Surgical excision and Mohs Micrographic Surgery for basal cell carcinoma : an evaluation from different perspectives

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An evaluation from different perspectives

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Surgical Excision and Mohs Micrographic Surgery for Basal Cell Carcinoma

An evaluation from different perspectives

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Life changes fast.
Life changes in the instant.
You sit down to dinner and life as you know it ends.
(Joan Didion: *The year of magical thinking*)

Ter nagedachtenis aan mijn zus

Contents

chapter 1

Introduction

Basal Cell Carcinom

Basal cell carcinoma (BCC) is the most common type of non-melanoma skin cancer worldwide.[1-2] The incidence of BCC is difficult to determine due to the fact that this type of skin cancer usually is excluded from national cancer-registries. In the Netherlands, estimates vary from approximately 26.000 to 30.000 new cases each year.[3-4]

Treatment modalities for BCC

A major risk factor for developing BCC is a patient's cumulative exposure to ultraviolet light.[5] Other risk factors include physical characteristics like a fair complexion, red or blond hair, light eye colour but also gender and genetic predisposition.[6] Although BCC is not a life-threatening disease and rarely metastasizes, it may grow aggressively and result in extensive tissue destruction. Since eighty percent of all BCCs are localized within the head and neck area[7], the disease and also its treatment can be associated with functional and cosmetic adverse effects. Therefore, the aim of a treatment when removing this type of skin cancer is not only to eradicate a tumour and to prevent a recurrence but also to achieve a good aesthetic outcome.

Treatment of BCC can be surgical or non-surgical.[2] The surgical approaches include curettage and electrodesiccation, cryosurgery, surgical excision (SE) and Mohs Micrographic Surgery (MMS).[2] Both SE and MMS have the advantage of histopathologic margin control.

Non–surgical treatments include radiotherapy, topical and injectable therapy, and photodynamic therapy.[2] The choice for a particular treatment depends on several factors like the size, the location of the tumour, histopathologic tumour subtype, age and health status of the patient, co-morbidity, the availability of therapies and the experience/preference of the dermatologist.[6]

Overall, the surgical procedures SE and MMS are the most frequently used. MMS is a specialised technique in which the tumour is removed layer by layer in successive stages. During the first stage, a bowl-shaped specimen is obtained and processed into horizontal frozen sections. These sections are histo-pathologically examined and if tumour cells are found, a second stage takes place. This procedure will be repeated until the complete area is tumour free. SE is a technique by which the obtained specimen is histopathologically examined by the bread-loafing (vertical sections) techniques or

the quadrant method afterwards. If the histopathological examination shows positive margins, a re-excision will be performed.
Since BCC has a very low potential to metastasize, the focus of therapy is local. The effectiveness of a treatment is usually expressed by recurrence of the tumour as primary clinical outcome measure.[8] Nevertheless, comparing studies reporting on the recurrence rates after different therapies for BCC is difficult due to a lack of uniformity in method of reporting and good quality research.[8-9] Results of a systematic review indicated that tumours treated with MMS appeared to have the lowest recurrence rate, followed by SE.[8] Still, MMS is also a more labour-intensive and thus a very costly procedure.

To examine whether the value or the benefit of MMS justifies the monetary investment, an economic evaluation in which costs and the effectiveness are compared is the appropriate method to perform.

Economic evaluation in health care

In general, economic evaluation involves the comparative analysis of alternative treatments in terms of both their costs and consequences. There are four basic types of evaluation:1) cost-minimization analysis, 2) cost-effectiveness analysis, 3) cost-utility and 4) cost-benefit analysis.[10]
Cost-minimization analysis involves a comparison of two treatments which differ in costs but are considered to be equally effective in their consequences. In cost-effectiveness analysis (CEA), both the effectiveness and costs of two alternative treatments are evaluated, resulting in a cost-effectiveness ratio which is essentially the incremental cost of obtaining one additional unit of health outcome.[11] The effectiveness measures used within CEA can range from intermediate outcomes such as blood-pressure reduction or recurrences avoided to years of lives saved. A cost-utility analysis can also be seen as a form of cost-effectiveness analysis, although the health outcomes of a treatment are measured and valued in Quality Adjusted Life Years (QALY's). The advantage of using a QALY is that it incorporates both duration of life and gains from reduced morbidity.[10] However, the method is less appropriate for measurement of outcomes related to treatment of BCC since both the disease and its treatment have neither effect on life expectancy nor on generic health related quality of life.
The cost-benefit approach expresses both the costs and the benefit of therapies in monetary units, making it possible to calculate the net benefit of

an intervention. A positive net benefit indicates that a health care intervention or a programme is worthwhile. From a theoretical perspective, cost-benefit analysis is preferred since it not only enables the comparison of programmes within health care but also can be used to inform resource allocation decisions both within and between sectors of economy.[12]
An important aspect to consider when conducting an economic evaluation is the perspective of the study. Analyses can be performed from the perspective of the patient, the health care provider, the insurance company or society. Generally, it is recommended to use the societal perspective since it includes all costs and health outcomes resulting from the intervention, regardless of who pays the costs or who benefits. However, a CEA can be done from a different perspective if certain outcomes or costs between treatments are not expected to differ.
In the past, there have been several studies that compared the costs of MMS and SE for various types of non melanoma skin cancer.[13-14] However, none of these studies related the effectiveness of both treatments to their costs, and as such described a cost-comparison analysis. Another study reported total costs of non melanoma skin cancer in a cost of illness study but did not calculate costs of separate treatment modalities.[15]
Therefore, a cost-effectiveness study in which costs are related to effectiveness, i.e. the recurrence rate, is essential in order to determine the cost-effectiveness of MMS versus SE for both primary and recurrent BCC.

Quality of life for patients with BCC

BCC is predominantly located in the head and neck, an area of the body which is visually conspicuous to the patient and to others. Disease progression and treatment may lead to functional and aesthetic problems.[16]
Research related to the impact of BCC on patients' lives has focused on the assessment of health related quality of life by using generic and dermatology specific questionnaires. Results of a study by Blackford et al. showed that patients seemed to experience little handicap from BCC.[17] Other studies showed similar results which indicated that this type of skin cancer had minimal impact on the health related quality of life of patients.[16,18-19] The measures used in those studies were the UK Sickness Impact Profile (UK-SIP), the Dermatology Life Quality Index (DLQI), the Skindex and the Short Form 36 item Health Survey (SF-36). Both the UKSIP and the SF-36 are questionnaires intended to measure general health related quality of life.

The Skindex and the DLQI are two dermatology specific instruments used to measure the effect of skin diseases on patient's health related quality of life. The DLQI contains 10 items that are strongly related to impaired functioning and physical disability while the Skindex includes 29 items to address dimensions like emotions, symptoms and functioning. However, both questionnaires seem more appropriate for patients suffering from a wide range of chronic skin diseases like psoriasis or eczema. Since the majority of the BCC is localized within the cervicofacial area, it can be assumed that problems specifically related to facial health and facial aesthetics are the most important issues for a patient. Therefore, developing a disease-specific questionnaire related to these issues is the first step in gaining insight in the impact of this type of skin cancer on patients.

Patient perceptions with facial health and aesthetics after surgery for BCC

Although BCC is not life threatening, it still is cancer. Moreover, the risk of subsequent skin cancer is close to 50% which almost makes it a chronic disease.[20] This can result in worrying about facial health or the severity of the condition. Patients may also think about their personal susceptibility for this type of skin cancer and be preoccupied with the impact of the disease and its treatment on their facial aesthetics. In addition, patients might have certain expectations regarding the results of their treatment. Some of these perceptions like susceptibility and severity are originally defined within the Health Belief Model (HBM).[21] This is basically a value-expectancy model originally developed to predict and explain health preventive behaviour. According to the HBM, an individual's state of readiness to take action for a health condition is not only determined by its "value" in terms of perceived susceptibility to a condition and the perceived severity of the condition but also by the "expectancy" based on an evaluation of the possible benefits and disadvantages of health behaviour to reduce susceptibility and/or severity.[21] Certain concepts of the HBM like the perception of susceptibility and severity can be seen as determinants for satisfaction of patients with their facial health and their facial aesthetics and thus are suitable to be included in a disease-specific questionnaire.

Preferences for surgical treatment

Cost-benefit analysis (CBA), as one of the methods of economic evaluation, expresses both the costs and the benefit of therapies in monetary units, making it possible to calculate the net benefit of an intervention. Within CBA, monetary values can be assigned to both health and non-health outcomes, making it possible to examine whether individuals derive benefit from other factors beyond the traditional health outcomes. One of the methods that is increasingly used within health care to identify the relative importance of attributes of a treatment and to determine the overall utility for a particular treatment or clinical service is the discrete choice experiment (DCE). The method is characterized by the presentation of hypothetical scenarios, each containing two or more options which describe different levels of various attributes. Individuals are presented with these scenarios and are asked which option they prefer. As such, DCE is firmly based in random utility theory (RUT), which assumes that an individual acts rationally and chooses the alternative with gives the highest utility. Moreover, a DCE closely resembles the actual choices that individuals have to make in every day life. A major advantage of the DCE is that the technique enables to combine outcome and process related attributes. As such, the method can be useful to examine which attributes of a surgical treatment for BCC are valued as important. If a cost variable is included, the possibilities of a DCE are enhanced since indirectly measures of welfare gain can be estimated like for instance the willingness to pay for MMS or SE and marginal willingness to pay for levels of different attributes of a surgical treatment. Consequently, results can be placed within the framework of a cost-benefit-analysis.

Still, the inclusion of a cost-attribute, particularly within collectively funded health care systems, can be problematic due to the fact that respondents are not used to pay for a service or a good at the point of consumption. Nevertheless, an increasing number of discrete choice experiments incorporate cost as an attribute.[22-25] So far, only one study by Brian et al. has examined the impact of a cost variable on individuals' preferences by comparing two DCEs, one including and one excluding the cost-attribute.[26] Since differences in results between a DCE with and without a cost attribute can alter policy recommendations and decisions, more research into the impact of a cost attribute on preferences is warranted. Therefore, a study was conducted in which the impact of a cost attribute on preferences for a surgical treatment to remove Basal Cell Carcinoma was investigated by

comparing the outcomes of two DCEs, one excluding and one including a cost-attribute.

Objective and outline of the thesis

The main objective of this thesis is to evaluate two surgical procedures, SE and MMS, for Basal Cell Carcinoma. To address this general objective, four studies from different perspectives have been performed:
The first study concerned an economic evaluation which was carried out alongside a prospective randomised clinical trial in which MMS was compared to SE. The objective of this study was to assess from a hospital perspective, the cost-effectiveness of MMS versus SE for both primary and recurrent BCC. Chapter 2 describes the results of this cost-effectiveness analysis. The second study was a prospective survey in which a newly developed disease-specific questionnaire was used. The objective was to examine determinants of satisfaction with facial health and aesthetics by using patient perceptions and expectations related to BCC and its treatment. The focus of this study was therefore the patient perspective. In order to examine the determinants of satisfaction with the facial health after surgery for BCC, two specific research questions were addressed:

1. Can pre-operative beliefs be used to predict patient satisfaction with the health state of the facial skin at six months after surgery.
2. Which pre- and/or postoperative beliefs do eventually explain satisfaction with the health state of the facial skin at six months after surgery.

For the analysis of perceptions on facial aesthetics after surgery for BCC, four research questions were formulated:

1. Is there a statistically significant improvement over time with regard to the perceptions of facial aesthetics in surgical patients.
2. Is there a statistically significant difference in perceptions of facial aesthetics between patients with primary and recurrent BCC.
3. Is there a statistically significant difference in perceptions of facial aesthetics between patients who had MMS or SE?
4. Which pre-operative perceptions and/or clinical parameters may predict the evaluation of facial aesthetics at six months after surgery.

Results regarding all research questions are described in chapter 3 and 4.
The third study included two discrete-choice experiments carried out among members of the general public and hence was performed from a societal perspective. The first objective of this study was to examine which attributes

of a surgical treatment for BCC are considered as important and to determine the incremental willingness to pay for MMS compared to SE (chapter 5.) The second objective was to examine if the inclusion of a cost attribute would change the rank order of preferences for a surgical treatment to remove BCC. For that purpose, the outcomes of two DCEs, one without and one with a cost attribute, were compared in terms of theoretical validity, relative importance of the attributes and the rank order of preferences. These findings are described in chapter 6.
The fourth study was a survey conducted among dermatologists in the Netherlands. The objective was to gain insight in the current state of affairs with respect to the incidence of primary and recurrent BCC, preferences for treatment modalities and specifically the use of MMS. The survey incorporated the perspective of the professional. Results are presented in chapter 7.
Finally, in chapter 8, the main findings of this thesis are summarized and discussed. In addition, some methodological and practical considerations are highlighted and recommendations for future research are presented.

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chapter 2

Cost-effectiveness of Mohs Micrographic Surgery versus Surgical Excision for Basal Cell Carcinoma of the face

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Abstract

Objectives. To assess the cost-effectiveness of Mohs Micrographic Surgery (MMS) compared with Surgical Excision (SE) for both primary and recurrent BCC.

Design. A cost-effectiveness study performed alongside a prospective randomised clinical trial in which MMS was compared with SE.

Setting. The study was carried out from 1999 till 2002 at the dermatology outpatient clinic of the University Hospital Maastricht, the Netherlands.

Participants. A total of 408 primary (374 patients) and 204 recurrent facial BCC (191 patients) were included.

Main Outcome Measure. The mean total treatment costs of MMS and SE for both primary and recurrent BCC; the incremental cost-effectiveness ratio, calculated as the difference in costs between MMS and SE divided by their difference in effectiveness. The resulting ratio is defined as the incremental costs of MMS compared with SE to prevent one additional recurrence.

Results. Compared with SE, the total treatment costs of MMS are significantly higher (primary: cost- difference €254, 95%CI €181 to €324; recurrent: cost-difference €249, 95%CI €175 to €323).
For primary BCC, the incremental cost-effectiveness ratio was €29,231.- while the ratio for the recurrent BCC amounted to €8,094. The acceptability curves showed that for these ratio's, the probability of MMS being more cost-effective than SE never reached 50%.

Conclusion. At this time, it does not seem cost-effective to introduce MMS on a large scale for both primary and recurrent BCC. However, since normally a five-year period is required to determine definite recurrence rates, it is possible that MMS may become a cost-effective treatment for recurrent BCC.

Introduction

Basal cell carcinoma (BCC) is the most common form of non-melanoma skin cancer worldwide. In the Netherlands, an estimated 30,000 new cases of BCC a year are diagnosed.[1] Although it is not a life-threatening disease, recurrence of this predominantly facial tumour may cause considerable morbidity related to functional and aesthetic problems. Prevention of a recurrence, particularly within the facial area, is therefore an important goal in the treatment of BCC. The main conclusion of a systematic review on recurrence rates after treatment for primary BCC was that recurrence rates for different therapies could not be compared because of a lack of uniformity in the method of reporting.[2] However, Mohs Micrographic Surgery (MMS) appeared to have the lowest recurrence rate, followed by Surgical Excision (SE). Still, MMS is also a more labour-intensive and thus a more costly procedure. To assess whether MMS is a cost-effective treatment for BCC, it is necessary to relate costs to effectiveness. Results of a cost-effectiveness study, performed alongside the first prospective randomised clinical trial in which MMS was compared with SE for both primary and recurrent BCC, are reported here.

Methods

Trial design

The following inclusion criteria for patients with a primary facial BCC were chosen: a histologically proven tumor of at least 1 cm in diameter, or with a histopathological aggressive subtype, located in the H-zone of the face. For patients with a facial recurrent BCC, first and second time recurred BCC were included. The exclusion criterion was a life-expectancy shorter than 3 years, based on expert opinion of the dermatologist. After patients signed the informed consent, separate randomisation procedures for both primary and recurrent BCC were performed. Since inclusion and randomisation were performed per BCC, patients with more than one BCC could be included multiple times. The clinical trial was designed to have a 90% power to detect a 6.5% difference in recurrence rate between MMS and SE for the primary BCC and a 13.5% difference for the recurrent BCC at the 5% level. Full details and results of the clinical trial are described elsewhere.[3]

Surgical procedures

All surgical procedures were performed under local anaesthesia at the outpatient clinic.

MMS is a specialised technique by which the tumour is removed layer by layer. During the first Mohs stage, a bowl-shaped specimen is obtained and processed into horizontal frozen sections. These sections are histopathologically examined and if tumour cells are found, a second Mohs stage takes place. The procedure will be repeated until the complete area is tumour free. The surgical excision is a technique by which the obtained specimen is histopathologically examined by the bread-loafing (vertical sections) techniques or the quadrant method. In case of positive margins, a re-excision will be performed. [3]

Clinical outcome and quality of life

The primary clinical outcome of both studies was recurrence of a BCC. Secondary outcomes were quality of life, anxiety and cost-effectiveness. Quality of life and anxiety were assessed at baseline and six months postoperatively by means of a generic instrument, the Dutch version of the Nottingham Health Profile (NHP) and a domain-specific questionnaire, the Dutch version of the State-Trait Anxiety Inventory (STAI).[4-5] The NHP is a 38-item questionnaire that produces binary responses to a series of items that are related to six following dimensions: physical mobility, sleep, bodily pain, energy level, emotional reactions and social isolation. Each dimension of the NHP gives a score between 0 and 100 with 0 being the best and 100 being the worst quality of life outcome. The assumption was that primarily the emotional reactions domain would show a difference between MMS and SE.

The Spielberger STAI consists of a 20-question assessment scale that measures to what extent personality traits are susceptible to anxiety and a 20-question assessment scale to measure anxiety in a certain state. The STAI gives a score between 20 and 80 with 20 indicating no anxiety and 80 a high anxiety level. In our study, only the State assessment scale was used to determine whether patients undergoing MMS showed a significant difference in anxiety level compared with the group undergoing SE, at baseline and six months postoperatively.

Economic evaluation

The economic evaluation was performed from a hospital perspective, because no difference in out of pocket costs or use of other health care and non health care services between the two surgical treatments was expected. In addition, the mean age for patients with this type of skin cancer is approximately between 60-65 years, as a result of which productivity losses were expected to be minimal. The costs and effects for primary BCC were collected during a time period of 30 months while the follow-up period for the recurrent BCC lasted 18 months. For both primary and recurrent BCC, costs and effects of MMS were compared to the costs and effects of SE. Given the time horizon of both studies, costs and effects occurring after 1 year were discounted at 4%.[6] The Incremental Cost-Effectiveness Ratio (ICER) was calculated as the difference in costs divided by the difference in effectiveness between MMS and SE. The result of this calculation was defined as the incremental costs of MMS to prevent an additional recurrence. For the cost-analysis, real resource consumption was measured and related to their costs, as recommended by the U.S panel on cost-effectiveness in health and medicine.[7] This approach is also known as 'micro-costing' which is a detailed inventory and measurement of resources consumed. A major advantage of micro-costing is that it allows others to see how well the analysis matches their own situation where patterns of care may differ.[7]

All volumes of use were based on the hospital information system and empirical time registrations. Unit costs were derived from the hospital financial department. Costs were calculated by multiplying volumes of use with the costs per unit. Direct costs of both treatments contained the personnel and material costs of all diagnostic procedures, surgery and all outpatient visits. Indirect costs included the general hospital overhead, which was allocated to the direct costs as an overall percentage of 35%, according to the Dutch guidelines for cost calculation.[6] All costs are presented in 2001 euros (1 euro=$0.89=£0.69). Table 1 provides an overview of the costs per unit.

The pre-operative costs consisted of a diagnostic procedure and a pre-operative outpatient visit. The personnel costs for surgery were determined by using empirical time registrations, whereby for every procedure (MMS or SE) the dermatologist who performed the surgery registered the exact starting and ending time. This allowed us to calculate the mean personnel costs based on a substantial number of procedures. Total operative costs included not only the costs of the surgical procedure but also the costs of a

possible re-excision as well as processing and examination of the histopathological slides. Based on expert opinion, it was assumed that complications would lengthen the usual duration of a control visit with fifty percent, as a result of which the costs of complications were calculated as half the costs of a post-operative control visit. The costs of any additional cosmetic treatments were already included in the personnel and material theatre costs if they were performed during the surgical procedure. However, if a cosmetic treatment like, for instance, laser therapy was performed after surgery, those costs were calculated separately based on cost information as provided by the hospital financial department. The costs of post-operative control visits consisted of five regular outpatient visits and any additional control visits.

Table 1 Unit costs used to value resource use within the clinical trial

	Unit	**Cost per unit in euros €**	**Source**
Direct healthcare costs:			
- pathology research-diagnostics	Test	61.45	University Hospital Maastricht*
- biopsy	Test	17.11	University Hospital Maastricht
Theatre:			
- team SE	Minute	1.53	Empirical time registration
- team MMS	Minute	1.59	Empirical time registration
- pathology research frozen sections	Four frozen sections	72.86	University Hospital Maastricht
- material SE	Procedure	17.49	University Hospital Maastricht
- material MMS	Procedure	20.55	University Hospital Maastricht
Outpatient visit:			
- pre-operative outpatient visit	Visit	68.57	Dutch Guidelines (Oostenbrink)[6]
- control outpatient visit	Visit	34.29	Dutch Guidelines (Oostenbrink)

*Abbreviations: MMS, Mohs Micrographic Surgery; SE, Surgical Excision * Maastricht, the Netherlands*

Sensitivity analysis

Univariate sensitivity-analyses were undertaken by varying a cost or an effectiveness parameter one at a time in order to investigate the impact on the incremental cost-effectiveness ratio. First, the personnel costs were varied by taking the upper and lower bound of the 95% CI of the procedure time. Second, the effect difference between MMS and SE as calculated for the power analysis at the start of the study, was used. Third, the actual recurrence rates after a follow up of 1,5 and 2,5 years for respectively recurrent and primary BCC were extrapolated to a 5-year period, to estimate the effect difference between the two treatments and subsequently, the 5-years incremental cost-effectiveness ratios. The assumption was that, within the observed follow up period, 70% of the recurrences for the primary and 50% of the recurrences of the recurrent carcinomas had occurred.[8-9]

Analysis

SPSS-PC for Windows, version 11.0 was used for statistical analysis. A p-value below 0.05 was considered to indicate statistical significance. Data of the cost-analysis were analysed by the intention to treat principle in which mean substitution for the missing cases was used. Data that combined both costs and effectiveness were, similar to the clinical results, analysed by modified intention to treat in which the missing cases were excluded.[3] The chi-square test was used to calculate log-likelihood. Regression analysis was used to investigate the effect of location and histopathologic subtype on the cost-difference between MMS and SE. If non-normal distributions were present, log-transformation of the costs was applied, after which a Kolmogorov-Smirnov test was used to test for normality. Confidence intervals for the mean differential costs were obtained by the bootstrap method. This method estimates the sampling distribution of a statistic through a large number of simulations, based on sampling with replacement from original data.[10] To account for the uncertainty surrounding the cost-effectiveness ratio's, bootstrapping was also used (1000 replications).[11] Results of the bootstrap analysis for the ICER's were presented in cost-effectiveness planes. A cost-effectiveness plane is a graphical presentation of four situations or quadrants in which additional costs and additional health outcome effects of a new therapy are compared to the standard therapy. Further-

more, acceptability curves were calculated which show the probability of a new therapy being more cost-effective than the usual treatment for various threshold value's, in this case being the maximum amount a hospital would be willing to pay extra for MMS in order to prevent one additional recurrence.
Quality of life scores were tested for normality by the Kolmogorov-Smirnov test. Differences in time of quality of life scores between MMS and SE were analysed by either a Mann-Whitney test or the independent group Student T-test.

Results

Clinical outcomes

Patient characteristics
In total 374 patients had 408 primary BCC. The mean age of the patients was 67,7 years (sd 12.65) and 60 % was male. There were 190 patients with 204 recurrent BCC. The mean age of this group was 67.9 years (sd 11.7). Fifty-eight percent was male.

Recurrence rates
408 primary BCC were included of which 204 were randomised to SE and 204 to MMS. For the 204 recurrent BCC, 102 were randomised to SE and 102 to MMS. Within the primary BCC group, five recurrences were found after SE and three after MMS at 30 months follow-up. Thirty-three (16%) patients of the SE-group and 44 (22%) patients in the MMS-group were lost-to follow-up.
For the recurrent BCC group, no recurrences were found after MMS while 3 recurrences after SE at 18 months follow-up. Nine patients of the SE-group (9%) and 7 patients (7%) of the MMS-group were lost to follow up.

Complications

No difference in postoperative complications between SE and MMS was seen in primary carcinomas (28[14%] versus 24 [12%]) while more complications occurred after SE than after MMS in recurrent carcinomas (19[19%] versus 8[8%], p-value=0.021)

Quality of life and anxiety

As given in Table 2, the number of patients included in the quality of life study is based on a subset of the total patient population due to a number of reasons. First, since inclusion was done per BCC, a patient with multiple BCC could be randomised to both SE and MMS. However, to determine whether there was a difference in quality of life between patients undergoing MMS or SE, only patients with a single BCC were interviewed. Second, a number of patients were lost due to administrative restrictions. Given that only one researcher was available to administer the questionnaires after the visit to the dermatologist, patients often had to wait in turn before they could be interviewed. A number of patients refused to do so, either because they had commitments elsewhere or they were not willing to wait.

The mean (sd) scores pre-and postoperatively for the NHP and STAI (Table 2) show that patients reported a good health related quality of life and a minimum level of anxiety. There was no statistically significant difference in NHP scores at six months after surgery compared with baseline between MMS and SE for both the group of primary and recurrent BCC. In addition, there was no statistically significant difference in anxiety level at six months compared with baseline between the two treatments.

Table 2 NHP and STAI Scores before and six months after surgery for primary and recurrent BCC

	Baseline		Six months		Difference in change MMS-SE	p-value
	MMS (n=45)	SE (n=65)	MMS (n=45)	SE (n=65)		
Primary BCC (n=110)						
NHP*						
emotional reactions	8.88 (13.93)	8.54 (14.13)	8.88 (15.81)	9.74 (16.37)	1.19	.677
energy	11.85 (25.78)	15.38 (28.31)	9.6 (22.04)	21.02 (33.62)	7.86	.214
pain	11.94 (22.91)	12.30 (22.91)	11.38 (21.29)	13.84 (22.65)	2.09	.445
sleep	11.55 (24.30)	17.84 (27.18)	14.66 (29.96)	13.23 (23.52)	-7.72	.091
social isolation	4.88 (10.57)	2.76 (6.96)	3.11 (8.48)	2.76 (7.80)	1.77	.316
physical mobility	9.44 (19.61)	13.46 (23.52)	10.83 (18.76)	15.96 (25.62)	1.11	.829
STAI**	32.86 (9.99)	33.64 (9.67)	29.77 (7.60)	31.69 (7.64)	-1.13	.46
Recurrent BCC (n=76)						
	Baseline		**Six months**		**Difference in change MMS-SE**	**p-value**
	MMS (n=40)	**SE (n=36)**	**MMS (n=40)**	**SE (n=36)**		
NHP						
emotional reactions	4.44 (11.19)	4.32 (8.51)	6.94 (13.93)	4.93 (9.73)	1.88	.37
energy	10.83 (26.56)	6.48 (17.49)	18.33 (30.15)	12.95 (24.26)	1.02	.40
pain	15.31 (25.23)	9.02 (19.73)	18.75 (29.95)	15.27 (24.66)	-2.81	.51
sleep	12.00 (21.62)	15.55 (23.95)	16.00 (28.71)	23.88 (34.08)	-4.33	.11
social isolation	.50 (3.16)	2.22 (6.37)	2.50 (8.06)	1.66 (5.60)	2.55	.07
physical mobility	15.31 (19.71)	9.02 (15.98)	16.87 (23.26)	12.50 (22.36)	1.86	.68
STAI	33.80 (11.23)	31.80 (7.99)	31.02 (8.46)	30.02 (7.52)	-.99	.61

** Best possible HRQOL is given by a score of 0, worst possible HRQOL by a score of 100*
***No anxiety is given by a score of 20 while a score of 80 indicates a high anxiety level*

Economic evaluation

Cost-analysis

Table 3 and 4 describe the mean costs (standard deviation) per primary and recurrent BCC. When comparing MMS with SE, the statistically significant differences were firstly related to the personnel costs of surgery due to longer theatre time (primary BCC: mean 155 min (sd 64) versus 60 min (sd 50); recurrent BCC: 190 min (sd 85) versus 91 min(sd 89) respectively) and

secondly to pathology costs. Both cost components were significantly higher for MMS, which resulted in a mean difference in total costs of €254,- per primary BCC and €249,- for a recurrent BCC.

Table 3 The total mean costs* of MMS and SE for primary BCC

Primary BCC	**MMS (N=204) Mean (sd) €**	**SE (N=204) Mean (sd) €**	**MMS versus SE** Difference in mean total costs (95% CI)†
Pre-operative costs	147	147	n.a.
Theatre related costs:			
- personnel	254 (107)	100 (77)	154 (135 to 172)
- material	21	21	n.a.
- pathology	112(50)	74 (34)	37 (30 to 45)
- costs clinical admission‡	19	17	n.a.
Total operative costs	406 (212)	212 (240)	194 (150 to 235)
Complications	2	2	n.a.
Cosmetic treatment	5	2	n.a.
Post-operative control visits	283	287	n.a.
Costs of consultation by telephone	-	5	n.a.
Post-operative costs	290	296	-6 (-18 to 8)
Total mean costs (excl. overhead)	843 (255)	656 (254)	186 (136 to 236)
Total mean costs (incl. overhead 35%)	1137 (362)	886 (343)	254 (181 to 324)

*Abbreviations: MMS, Mohs micrographic surgery;SE, surgical excision,BCC, basal cell carcinoma;CI, confidence interval;NA, not applicable; * cost-analysis is based on intention to treat analysis with mean substitution of the missing cases; † 95% non-parametric confidence interval obtained by bootstrapping (1000 replications); ‡based on a few patients*

Table 4 The total mean costs* of MMS and SE for recurrent BCC

Recurrent BCC	**MMS N=102 Mean (sd) €**	**SE N=102 Mean (sd) €**	**MMS versus SE** **Difference in mean total costs (95% CI)†**
Pre-operative costs	147	147	
Theatre related costs:			
- personnel	305 (137)	149 (143)	155 (117 to 195)
- material	21	24	n.a.
- pathology	149 (89)	103 (76)	45 (23 to 66)
- costs clinical admission‡	22	36	n.a.
Total operative costs	496 (276)	312 (381)	176 (79 to 260)
Complications	1	3	n.a.
Cosmetic treatment	.48	.97	n.a.
Post-operative control visits	204	196	n.a.
Costs of consultation by telephone	-	4.90	n.a.

Table 4 The total mean costs* of MMS and SE for recurrent BCC (continued)

Recurrent BCC	MMS N=102 Mean (sd) €	SE N=102 Mean (sd) €	MMS versus SE Difference in mean total costs (95% CI)†
Post-operative costs	206 (48)	205 (48)	1 (-11 to 15)
Total mean costs (excl. overhead)	845 (303)	664 (389)	169 (66 to 264)
Total mean costs (incl. overhead 35%)	1146 (387)	897 (525)	249 (175 to 323)

Abbreviations: MMS, Mohs micrographic surgery;SE, surgical excision,BCC, basal cell carcinoma; CI, confidence interval; NA, not applicable
** cost-analysis is based on intention to treat analysis with mean substitution of the missing cases ;† 95% non-parametric confidence interval obtained by bootstrapping (1000 replications)*
‡based on a few patients

Subgroup cost-analysis

Additional analyses (Table 5 and Table 6) were performed to test whether the cost-difference between MMS and SE was different for specific locations or (non) aggressive histology types. Dermatologists distinguish 7 facial locations (New York University Medical Centre): 1. forehead /temporal area;2. cheek /chin;3. nose/ peri-nasal area;4. lips;5. peri-ocular area; 6. ears;7. peri-auricular area. Results for the primary BCC indicated that interactions between treatment and location (location*therapy F=.478 6 by 324 df; p-value:.82) or histology subtype (aggressive subtype*therapy F=.051 1 by 324 df; p-value:.82) or both (location*aggressive subtype*therapy F=1.072 6 by 324 df; p-value:.38) were not statistically significant. This means that the difference in costs between MMS and SE applies for all locations and persists regardless whether histology type is aggressive or not. Results for the recurrent BCC also demonstrated that none of the interactions was statistically significant (location*therapy F=.441 6 by 181 df, p-value:.85; aggressive subtype*therapy F=0.05 1 by 181 df, p-value:.82; location*aggressive subtype*therapy F=.31 3 by 181 df, p-value:.82).

Table 5 Total mean treatment costs of primary and recurrent BCC per location

	N	MMS mean (sd) €	N	SE mean (sd) €	Recurrences MMS	Recurrences SE	ICER
Primary BCC							
1. Forehead/temporal	40	1039 (170)	58	839 (196)	2	3	28168
2. Cheek/chin	15	1064 (260)	13	793 (72)	-	-	Inferior
3. Nose/ paranasal	53	1132 (186)	50	885 (161)	-	1	12350
4. Lips	11	950 (116)	5	777 (18)	1	-	Inferior
5. Peri-ocular	12	1132 (226)	12	873 (200)	-	-	Inferior
6. Ears	6	1249 (169)	14	958 (201)	-	1	4157
7. Peri-auricular	18	1035 (204)	18	783 (77)	-	-	Inferior
Total	155	1132 (352)	170	866 (240)	3	5	
Recurrent BCC							
1. Forehead/temporal	37	1106 (319)	41	800 (356)	-	1	15300
2. Cheek/chin	10	953 (159)	9	831 (321)	-	1	1109
3. Nose/ paranasal	21	1146 (256)	25	843 (253)	-	1	7575
4. Lips	5	1247 (216)	1	724 (-)	-	-	Inferior
5. Peri-ocular	5	1153 (106)	4	865 (127)	-	-	Inferior
6. Ears	7	1311 (538)	3	972 (397)	-	-	Inferior
7. Peri-auricular	7	1008 (186)	7	976 (457)	-	-	Inferior
Total	92	1117 (298)	90	837 (324)	0	3	

Table 6 Total mean treatment costs of primary and recurrent BCC per histologic subtype

Histologic subtype	N	MMS mean (sd) €	N	SE mean (sd) €	Recurrences MMS	Recurrences SE	ICER
Primary BCC							
Aggressive	77	1105 (214)	73	899 (179)	1	1	Inferior
Non-aggressive	77	1061 (180)	97	819 (159)	2	4	15817
Total	154		170		3	5	
Recurrent BCC							
Aggressive	52	1140	42	871	-	3	3843
Non-aggressive	40	1086	47	800	-	-	Inferior
Total	92		89		0	3	

Cost-effectiveness analysis

As given in table 7, the difference in recurrence rate between MMS and SE for primary BCC at 30 months is 0.0091. Dividing the mean difference in costs by this effect difference, leads to incremental costs of €29231.- per recurrence avoided. For recurrent BCC, the effect difference after 18 months follow-up is 0.032, which gives an ICER of €8094.- per recurrence avoided. To estimate the uncertainty surrounding the cost-effectiveness ratio's, cost-effectiveness planes and acceptability curves were calculated.

Table 7 Incremental cost-effectiveness ratio of primary and recurrent BCC

	Costs* €	**Effectiveness**	**ICER**
Primary BCC (30 months)			
MMS (n=160)	1132.-	0.9812	
SE (n=171)	866,-	0.9725	
Increment	266	0.0091	29231
Recurrent BCC (18 months)			
MMS (n=95)	1159	1.000	
SE (n=93)	900	0.968	
Increment	259	0.032	8094

** based on modified intention to treat (exclusion of missing cases, i.e. no information on recurrence)*

The cost-effectiveness plane for the primary BCC (figure 1) shows that 69% of all ICER's are located in the quadrant where MMS is more effective but also more costly while 31% is in the quadrant where MMS is inferior (i.e. has higher costs and lower effectiveness). For the recurrent BCC as shown in figure 2, all cost-effectiveness pairs are situated within the quadrant where MMS is more effective but also more costly.

The acceptability curve for the primary BCC (figure 3) shows that, for the calculated ICER of €29231.-,the probability of MMS being cost-effective is 40%. For the group of recurrent BCC the acceptability curve demonstrates that based on the ICER of €8094.-, the probability that MMS is cost-effective amounts to 30%.

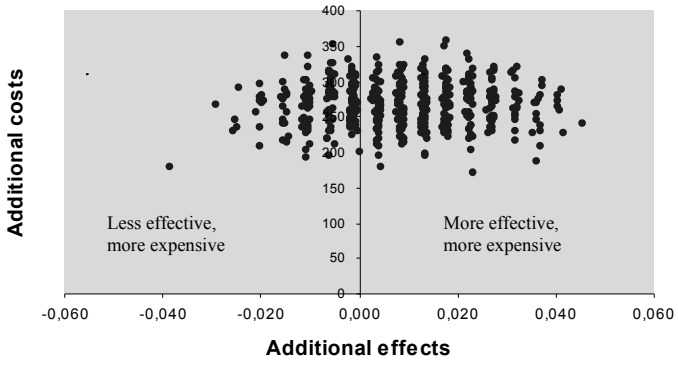

Figure 1 Cost-effectiveness plane MMS versus SE for primary BCC

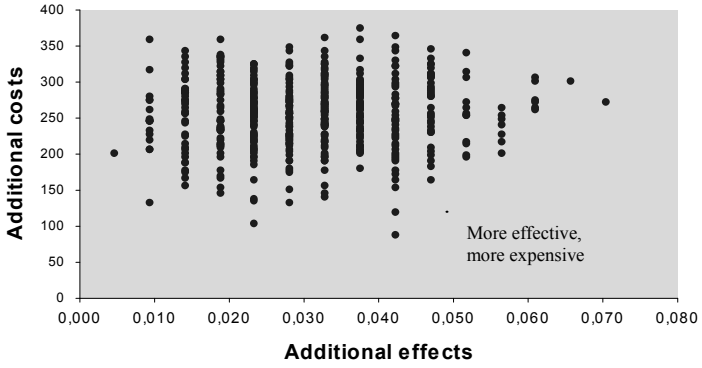

Figure 2 Cost-effectiveness plane MMS versus SE for recurrent BCC

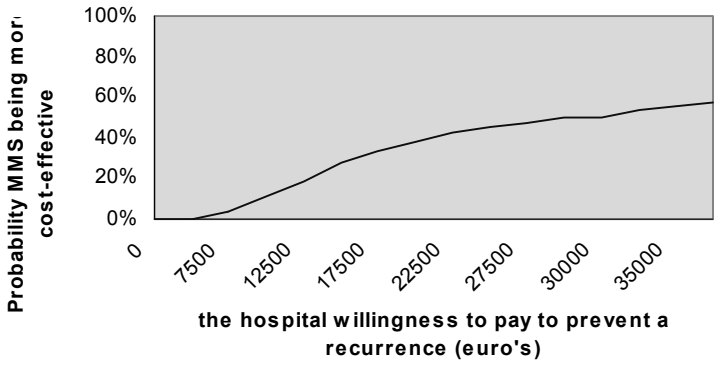

Figure 3 Acceptability curve of MMS versus SE for primary BCC

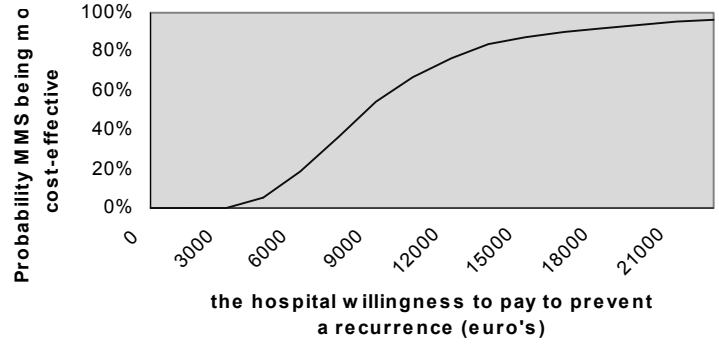

Figure 4 Acceptability curve of MMS versus SE for recurrent BCC

Sensitivity analysis

Results of the sensitivity analysis as presented in Table 8 demonstrate that taking the upper or lower bound of the 95% CI of the surgical procedure time has a minor effect on the incremental costs for both primary and recurrent BCC. The difference in effectiveness between both treatments has a significant impact on the cost-effectiveness ratio's. Based on the effect difference as calculated for the power analysis of the study, the cost-effectiveness ratio for primary BCC decreases to €3877.- per recurrence

avoided while the ratio for the recurrent BCC falls to €1844.-. Extrapolating the data of the observed effect-difference to a five year follow-up period shows that in particular the ratio for the recurrent carcinomas is reduced substantially, to € 4047.-

Table 8 Univariate sensitivity analysis incremental cost-effectiveness ratio primary and recurrent BCC

	MMS		**SE**		
	Costs €	**Effectiveness**	**Costs €**	**Effectiveness**	**ICER**
Variable					
Base case primary BCC	1132	0.9812	866	0.9725	29231
1. Duration					
- lower bound 95% CI MMS	1107	0.9812	866	0.9725	26483
- upper bound 95%CI MMS	1149	0.9812	866	0.9725	31098
- lower bound 95% CI SE	1132	0.9812	860	0.9725	29890
- upper bound 95% CI SE	1132	0.9812	871	0.9725	28681
2. Effectiveness					
- effect-difference of 6.5% (calculated for the power analysis of the clinical study)	1132	0.9812	866	0.9162	4092
- effect-difference of five-year follow-up period *	1132	0.9732	866	0.9607	21280
Base Case recurrent BCC	1159	1.000	900	0.9680	8094
1. Duration					
- lower bound 95% CI MMS	1114	1.000	900	0.9680	6688
- upper bound 95%CI MMS	1190	1.000	900	0.9680	9063
- lower bound 95% CI SE	1159	1.000	846	0.9680	9781
- upper bound 95% CI SE	1159	1.000	922	0.9680	7406
2. Effectiveness					
- effect difference of 13.5% (calculated for the power analysis of the clinical study)	1159	1.000	900	0.8650	1919
- effect-difference of five-year follow-up period**	1159	1.000	900	0.936	4047

** based upon extrapolation of 2,5 year recurrence rate*
*** based upon extrapolation of 1,5 year recurrence rate*

Discussion

To our knowledge, this is the first study investigating the cost-effectiveness of MMS compared with SE for the primary and recurrent BCC. Although retrospective research by Cook and Zitelli and a recent prospective study by Bialy et al. compared the costs of MMS and SE, they did not relate the effectiveness of both treatments to their costs.[12-13] As such, they describe a cost-comparison analysis. Moreover, both include various types of non-melanoma skin cancer while our study focuses exclusively on primary and recurrent BCC. Another study reported total costs of non-melanoma skin cancer treatment in general but did not calculate costs of the separate treatment modalities.[14]

Results of the clinical trial showed that the effect difference between the two surgical treatments was small for both groups. A possible explanation for the lower recurrence rate after SE is the fact that all incompletely excised BCC's were re-treated immediately.[3]

The quality of life results demonstrated that there was no statistically significant difference at six months compared with baseline between patients undergoing MMS or SE. However, it is possible that a generic measure like the NHP or even a domain-specific measure like the STAI is not sensitive enough to detect a difference in treatment effect for patients with this type of skin cancer. Since BCC often is localized in the facial area, it is likely that, for instance, psychosocial or functional issues resulting from the skin cancer and its treatment are more relevant. Therefore, we developed parallel to the clinical trial a disease-specific questionnaire focused on the perceptions of patients regarding the health and aesthetics of their facial skin. The outcomes of this study are described in a separate article.[15]

Results of the cost-analysis showed that the mean costs of MMS were significantly higher, mainly due to longer surgery time and higher pathology costs. More detailed analyses revealed that this cost difference persisted, irrespective of histology subtype and location.

Relating the costs of both surgical treatments to their effectiveness, resulted in a cost-effectiveness ratio of €29231.- per recurrence avoided for primary BCC, while the ratio for recurrent BCC was € 8094.-. The acceptability curves for the primary and recurrent BCC demonstrated that the probability of MMS being more cost-effective then SE, never reached 50% unless the hospital would be willing to pay even more than the calculated ICER's. The cost-effectiveness planes showed that the majority of all ratio's were located in

the quadrant where an increased effectiveness of Mohs is only achieved at higher costs. In such a situation, the decision to replace SE by MMS depends first on the threshold value, in this case the maximum amount the hospital would be willing to pay extra to prevent one additional recurrence and second whether the estimated ICER lies below this threshold value.[16] However, a maximum amount with respect to the treatment of a BCC has not yet been determined which makes interpretation and comparison of the ICER's difficult. This is often a problem when applying a disease-specific outcome measure instead of a more common measure for effectiveness like a Quality Adjusted Life Year (QALY).[17] The reason for not using the QALY as an outcome measure, was that BCC and its treatment would have no effect on life expectancy. In addition, it was expected that treating BCC had no substantial effect on general quality of life. Nevertheless, the ICER's of this study can be put into perspective by considering the consequences of a recurrent BCC from a hospital perspective. It is likely that a patient with a recurrent BCC will undergo a re-operation in the future. Therefore, it can be argued that an acceptable threshold value should at least include the hospital costs of repairing a recurrence. Furthermore, the value should account for the fact that not all recurrences can be repaired in the long run and that some patients will develop a second or third recurrence. Finally, although we did not examine the patient perspective, it is possible that a patient's willingness to pay to avoid a recurrence may provide important information with respect to a reasonable threshold value.

Still, even by taking three times the costs for repairing a recurrent BCC (that is, three times the costs of MMS = €3438.-), the ICER's for primary and recurrent BCC are still too high to recommend a broad implementation of MMS. When the threshold value of €3438.- is subsequently compared with the estimated ICER's for each location, it appears that, except for primary BCC of the ears and recurrent BCC of the cheek, MMS is not likely to be considered a cost-effective treatment. Furthermore, although the ICER's for primary BCC of the ears and recurrent BCC of the cheek seem more favourable, they should be interpreted with caution since they are based on small subgroups.

However, when the threshold value is compared with the ICER's per histology subtype, MMS might well be a cost-effective treatment for the group of aggressive recurrent BCC.

As shown by the sensitivity analysis, the ICER's for both primary and recurrent BCC were largely affected by the difference in recurrence rate.

Since normally a five-year period is required to determine definite recurrence rates, it is possible that in the near future the cost-effectiveness ratio of MMS for recurrent BCC's may become more acceptable.

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chapter 3

Determinants of satisfaction with the health state of the facial skin in patients undergoing surgery for facial basal cell carcinoma.

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Abstract

Objective. The main objective of the study was to assess which health beliefs predict and explain satisfaction with the facial health state of patients undergoing surgery for basal cell carcinoma.

Methods. Data were collected by administering a newly developed questionnaire pre-operatively and six months post-operatively (n=222).

Results. Results show that satisfaction as measured by postoperative worrying, susceptibility and fear of developing a new BCC at other facial sites can be predicted by pre-operative health beliefs. In addition, some patients experience an increase in perceived susceptibility, fear of recurrence of BCC on the same site or fear of developing a new BCC at other facial sites.

Conclusion. Our findings indicate that both pre-and post operative perceptions predict and explain for a substantial part the extent to which patients are satisfied with their facial health state six months after surgery.

Practice implications. Administering a short questionnaire at the start of the treatment period will give physicians a better understanding of how patients experience this skin disease. It will also help them to adjust information about BCC and its consequences to the needs of the patient.

Introduction

Basal cell carcinoma (BCC) is one of the most common type of (skin)cancer worldwide.[1] In the Netherlands, the number of newly diagnosed cases is estimated around 29.000 a year and the assumption is that this number will grow, due to ageing of the population and frequent exposure to sunlight.[2] Because most BCC are localized on the head and neck, this may result in significant morbidity with disfigurement, invasion of vital structures and mutilating local tissue destruction.[3] Nowadays, surgical excision, Mohs micrographic surgery, cryosurgery and radiotherapy are the most used treatment modalities for BCC. Their main goal is total removal of the skin cancer with preservation of healthy tissue. In addition to this, an optimal functional and cosmetic result is equally important. So far, research related to the impact of BCC on patients' lives has been concentrated on the assessment of health related quality of life. As shown in a study of Blackford, Roberts, Salek and Finlay, patients seem to experience little handicap from BCC.[4] However, it remains to be seen whether the generic measures used in their study are sensitive enough to measure the specific disease related aspects of this type of skin cancer. In this study, we decided to examine patient beliefs regarding BCC by using concepts of the Health Belief Model.[5] The assumption was that these beliefs might be indicators of the satisfaction of patients with the health state of their facial skin. To our knowledge, patient beliefs i.e. perceptions and expectations on facial BCC and its treatment have never been investigated. The main objective of our study was to assess which beliefs predict satisfaction with the health state of the facial skin at six months after surgery. For that reason, we developed a disease-specific questionnaire and used it parallel to a clinical trial.

Methods

Defining patient satisfaction with concepts from the Health Belief Model

Because of lacking valid and sensitive instruments to measure satisfaction with facial health status of non-melanoma skin cancer patients, the decision was made to develop a new disease-specific questionnaire inspired by concepts originally used in the Health Belief Model (HBM). The HBM is basically a value-expectancy model developed to predict and explain health preventive behavior.[5] According to the HBM, an individual's state of readi-

ness to take action for a health condition is not only determined by its "value" in terms of perceived susceptibility to a condition and the perceived severity of the condition but also the "expectancy" based on an evaluation of the possible benefits and disadvantages of health behaviour to reduce susceptibility and/or severity.[6] The model furthermore states that a stimulus is necessary to trigger appropriate health behaviour. This so-called "cue to action" might be internal (i.e. symptoms) or external like mass-media communications. However, patients enrolled in the clinical trial already had taken action for their health by making the decision to undergo treatment in order to remove the skin cancer.

Therefore, we did not consider a "cue to action" a relevant factor in this study, but we decided to use beliefs of the HBM as indicators for the extent to which patients are satisfied with the eventual facial health state at six months. Given these specifications and the objective of the study, we were interested in answering the following questions:

1. Can pre-operative beliefs be used to predict patient satisfaction with the health state of the facial skin at six months?
2. Which pre- and postoperative beliefs do eventually explain patient satisfaction with the health state of the facial skin at six months?

Definition of the concepts

First, we started to define which disease related concepts were relevant for patients with a primary or a recurrent BCC. This was achieved by discussing a list of relevant topics regarding patient's beliefs on skin cancer and its treatment within a panel of dermatologists. Then, after determining what kind of perceptions and expectations were relevant for patients with this type of skin cancer, questions and statements in item-form were devised and again discussed within the same panel of dermatologists.

Finally, the items were pre-tested on a group of 22 patients diagnosed with a primary or recurrent basal cell carcinoma. Analysing the data of this pre-testing led to some minor changes for a couple of items after which the final questionnaire was completed.

We used the following health perceptions: "Vulnerability for facial BCC ", "Susceptibility to facial BCC ", "Worrying about facial BCC", "Perceived severity of the facial skin affliction", "Perceived health status of the facial skin" and "Perceived size of the skin lesion". Within the context of this study, susceptibility and vulnerability refer both to a subjective perception of the

risk of developing skin cancer. However, we distinguished the two concepts by defining susceptibility as one's subjective perception of the risk relative to the one of their peer group and vulnerability as one subjective perception of the risk based on hereditary grounds. Perceived severity indicates not only the clinical but also the possible social consequences of the skin cancer on work and social environment. Next to this, patient expectations towards the surgical treatment in terms of a specific (dis)advantage includes fear for surgery, doubts about the results and fear of recurrence of BCC or fear of developing a new BCC on other facial sites. A conceptual framework is presented graphically in figure 1. A short hand form and a detailed description of the definition of the concepts are given in Table 1.

Table 1 Definition of variables used in this study

	Health perceptions
Vulnerability	The perceived vulnerability for BCC based on hereditary grounds (high-low)
Susceptibility	The perceived susceptibility for BCC compared with the peer group (high-low)
Size	The perceived size of the lesion (very big-small)
Severity	The perceived severity of the lesion (very serious . . . not serious)
Health status	The perceived overall health status of the facial skin (very good-very bad)
Worrying	Worrying about facial health problems (high-low)
	Expectations
Fear for surgery	Fear for the surgical treatment itself (high-low)
Doubts results	Doubts about the result of the surgical treatment (high-low)
Fear of recurrence of BCC	Fear of recurrence of BCC on the same facial site (high-low)
Fear of developing a new BCC	Fear of developing a new BCC on other facial sites (high-low)

Study design

From October 1999 till September 2002 a prospective randomised clinical trial was carried out by the department of Dermatology of the University Hospital Maastricht. The main goal of this trial was to compare two specific surgery modalities, Mohs micrographic surgery and surgical excision, with regard to the 18 months recurrence rate in patients with a primary or a recurrent facial BCC. Parallel to the clinical trial, a prospective study was performed in which a newly developed disease-specific questionnaire was

applied. At the baseline of the study, about 2 till 4 weeks before surgery, a one-hour personal interview took place in which data on socio-economic status were asked and the questionnaire was used. The patient could read the questions and items in a copy of the questionnaire while the interviewer scored the answers in the data form of the query sheet. The perceived size of the skin lesion and other patient characteristics have been measured by direct questioning with 5 categories to answer. Health perceptions, expectations and an overall satisfaction question were generally expressed as 5-point Likert scale items to which patients could agree or disagree. A sixth extra scale position was used to score patients who had "no opinion at all" or for items that did not apply to their situation. Co-morbidities were measured by using a list of diseases. After six months, a second personal interview took place in which a shorter version of the questionnaire was used. Evidently, expectations like fear for surgery and doubts about the operative result were left out.

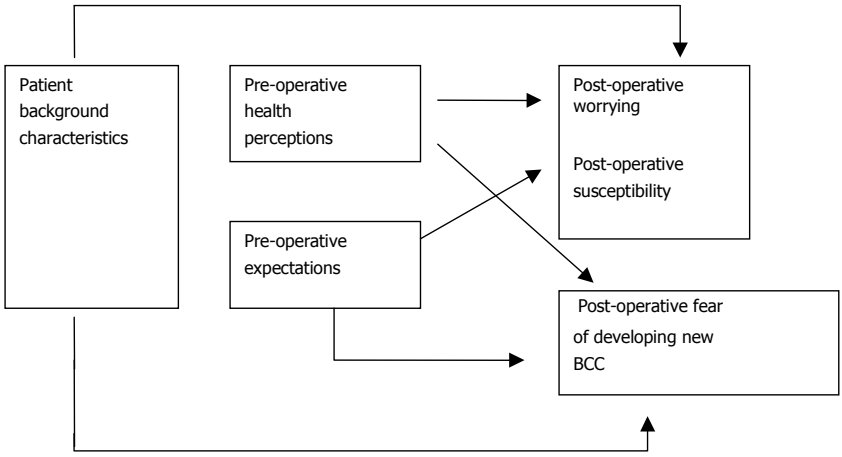

Figure 1 The conceptual framework for predicting post-operative health perceptions

Inclusion and exclusion criteria: patient eligibility criteria

The following eligibility criteria, for patients enrolled in the satisfaction study, were chosen:1) patients aged 18 years or older,2) patients presenting themselves with a single facial BCC. Excluded were patients who were not mentally capable of answering the questionnaire or not able to speak and understand the Dutch language. All eligible patients were asked if they were willing to participate in the satisfaction study after they had given informed consent to participate in the clinical trial. If they agreed to take part in the satisfaction survey, a personal interview preoperatively and another one six months postoperatively took place. It is possible that particularly the group with a primary BCC undergoing surgical excision is slightly underrepresented for patients coming from outside the region of Maastricht. This is due to the fact that many of these patients only visited the department of dermatology for a pre-visit while they were treated and had control visits in the hospital of their residence.

Statistical methods

Data of the questionnaire were analysed by using principal component and factor analysis. All items were clustered into provisional scales that were tested for internal consistency using Cronbach's alpha. The results lie between satisfactory and very good for all scales (alpha between 0.74 and 0.93).[7] Results of the factor analysis and the scale constructions are given in appendix table 1 and 2. At first, a paired t-test was carried out between baseline and postoperative scores. Next, a repeated measures ANOVA was performed to see if there were statistically significant differences in perceptions between treatment modalities. As a consequence of the two questions we posed at the start of the study, a distinction was made between "prediction models" and "models of explanation". Normally, if we wanted to predict postoperative perceptions using only pre-operative beliefs and patient background characteristics, a predictive analysis would suffice. However, in order to enhance and enlarge this prediction, some post-operative measurement was necessary to calculate changes in health beliefs over time and use them as additional predictors in the explanatory analysis. For both predictive and explanatory models, regression analysis was used, in which a health perception as an indicator for satisfaction at 6 months is regarded as "dependent" variable. Listwise deletion of missing cases was carried out. First, the follow-

ing baseline variables were used for the predictive models: age, gender, tumour (primary or recurrent), type of surgery, vulnerability, doubts about result surgery, fear for surgery, fear of recurrence of BCC, fear of developing a new BCC, socio-economic status, co-morbidities, perceived severity of skin lesion, perceived health status, perceived size and susceptibility. Then, in the explanatory models, the same dependent variable at six months was tested, but here next to the baseline variables, also the difference scores between the baseline and six months measurement were entered into the equation. All first order interactions between statistically significant direct effects of predictors were tested. The results of the predictive and explanatory models are presented in table 4 and 5. All analyses were done with SPSS-PC version 11.0. A p-value less than 0.05 is considered as statistically significant.

Results

Description of the study population

Initially, 374 patients with a primary BCC and 190 patients with a recurrent BCC were enrolled in the clinical trial. The questionnaire was tested at the beginning of the clinical trial and its final version could not be used until three months after start. As a consequence, we missed 42 patients with a primary and 9 patients with a recurrent BCC. Furthermore, patients were lost due to administrative restrictions. Since there was only one person who administered the questionnaire after the visit to the dermatologist, it meant that patients often had to wait in turn before they could be interviewed.

A number of patients refused to do so either because they had commitments elsewhere or they simply did not want to wait. Eventually, a total of 222 patients of which 133 with a primary BCC and 89 with a recurrent BCC were interviewed at baseline (39% of the total of 564). At six months, 22 patients with a primary BCC and 16 patients with a recurrent BCC were lost to follow-up. Of the total number of patients with a primary BCC, 111 persons completed the questionnaire at six months next to 73 patients of the recurrent group. Additional details of the two groups at baseline are described in table 2.

Table 2 Characteristics of the patient population

	Primary BCC (N=133)	Recurrent BCC (N=89)
Male/female	79 / 54	52 / 37
Age	65.61 (sd 12.51)	64.69 (sd 12.20)
Average number of co-morbidities (median)	2.06 (2)	1.86 (2)
Treatment modalities (excision/ mohs)	56 / 77	48 / 41

Results of the patient satisfaction questionnaire

Differences in health beliefs between baseline and six months

Results in table 3 show a significant decrease in worrying of patients about facial BCC, six months after surgery. The perceived size of the lesion/scar and the perceived severity also show a significant reduction while the perceived health status is significantly improving. On the other hand, there appears to be a slight but not statistically significant increase in perceived susceptibility for facial BCC of patients at six months. Fear of recurrence of a BCC or fear of developing a new BCC on other facial sites shows no statistically significant difference. Results of the repeated measures ANOVA showed no statistically significant difference in perceptions between the two surgical treatments (results not shown).

Table 3 Pre-and postoperative means of the health belief scales

Variable	N	Mean (sd) T0	Mean (sd) T1	p-value[a]
1. Worrying (much-not)[b]	184	2.67 (.75)	2.45 (.67)	.001
2. Susceptibility (high-low)	180	2.35 (.65)	2.43 (.70)	.051
3. Fear of recurrence BCC same site (high-low)	181	2.54 (.91)	2.50 (.86)	.537
4. Fear of developing new BCC other sites (high-low)	183	2.89(1.01)	2.82 (.92)	.263
5. Size of lesion/scar (very big-small) [c]	184	3.30 (.92)	3.92 (1.55)	.001
6. Severity (high-low) [c]	184	4.33 (1.58)	4.93 (1.12)	.001
7. Health status (very good-bad)	184	2.01(1.10)	1.62 (.85)	.001

[a] Paired Student t-test p-values are reported: significant differences at the .05 level.[b] Scales vary from 1-5. [c] A higher score indicates an improvement in perception of size or severity

Worrying about facial health

Comparing the results for both the predictive model and the model of explanation (table 4 and 5) for "Worrying", the most important effect proved to be the interaction between the baseline perception " Susceptibility" and the baseline expectation "Fear for surgery" (p-value: 0.001). Detailed analyses showed that in patients who are beforehand fearful for surgery, susceptibility has a larger impact on worrying at six months than in patients who are less fearful (beta:.547, p-value:.002 versus beta:.299,p-value: .001).

Fear of developing a new BCC on other facial sites is the second important factor in both predicting and explaining "Worrying". If patients, before surgery, already are fearful of developing a new BCC at other parts of their face, they tend to worry more at six months. In the model of prediction, no other variables had statistically significant effects.

Furthermore, the model of explanation showed that three difference scores had statistically significant effects. If a patient's fear of developing a new BCC or fear of recurrence of a BCC is increasing between baseline and six months, worrying will be higher. The third difference score indicates that a rising perception of susceptibility also tends to increase worrying at six months significantly. The last significant effect belongs to the baseline variable " Fear of recurrence of BCC" which indicates that patients who at baseline already are fearful of a recurrence, will also worry more at six months. All variables together explained 55 percent of the variance of worrying at six months. This is 23 percent higher than the variance explained in the predictive model.

Susceptibility for facial BCC

Three baseline variables in the predictive model as well in the explanatory model were statistically significantly related to " Susceptibility" at six months, that is "Fear of developing a new BCC on other facial sites", "Perception of facial health " and "Vulnerability ". However, the variables in both models differ in order of importance. For the predictive model, the three important effects are consecutively, "The perception of facial health", "Vulnerability" and "Fear of developing a new BCC on other facial sites". For the explanatory model, the most important effect belonged to "Fear of developing a new BCC on other facial sites" while the second important effect resulted from the difference score on this variable. So, if patients fear that a new BCC will develop on other facial sites and this fear grows between the period of baseline and the six months measurement, their perception of

susceptibility at six months will increase. The third and fourth significant effect came from the "Perception of facial health" and "Vulnerability". If patients perceive their facial health as low and if they think they are vulnerable for facial BCC, the perception of susceptibility at six months will increase. This last model has an explained variance of 41 percent that is seventeen percent higher than the variance explained in the predictive model. All tests for first-order interactions were not significant.

Table 4 Results of the linear regression analysis for prediction models

	B	Se	Beta	Sig t
Worrying about facial health				
Constant	.2.076	.434		.000
Susceptibility	-.177	.185	-.170	.340[a]
Fear for surgery	-.403	.164	-.533	.015[a]
Fear of developing new BCC other facial sites	.159	.045	.238	.000
Susceptibility*fear for surgery	.225	.066	.934	.001
Variance explained: .32				
Adjusted r-square:.31				
F: 21.2 by 4 and 176 df				
Susceptibility for facial BCC				
Constant	1.031	.199		.000
Health status	.229	.058	.271	.000
Vulnerability	.250	.067	.246	.000
Fear of developing new BCC other facial sites	.147	.048	.211	.003
Variance explained: .24				
Adjusted r-square:.22				
F: 18.24 by 3 and 175 df				
Fear of developing a new BCC other facial sites				
Constant	3.220	1.196		.008
Susceptibility	-.880	.469	-.619	.063[a]
Doubts result surgery	.253	.095	.175	.008
Comorbidities	.780	.220	1.409	.000[a]
Gender	.285	.117	.153	.016
Age	-.045	.018	-.596	.015[a]
Susceptibility*age	.0225	.007	1.195	.002
Comorbidities*age	-.0104	.003	-1.358	.001
Variance explained: .35				
Adjusted r-square:.32				
F:13.19 by 7 and 173 df				

[a] *these parameters are not interpretable because of the interaction*

Fear of developing a new BCC on other sites

For the predictive model, the most important significant effect was the interaction between "Co-morbidities and age". Further analysis showed that the effect of co-morbidities on fear for developing a new BCC was statistically significant for the patients younger than 65 who were suffering from multiple co-morbidities, but not for patients older than 65 years (beta:.386; p-value <0.001 versus beta:-.01, p-value:.888). A second significant interaction effect was between "susceptibility" and "age" which also proved to be the most important effect for the explanatory model (p-value: 0.008).

Detailed analyses showed that for patients older than 65 years the effect of susceptibility on fear of developing a new BCC is stronger than that for the group younger than 65 years (>65: beta:1.07 p-value <0.001 versus<65 beta:.533; p-value <0.001).

The second important factor for explaining "Fear of developing a new BCC on other facial sites" was the difference score of susceptibility. This means that the more susceptibility is increasing between baseline and six months, the more a patient will fear the development of a new BCC on other facial sites.

Parallel to the results of the predictive model, the baseline variable "Doubts about the result of the operation" is the third significant factor. If patients are doubtful about the result of the operation, they will fear the development of a new BCC on other facial spots. The factor "gender" turned out to have a significant fourth effect in both models, which means that women are more fearful of developing a new BCC then men. All variables together explain 46 percent of the variance of fear of developing a BCC on other facial sites at six months. This is 11 percent higher compared with the variance explained of the predictive model.

Table 5 Results of the linear regression analysis for models of explanation

	B	Se	Beta	Sig t
Worrying about facial health				
Constant	1.508	.367		.000
Fear of developing a new BCC other sites	.194	.066	.293	.004
Fear of recurrence BCC same site	.147	.064	.197	.023
Susceptibility	-.104	.157	-.102	.508 [a]
Fear for surgery	-.338	.135	-.454	.013 [a]
Difference score fear of developing a new BCC other sites	.181	.060	.261	.003
Difference score fear of recurrence BCC same site	.194	.055	.260	.001
Difference score susceptibility	.280	.072	.240	.000
Susceptibility* fear for surgery	.184	.055	.775	.001
Variance explained:.55				
Adjusted r-square:.54				
F: 26 by 8 and 169 df				
Susceptibility for facial skin afflictions				
Constant	.661	.183		.000
Fear for a new BCC other spots	.379	.053	.543	.000
Facial health status	.160	.052	.189	.002
Difference score fear of developing a new BCC other sites	.387	.054	.524	.000
Vulnerability	.187	.062	.180	.003
Variance explained:.41				
Adjusted r-square:.40				
F: 30.66 by 4 and 174 df				
Fear of developing a new BCC other facial sites				
Constant	3.138	1.071		0.004
Susceptibility	-.301	.419	-.213	.473 [a]
Difference score susceptibility	.697	.095	.435	.000
Age	-.052	.016	-.685	.002 [a]
Gender	.249	.105	.134	.019
Doubts result surgery	.305	.083	.211	.000
Susceptibility*age	.017	.006	.915	.008
Variance explained:.46				
Adjusted r-square:.44				
F: 24.70 by 6 and 173 df				

[a] *these parameters are not interpretable because of the interaction*

Conclusion and discussion

The primary aim of our study was to assess satisfaction with the health state of the facial skin in patients undergoing surgery for basal cell carcinoma. Overall, our results indicate that patients six months after surgery show a statistically significant decrease in worrying, the perceived size of the lesion/scar, their perceived severity while their perceived health status has improved. On the other hand, there appears to be a slight but not statistically significant increase in the perceived susceptibility for facial BCC of patients at six months. Moreover, both pre-and post operative perceptions predict and explain for a substantial part the extent to which patients are satisfied with their facial health state.

First, patients have certain perceptions and expectations beforehand, regarding BCC and its treatment, when visiting their dermatologist for the first time. These beliefs already predict for a large part their satisfaction with the facial health state after the operation.

For instance, being fearful at baseline of developing a new BCC on other facial sites will have an effect on both feelings of worrying and perceived susceptibility six months after treatment. Another result shows that doubts about the result of the surgery will be predictive for fear of developing a new BCC on other facial sites at six months.

Second, based on the results of this study, some patients experience an increase in their perceived susceptibility while others are increasingly fearful of recurrence of a BCC or developing a new BCC on other facial sites. A possible explanation for this increase might be that, at the start of the treatment period, patients are much less aware of the extent to which their skin has been damaged. Than later on, during their control visits at the hospital, they become more aware of the fact that recurrence of BCC or developing a new BCC on other facial sites can be a real threat.

Discussion

Recently, a study of Rhee et al. determined the general quality of life of patients with cervicofacial non-melanoma skin cancer by using the Short Form 36 item Health Survey (SF-36).[8] Results demonstrated a minimal impact of non-melanoma skin cancer on patients, although the authors conclude that a generic measure like the SF-36 may not be sensitive and

recommend the development of a more disease-specific instrument. In fact, within the field of dermatology, two instruments are available to measure the effects of skin diseases on patient's health related quality of life. The Dermatology Life Quality Index (DLQI) contains 10 items that are strongly related to impaired functioning and physical disability, while the refined version of the Skindex contains 29 items to address dimensions like emotions, symptoms and functioning.[9-10] Both questionnaires seem appropriate for patients suffering from a wide range of chronic skin diseases like psoriasis or eczema. It is questionable whether they are able to grasp the specific problems of having BCC, which is the main reason why we did not use these instruments.

Our assumption was that the most important issues for patients would be psychosocial problems resulting from the fact that this type of skin cancer is often localized in the facial area which could lead to cosmetic problems. These specific aspects are not included in both DLQI and Skindex. In order to examine the possible adverse consequences of BCC and its treatment, we chose to develop scales based on concepts originally used within the Health Belief Model. We considered health beliefs to be indicators for satisfaction with the eventual facial health state after surgery. A limitation of our study is that we tested the beliefs separately instead of a construct that combines them. Moreover, the correlation between health beliefs and other perhaps more commonly used satisfaction parameters should be further examined.

To test the internal consistency of our questionnaire, Cronbach's alpha was used. Results were between satisfactory till good for almost all scales (alpha between 0.74 and 0.93). The content validity was realised by consulting experts in the field of dermatology and testing the questionnaire within a group of patients. A limitation of our study is that reproducibility (test-retest) could not be achieved due to practical considerations. Administering the same questionnaire again would imply an additional visit for patients to the hospital within a very short time-period. Since a lot of patients came from outside the region of Maastricht, this would have been too burdensome at the time.

Practice implications

The results in this study show that both pre-and postoperative health beliefs as measured by worrying, fear and susceptibility determine for a large part the extent to which patients are satisfied with their facial health state after surgery. To gain insight in which patients are likely to be less satisfied and to reduce unnecessary feelings of worrying or fear, administering a short questionnaire at the start of the treatment period could be very useful to the process of informing patients about BCC and its consequences. Items regarding perceived susceptibility, vulnerability, health status of the facial skin, fear of recurrence, fear of developing a new BCC, fear for surgery and doubts about the results of the surgery are likely candidates to this end. In fact, such a questionnaire works both ways. On the one hand, the instrument may help physicians to a better understanding of how patients perceive this type of skin cancer and adjust their patient information accordingly. On the other hand, it may help patients to get information about BCC in a language they are familiar with. Additionally, since the main interest of clinical trials and intervention studies is whether a new treatment can be shown to be better than a standard or placebo treatment, this short questionnaire can be applied to assess if there's a difference in perceptions of patients undergoing therapy for non-melanoma skin cancer. Finally, although the questionnaire within our study is concentrated upon the health beliefs of patients with non-melanoma skin cancer, it could also be useful for other diseases with similar morbidity.

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Appendix

Table 1 Results on the factor analysis by Maximum Likelihood

(Items translated from Dutch to English version)

Items		Worrying about facial BCC	Vulnerability facial BCC	Susceptibility facial BCC	Com-munality
Item 1	Recently, I'm very worried about the health of my facial skin	**.85**	.042	.0073	.74
Item 2	Since I have this skin affliction, I often worry about the health of my facial skin	**.84**	.055	-.11	.67
Item 3	Recently, I'm concerned about the health of my facial skin	**.84**	.060	-.078	.67
Item 4	I'm absolutely not worried about the health of my facial skin	**-.76**	-.020	-.12	.67
Item 5	I'm not such a worrier about the health of my facial skin	**-.62**	.14	-.26	.55
Item 6	My facial skin health is rather vulnerable because skin afflictions often occur with family members	.040	**.94**	.024	.91
Item 7	I have more risk of skin afflictions because such health problems often occur within my family	.017	**.92**	.033	.88
Item 8	When I look at my family, then I have little risk of health problems with my facial skin, because they hardly occur there	-.034	**-.90**	-.025	.83
Item 9	I have such an oversensitive skin that I'm always having health problems	.029	-.11	**.88**	.74
Item 10	Compared with my peers my skin is much more sensitive to facial health problems	.058	.023	**.77**	.66
Item 11	When I compare my facial skin with that of my peers, I normally don't have such a sensitive skin type	.11	.038	**.73**	.63
Item 12	When I compare myself with peers, I tend to be more bothered by facial skin afflictions	-.13	.22	**.70**	.58
Cronbach's alpha		.86	.93	.82	

Table 2 Results on factor analysis by Maximum Likelihood

Items		Fear of developing new BCC other facial sites	Fear of recurrence BCC same facial site	Fear for surgery	Doubts results operation	Communality
Item 13	I fear that the skin affliction will develop at another facial site	**.99**	-.027	.015	-.006	.99
Item 14	I fear that in the long run the same skin affliction I now have, will develop at other facial sites	**.62**	-.088	.008	.22	.71
Item 15	I fear that the skin affliction after surgery once again will recur at the same facial site	.069	**-.99**	.06	-.15	.99
Item 16	I fear that in the long run the same skin affliction I have, will recur at the same facial site	.012	**-.74**	-.05	.24	.75
Item 17	When I think about the operation, I'm not looking forward to it	.129	.0042	**.83**	-.15	.71
Item 18	At this moment, I'm a bit fearful for operation	-.063	.033	**.79**	.09	.65
Item 19	I'm scared for the operation and everything surrounding it	-.045	-.06	**.75**	.11	.63
Item 20	Actually, I'm a bit doubtful about the result of the operation	-.046	-.123	.099	**.78**	.72
Item 21	I'm a bit doubtful about what the operation will bring me	.070	.064	.0052	**.57**	.38
Item 22	I'm doubtful whether the operation will bring me a good result	.10	-.032	.021	**.52**	.41
Cronbach's alpha		.88	.90	.85	.74	

chapter 4

Perceptions of facial aesthetics in surgical patients with basal cell carcinoma

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Abstract

Background. Basal Cell Carcinoma is a non-melanoma form of skin cancer that is frequently localized within the cervicofacial area. The aim of a treatment for BCC is not only to prevent a recurrence but also to achieve a good aesthetic outcome.

Objective. The main objective was to assess whether pre-operative perceptions of patients may predict their evaluation of facial aesthetics six months after surgery.

Methods. Parallel to a randomised clinical trial, a survey was carried out in which patients were asked about perceptions with regard to their facial aesthetics before and six months after surgery.

Results. Results showed that the evaluation of post-surgical facial aesthetics of primary BCC patients can be predicted by both visibility of the tumour and pre-operative perceptions.

Conclusion. It is recommended to administer before surgery a short questionnaire in which perceptions related to facial aesthetics are included. In doing so, physicians will become more familiar with the aesthetic problems patients might have regarding their afflicted facial site. It will enable them to provide those patients with information about the consequences of skin cancer and its treatment. Ultimately, it may help physicians in deciding whether patients will benefit from additional cosmetic procedures after surgery.

Introduction

Basal cell carcinoma (BCC) is a non-melanoma form of skin cancer that occurs in eighty percent of all cases within the cervicofacial area.[1] Given the cosmetic importance of this region, the aim of a treatment when removing this type of skin cancer is not only to eradicate the tumour and to prevent a recurrence but also to achieve a good aesthetic outcome. So far, little research is available that provides insight in perceptions of patients with regard to their facial aesthetics after treatment for BCC. For the comparison of the aesthetic outcome between a surgical and a non-surgical treatment, two studies have been performed.[2-3] Methods used to evaluate the aesthetic result by patients varied from rating the outcome in points from 1(very bad) to 10 (excellent) or on a 10-cm Visual Analogue Scale ranging from "not satisfied" to "satisfied". Overall, patients assessed the aesthetic result after surgical excision (SE) as better. Mohs Micrographic Surgery (MMS) is, next to SE, another surgical treatment modality that increasingly is used to treat non-melanoma skin cancer. In general, the assumption is that MMS may give good cosmetic results due to the fact that the tumour is removed in successive stages and thus unnecessary removal of unaffected tissue is minimised. Whether patients perceive their facial aesthetics after MMS as better, compared to those who underwent SE, has never been examined. From 1999 till 2002, a prospective randomised clinical trial was performed at the University Hospital Maastricht to determine the cost-effectiveness of MMS and SE for both primary and recurrent BCC. Parallel to this trial, a longitudinal survey in which patients were asked to evaluate their facial aesthetics, was carried out.

The objectives of this study were fourfold:

1) to analyse if there was a statistically significant improvement over time with regard to the perceptions of facial aesthetics in the total group of surgical patients, 2) to analyse if there was a statistically significant difference in perceptions of facial aesthetics between primary and recurrent BCC patients, 3) to analyse if there was a statistically significant difference in perceptions of facial aesthetics between patients who underwent MMS or SE, 4) to assess which baseline perceptions and/or clinical parameters may predict the evaluation of facial aesthetics at six months after surgery.

Methods

Study design

From October 1999 till September 2002, a prospective randomised clinical trial was conducted within the University Hospital Maastricht. Full details of this trial are described elsewhere.[4] Parallel to the clinical study, a survey was carried out in which patients by means of a newly developed disease-specific questionnaire were asked about perceptions with regard to their facial health and their facial aesthetics.[5] After patients had given their informed consent to take part in the clinical trial, they were subsequently asked if they were willing to answer the disease-specific questionnaire. If they agreed, they were interviewed a few weeks before surgery and six months post-operatively.

Power analysis indicated that for the group of primary BCC at least 102 patients were necessary to detect an effect difference of 12.5 percent between MMS and SE in the scale of very satisfied to not satisfied. For the group of recurrent BCC, 86 patients were required to detect an effect difference of 15 percent.

Aesthetic assessment methods

The assessment of the facial aesthetics included 5 specific questions about: the size of the facial site, the conspicuousness of the facial site, the extent to which the facial site was making the patient's appearance less beautiful, the appearance/beautifulness of the scar (this was only measured at six months) and the subjective burden caused by the facial site on the patient's appearance. In addition, perceptions like worrying about facial beauty, susceptibility for facial beauty problems and finding it difficult to be seen with facial beauty problems were expressed as blocks of 5-point Likert scale items to which patients could agree or disagree. From a clinical perspective, the assessment of an aesthetic outcome usually starts after surgery since the effect of the treatment then will be visible. However, because we were primarily interested in a patient's point of view and whether pre-operative perceptions may predict the evaluation of aesthetic results, we measured perceptions on aesthetics both before and after surgery. An exception was made for two direct questions about the appearance /beautifulness of the scar and the subjective evaluation of the result of surgery. These were asked exclusively six months after surgery.

The reconstruction techniques were categorized into 4 types: 'direct suture (1)', 'flaps (2)','grafts (3)' and a category (4) 'others' which consisted of a variety of reconstruction methods like delayed closure, closure by plastic surgeon and a combination of an advancement and a full thickness graft.[6]
Finally, to assess whether visibility of the afflicted site could predict the evaluation of facial aesthetics, the seven facial locations of the tumour as discerned by dermatologists were divided into four categories. [3] The first category was defined as "very highly visible" and included all BCC's located on the nose and peri-nasal area. The second category was labelled as "highly visible" and contained all BCC's on the forehead/temporal area and cheek/chin. Of the other two categories, one was defined as "moderately visible", encompassing all BCC's on the lips and peri-ocular area while the other one was defined as "lowly visible", including all BCC's on the ears and peri-auricular area.

Statistical analysis

Variables were at first tested for normal distribution by the Kolmogorov-Smirnov test.
For the comparison between response and non-response, a chi-square was used for categorical factors, a Student independent groups t-test for the normally distributed variables and the Mann-Whitney test when this was not the case. A repeated measures ANOVA was applied to analyse if there were statistically significant differences in evaluation of the facial aesthetics over time between patients with either a primary or a recurrent BCC. ANOVA was also carried out to determine if there were statistically significant differences in evaluation of the post-operative facial aesthetics between MMS and SE. Items on aesthetic perceptions were at first clustered into multiple provisional scales found by factor analysis. Scales were subsequently tested for internal consistency using Cronbach's alpha. To determine which baseline variables predict the evaluation on facial aesthetics, regression analysis in which scale perceptions at six months were regarded as outcome variables, was used. Listwise deletion of missing cases was carried out. The following baseline variables were used for the predictive regression models: age, gender, type of surgery, fear for scars, worrying about facial beauty problems, susceptibility to facial beauty problems, having difficulty about being

seen with facial beauty problems, the perceived size of the tumour, the defect size (cm), socio-economic status, the severity of the skin lesion, the perceived health status, reconstruction type and visibility (the last two variables represented as dummy variables). Regression models were applied separately for patients with a primary and a recurrent BCC. A p-value smaller than 0.05 was considered to be statistically significant. All data-analysis was performed with SPSS-PC, version 11.0.

Results

Description of the population

In total 222 patients of which 133 with a primary BCC and 89 with a recurrent BCC agreed to be interviewed before surgery. Twenty-two patients with a primary BCC and 16 patients with a recurrent BCC were lost to follow-up at six months. This resulted in 111 patients with a primary BCC completing the questionnaire at six months next to 73 patients of the recurrent group. Response and non-response were compared for both primary and recurrent BCC with regard to gender, age, type of surgery and co-morbidities. No significant difference was found between the patients who were lost to follow-up and the responders. Details of the primary and recurrent patients at baseline are described in Table 1.

Table 1 Descriptive data of primary and recurrent patients at baseline

	Primary BCC (N=133)	**Recurrent BCC (N=89)**
Male/female	79 /54	52 / 37
Age	65.61 (sd 12.51)	64.69 (sd 12.20)
Civil status		
-married	84	62
-single	49	27
Co-morbid conditions	2.06 (2)	1.86 (2)
Surgical procedure	77 MMS /56 SE	41 MMS /48 SE

Differences in aesthetic perceptions

As described in table 2, the perceptions on facial aesthetics of the total group of patients improved over time. This means that they generally believe they have improved with regard to all four facial aesthetic parameters (p-value <0.05).

Results also demonstrate that postoperatively there is no statistically significant difference between primary or recurrent BCC patients with regard to perceptions of the size, the conspicuousness and the extent to which the facial site is regarded as making the appearance less beautiful. Moreover, there is no significant difference in subjective burden caused by the afflicted facial site between both groups. Furthermore, results show that there is no statistically significant difference in perceptions on facial aesthetics between patients who underwent MMS or SE.

Table 2 Pre-and postoperative means (sd) of facial aesthetics for the total group of primary and recurrent BCC patients

			Baseline	6 months	Rep. Meas. Anova			
Aesthetic parameters	**N**		**Means (sd)**	**Means † (sd)**		**F**	**Df**	**p-value**
Extent to which the facial site is regarded as making the face less beautiful	89 77	MMS* SE	2.83 (.88) 3.04 (.76)	3.42 (.75) 3.42 (.71)	Time‡ Time*tumour# Time*surgery¶	32.53 3.54 1.14	1/162 1/162 1/162	<.001 .062 .286
Perception of the size of the facial site	100 83	MMS SE	3.27 (.90) 3.35 (.94)	4.06 (1.54) 3.71 (1.47)	Time Time* tumour Time*surgery	16.78 .17 2.82	1/179 1/179 1/179	<.001 .676 .065
Conspicuousness of the facial site	100 84	MMS SE	3.63 (.86) 3.46 (.78)	4.24 (.96) 4.14 (.76)	Time Time* tumour Time*surgery	70.69 .69 .73	1/180 1/180 1/180	<.001 .69 .39
The subjective burden by the facial site on the facial appearance	100 82	MMS SE	3.40 (1.24) 3.38 (1.22)	4.68 (.99) 4.61 (.84)	Time Time* tumour Time*surgery	142.58 1.06 .002	1/178 1/178 1/178	<.001 .30 .96

** MMS= Mohs micrographic surgery ; SE= surgical excision.*

*† A higher score indicates an improvement. ‡ Time: denotes the effect of the difference between 6 months postoperative score and baseline. # Time*tumour: denotes the difference of the time effect between primary and recurrent tumours.*

*¶ Time*surgery: denotes the difference of the time effect between MMS and SE*

Results of the predictive regression models for patients with a primary BCC

Results of the test for internal consistency using Cronbach's alpha were between satisfactory and very good for all scales (between 0.75 and 0.93). It turned out that for the group of recurrent BCC, the predictive model either had a very low explained variance (varying between 11 and 16 percent) or none of the entered variables were statistically significant (results not shown). Results of the predictive regression models for patients with a primary BCC are shown in table 3.

The extent to which the afflicted facial site is perceived as making the patient's appearance less beautiful.

The regression model shows that the perceived conspicuousness, the visibility and the type of reconstruction method are important in predicting whether patients postoperatively perceive the afflicted facial site as making their appearance less beautiful (explained variance of 44 percent). So, if patients before surgery already perceive their facial site as conspicuous, if the visibility of the site is high or very high or if the type of reconstruction falls into category 4 (delayed closure, closure by plastic surgeon or a combination of an advancement and a full thickness graft), then at six months after surgery they tend to think the site has made their appearance less beautiful.

Perception of the size of the facial site.

Two baseline variables, that is the perception of susceptibility to facial beauty problems and the perception of conspicuousness, are significantly related to the perception of the size of the facial site after surgery. If patients preoperatively think they are susceptible to facial beauty problems and if they perceive the skin lesion as conspicuous, they postoperatively will perceive the size of their afflicted site as larger. Both variables explain 22 percent of the variance of the perceived size of the facial site at six months.

Perception of the conspicuousness of the facial site

Both the perception of finding it difficult to be seen with the skin affliction and a very high visibility have statistically significant relationships with the extent to which patients think their facial site has become more conspicuous after surgery (explained variance of 25 percent).

Perception of the beautifulness of the facial site

Visibility of the afflicted facial site is the only significant factor in predicting how beautiful patients think their facial site has become. If visibility is very high, high or moderate, patients perceive their facial site after treatment as becoming less beautiful compared with patients who have a tumour on a lowly visible facial site (explained variance of 19 percent).

The degree to which patients find the afflicted site a burden for their facial appearance

The degree to which patients think the afflicted facial site has become a burden for their facial appearance is predicted by their perception of conspicuousness or the visibility of the lesion (explained variance of 25 percent).

Perception of the final result of surgery

If patients preoperatively perceive their tumour as conspicuous and the afflicted site is very highly or highly visible, then they tend to consider the result after surgery clearly as a scar.

Both variables explain 28 percent of the variance of the perceived final result at six months.

Table 3 Results of the regression models for patients with a primary BCC at 6 months after surgery

Outcome variables	B	Se	Beta	Sig
1. The extent to which the afflicted site is regarded as making the face less beautiful				
Constant	3.341	.472		.000
Perception of conspicuousness	.370	.096	.318	.000
Rec12 (direct suture-flaps)	-.087	.187	-.041	.643
Rec13 (direct suture-grafts)	-.451	.319	-.116	.161
Rec14 (direct suture-others)	-.632	.234	-.228	.008
Vis 14 (very high visibility-low visibility)	-1.206	.262	-.580	.000
Vis 24 (high visibility- low visibility)	-.772	.251	-.389	.003
Vis 34 (moderate visibility- low visibility)	-.331	.308	-.113	.285
Variance explained: .44				
F: 10.88 by 7 and 95 df				
2. How big or small has the afflicted facial site become?				
Constant	3.734	.919		.000
Susceptibility to facial beauty problems	-.423	.208	-.187	.045
Perception of conspicuousness	.437	.145	.289	.003
Vis 14 (very high visibility-low visibility)	-.646	.359	-.248	.075
Vis 24 (high visibility- low visibility)	-.628	.349	-.245	.075
Vis 34 (moderate visibility- low visibility)	-.325	.428	-.087	.448
Variance explained: .22				
F: 5.9 by 5 and 104 df				
3. How conspicuous has the facial site become?				
Constant	5.764	.307		.000
Having difficulty about being seen with beauty problems	-.344	.090	-.325	.000
Vis 14 (very high visibility-low visibility)	-.888	.253	-.466	.001
Vis 24 (high visibility- low visibility)	-.647	.249	-.346	.011
Vis 34 (moderate visibility- low visibility)	-.116	.306	-.042	.705
Variance explained: .25				
F: 8.93 by 4 and 105 df				
4. How beautiful has the facial site become?				
Constant	1.143	.239		.000
Vis 14 (very high visibility-low visibility)	1.371	.280	.667	.000
Vis 24 (high visibility- low visibility)	1.159	.275	.582	.000
Vis 34 (moderate visibility- low visibility)	1.143	.337	.394	.001
Variance explained: .19				
F: 8.27 by 3 and 104 df				

Table 3 Results of the regression models for patients with a primary BCC at 6 months after surgery (continued)

Outcome variables	B	Se	Beta	Sig
5. The subjective burden by the facial site on facial appearance				
Constant	3.439	.452		.000
Perception of conspicuousness	.442	.097	.400	.000
Vis 14 (very high visibility-low visibility)	-.577	.255	-.303	.026
Vis 24 (high visibility- low visibility)	-.399	.248	-.213	.111
Vis 34 (moderate visibility- low visibility)	-.161	.304	-.059	.598
Variance explained: .25				
F: 8.89 by 4 and 105 df				
6. If you closely examine the facial site that has been operated upon, do you see a scar (the perception of the final result) ?				
Constant	3.591	.567		.000
Perception of conspicuousness	-.466	.122	-.333	.000
Vis 14 (very high visibility –low visibility)	1.139	.322	.465	.001
Vis 24 (high visibility-low visibility)	.724	.313	.299	.023
Vis 34 (moderate visibility-low visibility)	.210	.392	.058	.593
Variance explained: .28				
F: 10.33 by 4 and 103 df				

Discussion

In this study, aesthetic perceptions of patients after surgical treatment for BCC were analysed. Results demonstrated that over time, facial aesthetics improved irrespective whether MMS or SE had been performed. In addition, at six months after treatment there was no statistically significant difference in perceptions between patients with a primary or a recurrent BCC. Furthermore, regression analysis results showed that the extent to which the facial aesthetics for patients with a primary BCC had improved could largely be predicted by subjective baseline perceptions and the visibility of the tumour within the facial area.

Comparing our results with those of other studies is difficult. First, studies that compared a surgical and a non-surgical treatment for BCC have mostly used a single global aesthetic outcome. Patients rated their evaluation either on a scale varying from satisfied to not satisfied, in points ranging from 1 (very bad) to 10 (excellent) or in terms of good, fair or bad. We considered a single outcome insufficient to measure a patient's opinion about facial aesthetics, which is why we chose to use perceptions related to six specific

aesthetic items like the perceived size or the perceived conspicuousness of the facial site.

Second, studies on aesthetic outcomes often make solely use of post-treatment measurements without allowing for pre-operative perceptions and expectations. We measured baseline variables because we were interested in whether they could predict the evaluation of an aesthetic outcome after treatment. We found that a pre-operative perception of conspicuousness and the visibility of the afflicted site were important variables in predicting the evaluation of facial aesthetics after surgery.

Several issues have to be taken into consideration when looking at the results of our study. It may be possible that the number of patients as calculated by the power analysis was insufficient to detect an effect difference. The actual difference in aesthetic perceptions between MMS and SE was much smaller than originally anticipated, which means that in future studies a larger number of patients will be necessary. However, the practical relevance of detecting such small differences is questionable. Another limitation of our study is that we used newly developed items and scales, although they all were carefully constructed in collaboration with dermatologists and patients.

In summary, dermatologists or other professionals involved in the treatment process of BCC have to be aware that, if patients have a tumour on a very highly or highly visible facial site, they generally will perceive the result of surgery as less beautiful. In addition, the extent to which patients believe that their facial aesthetics have improved after surgery can be predicted by pre-operative perceptions, independent of undergoing MMS or SE. Although these perceptions are subjective, they ultimately will influence satisfaction of patients with the treatment outcome. As such, it is preferable that, next to a more technical judgement by the physician, aesthetic patient evaluations are included in the assessment of the final surgical result.

In order to determine which patients will be likely to evaluate the aesthetic result as less beautiful, it is recommended to administer pre-operatively a short questionnaire in which items related to the perception of the size or the conspicuousness of the tumour are included. In doing so, the operating physicians will be more familiar with the individual problems some patients might have about their facial aesthetics. It will enable them to provide those patients with extra information about the consequences of skin cancer and its treatment. Ultimately, it may help physicians in deciding whether certain patients will benefit from additional cosmetic procedures after surgery.

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chapter 5

Assessing the public's choice for surgical treatment of Basal Cell Carcinoma: Results of a discrete choice experiment in the South of the Netherlands

In review

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Abstract

Background. Basal Cell Carcinoma (BCC) is a slowly growing non-melanoma type of skin cancer, which often is localized within the facial area. Surgical Excision (SE) and Mohs Micrographic Surgery (MMS) are the most well-known surgical procedures to treat BCC. The effectiveness, i.e. recurrence rate, and costs of MMS versus SE for primary and recurrent BCC have previously been compared in a cost-effectiveness study. Results showed that, from a health care perspective, it was not cost-effective to implement MMS on a large scale for primary BCC. This conclusion was based on the estimated incremental cost-effectiveness ratio in which solely the recurrence rate was incorporated as the primary clinical outcome measure. Still, it is possible that other factors related to treatment also play an important role in individuals' preferences for either MMS or SE.

Objectives. To examine which attributes of a surgical treatment for primary BCC are valued as important, and to determine the incremental willingness to pay for MMS versus SE.

Methods. Attributes and their levels were determined, based on the results of a cost-effectiveness study, a review and a focus group of patients. The discrete choice experiment was conducted among members of the general public by means of a telephone interview.

Results. Results showed that members of the general public were likely to prefer a surgical treatment with lower recurrence percentage, lower surgery time, lower travelling time, lower waiting time, no risk for a re-excision and lower costs, indicating that both outcome –and process variables were considered as being important. The incremental willingness to pay for MMS amounted to 848 euro. This means that, based on the attributes included in the experiment, MMS is preferred above SE.

Conclusions. Results from this DCE indicate that, when both outcome and process attributes are considered from a societal perspective, MMS is preferred to SE for primary BCC. Caution should be taken in that results cannot directly be generalized to patients and other contexts or settings.

Introduction

Basal Cell Carcinoma (BCC) is a slowly growing non-melanoma type of skin cancer, which often is localized within the facial area. Various therapies are available to treat a BCC among which Surgical Excision (SE) and Mohs Micrographic Surgery (MMS) are perhaps the most well-known surgical procedures. The effectiveness, i.e. recurrence rate, and costs of SE and MMS for both primary and recurrent BCC have been compared in a cost-effectiveness study.[1] Results showed that, from a health care perspective, it did not seem cost-effective to implement MMS on a large scale. This conclusion was based on the estimated incremental cost-effectiveness ratio in which solely the recurrence rate was incorporated as the primary clinical outcome measure. Although prevention of a recurrence is obviously the ultimate aim of a treatment, it is nevertheless possible that factors related to the process of treatment also play an important role in individual's preferences for either one of the surgical procedures. In this study, a discrete-choice experiment was designed to examine which attributes of a surgical treatment for primary BCC are valued as important. In addition, based on the attributes included in the experiment, the willingness to pay for MMS versus SE was determined.

Material and methods

Identifying attributes and levels

The first phase in conducting a discrete-choice experiment consists of identifying the relevant attributes and their levels. Since the expectation was that individuals might derive benefit from not only the outcome of treatment, i.e. the recurrence rate, but also from attributes related to the process of care, the decision was made to include both 'outcome' and 'process' attributes related to the surgical procedure. As presented in table 1, three attributes and their levels were derived from a review, a cost-effectiveness study, and a randomised clinical trial.[1-3] Two other attributes, 'waiting time till results surgery' and 'travel time' did not emerge from the sources mentioned above but were included because these factors differed between the surgical procedures. The attribute 'waiting time' was described as the length of time an individual has to wait for the results of the surgery. MMS is a specialised technique in which the tumour is removed in successive stages until the complete area is tumour free. Consequently, there is no waiting time. For

SE, the tumour tissue is histopathologically examined afterwards which means that patients have to wait for the results, varying from one to two weeks. In the Netherlands, SE is performed in almost every hospital while MMS is carried out in a selected number of clinics. As a result, travel time for a single trip to the hospital can vary from 15 minutes to a maximum of 1 hour. The sixth and final attribute 'cost' was defined as 'the price one has to pay for surgery'. Patients of the focus group were asked to value the aforementioned selected attributes on a 5-point Likert scale, varying from 1 'very important' to 5 'not important', and to determine the levels of the cost-attribute. In addition, they were asked if significant treatment related attributes were missing. Results (not shown) demonstrated that patients considered all attributes to be important aspects of a surgical treatment for BCC while no extra attributes were mentioned. It turned out that the levels of the cost-attribute as provided by the patients extended the actual costs of surgery as previously calculated within the cost-effectiveness study.[1]

Table 1 Treatment attributes, definitions and levels

Attribute	Definition	Levels
DIFREC	The possibility that a tumour recurs at the same site after initially successfully been removed (%)	1[3],2 [2],3 [2],5% [3]
DIFSURGTIME	Time between start and end of surgery	44, 52, 145, 165 minutes[1]
DIFTRAVTIME	Time it takes to travel a single trip from home till arrival in hospital	15, 30, 60 minutes
DIFWAITTIME	The length of time one has to wait before results of surgery are available	0, 1, 2 weeks
DIFRE-EXCISION	The possibility of having a second excision if results of the first excision show that the tumour is not completely removed	Nobody (0%), 1 in 5 patients (20%)[2]
DIFCOSTS	Price one has to pay for surgery	0, 200, 500, 1000, 1500 euro

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Experimental design

The attributes and their corresponding levels gave rise to 1440 possible scenarios. The SPSS software Orthoplan was used to reduce this number to a total of 32 scenarios. Orthoplan produces a fractional factorial orthogonal main effects design which assumes no interactions between attributes. The

32 scenarios were randomly divided into 16 pair-wise choices. To avoid respondent's boredom or tiredness, the decision was made to use a split-sample design and thus create two questionnaires, each containing eight pair-wise choices (an example of a choice set is presented in Table 2).
To avoid a preference towards a specific procedure irrespective of the levels, the hypothetical scenarios were not labelled (i.e. described as either Surgical Excision or Mohs Micrographic Surgery), but were described as 'treatment A' or 'treatment B'.

Table 2 Example of a choice set

Treatment characteristics	**Treatment A**	**Treatment B**
Probability of recurrence	2 in 100 (2%)	3 in 100 (3%)
Surgical procedure time	145 minutes	44 minutes
Travel time to hospital	15 minutes	30 minutes
Waiting time till results of surgery	1 week	No waiting time
Probability of having re-excision	No-one (0%)	1 in 5 (20%)
Costs of surgery	500 euro	200 euro

Which treatment do you prefer? A ❑ B ❑

I have no preference for either of the treatments ❑

Development of the questionnaires

Both questionnaires consisted of five parts, of which only part three differed. In the first part, respondents were provided with information regarding BCC and its consequences. In addition, the objectives of the study were explained. Part two of the questionnaire gave a description of the attributes and their levels. In part three, a total of nine choice sets (including an extra choice set to explore internal consistency of the preferences by means of a test-retest) were presented. Respondents were asked to indicate their preference for either 'treatment A' or 'treatment B', or to select the no-preference option. Part 4 contained questions regarding the feasibility of the questionnaire. In part 5 respondents were asked to provide some socio-demographic information. Furthermore, they were asked if they or one of their relatives ever had been diagnosed with skin cancer and which treatment they subsequently had received. Finally, they were also asked about their perception of susceptibility for BCC. A copy of the questionnaires (in Dutch) is available on request.

Data collection

Since we did not find clear guidelines or technical justifications for the calculation of the necessary number of respondents the decision was made that, in line with the numbers mentioned in the literature for previous DCEs, a total of 300 respondents was assumed to be sufficient for a meaningful analysis.[4-5]
Data were collected between April and July 2006 by means of telephone interviews. First, a letter explaining the purpose of the study was sent to a random sample of 820 residents (18 years and older) of the region Maastricht and Heuvelland. Following the letter, the residents were called and asked whether they were willing to participate in the study. If they gave informed consent, an appointment for the telephone interview was set. The questionnaire was sent to the participants with the instruction to read it carefully and fill in the choices before the interview took place.

Data-analysis

Data were analysed using the random effects ordered probit model in Limdep version 8.
Assuming a linear additive utility function, the main effect model to estimate the difference in utility between treatment A and treatment B was:
$\Delta U = \alpha_1$ DIFREC + α_2 DIFSURGTIME + α_3 DIFTRAVELTIME + α_4 DIFWAIT + α_5 DIFRE_EXCISION + α_6 DIFCOST + $\varepsilon + \mu$
Δ U is the change in utility when moving from treatment A to treatment B. DIFREC is the difference in probability of recurrence, DIFSURGTIME is the difference in duration of the surgical procedure, DIFTRAVELTIME is the difference in travel time, DIFWAIT is the difference in length of time one has to wait before results are available, DIFRE-EXCISION is the difference in probability of having a re-excision and DIFCOST is the difference in price of surgery, ε is the unobservable error term due to differences among observations while μ is the unobservable error term due to differences among respondents, α_1- α_6 are the parameters of the model to be estimated. Given that two indirect utility functions are compared and a linear additive model is assumed, terms common to both utility functions, like individual income (Y) and personal characteristics will drop out of the measurable part of the part of the utility function.

The ratio of any pair of parameter values shows the marginal rate of substitution between the attributes, while the ratio between α_j / α_6 (j=1,2,3,4,5) is the estimated willingness to pay for a certain attribute. The theoretical validity of the model was investigated by examining the sign of the estimated coefficients and their significance. The a-priori expectations were that lower levels of the probability of tumour-recurrence, duration of surgery, waiting time till results surgery, travel time, probability of having a re-excision and costs were preferred to higher levels for these attributes and thus a negative sign was expected. In addition, interaction terms were created between income* cost, education*cost and susceptibility*cost. The a-priori expectation for the interaction between income and cost was that respondents with an higher income would be willing to pay more for a surgical treatment. For the other two interaction terms, no a-priori expectations were made. Descriptive statistics were calculated for socio-demographic variables.

Results

Response

In total 820 information letters were sent to residents of the region Maastricht and Heuvelland. Initially, 395 individuals (48 percent) agreed to participate in the study while 312 were actually interviewed by telephone. This ultimately gave a response rate of 38 percent. The population characteristics are shown in Table 3.

Table 3 Characteristics of the study population

	N= 312
Age (range)	44 (24-79)
Male/female	49%/ 51%
Net household income	2695 (n=250)
Experience with skin cancer	3.8%
Perception of susceptibility for BCC	29%
Education (%)	
- lower	8%
- medium	33%
- higher	59%

Model results

Table 4 presents the results of the full sample main effects ordered probit model. The model appears to fit the data very well since 78 percent of the observations are correctly predicted. The estimated coefficients all have the anticipated negative sign and are statistically significant, providing evidence for the theoretical validity of the model and indicating that both outcome – and process attributes are considered as being important. Results indicate that respondents were likely to prefer a surgical treatment with lower probability of recurrence , lower surgery time, lower travelling time, lower waiting time, no risk for a re-excision and lower costs. The interaction model showed that people who think they are susceptible for developing BCC are willing to pay more for a surgical treatment (p-value 0.0017). No other interactions were found to be significant.

Table 4 Results of the main random effects ordered probit model

Variable	Coefficient	P-value
DIFREC	-.35776414	.0000
DIFSURGTIME	-.00490469	.0000
DIFTRAVTIME	-.00548437	.0000
DIFWAITTIME	-.12302631	.0000
DIFRE-EXCISION	-.04581133	.0000
DIFCOSTS	-.00077374	.0000

Willingness to pay

Table 5 shows the marginal willingness to pay for one unit improvement in the level of the attribute and the resulting overall willingness to pay of MMS versus SE. For example, respondents are willing to pay 462 euro for a surgical treatment with 1 percent less recurrence percentage and 159 euro for a reduction of a week in waiting time for results. When all the willingness to pay values for the statistically significant attributes are added up, the incremental willingness to pay for MMS amounts to € 847.67. This means that, based on the attributes included in the discrete choice experiment, MMS is preferred to SE.

Table 5 Incremental WTP-values for MMS vs SE

	marginal WTP per unit change	MMS vs SE	MMS	SE
DIFREC	€ 462.40	+ € 462.40	1%	2%
DIFSURGTIME	€ 6.33	- € 639.33	145	44
DIFTRAVTIME	€ 7.08	- € 318.60	60	15
DIFWAITTIME	€ 159	+ € 159.00	-	1
DIFRE-EXCISION	€ 59.21	+ € 1,184.20	-	20%
Incremental WTP	NA	€ 847.67		

Discussion

This study was designed to examine from a societal perspective which attributes of a surgical treatment for BCC are valued as important. In addition, based on attributes included in the experiment, the willingness to pay for MMS versus SE was determined. Results showed that respondents value both outcome and process attributes as important, since the estimated coefficients all had the anticipated negative sign and were statistically significant. These findings not only confirm the importance of using a clinical outcome parameter like probability of recurrence but also show that individuals might derive benefit from other more process related attributes like the chance of having a re-excision, travel-or surgical time. The interaction between susceptibility and the cost attribute turned out to be statistically significant, indicating that respondents who think they are susceptible for developing BCC, are willing to pay more for a surgical treatment.

Based on the willingness to pay results, MMS is preferred to SE for the surgical treatment of primary BCC, as members of the general public are prepared to pay an amount of €848. Comparing the willingness to pay values as obtained in our study with values derived from other studies within the same disease setting is difficult. To our knowledge, there has been one study performed by Weston and Fitzgerald which determined the willingness to pay for methyl aminole-vulinate photodynamic therapy (MAL-PDT) versus simple excision surgery (SE) for BCC among a group of 60 volunteers from the general public.[6] This DCE comprised the following attributes: risk of scarring, possibility of infection, treatment description but also costs and lesion response rate. The primary driver of the total willingness to pay of 940 australian dollars(= €588) for MAL photo-dynamic therapy was the risk

of scarring. However, as described by the authors, a limitation of this study was that long-term (longer than three months) recurrence rate data were not available. For our DCE, scarring as an attribute was not relevant since the comparison concerned two surgical procedures of which results on cosmetic aspects and aesthetic perceptions showed no difference.[2,7]

Results of a previous study on the cost-effectiveness of MMS versus SE showed that the ICER or the incremental costs to avoid one recurrence was € 29231, which is a large sum of money when compared to the actual costs of treating a recurrence.[1] These results led to the conclusion that, from a health care or hospital perspective, it would not be cost-effective to implement MMS on a large scale. However, it was also suggested that willingness to pay might be a method to gain more insight into the cost-effectiveness of MMS from a patient or societal perspective. The results from this DCE showed that members from the community are willing to pay €462 for a 1 percent reduction in recurrence rate. This indicates that they would be willing to pay €46200.- for a reduction of one recurrence. Putting these results in a cost-benefit perspective suggests that MMS is a cost-effective technique, as the incremental benefits (i.e. WTP for a reduction of one recurrence) exceed the financial investment of €29231.- to avoid a recurrence, as calculated within the cost-effectiveness study.[1]

When all the attributes of this discrete choice experiment are taken into account, the incremental willingness to pay of MMS compared to SE adds up to €848. If we again compare this amount with the incremental treatment costs of MMS versus SE of €254, as previously calculated within the cost-effectiveness study[1], one could argue that it might be cost-effective to implement MMS on a large scale since the incremental benefits (i.e. WTP) of MMS compared to SE exceed the incremental costs. However, these calculations are only for illustrative purposes, as costs within the cost-effectiveness study were determined from a health care perspective and willingness to pay in this DCE was determined from a societal perspective. In addition, the willingness to pay values in real life might be different from those deducted from a discrete choice experiment. In this respect, it is noteworthy that respondents are also prepared to pay a substantial amount of money of 159 euro for a reduction of one week in the waiting time period.

This study focused on eliciting preferences from members of the general public in the South of the Netherlands. Within health economics, it is generally recommended to use the societal perspective since it includes all costs and health outcomes resulting from an intervention, regardless of who pay

the costs or who benefits.[8] Nevertheless, it is possible that a DCE which involves patients with primary BCC would yield different results due to for example the influence of experience with the disease and/or treatment. However, the question of whose preferences should count within the context of a publicly provided health care system is still a topic for an ongoing discussion.[9-12]

The selection of the attributes included in our experiment was carefully done, based on the results of a cost-effectiveness study[1], a clinical trial[2], a review[3] and a focus group of patients who had received surgical treatment for BCC. Nevertheless, it is possible that in other countries, different treatment factors than the ones included in our DCE are considered to be important, which is why generalizing our findings should be done with caution. Still, this study has shown that the DCE can be a very useful method to assess community preferences for a surgical treatment to remove BCC. At this moment, cost-benefit analysis is not used as the sole basis for health care decision making, whereas the value of cost-effectiveness analysis is widely acknowledged. However, results from this DCE suggest that when both outcome and process attributes are considered from a societal point of view, MMS is preferred to SE. This information may be relevant in the context of health care decision making from a cost-benefit perspective.

From the context of clinical decision making, results of this study confirm the importance of recurrence as a clinical outcome parameter. In addition, our findings demonstrate that process attributes play a role in the public's preferences. This information could potentially also be helpful for both dermatologists and patients, when making an informed decision regarding surgical treatment options for BCC. In particular, if differences between treatments are expected to go beyond the clinical outcome, it might be useful to discuss process related treatment aspects in order to examine whether these factors could yield an additional level of benefit for patients.

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chapter 6

Does 'having to pay for it' change preferences for the surgical treatment of primary Basal Cell Carcinoma? A comparison of two discrete choice experiments

Submitted
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Abstract

Objectives. To assess the impact of a cost attribute on preferences for a surgical treatment, in particular Surgical Excision (SE) and Mohs Micrographic Surgery (MMS), to remove primary Basal Cell Carcinoma (BCC).

Methods. Six attributes (recurrence, re-excision, travel time, surgical time, waiting time surgical results, costs) and their levels were selected, based on results of a clinical trial, a cost-effectiveness study, a review and a focus group of patients who recently had received treatment for BCC. Two DCEs, one without (DCE_nocost) and one with a cost attribute (DCE_cost) were conducted among the general public. Outcomes of both DCEs were compared in terms of theoretical validity, relative importance of the attributes and the rank order of preferences.

Results. Except for travel time in DCE_nocost, respondents in both DCEs valued a surgical treatment with a lower level for all the selected attributes. Differences in ordering of attribute importance occurred with the attribute waiting time for surgical results which was third in DCE_nocost and ended as last in DCE_cost. The incremental utility score for DCE_nocost was 1.497 while the incremental willingness to pay for DCE_cost amounted to €848 in DCE_cost, both indicating a preference of MMS to SE.

Conclusion and discussion. From a policy perspective, results show that the inclusion of a cost-variable does not change the rank order of preferences for a surgical treatment to remove BCC. However, the results of our comparison are specific to the clinical setting of primary BCC and the surgical procedures MMS and SE. Further research within different settings will be needed to confirm our findings.

Introduction

For recent years, the discrete choice experiment (DCE) has gained popularity within the field of health care as a method to elicit preferences for health care interventions.

The DCE is a stated preference technique, which is characterised by presenting individuals with a number of choices, each consisting of two or more hypothetical alternatives. The individuals' preferences are measured by asking which alternative they prefer or choose. The technique is based on random utility theory(RUT) which assumes that an individual acts rationally and always chooses the alternative with the highest level of utility, i.e. the individual is a utility maximizer. The approach makes it possible to identify the relative importance of attributes included in an experiment and to determine the overall utility for a particular treatment or clinical service. If a cost-attribute is incorporated, the possibilities of a DCE are enhanced since willingness to pay can be estimated indirectly, and results can be placed within the framework of cost-benefit analysis. Nowadays, an increasing number of discrete choice experiments incorporate cost as an attribute[1-5] However, the inclusion of a cost-attribute, particularly within collectively funded health care systems, can be problematic due to the fact that respondents are not used to pay for a service or a good at the point of consumption. So far, only one study by Brian et al.[6] has examined the impact of a cost-attribute on individuals' preferences by comparing two DCEs, one including and one excluding the cost-attribute. Results showed that in both DCEs respondents valued the same attributes regarding the diagnosis and treatment of severe knee injuries as important. However, the cost-attribute was not statistically significant, indicating that this variable did not play an important role in the respondents' preferences. Several shortcomings in the study design like dissimilarity of the two study groups and an insufficiently large sample size were mentioned as possible explanations for the non-significance of the cost-variable. The current paper reports the results of a randomized study in which the impact of a cost attribute on preferences for a surgical treatment to remove Basal Cell Carcinoma was assessed. This was done by comparing the outcomes of two DCEs, one without and one with a cost attribute, in terms of theoretical validity, relative importance of the attributes and the rank order of preferences. In addition, feasibility and reliability were also examined.

Although the designs of the two DCEs are different with respect to the inclusion of the cost attribute, both are rooted in the same theoretical framework, that is Random Utility theory. Consequently, our a priori expectation was that the DCEs would result in the same rank order of preferences.

Clinical setting

The clinical setting of our study is the surgical treatment, in particular Surgical Excision (SE) and Mohs Micrographic Surgery (MMS), for primary Basal Cell Carcinoma (BCC). BCC is a non-melanoma form of skin cancer, which is not life-threatening and rarely metastasizes. The incidence of BCC is increasing worldwide with an estimated number of 26,000 primary cases in 2015 compared to 15,000 cases in 2000 in the Netherlands.[7]
MMS is a specialised surgical technique in which the tumour is removed layer by layer. During the first Mohs stage, a bowl-shaped specimen is obtained and processed into horizontal frozen sections. The sections are histopathologically examined, and if tumour cells are found, a second Mohs stage takes place. The procedure will be repeated until the complete area is tumour free. Consequently, there is no waiting time for surgical results. SE is a technique in which the obtained specimen is histopathologically examined afterwards, which means that waiting time for surgical results can vary from one to two weeks. If positive margins are found, a re-excision will be performed. The costs and effectiveness of MMS versus SE have previously been studied in a cost-effectiveness study.[8] Results showed that for primary BCC, the recurrence rate after MMS was lower than after SE although this was not a statistically significant difference. In addition, the total costs of MMS were higher, caused for a large part by longer surgery time. In the Netherlands, SE is performed in almost every hospital whereas MMS is carried out in a selected number of clinics. As a result, travel time for patients can vary from 15 minutes to 1 hour for a single trip from home to the hospital.

Methods

For this study, two discrete choice experiments were performed that were similar in all aspects, except for the cost attribute. The experiment excluding a cost attribute is further referred to as DCE_nocost whereas the experiment including a cost attribute is referred to as DCE_cost.

Establishing attributes and levels

Six attributes and their levels were selected, based on the results of a randomised clinical trial, a cost-effectiveness study, a review and a focus group of patients who recently had received treatment for BCC (Table 1).[8-10] The 'probability of tumour recurrence' was described as the possibility that a tumour recurs at the same site after it has initially successfully been removed. The attribute 'duration of the surgical procedure' was defined as the time between the start and the end of the surgical procedure. The 'probability of having a re-excision' was explained as the possibility that a second excision was necessary if results of the first surgical procedure showed that the tumour was not completely removed. The attribute 'waiting time' was described as the length of time an individual has to wait for the results of the surgery. Travel time was specified as the time it takes to travel a single trip from home till arrival in the hospital. The sixth and final attribute 'cost' was defined as 'the price one has to pay for surgery'. Patients of the focus group were asked to value the selected attributes on a 5-point Likert scale, varying from 1 'very important' to 5 'not important at all', and to determine the levels of the cost-attribute. In addition, they were asked whether important treatment or process related attributes were missing. Results demonstrated (not shown) that all patients considered the attributes to be important aspects of a surgical treatment for BCC and no extra attributes were mentioned. It turned out that the levels of the cost attribute as provided by the patients extended the actual costs of surgery as calculated within the cost-effectiveness study.[8]

Table 1 **Attributes and levels of a surgical treatment for primary BCC**

Attribute	Levels
Probability recurrence skin cancer	1 %,2 %, 3 %, 5 %
Duration of surgery (minutes)	44, 52, 145, 165 min
Probability of having a re-excision	0 20% (1 in 5 patients)
Waiting time (weeks)	0,1 week, 2 weeks
Travel time to hospital (minutes)	15, 30, 60 min
Costs of surgery	0 200 euro 500 euro 1,000 euro 1,500 euro

Experimental Design

For DCE_nocost, the five attributes and their levels led to a number of 288 possible scenarios while for DCE_cost, the six attributes and the levels gave rise to 1,440 possible scenarios. The SPSS software Orthoplan (SPSS version 11.0) was used to reduce these numbers to a total of 32 scenarios for both DCE_nocost and DCE_cost. Orthoplan produces a fractional factorial orthogonal main effects design that assumes no interactions between attributes. The 32 scenarios were randomly divided into 16 pair-wise choices for both DCEs. The number of pair-wise choices was kept equal in both experiments to avoid that differences in outcomes could be the result of different numbers of choices. To prevent fatigue or boredom, the decision was made to use a split sample design and thus to create four questionnaires (two for DCE_nocost and two for DCE_cost, each containing eight choice sets)
The hypothetical scenarios were not labelled (i.e. described as either Surgical Excision or Mohs Micrographic Surgery) but were described as 'treatment A' or 'treatment B' in order to avoid a preference towards a specific surgical procedure, irrespective of the levels of the attributes.

Developing the questionnaire

The questionnaire consisted of five parts. In the first part, respondents were provided with information regarding BCC and its consequences. In addition, the objectives of the study were explained. Part two of the questionnaire gave an explanation of the attributes and their levels. In part three, a total of nine choice sets (including an extra choice set to test internal consistency of the questionnaire) were presented and respondents were asked to indicate their preference for either treatment A or B, or to select the no-preference option. Part four contained the following three feasibility questions: 'How clear did you find the information as provided in this questionnaire?', 'How difficult did you find the questions that were asked in this questionnaire?' and 'What is your opinion about the number of questions?'. Responses to each question could be given on a 5-point Likertscale, with for example "1" indicating 'very clear' to "5" 'very unclear'. In part five respondents were asked to provide some socio-demographic information. Furthermore, they were asked if they or one of their relatives ever had been diagnosed with skin cancer, and which treatment they subsequently had received. Finally, a question was asked about their perception of susceptibility for BCC. Copies of the questionnaires (in Dutch) are available on request.

Data collection

The sample size was based on the numbers of respondents mentioned in the literature for previous DCEs that used a split sample design.[11-13] A total of 600 respondents (300 for DCE_ nocost and 300 for DCE_cost) was assumed to be sufficient for a meaningful analysis.
Data were collected between April 2006 and July 2006 by means of telephone interviews. First, a letter explaining the purpose of the study was sent to a random sample of 1,640 residents (18 years and older) of the region Maastricht and Heuvelland. Following the letter, the residents were called and asked whether they were willing to participate in the study. If they gave informed consent, an appointment for the telephone interview was set. Participants were randomly allocated to either DCE_nocost or DCE_cost. The questionnaire was sent to the participants with the instruction to read it carefully and fill in the choices before the telephone interview took place.

Data analysis

Data were analysed using a random effects ordered probit model (Limdep version 8.0).[14]
Assuming a linear additive utility function, the main effects model to estimate the difference in utility between treatment A and treatment B was:
$\Delta U = \alpha_1$ DIFREC + α_2 DIFSURGTIME + α_3 DIFTRAVELTIME + α_4 DIFWAIT + α_5 DIFRE_EXCISION + [α_6 DIFCOST] + ε + μ
Δ U is the change in utility when moving from surgical treatment A to surgical treatment B. DIFREC is the difference in probability of recurrence, DIFSURGTIME is the difference in duration of the surgical procedure, DIFTRAVELTIME is the difference in travel time, DIFWAIT is the difference in waiting time before results of the surgical procedure are known, DIFRE-EXCISION is the difference in probability of having a re-excision and DIFCOST is the difference in price of surgery (obviously this variable was not included in the model for DCE_nocost), ε is the unobservable error term due to differences among observations while μ is the unobservable error term due to differences among respondents, α_{1-} α_6 are the parameters of the model to be estimated. Given that two indirect utility functions are compared and a linear additive model is assumed, terms common to both utility functions such as individual income (Y) and personal characteristics will drop out of the measurable part of the part of the utility function.

Feasibility

Feasibility of both experiments was compared on the basis of the characteristics of respondents and the responses to the feasibility questions. Descriptive statistics were calculated for socio-demographic variables. To test for significant differences between respondents of the two studies, either a chi-square test (or fisher-exact test) was used for group variables or a Mann-Whitney-test for continuous variables. The expectation was that characteristics of the respondents and the answers to the feasibility questions between DCE_nocost and DCE_cost would not be statistically significantly different.

Reliability

Reliability was examined by including the same choice set twice. This meant that for each questionnaire, the third choice set was repeated as the ninth (final) choice set. The linear weighted kappa was calculated to measure agreement between the test and the retest.
The assumption was that the kappa values of DCE_nocost and DCE_cost would be comparable.

Theoretical validity

The theoretical validity of the models, i.e. the extent to which results are consistent with a priori expectations was investigated by examining the signs of the estimated coefficients and their significance. Given that lower levels of probability of recurrence, duration of surgery, waiting time, travel time, probability of having a re-excision and costs are preferred, we would expect these attributes to have a negative sign in the regression equations of both DCE_nocost and DCE_cost.

Relative importance of the attributes

Part-worth utilities were calculated by multiplying the coefficient of each attribute in the model with the range used for the attribute levels. Based on the part-worth utilities, the relative importance was determined for each attribute in both DCEs.[15] This was done by dividing the part-worth utility of each attribute by the sum of the part-worth utilities of all the attributes included in the experiment.
The expectation was that the order of relative importance of the attributes, except for the cost-attribute, would be the same for DCE_nocost and DCE_cost.

Rank order of preferences

Based on the results from DCE_nocost, the incremental utility score for MMS versus SE was calculated by multiplying the coefficient of each attribute with the range of the levels. The incremental willingness to pay for MMS versus SE was estimated by adding up the marginal willingness to pay values of all attributes included in DCE_cost. These values were calculated by dividing the coefficient of each attribute by the coefficient of the cost-attribute. The expectation was that respondents in both groups would show the same rank order of preference.

Results

Response

In total 1,640 information letters were sent to residents of the region Maastricht and Heuvelland. Initially, 1,034 individuals (63 percent) agreed to participate in the study while ultimately 615 respondents, 303 for DCE_nocost and 312 for DCE_cost were interviewed by telephone. This gave an overall response rate of 38 percent.

Feasibility

Respondents' characteristics
As shown in table 2, there were no significant differences in characteristics between respondents of DCE_nocost and DCE_cost.

Table 2 Characteristics of the population

	DCE_nocost N=302	DCE_cost N= 312	P-value
Age (range)	43 (21-88)	44 (24-79)	.577*
Male/female	53%/ 47%	49% /51%	.260#
Net total household income (euro)	2,685 (n=221)	2,695 (n=250)	.929*
Experience with skin cancer	3.6% (n= 11)	3.8% (n= 12)	.935+
Perception of susceptibility for BCC	30% (n=90)	29% (n=89)	.814+
Education)			.705+
- lower	10% (n=30)	8% (n=25)	
- medium	32% (n=96)	33% (n=102)	
- higher	58% (n=176)	59% (n=185)	

** Mann-Whitney test, + Chi-square test, # Fisher's Exact Test*

Feasibility questions

Table 3 presents the results of the feasibility questions. Respondents in both experiments did not differ significantly with regard to the perceived level of difficulty and their opinion about the number of questions. With respect to the clarity of the provided information, significantly more respondents in DCE_nocost answered that the information was not clear to them.

Table 3 Results of the feasibility questions

		Very clear	Clear	Neutral	Unclear	Very unclear	Total	p-value
1. How clear was the information provided in the questionnaire?	DCE _nocost*	65 (21%)	194 (64%)	23 (8%)	17 (6%)	3 (1%)	302	
	DCE _cost*	74 (24%)	210 (67%)	25 (8%)	3 (1%)	0 (0%)	312	.007
		Very Easy	Easy	Neutral	Difficult	Very difficult		
2.Did you find the questions easy or difficult to answer?	DCE_nocost	31 (11%)	144 (48%)	98 (32%)	22 (7%)	7 (2%)	302	
	DCE_cost	19 (6%)	146 (47%)	119 (38%)	26 (8%)	2 (1%)	312	.096

** statistically significant: P-value <0.05*

Table 3 Results of the feasibility questions (continued)

		Very many	Many	Neutral	Few	Very few	Total	p-value
3.What is your opinion about the number of questions?	DCE_nocost	1 (0%)	14 (5%)	211 (70%)	64 (21%)	12 (4%)	302	
	DCE_cost	0 (0%)	18 (6%)	226 (72%)	65 (21%)	3 (1%)	312	.123

Reliability

The linear weighted kappa demonstrated that the level of agreement for DCE_nocost was 0.68 (95% CI 0.52-0.84) and for DCE_cost 0.59 (95% CI 0.48-0.69). The kappa values are considered to be comparable since they lie within the range of each other's confidence interval.

Theoretical Validity

Table 4 reports the results of the random effects ordered probit models for DCE_nocost and DCE_cost. The estimated coefficients of the attributes, except for travel time in DCE_nocost, all have the anticipated negative sign and are highly significant. This indicates that respondents in DCE_nocost prefer a surgical treatment with a lower probability of recurrence, lower surgery time, lower waiting time, no risk for a re-excision and lower costs. Respondents in DCE_cost show the same preference but in addition to a lower level of recurrence, surgery time, waiting time, chance of re-excision and costs also prefer less travel time.

Table 4 Results of the main random effects ordered probit models

Variable	Coefficient	P-value
DCE_nocost		
DIFREC	-.36401437	.0000
DIFSURGTIME	-.00154723	.0001
DIFTRAVTIME	-.00031653	.8712
DIFWAITTIME	-.17433265	.0000
DIFRE-EXCISION	-.05576307	.0000
DCE_cost		
DIFREC	-.35776414	.0000
DIFSURGTIME	-.00490469	.0000
DIFTRAVTIME	-.00548437	.0000
DIFWAITTIME	-.12302631	.0000
DIFRE-EXCISION	-.04581133	.0000
DIFCOSTS	-.00077374	.0000

Relative attribute importance

Table 5 presents the relative attribute importance for both models. Respondents in DCE_nocost valued the probability of having a recurrence as most important when considering their preference for a surgical treatment, followed by the chance of a re-excision, waiting time for surgical results and the duration of surgery. In DCE_cost, the probability of having a recurrence is also valued as the most important attribute, followed by the cost of surgery, the chance of a re-excision, duration of surgical time, travel time and waiting time for results of the surgery. So, the order of relative importance between both experiments differs for the attribute "waiting time for surgical results".

Table 5 Relative attribute importance

Variable	**DCE_nocost**	**DCE_cost**
DIFREC	0.468608 (1)	0.311496 (1)
DIFSURGTIME	0.060251 (4)	0.129177 (4)
DIFTRAVTIME	*	0.053719 (5)
DIFWAITTIME	0.112211 (3)	0.053558 (6)
DIFRE-EXCISION	0.358930 (2)	0.199434 (3)
DIFCOSTS	-	0.252616 (2)

** the attribute "travel time" was not statistically significant in DCE_nocost*

Rank order of the preferences

As shown in table 6, the incremental utility score for DCE_nocost of 1.497 shows a preference for MMS to SE. This is supported by the results of DCE_cost, in which the incremental willingness to pay indicates that respondents also prefer MMS to SE.

Table 6 The incremental WTP and the incremental utility score

	MMS	SE	MMS vs SE DCE_nocost	MMS vs SE DCE_cost
Constant			+ 0.1032*	-
DIFREC	1%	2%	+ 0.3640	+ 462.40
DIFSURGTIME	145	44	- 0.1563	- 639.33
DIFTRAVTIME	60	15		- 318.60
DIFWAITTIME	0	1	+ 0.1743	+ 159.00
DIFRE-EXCISION	0	20%	+ 1.1153	+ 1,184.20
			+ 1.497	**€ 847.67**

** Limdep generated two threshold parameters: – 0.103 and 0.190. An incremental utility score in the area between these parameters indicates indifference; a score higher than 0.190 indicates a preference for MMS; a score lower than -0.103 indicates a preference for SE.*

Conclusions and discussion

This study was designed to examine whether the inclusion of a cost-attribute changes preferences for a surgical treatment to remove primary BCC. This was done by comparing the outcomes of two discrete choice experiments, one excluding (DCE_nocost) and one including a cost-attribute (DCE_cost), in terms of feasibility, reliability, theoretical validity, the relative importance of the attributes and the rank order of preferences. The strengths of our study are a randomized design and a sufficiently large sample size. Both aspects were reported as shortcomings in the study performed by Brian et al.[6]

First of all, the feasibility results show that the characteristics of the respondents between DCE_nocost and DCE_cost did not differ significantly. In addition, respondents in both experiments did not differ significantly with regard to the perceived level of difficulty and their opinion about the number of the questions. However, significantly more respondents in DCE_nocost answered that the provided information was not clear to them. It is difficult to explain this difference since both questionnaires gave the same informa-

tion, except for the additional information about the cost-attribute in DCE_cost. Second, results of the test-retest showed that the kappa values of DCE_nocost and DCE_cost were comparable as they fell within the range of each other's confidence interval. Third, the coefficients of the attributes, except for travel time in DCE_nocost, all had the expected negative sign and were highly significant, supporting the theoretical validity of both models. The non-significance of 'travel time' indicates that for respondents in DCE_nocost, this attribute does not play an important role in their preference for surgical treatment options. An explanation may be that the respondents in DCE_nocost do not care about the length of travel time to the hospital since it is the only investment they have to make before surgical treatment takes place. Respondents of DCE_cost, on the other hand, also need to think about the costs of surgery which is an additional investment they have to consider. As a consequence, they may want the other attributes to be as convenient as possible (a low probability of tumor recurrence, no waiting time for surgical results, a low duration of surgical time, no chance of a re-excision and less travel time). In contrast with the results of the study by Brian et al. the cost-attribute in our study was significant, indicating that this attribute does play an important role in respondents' preferences for a surgical treatment to remove BCC.[6] Fourth, the ordering based on the relative importance of the attributes suggest that respondents in both DCEs attach great importance to a low probability of having a recurrence. In fact, both the probability of a recurrence and the chance of a re-excision accounted for 83 percent in DCE_nocost, which means that the remaining attributes 'waiting time' and 'surgical procedure time' explained 17 percent. For DCE_cost, the probability of a recurrence and the chance of a re-excision together added up to 51 percent and when the cost-attribute (25%) was added, all three attributes accounted for 76 percent. The remaining attributes surgical procedure time, travel time, and waiting time accounted for 24 percent. Overall, this means that differences with respect to the significance and the order of relative importance between both models mainly occur with those attributes that relatively are the least important.

Fifth, the results of the rank order information show that 'having to pay for it' does not change the rank order of preferences since respondents in both DCEs preferred MMS to SE.

From a policy point of view, the results on the rank order information of the preferences indicate that either approach, i.e. a DCE with or without a cost-attribute, can be used as a method to elicit preferences. However, an advan-

tage of conducting a DCE including a cost attribute is that results can be placed within a cost-benefit framework, making it possible to estimate the net benefit of an intervention by converting all costs and benefits to monetary units. Still, there are many practical challenges related to the use of DCEs within cost-benefit analysis. McIntosh recommends a checklist for the development of DCE-derived Cost Benefit Analysis in healthcare.[16] Key areas to be considered are, for instance, the form and realism of the payment vehicle and the uncertainty surrounding the willingness to pay value. Other issues concerning the cost-attribute are for example the impact of the range and number of levels of a cost attribute or the ordering effects of a price-attribute.[13,17-19]

From an analytical perspective, some differences between the two studies were found. First, the attribute travel time in DCE_nocost was, in contrast with DCE_cost, not statistically significant. Second, the attribute 'waiting time for surgical results' was the third most important attribute in DCE_nocost although it ended as least important attribute in DCE_cost. It is questionable whether these differences are serious enough to conclude that either of the DCEs is not a suitable approach to derive preferences since the aforementioned attributes account for only a small percentage of the relative importance results. Still, the results of our study have shown that, from a societal perspective, the inclusion of a cost-variable or "having to pay for it" does not change the rank order of the preferences and as such provides valuable information about the willingness to pay for a certain treatment.

However, the results of our comparison are specific to the clinical setting of primary BCC and the surgical procedures MMS and SE. Moreover, the results of this comparative study show that in this population both approaches lead to the same direction of preferences. Whether these are actually true preferences can only be obtained by revealed preference information. So, further research within different settings will be needed to confirm our findings.

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chapter 7

Treatment of BCC by dermatologists in the Netherlands: results of a survey

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Abstract

Objectives. To gain insight in the state of affairs regarding the incidence of both primary and recurrent BCC, preferences for therapy and the use of a specialized surgical technique, that is Mohs micrographic surgery (MMS), a survey was sent to all dermatologists practising in the Netherlands.

Methods. A postal questionnaire consisting of a number of questions related to the incidence of primary and recurrent BCC, preferential treatment, and use of MMS.

*Results.*The response rate at individual level was 25%. An estimated number of 168 primary and 14 recurrent BCC were diagnosed per respondent in 2004. SE is considered to be the first preferential treatment for primary BCC. With respect to second (and third) line treatment, cryosurgery is selected for superficial and nodular BCC (at low-risk site) while radiotherapy is preferred for morphoic and nodular BCC at a high-risk site (facial area). For the recurrent BCC, SE is also preferred as first line treatment. Cryosurgery, radiotherapy and MMS are alternately mentioned as second or third treatment of choice. The percentage of dermatologists with a preference for MMS as first treatment increased if there was an unfavourable combination of factors like a tumour size larger than 2 cm with aggressive histologic subtype and a high risk site.

Conclusion and discussion. Overall, SE is considered to be the preferential treatment for both primary and recurrent BCC which corresponds with the Dutch guideline for treatment of patients with BCC. However, due to the low response rate, results cannot be generalized to the whole group of dermatologists practising in the Netherlands. Given the rising number of newly diagnosed BCCs in the near future, it is recommended to examine whether a national registration for BCC can be developed.

Introduction

Basal Cell Carcinoma (BCC) is one the most common types of skin cancer worldwide. Although it is rarely life-threatening, the tumour can cause functional and cosmetic adverse effects due to locally invasive and destructive growth.[1] In the Netherlands, approximately 26.000 primary BCC will be diagnosed in 2015 compared to 15.000 cases in 2000, indicating an increase of 78%.[2]

Of the many treatment modalities available for BCC, a distinction can be made between surgical and non-surgical therapies. Selection of a treatment can depend on several factors like the size of a tumour, the site, histologic subtype but also age and general condition of the patient. In 2003, the Dutch society for Dermatology and Venereology developed in collaboration with the Dutch Council for Public Health and Health Care, a guideline on the treatment of patients with BCC.[3] The primary aim was to provide an overview of all different treatment modalities based on the available strength of scientific evidence and thus facilitate the clinical decision making process for the dermatologist in practice. To gain insight in the state of affairs regarding the incidence of both primary and recurrent BCC, preferences for therapy and the use of a specialized surgical technique, that is Mohs micrographic surgery (MMS), a survey was sent to all dermatologists practising in the Netherlands. Results of this survey are reported here.

Methods

In April 2005, a total of 347 questionnaires was sent to the dermatologists. The questionnaire consisted of a number of questions related to the incidence of primary and recurrent BCC and the preference in treatment. For this purpose, a distinction was made between histologic subtype, the size and the site of the tumour which are the main prognostic factors related to the risk of a recurrence. Similar to the guideline "Treatment of patients with Basal Cell Carcinoma", location was classified into "low-risk" which meant that the tumour is located at the trunk (and/or extremities) and "high risk" referring to a tumour in the facial area. Furthermore, questions were asked about the use of MMS. This is a specialized surgical technique in which a tumour is removed layer by layer in successive surgical stages. During the first stage, a bowl shaped specimen is obtained and processed into horizon-

tal frozen sections. These sections are histo-pathologically examined and if tumour cells are found, a second stage takes place. The whole procedure will be repeated until the complete are is tumour free. For the analysis of the estimated incidence, a distinction was made between the group of respondents which answered that MMS was performed in their hospital and the group where MMS was not applied. For convenience, they are referred to as MMS and non-MMS group. Finally, a case was described of a patient presenting with a recurrent BCC. The dermatologist was asked to indicate his or her first line therapy to treat BCC. The survey was sent to all dermatologists practising in the Netherlands with the request to fill in and return the questionnaire as soon as possible. After three months, a reminder was sent to all the dermatologists who had not responded. Results of the questionnaire were analysed using SPSS version 11.5.

Results

Study population

In total 97 questionnaires were returned of which eleven were not filled in either because the dermatologist was no longer in practice, had a different area of clinical expertise or diagnosed too few patients with BCC. Ultimately, this led to a response rate of 25% (86/347). The 86 questionnaires were from 63 organisations of which 52 hospitals and 11 independent treatment centres. In the Netherlands, there are 94 hospital organisations which indicates that the response rate at organisational level was 55% (52/94).[4]
Seventy percent of the study population was male. The mean age was 48 years (sd 7,77) and the mean number of working years was 17,60 (range 2-36).

Incidence of the primary and recurrent BCC in 2004

In table 1, the incidence of the primary and the recurrent BCC in 2004 as estimated by the dermatologists is given. A total number of 21.628 primary BCC were diagnosed in the hospitals, which results in an average of 349 diagnosed primary BCC per hospital. Eighty percent of the study population diagnosed in total 11.468 primary BCC themselves, indicating an average of 168 primary BCC per dermatologist. For the MMS-group, the total number of diagnosed primary BCC is higher when compared with the non-MMS group (195 versus 163).

As for the recurrent BCC, fifty percent (n=43) of the study population estimated that in total 1.437 recurrent BCC were diagnosed, indicating an average of 33 recurrent carcinomas per hospital.
The dermatologists themselves diagnosed in total 820 recurrent BCC (an average of 14 recurrent BCC per dermatologist). Between the MMS-group and the non-MMS group, the mean number of diagnosed recurrent BCC does not differ much (15 versus 14).

Table 1 Incidence primary and recurrent BCC in 2004

Primary BCC	**Mean**	**Total (range)**
Hospital		
-no MMS (n=53)	350	18.561 (17-1100)
-MMS (n=8)	338	2.707 (250-1000)
Total (n=61)	349	21.268 (17-1100)
Dermatologist		
-no MMS (n=56)	163	9.128 (17-600)
-MMS (n=12)	195	2.340 (5-637)
Total (n=68)	168	11.468 (5-637)
Recurrent BCC	**Mean**	**Total (range)**
Hospital		
-no MMS (n=37)	32	1.197 (1-500)
-MMS (n=6)	40	240 (0-200)
Total (n=43)	33	1.437 (0-500)
Dermatologist		
-no MMS (n=47)	14	670 (5-200)
-MMS (n=10)	15	150 (2-60)
Total (n=57)	14	820

Preferential treatment primary and recurrent BCC

As shown in Table 2, the majority of the respondents prefer surgical excision (SE) as first line treatment for primary BCC, although for certain subtypes the percentage with a preference for cryosurgery and MMS increases.
A variety of different types of therapy were indicated as second and third preferential treatment. Cryosurgery is selected as second line treatment for superficial and nodular BCC (at low-risk site) while radiotherapy is preferred for morphoic and nodular BCC at a high-risk site (facial area).
Results of the survey (Table 3) demonstrate that for all histologic subtypes of the recurrent BCC, SE is preferred as first-line treatment. Next to this, the percentage of respondents with a preference for MMS, especially for nodular and morphoic types of recurrent BCC (larger than 2 cm and/or at a high risk

site), increased (10-30%). Cryosurgery, radiotherapy and MMS are alternately mentioned as second or third treatment of choice.

Table 2 Preferential treatments for primary BCC

	First preference	N	Second** preference	N	Third** preference	N
Superficial primary BCC						
< 2 cm						
Low risk site	SE (70%) Cryosurgery (19%) Curett. (5%) PDT (6%)*	85	Cryosurgery (59%)	66	Radiotherapy (44%)	38
High risk site	SE (89%) Cryosurgery(2%) Curettage (2%) PDT (5%) MMS (2%)	85	Cryosurgery (57%)	58	Radiotherapy (38%)	32
> 2 cm						
Low risk site	SE (67%) Cryosurgery(23%) Curettage (3%) PDT (7%)	84	Cryosurgery (51%)	61	Radiotherapy (47%)	34
High risk site	SE (76%) Cryosurgery (7%) MMS (7%) PDT (6%) Radiotherapy (2%) Curettage (2%)	84	Cryosurgery (61%) Radiotherapy	55	Radiotherapy Cryosurgery (66%)	30
Nodular primary BCC						
< 2 cm						
Low risk site	SE (93%) Curettage (4%) Cryosurgery (2%) PDT (1%)	86	Cryosurgery(47%)	49	Radiotherapie/ Cryosurgery (69%)	29
High risk site	SE (95%) MMS (3%) Cryosurgery (1%) Curettage (1%)	86	Radiotherapy (38%)	50	Cryosurgery (61%) Radiotherapy	28
>2 cm						
Low risk site	SE (95%) Cryosurgery (2%) Curettage (1%) MMS (1%) PDT (1%)	85	Cryosurgery (43%)	49	Radiotherapy (58%)	26
High risk site	SE (87%) MMS (12%) PDT (1%)	84	Radiotherapy (39%)	49	Cryosurgery(67%) Radiotherapy	28

Table 2 Preferential treatments for primary BCC (continued)

	First preference	N	Second** preference	N	Third** preference	N
Morphoic primary BCC						
< 2 cm						
Low risk site	SE (99%) MMS (1%)	86	Radiotherapy (41%)	39	Cryosurgery Radiotherapy (50%)	20
High risk site	SE (92%) MMS (8%)	85	Radiotherapy (41%)	44	MMS (24%) Radiotherapy (52%)	25
> 2cm						
Low risk site	SE (94%) MMS (5%) Cryosurgery (1%)	85	Radiotherapy (45%)	38	MMS (24%) Radiotherapy (40%)	21
High risk site	SE (76%) MMS (22%) Radiotherapy (2%)	83	Radiotherapy (36%) MMS (27%)	44	Radiotherapy (56%)	25

**PDT: Photodynamic therapy ** For the second and third preferential treatments, a variety of therapies was given. For convenience, only treatments with the highest percentage are given. Consequently, numbers do not add up to 100%.*

Table 3 Preferential treatment for recurrent BCC

	First preference	N	Second** preference	N	Third** preference	N
Superficial recurrent BCC						
< 2 cm						
Low risk site	SE (85%) Cryosurgery (9%) Curet/coag. (4%) PDT* (2%)	85	Cryosurgery (53%)	45	Radiotherapy (48%)	23
High risk site	SE (94%) MMS (3%) Cryosurgery (1%) Curet/coag. (1%) Radiotherapy(1%)	83	Cryosurgery (42%) Radiotherapy (28%)	45	Radiotherapy (46%)	24
> 2 cm						
Low risk site	SE (82%) Cryosurgery (11%) Curet/coag. (4%) PDT (2%) MMS (1%)	83	Cryosurgery (53%)	45	Radiotherapy (48%)	25
High risk site	SE (85%) MMS (7%) Cryosurgery (3%) Radiotherapy (3%) PDT (1%) Curet./coag (1%)	82	Cryosurgery/ Radiotherapy (71%)	46	Radiotherapy /cryosurgery (61%)	26

Table 3 Preferential treatment for recurrent BCC (continued)

	First preference	N	Second** preference	N	Third** preference	N
Nodular recurrent BCC						
< 2 cm						
Low risk site	SE (98%) MMS (2%)	85	Cryosurgery (32%) Radiotherapy (28%)	34	Radiotherapy (59%)	22
High risk site	SE (88%) MMS (11%) Radiotherapy (1%)	82	Radiotherapy (46%)	41	Cryosurgery (29%) Radiotherapy (29%)	21
>2 cm						
Low risk site	SE (98%) MMS (2%)	83	Cryochir/ Radioth. (31%)	36	Radiotherapy (50%)	22
High risk site	SE (83%) MMS (17%)	82	Radiotherapy (44%)	41	Radiotherapy (43%) MMS (35%)	23
Morphoic recurrent BCC						
< 2 cm						
Low risk site	SE (94%) MMS (6%)	86	Radiotherapy (44%)	36	Radiotherapy (45%) MMS (36%)	22
High risk site	SE (80%) MMS (20%)	83	Radioth. (42%)	45	Radiotherapy (52%) MMS (39%)	23
> 2cm						
Low risk site	SE (88%) MMS (10%)	83	Radioth. (42%) MMS (28%)	36	Radioth. (42%) MMS (28%)	21
High risk site	SE (70%) MMS (30%)	83	SE (43%) Radioth. (43%)	46	Radioth. (56%)	25

**PDT: Photodynamic therapy ** For the second and third preferential treatments, a variety of therapies was given. For convenience, only the treatments are given with the highest percentage. Consequently, numbers do not add up to 100%.*

MMS in practice

Twelve respondents (12/86) from 3 university and 4 general hospitals respectively indicate that MMS is applied in their hospital and performed by either respondents themselves, a colleague dermatologist or colleagues from other specialties (like Ear-Nose-Throat specialty). They estimate that MMS is performed in total 572 times for a primary BCC and 341 times for a recurrent BCC. Of the non-MMS group, 86 percent (61/71) refers to a centre where MMS is being performed. In 44 percent of all cases, this concerns

patients with an aggressive recurrent BCC, followed by an aggressive type of primary BCC (26%), or a primary-/recurrent BCC at a high risk site (25%). The remaining five percent is a mixture of aggressive primary or recurrent BCC, size larger than 2 cm, a high risk site or a BCC which has not been radically removed. An estimated number of 177 patients with a primary BCC and 190 patients with a recurrent BCC are being referred each year.

Case

The following case was presented to the respondents with the question to indicate their preferential treatment to remove the tumour. A sixty-year old male visits the outpatient clinic with a recurrent BCC localised at the right cheek. The tumour has a size of 19 mm and histologic examination has shown that it concerns a solid growing BCC. No further health problems are reported by the patient. Seventy percent (60/86) of the respondents answered that they would perform SE while 12 percent (10/86) choose MMS. The remaining 18 percent answered that they would refer to either a MMS-surgeon (7%) or a plastic surgeon (11%).

Conclusion and discussion

The results of this survey give insight in the incidence of the primary and recurrent BCC as estimated by the dermatologists, their type of preferential treatment and the use of MMS. The dermatologist in our study population diagnosed on average 168 primary and 14 recurrent BCC in 2004. Overall, SE is considered to be the preferential treatment for both primary and recurrent BCC which corresponds with the Dutch guideline for treatment of patients with BCC.[3] The percentage of dermatologists with a preference for MMS as first line treatment increased if there was an unfavourable combination of factors like a tumour size larger than 2 cm with aggressive histologic subtype and a high risk site.

A small percentage of the dermatologists indicate that both cryosurgery and radiotherapy are preferred as second or third therapy of choice for subtypes of primary and recurrent BCC. This differs to some extent with the guideline which states that cryosurgery can be applied for superficial and nodular

primary BCC, smaller than 2 cm and located at a low-risk site. However, for all other indications, a restrictive use is recommended. For radiotherapy, the guideline describes that this treatment can be applied for all subtypes of BCC but only in exceptional cases for primary and recurrent morphoic BCC, located in the facial area.

The results of the survey show that MMS is applied as treatment for certain subtypes of recurrent BCC and albeit to a lesser extent also for subtypes of primary BCC.

Comparing our findings with the results of a similar study performed by Thissen et al.[5], indicate that SE is still considered the preferential treatment for both primary and recurrent BCC. In addition, the order of preference for all other treatment has almost remained unchanged although within our study both MMS and Photodynamic therapy (PDT) are increasingly mentioned as treatment of choice.

A major imitation of our survey was the low response rate at individual level which limits the generalisability of the results to the whole group of dermatologists practising in the Netherlands. The reason for this low response is difficult to determine but it is possible that a number of dermatologists did not return the questionnaire because either they did not have treatment of skin cancer as specialty or did not perform surgical procedures. On the other hand, from the perspective of the hospital organisation, the response rate is higher, namely 55%. Hence, the results from our survey give to some extent insight in the diagnosis and treatment of BCC at hospital level. It is likely that the response rate would have been higher if data were collected by means of telephone interviews instead of a postal questionnaire. However, results of a survey conducted among general practitioners in Australia showed that a postal survey resulted in a higher response rate (59.9%) compared to interviews by telephone (40.6%).[6] Still, in this study, a reminder to fill in the questionnaire was sent three times while in our survey only one reminder was used.

Given the rising number of newly diagnosed BCCs in the near future, it is recommended to examine whether a national registration for BCC can be developed. In this way, not only the impact of the increasing incidence on the workload of the dermatologist and other specialities becomes more evident but also the costs associated with treatment of this type skin cancer can be determined. In addition, updating the clinical guideline with recent results of both clinical and cost-effectiveness studies on the treatment of BCC is recommended in order to support clinical decision-making.

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chapter 8

General discussion

Introduction

The main objective of this thesis was to evaluate the surgical treatment, SE or MMS, for Basal Cell Carcinoma. To address this general objective, four studies from different perspectives have been performed. This chapter gives a summary of the main findings. In addition, methodological and practical considerations resulting from these findings are presented and discussed. Finally, some recommendations for future research are given.

Main findings

Cost-effectiveness of MMS versus SE for facial primary and recurrent BCC

The cost-effectiveness study, in which effectiveness was expressed as the recurrence rate, was performed from a hospital perspective. Results of the cost analysis showed that the total treatment costs of MMS compared to those of SE were significantly higher. The cost-difference amounted to €254 (95%CI €181 to €324) for primary BCC and to €249 (95%CI €175 to €323) for recurrent BCC. The main drivers for this cost-difference were longer surgery time and higher pathology costs for MMS.

When combining the costs with the effectiveness of both treatments, the incremental cost-effectiveness ratio (ICER) was €29231 per recurrence avoided for primary BCC while the ratio for the recurrent BCC amounted to €8094. To account for the uncertainty surrounding the cost-effectiveness ratio's, bootstrapping was used (1000 replications).[1] The resulting acceptability curves demonstrated that for the calculated ICER's, the probability of MMS being more cost-effective than SE never reached 50% unless the hospital would be willing to pay more than the calculated ICER's. The cost-effectiveness planes also showed that the majority of all ratios was located in the quadrant where an increased effectiveness of MMS is only achieved at higher costs.

The findings indicate that from a hospital perspective, it does not seem cost-effective to implement MMS on a large scale for both primary and recurrent facial BCC. However, given the limited follow-up period, it is possible that MMS might become a cost-effective treatment for recurrent BCC.

Measuring determinants of satisfaction with the health state of the facial skin after surgery for BCC

A disease-specific questionnaire was developed in order to examine determinants of satisfaction with the health state of the facial skin and facial aesthetics. Overall, at six months after surgery, patients showed a significant decrease in worrying, their perception of the size of the lesion/scar and severity of the condition while their perceived health status was significantly improving. On the other hand, there appeared to be a slight but not statistically significant increase in their perceived susceptibility for facial BCC. Fear of recurrence of a BCC or fear of developing a new BCC at other facial sites showed no statistically significant difference at six months.

The first specific research question was: "Can pre-operative beliefs be used to predict patient satisfaction with the health state of the facial skin at six months after surgery?"

Results of the predictive regression models indicated that satisfaction of patients with their facial health state as measured by postoperative worrying, susceptibility, and fear for developing a new BCC at other facial sites can be predicted by pre-operative health beliefs. For example, the most important effect to predict 'worrying' of patients about their facial health six months after surgery, is a statistical interaction between 'susceptibility' and 'fear for surgery' at baseline. This means that in patients who are beforehand fearful for surgery, susceptibility has a larger impact on worrying than those who are less fearful. In addition, if patients before surgery already are fearful of developing a new BCC at other parts of their face, they tend to worry more at six months postoperatively.

The second research question was: " Which pre-and postoperative beliefs do eventually explain satisfaction with the health state of the facial skin at six months after surgery?"

Results showed that an additional explanation of the extent to which patients are satisfied with the health status of their facial health after surgery were changes in health beliefs. This means that between baseline and six months after surgery, some patients will experience an increase in susceptibility, fear for recurrence of BCC at the same site or fear of developing a new BCC at other facial sites.

Measuring perceptions of facial aesthetics after surgery for BCC

Results on facial aesthetics showed that all surgical patients improved over time with regard to their perceived facial aesthetics, irrespective whether MMS or SE had been performed. At six months after surgical treatment, there was no statistically significant difference in perceptions between patients with a primary or a recurrent BCC. Furthermore, regression analysis results showed that the extent to which patients thought their facial aesthetics had improved could largely be predicted by subjective preoperative perceptions like the conspicuousness of the facial site, the perceived susceptibility for facial beauty problems, finding it difficult to be seen with facial beauty problems and the visibility of the tumour within the facial area.

Preferences for a surgical treatment to remove BCC

A discrete-choice experiment was conducted from a societal perspective. Results showed that members of the general public were likely to prefer a surgical treatment with a lower probability of recurrence, lower surgery time, less travel time, no waiting time, no risk for a re-excision and lower costs. These findings suggest that from a societal perspective both outcome– and process variables are considered as being important and play a role in public's preferences for a surgical treatment to remove BCC. In addition, the willingness to pay for MMS amounted to 848 euro, which indicates that, based on the attributes and levels included in the discrete choice experiment, MMS is preferred to SE.

The impact of a cost-attribute on preferences for surgical treatment to remove BCC

The outcomes of two DCE's, one without a cost attribute (DCE_nocost) and one with a cost attribute (DCE_cost) were compared. Results showed that respondents in both DCE's preferred MMS to SE, which indicates that the inclusion of a cost attribute does not change the rank order of preferences. Differences between the two experiments were found with regard to the statistical significance of the attributes and their relative order of importance. First, the attribute travel time in DCE_nocost was, in contrast with DCE_cost, not statistically significant. Second, with regard to the order of the relative importance, the attribute waiting time for surgical results was the third most important attribute in DCE_nocost although it ended as the least important attribute in DCE_cost. It is questionable whether these

differences are serious enough to conclude that either of the DCEs is not a suitable approach to derive preferences since the aforementioned attributes account for only a small percentage of the relative importance results.

Treatment of BCC by dermatologists

Results of the survey showed that in 2004 respondents had diagnosed on average 168 primary and 14 recurrent BCC. Overall, SE was the first treatment of choice for both primary and recurrent BCC. This was followed by cryosurgery and radiotherapy. In addition, respondents preferred MMS as first-line treatment if it concerned a large tumour (> 2 cm), an aggressive histologic subtype and located in the H-Zone (facial area). However, since the response rate was very low (25% at individual dermatologist level) the results have to be interpreted with caution.

Methodological and practical considerations

All four studies have several methodological and practical issues that need to be considered.

First, the follow-up period in the cost-effectiveness study was, due to practical considerations, determined at 30 months for primary BCC and 18 months for recurrent BCC. It is likely that this period is too short to capture all recurrences as usually a minimum of a five-year period is required to determine definite recurrence rates. However, a sensitivity analysis was performed to extrapolate the observed effect difference to a five year period. Results showed that MMS still would not be cost-effective for primary BCC although the ICER for recurrent BCC decreased substantially.

Second, developing a new disease-specific questionnaire to measure satisfaction with the facial health and facial aesthetics for patients with BCC is an ongoing process. In our study, both content validity and internal consistency (Cronbach's alpha between 0.74-0.93) were achieved. In addition, the structure, i.e. the domains, within the questionnaire were thoroughly tested by using factor analysis. Still, reproducibility or test-retest could not be realised due to practical considerations. Administering the same questionnaire again would imply an additional visit for patients to the hospital within a very short time period. Since a lot of patients came from outside the region of Maastricht, this would have been too burdensome at the time. Furthermore, respondent's burden has to be diminished since the interview at baseline lasted one hour. Although the time for the second interview was

decreased to half an hour, it still limits the feasibility of the questionnaire for clinical practice and research.

Third, the power analysis indicated that for the group of primary BCC at least 102 patients were necessary to detect an effect difference of 12.5% between MMS and SE in the scale of very satisfied to not satisfied. For the group of recurrent BCC, 86 patients were expected to be necessary in order to detect an effect difference of 15% between MMS and SE. Our findings demonstrated that the observed difference in satisfaction with the health status of the facial skin and aesthetic perceptions between MMS and SE was much smaller than anticipated. This would imply that for future studies a larger number of patients would be necessary. However, the practical implications and relevance of detecting such small differences is questionable.

Fourth, the health beliefs were tested separately instead of a construct that combines them. We felt that averaging heterogeneous concepts like perceptions and expectations to one composite measure like patient satisfaction on the health state of the facial skin, could not be rightfully done. So, indicators in the analysis were kept apart to show more detail in approaching complex concepts like patient satisfaction.

Fifth, from the perspective of the general public, not only outcome but also process attributes were valued as important when considering preferences for surgical treatments to remove BCC. However, it is necessary to be cautious when generalizing the results to different settings or countries since our study was conducted in one region of the Netherlands. In addition, although the attributes included in the experiment were carefully selected, based on results of a clinical trial[2], a cost-effectiveness study[3], a review[4] and a focus group of patients who recently had received treatment for BCC, it is possible that in other countries different aspects of the treatment are considered to be important. In addition, the extent to which the preferences as obtained in our study are "true preferences' is unknown. For that purpose, respondents would actually have to pay the amount of money as determined within our experiment. Furthermore, it also is possible that using patient preferences instead of public preferences might result in different values due to for example experience with the disease (and its treatment). Although in economic evaluations, the societal perspective is generally recommended, research has shown that patient preferences regarding health outcomes systematically differ from societal preferences, and the discussion regarding which values are the most appropriate is still ongoing.[5-7]

Sixth, the results of the comparative study showed that the inclusion of a cost attribute did not have an impact on the rank order of preferences regarding surgical treatment to remove BCC. However, in line with the limitations mentioned above, the results are specific for the setting of BCC and the surgical procedures SE and MMS. Therefore, generalizing these findings to other settings, i.e. diseases and treatments, has to be done with caution.

Implications and future research

In Europe, some countries have introduced economic evidence as a formal requirement for resource allocation decisions. The National Institute for Health and Clinical Excellence (NICE) in the U.K. uses economic evidence to support decisions about the allocation of resources to publicly funded programmes involving medicine and other health technologies.[8] In the Netherlands, the Health Insurance Council demands pharmacoeconomic research when making decisions regarding the reimbursement of drugs.[9] Recently, the Dutch Council for Public Health and Health Care published a report called "Fair and Sustainable Care" in which they addressed issues such as which criteria should be applied in order to identify priorities for the funding of care from collective sources. They recommended that a decision should be given on the basis of disease burden and cost-effectiveness.[10] Nevertheless, the extent to which economic evidence directly influences different levels of decision-making is still considered moderate.[11-12]

The economic evaluation showed that the incremental costs per recurrence avoided (ICER) amounted to € 29231.- for primary BCC and to € 8094.- for recurrent BCC. The acceptability curves demonstrated that for these ICER's, the probability of MMS being more cost-effective than SE never reached 50% unless the hospital would be willing to pay more than the calculated ICER's. In such a situation, the decision to replace SE by MMS depends first on the threshold value, i.e. the maximum amount the hospital would be willing to pay extra to prevent one additional recurrence, and second whether the estimated ICER lies below this threshold value.[13] However, a threshold value with regard to the treatment of a BCC has not yet been determined which makes interpretation and comparison of the ICER's difficult. Overall, this is a problem when applying a disease-specific outcome measure, i.e. recurrence rate, instead of a more common and generic measure for effectiveness like a Quality Adjusted Life Year (QALY).[14] As men-

tioned in the introduction, the reason for not using QALY as an outcome measure was that BCC and its treatment would have no effect on life expectancy. In addition, it was expected that treating BCC would have no substantial effect on generic health related quality of life.

Nevertheless, the ICER's of this study can be put into perspective by considering the consequences of treating a recurrent BCC from a hospital perspective. It is likely that a patient with a recurrent BCC will receive surgery in the future. Therefore, it can be argued that an acceptable threshold value should at least include the hospital costs of treating a recurrence. Still, even by taking three times the costs for treatment of a recurrent BCC (that is, three times the costs of MMS = €3438.-), the ICER's for primary and recurrent BCC are still too high to recommend a broad implementation of MMS.

Ideally, the cost-effectiveness results should be incorporated into established guidelines to support decision-making on both a meso (organisation) and micro (professional) level.

In the Netherlands, the Dutch Institute for Health Care Improvement is involved in the development of evidence-based guidelines in close collaboration with professionals. For the treatment of BCC, a guideline was published in 2003.[15] MMS was primarily discouraged as treatment of choice for superficial and nodular primary and nodular recurrent BCC (<2cm, low risk site) but not for all the other types of BCC. Within our cost-effectiveness study, ICER's were calculated for the high-risk sites (facial area). Additionally, ICER's were also calculated for different locations in the facial area and histologic subtype. Results showed that, except for primary BCC of the ears and recurrent BCC of the cheek, MMS would not likely become a cost-effective treatment. On the other hand, the ICER (€3843.-) for aggressive recurrent BCC became more favourable, indicating that MMS might be cost-effective for this type of BCC. Since these results are based on smaller subgroups, they should however be interpreted with caution.

From a patient perspective, it is noteworthy that all patients improved, irrespective of MMS or SE.

The results on both facial health and facial aesthetics showed that before treatment, patients already have certain perceptions and expectations which for a large part will predict how they respond after therapy. Recently, the importance of pre-treatment characteristics as predictors for patient's post-treatment status have been confirmed by Chen et al.[16] They examined predictors of skin related quality of life (QOL) after treatment for non melanoma skin cancer (NMSC) by using a refined version of the dermatology

specific questionnaire Skindex 16-items version. The strongest independent and most consistent predictor of skin related QOL after treatment turned out to be pre-treatment skin-related QOL.

From a societal perspective, results of the DCE confirmed the importance of using recurrence as a primary clinical outcome. In addition, members of the general public also valued process related aspects of a surgical treatment as important which indicate that they derive benefit from other factors beyond a traditional clinical outcome like recurrence. As previous research[17-18] already has demon-strated, when differences in outcomes are expected to go beyond traditional health outcomes, the DCE can potentially be a very useful method to value other treatment related aspects, such as waiting time or location of a treatment. In this respect, an interesting area for future research is whether differences in preferences between patients and the general public are also present when it concerns process or non-health factors instead of health related outcomes. Given the recent advance in non-invasive therapies for BCC, the DCE seems a useful method to examine whether, next to the prevention of a recurrence, aspects like side-effects, duration of therapy or cosmetic results are also valued as important.

Comparing the incremental willingness to pay of €848, as derived from the DCE, with the incremental hospital costs of MMS versus SE of €254 (for primary BCC), as calculated within the cost-effectiveness study, suggest that MMS might be cost-effective if considered from a cost-benefit perspective, since the incremental benefits (i.e. WTP) of MMS compared to SE exceed the incremental costs. However, this comparison is only for illustrative purposes since cost-benefit analysis is not used as the sole basis for health care decision making.

Both DCEs, one without a cost attribute (DCE_nocost) and one with a cost attribute (DCE_cost), showed a preference of MMS to SE for primary BCC, indicating that the inclusion of a cost-attribute or "having to pay for it" does not change the rank order of the preferences. This indicates that from a policy perspective, either of the DCEs can be used to elicit preferences. However, as mentioned before, the inclusion of the cost-attribute makes it possible to estimate marginal and incremental willingness to pay values. Hence, it becomes possible to place the results within the framework of a cost-benefit analysis and stimulate resource allocate decisions, not only within health care but also between sectors of economy. Still, there are many methodological challenges related to the use of the cost-attribute like

the impact of the range, the number of levels and the ordering effects of a cost attribute.[19-21]

Conclusion

Results of a systematic review on recurrence rates after treatment of primary BCC indicated that tumours treated with MMS appeared to have the lowest recurrence rate, followed by SE.[4] However, at the time, the authors concluded that comparison of the recurrence rates for different therapies was difficult (i.e. impossible) due to a lack in uniformity of reporting and good quality research. This conclusion was confirmed by another more recent structured review on the assessment of recurrence rates after therapy for BCC.[22] Nevertheless, for a long period, a widespread conviction was that MMS would be the best therapy available although there was no scientific evidence to support this.

Given the results of all four studies as described in this thesis, an important question is therefore:

" How do the findings of the different studies support the decision-making process regarding MMS versus SE for primary and recurrent facial BCC?"

The results of the discrete choice experiment showed that, from a societal perspective, MMS is preferred to SE for primary facial BCC. As such, these findings demonstrate the strength of preferences, expressed as the incremental willingness to pay value of €848. However, the extent to which the results of a DCE at this moment actually can be used for decision making at a national level is limited.

The cost-effectiveness study was conducted parallel to a randomised controlled trial in which MMS was compared to SE for both primary and recurrent BCC. Results of the clinical trial showed that the difference in recurrence rates between MMS and SE for both primary and recurrent BCC was not statistically significantly different.[2] Relating the difference in recurrence rates to the difference in costs (incremental cost-effectiveness ratio) showed that MMS was not a cost-effective treatment for both primary and recurrent facial BCC although a longer follow-up period is perhaps necessary to determine the definite ratio for the last group.[3] As such, the cost-effectiveness analysis provides the strongest input and evidence to support decision-making on both a meso and micro level and indicate that it is not justified to perform MMS for every facial BCC.

Although the results from the survey have to be interpreted with caution, they seem to support the results of the cost-effectiveness study since the majority of the dermatologists who returned the questionnaire, preferred SE as first line treatment for both primary and recurrent BCC.
Finally, results from the disease-specific questionnaire showed that from a patient perspective, there was no statistically significantly difference in perceptions between the two treatments, i.e. patients improved irrespective of MMS or SE.
In conclusion, the conviction that MMS is the best therapy available (with respect to recurrence rates, cost-effectiveness, perceptions on facial health and aesthetics) is not confirmed by the results of this thesis. At his moment, SE should not be replaced by MMS for every facial primary BCC although it is possible that, in the near future, MMS might become cost-effective for the group of recurrent BCC.

Recommendations

Practical recommendations

To facilitate the decision-making process for treatment of non melanoma skin cancer on both a meso and micro-level, we recommend that cost-effectiveness results are incorporated into clinical guidelines. As such, they provide additional information as to whether the monetary investment of MMS is justified under certain circumstances.
A second practical recommendation concerns the administration of a short questionnaire before the start of a treatment. Items like perceived susceptibility for facial health and facial aesthetics, vulnerability, health status of the facial skin, fear of recurrence, fear of developing a new BCC, the conspicuousness of the facial site and the visibility of the tumour are likely candidates to be included. In fact, such an instrument might work both ways. It may help physicians to a better understanding of how patients experience this type of skin cancer and also give them insight which patients might benefit from pre-treatment counselling to reduce worrying. Next to this, it will help them to decide if certain patients might benefit from additional cosmetic procedures.

Recommendations for future research

Given the recent advance in non-invasive treatments such as imiquimod or photodynamic therapy (PDT) for certain types of BCC, research into the cost-effectiveness of these treatments should be stimulated and assessed. A randomised clinical trial is likely to be the first source of data collection. In addition, evidence synthesis and decision modelling[23] , including all data from other sources (if available), seem an appropriate framework to support the decision-making process regarding which treatment is the most cost-effective for different types of BCC.

Construct validity, i.e. concurrent validity, of our questionnaire should ideally be assessed in comparison with for instance a more recently developed questionnaire like the Facial Skin Cancer Index or the Skindex 16 (refined version of Skindex which includes 29 items). In addition, test-retest should be further investigated.

More research is needed regarding the external validity of the DCE results. To what extent are stated preferences actually true preferences? For that purpose, data regarding both hypothetical and actual behaviour will be necessary for comparison. Further research should aim to investigate whether differences in preferences between patients and the general public are also present when it concerns process factors or non-health outcomes.

Finally, more research is needed to examine the impact of the cost attribute on preferences in different settings.

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SAMENVATTING

Dit proefschrift heeft tot doel de chirurgische behandelingen Mohs Micrografische Chirurgie (MMS) en Standaard Excisie (SE) voor het primair en recidief Basaal Cel Carcinoom te evalueren. Daartoe zijn vier studies vanuit verschillende perspectieven uitgevoerd.

In hoofdstuk 2 worden de resultaten van de economische evaluatie beschreven. De kosteneffectiviteitsanalyse was uitgevoerd vanuit een ziekenhuisperspectief. De resultaten van de kostenanalyse toonden aan dat de totale behandelingskosten van MMS vergeleken met die van SE significant hoger waren. Het kostenverschil bedroeg €254 (95% BI €181-€234) voor primaire BCC en €249 (95% BI €175-€323) voor recidief BCC. Het kostenverschil werd voornamelijk veroorzaakt door een langere operatieduur en hogere pathologiekosten voor MMS. De incrementele kosteneffectiviteitsratio (IKER) per vermeden recidief was €29.231 terwijl de ratio voor het recidief BCC €8.094 bedroeg.
De resultaten van de bootstrap analyse toonden aan, dat de kans dat deze ratio's kosteneffectief zouden zijn, nooit hoger werd dan 50 procent tenzij het ziekenhuis bereid was meer te betalen dan de berekende IKER's. Bovendien bleek uit de presentatie van de IKER's in een 'kosten-effectiviteitsplane' dat de meerderheid gelokaliseerd was in het kwadrant waar een toename in effectiviteit van MMS alleen kon worden bereikt tegen hogere kosten. De resultaten geven aan dat het niet kosteneffectief is om MMS op grote schaal te implementeren voor zowel het primaire als het recidief BCC. Voor de laatste groep geldt echter dat de follow-up duur van 18 maanden wellicht te kort was hetgeen betekent dat MMS voor deze groep mogelijk in de toekomst kosteneffectief kan worden.

Hoofdstuk drie beschrijft de resultaten met betrekking tot de ontwikkeling en toepassing van een ziektespecifieke vragenlijst. Het doel was na te gaan welke determinanten de tevredenheid met de gezondheid van de gezichtshuid na een chirurgische behandeling voor BCC konden voorspellen en/of verklaren. Uit de resultaten bleek dat zes maanden na de operatie, patiënten zich minder zorgen maakten over de gezondheid van de gezichtshuid, de perceptie van de grootte van het aangedane plekje en de ernst van de aandoening afnam terwijl de perceptie van de status van hun gezichtshuid verbeterde. Desondanks bleek ook dat er een lichte maar niet statistisch significante toename in de perceptie van hun gevoeligheid voor BCC te constateren was. Uit de resultaten van de regressie analyse bleek dat de

tevredenheid van patiënten met de status van de gezondheid van de gezichtshuid zes maanden na de operatie voorspeld kon worden op grond van percepties over de gezondheid voorafgaand aan de operatie. Daarnaast toonden de resultaten aan dat de mate waarin patiënten tevreden waren met de gezondheidsstatus van hun gezichtshuid additioneel verklaard kon worden door veranderingen in health beliefs. Dit betekent dat in de periode tussen het eerste policonsult en zes maanden na de operatie, sommige patiënten een toename ervaren in hun gevoeligheid voor BCC, hun angst voor terugkeer van een BCC op dezelfde plek of hun angst voor het ontstaan van een nieuw BCC op andere gezichtsplekken.

De resultaten met betrekking tot de perceptie van de esthetiek van het gezicht worden in hoofdstuk 4 gepresenteerd. Alle patiënten gingen vooruit in hun perceptie van de gezichtsesthetiek, ongeacht of MMS of SE was uitgevoerd. Zes maanden na de operatie was er geen statistisch significant verschil in percepties tussen patiënten met een primair of een recidief BCC. Daarnaast toonden de resultaten aan dat de mate waarin patiënten van mening waren dat de esthetiek van hun gezicht verbeterd was, voor een groot deel voorspeld kon worden door subjectieve percepties voorafgaand aan de operatie zoals de perceptie van de opvallendheid van de plek in het gezicht, de perceptie van de kwetsbaarheid voor schoonheidsproblemen, het moeilijk vinden om gezien te worden met schoonheidsproblemen in het gezicht en de zichtbaarheid van de tumor in het gezicht.

Hoofdstuk 5 richt zich op de resultaten van een keuze-experiment uitgevoerd onder inwoners van Maastricht en Heuvelland. Het onderzoek werd verricht om inzicht te krijgen in welke attributen van een chirurgische behandeling voor BCC belangrijk worden gevonden. Daarnaast werd de bereidheid om te betalen voor MMS ten opzichte van SE bepaald. De resultaten gaven aan dat respondenten uit de algemene bevolking een voorkeur toonden voor een chirurgische behandeling met een lagere kans op een recidief, lagere operatieduur,minder reistijd, geen wachttijd met betrekking tot het beschikbaar zijn van de resultaten van een operatie, geen risico op een her-operatie en lagere kosten. Deze bevindingen suggereren dat vanuit een maatschappelijk perspectief niet alleen een klinische uitkomstmaat zoals het recidief maar ook proces variabelen zoals wachttijd, reistijd, en operatieduur belangrijk worden geacht en een rol spelen bij de voorkeur voor een chirurgische behandeling om een BCC te verwijderen. Bovendien bleek uit de

resultaten van het keuze-experiment dat men bereid was om €848 voor MMS te betalen.

Hoofdstuk zes geeft de resultaten weer van een vergelijking tussen een keuze-experiment met een kostenattribuut en een keuze-experiment zonder kostenattribuut. De vergelijking toonde aan dat respondenten in beide keuze-experimenten MMS boven SE prefereerden. Dit betekent dat in dit experiment, het kostenattribuut geen impact had op de sterkte van de voorkeur voor een chirurgische behandeling. Verschillen tussen de twee keuze-experimenten werden gevonden met betrekking tot de statistische significantie van de attributen en de volgorde waarin de attributen van belang werden geacht. Ten eerste bleek dat het attribuut 'reistijd' in het keuze experiment zonder kostenattribuut niet statistisch significant was. Op de tweede plaats bleek het attribuut wachttijd voor resultaten van de operatie het derde belangrijkste attribuut te zijn in het keuze-experiment zonder kosten maar als minst belangrijk attribuut te eindigen in het keuze experiment met een kosten.

In hoofdstuk 7 worden de resultaten van de vragenlijst onder dermatologen beschreven. In 2004 werd er per respondent gemiddeld 168 primaire en 14 recidief BCC gediagnosticeerd.De Standaard Excisie (SE) werd overwegend als eerste voorkeur opgegeven voor de behandeling van zowel het primair als het recidief BCC, gevolgd door cryochirurgie en radiotherapie. De voorkeur voor MMS als eerste keuze nam toe indien het ging om een grote tumor (> 2 cm), een agressief histologisch subtype en gelokaliseerd in het gezicht (H-zone). Echter, de resultaten van de vragenlijst dienen met de nodige voorzichtigheid te worden geïnterpreteerd aangezien de response laag was (25% op individueel dermatoloog niveau).

Tenslotte wordt in hoofdstuk acht, een samenvatting gegeven van de belangrijkste resultaten van de verschillende studies. Daarnaast worden de bevindingen bediscussieerd, methodologische en praktische overwegingen aangekaart terwijl implicaties voor beleid en aanbevelingen voor toekomstig onderzoek worden aangegeven.

DANKWOORD

Dankwoord

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Curriculum vitae

Curriculum vitae

Brigitte Essers was born on May the 21st 1968 in Maastricht. After finishing high school (Gymnasium, Jeanne D'Arc College) in 1986, she studied Law for two years at the University of Leiden. She then decided to study Health Sciences with main subject Health Policy and Administration at the University of Limburg. After graduating in 1993, she started to work at the University Hospital Maastricht as policymaker for the Medical Intervention Centre and as project assistant for the patient-classification Diagnosis Related Groups (DRG)-project, at the Research unit of Patient Care (now called: Department of Clinical Epidemiology and Medical Technology Assessment).
At the end of 1999, she became part-time researcher for the Mohs trial in which both the effectiveness and cost-effectiveness of Mohs Micrographic Surgery (MMS) versus Surgical excision (SE) were compared for primary and recurrent Basal Cell Carcinoma (BCC). Simultaneously, she became project manager for the DRG-project. In this position, she was also involved with developments regarding a new Dutch national financing system, the Diagnosis Treatment Combination. In 2004, she completed the education for epidemiologist at the department of Epidemiology of the University of Limburg.
Since 2005, she works for the Scientific Advisory Board of the University Centre Maastricht UMC^{+} and as co-ordinator for the ZonMw-Health Care Efficiency Research Programme. Furthermore, she is involved with several research projects. One of them is a ZonMW project (project leader Dr.N. Smeets of the department of Dermatology) which among other things concerns a cost-minimisation analysis and a discrete choice experiment regarding three non-invasive therapies (photodynamic therapy, imiquimod and efudix) for the treatment of superficial BCC.

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