SUMMARY AND GENERAL DISCUSSION

This thesis describes several studies conducted with the aim to optimize care for patients with sBCC. In this chapter, the conclusions of my research will be summarized and discussed.

The aim of this thesis was to create optimal conditions in which to treat patients with sBCC. The current guidelines and the latest Cochrane review on the management of BCC identify several treatment options for sBCCs. [1-3] First and foremost, surgery is the most effective treatment. Non-invasive and destructive options are less effective compared to surgery, but are relevant alternatives all the same because of other advantages. Several aspects play a role in optimizing care of patients with sBCC. The risk of misclassification of the BCC subtype has to be minimized, available non-invasive treatment strategies should be optimal, cost-effectiveness should be taken into account (which is absolutely vital from a healthcare perspective), and last but not least, patient preferences should be considered. In this respect, it is fundamental to provide patients with tools that enable them to make a well-informed and optimal treatment decision.

A patient decision aid for patients with superficial basal cell carcinoma
Chapter 2 entails all of the research concerning the development and testing of a patient decision aid (PDA) for patients with sBCC.

A quantitative survey study was conducted, described in Chapter 2.1, to evaluate patients’ recollections of the treatment choices for their BCC and what kind of information they valued most. Patients of a large Dutch patient panel (25,000 members) were asked if they ever had been diagnosed with a BCC, what their recollections were of the treatment options they were offered, and what kind of information they valued. In total, 309 panel patients with a BCC in their history responded. Most of these patients remembered that surgery was an option (71%), followed by cryotherapy (34%), Mohs micrographic surgery (20%), 5FU (23%), PDT (19%), and imiquimod (15%). Strikingly, cryotherapy was very often recalled as a treatment option, even though it is not a standard treatment for BCC according to the Dutch guidelines, but should be reserved for patients with low-risk BCC who prefer a quick-and-easy treatment over a more burdensome surgical treatment with higher effectiveness and a good cosmetic outcome. [1, 2, 4] This explorative study also showed that more than 25% of the patients would have
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liked additional information on the diagnosis and treatment options, even many years post-treatment. Van Egmond et al. came to the same conclusion in their focus group study on needs and preferences of patients with BCC and SCC. Patients emphasized the importance of receiving all relevant information specifically tailored to their situation. [5] Subsequently, it was important to find out what information should be included in a future PDA for patients with a BCC. From most to least important, patients wished for information on risk of recurrence, risk of complications and side-effects, the setting of the treatment (at home or at the hospital), and finally cosmetic outcome and costs which is in line with former research. [6]

The development of the actual PDA for patients with a sBCC was described in Chapter 2.2 and consisted of three phases. [7] In phase 1 the content for the PDA was created using the results from the survey study in Chapter 2.1 and an extensive literature search that was performed on treatment options, characteristics of treatments, and additional information on patient values. It was during this phase, that we made the decision not to include destructive treatments like cryotherapy and curettage and electrodesiccation (C&E) in the PDA. These options are directly applied treatments that are reserved for patients with low-risk sBCC that opt for a quick-and-easy treatment. It was assumed that patients who opt for these on-the-spot therapies will probably not be offered the PDA. A first draft of the PDA was developed as a mock-version and tested in a focus group with patients and a separate focus group with professionals. Three important topics arose: to make visual aids (e.g. photographs of BCCs) optional, to nuance the information on rare metastatic potential, and to exclude the information on Mohs micrographic surgery. The PDA was altered accordingly. Next, feedback was gathered from a predetermined project-team consisting of stakeholders (academic and general dermatologists, specialized nurses, patients, a digital dermatologist, a representative of the Dutch patient federation). Finally, five patients went through the PDA during a ‘think-aloud’ interview to remove the final bugs. The PDA was ready to be implemented.

Following the development of the PDA, it would have been possible to directly deploy and implement the PDA. However, it seemed necessary to evaluate the effect of the PDA in patients with sBCC. Several questions were raised: 1) would the PDA help to decrease decisional conflict? 2) Would employing the PDA lead to an improved understanding of the information (improved knowledge)? 3) Would it change actual decision-
making, or in other words, would patients who used the PDA more often prefer a non-invasive treatment to a control group without PDA?

We aimed at answering the first two questions in Chapter 2.3. A prospective multicentre observational pre- and post-implementation study in patients with a newly diagnosed sBCC was performed. The objective was to investigate whether using the PDA in a target population of patients led to a reduction in decisional conflict level and increased knowledge of the diagnosis and treatment options. Decisional conflict levels were measured using the decisional conflict scale (DCS). The DCS consists of 16 statements gathered into subscales: 1) ‘uncertainty’, 2) ‘factors contributing to uncertainty’ (consists of ‘informed decision’, ‘values clarity’, and ‘support’), and 3) ‘effective decision making’. [8] Higher scores on the DCS indicate that patients have more decisional conflict, are inclined to regret their choice, and/or ‘fail’ on a knowledge test. Lower levels of decisional conflict (<25) mean that patients are more inclined to follow through on their decision. [9, 10] All patients completed the DCS directly after making the treatment decision and before treatment and completed a knowledge questionnaire that was adapted from an existing knowledge instrument for patients with melanoma. [11, 12]

Patients were included before and after implementation of the PDA. Data was available for a total of 103 patients in the control group that did not use a PDA, and 109 patients in the group that did use the PDA before making the treatment decision (PDA-group). The total score on the DCS in the control group was 22.78 versus a score of 22.34 in the PDA-group (mean difference -0.44, p=0.828). We found no significant difference in levels of decisional conflict between patients in the PDA-group compared to the control group, which was the primary outcome of our study, probably because decisional conflict was low to begin with; there was very limited room for improvement. Post-hoc subgroup analyses showed that patients with a sBCC in the head and neck area, patients without a history of BCC and patients with a higher educational level seemed to benefit more from using the PDA, but these results were not significant.

However, the patients in the PDA-group did have improved knowledge. The average percentage correct score on the knowledge questionnaire in the control group was 76.5% versus 80.5% in the PDA-group (p=0.044). To the question on recognition of a sBCC, the average percentage correct score increased significantly from 71.8% in the control group to 78.9% in the PDA-group (p=0.007). Knowledge on sun-protection, risk factors for developing a BCC, and treatment options for sBCC
also increased, but the increases were not statistically significant. Furthermore, 75.9% of the patients in the control group indicated that they would have wanted additional information compared to only 15% in the PDA-group. We might conclude that the information provided through the PDA was sufficient and was better absorbed by patients in the PDA-group compared to the control group who only received vocal information from their physician. It is a fact that physicians sometimes (unintentionally) guide patients towards a certain decision. [13, 14] The PDA can be used as an objective tool that gives unbiased information. A limitation of this study was that it was designed as a pre – and post implementation study, and not as a randomized controlled trial (RCT) because cluster randomization of clinicians was not feasible. Patient groups were included during different time periods and multivariate regression analyses were used to adjust for potential between-group differences in baseline characteristics. All in all, it seems that patients value unbiased information tailored to their level to increase their knowledge. Even if patients do not experience a high level of decisional conflict, information is indispensable for making a treatment decision that fits a patient’s personal situation.

Finally, the third question remained whether using a PDA changes the actual treatment decision? Within the dermatological field, not much is known about the effects of using a PDA on treatment decisions or if there are any tumour – or patient related characteristics of influence on this decision. Research showed that patients with non-dermatological conditions who used a PDA choose treatment options with fewer risks of complications or side-effects. The primary goal of Chapter 2.4 was to investigate whether patients with a sBCC who used a PDA more often prefer non-invasive treatment options when compared to a control group, and whether patients were still satisfied with their decision post-treatment. It was also investigated whether patients are still satisfied with their treatment decision after treatment measured on the 'effective decision making' subscale on the DCS. For this purpose, we used the data of the observational study described in Chapter 2.3. In both the control group and the PDA-group, more than half of the patients preferred surgery to non-invasive treatment. In the PDA-group the proportion of patients who chose non-invasive treatment was slightly higher than in the control group (48.6% vs 40.8%), but the difference was not statistically significant (p=0.255). An analysis was performed concerning the association between preference for non-invasive treatment and specific patient- and tumour characteristics. Patients with a positive history of BCC significantly more often chose
non-invasive treatment compared to patients with a first-time BCC (OR 2.28, p=0.014). Furthermore, three months after treatment, the mean score on the ‘effective decision making’ scale for the PDA-group was 10.33 (SD 12.85) compared to 14.92 (SD 18.04) in the control group (mean difference of -4.10, p=0.082, effect size=0.3). Lower scores indicate more satisfaction with the treatment decision in hindsight. Patients who used the PDA seemed more likely to feel they had made an ‘effective decision’. The effect size was near 0.3 defined as clinically relevant in the user manual of the DCS although the between-group difference was not significant. [10]

Systematic review of economic evaluations of treatment options for superficial basal cell carcinoma

The rising incidence of sBCC puts a large burden on healthcare budgets worldwide. [15, 16] Multiple treatment options are available that differ in terms of their costs and effectiveness. Economic evaluations are valuable to determine whether the investment made is in balance with the effect that is achieved. [17, 18] Many healthcare decisions are still based on effect outcomes like recurrence rates alone. If effects are not related to costs, this may lead to inefficient use of resources. [19] Economic evaluations such as Cost-Effectiveness Analyses (CEA), Cost Benefit Analyses (CBA), and Cost-Utility Analyses (CUA) are helpful to determine which treatment options are cost-effective. [19]

In Chapter 3 we describe a systematic review of the available economic evaluations on interventions for sBCC. The aim of the review was to give an update of the currently available evidence, to discuss whether the different treatments provide value for money, and to address potential gaps in current cost-effectiveness research for sBCC.

A search through four large databases resulted in 710 articles. Original articles were included when they reported both costs and effects (treatment success) of either surgical excision, 5FU, imiquimod, PDT, cryotherapy, or C&E for the treatment of sBCC. Four articles were identified that met the inclusion criteria. [20-23] Two articles described a trial based economic evaluation [20, 21], two studies developed a decision analytic model. [22, 23] Different interventions were compared. Imiquimod and 5FU were compared to MAL-PDT in one study [20], two studies compared imiquimod to surgery [21, 23], and one study compared MAL-PDT to surgery. [22] The studies were evaluated for possible bias using the extended version of the Consensus on Health Economic Criteria. [24, 25] Due to heterogeneity between the studies, the results could not be pooled. The conclusion of the methodological quality assessment was that the quality of the studies was moderate.
Summary and general discussion

One of the issues was that uncertainty around the input of data and the Incremental Costs and Effects Ratios through bootstrap analyses and sensitivity analyses was not or insufficiently addressed. The conclusions of the authors could not be corroborated in all cases. Treatment of sBCC with imiquimod as well as surgery seemed to provide value for money. Superficial BCCs have little impact on quality of life and mortality, the use of a QALY as an outcome measure for the economic evaluation seems less relevant. However, in that case, it is important to use clearly defined clinical outcomes for the cost-effectiveness ratio.

Photodynamic therapy for superficial basal cell carcinoma: MAL versus fractionated 5-ALA

Between 2008 and 2010, a large RCT was performed by our research group comparing imiquimod, 5FU, and PDT for patients with sBCC. The conclusion of this trial was that imiquimod was the preferred and cost-effective treatment. [26, 27] After 5 years of follow-up, MAL-PDT was effective in only 62.7% of the cases versus 80.5% of the patients treated with imiquimod. [27] Even though MAL-PDT was not as effective as imiquimod and 5FU, there are several reasons for patients to still prefer PDT despite its lower effectiveness. First of all, it is a good alternative for patients that prefer non-surgical treatment but do not want to or are not able to apply cream, for instance due to the location of the sBCC. Secondly, PDT has an excellent cosmetic result. [28] Optimization of PDT was therefore needed in order to maintain PDT as an option for a certain group of patients.

Several animal and clinical studies showed that fractionated PDT with 5-aminolevulinic acid (5-ALA) as photosensitizer increased the effectiveness of PDT substantially. [29, 30] Therefore, a multicentre RCT was conducted comparing the 1-year risk of treatment failure after MAL-PDT versus fractionated ALA-PDT for patients with sBCC in 2013. [31] In Chapter 4 effectiveness and cosmetic outcomes after 5 years of follow-up were compared. All patients who were included in the initial trial were invited for a visit 5 years post-treatment. The 5-year tumour-free survival rate was 70.7% for ALA-PDT and 76.5% for MAL-PDT. At 5-year follow-up, 20 treatment failures had occurred after treatment with ALA-PDT of which 14 were diagnosed after the first year of follow-up. Following MAL-PDT, the total number of treatment failures was 16 of which 5 were diagnosed after the first year of follow-up. The survival curves intersected at around 3 years post-treatment, and the proportional hazard assumption did not hold (p = 0.006). Therefore, period-specific hazard ratios (HR) for treatment failure with p-values were calculated for the first 3 years and last 2 years of follow-
up. Within the first period, the HR (for MAL-PDT vs. ALA-PDT) was 1.53 (95% CI: 0.70–3.33, p = 0.283). Within the second period, the HR was 0.125 (95% CI: 0.016–0.987, p=0.049), indicating a significantly lower risk of treatment failure in the MAL-PDT group later during follow-up. There was no difference in cosmetic result between the two treatments as judged by either patients or physicians. The aim of this study was to optimize treatment with PDT, which was not achieved, for fractionated ALA-PDT did not lead to an improved effectiveness in the long run. We did not find any explanation in literature why the majority of recurrences occurred later during follow-up after ALA-PDT. There is a discrepancy in the 5-year probability of remaining free from treatment failure after MAL-PDT between this study and the trial comparing MAL-PDT with imiquimod and 5FU (76.5% versus 62.7%). [27] This difference may be explained because BCCs in the first trial were more frequently located in the head and neck area. Former research showed that BCCs in the head and neck area are more often of a mixed subtype. Mixed subtype BCCs are more prone to sampling error of the diagnostic punch biopsy. If a mixed BCC is underdiagnosed as a sBCC and treated non-invasively, this treatment might be less effective. Thus, sampling error of mixed BCCs might lead to more recurrences following non-invasive treatment in the head and neck area.

Optimization of diagnosing and subtyping superficial basal cell carcinoma

The current guidelines advise to reserve non-invasive treatments for low-risk superficial, and sometimes nodular, BCCs. [1, 2] The gold standard for the histological subtyping of BCCs is the punch biopsy, which is a 3 mm sample of the lesion. The correct subtyping of a sBCC is a prerequisite for prescribing non-invasive therapies, but due to sampling error there is a risk of missing non-superficial components in mixed BCC subtypes. An alternative hypothesis that has been put forward is that non-invasive treatment can result in transformation of sBCCs into non-superficial subtypes. [32-34] Chapter 5.1 describes an observational study with the aim to examine the hypothesis that misclassification rather than transformation is the most plausible explanation for non-superficial recurrences following non-invasive therapy of a primary sBCC. The required data was derived from the multicentre RCT comparing imiquimod, 5FU, and PDT for patients with sBCC. [27] In this trial, a histologically confirmed treatment failure occurred in 166 out of 601 randomized patients. A non-superficial subtype was diagnosed in 64 of these 166 (38.6%) treatment failures, which is 10.6% (64/601) of the initially treated tumours. The proportion of recurrences with a non-superficial
subtype was 51.3% (38/74) for treatment failures that occurred within the first 3 months post-treatment and 28.3% (26/92) for later treatment failures (p=0.003). Furthermore, these proportions were also higher in the head and neck area compared to the extremities and trunk: (100% versus 41.9% in early treatment failures, p=<0.01) and 60% versus 22.1% in later treatment failures, p=0.006). These findings support the hypothesis that underdiagnosis of a more aggressive component in the primary BCC rather than transformation results in treatment failures with non-superficial subtypes after non-invasive treatment of patients with sBCC. Thus, in approximately 10% of the cases, the starting position for initiating non-invasive therapy were not optimal. After consulting several pathologists, it seemed that the number of levels of a punch biopsy evaluated by pathologists to determine the diagnosis and subtype of a BCC varied between labs. In Chapter 5.2 we evaluated whether the risk of misclassification of more aggressive subtypes as sBCC could be reduced by evaluating four levels of a punch biopsy instead of one or two levels. In a retrospective study we evaluated punch biopsies of histologically confirmed BCCs. The primary outcome was the proportion of ‘more aggressive’ BCCs (non-superficial versus superficial, infiltrative versus nodular subtype) which were missed by evaluation on one or two levels, using four level diagnosis as reference standard. Eighty-five BCCs were evaluated on all separate levels with a maximum of 4 levels per biopsy and compared to the initial evaluation of the pathologist. Histological subtyping based on one level only, resulted in discrepancies with four level diagnosis in 14 (16.5%) cases. Underdiagnosis occurred in 14 of 58 non-superficial BCCs (24.1%, 95%CI: 13.9-37.2). Seven of 38 nodular BCCs were under diagnosed as superficial and 7 of 20 infiltrative BCCs were diagnosed as superficial (N=2) or nodular (N=5). Thus, evaluation of two or more levels led to improved identification of non-superficial components compared to evaluation of one level. Underdiagnosis may lead to non-invasive treatment of supposed sBCCs that are actually of a non-superficial subtype, which consequently leads to more recurrences with additional treatment cost and inconvenience for patients. Thus, it is prudent to evaluate at least two and preferably more levels of a punch biopsy to determine the subtype of a BCC correctly and prevent underdiagnosis and subsequent undertreatment.

**GENERAL DISCUSSION**

This thesis focused on optimizing the conditions for care of patients with sBCC by addressing current gaps in the evidence. The previous chapters provided answers to the general questions that were posed