherence tomography is a non-invasive imaging technique that enables high-resolution *in vivo* imaging of skin. Although optical coherence tomography is promising for diagnosing basal cell carcinoma, its limited penetration depth may impede basal cell carcinoma subtyping. This study evaluated whether topical application of glycerol can increase penetration depth and improve the image quality and visibility of characteristic features of basal cell carcinoma.

A total of 61 patients with a total of 72 basal cell carcinomas were included. Optical coherence tomography scans were obtained before and after application of an 85% glycerol solution. The mean penetration depth of each optical coherence tomography scan was acquired by automatically tracing both skin surface and the point of signal loss using a custom-made MATLAB program. Mean ± standard deviation penetration depth increased from 883 ± 108 to 904 ± 88 µm before and after glycerol application, respectively ($p$=0.005).

Topical application of glycerol leads to a significant 2.4% increase in penetration depth. However, no significant differences in image quality and visibility of basal cell carcinoma features were found.

# Introduction

The incidence of non-melanoma skin cancer (NMSC) is increasing globally, with basal cell carcinoma (BCC) being the most prevalent skin cancer diagnosed among the Caucasian population.[1] Histopathological examination of a punch biopsy remains the gold standard for confirming BCC diagnosis and subtype.[2,3] However, a punch biopsy is a minor invasive procedure.

Optical coherence tomography (OCT) has emerged as a promising non-invasive imaging technique for the diagnosis of BCC, showing improved specificity and sensitivity when used in addition to clinical examination and dermoscopy.[3-6] OCT uses the reflection of an optical beam to acquire real-time cross-sectional images of the skin with a <7.5 µm lateral and <5 µm axial optical resolution, and a penetration depth of approximately 1-1.5 mm. Based on the optical reflections, the epidermis, dermis, and skin appendages can be distinguished.[6,7] However, as the mean tumour depth of aggressive BCC subtypes, including infiltrative and micronodular BCC, is estimated at approximately 1.5 mm, the penetration depth may be insufficient to detect deeper located and smaller BCC tumour nests.[8]

By reducing light scattering in OCT scans, the penetration depth may be enhanced. Light scattering occurs mainly at the tissue interfaces whose refractive indices mismatch, such as the surface of skin and the dermal-epidermal border. In pursuance of enhancing OCT image quality and penetration depth, hyperosmotic chemical agents, called optical clearing agents (OCAs), have been applied to the skin to match refractive indices. These OCAs reduce light scattering and thereby enhance optical penetration depth.[9,10] Glycerol, a hydrophilic trihydroxy alcoholic substance, has been used as OCA in multiple studies, demonstrating increased penetration depth and enhanced contrast in OCT diagnostics.[9-14] However, the reported increase in penetration depth has not yet been quantified.

The aims of this study were to evaluate whether topical application of glycerol solution on BCCs improves optical penetration depth. In addition, the effect of glycerol application on image quality and visibility of characteristic BCC features was evaluated.[15]

# Materials and methods

Patients, aged 18 years or older, visiting the Department of Dermatology of the Maastricht University Medical Centre+ (MUMC+) with 1 or more histopathologically confirmed BCCs were included between January and May 2019. The study was approved by the local ethics committee (METC 16-4-197) and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to inclusion.

## Optical coherence tomography imaging

OCT imaging of the BCC(s) was performed both before and immediately after topical application of glycerol 85% (0.01 ml) solution on the skin lesion. All OCT scans were acquired by a single physician using a commercially available OCT device (VivoSight; Michelson Diagnostics Ltd, Maidstone, UK) equipped with a 6-mm probe (axial resolution 15 μm). Prior to OCT imaging, a medical photograph was taken of each lesion.

## Image analysis

For all OCT images the mean penetration depth was assessed using a custom-made MATLAB (version 2018b; The Mathworks, Natick, MA, USA) script. This program automatically traced the skin surface and the point of signal loss for each location in the image based on the (differences in) signal intensity, represented by blue and red lines in the OCT image, respectively (Figure 2.3.1). Penetration depth was defined as the mean distance between these 2 lines. Subsequently, all OCT images were presented in random order to 3 observers who were blinded to any patient data and did not know whether the OCT image was taken before or after application of glycerol: 1 dermatologist with extensive OCT imaging experience (EvL) and 2 dermatology residents with moderate OCT imaging experience (EO and GD).

Observers scored the overall image quality (determined by the noise level and shadows casted by keratosis and/or crusts/ulcerations), and visibility of the most common features of BCC (as identified previously by Hussain et al.[15]). Both parameters were scored separately using a 4-point Likert-scale (1: low, 2: medium, 3: high, and 4: very high). Since lower image quality has been reported for BCCs presenting with keratosis and with crusts and/or ulcerations, lesions with these features were classified into 2 subgroups based on clinical presentation.[16]

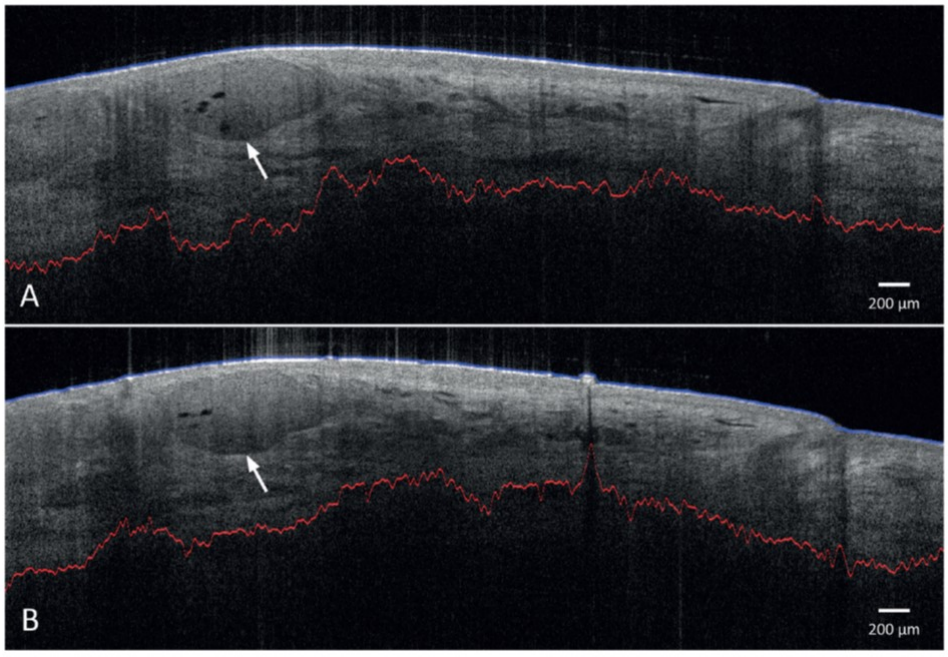


**Figure 2.3.1**: Optical coherence tomography (OCT) images of the same basal cell carcinoma (BCC) acquired before (image A) and after (image B) application of glycerol. A custom-made MATLAB program was used to automatically analyse the images: the blue line traces the skin surface, while the red line traces the point of signal loss. The distance between these 2 lines was calculated at all positions to obtain mean penetration depth. A signal-poor ovoid nest (corresponding to a basaloid cell nest) is indicated by the white arrow. At approximately 1-mm depth the signal intensity drastically decreases, which might make it difficult to identify features of BCC in deeper skin layers. Note that images (A) and (B) differ slightly in image position as the OCT imaging probe was removed for application of glycerol.

## Statistical analysis

The sample size calculation was based on the mean penetration depth, the primary outcome measure. An increase in mean penetration depth after glycerol application of half the standard deviation (SD) of the difference (effect size 0.5) was considered as minimally clinically relevant. To enable detection of such a difference between the 2 conditions (before and after topical application of glycerol) with a power of 80% and 2-sided alpha of 5%, 64 BCCs were required. To account for a 10% drop-out rate 72 BCCs were included.

Results are expressed as mean ±SD or as percentage, unless otherwise specified. Differences in mean penetration depth before and after topical application of glycerol were evaluated using either a paired-samples Student's *t*-test (in case of normally distributed data) or a non-parametric Wilcoxon signed-rank test (in case of non-normally distributed data). Normality of the data was evaluated using the Shapiro–Wilk test. Differences in image quality and visibility of characteristic BCC features before and after topical glycerol application were evaluated using the McNemar's test for paired proportions. The proportions of OCT scans with higher scores after application of glycerol (improved outcome) were compared with percentages with lower scores after application of glycerol (worsened outcome). Separate analyses were performed for the 2 subgroups of BCCs presenting with keratosis, or crusts and/or ulcerations and for superficial BCCs. All statistical analyses were performed using SPSS Statistics 25 (International Business Machines (IBM), Armonk, NY, USA).

Two-sided *p*-values <0.05 were considered statistically significant.

## Results

Sixty-one patients (35 male, median age 70 years, age range 44–95 years) with a total of 72 BCCs were included. Baseline characteristics of the study sample are summarized in Table 2.3.1. OCT imaging was performed successfully before and after topical application of glycerol in all patients. The mean ± SD penetration depth increased significantly after topical application of glycerol (883 ± 108 vs 904 ± 88 µm, $p$=0.005). The 21-µm difference represented an increase by 0.34 SD of the difference corresponding with an effect size of 0.34.

The numbers and proportions of BCCs with improved and reduced scores on the 4-point Likert scale, with respect to overall image quality and visibility of characteristic BCC features after glycerol application, are shown in Table 2.3.2. Regarding overall image quality after glycerol application, no significant improvement was found for observers 1 and 3. For observer 2, the proportions with improved scores were substantially higher than the proportions with reduced scores, but only statistically significant for BCC with crusts and/or ulcerations ($p$=0.04). Regarding the visibility of BCC features, there was a trend toward improved scores for observers 1 and 2, but the results were not statistically significant. For observer 1, the visibility of BCC features for superficial BCCs significantly decreased ($p$=0.01).

**Table 2.3.1**: Baseline characteristics of the study sample (61 patients with a total of 72 basal cell carcinomas (BCCs)).

| **Characteristics** | |
|---|---|
| Sex (male), n (%) | 35 (57.4) |
| Age, years, median (range) | 70 (44–95) |
| **Number of lesions per patient, n (%)** | |
| 1 | 53 (86.9) |
| 2 | 6 (9.8) |
| 3 | 1 (0.02) |
| 4 | 1 (0.02) |
| **Lesion location n (%)** | |
| Head and neck region | 23 (31.9) |
| Upper chest | 6 (8.3) |
| Back/abdomen | 27 (37.5) |
| Extremities | 16 (22.2) |
| **BCC subtype** | |
| Superficial | 26 (36.1) |
| Nodular | 28 (38.9) |
| Mixed nodular/superficial | 13 (18.1) |
| Infiltrating/morpheaform | 2 (2.8) |
| Mixed nodular/morpheaform | 1 (1.4) |
| Mixed superficial/micronodular | 1 (1.4) |
| Mixed nodular/micronodular | 1 (1.4) |

**Table 2.3.2**: Proportions of improved score, equal score, and reduced score for overall image quality and visibility of basal cell carcinoma (BCC) features after topical glycerol application for all 3 observers.

| **Outcome** | **Observer** | **Improved score[a] % (*n*)** | **Equal score % (*n*)** | **Reduced score % (*n*)** | ***p*-value** |
|---|---|---|---|---|---|
| **All (*n* = 72)** | | | | | |
| Overall image quality after | 1 | 26.4 (19) | 41.7 (30) | 31.9 (23) | 0.79 |
| glycerol application | 2 | 38.9 (28) | 45.8 (33) | 15.3 (11) | 0.08 |
| | 3 | 22.2 (16) | 47.2 (34) | 30.6 (22) | 0.20 |
| Visibility of BCC features after | 1 | 25.0 (18) | 56.9 (41) | 18.1 (13) | 0.70 |
| glycerol application | 2 | 38.9 (28) | 31.9 (23) | 29.2 (21) | 0.49 |
| | 3 | 18.1 (13) | 56.9 (41) | 25.0 (18) | 0.06 |
| **Keratosis (*n* = 42)** | | | | | |
| Overall image quality after | 1 | 28.6 (12) | 45.2 (19) | 26.2 (11) | 0.84 |
| glycerol application | 2 | 42.9 (18) | 45.2 (19) | 11.9 (5) | 0.07 |
| | 3 | 19.0 (8) | 57.1 (24) | 23.8 (10) | 0.64 |
| Visibility of BCC features after | 1 | 28.6 (12) | 52.4 (22) | 19.0 (8) | 0.22 |
| glycerol application | 2 | 42.9 (18) | 31.0 (13) | 26.2 (11) | 0.51 |
| | 3 | 19.0 (8) | 54.8 (23) | 26.2 (11) | 0.37 |

**Table 2.3.2**: (continued)

| Outcome | Observer | Improved score[a] % (*n*) | Equal score % (*n*) | Reduced score % (*n*) | *p*-value |
|---|---|---|---|---|---|
| **Crust/ulceration (*n* = 19)** | | | | | |
| Overall image quality after | 1 | 26.3 (5) | 47.4 (9) | 26.3 (5) | 0.48 |
| glycerol application | 2 | 52.6 (10) | 31.6 (6) | 15.8 (3) | 0.04 |
| | 3 | 26.3 (5) | 52.6 (10) | 21.1 (4) | 0.56 |
| Visibility of BCC features after | 1 | 26.3 (5) | 57.9 (11) | 15.8 (3) | 0.77 |
| glycerol application | 2 | 47.4 (9) | 36.8 (7) | 15.8 (3) | 0.16 |
| | 3 | 21.1 (4) | 57.9 (11) | 21.1 (4) | 0.76 |
| **Superficial BCC (*n* = 26)** | | | | | |
| Overall image quality after | 1 | 38.5 (10) | 19.2 (5) | 42.3 (11) | 0.15 |
| glycerol application | 2 | 38.5 (10) | 46.2 (12) | 15.4 (4) | 0.46 |
| | 3 | 15.4 (4) | 65.4 (17) | 19.2 (5) | 0.74 |
| Visibility of BCC features after | 1 | 27.0 (7) | 15.4 (4) | 57.7 (15) | 0.01 |
| glycerol application | 2 | 46.2 (12) | 15.4 (4) | 38.5 (10) | 0.88 |
| | 3 | 19.2 (5) | 61.5 (16) | 19.2 (5) | 0.78 |

Results are presented as % (n) with corresponding p-values (McNemar's test).
[a]An improved score is defined as an increase on the 4-point Likert scale. 1: EvL, 2: EO, and 3: GD.

## Discussion

The main objective of this study was to evaluate whether topical application of glycerol increases the optical penetration depth, which may aid the detection of deeper located BCC tumour nests. This study demonstrates that application of glycerol increases penetration depth from 883 to 904 µm, corresponding to an effect size of 0.34. This limited increase, however, may not be sufficient to detect aggressive BCC tumour nests, which can reach an estimated mean depth of 1,500 µm.

The observed penetration depth was remarkably lower than expected, as a systematic review reports a mean penetration depth of 1.2–2 mm with the same OCT device as the one used in the current study.[17] We found that beyond 1-mm depth the signal intensity decreases drastically (Figure 2.3.1), even after application of glycerol. Reported penetration depths of other devices vary from 1–1.6 mm (Thorlabs, Newton, NJ, USA), 1.3 mm (Risø National Laboratory, Roskilde, Denmark) and 2.0–2.5 mm (an OCT device developed at the Technical University of Denmark).[17]

Despite the increase in penetration depth, no improvement in image quality and visibility of BCC features was found. This may be explained by the fact that resolution,

more than penetration depth, determines image quality and how well BCC features can be distinguished from surrounding tissue.

Although OCAs may be useful for OCT imaging, Welzel et al. concluded that topical treatment of the skin prior to OCT imaging is not imperative, but gives a non-specific increase in optical penetration depth due to the lower surface reflectivity.[14] They found that a decrease in the light attenuation coefficient implies an increase in optical penetration depth, although this increase was not exactly quantified. Different solutions, including glycerol, ultrasonic gel, urea, petrolatum and paraffin oil, were tested on healthy skin of the fingertips in 15 patients. OCT images were obtained directly after application and compared with the untreated fingertips of the other hand.[14] All investigated solutions resulted in a comparable decrease in surface reflectivity and increase in optical penetration depth. Wang et al. used a combined liquid paraffin and glycerol mixture to reduce light scattering in tissue and achieve more optical penetration depth.[10] Eight OCT images of human fingers were obtained at 0–40 min after application, with a 5-min interval between each image. The time to reach the optimal optical clearing effect, defined as an OCT image with enhanced contrast, was around 10–30 min after application of a mixture with 70% glycerol concentration. The authors concluded that applying the liquid paraffin and glycerol mixture led to an OCT scan with enhanced contrast and assumed that this indicated an increase in optical penetration depth, although this increase was not exactly quantified.

Even though the above-mentioned studies report an increase in optical penetration depth and enhanced contrast after glycerol application, it was not reported whether these findings led to improved image quality and visibility of BCC features in OCT images. Wang et al.[10] observed enhanced contrast after application of glycerol, but in the current study an improvement in image quality and visibility of BCC features was not observed.

## Conclusion

Topical application of glycerol increases the optical penetration depth in OCT imaging of skin lesions suspected for BCC. However, this limited increase may not be clinically relevant. No significant differences were found in image quality and visibility of BCC features after topical application of glycerol.

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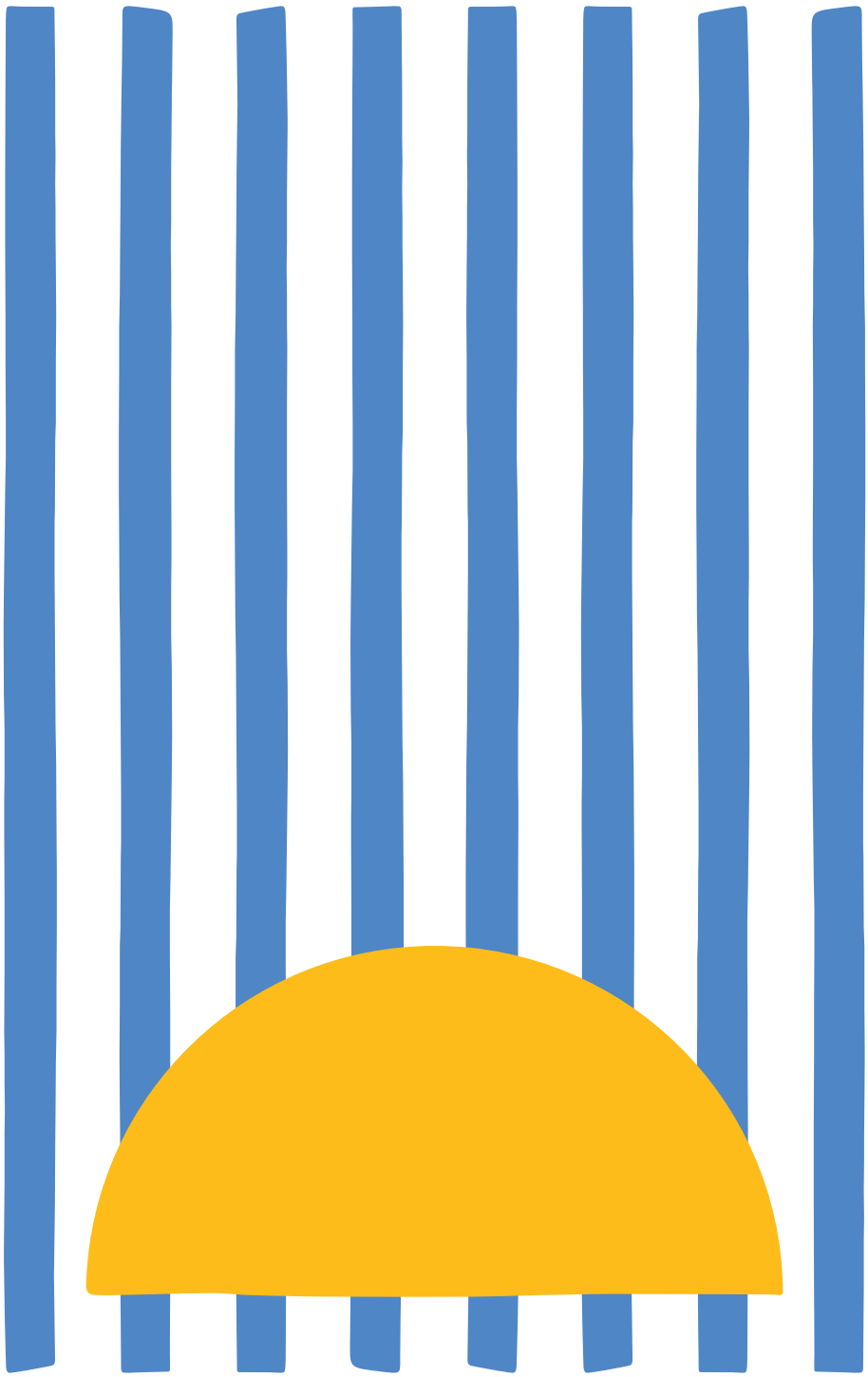
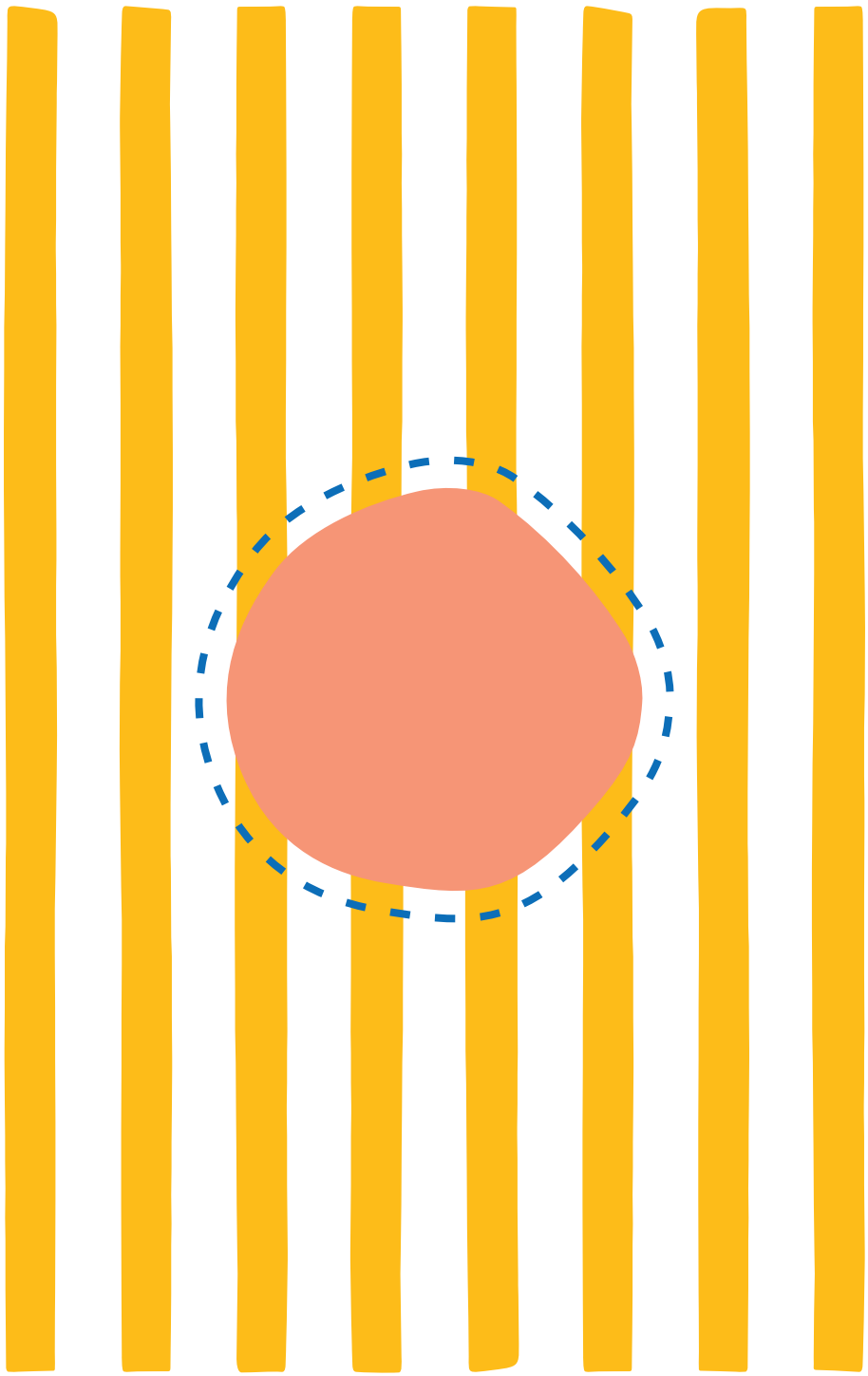


# PART TWO

## Surgical treatment of basal cell carcinoma



# CHAPTER 3.1

## Are the recommended excision margins for basal cell carcinoma too defensive? A retrospective chart study and evaluation of the Dutch guideline

Eva van Loo · Patty J. Nelemans · Corine Peters · Myrurgia Abdul-Hamid · Nicole W.J. Kelleners-Smeets

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## Introduction

The optimal surgical margin width for basal cell carcinoma (BCC) is currently unclear, and the guidelines are inconsistent.[1-3] In 2007, recommendations on excision margins were introduced in the Dutch BCC guideline. Surgical margins of 3 mm in small (≤10 mm) primary BCC and 5 mm in large (>10 mm), high-risk (aggressive histological subtype) or recurrent BCC were advised.[4] In 2015 the guideline was updated with the margin for low-risk BCC being adjusted to 3-4 mm, the size-threshold for high-risk BCC increased to 20 mm, and H-zone location was incorporated as a high-risk BCC.[2] The aim of this study is to assess the risk of incomplete excision in case of adherence and non-adherence to the recommended surgical margins according to the 2007 and 2015 Dutch BCC guidelines.

## Materials and methods

The 'Pathologic-Anatomic National Automated Archive' (PALGA) database was searched for cases of BCC. Inclusion criteria were: BCCs treated with conventional excision at the Dermatology department of the Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands, in 2010; with histopathological evaluation of the excision specimen by a pathologist of MUMC+. The institution's medical ethics committee approved the study. Retrospectively, for each BCC, tumour characteristics were recorded to enable categorization into low-risk versus high-risk BCC. The actual excision margin and the optimal margin according to the guidelines were recorded, as well as the histopathological completeness of the excision. Non-adherence was defined as the use of an excision margin smaller than recommended by the guidelines. This study evaluates actual non-adherence for the 2007 guideline (as this guideline was valid at the time of the excisions in 2010 included in this study) and theoretical non-adherence for the 2015 guideline. To evaluate whether risk of incomplete excision increases in case of non-adherence, relative risks (RR) of incomplete excision with 95% confidence interval (CI) were calculated. For statistical analysis, the Statistical Package for Social Sciences (SPSS, version 23) and Openepi.com were used. *P*-values <0.05 were considered to indicate statistical significance.

# Results

A search of the PALGA database for BCC diagnosis in 2010 resulted in 589 BCC in 469 patients eligible for the study. Patients had a mean age of 69.1 (±12.4) years and 54.4% were male. In total, 83.2% (*n*=390) of patients had 1 BCC, 11.1% (*n*=52) had 2 BCCs, 4.1% (*n*=19) had 3 BCCs and 1.7% (*n*=8) had 4-8 BCCs excised. All included tumours were excised with a 2-, 3- or 5-mm margin (n=19, 442 and 128 respectively). Mean tumour size was 8.2 (±5.2) mm and 52.8% (*n*=311) was located in the head- and neck area, 30.2% (*n*=178) on the torso and 17% (*n*=100) on the extremities. In low-risk BCC, the risk of incomplete excision was 2.5% and 0.4% after adherence to the 2007 guideline and 2015 guideline, respectively (Table 3.1.1). For low-risk BCC, non-adherence to the 2015 guideline was associated with a significantly increased risk of incomplete excision (RR=41.27; 95% CI: 4.05-421.3, *p*=0.003) and a trend towards increased risk in case of non-adherence to the 2007 guideline (RR=2.88 ;95% CI: 0.38-21.81, *p* =0.187).

For high-risk BCCs, the relative risks associated with non-adherence to guidelines were smaller and non-significant (Table 3.1.1). In case of non-adherence, the percentage of incomplete excisions in high-risk BCC increased only slightly from 6.1% to 7.3% (2007 guideline) and from 6% to 7.7% (2015 guideline). Non-adherence to the 2007 guideline occurred more frequently in high-risk BCC (60.8%) than in low-risk BCC (5.0%).

**Table 3.1.1**: Comparison of percentages with incomplete excision between basal cell carcinoma (BCC) excisions performed with compliance and without compliance to the 2007 and 2015 guidelines.

| | **BCC excisions with guideline compliance, % (*n*/total)** | **Incomplete excisions in BCC excisions without compliance to guideline, % (*n*/total)** | **Incomplete excisions in BCC excisions with compliance to guideline, % (*n*/total)** | **Relative risk** | **95%-CI** | ***p*-value[d] (2-sided)** |
|---|---|---|---|---|---|---|
| *High-risk BCC (ref: 2007 guideline)*[a] | | | | | | |
| All (n=293) | 39.2 (115/293) | 7.3 (13/178) | 6.1 (7/115) | 1.20 | 0.49-2.92 | 0.868 |
| >10 mm (n=117) | 32.5 (38/117) | 10.1 (8/79) | 5.3 (2/38) | 1.92 | 0.43-8.63 | 0.413 |
| aBCC (n=199)[b] | 51.8 (103/199) | 7.3 (7/96) | 6.8 (7/103) | 1.07 | 0.39-2.95 | 0.888 |
| Recurrence (n=28)[b] | 10.7 (3/28) | 8.0 (2/25) | 66.7 (2/3) | 0.24 | 0.03-1.92 | 0.321 |
| *High-risk primary BCC (ref: 2007 guideline)*[a] | | | | | | |
| All (n=265) | 42.3 (112/265) | 7.2 (11/153) | 4.5 (5/112) | 1.61 | 0.58-4.51 | 0.510 |
| >10 mm (n=110) | 31.8 (35/110) | 9.3 (7/75) | 0.0 (0/35) | na | na | 0.062 |
| aBCC (n=191)[b] | 52.9 (101/191) | 7.8 (7/90) | 5.0 (5/101) | 1.57 | 0.52-4.78 | 0.614 |
| *High-risk BCC (ref: 2015 guideline)*[a] | | | | | | |
| All (n=351) | 33.3 (117/351) | 7.7 (18/234) | 6.0 (7/117) | 1.29 | 0.55-2.99 | 0.714 |
| ≥20 mm (n=31)[c] | 58.1 (18/31) | 0.0 (0/13) | 11.1 (2/18) | na | na | 0.329 |
| H-zone location (n=209) | 25.8 (54/209) | 9.0 (14/155) | 7.4 (4/54) | 1.22 | 0.42-3.55 | 0.749 |
| *High-risk primary BCC (ref: 2015 guideline)*[a] | | | | | | |
| All (n=323) | 35.3 (114/323) | 7.7 (16/209) | 4.4 (5/114) | 1.75 | 0.66-4.64 | 0.367 |
| ≥20 mm (n=27)[c] | 55.6 (15/27) | 0.0 (0/12) | 0.0 (0/15) | na | na | na |
| H-zone location (n=204) | 25.4 (52/204) | 9.2 (14/152) | 5.8 (3/52) | 1.60 | 0.48-5.34 | 0.468 |
| *Low-risk BCC* | | | | | | |
| Low-risk, 2007 guideline (n=296) | 95.3 (282/296) | 7.1 (1/14) | 2.5 (7/282) | 2.88 | 0.38-21.81 | 0.187 |
| Low-risk, 2015 guideline (n=238) | 95.4 (227/238) | 18.2 (2/11) | 0.4 (1/227) | 41.27 | 4.05-421.1 | 0.003 |

[a]The criteria for low- and high-risk basal cell carcinoma (BCC) also differ between the 2007 and 2015 guidelines. Excision margins according to guideline 2007: 3 mm low risk BCC, 5 mm high risk BCC (>10 mm, infiltrative subtype, recurrence). Excision margins according to guideline 2015: 3-4 mm low risk BCC, 5 mm high risk BCC (>20 mm, infiltrative subtype, H-zone location, recurrence). [b]Risk factors and values also apply to the 2015 guideline. [c]Since there was no case of therapy failure in the assessed risk factor, calculation of a risk ratio was not possible. [d]*p*-values were derived from the Yates corrected $\chi 2$ or in case of at least one expected value (row total*column total/grand total) <5, the Mid-P exact test. CI: confidence interval, aBCC: aggressive basal cell carcinoma, na: not available, ref: reference.

## Discussion

In this study, the highest relative risk of incomplete excision was observed for low-risk BCCs excised with a smaller margin than recommended by the guidelines. Overall adherence in low-risk BCC was high. In high-risk BCC, relative risks associated with non-adherence were lower and non-significant whilst adherence to recommended margins was rather poor.

These results imply that physicians may have a well-developed sense for which high-risk BCCs the use of a margin smaller than recommended in the guideline might be acceptable. Non-adherence rates were especially high for tumours larger than 10 mm and recurrent tumours. Due to the retrospective nature of this study, it was not possible to track down the reasons for guideline deviations for high-risk BCC. It is likely that a 5-mm margin for these tumours was considered too large by the treating physician. In fact, high-quality evidence for the 10-mm size threshold in the 2007 guideline was lacking and may have been rather arbitrary, because in the 2015 guideline it was adjusted to 20 mm without new studies to substantiate this modification. Also, most recurrent BCCs occurred after non-invasive treatment of superficial BCCs and recurrence was not accompanied by other high-risk features in the majority of cases. For non-melanoma skin cancer, guideline deviation associated with patient's age, tumour localization and surgeon's experience has been reported.[5] According to a systematic review, non-adherence to clinical (non-dermatological) guidelines is often intentional and due to valid reasons such as comorbidity and contra-indications, which does not necessarily lead to impaired quality of care.[6] This is probably also the case in the current study. The poor adherence in high-risk BCCs is in line with the results of another study in the Netherlands, in which self-reported BCC guideline adherence with respect to excision margins was 37.9%.[7]

For low-risk BCC, non-adherence occurred in only 5% of cases and with a more straightforward reason: these excisions served a diagnostic rather than a therapeutic purpose because of a differential diagnosis including an atypical melanocytic lesion. In these diagnostic cases, the use of a 2-mm margin is prescribed by the Dutch melanoma guideline.[8]

Currently, both the Dutch and the recent European consensus-based guideline on BCC advise margins of 3-4 mm in low-risk BCC and a minimal margin of 5 mm (Dutch guideline) or 5-15 mm (European guideline) in high-risk BCC.[2,3] In our study population, a margin of 3 mm was sufficient in no less than 99.6% of BCCs categorized as low risk by

current guidelines.[2,3] Also, a margin of 5 mm for high-risk BCC was effective and led to complete tumour removal in 94% of cases. The study population did not include high-risk facial BCCs for which micrographic surgery with 3D margin evaluation, rather than larger margins, is preferred.[9]

Finding the optimal surgical margin is always a balance between complete tumour removal, for which higher margins are more effective, and unnecessary removal of healthy tissue, for which smaller margins are preferable. The findings of this study indicate that, for high-risk BCC, attempts to prevent incomplete excision have resulted in recommendations by the various guidelines that do not match the desire of treating dermatologists to take into account other factors that drive their decisions regarding the optimal excision margin. Adherence to the guideline in high-risk BCC was poor, but lack of adherence had limited effect on the risk of incomplete excision. Current guidelines seem to be very cautious and defensive, and do not represent clinical practice. Therefore, revision of the guideline recommendations on the excision margin for high-risk BCC may be warranted. However, a problem in providing evidence-based recommendations is the lack of high-quality research on this subject.

A limitation of this study is the relatively low sample size. As a result, the power to detect small but relevant increases in risk of incomplete excision due to non-adherence is limited. Furthermore, the study has been performed in a single center, which may limit the generalizability of the results.

## Conclusion

The results of this study suggest that non-adherence to guidelines is associated with an increased risk of incomplete excision for low-risk BCC. For high-risk BCC, guideline adherence was poor but the observed increase in risk of incomplete excision was less substantial, so clinicians seem to be able to judge in which cases deviations from guideline recommendations can be deemed acceptable. With high-quality evidence still lacking, we need to be wary of advising unnecessary large margins for situations in which micrographic surgery might be the better option.

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# CHAPTER 3.2

## Safety margins for surgical excision of basal cell carcinoma: a systematic review and meta-analysis

Eva van Loo · Lieke C.J. van Delft · Melis Altan · Klara Mosterd · Patty J. Nelemans[1] · Nicole W.J. Kelleners-Smeets[1]

[1] Authors share senior authorship

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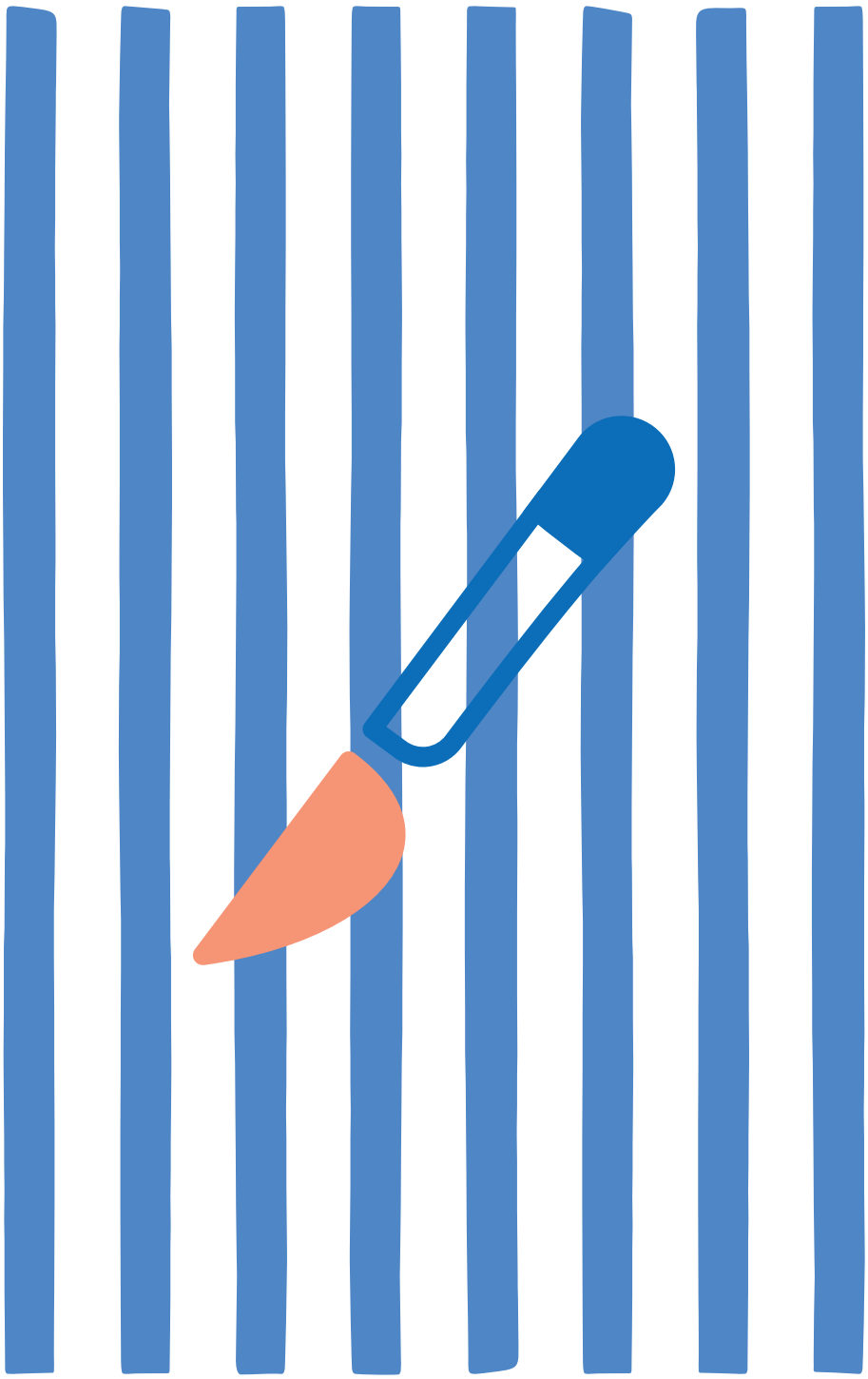

# CHAPTER 4

## Surgical excision versus Mohs micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10-year follow-up

Eva van Loo · Klara Mosterd · Gertruud A.M. Krekels · Marieke H. Roozeboom · Judith U. Ostertag · Carmen D. Dirksen · Peter M. Steijlen · H.A. Martino Neumann · Patty J. Nelemans · Nicole W.J. Kelleners-Smeets

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# Abstract

**Background**

Basal cell carcinoma (BCC) is the most common form of cancer among Caucasians and its incidence continues to rise. Surgical excision (SE) is considered standard treatment, though randomised trials with long-term follow-up are rare. We now report the long-term results of a randomised trial comparing surgical excision with Mohs micrographic surgery (MMS) for facial BCC.

**Methods**

408 facial, high risk (diameter at least 1 cm, H-zone location or aggressive histological subtype) primary BCCs (pBCCs) and 204 facial recurrent BCCs (rBCCs) were randomly allocated to treatment with either SE or MMS between 5th October 1999 and 27th February 2002. The primary outcome was recurrence of carcinoma. A modified intention to treat analysis was performed.

**Findings**

For primary BCC, the 10-year cumulative probabilities of recurrence were 4.4% after MMS and 12.2% after SE (Log-rank test $\chi^2$ 2.704, $p$=0.100). For recurrent BCC, cumulative 10-year recurrence probabilities were 3.9% and 13.5% for MMS and SE, respectively (Log-rank $\chi^2$ 5.166, $p$=0.023). A substantial proportion of recurrences occurred after more than 5 years post-treatment: 56% for pBCC and 14% for rBCC.

**Interpretation**

Fewer recurrences occurred after treatment of high risk facial BCC with MMS compared to treatment with SE. The proportion of recurrences occurring more than 5 years post-treatment was especially high for pBCC, stressing the need for long-term follow-up in patients with high risk facial pBCC.

# Introduction

Basal cell carcinoma (BCC) is the most common form of cancer among Caucasians worldwide. The incidence has increased with 5.5% per year over the past decades and is predicted to continue rising.[1] In the Netherlands, the lifetime risk of developing a BCC is one in every 5–6 persons.[2] The disease related mortality is very low due to the low rates of metastatic disease.[3] However, morbidity can be high due to local tissue destruction, especially since most tumours occur in functional areas such as the head and neck.[4] Although many therapeutic options are available today, standard surgical excision (SE) is still the most common form of treatment for BCCs.[4] Mohs micrographic surgery (MMS) is a specialised surgical technique and its use is increasing.[5] The main difference between both treatments is the method of histological margin examination. In standard SE, surgical margins are mostly examined on random vertical sections, the so-called bread loaf technique. In MMS, the specimen is flattened and sliced horizontally. This offers the possibility to examine 100% of the resection margins, in contrast to the small percentage of margin control in SE. Therefore, MMS should theoretically lead to fewer recurrences with maximal sparing of surrounding healthy tissue.[6] We previously showed that, after a period of 5 years, treatment with MMS led to significantly fewer recurrences than SE in recurrent facial BCC.[7] However, consensus on treatment is difficult to reach since prospective randomised studies are rare.[4] Furthermore, most non-comparative studies only report 5 year recurrence rates, but there have been reports that recurrences may develop even later.[7-13] BCC located in the H-zone of the face, with positive excision margins in previous resections or with an aggressive histological growth pattern show higher recurrence rates.[14,15]

The goal of this study is to provide evidence on the long-term efficacy of MMS and SE in high risk facial BCC. In 1999, a randomised controlled trial was initiated and we previously reported the results after 2 and 5 years of follow-up.[7,16] To our knowledge, this is the first randomised controlled trial on treatment of BCC which provides data that enable estimation of recurrence probability after a 10-year follow-up period.

# Materials and methods

A prospective randomised controlled trial was started at the Maastricht University Medical Centre in 1999, comparing MMS with SE in facial BCC.[7,16] The primary outcome of this trial was recurrence of tumour. Patient selection and techniques were described in the previous publications on this trial, but will be briefly described here.[7,16]

## Patient selection

Patients were recruited during a visit to a dermatology outpatient clinic of one of the seven participating hospitals in the southern part of the Netherlands between 5th October 1999 and 27th February 2002. Patients were included in the primary basal cell carcinoma (pBCC) group if they presented with a primary facial BCC of 1 cm or more in diameter, and were either located in the H-zone of the face or were of an aggressive histological subtype (micronodular, morpheaform, BCC with squamous differentiation, infiltrative). Patients were included in the recurrent basal cell carcinoma (rBCC) group if they had at least one facial BCC recurring for the first or second time. The diagnosis of BCC had to be histologically confirmed before treatment. Patients with a life expectancy of less than 3 years were excluded from participation. The trial was approved by the ethics and scientific committee of the University Hospital Maastricht and has been carried out in accordance with The Code of Ethics of the World Medical Association. All patients gave written informed consent for study participation.

## Randomisation and masking

Tumours of eligible patients were randomly assigned to either SE or MMS by use of a computer-generated allocation scheme (Sampsize 2.0). Randomisation occurred by telephone, by an independent person not involved in the trial and separately for the pBCC and rBCC groups. For practical reasons no blinding was performed for the allocated treatment.

## Procedures

Patients with tumours assigned to SE were referred for treatment to either the Maastricht University Medical Center (Maastricht, the Netherlands) or the Laurentius Hospital Roermond (Roermond, the Netherlands), in which SE was performed under the same conditions and by the same three surgeons (JUO, GAMK and NWJK-S). In most patients the procedure was performed under local anaesthesia. In both the pBCC and rBCC group, a tumour assigned to SE was excised with a 3-mm clinically tumour free resection margin at a 90° angle into the subcutaneous fat. Histological margin examination with the bread loaf-technique was performed if the tumour diameter was 16 mm or less. In larger sized tumours the quadrant method was applied.[17] In case of an incomplete excision, re-excision with a 3-mm margin followed. In case of two incomplete excisions, tumours were treated with MMS.

Patients with tumours assigned to MMS were referred for treatment to the Maastricht University Medical Center and treated by the same three surgeons formerly mentioned. The tumour was excised with a 3 mm clinically tumour free resection margin at a 45° angle in order to obtain a bowl-shaped excision sample. For histological margin examination, this sample was compressed and sliced horizontally. In case of residual tumour the procedure was repeated until no more tumours were seen in the specimen.

## Follow-up information

The primary outcome of this study was tumour recurrence defined as a histologically confirmed BCC in a skin biopsy of a clinically suspect area within 5 mm of the surgical scar. Patients were seen once every year by their own dermatologist, generally until 5 years after treatment. Long-term follow-up was conducted by the patient's own dermatologist if indicated, e.g. in patients with multiple skin cancers. For this study, the remaining patients who did not complete a follow-up of at least 10 years received an invitation for skin examination by the research physician. At follow-up visits the treatment site was inspected. The collection of follow-up data for pBCC and rBCC groups ended on 19th June 2012.

## Statistical analysis

The sample size calculation for this study has been described in previous publications on this trial.[7,16] For estimation of cumulative probabilities of recurrence, Kaplan–Meier survival analysis was used. Patients were censored at the date of histological confirmation of a recurrence or the date of the last follow-up visit. Differences in cumulative probability of recurrence between treatment groups were tested for statistical significance with the log-rank test. Differences in tumour characteristics between tumours with and without a follow-up period of at least 10-years were tested for statistical significance with the Fisher-exact test (categorical data) or Student's *T*-test (continuous data). Unless stated otherwise, analyses were performed per included tumour and not per patient. A *p*-value below 0.05 was considered to indicate statistical significance. A modified intention to treat analysis was applied: randomised tumours that were not treated were excluded from further analysis. All data analyses were performed with SPSS version 18.0 (SPSS, Chicago, IL, United States of America (USA)) and STATA version 11_0 (Stata-Corp, USA).

## Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

# Results

## Primary basal-cell carcinomas

Between October 1999 and January 2001, 408 pBCCs in 374 patients were randomly assigned to treatment with SE or MMS (Figure 4.1). 11 Allocated patients were not treated. A total of 363 patients with 397 tumours were treated. Of the 374 randomised patients, 30 patients had two and two patients had three tumours. Treatment characteristics, nature and prevalence of complications were described previously.[7,16] Baseline characteristics were comparable between the randomised groups (Table 4.1). The median follow-up period for pBCC was 79.2 months (range 0.0–150.3). Follow-up data for at least 10 years post-treatment were available for 140 (35.3%) of 397 treated tumours in 129 patients. Reasons for not completing the 10-year follow-up were: death due to causes unrelated to BCC or treatment, refusal to attend follow-up visits, and other reasons such as inability to contact the patient or inability of the patient to visit the hospital (Figure 4.1). Reasons for loss to follow-up were comparable between SE and MMS treatment groups (Figure 4.1). The mean age of patients lost to follow-up was significantly higher than that of patients who completed a 10-year follow-up period (72.1 versus 60.3 years respectively, $p<0.001$). There was no significant difference in the mean age of patients lost to follow-up between the two treatment groups. Comparison of other characteristics such as tumour location, allocated therapy, gender and aggressive histological subtype did not reveal any important differences.

During the 10-year follow-up period, 21 recurrences were registered in the pBCC group; 15 after SE and 6 after MMS. Two more recurrences occurred in each treatment group more than 10-years post-treatment. The 10-year cumulative probability of recurrence is 4.4% (95% confidence interval (CI): 1.9–9.8%) after MMS and 12.2% (95% CI: 7.3–19.8%) after SE (Log-rank test $\chi^2$ 2.704, $p=0.10$, Table 4.2, Figure 4.2). Of all recurrences, 11 (44.0%) were registered in the first 5-years after treatment, 10 (40.0%) were registered between 5 and 10-years post-treatment and another 4 (16.0%) even past 10-year follow-up. Of the patients who had more than one pBCC, none had more than one recurrence. Characteristics of recurrent tumours are shown in Table 4.3.

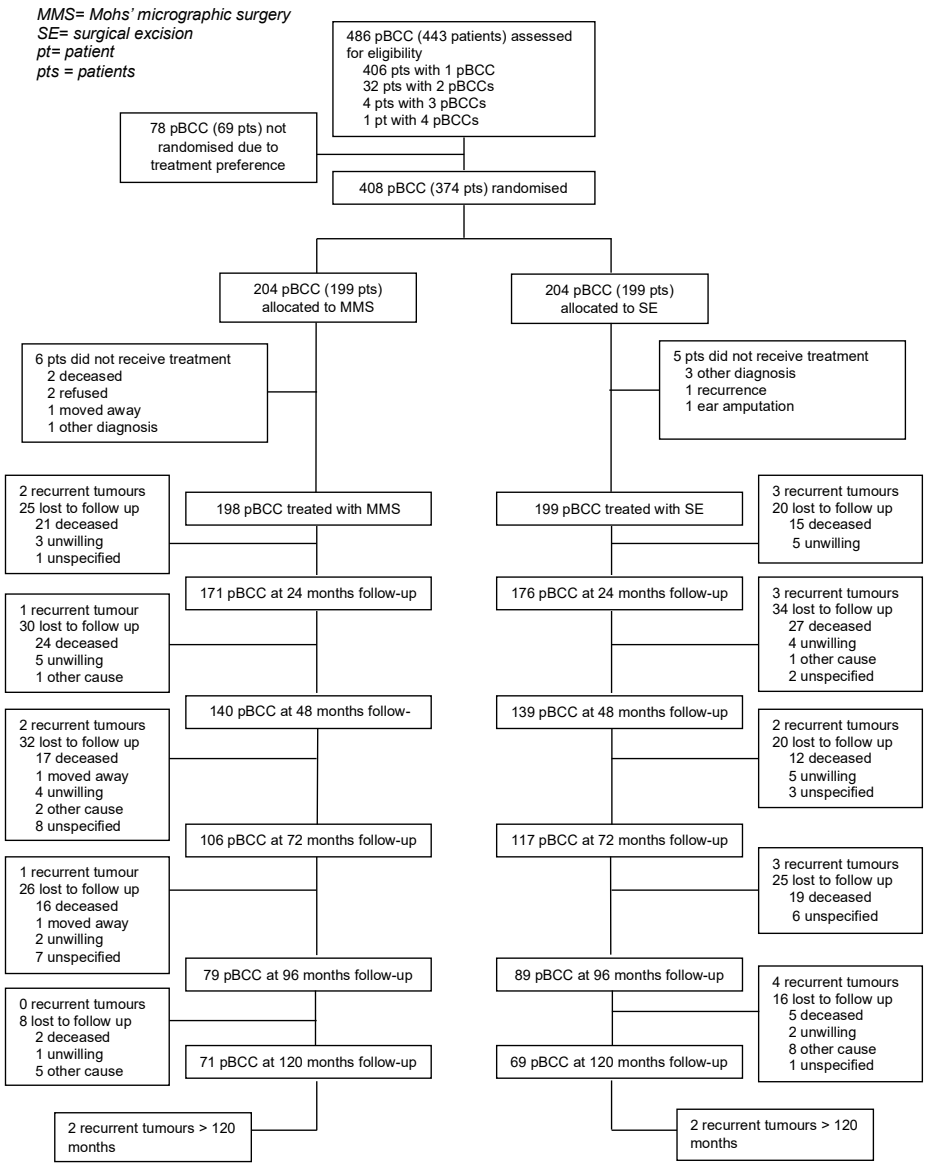



**Figure 4.1**: Trial profile of the primary basal cell carcinoma (pBCC) group.

**Table 4.1**: Baseline patient and tumour characteristics separated for primary and recurrent BCC and treatment group.

| | pBCC | | rBCC | |
|---|---|---|---|---|
| | **MMS (n=204) n, (%)** | **SE (n=204) n, (%)** | **MMS (n=102) n, (%)** | **SE (n=102) n, (%)** |
| Mean age at treatment, y | 67.4 (SD 12.7) | 68.7 (SD 12.2) | 69.2 (SD 10.6) | 67.1 (SD 12.4) |
| Gender | | | | |
| Male | 123 (60.3) | 126 (61.8) | 54 (52.9) | 62 (60.7) |
| Female | 81 (39.7) | 78 (38.2) | 48 (47.1) | 40 (39.3) |
| Location | | | | |
| Frontal/temporal | 53 (26.0) | 65 (31.9) | 38 (37.3) | 46 (45.0) |
| Cheek/chin | 19 (9.3) | 16 (7.8) | 12 (11.7) | 10 (9.8) |
| (Peri)nasal | 69 (33.8) | 62 (30.4) | 23 (22.5) | 29 (28.4) |
| Lips/perioral | 14 (6.9) | 8 (3.9) | 6 (5.9) | 1 (0.9) |
| Periocular | 16 (7.8) | 16 (7.8) | 6 (5.9) | 5 (4.9) |
| Ears | 9 (4.4) | 16 (7.8) | 8 (7.8) | 4 (3.9) |
| Periauricular | 24 (11.8) | 21 (10.3) | 9 (8.8) | 7 (6.8) |
| H-zone | 184 (90.0) | 197 (97.0) | 85 (83.3) | 81(79.4) |
| Aggressive histological subtype | 105 (51.5) | 88 (43.1) | 60 (59.4) | 49 (48.5) |
| First recurrence | - | - | 83 (81.4) | 82 (80.4) |

pBCC: primary basal cell carcinoma; rBCC: recurrent basal cell carcinoma; MMS: Mohs micrographic surgery; SE: surgical excision; BCC: basal cell carcinoma; Y: years; SD: standard deviation

**Table 4.2**: Estimated cumulative probabilities of recurrences for primary and recurrent basal cell carcinoma treated with Mohs micrographic surgery (MMS) or surgical excision

| | **Kaplan-Meier cumulative probability of recurrence (95% confidence interval)** | | | |
|---|---|---|---|---|
| | **Primary basal cell carcinoma** | | **Recurrent basal cell carcinoma** | |
| **Follow-up (months)** | **MMS** | **Surgical excision** | **MMS** | **Surgical excision** |
| **12** | 0.005 (0.001-0.037) | 0.005 (0.001-0.037) | 0.00 (-) | 0.00 (-) |
| **24** | 0.011 (0.003-0.043) | 0.016 (0.005-0.049) | 0.00 (-) | 0.032 (0.011-0.097) |
| **60** | 0.024 (0.009-0.063) | 0.041 (0.020-0.084) | 0.023 (0.006-0.090) | 0.118 (0.065-0.208) |
| **120** | 0·044 (0.019-0.098) | 0·122 (0.073-0.198) | 0.039 (0.013-0.117) | 0·135 (0.076-0.232) |

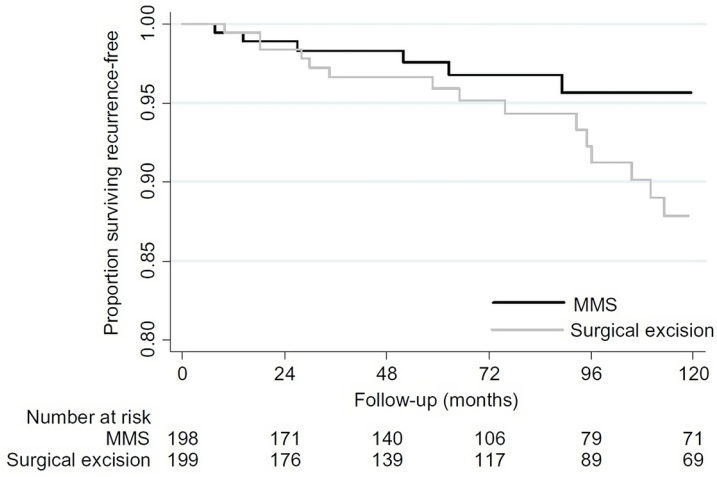



**Figure 4.2**: Kaplan–Meier survival analysis of primary basal cell carcinoma (pBCC) treated with Mohs micrographic surgery (MMS) or surgical excision.

## Recurrent basal-cell carcinomas

Between October 1999 and February 2002, 204 rBCCs in 191 patients were assigned to one of the treatment groups (Figure 4.3). Two patients, randomised to MMS, deceased before treatment so 202 patients were treated. Of the 191 randomised patients with rBCC, 10 patients had 2 and 1 had 4 rBCCs. Previous treatments of rBCC consisted mainly of SE (53.9%), cryotherapy (28.9%) or radiotherapy (5.4%). Baseline characteristics are presented in Table 4.1. The median follow-up period for rBCC was 85.0 months (range 0.0–149.3). 10-year follow-up data were complete for 78 (38.6%) of 202 treated tumours in 74 patients (Figure 4.3). The most common reasons for not completing follow-up were death and inability to reach the patient or no-show at appointments (Figure 4.3). Percentages of reasons for loss to follow-up were comparable between treatment groups. Patients lost to follow-up were older than patients who completed a 10-year follow-up period (mean age 70.4 versus 64.5 years respectively, $p<0.001$). The mean age of patients lost to follow-up did not differ significantly between treatment groups. Other characteristics such as histological subtype, tumour location, gender, Fitzpatrick skin type and number of recurrence showed no statistical differences between patients with and without a complete 10-year follow-up. During the 10-year follow-up period, 14 recurrences were registered in the rBCC group, 11 after treatment with SE and 3 after treatment with MMS. The cumulative probability of recurrence after MMS was 3.9% (95% CI: 1.2–11.7%) and

after SE 13.5% (95% CI: 7.6–23.2%) at 10-years post-treatment (log-rank $\chi^2$=5.166; *p*=0.023, Table 4.2, Figure 4.4). Of the cumulative number of recurrences, 12 (86%) were registered in the first 5-years and 2 (14%) between 5 and 10-years post-treatment. No recurrences were registered more than 10-years post-treatment. Of the patients who had more than one rBCC, none had more than one recurrence. Characteristics of recurrences are shown in Table 4.4.

**Table 4.3**: Patient and tumour characteristics for primary basal cell carcinoma that recurred.

| | Survival (months) | Sex | Age (years) | Histological subtype | Tumour location | Allocated treatment |
|---|---|---|---|---|---|---|
| 1 | 7.7 | M | 54.0 | Aggressive | Frontal/temporal | MMS |
| 2 | 9.9 | M | 69.7 | Non-aggressive | Frontal/temporal | SE |
| 3 | 14.3 | F | 52.6 | Non-aggressive | Frontal/temporal | MMS |
| 4 | 18.2 | M | 73.5 | Non-aggressive | Ears | SE |
| 5 | 18.2 | M | 72.2 | Non-aggressive | Frontal/temporal | SE |
| 6 | 27.0 | F | 70.5 | Non-aggressive | Frontal/temporal | MMS |
| 7 | 27.9 | F | 82.7 | Aggressive | (Peri)nasal | SE |
| 8 | 29.9 | M | 40.9 | Non-aggressive | Frontal/temporal | SE |
| 9 | 34.5 | F | 62.7 | Non-aggressive | Frontal/temporal | SE |
| 10 | 51.9 | M | 58.9 | Aggressive | (Peri)nasal | MMS |
| 11 | 58.8 | M | 74.7 | Non-aggressive | Frontal/temporal | SE |
| 12 | 62.7 | M | 74.9 | Non-aggressive | (Peri)nasal | MMS |
| 13 | 65.0 | M | 70.9 | Aggressive | (Peri)nasal | SE |
| 14 | 75.8 | M | 77.2 | Non-aggressive | (Peri)nasal | SE |
| 15 | 89.1 | M | 61.5 | Non-aggressive | Frontal/temporal | MMS |
| 16 | 92.6 | F | 90.9 | Aggressive | Frontal/temporal | SE |
| 17 | 95.0 | F | 86.5 | Non-aggressive | Ears | SE |
| 18 | 96.1 | M | 52.6 | Non-aggressive | (Peri)nasal | SE |
| 19 | 105.6 | M | 71.2 | Non-aggressive | (Peri)nasal | SE |
| 20 | 110.0 | F | 78.0 | Non-aggressive | (Peri)nasal | SE |
| 21 | 113.1 | F | 49.4 | Non-aggressive | Frontal/temporal | SE |
| 22 | 127.2 | F | 68.8 | Non-aggressive | Frontal/temporal | MMS |
| 23 | 131.6 | M | 71.3 | Non-aggressive | Frontal/temporal | MMS |
| 24 | 139.4 | M | 60.9 | Aggressive | Frontal/temporal | SE |
| 25 | 143.6 | F | 69.1 | Non-aggressive | (Peri)nasal | SE |

M: male; F: female; MMS: Mohs micrographic surgery; SE: surgical excision

**Table 4.4**: Patient and tumour characteristics for recurrent basal cell carcinomas that recurred during the study period.

| | Survival (months) | Sex | Age (years) | 1st/2nd recurrence | Histological subtype | Tumour location | Allocated treatment |
|---|---|---|---|---|---|---|---|
| 1 | 18.0 | M | 44.0 | 1st | Non-aggressive | (Peri)nasal | SE |
| 2 | 18.2 | F | 75.2 | 1st | Aggressive | Cheek/chin | SE |
| 3 | 20.7 | F | 82.6 | 1st | Non-aggressive | Frontal/temporal | SE |
| 4 | 25.3 | M | 73.3 | 1st | Aggressive | Frontal/temporal | SE |
| 5 | 27.1 | M | 60.4 | 2nd | Aggressive | (Peri)nasal | MMS |
| 6 | 29.2 | F | 74.0 | 1st | Aggressive | Cheek/chin | SE |
| 7 | 29.2 | F | 82.0 | 1st | Aggressive | Frontal/temporal | SE |
| 8 | 31.9 | F | 82.2 | 1st | Aggressive | (Peri)nasal | MMS |
| 9 | 39.1 | M | 71.7 | 2nd | Aggressive | Perioculair | SE |
| 10 | 45.8 | F | 71.4 | 1st | Aggressive | Frontal/temporal | SE |
| 11 | 46.9 | M | 47.9 | 1st | Aggressive | Frontal/temporal | SE |
| 12 | 53.1 | M | 56.8 | 1st | Aggressive | (Peri)nasal | SE |
| 13 | 74.6 | M | 61.8 | 1st | Non-aggressive | Frontal/temporal | MMS |
| 14 | 77.1 | F | 54.7 | 1st | Non-aggressive | Perioculair | SE |

M=male; F=female; MMS=Mohs micrographic surgery; SE=surgical excision.

## Subgroup analyses

Additional analyses were performed within subgroups according to histological subtype. Results are presented in Table 4.5, which shows that 10-year risk of recurrence was consistently higher after treatment with SE when compared to treatment with MMS. The largest difference between SE and MMS was found for aggressive rBCC.

**Table 4.5**: Percentages cumulative recurrence free survival in the subgroups according to histological subtype.

| | % cumulative recurrence free survival | | *p*-value |
|---|---|---|---|
| | MMS | SE | |
| pBCC | | | |
| Aggressive histological subtype | 97.5 | 94.1 | 0.313 |
| Non-aggressive histological subtype | 93.7 | 83.6 | 0.293 |
| rBCC | | | |
| Aggressive histological subtype | 96.1 | 80.7 | 0.021 |
| Non-aggressive histological subtype | 96.0 | 91.8 | 0.362 |

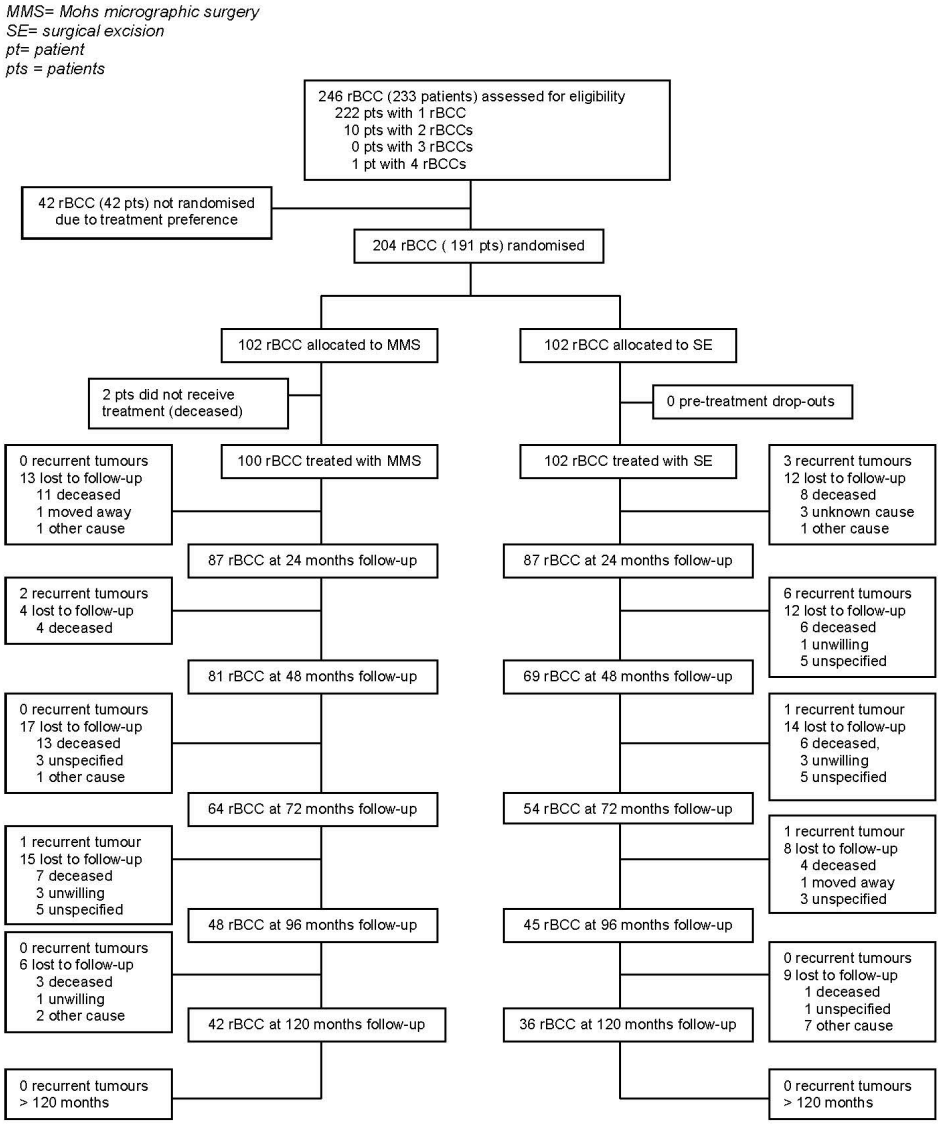
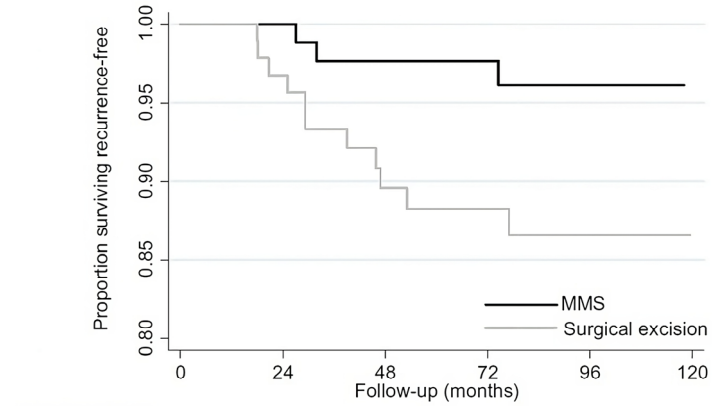



**Figure 4.3**: Trial profile for recurrent basal cell carcinoma (rBCC).




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| MMS | 100 | 87 | 81 | 64 | 48 | 42 |
| Surgical excision | 102 | 87 | 69 | 54 | 45 | 36 |

**Figure 4.4**: Kaplan-Meier survival analysis of recurrent basal cell carcinoma (rBCC) treated with Mohs micrographic surgery (MMS) or surgical excision.

## Discussion

To our knowledge, this is the first prospective randomised study that compares SE and MMS for treatment of high risk primary and recurrent facial BCC with a long-term follow-up of 10 years. We observed substantial differences in estimated 10-year recurrence rates of 7.8% for pBCC and 9.6% for rBCC, favouring MMS. Our results show that, compared to SE, MMS is more effective in preventing recurrences for both high-risk pBCC and rBCC in the face.

Several prospective, non-randomised studies reported a 5-year recurrence percentage for MMS of 1.0–6.5% for primary and 4.0–10.0% for recurrent tumours.[8,10-13,18-21] The 5-year percentages in our study are comparable for pBCC and somewhat lower for rBCC (Table 4.2). For SE, reported 5-year recurrence rates are 1.3–10.1% for pBCC and 11.6-17.4% for rBCC.[9,13,18,22,23] The 5-year percentages of recurrences after SE in this study are comparable. Multiple retrospective studies have reported on recurrences more than 5 years post-treatment.[7-13] In the current prospective study more than half of all recurrences in the pBCC group occurred more than 5 years post treatment, a finding which justifies the assumption that longer follow-up periods are required for evaluation of treatments for high-risk facial BCC. For pBCC, the effect of MMS appears visually more impressive in the late study period since a relatively large number of

events occurred (in the SE group) in a smaller number at risk. However, after testing we found that the proportional hazards assumption was met for the whole study period, hence the relative efficacy remains constant also for the whole study period. Notably, in the rBCC group only few extra recurrences occurred between 5 and 10 years post-treatment. We hypothesise that primary tumours and their first recurrences show less aggressive biological behaviour than tumours recurring for the second time or more, and therefore first recurrences of pBCC are discovered after a longer period of time.

Our study has several limitations. In the trial, a total of 13 patients received no treatment after randomisation and were excluded from analysis. For this reason, a modified intention to treat analysis had to be applied. Bias of results is unlikely, because reasons for exclusion were not related to tumour characteristics. A second limitation of our study is that only around 35–40% of all patients completed a 10-year follow-up. BCC generally affects people at higher age and it is known that loss to follow-up in older patient populations is substantial. In this study, death (unrelated to BCC) occurred in 30–40% of all patients. Another 20% of cases was lost to follow-up because of other reasons. However, these percentages still compare favourably to loss to follow-up rates reported in some of the few available long-term studies on BCC, in which percentages range from approximately 36% with more than 5-years of follow-up to 88% loss to follow-up at 10-years post-treatment.[21,24] The substantial loss to follow-up may have resulted in less precise estimates of recurrence-free survival, but the comparable loss to follow-up percentages in both treatment groups make biased comparison of the recurrence estimates unlikely.

At present times, a clinically tumour free margin of at least 4–5 mm is generally chosen in these high risk primary and recurrent facial BCCs. However, when this study was designed (in 1998) guidelines were lacking and an appropriate excision margin was based on the available literature at that time.[25,26] The benefit of larger margins (less incomplete excisions) was carefully weighed against the disadvantage of larger defects. Furthermore, the same resection margin (3 mm) was chosen for both SE and MMS to standardise both treatments and enhance comparability. We aimed at clear margins in both treatments, without an additional histological margin. However, if there was any doubt on the completeness of the SE, we performed a second excision with again 3 mm margin. The large number of incomplete excisions (18% of pBCC and 32% of rBCC assigned to SE were incompletely removed after the first excision) shows that a surgical margin of 3 mm is not sufficient in these high risk BCCs.[7] Although surgery was repeated in the SE group until histological tumour free margins were obtained, it may be possible that less long term recurrences would have occurred in the SE group if a

larger resection margin had been chosen. Nevertheless, the consequence of a larger surgical margin is a larger defect. This worsens aesthetic outcome and may in some cases lead to reduced functionality. Clinicians that treat facial skin tumours, face that dilemma on daily basis.

Indications for MMS have been broadened in the past years and if we would perform MMS on all indications that are mentioned in a recent published article on indications for MMS, this would mean a great burden on the dermatologists practice.[5] Furthermore, as the incidence of BCC still increases, there is a huge rise in treatment costs of this tumour. Since costs of MMS are higher than costs of SE, MMS should be reserved for indications for which superior effectiveness has been proven.[27] In this study, we included only high risk facial primary BCC and facial recurrent BCC. A high risk facial primary BCC is defined in this study as a BCC of at least 1 cm diameter either located in the H-zone of the face or being of an aggressive histological subtype. At this moment, only for these indications we consider MMS superior to SE. We think that more research is needed before MMS is introduced on a much larger scale.

## Conclusion

We showed that recurrences after surgical treatment of both rBCC and pBCC can still occur up to and even after 10-years post treatment. In BCC treated with MMS, fewer tumours recurred during long term follow-up. We therefore consider MMS as the most effective treatment for rBCC and high risk pBCC located in the face for prevention of recurrence on the long-term.

### Acknowledgements

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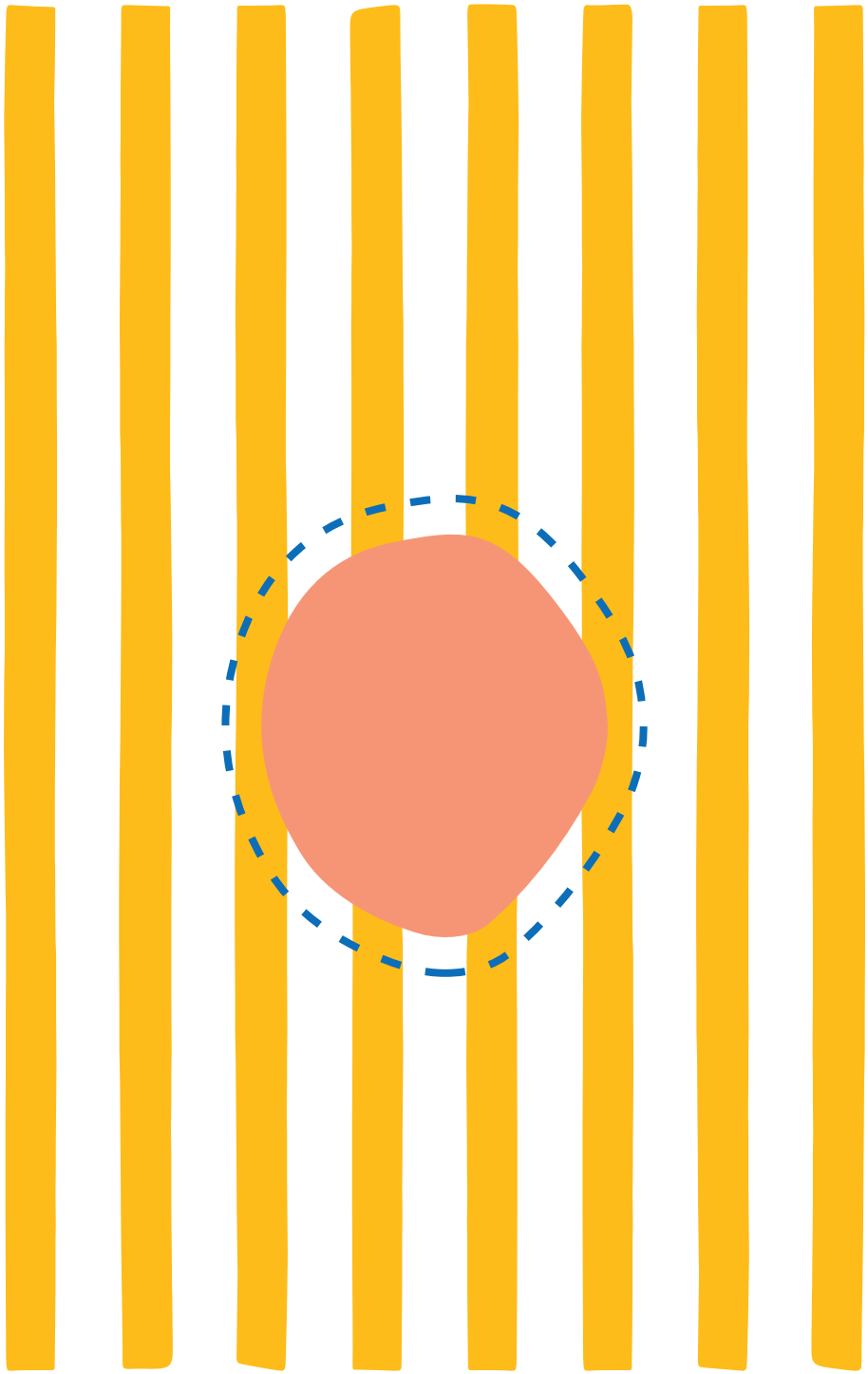

# CHAPTER 5

## Pain in dermatologic surgery: A prospective quantitative study

Eva van Loo · Gabrielle Westerveld · Patty J. Nelemans · Nicole W.J. Kelleners-Smeets

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The number of surgical procedures in dermatology has increased substantially during the last decades.[1] Intraoperative pain is still scantly reviewed in dermatologic surgery.

The objective of this prospective observational study was to assess the prevalence and degree of intraoperative pain in outpatient dermatologic surgery and to identify patient and treatment characteristics associated with an increased risk of severe intraoperative pain. The study was conducted at the Dermatology Department of the Maastricht University Medical Center+, Maastricht, the Netherlands, and approved by the center's medical ethics board. Between October 1, 2016 and January 31, 2017, patients undergoing a surgical treatment (Mohs or conventional excision) under local anaesthesia were asked to complete a pain assessment questionnaire after written informed consent. Patients rated their pain using the pain intensity numeric rating scale (PI-NRS)- 11 (with 0 indicating no pain and 10 indicating the worst pain imaginable).[2] Local anaesthesia consisted of a 10:1 mixture of lidocaine 1% with epinephrine 1:100.000 and sodium bicarbonate 8.4%. Patients undergoing Mohs surgery had additional bupivacaine 0.5% after each stage. Dermatologic surgeons and residents were educated on pain-minimising techniques in local anaesthesia prior to the start of the study.[3]

A total of 199 patients were included, 163 (81.9%) with 1 and 36 (18.1%) with more than 1 surgical site. The baseline characteristics of patients with 1 site are presented in Table 5.1. In total, 169 of 199 (84.9%) patients reported pain (PI-NRS ≥1) during injection of local anaesthetics, with the majority of scores on the lower end of the spectrum (Table 5.1). Overall, 27 of 199 (13.6%) reported severe pain (PI-NRS ≥6). During surgery, 77 of 199 patients (38.7%) reported pain (PI-NRS ≥1) with predominantly low scores of 1 or 2. Severe pain was reported by 8.5%. The risk of severe intraoperative pain was significantly increased in patients with a high pain expectation, a preference for sedation and a PI-NRS score ≥ 6 during anaesthesia (Table 5.2). Furthermore, the relative risk of severe pain was especially high in patients with melanoma requiring a deep excision compared to patients treated with a superficial excision for non-melanoma skin cancer (relative risk 21.7).

In general surgery, the association of pain expectation and anxiety with postoperative pain has previously been reported.[4] The explanation for the observed high risk of severe pain in melanoma patients may be that in our center, these patients receive surgery on a short term and may have high anxiety levels. The hypothesis that anxiety contributes to higher risk of severe pain could not be evaluated in this study because we did not use a validated anxiety scale.

Maastricht University Medical Center+ is an academic hospital with a regional function and serves a broad spectrum of dermatologic surgery patients, but as this is a single-center study generalizability of the results may be a concern.

In conclusion, most patients report only minor pain during dermatologic surgery under local anaesthesia. A small group experiences severe intraoperative pain. Awareness of risk factors for severe pain helps improving pain management and selection of candidates for pain-reducing interventions. High-risk patients might benefit from conscious sedation (limited to hospital setting) or oral anxiolytics.[5]

**Table 5.1**: Patient and treatment characteristics of patients with 1 surgical site.

| **Patient/treatment characteristic** | **Value (N=163)*** |
|---|---|
| Sex, n (%) | |
| Male | 84 (51.5) |
| Female | 79 (48.5) |
| Age, y, mean ± SD | 67.1 ± 14.6 |
| Location (%) | |
| Nose | 29 (17.8) |
| Ear | 16 (9.8) |
| Lip | 5 (3.1) |
| Periocular | 9 (5.5) |
| Frontotemporaal | 13 (8.0) |
| Cheek | 11 (6.7) |
| Skull | 15 (9.2) |
| Neck | 3 (1.8) |
| Trunk | 30 (18.4) |
| Extremities | 32 (19.6) |
| Defect size, mm, mean ± SD | 26 ± 17.2 |
| Type of surgery, n (%) | |
| Mohs surgery | 42 (25.8) |
| Conventional excision, surgical level | |
| Subcutaneous fat | 92 (56.4) |
| Subgaleal, periosteum or cartilage | 12 (7.4) |
| Muscular fascia | 17 (10.4) |
| Diagnosis , n (%) | |
| Non-melanoma skin cancer | 140 (85.9) |
| Melanoma | 12 (7.4) |
| Benign tumour | 11 (6.7) |

**Table 5.1**: (continued)

| Patient/treatment characteristic | Value (N=163)* |
|---|---|
| Pain scores during local anaesthesia, n (%) | |
| 0 | 26 (16.0) |
| 1 | 33 (20.2) |
| 2 | 34 (20.9) |
| 3 | 22 (13.5) |
| 4 | 14 (8.6) |
| 5 | 14 (8.6) |
| 6 | 4 (2.5) |
| 7 | 5 (3.1) |
| 8 | 8 (4.9) |
| 9 | 1 (0.6) |
| 10 | 2 (1.2) |
| Pain scores during surgery | |
| 0 | 103 (63.2) |
| 1 | 19 (11.7) |
| 2 | 12 (7.4) |
| 3 | 5 (3.1) |
| 4 | 8 (4.9) |
| 5 | 2 (1.2) |
| 6 | 5 (3.1) |
| 7 | 3 (1.8) |
| 8 | 2 (1.2) |
| 9 | 1 (0.6) |
| 10 | 3 (1.8) |

SD: standard deviation.

*Only pain scores of patients with 1 lesion are reported. Distribution of pain scores in patients with more than 1 lesion was similar (results not shown).

**Table 5.2**: Relative risks (RR) with 95% confidence intervals (CI) of severe pain associated with patient, tumour and treatment characteristics.

| Characteristics | N (n=163) | PI-NRS ≥6 | PI-NRS <6 | RR (95% CI) | *P*-value* |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 84 | 6 (7.1%) | 78 (92.9%) | ref | |
| Female | 79 | 8 (10.1%) | 71 (89.9%) | 1.42 (0.51-3.90) | 0.689 |
| Age | | | | | |
| 0-70 years | 86 | 9 (10.5%) | 77 (89.5%) | ref | |
| >70 years | 77 | 5 (6.5%) | 72 (93.5%) | 0.62 (0.22-1.77) | 0.533 |
| Pain expectation | | | | | |
| 0-5 | 133 | 8 (6.0%) | 125 (94.0%) | ref | |
| 6-10 | 30 | 6 (20.0%) | 24 (80.0%) | 3.33 (1.25-8.88) | **0.030** |
| Sedation preference | | | | | |
| No | 145 | 6 (4.1%) | 139 (95.9%) | ref | |
| Yes | 18 | 8 (44.4%) | 10 (55.6%) | 10.74 (4.20-27.45) | **<0.001** |
| Pain score anaesthesia | | | | | |
| 0-5 | 143 | 6 (4.2%) | 137 (95.8%) | ref | |
| 6-10 | 20 | 8 (40.0%) | 12 (60.0%) | 9.53 (3.69-24.64) | **<0.001** |
| Defect size | | | | | |
| 0-20 mm | 59 | 6 (10.2%) | 53 (89.8) | ref | |
| >20 mm | 104 | 8 (7.7%) | 96 (92.3%) | 0.76 (0.28-2.01) | 0.801 |
| Diagnosis | | | | | |
| NMSC | 140 | 8 (5.7%) | 132 (94.2%) | ref | |
| Benign | 11 | 1 (9.1%) | 10 (90.9%) | 1.60 (0.22-11.60) | 0.635 |
| Melanoma | 12 | 5 (41.7%) | 7 (58.3%) | 7.30 (2.82-18.84) | **0.001** |
| Diagnosis and excision type | | | | | |
| NMSC - superficial | 76 | 2 (2.6%) | 74 (97.4%) | ref | |
| NMSC- Mohs | 42 | 4 (9.5%) | 38 (90.5%) | 3.62 (0.69-18.94) | 0.139 |
| NMSC – deep** | 22 | 2 (9.1%) | 20 (90.9%) | 3.46 (0.52-23.13) | 0.251 |
| Benign - superficial | 11 | 1 (9.1%) | 10 (90.9%) | 3.46 (0.34-35) | 0.378 |
| Benign – deep** | 0 | - | - | - | - |
| Melanoma – superficial (diagnostic) | 5 | 1 (20.0%) | 4 (80.0%) | 7.6 (0.82-70.2) | 0.185 |
| Melanoma –deep **(therapeutic) | 7 | 4 (57.1%) | 3 (42.9%) | 21.71 (4.80-98.34) | **<0.001** |
| Re-excision | | | | | |
| No | 146 | 8 (5.5%) | 138 (94.5%) | ref | |
| Yes, melanoma | 7 | 4 (57.1%) | 3 (42.9%) | 10.43 (4.11-26.44) | **<0.001** |
| Yes, other | 10 | 2 (20.0%) | 8 (80.0%) | 3.65 (0.89-14.96) | 0.145 |

PI-NRS: pain intensity -numeric rating scale; RR: relative risk; CI: confidence interval; ref: reference; NMSC: non-melanoma skin cancer; CE: conventional excision.

**P*-values were derived from the Yates corrected chi-square test or from the mid-P exact test in case of at least 1 expected value (row total X column total/grand total) <5.

** 'Deep' includes all conventional excisions beyond the level of the subcutis (muscular fascia, subgaleal, periosteum or cartilage).

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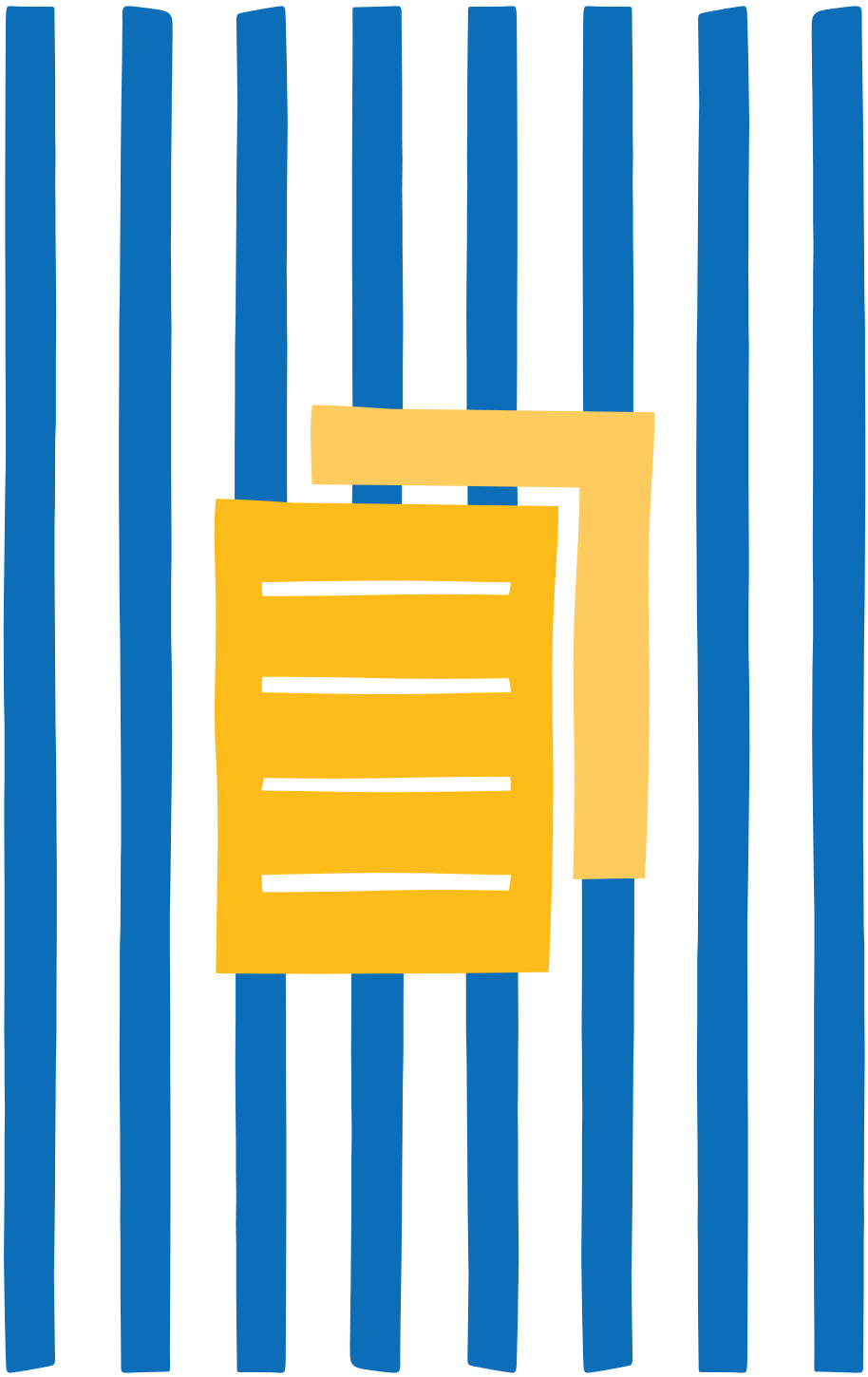
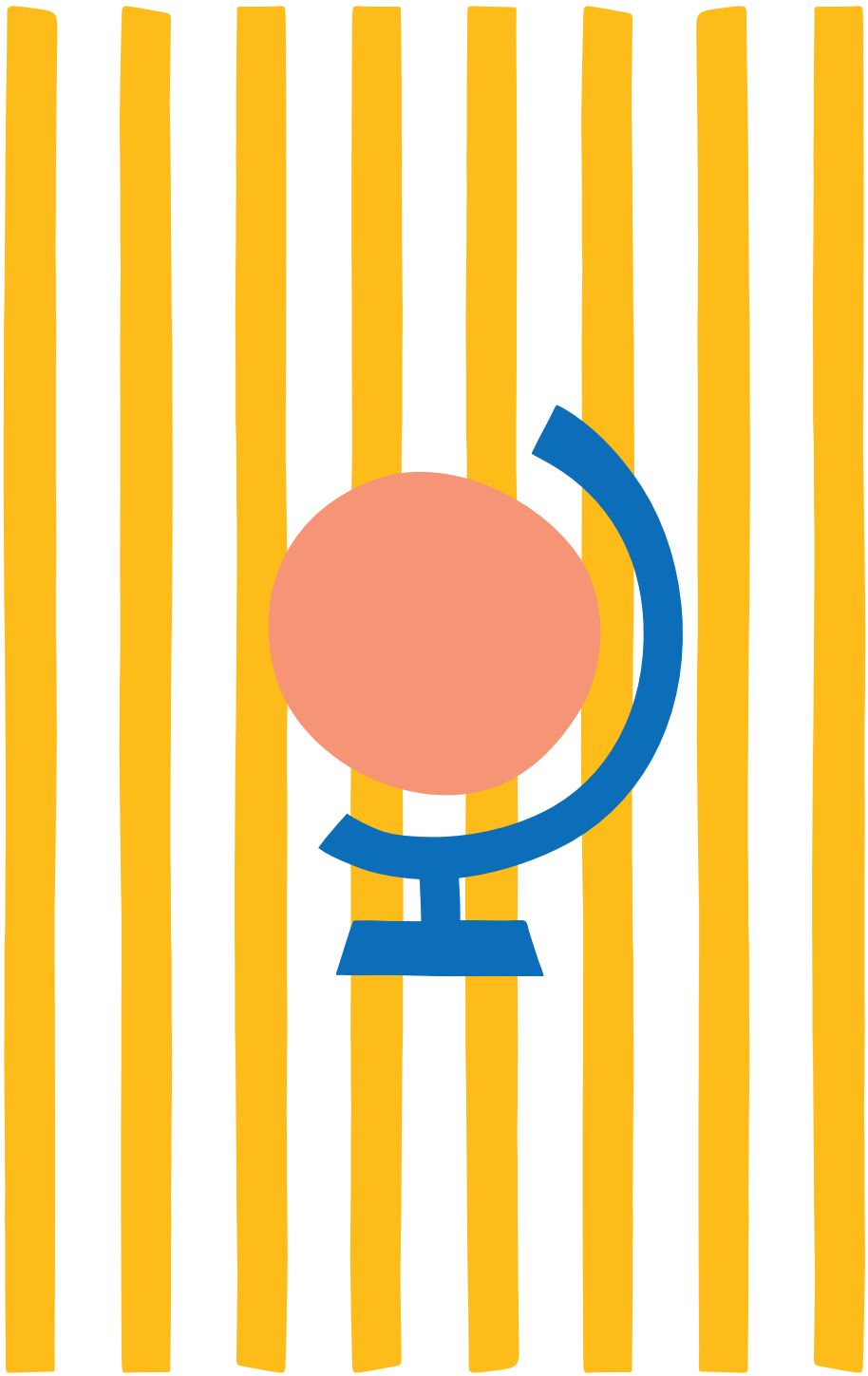
# GENERAL DISCUSSION

# SUMMARY



# DUTCH SUMMARY



# IMPACT PARAGRAPH

# ADDENDUM

Curriculum vitae

List of publications

Acknowledgements

# Curriculum vitae

Eva van Loo werd op 3 september 1988 geboren te Sittard. Zij groeide op in Landgraaf met haar ouders en zus. Na het cum laude behalen van haar diploma tweetalig VWO voor 2 profielen (natuur en techniek en natuur en gezondheid, extra vak: economie), aan het Eijkhagen College te Landgraaf, startte zij met de opleiding geneeskunde aan de Universiteit Maastricht. Uit een keuze-coschap kinderlonggeneeskunde in het Children's Hospital of Westmead, Sydney, Australië, volgde een eerste wetenschappelijke publicatie. De interesse voor dermatologie werd gewekt tijdens haar coschap op de afdeling Dermatologie in het Maastricht UMC+. Hier doorliep zij ook haar wetenschappelijke stage in het laatste jaar van de master, waarbij zij onderzoek deed naar de 10-jaars resultaten van het Mohs project. De resultaten hiervan staan beschreven in dit proefschrift. Na het behalen van het artsenexamen in 2012 werkte zij als ANIOS Interne Geneeskunde in het VieCuri MC te Venlo en later als ANIOS Dermatologie bij de Dr. Kolbach Kliniek (ZBC) te Maastricht. In september 2014 werd ze aangenomen voor de opleiding Dermatologie en Venereologie in het Maastricht UMC+. In 2016 startte zij naast haar opleiding met promotieonderzoek, onder begeleiding van dr. Kelleners-Smeets, prof. dr. Steijlen en prof. dr. Mosterd. In 2018 rondde zij haar opleiding tot dermatoloog af en sindsdien is zij werkzaam als staflid in het Maastricht UMC+, met aandachtsgebieden dermato-oncologie en dermatochirurgie (waaronder Mohs chirurgie). Van maart tot juni 2020 maakte zij een korte uitstap om in samenwerking met Netwerk Acute Zorg Limburg (NAZL) een Regionaal Centrum Patienten Spreiding Limburg op te zetten in het kader van de COVID pandemie**.** Eva is lid van het multidisciplinaire hoofd-hals huidtumoren team van het Maastricht UMC+ en sinds 2022 van de Nederlandse werkgroep Mohs chirurgie. Zij woont in Maastricht met haar man en dochter.

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Cumulative sum analysis for the learning curve of optical coherence tomography assisted diagnosis of basal Cell carcinoma. *Oral presentation.* 21th Annual scientific

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