CHAPTER 4

Discussion and valorization
Despite skin cancer prevention campaigns on sun avoidance, little behavior change is seen and the incidence of skin cancer continues to rise. About 80% of skin cancers are basal cell carcinoma (BCC). Nowadays, the lifetime risk of developing a BCC before the age of 85 years is 1 in 5-6 persons. Predictions for the future incidence are even more alarming. One should keep in mind that incidence studies are based on data from cancer registries which often only register the first, histologically confirmed BCC. Within 5 years after the first BCC diagnosis, 29% of patients will develop another BCC. Therefore, only the tip of the iceberg is measured and actual incidence rates will be higher. BCC may be regarded as a chronic disease which poses a large burden on dermatologic health care services.

A century ago, surgery was the only treatment option for BCC and was mostly performed by general surgeons. Surgical excision is a treatment that enables histological verification of complete tumor removal. It therefore was (and still is) the most effective treatment in BCC. The first non-invasive option that emerged more than 50 years ago was 5-fluorouracil (5-FU). This therapy probably became abandoned as more dermatologists were expanding their surgical skills and a treatment was developed that resulted in nearly 100% cure rates (Mohs’ micrographic surgery). Furthermore, in the 1960-1980s, incidence of skin tumors was still not that high that alternative treatments were in high demand. It is conceivable that in those days patients were glad their tumor was removed and were not that concerned about the aesthetic outcome. The situation changed in the late 20th century, when the incidence rates of BCC increased rapidly, more young patients were affected and patients became more demanding. At that time, the second non-invasive treatment was developed: photodynamic therapy (PDT). The concept of PDT was already initiated 100 years earlier by Von Tappeiner: an interaction between light, a photosensitizer and oxygen. It is interesting to observe how PDT suddenly gained popularity based on a few small-sized studies with a short follow-up period. One of the reasons was probably the strong need for non-surgical therapies that could be executed by nurses, relieving the busy dermatologic practice. PDT became a competitor of surgery with a promised high treatment success and excellent aesthetic outcome. PDT was incorporated in (inter)national guidelines on treatment of superficial BCC (sBCC). With the introduction of imiquimod in 2004 competition came into play. Imiquimod cream is less expensive than the in-hospital PDT. Another advantage of imiquimod is that patients can apply the cream themselves at home. Consequently, imiquimod became also incorporated in guidelines on BCC treatment. Guidelines agree that surgical excision should still be considered as first choice treatment for sBCC but excision is not always needed and often considered as overtreatment. Despite the
acknowledgement that in some instances non-invasive therapies may be preferred, there was no consensus on the best non-invasive treatment choice in sBCC.

In the last decades, the need for consensus has increased due to the observed shift towards sBCC. sBCC can be treated non-invasively and this provides the opportunity to reduce the workload for dermatologists. As a result, non-invasive therapies such as PDT, imiquimod and 5-FU have become increasingly popular. These trends highlight the need for evaluation of diagnostic and treatment options for optimal management of sBCC. First, the development of these non-invasive therapies demands an accurate diagnostic tool with the ability to discriminate between BCC subtypes. Knowledge of subtypes is important as sBCC can be treated non-invasively while nodular BCC (nBCC) and aggressive BCC (aBCC) mostly require a surgical treatment. The need for distinction between sBCC and other types of BCC asks for diagnostic strategies that can meet this requirement. Secondly, the availability of various non-invasive treatment options for patients with sBCC asks for comparison of the effectiveness of these treatments and other aspects such as cosmetic results, adverse effects and costs. Such results are pivotal for reaching consensus on the most effective non-invasive treatment option in patients with sBCC. A third issue is whether treatment needs to be tailored based on patient and tumor characteristics. It may well be that subgroups of patients benefit more or less from specific treatment options.

**Diagnosis**

Optimal management of BCC relies on early and accurate diagnosis in order to optimize outcome and minimize morbidity. Current national and international guidelines on BCC recommend a punch biopsy of clinically suspected BCC prior to treatment to facilitate treatment choice based on the histological BCC subtype. We performed two studies to evaluate the diagnostic accuracy of a punch biopsy. In one study on the agreement between the results of punch biopsy and surgical excision, we found that punch biopsies can detect the most aggressive subtype in 83.4% of cases when compared with surgical excision, resulting in a correct staging in 5 out of 6 primary BCC. Our findings corroborate results of previous studies that also showed high percentages of 79-89%. An explanation for the fact that the most aggressive subtype is not detected in all cases is that a punch biopsy, often 3-4 mm, represents only a small sample of the tumor. The majority of BCC (74%) consists of a ‘mixed’ histological subtype and the most aggressive component can be missed in a small tumor sample. However, we can
conclude that a punch biopsy has a high sensitivity to identify nBCC and aBCC that qualify for surgery instead of a non-invasive treatment.

In another study, the accuracy of punch biopsy was compared with that of a clinical diagnosis by a dermatologist. The diagnosis based on the surgical excision specimen was used as gold standard. It is assumed that dermatologists can diagnose a BCC fairly well by their clinical observation. The advantage of clinical diagnosis is that it is a painless, time saving and presumably also a cost saving procedure. But a relevant question is: how many tumors will be over- or understaged and consequently how many tumors would be over- or undertreated when omitting a punch biopsy? We performed a study to compare the diagnostic accuracy of clinical assessment and histological diagnosis by punch biopsy for subtyping BCC. In this study, a punch biopsy appeared to be a more accurate diagnostic tool than the clinical diagnosis for detection of the histological BCC subtype. Omission of a punch biopsy resulted in overstaging of 1 in 4 sBCC as nodular or aggressive and in understaging in about 1 in 4 aBCC as nBCC. The question can be raised whether these diagnostic errors result in inadequate treatment. In case of overstaging, the physician will almost certainly advise surgery and the patient will be denied the choice between surgery and less invasive alternatives. However, some patients will be satisfied with a surgical excision as they are content that their tumor has been removed. In case of understaging, patients are at risk of having their BCC excised with too small margins. However, a BCC is a tumor with a low mortality rate and any residue or recurrence following therapy can be diagnosed and retreated easily in most cases. Based on these findings, it may be justified in a few cases to omit a punch biopsy, especially if the tumor is located on a low risk area. It would be interesting to find out whether the accuracy of clinical diagnosis approaches that of a punch biopsy when the degree of confidence in the diagnosis of BCC subtype is taken into account. In situations where physicians are very confident of their clinical diagnosis on BCC subtype, the need for a punch biopsy may be less obvious. Furthermore, the subtyping of BCC might further be improved by the use of a dermatoscope, which enables detection of certain clinical features that are characteristic for BCC subtypes. The hypothesis, that a clinical diagnosis of BCC subtype made with a dermatoscope and high confidence may exclude the necessity of a punch biopsy prior to treatment, needs to be confirmed in a well-designed prospective study.
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Treatment

The equivocal guidelines and the large web of treatment options presented in guidelines on sBCC can hamper physicians in making well-informed treatment choices. Due to the current lack of evidence on relative effectiveness of therapies, treatment choice is nowadays partly based on the doctors’ own experience and education. More evidence on relative effectiveness of treatments is needed. We performed a systematic review and meta-analysis of published studies to compare the tumor-free survival of patients with primary sBCC treated with the most frequently used non-invasive therapies. The majority of the included studies reported on treatment with imiquimod or PDT, which enabled a meta-analysis on treatment success of these therapies. The pooled estimates for one year tumor-free survival were 87.3% for imiquimod and 84.0% for PDT. However, restriction of the analysis to PDT studies with only one PDT cycle resulted in a lower pooled estimate of tumor-free survival of 76.2%. These results provided evidence that imiquimod and PDT are nearly equally effective in treatment of sBCC at one year post treatment. The meta-analysis also revealed that head-to-head comparison studies and studies with a long-term follow-up were lacking. Closing this gap in knowledge is essential to enable better recommendations in guidelines on sBCC treatment.

To fulfill the need for a head-to-head comparison study with long-term follow-up, a non-inferiority randomized controlled trial in 601 patients with sBCC treated with methylaminolevulinate (MAL)-PDT, imiquimod or 5-FU has been performed. The one year follow-up results indicated that both creams are not inferior to MAL-PDT in terms of effectiveness and that imiquimod was even superior to MAL-PDT. One year tumor-free survival for imiquimod was 83.4% versus 72.8% for MAL-PDT with a difference of 10.6% (95% CI 1.5%-19.5%) favoring imiquimod. Extra data during a three year follow-up period were collected. At three years post treatment, imiquimod and 5-FU remained non-inferior to MAL-PDT, but the gap between imiquimod and MAL-PDT widened even more. Imiquimod showed a large advantage in three year tumor-free survival of 79.7% compared with 68.2% for 5-FU and only 58.0% for MAL-PDT. The conclusion is that based on effectiveness, imiquimod should be considered as the first treatment choice in primary, low-risk sBCC.

The trial was designed as a non-inferiority trial because before the start of the trial it was assumed that MAL-PDT was the most effective treatment and that both creams might be less effective in terms of tumor-free survival. However, it was expected that the creams would have advantages such as lower costs and reduction of workload on dermatologists, because creams can be applied by the patient at home. Because of these
advantages and the possibility to fall back on excision in case of a recurrent BCC, a loss in one year tumor-free survival by 10% was deemed acceptable. The choice of MAL-PDT as reference therapy was based on a review of the Cochrane Collaboration which concluded that surgical excision should be the first choice therapy for sBCC but that PDT can be considered as a good alternative because of better cosmetic outcomes and a greater patient tolerability.\textsuperscript{18} It was assumed that the one year cumulative probability of tumor-free survival after PDT would be about 80%, based on the average of the estimates for PDT from the meta-analysis. However, the trial results seem to contradict the correctness of this assumption. This faulty assumption is partly due to the scarcity of randomized controlled trials comparing MAL-PDT with surgery. Before the start of the trial, only one randomized controlled trial had compared MAL-PDT with surgical excision at one year post treatment and estimates of treatment success after PDT may have been overoptimistic.\textsuperscript{19} The one trial included 128 histologically proven primary sBCC that were treated with one or two MAL-PDT cycles. In this study, 90 of 128 (70.3%) sBCC responded to one MAL-PDT cycle, but the non-responders and incomplete responders received two additional MAL-PDT sessions after a period of three months. This increased the overall cumulative probability of sustained clearance to 90% at one year post treatment for MAL-PDT. A reason for the observed discrepancy with the expected 80% treatment success after PDT may be that the most frequently used European PDT protocol was applied very strictly in this trial. This protocol for MAL-PDT is advised by the company producing MAL and prescribes one MAL-PDT cycle consisting of two treatments with one week interval.\textsuperscript{20} Repeating treatments would probably improve treatment success but increases the dermatologist’s workload and treatment costs.

The trial results indicate that PDT is not the most effective non-invasive treatment option. However, PDT has the benefit of being a two-day treatment with less side effects and a more rapid recovery compared with imiquimod. In this respect, further research to improve PDT and its illumination protocol seems worthwhile.

Now we have concluded that imiquimod should be the first choice therapy in primary sBCC, the question raises whether imiquimod is the most effective therapy for every patient with a sBCC. Based on data derived from the above mentioned non-inferiority trial, subgroup analyses were performed to explore whether the relative treatment effect of MAL-PDT and imiquimod is consistent across subgroups of patients and tumors.\textsuperscript{21} A higher probability of treatment success for imiquimod versus MAL-PDT at three year follow-up was confirmed in most subgroups. An interesting finding was that in patients >60 years with a sBCC on the lower extremities, MAL-PDT was more effective than imiquimod (tumor-free survival of 93.8% vs. 36.2%). This finding coming from an ex-
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Plorative analysis needs to be confirmed in future studies, but for the time being these results suggest that MAL-PDT can be considered as a treatment option for older patients with sBCC on the lower extremities, in whom the imiquimod induced erosion might cause local wound infections, ulcerations or erysipelas. There are other situations wherein imiquimod may not be the optimal choice for an individual patient. Imiquimod requires compliance with a treatment regimen which prescribes application once daily, five times a week for six weeks. Therefore, this treatment is not indicated when the sBCC is situated inconveniently on a body site that is out of reach of a patient or when there is another reason why patients are not capable of applying the cream. In these cases, PDT may be an option, but surgery may also be considered depending on the comparative assessment between effectiveness and cosmetic aspects.

It was also evaluated whether tumor thickness and adnexal extension might influence response to non-invasive treatments. The superficial growth pattern is easily accessible for topical treatments. We defined a sBCC as a tumor existing of small buds of proliferating basal cells that grow down from the epidermis into the superficial dermis, whilst maintaining their attachment to the base of the epidermis. However, it might be that there is a threshold thickness above which sBCC do not respond well to PDT, imiquimod and 5-FU. We measured tumor thickness in 336 sBCC with a median thickness of 0.35 mm and a range of 0.2-1.0 mm. Our results showed that tumor thickness and adnexal extension of sBCC were not significantly associated with treatment failure following MAL-PDT, imiquimod or 5-FU.

International guidelines recommend PDT as treatment option for sBCC, but also for ‘thin’ nBCC that cannot be surgically excised. Thin tumors are likely to respond to the superficially working PDT. We analyzed the effect of nBCC thickness on treatment failure five years after treatment with fractionated aminolaevulinic acid (ALA)-PDT. The cumulative probability of tumor-free survival after ALA-PDT was 65.0% for tumors measuring > 0.7 mm in thickness compared with 94.4% in tumors ≤ 0.7 mm. The finding that thin nBCC in this trial responded more often to PDT than the sBCC in the non-inferiority trial (treatment success of 94.4% vs. 58.0%) might be explained by the partial debulking prior to PDT.

Another explanation might be that nBCC were treated with ALA-PDT instead of MAL-PDT. According to the literature, the effectiveness in terms of clearance rates of sBCC is lower for MAL-PDT in two sessions compared with fractionated ALA-PDT: 73% vs. 88% at five years post treatment. Based on these results, fractionated ALA-PDT with partial debulking might be considered as an acceptable non-invasive treat-
ment option in a selected population of inoperable patients with nBCC measuring ≤ 0.7 mm in thickness.

Based on the data in this thesis, we can conclude that a punch biopsy is preferred in clinically suspected BCC in order to confirm the diagnosis but, even more important, to identify the most aggressive subtype. Omission of a punch biopsy may be justified in few cases, but the possible consequences should always be discussed carefully with the patient. First choice treatment for sBCC is imiquimod cream whereas PDT might be a treatment option in elderly patients with sBCC on the lower extremities or in patients for whom cream application is not feasible for practical reasons. It will remain a goal but also a challenge for dermatologist and other physicians to provide clear guidance in treatment of an individual patient with sBCC.
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References


