Paving the pathway toward non-invasive diagnosis and treatment of basal cell carcinoma

PAVING THE PATHWAY TOWARD NON-INVASIVE DIAGNOSIS AND TREATMENT OF BASAL CELL CARCINOMA

Kelly Sinx

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CHAPTER 1

General introduction

1.1 INTRODUCTION

At the moment there is a trend in dermatological health care toward more non-invasive diagnostic methods and treatments. If non-invasive options become more implemented in the current clinical setting, this could cause a reduction of workload for dermatologists and costs of medical care might be reduced in the future. Diagnoses could be made in a 'one-stop-shop' setting and patients would become more self-sufficient by treating themselves at home. Therefore, a non-invasive approach would be beneficial to caretakers and patients. In dermatology, basal cell carcinoma (BCC) is ideally suited for such an approach since it is a type of skin cancer with a benign growth character, a good prognosis and a negligible risk of metastasis. In this thesis we investigated options for non-invasive diagnosis and treatment of low risk basal cell carcinoma, paving the way toward implementation in clinical practice in the future.

Basal cell carcinoma

Epidemiology

Over the last decades, the incidence of skin cancer has been increasing worldwide. In the Netherlands, basal cell carcinoma (BCC) is the most prevalent form, with a lifetime risk of 16-20 per cent.(1, 2) Although the mortality is low, morbidity can be substantial in case of an aggressive local invasive growth pattern and due to its frequent localization in the head and neck area.(3)

For the rising incidence of BCC, ultraviolet light exposure is an important etiological factor. Increasing life-expectancy and recreational exposure to sunlight may explain the worldwide increase.(4) Genetic predisposition seems to be important in the development of BCC. Male sex, fair skin types I and II, immunosuppression and arsenic exposure are other recognized factors for the development of BCC.(1) BCCs can be classified with a 'low risk profile' or a 'high risk profile'. The profile is determined by the tumour recurrence probability after treatment, which could be influenced by four prognostic factors: histopathological growth pattern, localisation, size and whether it is a primary or recurrent BCC.(5)

Pathogenesis

The vast majority of BCCs occur sporadically due to a genetic mutation that enhances sonic hedgehog (SHH) pathway signalling. In approximately 80% of sporadic BCCs, genetic mutations can be found in at least one allele of the tumour suppressor gene patched 1 (PTCH1), which acts as an primary inhibitor of the SHH-signalling pathway.(6, 7)

Cessation of the inhibition of the oncogene SMO caused by inactivating mutations of PTCH1 or loss of heterozygosity, leaves SMO in an activated state and downstream effectors are switched on (SUFU, GLI2), leading to enhanced cell proliferation and

development of BCC (Fig. 1).(8) Furthermore, activating mutations in the oncogene smoothened (SMO) can cause BCC development.(9)

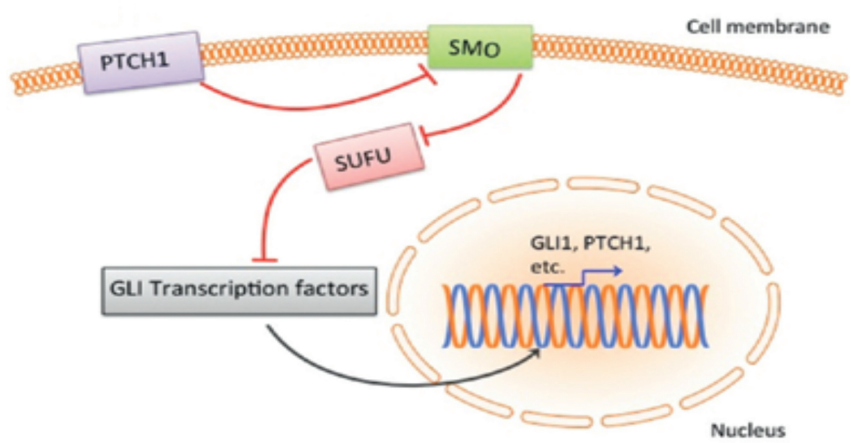

Figure 1. Hedgehog signalling pathway.

Figure reprinted with permission: *Booms P, Harth M, Sader R, Ghanaati S. Vismodegib hedgehog-signaling inhibition and treatment of basal cell carcinomas as well as keratocystic odontogenic tumors in Gorlin syndrome. Ann Maxillofac Surg. 2015;5(1):14-9.*

Clinical and histopathological presentation of BCC subtypes

A simplified histopathological classification of BCCs includes the following three subtypes: nodular, superficial and aggressive variants.(14) The most common subtype is nodular representing 40.6%-57.1% of the BCCs, followed by the superficial (19.5%-30.7%) and the aggressive subtype(14.1%-28.7%).(14, 15)

Superficial BCCs are mainly located on the trunk and clinically show an erythematous and sometimes mildly squamous papule or plaque (Fig. 2A).(16) Histopathologically, these superficial BCCs are characterized by basaloid cells/nests that are attached to or lie in the epidermis.(17, 18)

Nodular BCCs clinically show erythematous papules or nodules with a pearly, shiny aspect and arborizing vessels (Fig. 2B). When the BCC enlarges, a typical central ulcer may appear (rodent ulcer).(16) Histopathology presents large nests of basaloid cells in the papillary or reticular dermis.(17, 18)

Aggressive BCC subtypes include the morpheaform/infiltrative, micronodular, and basosquamous BCC.(16) This type of BCC is clinically difficult to diagnose, since it does not have the typical clinical appearance. It usually appears as a pink to red plaque with ill-defined margins (Fig. 2C).(18)

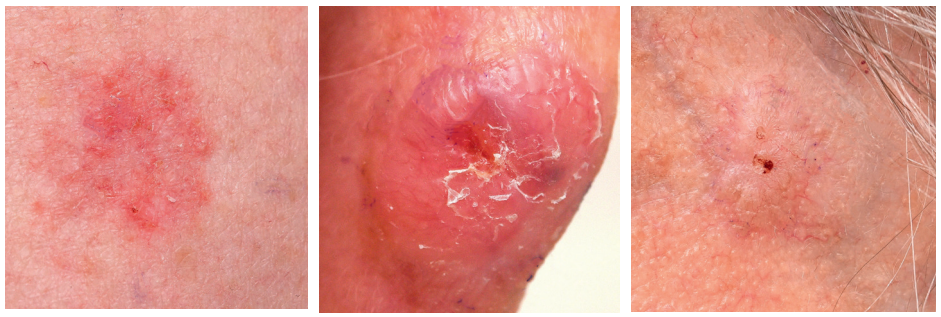

Figure 2. *A.* **Superficial BCC,** *B.* **Nodular BCC,** *C.* **Infiltrative BCC**

Histopathologically, micronodular BCC presents as nodular BCC, however, with remarkably smaller nests, also on histopathological slides the lesion is often difficult to demarcate. Morpheaform/infiltrative BCC is characterized by a few layers of basaloid cells invading collagenized stroma.(18) Basosquamous or metatypical BCC consists of a mix between basaloid and squamous cells and represents a collision between two skin neoplasms with a more aggressive growth pattern.(17, 18)

A BCC can also consist of a combination of the above mentioned subtypes within one lesion.(17)

If a BCC is inoperable due to its size and/or location this is considered a locally advanced BCC Even though BCCs are slow-growing indolent tumors, in rare cases BCC can metastasize. Estimates of the prevalence of metastases vary between 0.003% to 0.55%. (19, 20) Both locally advances and metastasized BCC are referred to as advanced BCC. (21)

Basal cell nevus syndrome

A rare genetic disorder caused by an inherited germline mutation in *PTCH1* is called basal cell nevus syndrome (BCNS), also known as Gorlin syndrome. Patients are born with an already excisting PTCH1 mutation in one of the two alleles.

Alterations in both alleles of a tumour suppressor gene are required to initiate carcinogenesis. Since patients with Gorlin syndrome already have a germ line mutation in *PTCH1*, just one additional somatic inactivating mutation or deletion (leading to loss of heterozygosity, LOH) is sufficient (second hit), resulting in gene deficiency and initiating development to BCC. This makes BCNS patients more susceptible to develop BCC.(10, 11) Therefore, BCNS is characterized by the development of multiple basal cell carcinomas (BCCs) at a young age. Other manifestations of BCNS comprise keratocystic odontogenic tumours of the jaw and palmar pits.(12)

The following criteria establish the diagnosis of BCNS; (1) one major criterion and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria. (13) The criteria are presented in Table 1.

Table 1. BCNS criteria according to Bree et al.

Major criteria	Minor criteria
1. BCC prior to 20 years old or excessive numbers of BCCs out of proportion to prior sun exposure and skin type;	1. Rib anomalies
2. Odontogenic keratocyst of the jaw prior to 20 years of age;	2. Other specific skeletal malformations and radiologic changes (i.e., vertebral anomolies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)
3. Palmar or plantar pitting;	3. Macrocephaly
4. Lamellar calcification of the falx cerebri;	4. Cleft/lip palate
	5. Ovarian/cardiac fibroma
5. Medulloblastoma, typically desmoplastic;	6. Lymphomesenteric cysts
6. First degree relative with BCNS.	7. Ocular abnormalities

Diagnostic methods

Clinical examination seems to be very sensitive for diagnosing BCC (90%), but the specificity has been reported to be low (28.6-48.9%).(22, 23) Addition of dermoscopy can increase the specificity to 54.3%-55.6% compared to clinical examination alone. (22, 23) With respect to discrimination between superficial and non-superficial clinical examination shows 89% sensitivity and a specificity of 64%.(24) Data on accuracy of dermoscopy in subtyping BCCs is not available.(25) Since these diagnostic methods are not optimal, most patients still undergo biopsy to confirm the diagnosis of BCC and to define the subtype. Biopsy is considered as the gold standard for diagnosis and subtyping of BCC.(5, 26) It is important to distinguish between the subtypes of BCC, since a different therapeutic approach is necessary to decrease the risk of recurrences.(5)

A biopsy is an invasive procedure and can be complicated by pain, bleeding, infection or scarring. Furthermore, the potential waiting period for histopathological assessment could be stressful for patients, but also leads to delay of treatment.

According to international guidelines, a biopsy can sometimes be omitted, but only in cases with a high clinical suspicion for a low risk BCC or in patients with multiple BCCs. (26) In the last years there is a trend toward the development of more non-invasive and less time consuming techniques to diagnose and subtype BCCs.

Optical coherence tomography (OCT)
OCT is a non-invasive imaging technique, producing real-time, in vivo, cross-sectional images of lesions with a depth of 1,5-2 mm. Although OCT is a well-established diagnostic tool in ophthalmology, the use of optical coherence tomography in dermatology is fairly new. The principle of OCT is based on light interferometry. The signal of extraction leads to a black and white scan, similar to an ultrasound.(27) The use of light instead of sound results in a higher resolution than ultrasonography.(28)

OCT provides a field of view of 6mmx6mm and a depth up to 2mm. This makes it possible to get a horizontal view of the different skin layers and adnexa. These horizontal images allow to assess the lesion and skin layers in the same direction as a histopathological section, making it easier to interpret for clinicians/dermatologists who are already used to histopathological assessment.

The machine contains a probe, which is placed on the skin lesion and within 30 seconds an image is made (Fig. 3.)

Figure 3. Vivosight OCT

Various histopathological structures are known to be characteristic for BCC and BCC subtypes.(16) These characteristics can also be recognized on OCT images. BCC in general can be recognized by the following characteristics on OCT: change or rupture of

the dermo-epidermal junction; dark ovoid nests with or without a dark, hyporeflective halo and dilated dermal capillaries, directed toward the basal cell islands and signal free lateral edges (Fig. 4).(29)

Superficial BCC becomes visible on OCT in black and white nest structures originating from the epidermis or dermo-epidermal junction.(29, 30)

Nodular BCC on OCT shows basal cell nests localized in the papillary or superficial reticular dermis with no attachment to the epidermis. Around the nests a hypo reflective border is visible followed by a darker halo representing peripheral palisading. Sometimes, dilated vascular structures are seen.(29, 30)

The typical appearance of micronodules are also visible on OCT image in micronodular BCC.(30)

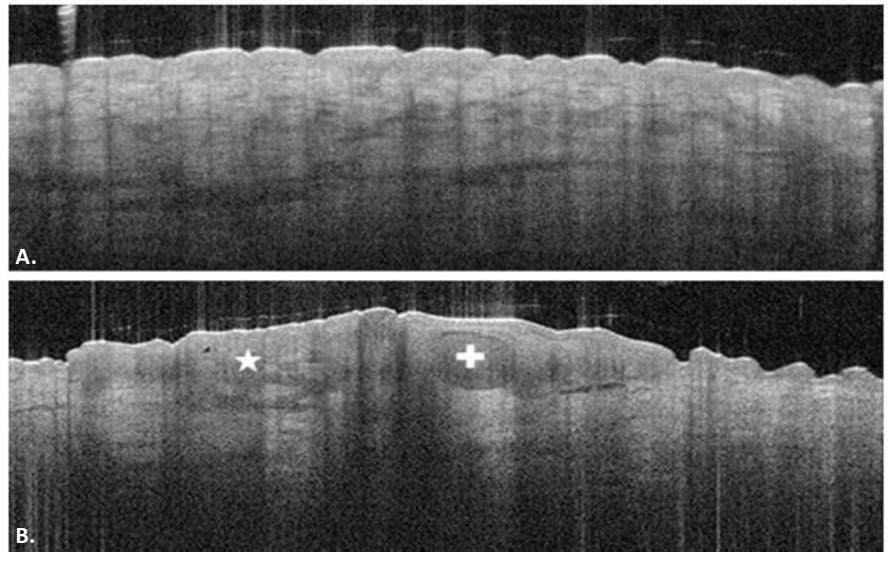

Figure 4. Images made with OCT (Maastricht UMC+, Dermatology deparment).

A. Normal skin. B. Basal cell carcinomwa with visible ovoid nests+, ruptured dermo-epidermal junction*.

Previous studies have shown that this OCT allows discrimination of BCC from non-BCC. (22, 23, 31-35) The method also has the ability to distinguish between superficial BCC and other subtypes in patients with clinical suspicion of superficial BCC.(31) Based on these studies, it seems a promising method for non-invasive diagnosis of BCC with the potential to avoid biopsy in a substantial part of patients. Furthermore, OCT can be

used in the management of basal cell carcinomas such as evaluating therapy progress, as well as in the pre-surgical assessment of tumour resection margins.(29, 31)

If OCT appears to be a valuable diagnostic technique, this might lead to a reduction of the number of biopsies in the future. Before wide scale implementation of OCT in clinical practice, it is important to evaluate the accuracy and applicability of this technique when compared with standard care.

Treatment

Several different treatment options are available for BCC depending on subtype, localisation and whether it is a primary or secondary BCC.(3, 36-38) Age and cosmetic results are taken into account when discussing therapeutic options with the patients. Overall, costs of a treatment can also be an important determinant in the choice for a treatment, as insurance companies may steer in the choice between otherwise comparable treaments. A positive development nowadays is the increased involvement of patients in the process of choosing a treatment. Discrete choice experiments are performed to evaluate which aspects of a treatment determines the preferences of patients.(39, 40) Patients become more informed about their treatment in advance by clinicians and online information tools, making them more capable to make their own treatment decision. (41) The treatment of BCC is a good example in this process because of the multiple treatment options.

Surgical excision is still the gold standard for the treatment of BCC regardless of the subtype.(42-44) Approximately 30% of BCC patients will develop one or more subsequent BCCs, which leads to multiple excisions.(45)

Due to possible adverse events, such as infection and scarring and the fact that BCC usually shows a fairly benign growth pattern, non-invasive treatments become increasingly interesting as alternative treatment for excision, especially in patients with frequent excisions and consequently multiple scars.

For superficial BCCs non-invasive treatments, such as topical imiquimod 5% cream, 5– fluorouracil (5-FU) or photodynamic therapy (PDT) are already commonly used. (26) A large randomized controlled trial that compared these three treatments in the treatment of superficial BCC found that 5 years after treatment imiquimod 5% cream was associated with a significant lower risk of recurrence compared to 5-fluorouracil and PDT.(46) With a 5-year clearance rate of 82.5%, imiquimod 5% cream is therefore considered as the most effective non-invasive treatment. The cure rate of surgery for low risk BCCs is 96%-97.7% after 5 years follow-up.(5, 47) Surgery is therefore still the gold standard regarding efficacy, however, guidelines state that imiquimod 5% cream is a good alternative in patients with sBCC who prefer the benefits of non-invasive treatment over efficacy.(5)

For nodular BCCs, surgical excision is still considered as the first treatment option in (inter)-national guidelines.(26) Since nodular BCC is a low risk BCC with a compact, not deeply infiltrating growth, non-invasive treatment with imiquimod 5% cream was also expected to be a good treatment option for this indication. It has the advantage of less scarring and could provide a tool to treat more patients on a short notice, because treatment can take place directly and performed by the patients themselves. Williams et al compared treatment with imiquimod 5% cream to treatment with surgical excision for nodular BCC and found an a succes rate of imiquimod 5% cream of 81.1%, which was inferior to excision with a success rate of 98.8% after 5 years of follow-up.(47) Combining treatments might improve efficacy of imiquimod 5% cream. For example, the efficacy and penetration of imiquimod 5% cream treatment for nodular BCC might be increased by prior debulking of the tumour with curettage. Possibly, cure rates can be obtained comparable to those of non-invasive treatment of superficial BCC. Several small studies have investigated the treatment of imiquimod 5% cream with prior curettage and found high sustained clearance rates (90-100%)with different follow-up periods from 6 weeks to 1 year. However randomized controlled trials with head to head comparison of imiquimod 5% cream and curettage to excision are lacking.(48-51)

Most non-invasive treatments for BCC are topically applied and prescribed very often. However, in advanced BCC, where surgery and radiotherapy are not possible anymore, the only alternative is systemic treatment with a smoothened inhibitor, which specifically targets the hedgehog pathway. Available are the substances vismodegib and sonidegib, of which vismodegib is the only one that is FDA)Food and Drug Administration) and EMA (European Medicines Agency) approved for the treatment of advanced BCC.(52) Treatment with systemic hedgehog inhibitors could also be an option for patients with syndromal development of multiple BCCs, basal cell nevus syndrome. Due to the development of these multiple BCCs, surgical excision can become an unwanted treatment due to the excessive scarring.

This thesis focusses on surgical excision and non-invasive treatment with curettage/ imiquimod 5% cream and vismodegib. Therefore, a more detailed description of these treatment options for BCC is given.

Excision

For superficial and nodular BCC a 3mm clinical excision margin is accepted in the Netherlands, whereas for aggressive subtypes a 5mm clinical safety margin is required. (26) Surgical excision is generally performed under local anaesthesia in a hospital setting. Clearance rates after 5 year follow up are 87.9% for high risk BCC and up to 98% for low risk BCC.(47, 53) An advantage of excision is that it enables confirmation of tumour clearance by histopathological examination.

Curettage
A curette is a round shaped scraper, that only shaves away superficial skin. Curettage is the procedure in which the curette is used to scrape away lesions, usually until the level of normal dermis. There is only an erosion visible which usually heals within 1 week.

According to the British guidelines for treatment of BCC, curettage and electrodessication (C&E) is a good treatment option for low-risk nBCCs.(42) It is a quick, relatively painless procedure and does not require extra hospital visits for dressing changes or suture removal.

However, reported recurrence rates for BCCs treated with C&E range from 7.7% to 47%. More importantly, treatment with C&E often leads to a poor cosmetic result with hypertrophic scarring.(54, 55) The risk of hypertrophic scarring is generally attributed to the electrodessication component(56). Although curettage alone is not an accepted treatment modality for nBCC, in combination with a different therapy it could be an option.(57)

Imiquimod 5% cream
Imiquimod 5% cream is an immune-response modifier. It functions as an agonist of Toll-like receptor-(TLR)-7 and TLR-8. Due to activation of TLR7 and 8, a cascade of cytokines and chemokines is released followed by induction of an innate and cellular immune response against the tumour cells.(58, 59) Furthermore, imiquimod 5% cream has been reported to induce apoptosis on tumour cells.(60) A study on cell cultures suggests that imiquimod 5% cream might be able to directly inhibit sonic hedgehog signalling by negatively modulating GLI activity, however, evidence is still scarce .(61)

Imiquimod 5% cream is approved by the FDA and EMA for the treatment of condylomata acuminata, actinic keratotis and superficial BCC. In superficial BCC, imiquimod 5% cream is applied for 6 weeks, 5 days in a row once daily. Application should last approximately 6-10 hours, so patients are advised to apply imiquimod 5% cream in the evening and remove it the next morning. Side effects include erythema, crusting, erosions, oedema, vesicles and even flu-like symptoms.(62)

Vismodegib (systemic smoothened inhibitor)
Smoothened (SMO) is the primary target for the development of systemic smoothened-inhibitors for the treatment of BCC. SMO inhibition prevents the downstream activation of GLI transcription factors, leading to suppression of downstream genes associated with BCC development. Vismodegib is a hedgehog pathway inhibitor that prevents activation of the sonic hedgehog pathway by inhibition of the smoothened (SMO) protein (Fig. 5).(63) Vismodegib capsules are taken daily by the patients in a dosage of 150mg once a day. Response rates in locally advanced BCC and metastasized BCC are approximately 42.9 %- 66.7% and 30.3%- 37.9%, respectively.(52, 64, 65) Unfortunately, the efficacy is

lower than first expected and adverse events are a frequent cause for discontinuation of vismodegib.(21) Moreover, resistance against vismodigib has been demonstrated.(21) In the majority of cases this resistance is due to *SMO* mutations and to a lesser extent also *SUFU* and *GLI2* mutations are found.(66, 67) The use of vismodegib should therefore be well considered and discussed with the patient.

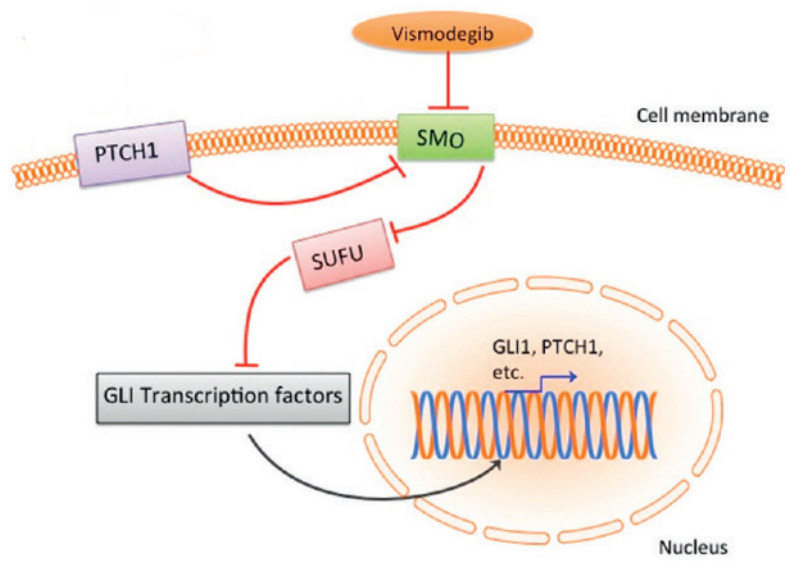

Figure 5. Hedgehog signalling pathway. The mechanisme of action of vismodegib by binding to SMO.
Figure reprinted with permission: *Booms P, Harth M, Sader R, Ghanaati S. Vismodegib hedgehog-signaling inhibition and treatment of basal cell carcinomas as well as keratocystic odontogenic tumors in Gorlin syndrome. Ann Maxillofac Surg. 2015;5(1):14-9.*

Treatment in basal cell nevus syndrome
Although most BCCs can easily be treated with excision or topical non-invasive therapy, treatment is often challenging because patients can develop hundreds to thousands of BCCs during their lives. Radiotherapy is contraindicated, since radiation enlarges the susceptibility of a second hit mutation thus BCC development.(68) And even though the FDA only approved systemic therapy with vismodegib for the indication laBCC or mBCC, vismodigib seems to be valuable in the treatment of BCNS patients. BCNS patients have been treated with vismodegib in studies, since they also develop laBCC and mBCC and therefore participated in clinical trials. (21, 69) Furthermore, a treatment indication can be present with inoperability due to the high number of BCCs of up to hundreds.(70, 71) However, the disadvantages of vismodegib including adverse events and resistance should also be accounted for during the treatment of patients with BCNS. Until now, no overview of literature concerning vismodegib use in BCNS was available. Nevertheless, such an overview is of importance to provide the correct

practical work-up for this group that needs life-long treatment. Combined with other treatment options (e.g. excision and topical therapies), vismodegib could be valuable in a personalized treatment strategy for patients with BCNS.

Aims and outlines of this thesis

Currently, a lot is changing in the field of diagnosis and treatment of BCC. Since BCC is a relatively harmless tumour, non-invasive options are being explored. This thesis contributes to the development and the possible further applicability of non-invasive tools and treatments for basal cell carcinoma and in basal cell nevus syndrome.

Non-invasive diagnosis of basal cell carcinoma: optical coherence tomography.

In *Chapter 2.1* the accuracy of OCT in non-invasive diagnosis and subtyping of BCC compared to clinical examination was investigated in a cohort study using punch biopsy as the gold standard. Furthermore, it was estimated in which proportion of patients with clinical suspicion of BCC a biopsy could be avoided in the future by the use of OCT.

Chapter 2.2 illustrates how a learning curve can be used to estimate the number of cases that need to be assessed with OCT to achieve an adequate level of performance .

Non-invasive treatment in basal cell carcinoma: therapies and preferences

Chapter 3.1 presents the results of a non-inferiority randomised controlled trial investigating the efficacy of treatment with curettage and imiquimod 5% cream compared to surgical excision in patients with nodular BCC . Furthermore, the relative frequency of adverse events, good cosmetic outcome and patient satisfaction is reported.

Patient preferences were evaluated with the use of a discrete choice experiment in *Chapter 3.2*, regarding the treatment with either curettage and imiquimod 5% cream or surgical excision taking into account the efficacy, adverse events, cosmetic outcomes and waiting period.

Non-invasive treatment with vismodegib and other hedgehog inhibitors.

A review of literature of the treatment with vismodegib and other hedgehog inhibitors in BCNS patients and patients with high frequency (HF) BCC patients is given in *Chapter 4.1* of this thesis. The aim of this review was to provide estimates of the frequency of successful treatment, adverse events and development of resistance of the available data on hedgehog inhibitors concerning its use and to discuss and provide a specific work-up for these patients who need life-long treatment. These estimates serve as a basis for suggestions for the clinical management of BCNS- and HF-BCC patients.

In *Chapter 4.2* we discussed a patient with basal cell nevus syndrome (BCNS) with multiple BCCs treated with vismodegib. We describe the resistance to vismodegib which

this patient developed in small BCNS-related BCCs, which is very rare. We performed mutation analyses of these BCCs to clarify the cause of resistance.

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CHAPTER 2

Non-invasive diagnosis of basal cell carcinoma: Optical coherence tomography

CHAPTER 2.1

Optical Coherence Tomography for Noninvasive Diagnosis and Subtyping of Basal Cell Carcinoma: A Prospective Cohort Study

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ABSTRACT

Noninvasive 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 patients with 250 lesions suspected for non-melanoma skin premalignancies requiring a biopsy. Accuracy of BCC diagnosis and subtype on the basis of 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 histopathologic 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 nonsuperficial BCC subtypes and seemed to be a valuable addition to CE alone in the diagnosis and subtyping of BCC.

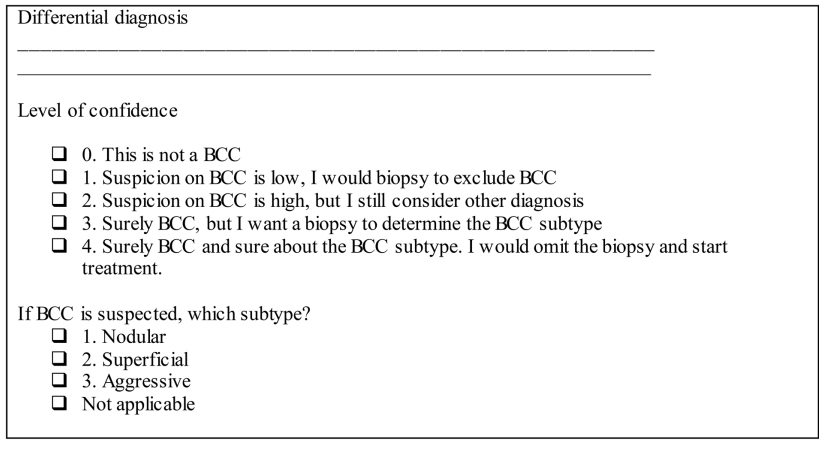
INTRODUCTION

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 (Flohil et al., 2011). A punch biopsy is required to discriminate BCC from alternative diagnoses and to determine the histopathologic subtype (NVDV, 2015, Work Group et al., 2018). Knowledge of the histopathologic subtype is especially relevant in determining the optimal treatment. In case of superficial BCC, treatment with a topical therapy may be prescribed. In nonsuperficial 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 histologic 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 noninvasive 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 (Cheng and Guitera, 2015). 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 (Hussain et al., 2015). 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 (Cheng et al., 2016, Markowitz et al., 2015, Ulrich et al., 2015). 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 methodologic quality make it impossible to guide practice (Ferrante di Ruffano et al., 2018). 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) superficial and nonsuperficial (nodular and aggressive) subtypes of BCC. An additional objective was to evaluate how often OCT scans, in conjunction with clinical images of lesions (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.

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.

CE consisted of macroscopic and/or 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 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 × 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.


Differential diagnosis

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Level of confidence

- ❑ 0. This is not a BCC
- ❑ 1. Suspicion on BCC is low, I would biopsy to exclude BCC
- ❑ 2. Suspicion on BCC is high, but I still consider other diagnosis
- ❑ 3. Surely BCC, but I want a biopsy to determine the BCC subtype
- ❑ 4. Surely BCC and sure about the BCC subtype. I would omit the biopsy and start treatment.

If BCC is suspected, which subtype?

- ❑ 1. Nodular
- ❑ 2. Superficial
- ❑ 3. Aggressive
- ❑ Not applicable

Figure 1. Classification of diagnosis according to level of confidence in BCC diagnosis and BCC subtype. BCC, basal cell carcinoma; DD, differential diagnosis.

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 the criteria for OCT assessment, as previously described (Hussain et al., 2015). 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 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 premalignancy was about 45% (on the basis of retrospective unpublished data of our department). The goal was to evaluate whether the use of cOCT will result in an increase of 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 (Markowitz et al., 2015, Ulrich et al., 2015). Thus, 100 patients without BCC (55% of 182) were expected to be available for evaluation of specificity. This number enabled 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 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 (Obuchowski, 2003).

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 nonsuperficial 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 (DeLong et al., 1988).

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.

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 to 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 1.

Table 1. Baseline Characteristics of Patient and Lesion-Based Analysis; For Categorical Variables Percentages (Absolute Numbers) Are Given

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)	
Histologic 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)

Table 1. Continued

Characteristic	Patient-Based	Lesion-Based
Aggressive BCC	21 (25.3)	26 (22.4)
Other diagnoses (non-BCC), n(%)		
Benign1	48 (48.4)	62 (46.3)
SCC	19 (19.2)	23 (17.2)
Actinic keratosis	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)

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

Ability to distinguish basal cell carcinoma from non–basal cell carcinoma

The area under the receiver operating characteristic curve (AUC) was 85.6% (95% confidence interval = 80.2–89.0%) for clinical examination (CE) alone and 91.2% (95% confidence interval = 86.7–95.8%) for cOCT improvement in diagnostic performance (*P* = 0.061) (Figure 2).

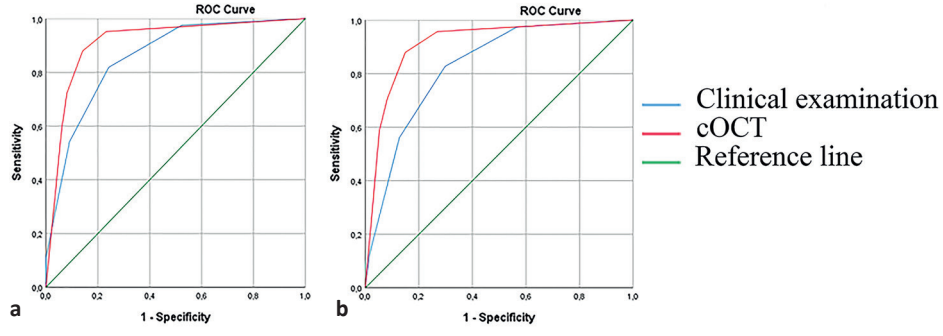

Figure 2. ROC curves for clinical examination and cOCT. cOCT, optical coherence tomography in conjunction with clinical images; ROC, receiver operating characteristic.

ROC curves of both patient (a) - and lesion based (b) analysis

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 (Table 2). When confidence scores 1–4 were considered as test positives and 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.

Table 2. Diagnostic Performance of CE and OCT in cOCT from Patient-Based (182) and Lesion-Based (250) Analyses. Sensitivity and Specificity are Given for Various Cutoff Values of the Confidence Score

	Patient-based CE, % (CI)	Patient-based cOCT, % (CI)	Lesion-based CE, % (CI)	Lesion-based cOCT, % (CI)
		Cutoff 1234 versus 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)
		Cutoff 234 versus 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)
		Cutoff 34 versus 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)
		Cutoff 4 versus 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)

Abbreviations: 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.

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 that of cOCT (59.0%) ($P < 0.001$). The positive predictive values increased to 100% for CE and 89.1% for cOCT, whereas negative predictive value decreased to 57.2% for CE and 73.2% for cOCT.

Ability to distinguish between subtypes of basal cell carcinoma

Accurate subtyping of BCCs is important to decide whether an excision is indicated (nonsuperficial BCC) or whether the BCC can be treated noninvasively (superficial BCC). There were 83 histologically confirmed BCCs in the database (57 nonsuperficial 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 nonsuperficial BCCs and 23 superficial BCCs), which were used for the paired comparison of subtyping ability of CE and cOCT (Table 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 3. Ability to Distinguish between Superficial and Nonsuperficial BCC of CE and OCT in cOCT

	Patient-based CE, % (CI)	Patient-based cOCT, % (CI)	*P*-value (McNemar test)	Lesion-based CE, % (CI)	Lesion-based cOCT, % (CI)	*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

Abbreviations: 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 nonsuperficial 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 histopathologic 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 4). According to histopathology, 49 of those 55 lesions were BCCs (positive predictive values = 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.

Table 4. BCC Diagnosis and Subtyping by cOCT Correlated to Histopathologic Diagnosis for Patient-Based (55) and Lesion-Based (75) 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
Nonsuperficial	3	2	32	37	4	2	41	47
Total	6	15	34	55	7	20	48	75

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

According to histologic subtyping, those 49 BCCs consisted of 15 superficial BCCs and 34 nonsuperficial BCCs. With respect to subtyping, sensitivity to detect nonsuperficial BCCs was 94.1% (32 of 34) for cOCT compared with 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 3).

Table 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 nonsuperficial 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 nonsuperficial BCC by cOCT. Of those, 32 were indeed nonsuperficial 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.

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 1. The 250 lesions consisted of 116 BCCs and 134 non-BCCs, corresponding to 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 when compared with 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 (Cheng et al., 2016, Markowitz et al., 2015, Ulrich et al., 2015).

This study showed that the ability of cOCT to discriminate between superficial and nonsuperficial 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 nonsuperficial 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 tumor. 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 analyses. 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 led 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 noninvasive 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 (Cheng et al., 2016, Markowitz et al., 2015). 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 of 182) of patients.

Within the subgroup of 55 lesions in which BCC was diagnosed with high confidence by cOCT, six lesions turned out not to be BCC after histologic 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 squamous cell carcinoma that was diagnosed as nodular BCC by cOCT. Treatment would have been surgery, but misclassification of invasive tumors like squamous cell carcinoma 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 noninvasive 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 (Williams et al., 2017). 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 overtreated with noninvasive 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

described above is a hypothetic scenario, and whether OCT-guided diagnosis and treatment compromised effectiveness in terms of remaining free from recurrences in 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 and the opportunity to obtain a second scan of a different area within the tumor in case of doubt of the diagnosis, a real-time scanning could benefit the outcome of the OCT-guided strategy. 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.

In conclusion, this study shows that the use of cOCT improves ability to distinguish between BCC and other diagnoses in patients with lesions clinically suspected 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

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ABSTRACT

The amount of training needed to correctly interpret optical coherence tomography (OCT) is undefined. The objective of this study was to illustrate how cumulative sum (CUSUM) charts can be used in determining how many OCT scans novice assessors should evaluate in order to obtain competence in diagnosing basal cell carcinoma. Four hundred lesions suspect for non-melanoma skin cancer were evaluated by OCT in combination with clinical photographs, using a five-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 seems substantial.

ABBREVIATIONS
OCT: optical coherence tomography; BCC: basal cell carcinoma; CUSUM: cumulative sum; NMSC: non-melanoma skin cancer

INTRODUCTION

The incidence of non-melanoma skin cancer (NMSC) has risen over the past decades with basal cell carcinoma (BCC) being the most prevalent cancer in the Caucasian population worldwide.(1-3) BCC diagnosis is often confirmed histopathologically by a biopsy, which also allows BCC subtyping and accommodates choosing 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 the last years, non-invasive diagnostic techniques have improved and interest in its 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 microns and a detection depth of around 1.5 mm.(7) Real time, in vivo images of tissue microarchitecture are provided. For BCC, morphological features on OCT have been defined which show high concordance with regular histopathology slides.(8-11) Several studies explored the diagnostic value of OCT for discrimination between BCC and other diagnoses and 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 consider working with OCT. We studied the learning curve for OCT-assisted diagnosis of BCC using cumulative sum (CUSUM) analysis. Our aim was to illustrate how CUSUM charts can be used to determine how many OCT scans have to be evaluated by novice assessors to achieve an adequate level of competence in distinguishing BCC from other diagnoses.

MATERIAL AND METHODS

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

Patients, 18 years or older, receiving a skin biopsy of a lesion clinically suspect for a NMSC or pre-malignancy were included between February 15 and June 29, 2017. Written informed consent was obtained. Excluded were patients incompetent 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) and consecutively a 3-mm punch biopsy was taken. Histopathology was assessed by independent pathologists, unaware of the OCT diagnosis.

OCT images were coded and saved anonymously. OCT assessment was performed by two 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 (Table 1).(8, 18) Level of confidence in the diagnosis of BCC was documented using a 5-point Likert-scale (range: 0-4, Table 2).

Table 1: Criteria used for assessing optical coherence 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. and vivosightatlas.com

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

Table 2: Level of confidence in diagnosis of BCC on OCT and definition of positive and negative OCT test results according to two 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)

OCT= optical coherence tomography, BCC= basal cell carcinoma

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.

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 of the manufacturer. Also literature on OCT in dermatology was studied and an OCT convention was attended.(19) Around 20 OCT scans were assessed purely for educational purposes and to get 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 spread sheet.(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 one of two 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 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 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). 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

400 OCT scans with corresponding clinical images of 400 lesions in 289 patients were included. All lesions were clinically suspicious for NMSC or pre-malignancy. Of all 289 patients, 208 had one lesion, 63 had two, ten had three, six had four and two had six lesions. Lesion characteristics are presented in Table 3. Histopathology results revealed a total of 192 BCCs and 208 other diagnoses.

Table 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 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.

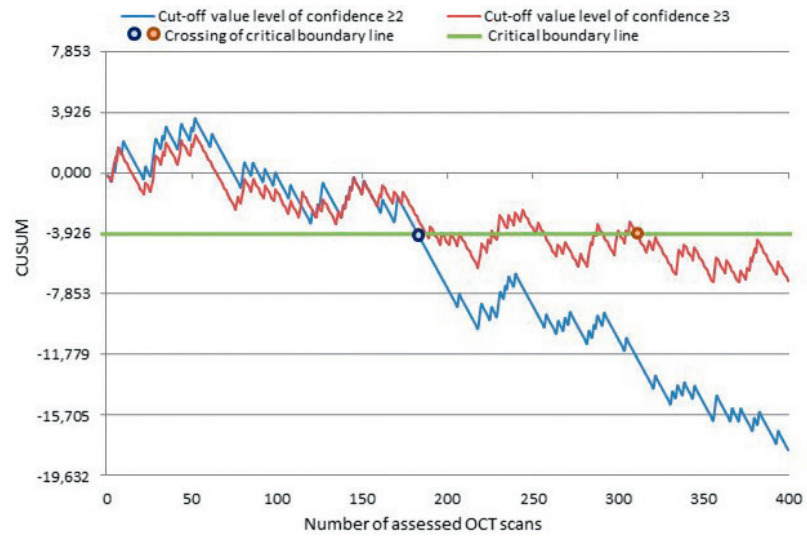

Figure 1: Cumulative sum (CUSUM) curve for optical coherence tomography (OCT) assisted diagnosis of basal cell carcinoma (n=400), with p_0 = 16% and p_1 = 25% for cut-off value level of confidence ≥2 and ≥3.

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 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.

DISCUSSION

With this study we illustrated 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 programs.(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 confident 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. But 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 two (industry-initiated) studies on diagnostic performance of OCT. (13, 14) However, the prevalence of BCC was higher than in our 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, two OCT users with 23 and 8 years of experience (JW and SS) assessed a randomly chosen subset of 100 scans of 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 felt 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 should be assessed with OCT before being able to discriminate BCC from other diagnoses. 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-minute instruction of 50 OCT images or a 20-minute lecture on OCT.(12, 16) In the current study, training was more extensive. We think that a basic level of background knowledge is necessary in order to understand the structures visible on the scans and a similar two-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. So, it seems that a substantial number of scans needs to be evaluated to achieve adequate competence in diagnosing BCC with OCT.

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SUPPLEMENTARY MATERIAL

Appendix 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

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

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

CHAPTER 3

Minimal-invasive treatment in basal cell carcinoma: therapies and preferences

CHAPTER 3.1

Surgery versus combined treatment with Curettage and Imiquimod for Nodular basal cell carcinoma (SCIN): 1-year results of a non-inferiority, randomized controlled trial.

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ABSTRACT

Purpose: Nodular basal cell carcinoma (nBCC) is mostly treated with surgical excision. Interest in minimally invasive treatment of these low-risk tumors is increasing. We assessed the effectiveness of nBCC treatment with curettage and imiquimod cream compared with surgical excision.

Methods: Patients with nBCC included in this randomized, controlled noninferiority trial were randomly assigned to either a curettage and imiquimod cream group or a surgical excision group. The primary endpoint was the proportion of patients free from treatment failure 1 year after the end of treatment. A prespecified noninferiority margin of 8% was used. A modified intention-to-treat and a per-protocol analysis was performed (ClinicalTrials.gov identifier NCT02242929).

Results: One hundred forty-five patients were randomized: 73 to the curettage and imiquimod cream group and 72 to the surgical excision group. The proportion of patients free of recurrence after 12 months was 86.3% (63/73) for the curettage and imiquimod group and 100% (72/72) for the surgical excision group. The difference in efficacy was -13.7% (95% confidence interval -21.6% to -5.8%; 1-sided P = .0004) favoring surgical excision.

Conclusion: Noninferiority of curettage and imiquimod cream cannot be concluded. Given the still high efficacy of curettage and imiquimod cream and the indolent growth pattern of nBCC, curettage and imiquimod could still be a valuable treatment option with the possibility to prevent overuse of excisions. However, it cannot replace surgical excision.

INTRODUCTION

Basal cell carcinoma (BCC) is a slowly growing, locally invasive skin tumor and the most common malignant disease in white patients.[1] A simplified histologic classification of BCCs distinguishes between nodular, superficial, and infiltrative variants, with nodular BCC (nBCC) being the most frequent subtype.[2] Standard treatment of nBCC is surgical excision (SE). Because of the increasing incidence of BCC, its treatment puts a high burden on dermatologic practice. Superficial and nBCCs in low-risk areas are generally accepted to be low-risk tumors with a slow growth pattern and low invasive potential, which has encouraged research on the effectiveness of noninvasive and minimally invasive treatment options. Surgical excision may be accompanied by complications (postoperative bleeding, secondary infection, and disfiguring scars), which is even more relevant in patients who develop multiple BCCs.[3] Noninvasive treatments, such as imiquimod cream, 5-fluorouracil, or photodynamic therapy are currently registered and commonly used for treatment of superficial BCC. Of those, imiquimod proved to be superior with clearance rates of 80.5% at 5 years after treatment.[1,4] Imiquimod cream treatment for nBCC has been investigated in a randomized, controlled, double blind, dose response trial with a surgical excisional endpoint by Shumack et al,[5] and optimal cure rates were found for once daily dosing for 7 days per week. Clearance was evaluated after treatment and cure rates were 71% and 76% after 6- and 12-week daily treatment regimens, respectively.[5] Recently, Williams et al[6] compared the effectiveness of a 12- week imiquimod cream treatment regimen to surgical excision of low-risk superficial BCC and nBCC after 3 and 5 years of follow-up. Imiquimod already showed a high efficacy of 82.5% after 5 years of follow-up but was still inferior to surgery.[6] A treatment strategy mentioned in guidelines for low-risk nBCC is curettage and electrodesiccation, but it often leads to a poor cosmetic result with hypertrophic scarring, probably because of the destruction after electrodesiccation.[1,7,8] Curettage alone is not deemed an accepted treatment modality for nBCC.[9] We hypothesized that combining the mechanic effect of curettage with the immunologic antitumor effect of imiquimod cream could enable a deeper penetration of imiquimod into the tumor. Combining curettage with imiquimod cream for nBCC was already investigated in some small phase II and III pilot studies, showing efficacy rates (initial and sustained tumor clearance) ranging from 94% to 100% with follow-up of 6 weeks to 1 year.[10-12] We aimed to evaluate whether curettage followed by imiquimod cream 5% is noninferior to surgical excision in the treatment of patients with low-risk nBCC.

METHODS

A multicenter, randomized, controlled noninferiority trial was performed at the outpatient clinics of the Maastricht University Medical Centre, Maastricht, and Catharina Hospital, Eindhoven. Eligible patients had a primary nBCC of 4 mm to 20 mm, histologically proven by a specialized dermatopathologist froma 3-mm biopsy

specimen.[13] Mixed type BCCs having a superficial and nodular component were also included. One lesion per patient was included to ensure independence of observations. When patients had >1 BCC, the most accessible lesion or the largest lesion was chosen. Exclusion criteria were: localization in the H-zone of the face or on the hairy scalp, recurrent BCC and BCC with (partly) an aggressive histopathologic subtype (infiltrative, BCC with squamous differentiation), patient life expectancy of\5 years, breastfeeding or pregnancy, serious comorbidities (overall health status/diseases of the patient that makes follow-up impossible), genetic skin cancer syndromes, or the use of immunosuppressive medication during the trial period until 3 months after the end of treatment or within 30 days before enrollment. This trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the local independent ethics committee and all patients provided written informed consent.

The primary study endpoint was the proportion of patients free from treatment failure 1 year after the end of treatment, defined as the absence of residual tumor after 3 months or of local recurrence after 1 year posttreatment.

Patients treated with imiquimod cream had a follow-up visit scheduled at 3 months and both treatment groups had a visit at 12 months after treatment. Two investigators independently examined patients for clinical signs (shiny border, telangiectasia, and ulceration) and dermoscopic characteristics (telangiectasia or ovoid nests) of residual or recurrent tumor as is usually done in standard care. In the event that one of the investigators suspected initial treatment failure or recurrence, a 3-mm punch biopsy specimen was obtained for histologic verification. Only in cases of histologic confirmation of BCC was the lesion considered as a treatment failure.

Secondary endpoints were compliance, cosmetic outcomes, patient satisfaction, and pain and adverse events 1 year posttreatment. Cosmetic outcome was assessed independently by 2 investigators and the patients on respectively a 4-point scale (poor, fair, good, or excellent) and patient and observer scar assessment scale.[14]

Patients were asked for adverse reactions during follow-up visits, completed diaries to report daily on compliance and pain (on a 10-point visual analogue scale where 0 represents ‘‘no pain’’ and 10 represents the ‘‘most severe pain imaginable’’) during treatment and 2 weeks after treatment. Patient satisfaction was evaluated by asking 3 standard questions.

Procedures

Patients allocated to surgical excision could undergo this procedure on the day of randomization. The nBCC was excised under local anesthesia (lidocaine 1%) with a 3-mm clinically tumor-free safety margin into the subcutaneous fat.15 Sutures were removed 1 to 2 weeks postoperatively, depending on tumor localization. Histologic

examination was performed by pathologists on tumor margins using postoperative hematoxyline eosin-stained vertical sections taken from formalin-fixed, paraffin-embedded tissue. Patients assigned to the curettage and imiquimod 5% cream group underwent curettage only of the elevated tumor tissue, up to the level of normal skin at the day of randomization. To allow healing of the erosion, imiquimod 5% cream was started 1 week after curettage. The dosing regimen was a 6-week application, 5 days a week, once a day. Patients were instructed to apply the cream in a thin layer on the tumor including 5 mm to 10 mm of the surrounding skin, to use no occlusive dressing, and to apply the cream at least 1 hour before going to bed and to wash it off the next morning. All suspected unexpected serious adverse reactions were recorded in the national registry (toetsingonline.com).

Randomization and masking

Patients were randomly assigned to either topical imiquimod 5% cream and curettage or surgical excision groups using a computer-generated randomization list with random permuted blocks of 4. Randomization was stratified for participating center. Blinding of patients and physicians to treatment assignment was not feasible because of different scarring.

Statistical analysis

The prespecified noninferiority margin was set at 8% (assuming an efficacy of 98% after surgical excision and considering that curettage with imiquimod 5% cream is inferior if the efficacy would fall below 90%). A sample size of 130 patients (65 per group) was required to be 90% sure that the lower limit of a 2-sided 95% (1-sided 97.5%) confidence interval would exclude a difference in favor of the standard group of [8%. To account for a loss to follow-up of 10%, 144 patients were needed. The absolute difference in the proportion of participants without treatment failure between randomized groups at 1 year posttreatment was calculated with a 2-sided 95% confidence interval (95% CI). Negative differences indicate lower success rates for curettage with imiquimod 5% cream compared with excision. Both an intention to treat and a per protocol analysis were performed. Differences in secondary endpoints were calculated with the chi-square test and t test for independent samples. All data were analyzed with SPSS software (v 23.0; IBM Corp, Chicago, IL). This study is registered on clinicaltrials.gov (NCT02242929).

RESULTS

Between January 2016 and November 2017, 310 patients were assessed for eligibility (Fig 1). Of those, 165 declined to participate because of a strong preference for 1 of the 2 treatments, difficulties to apply cream because of lesion location, older age, or comorbidities. The BCC size of patients declining participation were comparable to those of the included participants. One hundred forty-five patients were included and

randomly assigned to treatment with either curettage and imiquimod cream (n = 73) or surgical excision (n = 72) in 2 hospitals: Maastricht University Medical Centre (n = 137) and Catharina Hospital Eindhoven (n = 8). All patients received the allocated treatment. Four patients (2.8%) were lost to follow-up (Fig 1). Baseline characteristics are shown in Table I. There were slight imbalances between the treatment groups, with higher frequencies of female sex, Fitzpatrick skin type 1, and location of the lesion in head and neck region in the patients assigned to the curettage and imiquimod group. Positive history of BCC was less often reported in this group.

Primary endpoint

One year after treatment, the proportion of patients free from treatment failure was 86.3% (63/73) for the curettage and imiquimod cream group and 100% (72/72) for the surgical excision group.

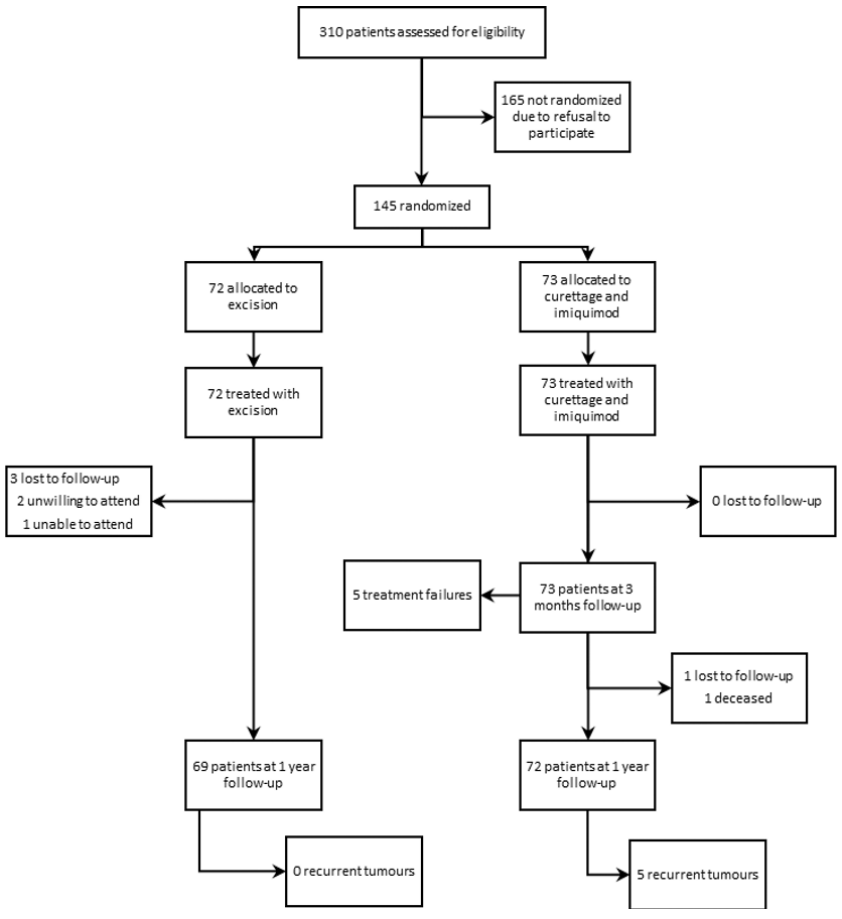

Fig 1. Study flowchart

Table 1. Distribution of patient and tumor characteristics

Characteristics	Total (n= 145)	Curettage and imiquimod (n=73)	Excision (n=72)
Sex			
Male	77 (53.1%)	33 (45.2%)	44 (61.1%)
Female	68 (46.9%)	40 (54.8%)	28 (38.9%)
Age in years median (range)	68 (31-89)	68 (38-89)	67 (31-87)
Skin type			
I	55 (37.9%)	35 (47.9%)	20 (27.8%)
II	90 (62.1%)	38 (52.1%)	52 (72.2%)
History of BCC			
Yes	89 (61.4%)	38 (52.1%)	51 (70.8%)
No	56 (38.6%)	35 (47.9%)	21 (29.2%)
Sun exposure			
Mild	1 (0.7%)	0 (0%)	1 (1.4%)
Moderate	121 (83.4%)	58 (79.5%)	63 (87.5%)
Severe	23 (15.9%)	15 (20.5%)	8 (11.1%)
Size BCC			
Median in mm (range)	7 (4-20)	8 (4-20)	7 (4-20)
≤7mm	75 (52.8%)	34 (46.6%)	41 (59.4%)
>7mm	67 (47.2%)	39 (53.4%)	28 (40.6%)
Location			
Head/Neck	43 (29.7%)	25 (34.2%)	18 (25%)
Trunk	56 (38.6%)	25 (34.2%)	31 (43.1%)
Upper extremities	23 (15.9%)	12 (16.4%)	11 (15.3%)
Lower extremities	23 (15.9%)	11 (15.1%)	12 (16.7%)
Study site			
Maastricht	137 (94.5%)	69 (94.5%)	68 (94.5%)
Eindhoven	8 (5.5%)	4 (5.5%)	4 (5.5%)

The absolute difference was -13.7% (95% CI -21.6% to -5.8%; 1-sided P = .0004) favoring surgery. The lower limit of the 95% CI exceeds the noninferiority margin of -8% and so it cannot be concluded that curettage with imiquimod is noninferior to surgical excision (Fig 2). Per-protocol analyses resulted in similar results with an absolute difference of -12.5% (95% CI -20.1% to -4.7%; 1-sided P = .0009). Residual or recurrent tumors in the curettage and imiquimod group were found on the trunk (n = 4), head/neck (n = 4),

and lower extremities (n = 2). Histopathology showed 1 superficial, 7 nodular, and 2 aggressive BCCs (1 infiltrating, 1 basosquamous).

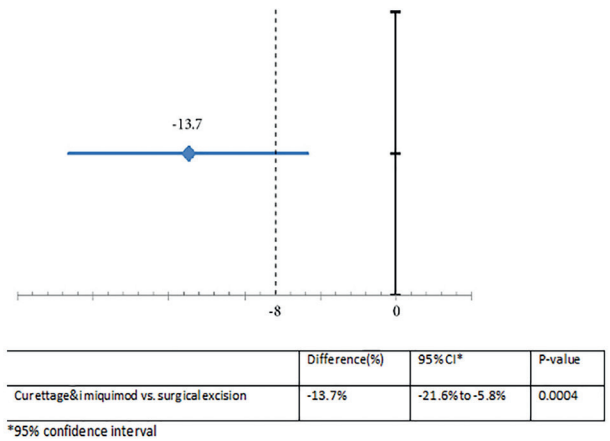

Fig 2. *Absolute difference in efficacy between curettage and imiquimod versus surgical excision.*

The figure shows the absolute difference in treatment efficacy 1 year after treatment (-13.7%) and the horizontal line represents the 95% confidence interval (-21.6% to -5.8%). The lower boundary of the 95% confidence interval crosses the noninferiority limit of -8%.

Subgroup analyses

The median value of BCC size (7 mm) was used as the cutoff for subgroup analyses of the nBCC size. For patients with BCCs ≤7 mm, the absolute difference was -14.7% (95% CI -26.6% to -2.8%; 1-sided P = .008), and for patients with BCCs >7 mm the difference was -12.8% (95% CI -23.3% to -2.3%; 1- sided P = .03), both in favor of surgical excision.

Secondary endpoints

The proportions of patients with residual tumor at 3 months after treatment were 6.8% (5/73) in the curettage and imiquimod group and 0% (0/72) in the surgical excision group (1-sided P = .030). Pain scores revealed that patients treated with curettage and imiquimod cream less often reported moderate to severe pain (13.5%) compared with patients in the excision group (27%), but the differences were nonsignificant (P = .208; Table II). The proportions of patients receiving curettage and imiquimod that reported moderate to severe adverse events varied from 1.7% (for squamae) to 30% (for redness) (Table II). Patients did not report flu-like symptoms in their diaries.

Table II. Pain and adverse events during and 2 weeks after treatment reported by patients*

Pain score (VAS)	Curettage and imiquimod	Surgery
Absent/mild	51/ 59(86.4%)	38/52 (73%)
Moderate	6/59 (10.2%)	11/52 (21%)

Pain score (VAS)	Curettage and imiquimod	Surgery
Absent/mild	51/ 59(86.4%)	38/52 (73%)
Severe	2/59 (3.4%)	3/52 (6%)
Curettage and imiquimod treatment Adverse events	**Absent/mild**	**Moderate/severe**
Redness	42 (70%)	18 (30%)
Erosion	45 (75%)	15 (25%)
Crusts	45 (75%)	15 (25%)
Squamae	59 (98.3%)	1 (1.7%)
Itching	57 (95%)	3 (5%)

VAS, Visual analogue scale.
**Pain and adverse events were recorded in diaries, so data were missing for some participants. Pain scores are categorized into 3 groups: absent/mild, 0-3; moderate, 4-6; and severe, 7-10. Adverse events are categorized into 2 groups: absent/mild and moderate/severe.*

No suspected unexpected serious adverse events occurred in this study. Data on cosmetic outcomes are shown in Table III. Investigator-reported cosmetic outcome after curettage and imiquimod was significantly better than after surgical excision, but patient ratings of cosmetic results were similar in both treatment groups (Table III). An exception concerned the subgroup of BCCs located in the head and neck, where the patient reported that cosmetic outcome was significantly better after curettage and imiquimod than after surgical excision (P = .02). Patient satisfaction results are shown in Table IV. Compliance was 100% in the excision group. Complete compliance was reported in 76.3% (45/ 59) of patients in the curettage and imiquimod group.

Table III. Cosmetic outcomes

	Curettage and imiquimod	Surgery	**P-value (2-tailed)**
Four point scale (N (%))	**Good/excellent**	**Good/excellent**	
Observer 1	61/71 (85.5%)	47/69 (68.1%)	0.012
Observer 2	59/71 (83.1%)	31/68 (45.6%)	<0.001
Patient	67/67 (100%)	60/63 (95.2%)	0.071
POSAS researchers Mean (standard deviation)	**Overall opinion**	**Overall opinion**	
Observer 1	2.3 (1.8)	3.4 (1.9)	0.001
Observer 2	2.7(2.0)	4.2 (2.6)	<0.001
Patient	2.0 (1.7)	2.4 (2.0)	0.282

POSAS, Patient and Observer Scar Assessment Scale; SD, standard deviation.

Table IV. Patient reported satisfaction of the allocated treatment

Patient satisfaction		
	Curettage and imiquimod	Surgery
I would undergo this treatment again		
I agree	57 (85.1%)	63 (95.5%)
I do not agree	8 (11.9%)	2 (3%)
I do not know	2 (3%)	1 (1.5%)
I would recommend this treatment to others		
I agree	59 (88%)	57 (86.4%)
I do not agree	3 (4.5%)	2 (3%)
I do not know	5 (7.5%)	7 (10.6%)
I am satisfied about the cosmetic result		
I agree	59 (88%)	64 (97%)
I do not agree	4 (6%)	1 (1.5%)
I do not know	4 (6%)	1 (1.5%)

DISCUSSION

Surgical excision was significantly more effective than curettage and imiquimod in this study. With a difference of -13.7% and the lower limit of the CI falling below the prespecified noninferiority margin of -8%, it cannot be concluded that curettage followed by imiquimod cream is noninferior to surgical excision. This conclusion also

holds for smaller nBCCs (≤7 mm). The probability of being free from treatment failure at 1 year after the end of treatment was 86.3% and comparable to the 1-year success rate of 85.6% that was found in the excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma (SINS) trial for the subgroup with nBCC. No curettage was performed in the SINS trial, but imiquimod treatment was applied for 12 weeks instead of 6 weeks. Previous phase II to III pilot studies already found higher efficacy rates of 94% to 100% after curettage and imiquimod in the treatment of nBCC. However, these studies had shorter follow-up, used study populations that also included patients with superficial BCC, or applied imiquimod during a longer period (≤12 weeks of treatment).[10-12] The similar success rates after imiquimod treatment of nBCC in this trial and the SINS trial raise the question whether the addition of curettage increases the effectiveness of imiquimod treatment. Curettage may allow for a shorter imiquimod application period of 6 weeks instead of 12 weeks, but this needs to be investigated. This trial does not allow the conclusion that imiquimod treatment with curettage is noninferior to surgical excision. Nevertheless, the success rates of curettage and imiquimod still represent a substantial response. In international guidelines, noninvasive treatment is already generally accepted as standard care for superficial BCC. There seems to be no obvious reason to follow another approach for nBCC than for superficial BCC, because both subtypes are considered low risk and in the SINS trial 3-year clearance rates for nBCC were not much lower than for sBCC (81.8% and 85.1%, respectively). The high incidence of BCC puts a burden on the workload of dermatologists, and therefore curettage and imiquimod can be a valuable treatment alternative. Especially in patients with multiple lesions, this treatment increases capacity and might be cost effective. We found that clinical observers rated the cosmetic outcomes after curettage and imiquimod 5% cream significantly better than after surgery.

Patients reported that the cosmetic outcomes of curettage and imiquimod were significantly better for nBCC localized in the head and neck region compared with excision. The visibility of this region and the possible avoidance of reconstructive surgery can be causes for this finding. There were no flu-like symptoms reported. This is possibly because imiquimod cream was only applied to 1 small, solitary lesion.

A limitation of our study is that a total of 53.2% of the patients eligible for this study did not want to participate. Although it seems unlikely that this selection bias affects the estimate of efficacy, this problem, common to randomized controlled trials, may threaten external validity.

A second limitation is that no adjustment was possible for the slight imbalances in the baseline characteristics between the randomized groups because of the lack of treatment failures in the excision group. Randomization ensures that the allocation of treatment to patients is left purely to chance, but there is no guarantee that all baseline characteristics will be evenly distributed between groups.[16] A third limitation

is the 1-year follow-up period. Longer observation is required to ensure that late recurrences are not missed. However, the 5-year results in the SINS study showed that most treatment failures were identified early within the first year after treatment and that recurrences of low-risk BCC after topical imiquimod did not appear to be difficult to treat.[6] Overall, in the treatment decision for nBCC the benefits of curettage and imiquimod should be weighed against the decrease in effectiveness compared with excision. Given the still high efficacy and the fairly indolent growth pattern, curettage and imiquimod could still be a valuable treatment option in nBCC, with the possibility to decrease the workload in clinical practices. It cannot, however, replace surgical excision as the first treatment choice. We thank MEDA pharma for donating 5% imiquimod cream free of charge. We thank Kiki Frencken for her enthusiasm and her contribution to the design of this study.

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CHAPTER 3.2

Patient preferences for curettage followed by imiquimod 5% cream versus surgical excision for the treatment of nodular basal cell carcinoma: A discrete choice experiment

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Submitted

ABSTRACT

Background: Nodular basal-cell carcinoma (nBCC) is most commonly treated with surgical excision. Since nodular BCC is a indolent growing skin cancer, non-invasive treatments like imiquimod 5% cream could become an option. Recently, a non-inferiority randomised controlled trial was conducted comparing the efficacy of curettage followed by imiquimod 5% cream to surgical excision for nBCC (SCIN-trial, Maastricht UMC+, the Netherlands). We performed a discrete choice experiment along this trial to investigate the preferences of patients for curettage followed by imiquimod 5% cream or surgical excision.

Methods: A discrete choice experiment is an attribute-based survey method for measuring preferences. The participants were asked to choose between surgery and curettage followed by imiquimod 5% cream. Both treatments were described according to four attributes: efficacy, side effects, cosmetic outcomes and waiting time.

Results: In this study, we enrolled 110 patients with a histologically proven nodular basal-cell carcinoma at Maastricht UMC+, the Netherlands. Participants preferred surgery in 60% of the choice sets compared to 40% for curettage followed by imiquimod 5% cream. Overall, better cosmetic outcomes, no side effects and higher efficacy were valued the most when choosing either one of the treatments. Waiting time was not significant. Cosmetic outcomes and side effects were valued as most important.

Conclusions: This DCE represents the average preferences of a patient sample, weighing the importance of different treatment aspects of nBCC. Discussing every aspect of a treatment allows patients to make the decision that fits specifically to their needs. Therefore, treatment with curettage and imiquimod could still be a valuable option in different circumstances.

INTRODUCTION

Basal-cell carcinoma (BCC) is a slow-growing, locally invasive epidermal skin tumour mainly caused by exposure to ultraviolet radiation.(1) Even though this skin tumour metastasizes rarely, it may cause significant morbidity due to the frequent localization in the face and its ability to infiltrate and damage local tissue, which can cause functional impairment and cosmetic problems.(2, 3) Caucasian people have a life time risk of 20% to develop a BCC.(3, 4) BCC consists of roughly three subtypes: superficial, nodular and aggressive. The superficial as well as the nodular form are known for their indolent growth pattern. Currently, non-invasive treatment options gain more interest. For the treatment of superficial BCC (sBCC), topical treatment with imiquimod 5% cream, photodynamic therapy (PDT) and 5-fluorouracil cream (Efudix) are already frequently investigated and applied. Imiquimod 5% cream was proven to be the best non-invasive treatment for superficial BCC.(5) However, for nodular BCC, surgical excision is still the standard treatment. Excision has possible complications such as post-operative bleeding, secondary infections and scarring and could be seen as overtreatment for a indolent skin tumour as nodular BCC. Imiquimod 5% cream might be a treatment option for nodular BCC, but in a previously performed randomized controlled trial, imiquimod 5% cream was found be inferior to surgery after five year follow-up (IMQ 82.5% v.s. surgery 97.7%). (6) To improve the efficacy of imiquimod 5% cream treatment, curettage could be added prior to application with imiquimod, to debulk the tumour and provide better uptake of imiquimod. In Maastricht UMC+, the Netherlands, we investigated the efficacy of imiquimod 5% cream with prior curettage compared to surgical excision in a non-inferiority randomised controlled trial (SCIN-trial).(7) In addition, we were interested what other aspects of treatment patients might consider important. Therefore, we investigated patient preferences for either curettage followed by imiquimod 5% cream or surgical excision in the treatment of nodular BCC with the use of a labelled Discrete Choice Experiment (DCE).

MATERIALS AND METHODS

A Discrete Choice Experiment was performed at the Maastricht University Medical Centre (MUMC+). Adults patients (≥18 years) with a nodular BCC were included. Both patients willing to participate in the SCIN-trial and patients not participating in the trial were included. The DCE was filled out by the patient either before randomisation in the study or before treatment of the nodular BCC at our outpatient clinic. Written and spoken informed consent was provided.

Discrete choice experiment

A Discrete Choice Experiment (DCE) is often used in health care to elicit preferences for treatments, products and programs. (8-10)

The underlying assumption of a DCE is that a treatment or intervention can be described by different attributes. These attributes describe characteristics of a certain treatment like efficacy, cosmetic outcomes, side effects or process related aspects like waiting time. Each attribute has different levels that can be expressed as a continuous or a categorical level.

Based on the attributes and their levels, hypothetical choice sets are created.
A DCE might be labelled which means that the name of the treatment is explicitly mentioned (like surgery versus curettage followed by imiquimod 5% cream) or unlabelled (treatment A or treatment B). In this study a labelled design was used because both treatments, one non-invasive and the other one invasive, have specific levels for each attribute

Attributes and levels
To identify and select the attributes for the DCE, interviews were performed with two focus groups (patients and dermatologists). Participants of the focus groups were asked to value different attributes with the use of a 5-point Likert scale (1 not important until 5 very important). Eventually, the four most important attributes were chosen as input for the DCE; chance of complete clearance (%) after one year of treatment (efficacy), cosmetic outcomes (good, moderate, bad), waiting time (weeks), side effects (no, mild-moderate, severe) during and after treatment (table 1).

Three attributes consisted of three levels and one attribute of four levels.
Based on literature, the lower levels of the treatment success of curettage following IMQ after one year was put on 86% and 94% for surgery. The upper level for surgery is between 90 – 100%, and for curettage following IMQ 94% considering this treatment option will not be more effective than surgery (6, 11-16). The levels for cosmetic outcomes and side effect were defined as a 3-point scale partly based on the DCE of Tinelli et al. 2012, since the attributes show overlap with this DCE.(11) The description of the levels for cosmetic outcomes and side effects differs between curettage followed by imiquimiod 5% cream and excision according to their treatment-specific characteristics. (Table 1) Waiting time for surgical excision included 4 levels, varying from no waiting time to 8 weeks based on expert opinion. The list of attributes and their levels and descriptions are shown in table 1.

Study design
An efficient labelled design was created using Ngene software (version 1.1.1) with priors set to zero because no information was available. Then, a pilot study was performed after which an update of the design was executed with information from the pilot study. In total thirty-six hypothetical choice sets were generated and blocked into three sets of 12. This means that each respondent received 12 choice sets. Respondents were randomly divided over the three blocks. In addition, the order of the attributes (the first and last attribute) was changed in each block to avoid an 'ordering effect', which could potentially lead to patients thinking the first attribute would be the most important.

Table 1: DCE attributes and their levels

ATTRIBUTES	TREATMENT OPTIONS	
	SURGERY	**CURETTAGE + IMQ**
Cosmetic outcomes	**Good** Scar is barely visible	**Good** Treated skin has the same colour as normal skin
	Moderate Visible scar	**Moderate** Treated skin is slightly darker/ lighter than normal skin
	Bad Clearly visible scar	**Bad** Treated skin shows strong discolouration/uneven surface compared to normal skin.
Chance of treatment success one year after treatment (%)	98% 96% 94%	94% 90% 86%
Waiting time	0 weeks 4 weeks 6 weeks 8 weeks	0 weeks
Side effects	**No side effects**	**No side effects**
	Mild- moderate Pain, but no need for pain medication/ disturbing sleep	**Mild- moderate** Mild to moderate irritation, burning or redness, mild to moderate pain or superficial erosions
	Severe Pain with need for pain medication/ disturbing sleep	**Severe** Severe irritation, burning or redness, pain, deep erosions. Flu-like symptoms.

DCE questionnaire
The questionnaire started with a short introduction that described the background and rationale for this study. Then an example of a discrete choice set was presented and explained, followed by a description of the attributes and levels of both treatments (table 1.) Subsequently, 12 choice sets were presented. An example of a choice set is shown in table 2. At the end of the questionnaire, a few sociodemographic questions were asked like age, education and whether patients were previously treated for nBCC as well as questions about the difficulty of the questionnaire.

Table 2: Example of a choice-set

	CURETTAGE + CREAM	SURGERY
Chance of treatment success one year after treatment (%)	90%	94%
Waiting time	0 weeks	8 weeks
Cosmetic outcome after treatment	**Bad** Severely discoloured skin, possibly scar or depression	**Moderate** Visible scar
Side effects during/after treatment	**Mild - moderate** Mild to moderate irritation, burning or redness, mild to moderate pain	**None**
Which treatment do you prefer? (Choose 1 box)	☐	☐

Sample size

Sample size calculation for stated-preference studies is difficult as it depends on the true values of the unknown parameters estimated in the DCE.(8) Given the lack of a definite method for calculating a sample size, we used the rule of thumb as proposed by Johnson and Orme which showed that 100 participants would be required.(17)

Statistical analysis

Data analysis was performed using a multinominal logit (MNL) model with Nlogit software version 5 (Econometric Software Inc.). This model has the following regression equation:

*V(curettage+imiquimod) =β0+ β1*efficacy + β2* cosmetic outcomes + β3* side-effects +ε*
*V(surgery)= β4*efficacy + β5* cosmetic outcomes + β6* side-effects + β7 * waiting time + ε*

V: represents the relative utility that a respondent derives from choosing curettage followed by imiquimod 5% cream or surgery. β0= the alternative specific constant, reflecting a preference for the label curettage followed by imiquimod 5% cream or surgery.
β1- β7= the alternative specific coefficients of each attribute.

A priori, we expected that patients prefer a higher level of efficacy after one year (positive coefficient), and lower levels of waiting time (negative coefficient). For cosmetic outcomes, we hypothesized that a good and moderate result would be valued positive and a bad result negative. With regard to side-effects, we expected no side-effects to be positive and mild-moderate as well as severe side-effects to be negative.

β1; ε= unobserved component of the utility function or error term. Efficacy and waiting time were included as continuous variables while for cosmetic outcomes and side effects effect coding was used. When effects coding is used, zero corresponds to the mean effect for each attribute, rather than the combination of all the omitted categories, and the parameter for the omitted category is the negative sum of the included-category parameters.(18)

In addition, a simulation analysis was applied to test how changes in the attribute levels may impact the choice shares for curettage followed by imiquimod 5% cream or excision using the MNL model results. To that end, we first estimated a scenario using the estimates of the main model. A second and third scenario included the best level in efficacy for both therapies (94% for curettage followed by imiquimod 5% cream and 98% for excision) and the lowest level for curettage followed by imiquimod 5% cream (86%) and the highest level for excision (98%).

The relative importance of the attributes was calculated by multiplying the coefficient of an attribute with the range used for the attribute levels or using the difference in coefficients between the best and worst level of the same attribute (in case of dummy coding). Subsequently, the resulting part-worth utility of each attribute was divided by the sum of all part-worth utilities which gives the relative importance per attribute.(19, 20)Patient characteristics were analysed using descriptive statistics in SPSS software version 23.

RESULTS

In total, 110 patients completed the questionnaire from January 2016 until March 2017. All patients gave informed consent. Of these patients, 41 (37%) participated in the SCIN-trial, 69 (63%) did not. The median age of the participants is 67 years. In total, 87 (79.1%) of the participants considered the questions clear/very clear and 66 (60%) of the participants had previous experience with any kind of treatment of a BCC. Baseline patient characteristics are shown in Table 3.

Table 3: Patient characteristics

Patient characteristics	N Total (n=110)
Age	
Median (range)	67 (28 - 91)
Experience with previous treatment	
None	43 (39.1%)
Cream	4 (3.6%)
Surgical excision	30 (27.3%)
Both	32 (29.1%)
Missing	1 (0.9%)
Education (n=108)	
Primary education	5 (4.5%)
Vocational education	17 (15.5%)
Intermediate general secondary education	21 (19.1%)
Secondary vocational education	22 (20%)
General secondary education	9 (8.2%)
Higher professional education	20 (18.2%)
University	14 (12.7%)
Missing	2 (1.8%)
Clarity of questionnaire (n=106)	
Very clear	25 (22.7%)
Clear	62 (56.4%)
Not clear/unclear	16 (14.6%)
Unclear	3 (2.7%)
Very unclear	0 (0%)
Missing	4 (3.6%)
Patients inside/outside RCT	
Inside RCT	41 (37.3%)
Outside RCT	69 (62.7%)

Results main model

The results of the DCE analysis are presented in Table 4. When making a choice for either one of the treatments, respondents preferred a higher level of efficacy and no side effects. Both a good and a moderate cosmetic outcome with curettage followed by imiquimod 5% cream were positively valued. For excision, a good cosmetic outcome was positively appreciated, however, both moderate and bad cosmetic outcomes were

considered negative. Severe side effects are negatively valued in both treatments, while the attribute waiting time was not statistically significant.

The constant, which measures whether respondents show an preference for the label of one of the two treatments, regardless of the attributes, is not significant (1.332 (-7.32 – 9.98)).

Based on the main effect model, the simulated choice shares for surgery is 60% compared to 40% for curettage followed by imiquimod 5% cream. Using a scenario with the highest level of efficacy for both treatments, the choice shares for curettage followed by imiquimod 5% cream marginally increase to 41%. However, with the use of the lowest level for curettage followed by imiquimod 5% cream and the highest level for excision the choice shares decreased to 33% for curettage followed by imiquimod 5% cream.

Table 4: Main effect multinomial model

	Whole sample N = 110		
	Regression		
	Coefficient	**95% CI**	
Constant	**1.332**	-7.32 – 9.98	Relative importance (part-worth utility)
Curettage followed by imiquimod 5% cream			
Efficacy	**0.057*** **	0.017 – 0.096	0.456
Cosmetic outcomes			
Good	**0.414*** **	0.223 – 0.605	1.063
Moderate	**0.234** **	0.050 – 0.419	
Bad	**-0.649*** **	-0.843 - -0.454	
Side effects			
No	**0.443*** **	0.265 – 0.621	0.976
Mild-Moderate	**0.090**	-0.090 – 0.270	
Severe	**-0.533*** **	-0.729 - -0.337	
			Sum of all part-worth utilities 2.495
Excision			
Efficacy	**0.073***	-0.007 – 0.153	0.292
Cosmetic outcomes			
Good	**0.586*** **	0.398 – 0.775	0.91
Moderate	**-0.263*** **	-0.451 - -0.074	
Bad	**-0.324*** **	-0.509 - -0.138	
Side effects			
No	**0.480*** **	*0.288 – 0.672*	1.026
Mild-Moderate	**0.066**	-0.120 – 0.252	
Severe	**-0.546*** **	-0.723 - -0.369	
Waiting time	**-0.014**	-0.090 – 0.063	
			Sum of all part-worth utilities: 2.228
Number of observations	**1320**		
Log-likelihood function	**-** 762.67		

* *significance at 10% level*
** *significance at 5% level*
*** *significance at 1% level*

Relative importance
When the part-worth utility of each attribute was divided by the sum of all part-worth utilities, this gives the relative importance per attribute in percentages. For curettage followed by imiquimod 5% cream the cosmetic outcome was the most important attribute in order of importance (43%) , followed closely by side effects (39%) and finally efficacy (18%). For excision, side effects was considered the most important attribute (46%), followed by cosmetic outcomes (41%) and efficacy(13%).

DISCUSSION

This study examined the preferences of patients concerning the treatment of nodular BCC with either curettage and imiquimod 5% cream or surgery using a DCE. Our results show that patients when making a choice significantly preferred a higher efficacy, better cosmetic outcomes and no side effects. Overall, patients preferred surgery (60%) in the majority of the choice sets over curettage followed by imiquimod 5% cream (40%).

Previous studies that investigated preferences in BCC treatments showed preferences toward treatment with imiquimod 5% cream. The DCE study of Tinelli et al. concluded that participants preferred imiquimod 5% cream over excision for the treatment of both superficial and nodular BCC and that all treatment characteristics influenced their decision.(11) In addition, their study showed that patients were more likely to be worried about their cosmetic outcomes and side effects than for chance of clearance and costs. Our results showed that, in order of importance, both cosmetic outcome and the chance of side effects are valued as most important when making a choice for either the combined treatment curettage followed by imiquimod 5% cream or surgery. The importance of a good cosmetic outcome was also shown in another DCE that compared different treatment options for BCC in general. It turned out that patients with a BCC in the head neck area were particularly interested in cosmetic outcome.(2) However, in our DCE questionnaire, we described that the nBCC for the hypothetical choice sets was located on the body and not in de head and neck area. Possible explanations in our case for the ordering of cosmetic outcomes and side effects could be that we explained that a nodular BCC is not life threatening and a recurrence can easily be treated with an excision. In addition, the majority of the patients already had experience with BCC and different treatments. As a consequence, they might be less worried about the efficacy and more about potential side-effects of a treatment and cosmetic outcomes. However, we would like to note that although efficacy was last with regard to the order of importance, it is still an important attribute influencing the preference for a treatment as shown by our results. In this DCE, patients preferred excision more often than curettage and imiquimod. An explanation could be the inclusion of patients inside and outside the RCT. Patients that are willing to participate in a randomised trial often are open to new treatments. It seems plausible that patients outside the trial were inclined to choose surgical excision more often since that is the standard therapy

they are familiar with. Although this could introduce status quo bias which means that patients prefer what they have experienced or know, we think that including patients from in- and outside the trial resulted in a higher patient diversity that is a better reflection of the population with a nBCC.

This DCE was performed alongside a randomized non-inferiority study investigating the efficacy of curettage followed by imiquimod 5% cream versus excision.(7) The non-inferiority margin was set at 8%, assuming an efficacy of 98% after surgical excision and considering that curettage followed by imiquimod 5% cream is inferior if the efficacy would fall below 90%. The clinical results show an efficacy of 86.3% for curettage followed by imiquimod 5% cream compared to 100% efficacy in surgical excision one year after the end of treatment. However, the lower limit of the 90% confidence interval exceeds the -8%, which means it could not be concluded that curettage with imiquimod is non-inferior to surgical excision. The rationale behind the non-inferiority design was that, even though it is expected that curettage followed by imiquimod 5% cream is not more effective than excision, it might have benefits in other outcomes like cosmetic outcomes or side effects. The results of this DCE indeed show that not only efficacy but also other aspects like cosmetic outcome and side effects influence the choice for a treatment.

In this DCE a moderate cosmetic outcome is positively valued in curettage followed by imiquimod 5% cream and negatively in excision. Different descriptions of the cosmetic outcomes were given for curettage followed by imiquimod 5% cream and excision. Based on these results, a moderate cosmetic outcome in excision (visible scar) has different implications than the description of a moderate cosmetic outcome in curettage followed by imiquimod 5% cream (discolouration). It seems that discolouration is a more acceptable cosmetic outcome than a visible scar.

We did not include an opt-out option, i.e. described as no treatment, because all included patients desired treatment for their nodular BCC.

In this study a labelled design was chosen since the levels of the different attributes were specific for either IMQ or surgical excision. In addition, the choice between an invasive and a non-invasive therapy makes the use of a labelled design more realistic and in this case is a better reflection of the choices patients face in clinical practice instead of a treatment A or B. A potential limitation is that we administered the DCE before the start of the treatment. It is possible that the experience with the treatment, in particular for patients that had no experience with any therapy, might impact their preference. In addition, it could be informative to perform a DCE before and sometime after the treatment to explore if the experience and the long term outcome of the treatment changes the preferences of patients.

Our results represent the average preference of a patient sample, weighing the importance of different aspects of treatment of nBCC: efficacy, side-effects, cosmetic outcomes and waiting time. The clinical trial (SCIN-trial) showed a lower efficacy for curettage followed by imiquimod 5% cream (86.3%) as compared to surgical excision (100%) one year after the end of treatment.(7) But, since the 86.3% efficacy of curettage followed by imiquimod 5% cream is still high and given the indolent growth pattern of nBCC, this minimal invasive treatment could still be a valuable treatment option in specific cases. The results of this DCE also show that there is a place for curettage followed by imiquimod cream 5% since. Even with the lowest efficacy level, there are still patients choosing curettage followed by imiquimod 5% cream. This means that the other attributes like cosmetic outcomes and side effects also play a role in the choice of patients for a specific treatment. This DCE should merely be seen as guidance in underlining the importance of discussing every aspect of a treatment with patients. This approach allows patients to make the decision that fits specifically to their needs.

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CHAPTER 4

Non-invasive treatment with vismodegib
and other hedgehog inhibitors

CHAPTER 4.1

Update on hedgehog pathway inhibitor therapy for patients with basal cell nevus syndrome or high-frequency basal cell carcinoma: A systematic review

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Submitted

INTRODUCTION

A subset of basal cell carcinoma (BCC) patients will develop a large number of BCCs during their lives. The most common underlying genetic disease that causes multiple BCCs is basal cell nevus syndrome (BCNS), which has an estimated incidence ranging from 1:56.000-256.000.[1] In up to 85% of all BCNS patients, a germline mutation in the tumor suppressor gene patched-1 (PTCH1), part of the hedgehog signaling pathway, is responsible.[1] In a smaller proportion of BCNS patients, a causative germline or postyzygotic mutation in another hedgehog pathway gene such as smoothened (SMO) or supressor of fused (SUFU), can be found.[2, 3] Apart from BCNS patients also xeroderma pigmentosum, Bazex-Dupré-Christol and Rombo syndrome patients are prone to develop multiple BCCs.

In a subset of patients with multiple BCCs the underlying cause is unknown. These patients are referred to as high-frequency BCC (HF-BCC) patients, although there is no clear definition for the number and frequency of BCCs in HF-BCC patients yet. Recently, a prevalence of HF-BCC patients of 49.39 per 100.000 was found in the Danish population.4 In this study, HF-BCC patients were defined as patients with at least 9 BCC surgeries in a 3 year time period.[4]

In general, BCCs in BCNS and HF-BCC patients can be treated according to standard of care with local surgery. However, there is an unmet need for new treatment options for BCNS and HF-BCC patients as some patients develop >100 BCCs during their lives and therefore surgical treatment can be very challenging.[5] Furthermore, the impact of multiple BCCs on the health-related quality of life (HRQoL) can be substantial, as was found in a small cohort of BCNS patients.[6] A treatment that could cure all lesions at once without major side effects is therefore very desirable.

In 2012 the U.S. Food and Drug Administration approved the first hedgehog pathway inhibitor (HPI), vismodegib, for the treatment of advanced BCC.[7] Its mechanism of action consists of inhibition of SMO and consequently inactivation of the hedgehog pathway. Unfortunately, tumor resistance, predominantly caused by SMO mutations, is a common problem in the treatment of advanced BCC with vismodegib.[8, 9]

Vismodegib was the first HPI investigated in HF-BCC and BCNS patients, but other types of HPIs have been investigated in BCNS and HF-BCC patients as well. In general, side effects such as muscle spasms, alopecia and dysgeusia eventually lead to treatment discontinuation in the BCNS and HF-BCC population, who need long-term treatment.[10]

The aim of this review is to outline the available clinical data in BCNS and HF-BCC patients treated with any type or dosing of oral and topical HPIs.

METHODS

This systematic review, conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, was performed in the following 4 areas of interest: 1. efficacy, 2. safety, 3. tumor resistance and reoccurrence, and 4. HRQoL in BCNS and HF-BCC patients that were treated with HPI. Systematic reviews are exempted for institutional board review at our institution.

First, a broad search was performed in clinicaltrials.gov, ISRCTN.org and clinicaltrialsregister.eu to determine which HPIs have been used for the treatment of BCCs. The following HPIs were identified: oral; vismodegib/GDC-0449, sonidegib/LDE225, saridegib/IPI-926, itraconazole, BMS-833923, LEQ506 and TAK-441, and topical; patidegib/IPI-926, sonidegib/LDE225 and itraconazole. Multiple searches were performed using either “basal cell nevus syndrome/Gorlin syndrome,” “high-frequency basal cell carcinoma,” “multiple basal cell carcinoma,” or “basal cell carcinoma” in combination with one of the HPIs to identify suitable articles in clinicaltrials.gov, PubMed, Embase and Cochrane Central Register of Controlled Trials from database inception to 1st of July, 2020. English written results on HPI monotherapy for BCCs were included.

Two authors (BV and KS) performed the searches and independent review of the titles and abstracts. English written studies describing treatment of BCNS or HF-BCC patients with HPI monotherapy, that were relevant for the areas of interest were selected for full article review. To assess efficacy and safety, randomized and non-randomized clinical trials (RCT), open-label trials and retrospective cohort studies were included, regardless of the used outcome and safety measurements. To evaluate tumor resistance and reoccurrence also case reports or series were included. Reference lists of included articles were checked for missing studies.

The following information was extracted: type and dosage of HPI, study design, level of evidence, treatment indication, number of participants, duration of treatment and follow-up, response criteria, efficacy, industry driven. Quality of evidence was assessed by using Oxford Center for Evidence-Based Medicine levels. A list of common adverse events and reasons for treatment discontinuation were also collected. Additional information on mutation analysis, resistance criteria, time to reoccurrence, and a brief summary was collected from tumor resistance and reoccurrence studies.

Additional information on type of questionnaire and time points of its measurements were collected for HRQoL studies.

RESULTS

A total of 347 articles were identified, of which 266 were removed after review of the titles and abstracts, and another 70 were removed after full-text review (Figure 1). Eventually, 11 studies were included that discussed results on either efficacy (n=6), safety (n=6), tumor resistance and reoccurrence (n=5), or HRQoL (n=2) in BCNS and HF-BCC patients. (Figure 1)

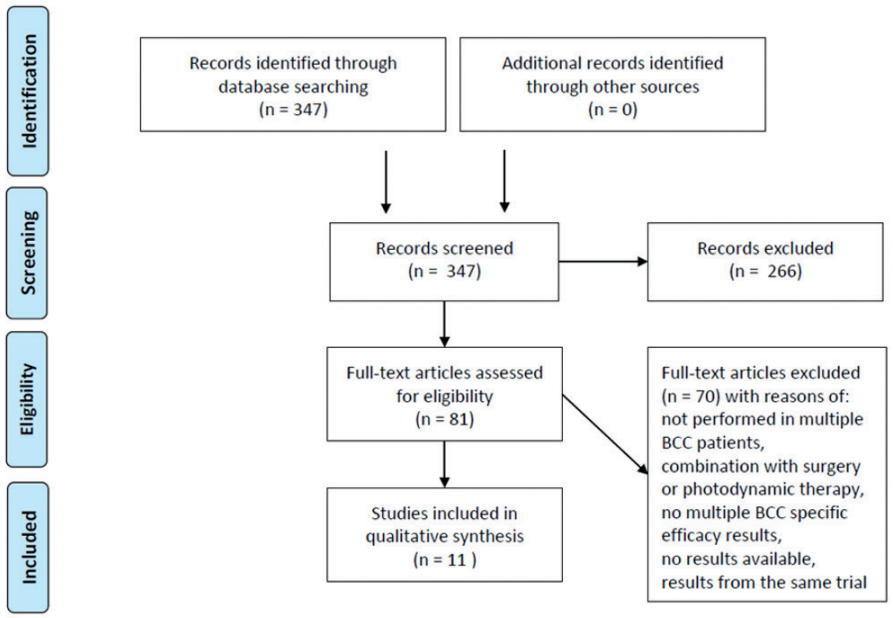

Figure 1. PRISMA flow diagram.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. BCC = basal cell carcinoma.

Efficacy

Efficacy results of all HPIs are shown in Table I.

Oral HPIs

Three phase-2 RCTs were executed to study oral HPIs, 2 investigated continuous therapy and 1 investigated two different treatment regimens.11-14

Treatment with vismodegib 150mg daily (n=26) compared to placebo (n=15) resulted in a mean rate of 2 new surgically eligible BCCs (SEBs) per year compared to 34 in the placebo group. Furthermore, the vismodegib group showed a 65% reduction in mean size of existing SEBs.11, 12 A SEB was defined as clinically diagnosed BCC of ≥5 millimeters (mm) in diameter on the face or ≥9 mm on other body parts.

Treatment with sonidegib 400mg daily (n=7) resulted in a 100% clinical clearance rate in 3 patients, 76-99% in 3 other patients and 26-75% in 1 patient, which was higher than placebo (n=2).13 The total number of BCCs decreased from 566 at baseline to 309 after 3.7 months in the sonidegib group and increased from 510 to 619 after 3.7 months in the placebo group.

One RCT determined the efficacy of 2 vismodegib regimens in 85 BCNS and 144 HF-BCC patients.14 Group A received 12 weeks of vismodegib 150mg/day alternated with 8 weeks of placebo and group B received 24 weeks of vismodegib 150mg/day followed by 8 weeks placebo, which was then alternated with 8 weeks of vismodegib 150mg/day. The mean relative reduction of the number of clinical BCCs was 62.7% in group A and 54.0% in group B after 16.8 months of treatment.

Topical HPIs

Three randomized-vehicle-controlled phase-2 trials investigating twice daily application of topical HPIs were registered at clinicalrials.gov and had results.15-18

The first compared itraconazole 0.7% gel for 47 BCCs with vehicle for 25 BCCs within the same 9 patients (6 BCNS and 3 HF-BCC patients).15 The change in tumor area was +0.04% in the itraconazole 0.7% BCCs compared to -10.9% in the vehicle BCCs after 4 weeks compared to baseline. After 12 weeks the change in tumor area was +8.9% in the itraconazole 0.7% gel and +26.5% in the vehicle BCCs.

The second compared patidegib 2%, 4% and vehicle gel in BCCs >5mm at baseline in 17 BCNS patients.16 After 26 weeks of application, the tumor size decreased with 51.3% in the patidegib 2% group, 26.6% in the patidegib 4% group and 21.8% following vehicle application.

In the third trial, LDE225 0.75% cream on 13 BCCs was compared with vehicle on 14 BCCs within the same 8 BCNS patients.17 The mean decrease in 3 dimensional tumor size was 35.3% after four weeks of treatment in the LDE225 0.75% group compared to an increase of 7.0% in the placebo group. In part two of the trial, LDE225 0.75% cream was compared with LDE225 0.25% cream and showed a mean decrease in 3 dimensional tumor size of 43.4% and 19.3% respectively after four weeks of treatment.[18]

Table 1 – Studies on hedgehog pathway inhibitors for high-frequency BCC patients

Study	HPI	Drug administration	Study type	Quality of evidence	Response criteria	Total patients – BCNS patients, n	Randomization: n	Baseline tumors	Primary outcome	Secondary outcome	Completion of treatment until primary outcome?
Tang et al.[11,12]	Vismodegib 150mg	Oral	Phase-2 double-blind RCT (placebo)	1	Reduction in rate of new surgically eligible BCCs (nSEBs) after 3 months compared to placebo	41 – 41	Vismodegib: 26 Placebo: 15	Mean number of nSEB at baseline: 44 37	Mean rate nSEBs per year at month 3: 2 34 *p<0.0001*	Change in size of existing SEBs: -60mm +55mm *p<0.0001*	38 patients completed
Lear et al.[13]	Sonidegib 400mg	Oral	Phase-2 double-blind RCT (placebo)	1	Clinical clearance rate of main target BCC using a 6-point scale (worsening, no change, 1-25%, 26-75%, 76-99% or 100% improvement)	10 – 10	LDE225: 8 Placebo: 2	Total number of BCCs at baseline: 566 510	Clinical clearance rate main target BCC at day 113: 100%: 3 76-99%: 3 26-25%: 1 1-25%: 1 worsening: 1	Disease burden by BCC tumor count at day 113: 309 619	All patients completed. Only 7 LDE225 allocated patients included in efficacy analysis due to receipt of placebo in 5 of 13 doses in 1 patient.
Dreno et al.[14]	Vismodegib 150mg alternated with placebo	Oral	Phase-2 double-blind RCT (two different treatment schedules)*	2	Percentage reduction in number of clinically evident BCCs at week 73	229 – 85	Group A: 116 Group B: 113	Mean number of BCCs at baseline: 9.8 9.1	Mean relative reduction in number of BCCs at week 73: 55.2% 56.6% p=0.21	Mean relative reduction of total size 3 target BCCs at week 73: 82.9% 68.8% p=0.02	55% in group A and 50% in group B completed 73 weeks of treatment. Median treatment duration was 71.4 weeks.

Table 1 Continued

Study	HPI	Drug administration	Study type	Quality of evidence	Response criteria	Total patients – BCNS patients, n	Randomization: n	Baseline tumors	Primary outcome	Secondary outcome	Completion of treatment until primary outcome?
Sohn et al.[15]	Itraconazole	topical	Phase-2 open-label intrapatient (vehicle and 0.7%)	3	Change in BCC tumor area	9 – 6	Itraconazole 0.7%:9 Vehicle: 9	Total BCCs treated: 65 42	Change in tumor area at week 4: 0.04% -10.9% p=0.40	Change in tumor area at week 12: 8.9% 26.5% p=0.40	All patients completed
Epstein et al.[16]	Patidegib	Topical	Phase-2 double-blind parallel assignment (vehicle, 2%, 4%)	1	Percent change in tumor size of treatment-targeted SEBs at week 26	17 – 17	Patidegib 2%: 6 Patidegib 4%: 6 Vehicle: 5	Total number of SEBs at baseline: 21 24 16	Percent change in tumor size of SEBs at week 26 51.3% (*P=0.03*) 26.6% (P=0.76) 21.8%	Mean number of nSEBs at week 26: 0.4 (2% and 4% combined) 1.4 *P=0.048*	15 patients completed 1 subject in 2% and 1 subject in vehicle group did not
Skvara et al.[17,18]	Sonidegib	Topical	Phase-2 double-blind, 2 parts, parallel assignment (vehicle, 0.25%, 0.75%)^	1	Percentage of BCCs with complete and at least partial clinical clearance	18 - 18	Part 1 – 4 weeks Vehicle: 8 LDE225 0.75%: 8 Part 2–6 weeks LDE225 0.25%: 3 LDE225 0.75%: 7	Total number of BCCs at baseline: 14 13 12 22	Percentage BCCs with partial/ complete clearance at week 4: 7% / 0% 92% / 23% 83% / 0% 77% / 0%	Mean % change in 3D tumor size at week 4: 7.0 -35.3 -19.3% -43.4%	All patients completed part 1 1 subject in part 2 - LDE 0.75% did not complete

HPI = hedgehog pathway inhibitor, RCT = randomized controlled trial, BCCs = basal cell carcinomas, SEBs = new surgically eligible basal cell carcinomas, nSEBs = new surgically eligible basal cell carcinomas (SEBs were defined as clinically diagnosed basal cell carcinoma (BCC) 5 millimeters (mm) or greater in diameter on the face, excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face), CI = confidence interval. Consisted of two groups; group A: 12 weeks vismodegib 150mg/day – 8 weeks placebo alternately, group B: 24 weeks vismodegib 150mg/day followed by 8 weeks placebo – 8 weeks vismodegib 150mg alternately. ^Part 1: participants were exposed to both topically applied 0.75% LDE225 cream and LDE225 vehicle cream twice daily for 28 days where each treatment was randomized to two different test areas on each participant, part 2: participants were exposed to topically applied 0.25% or 0.75% LDE225 cream twice daily for 6 weeks or 0.75% LDE225 cream twice daily for 9 weeks.*

Safety

The most commonly reported adverse events and reasons for treatment discontinuation of oral HPIs are shown in Table II.

Oral HPIs

In the trial of Tang et al., 40 patients were eventually treated with vismodegib. Thirty-one patients (78%) needed temporarily (n=19, 48%) or permanent (n=12, 30%) treatment interruptions due to adverse events during a maximum treatment period of 18 months.[11, 12]

Two of the 8 (25%) patients treated with continuous sonidegib discontinued treatment due to side effects during the overall 3.7 months of treatment.[13]

In the trial of Dreno et al., 23 of the 116 (19.8%) in group A and 30 of the 113 (26.5%) patients in group B discontinued due to adverse events.[14] The median duration of treatment was 16.5 and 15.7 months in group A and B respectively.

Topical HPIs

All three topical HPIs were applied twice daily on several BCCs within a patient.

Itraconazole 0.7% gel for 4 weeks caused application site reaction and pruritus in 4/9, lesion pain in 3/9, and xerosis and dysgeusia in 1/9 patients.[15]

Patidegib 4% gel lead to application site alopecia, dermatitis, pain and rash in 1/6 patients during 26 weeks of treatment.[16] None of these adverse events occurred in the 6 patients treated with patidegib 2% gel.

LDE225 0.75% cream lead to local skin irritation in 4/8 patients and skin fissures in 1/8 patients.[17] Urticaria and increased hepatic enzyme activity in blood investigations were seen in 1/8 patients. None of these adverse events occurred in the 3 patients treated with LDE225 0.25% cream.[18]

Table II - Prevalence of side effects in oral HPIs

	Tang et al.[11, 12]	Lear et al.[13]	Dreno et al.[14] Group A*	Dreno et al.[14] group B*
HPI	Vismodegib	Sonidegib	Vismodegib	Vismodegib
Dosage	150mg daily	400mg daily	150mg daily alternated with placebo	150mg daily alternated with placebo
Treatment duration	Unknown, 10 patients were treated for more than 15 months continuously	113 days	71.6 weeks	68.4 weeks
Patients available for safety results	40	8	114	113
Alopecia	100% (40)	25% (2)	63% (72)	65% (73)
Muscle spasms	100% (40)	38% (3)	73% (83)	83% (93)
Dysgeusia	93% (37)	13% (1)	66% (75)	67% (75)
Weight decreased	78% (31)	NM	21% (24)	19% (21)
Gastrointestinal upset/ diarrhea	65% (26)	13% (1)	18% (20)	16% (18)
Fatigue	48% (19)	25% (2)	21% (24)	23% (26)
Nausea	10% (4)	25% (2)	20% (23)	13% (15)
Runny nose/ nasopharyngitis	18% (7)	25% (2)	NM	NM
Common cold/asthenia	20% (8)	NM	13% (15)	18% (20)
Headache	NM	25% (2)	10% (11)	11% (12)
Treatment discontinuation	21/40 within 18 months	2/8 within 113 days	50/116 within 73 weeks	57/113 within 73 weeks
Reason for treatment discontinuation				
AE / lab abnormalities	30% (12)	25% (2)	20% (23)	27% (30)
Patients decision/ refused treatment	NM	NM	6% (7)	3% (3)
Patient satisfaction	3% (1)	NM	NM	NM
Site method	15% (6)	NM	NM	NM
Withdrew consent	NM	NM	10% (12)	12% (13)
Investigators decision	NM	NM	2% (2)	5% (6)
Disease progression	NM	NM	3% (3)	3% (3)
Died	5% (2)	NM	NM	NM

*AE = adverse event, HPI = hedgehog pathway inhibitor, NM = not mentioned, *Group A: 12 weeks vismodegib 150mg/day – 8 weeks placebo alternately, group B: 24 weeks vismodegib 150mg/ day followed by 8 weeks placebo – 8 weeks vismodegib 150mg alternately.*

Tumor resistance and reoccurrence

In table IV the limited publications on tumor resistance and/or reoccurrence in BCNS and HF-BCC patients are summarized.[11, 12, 19-23] All studies reported on resistance and/or reoccurrence during or after vismodegib treatment.

Resistance

In the trial of Tang et al., 2 resistant BCCs out of 41 BCNS patients with a total of >2000 BCCs were observed.[11, 12] Resistance was defined as tumors that continued to grow or did not shrink while the patient was taking vismodegib. Both were histological confirmed BCCs; one did not reveal mutations in SMO and in the other a known resistance-causing SMO mutation (Val321Met) was identified. In none of the 41 BCNS patients the underlying germline mutation was mentioned.

A retrospective cohort series reported on secondary resistance, defined as BCC regrowth within or immediately adjacent to (<1cm) a vismodegib-responsive tumor during continuous vismodegib treatment.[19] In 3 of the 5 BCNS patients a total of 6 out of 133 BCCs reoccurred during treatment.

Lastly, a case report in a BCNS patient, who was treated with vismodegib for multiple BCCs during 3 years, described the regrowth during treatment of 2 BCCs after initial response.20 Both BCCs harbored SMO mutations on known hotspots for mutations causing resistance (Ser241Phe and Asp473Asn).

Reoccurrence

In the trial of Tang et al., reoccurrence of BCCs during treatment breaks was noticed in 4 patients. Unfortunately, no exact prevalence number of reoccurring BCCs was provided.[11, 12]

In a retrospective case series including 4 BCNS patients, reoccurrence of BCCs was specifically mentioned in 1 patient, 3 months after 54 months of vismodegib treatment.[21]

In another case series including 3 BCNS patients, reoccurrence of BCCs was mentioned in all 3 patients within 2 years after vismodegib discontinuation.[22]

In a case report, 10 out of 19 BCCs reoccurred 24 months after 7 months of vismodegib treatment.[23]

In another case report, 2 months after a 3 year treatment period an unknown number of BCCs reoccurred.[20]

Table IV – Tumor resistance & reoccurrence

Study	Indication	Study type – Quality of evidence	BCNS patients, n	BCCs described, n	*Resistance* during vismodegib treatment, primary or secondary	*(Re)occurrence* after discontinuing vismodegib treatment
Tang et al.[11, 12]	Multiple BCCs	Phase-2 double-blind RCT (placebo) –1	41	>2000	During vismodegib treatment: - Two pre-existing BCCs did not respond - Mutational profile: one had a vismodegib-resistant SMO mutation (Val231Met) No information on secondary resistance described	- During treatment breaks BCC reoccurred, no exact number or percentage was provided
Chang and Oro[19]	Multiple BCCs	Retrospective cohort –2	3	133	During vismodegib treatment: - After a mean period of 55.3 weeks - 6 out of 133 BCCs regrew	Not described
Sinx et al.[20]	Multiple BCCs	Case report – 5	1	>3	During 3 years vismodegib treatment: - 2 BCCs regrew after initial complete response - Mutational profile: both had vismodegib-resistant SMO mutations (Ser241Phe and Asp473Asn)	- Two months after discontinuing 3 years vismodegib treatment, BCCs reoccurred at their pre-treatment locations. - Number unknown
Banvolgyi et al.[21]	Multiple BCCs	Retrospective cohort – 5	4	Unknown	Not described	- Three months after discontinuing 4 years vismodegib treatment, BCCs reappeared in 1 patient
Valenzuela-Onate et al.[22]	Multiple BCCs	Case series – 5	3	5	Not described	- In 3 cases, at least 19 BCCs developed within 2 years after discontinuing vismodegib of unknown treatment duration.
Wolfe et al.[23]	Multiple BCCs	Case report – 5	1	19	Not described	- Two years after discontinuing 7 months vismodegib treatment, 10 out of 19 BCCs on the head & neck reoccurred

Health-related quality of life

Only Dreno et al. measured HRQoL with a validated questionnaire.14 The Skindex-16 questionnaire, which comprises 3 domains (symptoms, emotions and function) was measured 8 times between baseline and end-of-treatment (week 73), and at 12, 24 and 52 weeks follow-up.[24] Outcomes ranged from 0 (never bothered) to 100 (always bothered). Both treatment regimens showed a decrease of ≥10 points from baseline from week 9 and every point post-baseline in all domains, which was considered to be a clinical meaningful improvement.[25] A decrease in HRQoL was seen in all domains after treatment discontinuation, but HRQoL scores were not returned to baseline scores yet after 52 weeks of treatment discontinuation.

Furthermore, Tang et al. reported that 23 of the 41 included BCNS patients responded to a telephone questionnaire evaluating vismodegib treatment of which 18 preferred treatment with vismodegib over surgery.[11, 12]

DISCUSSION

This review shows that there is little evidence for HPI therapy in BCNS and HF-BCC patients. Continuous oral HPI therapy has been proven effective in BCNS patients. Resistance during continuous oral HPI in BCNS patients is uncommon, but can occur in a small subset of BCCs in this population. Adverse events are very common and the reason for treatment discontinuation in 20-74% of patients. Unfortunately, it is not clear which adverse events at what grades are causative for treatment discontinuation. After discontinuation of oral HPI therapy most BCCs reoccurred. The information on improvement of HRQoL is very scarce.

Although direct comparison between oral continuous vismodegib and sonidegib was not possible, side effects and treatment discontinuation seemed to occur less in the oral HPI sonidegib. This is probably caused by the small population and short treatment period of 3.7 months in the sonidegib trial, which also does not reflect the long-term treatment needed in BCNS and HF-BCC patients. In general, the total number of patients discontinuing treatment due to side effects is probably underreported in studies, as ‘patient’s decision,’ ‘withdrawal of consent,’ and ‘refusing of treatment,’ are often mentioned as additional reasons for treatment discontinuation.

Intermittent dosing of oral HPIs has been proposed to endure these side effects. As only one RCT investigated intermittent dosing, conclusions should be drawn with consideration. However, patients were treated for a median duration of 16.8 months, which is longer than in the continuous oral HPI trials and above that, HRQoL improved during and after the trial on the emotional well-being domain compared to baseline HRQoL. Vismodegib Monday-Friday or every other day, but also several months on and off continuous therapy were reported successful in a few case reports and series.[22, 26, 27]

Such personalized schedules may enable long-term treatment, but long-term efficacy results and resistance development during treatment regimens are lacking.

Topically applicable HPIs have been developed to avoid side effects in patients requiring long-term treatment for multiple BCCs. However, the available evidence for topical HPIs is scarce. From the 3 phase-2 trials on 3 different HPIs it can be concluded that topical itraconazole 0.7% gel was not effective, but topical patidegib 2% and LDE225 0.75% showed more promising results and limited side effects. Larger trials confirming efficacy, but also addressing possible development of tumor resistance and HRQoL improvement are needed.

In conclusion, there is very little evidence for HPI treatment in BCNS and HF-BCC patients. Continuous oral HPIs are effective, but at least 20-74% of BCNS and HF-BCC patients discontinue due to adverse events. Personalized rotational schedules for oral HPIs can be effective and tolerable for a small subgroup of BCNS and HF-BCC patients. As topical HPIs showed little side effects in phase-2 trials, this might be a more suitable long-term treatment for BCNS and HF-BCC patients, but results of larger phase-3 trials will have to be awaited.

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CHAPTER 4.2

Vismodegib-resistant basal cell carcinomas in basal cell nevus syndrome: Clinical approach and genetic analysis

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INTRODUCTION

Basal cell nevus syndrome (BCNS, Gorlin syndrome) is a rare inherited disorder characterized by the development of multiple basal cell carcinomas (BCCs), odontogenic keratocysts, and palmar pits.1

BCC development is caused by sonic hedgehog pathway (SHH) activation caused by mutations in tumor suppressor gene patched 1 (*PTCH1*) or activating mutations in the oncogene smoothened (*SMO*).2 Because patients with BCNS carry a germ-line mutation in *PTCH1*, one additional somatic mutation (second hit) results in BCC development at a young age.

In 2012, the US Food and Drug Administration approved vismodegib for treatment of locally advanced BCC (laBCC) or metastatic BCC (mBCC). Vismodegib prevents activation of the SHH pathway by binding and inhibiting the SMO protein.3 Vismodegib resistance, mainly caused by *SMO* mutations, is an important problem seen in laBCC or mBCC in patients with and without BCNS.4, 5 Vismodegib resistance in smaller BCCs, which are far more frequent in BCNS patients, is only described once.6 Here, vismodegib resistance of those smaller BCCs in a BCNS patient is genetically explained, and a clinical treatment approach is given.

Case report

A 59-year-old man with BCNS (Gorlin syndrome) was seen at our dermatology outpatient clinic with a history of multiple BCCs, palmar pits, and hypertelorism. After former extensive mutilating surgical procedures, surgery was not feasible. Vismodegib treatment was started at 150 mg/d in a clinical trial (STEVIE; NCT01367665). There was a reduction of the amount and size of the BCCs until no BCCs were clinically detectable and also palmar pits disappeared (Fig 1, A and B). Adverse events included hair loss, muscle cramps, a total lack of taste, and weight loss of 15 kg. After 3 years of continuous vismodegib therapy, 3 lesions developed (preauricular and 2 on his back) suspect for recurrent BCC (Fig 1, C). After excision of the 3 lesions, 2 lesions (preauricular and on his back) were histologically confirmed to be superficial BCCs, whereas one of the lesions on his back showed no histologic signs of malignancy. Following the study protocol, treatment was discontinued (resistance). Written informed consent was obtained to perform genetic analysis on their tissue.

Two months after discontinuing vismodegib treatment, multiple BCCs (re)developed on their original locations and with the exact sizes as before treatment. Currently, he is treated intermittently with vismodegib (4-5 months on and 6-7 months off), depending on response and side effects. Resistant tumors are surgically excised at the end of each treatment cycle.

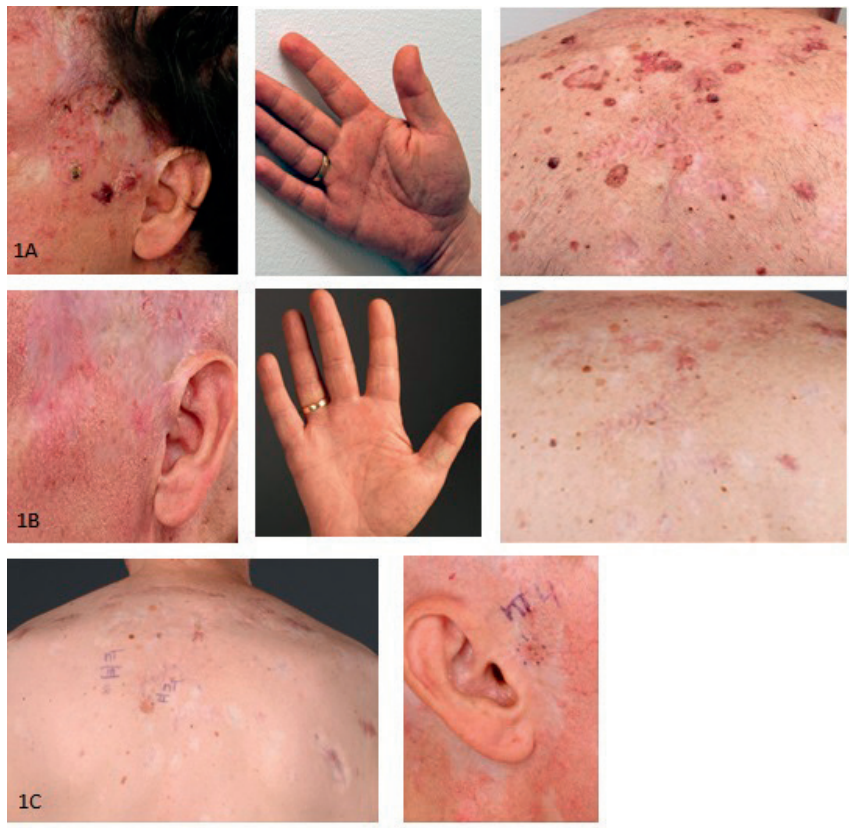

Figure 1

BCNS patient. **A**, Before starting vismodegib. **B**, Clearance after 3 months of vismodegib treatment. **C**, BCC redevelopment (resistance).

METHODS

Directly after excision, biopsy samples (3 mm) were taken from the 3 clinically suspect BCCs preauricular and on the back. The samples were freshly frozen and stored at e808C, and subsequently DNA was extracted (DNeasy Blood & Tissue Kit, Qiagen, Hilden, Germany) and analyzed using single molecule molecular inversion probes (smMIPs).7

An smMIP-based library preparation was used to target coding sequences of genes involved in the SHH pathway: PTCH1, PTCH2, SMO, SUFU, GLI2, and TP53(resp. NCBI RefSeq: NM_000264.3, NM_ 003738.4, NM_005631.4, NM_016169.3, NM_0052 70.4, M_000546.5/NM_001126113.2/NM_0011261 14.2). Subsequently, the samples were sequenced on a MiSeq system (Illumina, San Diego, CA) nextgeneration sequencer.

RESULTS

Table I. Mutational analysis: Resistant basal cell carcinomas analyzed using molecular inversion probes

Sample	Mutation	Gene	Protein change	Type
Sample 1 (BCC)	c.747-2A>G 59.8%	PTCH1	p.?[1]	Germ line splice site mutation with LOH of other allele (skewed %)
Sample 1 (BCC)	c.1417G>A 14.1%	SMO	p.Asp473Asn	Somatic missense mutation (responsible for vismodegib resistance)
Sample 2 (BCC)	c.747-2A>G 47.4%	PTCH1	p.?[1]	Germ line splice site mutation
Sample 2 (BCC)	c.1804C>T 26.8%	PTCH1	p.Arg602*	Somatic nonsense mutation Second hit
Sample 2 (BCC)	c.1406G>A 23.5%	SMO	p.Cys469Tyr	Somatic missense mutation (responsible for vismodegib resistance)
Sample 2 (BCC)	c.722C>T 26.4%	TP53	p.Ser241Phe	Somatic missense mutation
Sample 3 (histologically normal skin)	c.747-2A>G 47%	PTCH1	p.?[1]	Germ line splice site mutation

[1] The germ line mutation is located at the splice acceptor site of intron 5 (at the exon 6 border). Splice site software tools (integrated in the Alamut V2.10 software) predict the acceptor splice site to be lost by the mutation. Since the mRNA cryptic splicing needs to be experimentally verified, the resulting putative protein is unknown (p.?).

All 3 samples showed a germ-line mutation in *PTCH1*, located in the splice acceptor site of intron 5, c.747-2A>G and predicted to affect the conical splice site, which putatively results in aberrant splicing of the *PTCH1* transcript and is presumably causal to BCNS. The represented percentage of this *PTCH1* mutation was 47.0% for histologically normal skin, and no additional mutations were found (sample 3). In sample 1 (BCC), the germ-line *PTCH1* mutation skewed to 59.8%. Furthermore, a *SMO* mutation c.1417G>A (p.(Asp473Asn)) was detected, representing 14.1% in the sample and a known mutation causing vismodegib resistance.4 In sample 2 (BCC) the *PTCH1* germ-line mutation percentage was 47.4%, similar to that of normal skin. Additionally, a second nonsense mutation in *PTCH1* c.1804C>T (p.(Arg602*)) was detected as second hit (26.8%). In this sample, a different causal SMO mutation c.1406G>A (p.(Cys469Tyr)) was found (23.5%).5 Furthermore, a *TP53* mutation c.722C>T(p.(Ser241Phe)), previously described as germ-line mutation in sarcoma, was found (Table I).8

DISCUSSION

Here, a BCNS patient with vismodegib resistance in small, BCNS-related BCCs and the clinical course are described. To our knowledge, resistance of non-laBCCs was only documented in 1 of the 41 included BCNS patients in a phase 2 trial by Tang et al6 This resistance is probably much less frequent than vismodegib resistance in laBCC, which occurs in approximately 20% of patients.9

Both detected *SMO* mutations in the resistant BCCs were found before.4, 5 The few different *SMO* mutations reported to date suggest the presence of hotspot regions in *SMO*, responsible for resistance.4, 5 We used smMIP-based analysis, because it is relatively easy in determining SMO-associated tumor resistance with low costs.7 In a clinical setting, this may be valuable and even cost effective if the decision to continue therapy depends on one or a few lesions. Vismodegib resistance in BCNS does not have the same clinical implications as in laBCC/mBCC, because the few resistant BCCs can easily be treated otherwise.

Vismodegib discontinuation led to reoccurrence of BCCs at their original locations, suggesting that tumors are not completely eliminated. Indolent cancer stem cells, capable of redeveloping cancer cells when treatment is discontinued are hypothetically debit.4 The fact that treatment with vismodegib is only of suppressive nature is important to discuss with the patient.

In BCNS patients with non-laBCCs only, 17% tolerate continuous vismodegib treatment during 3 years, and side effects are the major reason for discontinuation of treatment.6 In these patients with long-term treatment need, rotational schedules have been applied (12 weeks of 150 mg/d vismodegib rotated with 8 weeks of placebo, or starting with 24 weeks vismodegib followed by 8 weeks of placebo rotated with 8 weeks vismodegib), but even then, adverse events cause high treatment discontinuation (23%).10 Probably, these schedules are still too stringent. Because BCNS patients need lifelong treatment, intermittent vismodegib therapy seems preferable and can be combined with excision or topical treatment of the few resistant tumors. In our experience, the development of response and severity of side effects varies, so discontinuation and restart of the therapy should be guided by the burden of the patient.

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CHAPTER 5

Discussion and valorisation

This thesis describes the results of multiple studies concerning the minimally and non-invasive diagnosis and treatment of basal cell carcinoma (BCC). In this chapter the major conclusions of this thesis will be summarized. The results will be discussed and the relevance for clinical practice will be outlined.

Why this research is relevant

The incidence of basal cell carcinoma (BCC) is increasing with a current life time risk of 1 in 5-6 people in the Netherlands.(1) In practice, these patients often develop multiple BCCs due to sun-damaged skin .(2) One of the main causes potentially lies in the recreational sun behaviour in the 60s and 70s without the use of sun protection. Today, the consequences of this behaviour become visible with a high incidence of sun damaged skin (actinic keratosis) and the development of non-melanoma skin cancer; basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).(3) Although, there is more attention and awareness of the negative effects of UV radiation nowadays, an increase of BCC is seen in the younger population (below the age of 40 years) over the last years.(4) It seems that getting a tan, by either sunlight or a sun bed is still seen as attractive to many people. Furthermore, people do not seem to associate cycling, walking and outdoor swimming to increased sun exposure. In addition, as people get older, an increase in BCC incidence is expected over the next years. So, even more awareness is necessary to change the current sun behaviour of people and hopefully decrease the incidence of BCC in the future. Until then, it is important to optimize diagnosis and treatment of BCC to provide the most optimal care for patients. As far as diagnosis and treatments are concerned, minimally and non-invasive options are being sought and investigated.

Although BCCs are considered to be skin cancers, especially the superficial and nodular subtypes have fairly indolent characteristics: these BCCs grow slow, hardly ever metastasize and do not influence life expectancy. Still, longer existing tumours can grow into deeper tissues and can cause persisting wounds. Moreover, several other subtypes (micronodular, morpheaform) are associated with a more aggressive growth. Therefore, correct diagnosis to guide decisions on optimal treatment is essential. Aggressive BCCs (i.e. micronodular, morpheaform) require surgical excision, but in recent years there has been a trend toward the development of non-invasive and less invasive methods for the treatment of less aggressive BCCs (superficial, nodular). Given the high volume of BCC in dermatological practices, less and non-invasive diagnostic tools and treatments provide the opportunity to reduce the work load for dermatologists caused by the high number of biopsies and surgical excisions. Besides, it would be possible to give patients more control over their own treatment. Herewith , we (clinicians) must remain critical regarding the application of non-invasive diagnostic methods and treatments in clinical practice, in a way that accuracy and effectiveness remains warranted. In this context, we have to keep searching for new technologies and treatments that will make healthcare not only more efficient, but also more patient friendly.

Diagnosis of basal cell carcinoma

Over the years the carcinogenic aspect of basal cell carcinoma, especially of superficial and nodular basal cell carcinoma has been increasingly questioned. Since these types of BCC hardly metastasize (0.0003-0.55%) and grow slowly, the question is whether invasive diagnosis and treatment is still necessary.(5) Being an indolent form of skin cancer it gives clinicians the opportunity to look out for different types of diagnostic tools to diagnose BCC. Currently, a skin biopsy is the first choice when it comes to BCC diagnosis and subtyping.(6) Obtaining a biopsy is an invasive procedure which can cause pain and bleeding during the procedure and complications such as infection and scarring afterwards. Histopathological assessment takes approximately 1 week and during this period the uncertainty may cause stress for patients. Moreover, it results in a treatment delay since treatment will not be started before definitive histopathological results are available.

Within the dermatology field, various alternative, non-invasive imaging techniques are in development. In the Netherlands, there is much experience with reflectance confocal microscopy (RCM, Vivascope), in research settings. RCM is a non-invasive technique, that is currently not yet ready for clinical use by general dermatologists, because it is difficult to use or interpret.(7, 8) Compared to RCM, OCT has the advantage that images are shown in a vertical plane and therefore resemble histological slides making them easier to interpret. Besides that, penetration of the OCT is deeper, giving more information about deeper invading subtype or depth of the tumour. These characteristics together with specific BCC characteristics seen on the OCT image makes it a more usable option in clinical practice.

Clinical examination alone is already associated with a high sensitivity of at least 90% to diagnose a BCC.(9, 10) Specificity of clinical examination is known to be low, 28.6% as shown in the study by Ulrich et al. These authors compared the diagnostic accuracy of clinical and dermatoscopic evaluation of suspected lesions with that of OCT using histopathological results as gold standard.(10) The low specificity is probably the main reason why the number of biopsies taken in patients who do not have BCC is still high**.**

In order to reduce the amount of biopsies in the future, OCT should offer a better accuracy than clinical examination. In **Chapter 2.1** we conducted a clinical cohort study comparing clinical examination alone to OCT using biopsy as gold standard test in the diagnosis and subtyping of BCC. We found that the accuracy of diagnosing BCC improved when OCT (together with clinical photographs of the lesion) was used. The area under the ROC curve was 91.2% as compared to 85.6% after clinical examination alone (P=0.061). The specificity increased significantly with the use of OCT (76.8%) as compared to clinical examination (47.5%) at similar sensitivity (95.2% and 97.6%, respectively). These results confirm that OCT can be a promising new method to confirm the diagnosis of a BCC if there is still doubt after clinical evaluation. However, it showed

that subtyping of BCCs is still difficult with OCT. If it had been f feasible to evaluate the OCT scans directly, alongside the patient in the study, the ability to discriminate between nodular BCC and other BCC subtypes might have been better, because nodular BCCs are clinically well recognizable and have 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. Due to the design of the study, the assessors of OCT images had to do with photographs of the lesion in which elevation and shiny appearance are obviously less clear.

Another explanation for the difficulty in subtyping could be the still limited resolution of OCT, which makes it more difficult to differentiate in cases where subtypes show overlap. Often it is difficult to determine if a BCC is only superficial or already starting to become nodular (mixed subtype). However, this is a shared problem with histopathology and this will remain a matter of clinical interpretation.

When the use of OCT is evolving, it is most likely that in part of the patients biopsies could be avoided in the future. If a biopsy can be avoided by accurate OCT diagnosis of BCC, the BCC diagnosis could be discussed on the same day and treatment could be started or planned directly. This is more convenient for the patients and it may also reduce anxiety and stress. This is an already existing concept and is called the one-stop-shop concept.

We found that the percentage of biopsies that could be avoided in the future is around 30%. However, it is important to realize that inaccurate diagnosis by OCT which is not verified by punch biopsy harbours the risk of over- or under treatment. Further research is necessary to find out whether the accuracy of OCT improves even more when scans are evaluated in a clinical setting and whether use of OCT actually reduces the necessity of a biopsy in clinical practice. The study discussed in chapter 2.1 was the basis for a multicentre randomised controlled trial which is currently ongoing with the Maastricht UMC as the coordinating centre. This randomised controlled trial directly compares OCT-guided diagnosis and treatment with standard care, where a biopsy is always taken to verify the clinical diagnosis. It evaluates whether effectiveness in terms of remaining free from recurrences in the long term is comparable between the two study arms.

4Accuracy of diagnosing BCC with OCT can improve with training. Therefore, with the use of learning curves we investigated the number of OCT assessments necessary to reach an adequate level of performance **(chapter 2.2).** Cumulative sum analyses showed that an acceptable performance was reached after assessing 183 to 311 scans. The minimal number of OCT scans that need to be assessed depends on pre-set acceptable and unacceptable error rates, but also on cut-off values for the definition of a positive test. The OCT-researchers 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. In a scenario where the aim is not to miss a BCC, one may opt for a confidence level ≥ 2 (either high suspicion or certainty of BCC presence) as the cut-off point for a positive BCC diagnosis according to OCT. In this scenario the required number of 183 cases that need to be evaluated before reaching acceptable performance was lower compared with a scenario using a more strict threshold of ≥ 3 (only certainty of BCC presence was defined as a positive test result). The latter threshold may be more appropriate when the ultimate goal of OCT is to be able to omit punch biopsy if OCT diagnosis is positive. Then it becomes important to monitor the ability to make both accurate and confident diagnoses. However, such ability requires more and longer training as was indicated by the finding that at least 311 OCT scans had to be evaluated to achieve competence.

These results cannot be universally applied to other centres, because previous experience with OCT may differ as well as targets that are considered feasible or acceptable. However, the learning curves in our study provide more insight into the learning process and the expertise required to master a new skill and therefore will be important for further use and implementation of OCT in clinical practice.

Treatment of basal cell carcinoma

The majority of basal cell carcinomas is still treated with surgical excision.(6) But the same discussion that plays a role in de diagnosis of BCC is also applicable to the treatment of BCC. Given the indolent growth pattern and the possibility of non-invasive diagnosis, this type of skin cancer is also well-suited for less invasive treatment. Cancer medicine is increasingly focussing on topical non-invasive treatments like imiquimod and 5-fluorouracil.(11) This development enables patients to treat themselves in an out-of- hospital setting. Besides, if there are more treatment options available, it will be possible for patients to choose the treatment they prefer most. With the excessively rising incidence of skin cancer, a second important advantage that treatment by patients themselves offers is relieving some of the pressure put on dermatological practices by reducing surgical excisions . We conducted a non-inferiority randomized controlled trial **(Chapter 3.1)** comparing the efficacy of imiquimod with prior curettage with that of surgical excision in patients with nodular BCC. A predefined non-inferiority margin of 8% was used. One year after treatment, the proportion of patients free from treatment failure was 86.3% (63/73) for curettage and imiquimiod cream and 100% (72/72) for surgical excision. The absolute difference was -13.7% (95% CI: -21.6% to -5.8%, one-sided p=0.0004) favouring surgery. The lower limit of the 95% CI exceeds the non-inferiority margin of -8% and so it cannot be concluded that curettage with imiquimod is non-inferior to surgical excision.

Over the years, more topical therapy options became available for the treatment of superficial BCC and nodular BCC, however, to date the efficacy does not equal that of surgical excision. An alternative therapy (that is not as effective as the standard treatment) is only acceptable if it has other advantages like better cosmetic outcomes,

less adverse events or other benefits that lead to more patient satisfaction. It was expected that minimal invasive treatment of nodular BCC by curettage and imiquimod would result in improved cosmetic appearance of treated skin compared to surgical excision. Remarkably, from the patient perspective there was no difference in cosmetic outcome, whereas the clinical investigators did value cosmetic appearance significantly better after curettage and imiquimod treatment than after surgical excision. This finding could be explained by a high number of older patients in the study population and in practice it seems that this group does not attach high value to cosmetic appearance. However, patients did care for the cosmetic appearance if the BCC was located at a visible part of the body: the head and neck area. In this area the cosmetic outcome of curettage and imiquimod was valued significantly better than after surgical excision.

Patients attach different values to different treatments, depending on the situation and location. The choice of treatment will possibly differ between patients, as they will have different needs and require different treatment approaches. In a discrete choice experiment (DCE) including patients inside and outside the trial **(Chapter 3.2),** we aimed to investigate which attributes of a treatment are important to patients and to elicit preferences. Based on important attributes like efficacy, cosmetic results, side effects and waiting period, patients could make a choice between surgical excision or curettage and imiquimod cream as a treatment option. Surgery was chosen most of the times (60%), whereas 40% of the patients chose curettage and imiquimod. The relative importance of the attributes cosmetic results, adverse events and efficacy were calculated. It showed that for both surgical excision and curettage and imiquimod efficacy was considered the least important attribute. The most probable explanation for this finding could be that the efficacy of both treatments was high, which may have geared patients to focus more on other aspects. The DCE helps us to gain more insight in what aspects of a treatment are most important to patients, which may differ from those of medical workers, because patients often have different goals or associations with different treatments. Therefore, cooperation with patients in future randomized controlled trials is essential. Especially, because nowadays, not only efficacy, but many other aspects play important roles in the choice for a treatment.

Overall, surgical excision is still the most effective treatment in the treatment of nodular BCC. It also offers other advantages such as the possibility of histological assessment of the excision specimen and short treatment duration. After treatment with curettage and imiquimod cream in our study, the proportion of patients without treatment failure at 1 year follow-up of 86.3% was still very high. Also, in international guidelines, non-invasive treatment is already generally accepted as standard care for superficial BCC .(12) There seems to be no obvious reason to follow another approach for nodular BCC than for superficial BCC, since both subtypes are considered low risk. (13) Despite a slightly lower efficacy, curettage and imiquimod can be a valuable treatment alternative as the high incidence of BCC puts a burden on the workload of dermatologists,. Especially in

patients with multiple lesions, this treatment increases capacity and might be more cost-effective.

Hedgehog inhibitors

Treatment of BCCs in basal cell nevus syndrome (BCNS) patients and high-frequency BCC (HF-BCC) patients remains a challenge in dermatology. Usually the problem is not the subtype or size of the BCC, but the development of a high number of BCCs in patients.(14) Patients often require many repeated surgical excisions, leaving them with multiple scars. Difficult localisations in the head and neck area or new BCCs in areas with many scars increase the complexity of treatment of BCNS patients.(15) Furthermore, patients will develop new BCCs for the rest of their lives. Altogether the burden is high. Non-invasive topical therapies like imiquimod or curettage and imiquimod could be alternatives for surgery, but not every subtype is suited for this approach. Besides, sometimes there are just too many lesions and it is difficult to treat this high tumour burden with regular therapy. Hedgehog inhibitors might offer a solution in this selected population.

The review in **chapter 4.1** gives an reflection on the treatment with hedgehog pathway inhibitors (HPIs) in BCNS and HF-BCC patients. Treatment with oral hedgehog pathway inhibitors is initially effective, but adverse events, drug resistance and moderate efficacy undermine the potential for long-term use. Most studies have been carried out with patients who had locally advanced BCC (laBCC) or metastasized BCC (mBCC), among which were also patients with BCNS who had a locally or metastasized BCC.(16-18) Only one study specifically investigated the efficacy of vismodegib in BCNS patients with multiple small BCCs, in whom the treatment indication was not locally advanced or metastasized BCC.(19) This study showed a decreased frequency of new BCCs and remission of existing BCCs.

Patients on HPIs frequently discontinue their treatment due to adverse events. Diarrhoea, nausea, fatigue and hair loss are common side effects. Personalized medicine is the key word in these patients, who will develop new BCCs for the rest of their lives. Therefore it is important to adjust a treatment to the patient. Resistance and side effects need to be overcome with the development of new treatment strategies. Intermittent dosing of oral HPIs has been proposed to decrease the severity of side effects and to make continuation of treatment possible. One randomized controlled trial investigated intermittent dosing of vismodegib.(20) In this study patients were treated for a median duration of 16.8 months, which is longer than in the continuous oral HPI trials. Besides, HRQoL improved during and after the trial on the emotional well-being domain compared to baseline HRQoL. However, there are no data on efficacy or resistance with this intermittent treatment. Although the possibility for longer treatment seems promising, this was the only randomized trial which investigated intermittent dosing, so conclusions should be drawn with caution. To ensure efficacy

during temporary discontinuation a combination of HPIs with regular treatment could also be an option. Furthermore, topically applicable HPIs could be a solution for some patients requiring long-term treatment for multiple BCCs. Research on topically applicable HPIs is still scarce, but recently a phase 3 randomised controlled trial was started, investigating topical treatment with the hedgehog inhibitor patidegib for BCNS patients. The Maastricht University Medical Centre is one of the participating centres in this international multicentre study.

Drug resistance remains a major problem for laBCC or mBCC treated with vismodegib. Vismodegib resistance in BCNS with laBCC occurs in approximately 20% of patients.(21) However, vismodegib resistance in small BCCs (non laBCC or mBCC) is rare. In **chapter 4.2** we described a BCNS patient with multiple small BCNS-related BCCs who initially had a favourable response, but who developed vismodegib resistance over time. This is only the second case that describes vismodegib resistance in BCNS without laBCC/mBCC, indicating its rarity. (15) Although this report shows that vismodegib resistance does occur in BCNS-related BCCs, it does not have the same clinical implications as in laBCC/mBCC, because the few resistant BCCs in BCNS can easily be treated with surgical excision or topical treatments. However, these results should be interpreted with caution, due to the low number of patients and scarce available research in this BCNS group.(19)

CONCLUSION

In this thesis we paved the way toward a more non-invasive diagnosis and treatment of basal cell carcinoma. Even though the options of new diagnostic tools like OCT and treatments like imiquimod with prior curettage are promising, optimisation is necessary. Personalized treatment becomes increasingly important and should be based on the number and characteristics of the BCCs, location on the body and personal patient preferences. Non-invasive management should become a part of this personalized treatment, because it gives patients more options and the possibility to be actively involved in the process.

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CHAPTER 6

Summary / Samenvatting

SAMENVATTING

Basaalcelcarcinoom (BCC) is de meest voorkomende vorm van huidkanker, ongeveer 20% van de Nederlanders ontwikkelt ergens in het leven een BCC. Er wordt onderscheid gemaakt tussen drie subtypen : oppervlakkig, nodulair en agressief. Het subtype bepaalt voor een belangrijk deel welke behandeling het meest geschikt is. Hoewel chirurgie nog steeds de standaard behandeling is, is er momenteel een trend naar minder invasieve vormen van diagnose en behandeling. Als deze minder invasieve opties meer worden geïmplementeerd in de huidige klinische setting, kan dit de werklast voor dermatologen verminderen, kan de zorg patiëntvriendelijker zijn en kunnen de kosten van medische zorg in de toekomst worden verlaagd. In de dermatologie is het BCC bij uitstek geschikt voor een niet-invasieve aanpak omdat het een type huidkanker is met een indolent groeikarakter, een goede prognose en een uiterst klein risico op metastasering. Dit proefschrift richt zich op minimaal invasieve methoden voor diagnose en behandeling van het BCC, gepresenteerd in 6 onderzoeken.

In *hoofdstuk 1* wordt een algemene introductie gegeven betreffende de onderwerpen die aan bod komen in dit proefschrift. Epidemiologie, ontstaanswijze, diagnostiek en behandeling van het BCC worden besproken. Ook wordt de behandeling van het basaalcelnaevus syndroom met vismodegib besproken. Daarnaast worden de doelstellingen van dit proefschrift beschreven.

Niet-invasieve diagnostische strategieën maken gedetailleerd onderzoek naar de architectuur van huidweefsel mogelijk te maken en hebben potentieel voor identificatie en subtypering van het BCC. Een van deze technieken is *optical coherence tomografie* (OCT) beschreven in *hoofdstuk 2*. OCT is een beeldvormende techniek met veilig laser licht, die direct in vivo dwarsdoorsnedes afbeeldingen maakt van de huid. Hiermee kan men ongeveer 1,5-2 mm diep 'in de huid kijken'. Het is een patiëntvriendelijke methode waarbij de scanner op de huid kan worden gezet en binnen 30 seconden een afbeelding wordt gemaakt van de laesie. Deze informatie kan worden gebruikt ter identificatie en subtypering van basaalcelcarcinomen.

Om de aanvullende diagnostische waarde van OCT te evalueren, hebben we in *hoofdstuk 2.1* een prospectieve cohortstudie uitgevoerd waarbij 182 patiënten met in totaal 250 laesies werden geïncludeerd . Hierbij bestond de klinische verdenking op niet-melanoom huidkanker of voorlopers hiervan. Alleen patiënten waarbij een biopt moest worden afgenomen voor de diagnose werden geïncludeerd. Het eerste doel van de studie was om vast te stellen of OCT als aanvulling op de klinische beoordeling het mogelijk maakt om beter onderscheid te maken tussen aan- en afwezigheid van BCC. Het tweede doel was om na te gaan of gebruik van OCT bij patiënten met BCC leidt tot een accurate diagnose van het histologische subtype. De mate van vertrouwen in de OCT diagnose werd geregistreerd op een vijfpuntschaal, waarbij score 0 duidde

op zekerheid over afwezigheid van BCC en scores 1-4 op toenemende zekerheid over aanwezigheid van BCC. Voor het schatten van diagnostische parameters werd de histopathologische diagnose met het punch biopt als gouden standaard gebruikt.

Bij gebruik van OCT als aanvulling op de klinische beoordeling nam het vermogen om te discrimineren tussen BCC en niet-BCC toe. Bij diagnose op basis van de klinische blik was de oppervlakte onder de ROC curve (area under the curve) gelijk aan 85.6%. Bij aanvullend gebruik van OCT nam de area under the curve toe tot 91.2% (p = 0,061). Indien een positieve OCT uitslag werd gedefinieerd als enig vermoeden op de aanwezigheid van een BCC (Likert scale score 1-4), nam de specificiteit op patiëntniveau toe van 47,5% (alleen klinisch onderzoek) tot 76,8% (OCT) bij vergelijkbare sensitiviteit (respectievelijk 97,6% en 95,2%). OCT verbeterde tevens het vermogen om onderscheid te maken tussen oppervlakkige en niet-oppervlakkige BCC-subtypen.

In een aanvullende analyse werd onderzocht of een diagnose op basis van OCT nauwkeurig genoeg is om bij een positieve OCT uitslag een punch biopt achterwege te kunnen laten. Het voordeel is dat het dan niet meer nodig is om de uitslag van het biopt af te wachten en men in overleg met de patiënt direct kan overgaan tot een keuze voor behandeling. Voor deze analyse werden de patiënten geselecteerd bij wie de diagnose op basis van OCT een hoge zekerheid had voor de diagnose BCC en ook het subtype. Dit was het geval in 55 van de 182 patiënten (30%). Volgens histopathologie was er bij 49 van deze 55 patiënten (89.1%) inderdaad sprake van een BCC en in de overige 6 gevallen betrof was het goedaardige aandoeningen. De consequenties van inaccurate diagnose op basis van OCT in termen van over- en onder behandeling lijken beperkt. Echter de vraag of OCT-geleide diagnose en behandeling van laesies met verdenking op BCC mogelijk is zonder de prognose van patiënten in gevaar te brengen kan alleen beantwoord worden met een gerandomiseerde trial.

Ten aanzien van het adequaat beoordelen van OCT afbeeldingen, dient een trainingsperiode in acht te worden genomen. In *hoofdstuk 2.2* worden leercurves gepresenteerd die illustreren hoeveel OCT scans minimaal dienen te worden beoordeeld om foutpercentages binnen acceptabele marges te houden. Deze aantallen hangen af van vooraf ingestelde criteria voor acceptabele en onacceptabele foutenpercentages en afkapwaarden voor de definitie van een positieve test. De OCT-onderzoekers rapporteerden de mate van vertrouwen in hun diagnose op een 5-punts Likertschaal. In een scenario waarin OCT diagnoses met een score ≥ 2 (hoge verdenking op BCC of zekerheid over aanwezigheid van BCC) als positieve testuitslag werden gedefinieerd waren minimaal 183 oefenscans nodig om de foutenpercentages van onderzoekers binnen acceptabele grenzen te houden. In een scenario, waarin men bij de uitslag van OCT gebruikt om een punch biopsie achterwege te laten, ligt het meer voor de hand om alleen zekere OCT diagnoses (met scores 3 en 4) als een positieve OCT uitslag te

beschouwen. In dit geval is er meer training vereist en dienen minimaal 311 OCT scans te worden beoordeeld.

In *hoofdstuk 3.1* presenteren we de resultaten van een non-inferiority gerandomiseerde studie waarin werd nagegaan of behandeling van het nodulaire BCC met curettage en imiquimod crème niet-inferieur is aan chirurgische excisie. Patiënten met een met biopt bewezen nodulair BCC werden via randomisatie in een van de twee behandelgroepen ingedeeld. Het primaire eindpunt was het percentage patiënten dat één jaar na het einde van de behandeling geen falen van de behandeling had. Behandelfalen werd gedefinieerd als de afwezigheid van residu tumor na 3 maanden of recidief na 1 jaar. Er werd een vooraf gespecificeerde non-inferioriteitsmarge van 8% gebruikt. Een daling in het succespercentage van maximaal 8% na behandeling met curettage en imiquimod-crème werd als acceptabel beschouwd vanwege verwachte gunstige effecten op cosmetiek en patiënt-tevredenheid. In totaal werden 145 patiënten gerandomiseerd, waarvan 73 naar curettage en imiquimod crème en 72 naar chirurgische excisie. Het percentage recidiefvrije patiënten na 12 maanden was 86,3% voor curettage en imiquimod (63/73) en 100% voor excisie (72/72). De daling in succespercentage in de groep behandeld met curettage en imiquimod was 13.7% . De bovenste grens van het 95% betrouwbaarheidsinterval (5.8%-21.6%) sluit een daling van meer dan 8% niet uit.

Niet-inferioriteit van curettage en imiquimod-crème aan chirurgische excisie kan derhalve niet worden geconcludeerd. In geselecteerde gevallen kunnen curettage en imiquimod een waardevolle behandelingsoptie zijn met de mogelijkheid om overmatig gebruik van excisies te voorkomen. Het kan echter chirurgische excisie niet vervangen.

Hoofdstuk 3.3 beschrijft de resultaten van een discrete choice experiment onder patiënten met een nodulair basaalcelcarcinoom. Een dergelijke vragenlijst geeft op basis van een aantal attributen, zoals cosmetiek, effectiviteit, wachttijden bijwerkingen, de patiënten keuzeopties tussen de twee behandelmogelijkheden door middel van verschillende levels (bijvoorbeeld percentage effectiviteit). De vragenlijst bestond uit 12 verschillende keuzesets, elke keuzeset verschilt in de levels van de attributen. Per keuzeset werd aan patiënten gevraagd voor welke behandeling zij op dat moment de voorkeur hadden: curettage en imiquimod of excision. Patiënten kozen in 60% van de gevallen voor excisie en in 40% voor curettage en imiquimod. Het bleek dat cosmetische resultaten en bijwerkingen als de belangrijkste attributen werden gewaardeerd.

Tot slot hebben we een hoofdstuk *(4.1 en 4.2)* gewijd aan studies betreffende de behandeling met hedgehog pathway inhibitoren van basaalcelcarcinomen bij patiënten met het basaalcelnaevus syndroom (BCNS) en hoog-frequent BCC (HF-BCC) patiënten. BCNS is een syndroom veroorzaakt door een genetische afwijking die ervoor zorgt dat patiënten zeer veel basaalcelcarcinomen ontwikkelen en vaak al vanaf jonge leeftijd. De hedgehog pathway is essentieel in de ontwikkeling van een BCC en is geactiveerd in

de meeste BCC's. HF-BCC patiënten worden gedefinieerd als patiënten met minstens 9 BCC excisies binnen een periode van 3 jaar. In de review in hoofdstuk 4.1 werd het overzicht gegeven van de huidige beschikbare kennis op het gebied van behandeling met hedgehog inhibitoren bij zowel BCNS patiënten als bij HF-BCC patiënten op het gebied van effectiviteit, veiligheid, tumor resistentie en recidief en kwaliteit van leven. Vooral bij deze patiënten lijkt de geregistreerde dosering niet optimaal en zal een patiënt vermoedelijk meer gebaat zijn bij een gepersonaliseerde behandeling.

Daarnaast beschreven we in hoofdstuk 4.2 een casus waarbij een met vismodegib behandelde patiënt met BCNS gerelateerde BCC's resistent was voor de behandeling. Met genetisch onderzoek middels molecular inversion probes (MIP) op het tumormateriaal van zowel resistente als niet-resistente BCCs toonden we aan dat de oorzaak van deze resistentie vermoedelijk werd veroorzaakt door een mutatie in het gen smoothened, het gen dat normaliter wordt geremd door vismodegib. De therapeutische consequenties van resistente tumoren in patiënten met BCNS kwamen aan bod.

Hoofdstuk 5
Dit hoofdstuk besluit het proefschrift met een discussie en valorisatie waarin we de uitgevoerde onderzoeken bediscussiëren en het belang van het onderzoek voor de dagelijkse praktijk bespreken.

SUMMARY

Basal cell carcinoma (BCC) is the most common form of skin cancer in the Netherlands with a life time risk of 20% to develop BCC. BCC generally can be categorized into three subtypes: superficial, nodular and infiltrative BCC. The subtype is of importance for the choice of optimal treatment. Although currently surgery is still the standard treatment, there is a trend toward less invasive diagnosis and treatment. More frequent use of non-invasive options in the current clinical setting, could result in a reduction of the workload for dermatologists, could be more patient friendly and might reduce costs of medical care. In dermatology, BCC is especially suited for a non-invasive approach since it is a type of skin cancer with an indolent growth character, a good prognosis and a very low risk of metastasis. This thesis focuses on minimally invasive methods for diagnosis and treatment of basal cell carcinoma, presented in 6 studies.

In *chapter 1,* the topics that will be discussed in this thesis are presented in a general introduction. The background, regarding epidemiology, origin, diagnosis and treatment of basal cell carcinoma and basal cell nevus syndrome is discussed and objectives of this thesis are described.

Non-invasive diagnostic strategies enable detailed investigation of skin tissue architecture and have the potential for identification and subtyping of basal cell carcinoma. One of these techniques is optical coherence tomography (OCT) as described in *chapter 2*. OCT is a safe laser light imaging technique that provides real-time, in vivo, cross-sectional images of lesions with a depth of about 1.5-2 mm. A scan probe is placed on the skin and an image of the lesion is made within 30 seconds. The speed and non-invasive aspects makes OCT a very patient friendly method .

To evaluate the diagnostic value of OCT for identification and subtyping of BCC, we conducted a prospective cohort study in *chapter 2.1* that enrolled 182 patients with a total of 250 lesions suspected of non-melanoma skin cancer or its precursors. Only patients requiring a biopsy for diagnosis were included. The first aim of the study was to determine whether OCT in addition to clinical images (cOCT) could increase the ability to distinguish between the presence and absence of BCC. The second aim was to determine whether the use of OCT in patients with BCC leads to an accurate diagnosis of the histological subtype. Confidence levels were recorded on a five-point scale, with score 0 indicating absence of BCC and scores 1-4 indicating increasing certainty of diagnosis. Diagnostic parameters were compared to histopathological diagnosis with the use of punch biopsy as gold standard.

cOCT increased the ability to discriminate between BCC and non-BCC. At patient level, the area under the curve increased from 85.6% for the clinical examination alone to 91.2% for cOCT ($p = 0.061$) and at lesion level from 82.7% to 91.3% ($p < 0.001$) in favor of

OCT. When a certainty on the 5-point scale 1-4 was defined as positive (some suspicion of BCC), specificity at the patient level increased from 47.5% (clinical study only) to 76.8% (OCT) at comparable sensitivity (97.6% and 95.2%). cOCT slightly improved the ability to distinguish between superficial and non-superficial BCC subtypes and appears to be a valuable addition to clinical examination in the diagnosis and subtyping of BCC.

An additional analysis was performed to investigate whether a BCC diagnosis based on OCT is accurate enough to omit a punch biopsy in the future. 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 (highest confidence). This level of certainty about the presence of BCC and the subtype according to cOCT was seen in 55 of 182 patients (30%). According to histopathology, 49 of these 55 patients (89.1%) indeed had a BCC and the remaining 6 diagnoses were benign conditions. The consequences of inaccurate diagnosis based on OCT in terms of over- and under treatment appear to be limited. However, the question of whether OCT-guided diagnosis and treatment of lesions with suspected BCC is possible without jeopardizing the prognosis of patients can only be answered with a randomized trial.

Accuracy of diagnosing BCC with OCT can improve with training. In chapter 2.2 learning curves are presented that illustrate the minimum number of OCT scans that should be assessed in order to keep error rates within acceptable margins. This number also depends on preset acceptable and unacceptable error rates and cut-off values for the definition of a positive test. The OCT researchers reported their diagnosis on a 5-point scale, which allowed evaluation of their performance using different thresholds. When OCT diagnoses made with a confidence level ≥ 2 (either high suspicion or certainty of presence of BCC) was defined as test positive results, the minimally required number of training scans before achieving acceptable performance was 183 cases. In a scenario where a biopsy would be omitted if the OCT result is positive, it makes sense to use only certain OCT diagnoses (with scores 3 and 4) as positive. In this case, more training is required and a minimum number of 311 OCT scans must be assessed.

In *chapter 3.1* a non-inferiority randomized trial is discussed which aimed to evaluate whether minimally invasive treatment of nodular basal cell carcinoma (nBCC) with curettage and imiquimod cream is non-inferior to standard treatment with surgical excision. Patients with a biopsy-proven nodular BCC were randomized into one of the two treatment groups. The primary endpoint was the percentage of patients without treatment failure one year after the end of treatment. A pre-specified non-inferiority margin of 8% was used. A decrease in the success rate of up to 8% after treatment with curettage and imiquimod cream was considered acceptable because of expected

beneficial effects on cosmetic outcomes and patient satisfaction. A total of 145 patients were randomized, of which 73 to curettage and imiquimod cream and 72 to surgical excision. The proportion of patients without treatment failure at 12 months was 86.3% for curettage and imiquimod (63/73) and 100% for excision (72/72). The reduction in success rate of curettage and imiquimod compared to excision was 13.7%. The upper limit of the 95% confidence interval (5.8% -21.6%) did not exclude a decrease of more than 8%. Non-inferiority of curettage and imiquimod cream cannot be concluded. However, given the still relatively high efficacy, curettage and imiquimod can be considered as a treatment option in selected cases or in a situation where it is beneficial to avoid overuse of excisions. However, it cannot replace surgical excision.

In addition, a discrete choice experiment was performed among patients with nodular BCC (*chapter 3.2*). The attributes used in this study that were marked as important for treatment were cosmetic outcomes, effectiveness, waiting time and side effects. The questionnaire consisted of 12 different choice sets, depending on different attribute levels. Per set, patients were asked what treatment they preferred in that specific choice set: curettage and imiquimod or surgical excision. In 60% of the cases, patients opted for excision and in 40% for curettage and imiquimod. It turned out that cosmetic results and adverse events were valued as the most important. These attributes were valued more than efficacy.

In the last chapter (4.1 and 4.2) studies on hedgehog inhibitors in the treatment of basal cell carcinomas in patients with basal cell nevus syndrome (BCNS) and high-frequency BCC patients (HF-BCC patients) are discussed. BCNS is a syndrome caused by a genetic abnormality that causes patients to develop many basal cell carcinomas, often from an early age. The genetic defect is situated in the patched gene, a gene of the hedgehog pathway. The hedgehog pathway is not only defective in BCNS patients, but also essential in the development of a BCC and is activated in most BCCs. HF-BCC patients were defined as patients with at least 9 BCC surgeries in a 3 year time period. We reviewed the literature on hedgehog pathway inhibitors in BCNS and HF-BCC patients to provide an overview on efficacy, safety, tumor resistance and reoccurrence, and health-related quality of life. Especially in patients with BCNS, the registered dose does not seem optimal and patients will probably benefit more from a personalized treatment.

In addition, in chapter 4.2 we described a case study in which with vismodegib treated patients with BCNS-related BCCs were resistant to the treatment. Genetic research using molecular inversion probes (MIP) on the tumor material of both resistant and non-resistant BCCs showed that this resistance was probably caused by a mutation in the smoothened gene, the gene that is normally inhibited by vismodegib. The therapeutic consequences of resistant tumors in patients with BCNS were discussed.

Chapter 5
This chapter concludes the thesis with a discussion and valorization in which we discuss the research done and the importance of the research for daily practice.

CURRICULUM VITAE

Kelly Anna Emma Sinx werd op 23-02-1990 geboren te Oosterhout, Noord-Brabant. Zij groeide op als oudste in een gezin met een jongere broer. Zij doorliep in 6 jaar het atheneum van het Monsigneur Frencken college te Oosterhout en nam in 2008 haar diploma in ontvangst. Van 2008-2015 studeerde zij geneeskunde aan de Radboud universiteit Nijmegen waarbij al vroeg in de opleiding interesse in de Dermatologie ontstond. Aan het einde van de coschappen werden de onderzoeksstage en het eindcoschap bij de Dermatologie in het RadboudUMC gedaan. Alvorens te starten aan haar promotieonderzoek bij de Dermatologie in het Maastricht UMC+, heeft zij 7 maanden als ANIOS Ouderengeneeskunde gewerkt in Arnhem. In november 2015 startte zij met haar promotieonderzoek. Kelly is sinds mei 2018 in opleiding tot dermatoloog in het Maastricht UMC+.

LIST OF PUBLICATIONS

- Optical Coherence Tomography for Noninvasive Diagnosis and Subtyping of Basal Cell Carcinoma: A Prospective Cohort Study. Sinx KAE, van Loo E, Tonk EHJ, Kelleners-Smeets NWJ, Winnepenninckx VJL, Nelemans PJ, Mosterd K. J Invest Dermatol. 2020 Oct;140(10):1962-1967

- Surgery versus combined treatment with curettage and imiquimod for nodular basal cell carcinoma: One-year results of a noninferiority, randomized, controlled trial. Sinx KAE, Nelemans PJ, Kelleners-Smeets NWJ, Winnepenninckx VJL, Arits AHMM, Mosterd K. J Am Acad Dermatol. 2020 Aug;83(2):469-476.

- Commentary on “Long-Term Follow-Up Results of Topical Imiquimod Treatment in Basal Cell Carcinoma”. Jansen MHE, Sinx KAE, Kelleners-Smeets NWJ, Mosterd K. Dermatol Surg. 2019 Jan;45(1):144-145.

- Vismodegib-resistant basal cell carcinomas in basal cell nevus syndrome: Clinical approach and genetic analysis. Sinx KAE, Roemen GMJM, van Zutven V, Janssen R, Speel EM, Steijlen PM, van Geel M, Mosterd K. JAAD Case Rep. 2018 Apr 30;4(5):408-411. doi: 10.1016/j.jdcr.2017.11.011.

- Erythema annulare centrifigum bij een patiënt met polycythemia vera. K.A.E. Sinx en W.H.P.M.Vissers. Nederlands Tijdschrift voor Dermatologie en veneorologie september 2015.

GRANTED PROPOSALS

2018

ZonMw Grant Doelmatigheidsonderzoek 2018 *Project*: (Cost)-effectiveness of optical coherence tomography versus regular punch biopsy in the diagnosis and subtyping of basal cell carcinoma: a multi-center randomized non-inferiority trial. € 295.500,00

December 2016

Travel Grant, Fondation René Touraine, Paris. Mice studies for the treatment of basal cell carcinoma with imiquimod creme and diclofenac gel. Laboratory of prof. C. Blanpain, Brussels, Belgium. €1.650

April 2016

Grant Maurits en Anna de Kock stichting, Amsterdam. Support for the purchase of optical coherence tomography device. € 40.000

PRESENTATIONS AND CONGRESSES

October 2020

Oral presentation online: Surgery versus combined treatment with curettage and miquimod for treatment of nodular basal cell carcinoma(SCIN): 1-year results of a non-inferiority, randomized controlled trial. European association of Dermato Oncology (EADO)

September 2018

Oral presentation: Optical Coherence Tomography for non-invasive diagnosis and subtyping of Basal Cell Carcinoma, a prospective cohort study. Congress European Academy of Dermatology and Venereology (EADV) Paris, France.

May 2017

Poster presentation: Vismodegib resistant basal cell carcinoma in Gorlin syndrome. Congress European association for Dermatology and Venereology. EADV Athens, Greece

Feb 2017

Oral presentation: Vismodegib resistant basal cell carcinoma in Gorlin syndrome, NVED 2017, Lunteren

2015

Poster presentation: Risk of photosensitive diuretics on developing skin malignancies in immunocompromised renal transplant patients, NVED 2015, Lunteren.

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