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

# 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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