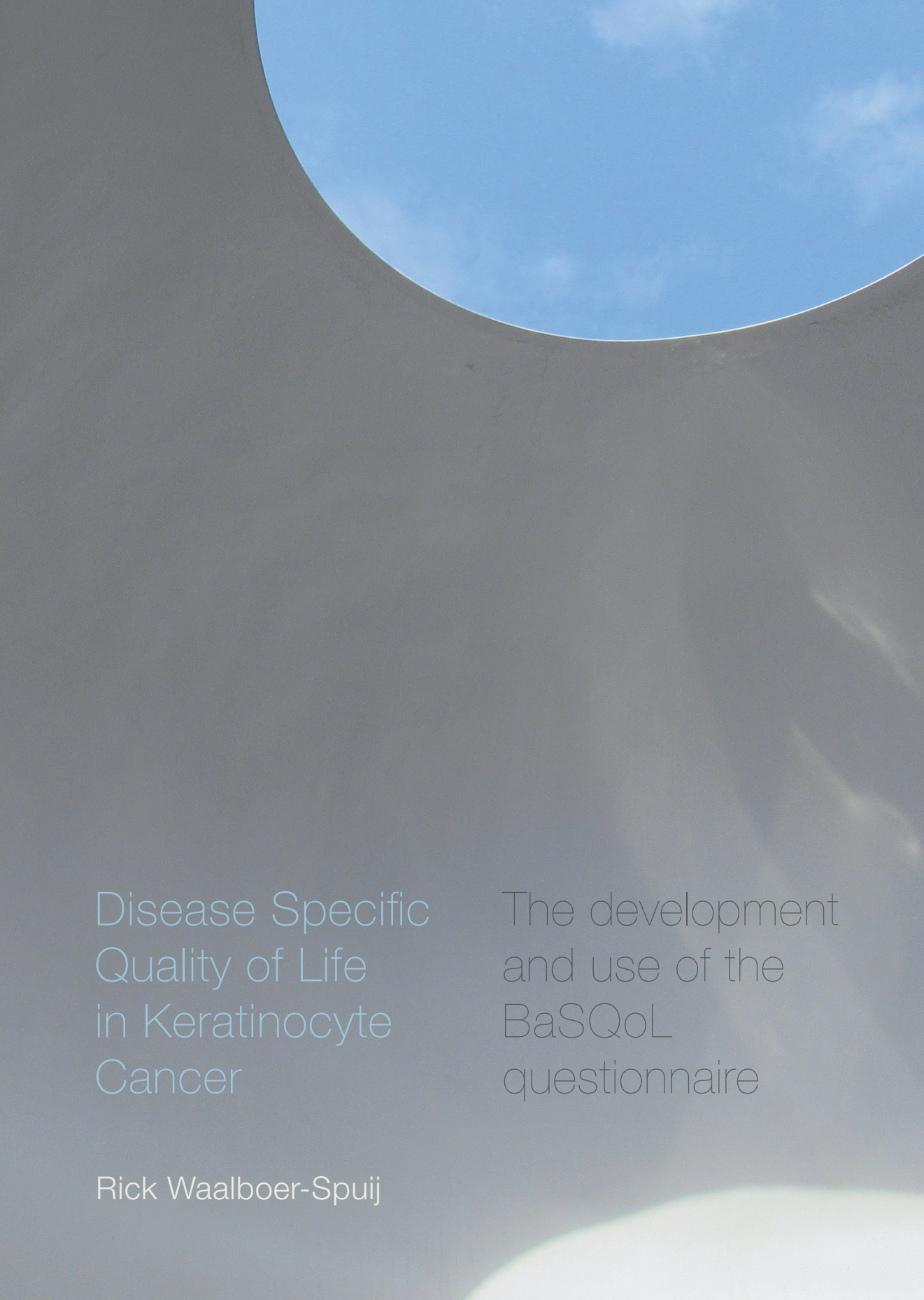

Disease Specific Quality of Life in Keratinocyte Cancer

The development and use of the BaSQoL questionnaire

Rick Waalboer-Spuij

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Disease Specific Quality Of Life In Keratinocyte Cancer

The development and use of the BaSQoL questionnaire

Ziektespecifieke kwaliteit van leven bij keratinocytkanker

De ontwikkeling en het gebruik van de BaSQoL vragenlijst

Proefschrift

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	Prof. dr. L.V. van de Poll-Franse
Overige leden:	Prof. dr. C. Verhoef
	Prof. dr. J.J. van Busschbach
	Prof. dr. I.M. Verdonck-de Leeuw
Copromotor:	Dr. L.M. Hollestein

CONTENT

Chapter 1

General introduction

Rick Waalboer-Spuij
Tamar E.C. Nijsten

Based on:
A review on quality of life in keratinocyte carcinoma patients G Ital Dermatol Venereol. 2013 Jun;148(3):249-254.

The incidence of skin cancer is increasing in the Netherlands the past decades [1, 2]. Basal cell carcinoma (BCC) is the most common skin cancer, followed by squamous cell carcinoma (SCC) and melanoma. The term non-melanoma skin cancer (NMSC) is often incorrectly used for BCC and SCC together. NMSC also could include other types of skin cancer such as Merkel cell carcinoma, atypical fibroxanthoma and cutaneous T cell lymphoma. Therefore we prefer to use keratinocyte carcinoma (KC).

More than 49,000 patients were newly diagnosed with skin cancer in the Netherlands in 2015 [3]. This included 5,978 new patients with melanoma, ~ 34,000 patients with BCC and 8,902 newly diagnosed SCC patients. This large amount of new patients does not even reflect the total number of skin cancers, as the Netherlands Cancer Registry only registered the first BCC and/or SCC per patient up to mid-2016, while many KC patients will develop subsequent skin cancers [4].

The mortality of KC is generally low and treatment is usually surgical or topical [5]. It usually does not involve lengthy systemic treatments with associated (severe) side effects.

Patient reported outcomes and quality of life

Patient reported outcomes (PROs) are outcomes about a disease, health or treatment directly from patients without interpretation. It includes quality of life (QoL), but also other outcomes such as treatment satisfaction, functional status and well-being and it reflects how patients feel [6].

QoL is defined by the World Health Organization (WHO) as 'an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns. This broad ranging concept is in a complex way affected by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment'. Health-related quality of life (HRQoL) concerns only the health aspects of QoL, but this is considered as a fluid construct. Because if the disease is severe enough, it will impact the whole QoL domain.

Health-related quality of life in dermatologic oncology

Over the past decades PRO and HRQoL more specifically, became increasingly important in dermatology patients . The focus of HRQoL assessments at first was on common chronic non-life-threatening diseases such as psoriasis and atopic dermatitis and it has proven to be an essential outcome for studies and in daily practice [7]. Subsequently, the measurement of PROs has spread to other chronic less common skin diseases as well. However, PRO in cutaneous malignant tumours were not widely studied which may be due to fact

that having a skin cancer was considered a discrete event instead of possibly being part of a chronic disease (with multiple tumours). Also preliminary studies yielded little to no impairment on generic or dermatology specific instruments [8-21].

When you also take the rapidly increasing incidence in skin cancers in account, implementation of PRO and HRQoL in diagnosis and treatment is necessary, especially in KC with the high incidence [2, 22, 23].

With the introduction of the concept of skin cancer as a chronic disease, new non-invasive treatments for cutaneous (pre)malignancies and the development of skin cancer specific tools, the lack of knowledge on PRO in this context should be re-explored.

In the past, most attention in PRO and HRQoL research in dermatologic oncology has focused on malignant melanoma (MM) patients, because of the associated mortality and the impact of systemic therapies. It was found that the HRQoL impact in these patients is comparable to that of others cancers and that assessment is pivotal for further disease management [24]. KCs however are rarely life-threatening, but may be associated with HRQoL impairment. Because of low mortality, many KC patients are likely to develop multiple carcinomas and actinic keratoses (AK) during their lives. Having multiple carcinomas has been regarded as discrete events in the past, but is increasingly being recognized as a chronic illness [25]. The condition “actinic neoplasia syndrome (ANS)”, as proposed by Weinstock et al., is possibly the best way to consider this emerging group of patients and one of the main reasons to investigate the impact of this chronic condition on the HRQoL [20].

As in all other chronic diseases in dermatology, assessment of the HRQoL is pivotal for optimizing disease management, supportive care and integrating patient preferences. Evaluation of the impact on PRO is a way in which new treatments can discriminate themselves from conventional treatments including surgery. If treatments are equally (or even less) effective, PROs may shift the balance in favour of innovative therapies.

First study on HRQoL impact of KC

One of the first published studies addressing the impact of BCC on HRQoL demonstrated little impact with only minimal differences before and after treatment [26]. Measurements were performed using the UK Sickness Impact profile (UKSIP), a measure of general health status, and the Dermatology Life Quality Index (DLQI), a dermatology specific questionnaire. In this study the authors noticed very low overall scores (implying low impact on HRQoL), with only a minimal rise one week after treatment (excision, curettage and cautery, cryotherapy or excision and flap). Therefore they concluded that BCCs cause little handicap.

Generic questionnaires

Many studies in BCC and SCC patients, using multiple generic questionnaires (such as Short Form 36-item Health Survey (SF-36), Functional Assessment of Cancer Therapy-General (FACT-G)), reported a general health status comparable to the normal population in all domains of the SF-36 [10, 14, 16]. FACT-G scores were high compared with other malignancies suggesting little impairment on the subscales emotional, functional, physical and social well-being. It only demonstrated a slight improvement in emotional well-being after treatment [16]. The relevance of many items was frequently questioned by the study participants.

Another study focused on distress and coping strategies by using the Hospital Anxiety and Depression Scale (HADS) and the Ways of Coping Questionnaire – Cancer Version (WOC-CA) [17]. They reported that 19% of the NMSC patients experienced significant levels of distress (HADS score ≥ 13). The most often used coping strategies were behavioural escape avoidance and distancing.

Concluding, it is possible that the affected domains of HRQoL in KC patients are not fully captured by the generic questionnaires (SF-36 and FACT-G) since they show little impairment whilst HADS display distress in 19% of the KC patients.

Dermatology specific questionnaires

In a cross-sectional study among 52 German patients diagnosed with AK, BCC, SCC or Bowen's disease [19], the majority of the patients reported no to slight HRQoL impairment using the DLQI. However, a third of patients reported a moderate to large impairment, especially in the subscales "symptoms and feelings", "leisure" and "daily activities".

In a prospective US cohort study, BCC was associated with low DLQI scores indicating little HRQoL impairment. Four months after therapy, only the items focusing on physical improvement and embarrassment decreased significantly, suggesting suboptimal responsiveness of the DLQI. Moreover, lack of relevance of several items was mentioned by many participants [15, 21]. In both studies, the low scores indicate a lack of HRQoL impact or otherwise a poor content validity in the studied populations.

A large study among 931 patients with a history of KCs demonstrated a higher effect on each of the three domains of the Skindex-29 compared to a historical reference sample of persons without skin disease [20]. The main items responsible for this impairment were: 'worrying about seriousness of the skin condition' and 'worrying about it getting worse' in the emotions subscale. The most prominent predictive factors for worse Skindex-29 scores were AK count, ever-use of 5-fluorouracil (5-FU) and younger age [20]. Six KC-specific

items were added to the Skindex-29, suggesting a possible problem with content validity. The topics of these items were about bother (from scars, about appearance and about persistence of skin condition) and worry (about treatment and that the skin condition will spread) and were scored similar to the Skindex items.

A prospective trial by the same group with the Skindex-29 was performed to investigate the HRQoL effects of developing new KCs over a 36 month course. The 6 item KC-specific questions used in the previous mentioned study were also used. They reported no difference in Skindex-29 or KC-item scores in patients with new KCs, in comparison to their own scores 12 months prior. The only exception were the KC-specific items at 12 months, however this was not found at the 24- or 36-month assessment [12].
A prospective cohort study using the Skindex-16 to measure HRQoL in patients undergoing treatment (electrodessication and curettage, excision and Mohs surgery) reported worse scores on the emotions domain before treatment in the Mohs surgery group [8, 11]. There were no significant differences in functional outcomes, but the electrodessication and curettage group did not improve, whereas the excision and Mohs surgery group did [9].

The newer, Rasch-reduced Skindex-17 has been used in one more recent study comparing the field performance of the Skindex-29 with the Skindex-17 [18]. In this study with 2487 patients in total, 79 patients had NMSC. The mean scores in this subgroup were published for both questionnaires, showing a mean value of 18.2 (Skindex-29) and 19.6 (Skindex-17) in the symptoms domain, and a mean of 12.8 (Skindex-29) and 9.2 (Skindex-17) in the psychosocial domain. There was also a very high concordance between the Skindex-29 and Skindex-17 overall [18].

Concluding, dermatology specific tools such as the DLQI and to a lesser extent the Skindex questionnaires lack face validity and are not specific enough to capture KC patients concerns in detail.

Skin cancer specific questionnaires

Fortunately, several attempts have been made to develop skin cancer specific tools, since the above mentioned general and dermatology specific HRQoL instruments are not specific enough.

The Skin Cancer Index (SCI) was the first, developed after a thorough process using semi-structured interviews (20 patients and 6 healthcare providers) for item generation in stage I and rating of importance by a second sample of patients for item reduction in stage II (52 patients) [27]. The final 36 remaining items were captured within 6 domains: emotional, appearance, work / financial, lifestyle / recreation, social / family and physical / function-

ing. Based on test-retest reliability, validation and sensitivity testing the authors created a 15-item questionnaire with three domains: emotional, social and appearance [28, 29]. In a prospective study with 183 patients the SCI was tested in a tertiary care Mohs surgery clinic at initial consultation and four months after treatment. The average SCI total score post-surgery was 77.3 (vs. 68.3 pre surgery) and all three domain scores improved with treatment [21]. Paired *t* tests were used to assess responsiveness and showed P values <.001 in all three domains and in the total score. These findings were confirmed in a prospective study of 53 KC patients attending a plastic surgery clinic [30]. The SCI fails to capture one of the most reported issues in skin cancer patients; the often required behavioural changes (and related psychological issues) to reduce sun exposure.

The Skin Cancer Quality of Life Impact Tool (SCQOLIT) was created as a versatile questionnaire for use in nonmetastatic skin cancer (MM and NMSC) including HRQoL issues as mentioned before [31, 32]. The target population was patients with nonmetastatic skin cancer including MM patients [31]. The researchers collected data by asking 100 (50 MM and 50 NMSC) patients to fill in an open-ended anonymous 'Skin Cancer Quality of Life Question Sheet'. The most reported themes were 'concern about the public's lack of understanding and recognition of skin cancer', 'awareness of the importance of avoiding excess sun exposure' and 'concern that skin cancer could spread, recur or develop'. The HRQoL themes were then transformed by the authors into ten items in the questionnaire. In a prospective study with 120 patients (60 MM and 60 NMSC) the questionnaire was tested and validated. It has not been used in other studies yet. One major flaw in the SCQOLIT is the use of multiple issues and questions combined in one item. For example, the 5th item; "over the last week, how much have you felt emotional, anxious, depressed, guilty or stressed, in respect to your skin cancer or its treatment" tries to capture five psychological issues regarding two different aspects of the skin cancer in one item. Therefore, the interpretability of the questionnaire is insufficient. Similar to the SCI, the SCQOLIT also does not measure the impact of behavioural changes to reduce sun exposure.

Both the SCI and the SCQOLIT were both developed in a step-by-step approach to first generate and later reduce items [28, 32]. Most of the HRQoL instrument characteristics (validity (concept, construct and convergent), reliability, structure, responsiveness, floor and ceiling effects, item bias, respondent and administrative burden), as proposed by Both et al., apply for these instruments [33].

A recent Danish study described the development of the Actinic Keratosis Quality of Life (AKQoL) questionnaire focussing entirely on AK while using a similar approach as used in the SCI to first generate and later reduce items [27, 34]. They produced four domains

(functions, emotions, control and global) and 9 items. The AKQoL was tested and validated and is a promising instrument for use in studies comparing treatments for AK.[35]

In contrast to the before mentioned SCI and SCQOLIT, the Skin Cancer Quality of Life (SCQoL) questionnaire was developed and validated by using modern test theory, namely Rasch analysis [36]. The instrument was, however, derived from the previously developed AKQoL and only pre-tested in a very small sample (18 AK patients, 14 skin cancer patients) with the objective of distinguishing between patients with AK and those with skin cancer. From a content validity perspective, the above-mentioned questionnaires do not capture the psychological issues due to the behavioural changes often required to reduce sun exposure.[36, 37]

In conclusion, existing HRQoL measures are limited because they fail to capture important behavioral changes of KC patients, interpretability is questionable due to multiple items into 1 question and face and content validity are lacking. Therefore, a KC HRQoL instrument needed to be developed, which captures all important aspects and is easy to interpret.

Aims for this thesis

The aims of this thesis were to assess HRQoL and patient perception on disease, treatment and provided information in KC patients.

First we performed a review of the available literature to assess the available questionnaires (this chapter). Second, a dermatology specific HRQoL questionnaire and an existing disease-specific HRQoL questionnaire were used to assess the sensitivity of the questionnaires around an intensive treatment with topical imiquimod (chapter 2). The perception of the patients on treatment was also assessed. Since the existing questionnaires did not capture some important aspects of HRQoL or had major methodological flaws, we developed and validated the basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire (chapter 3) and additionally validated the English translation of the BaSQoL (chapter 4). Finally, to assess the impact of KC diagnosis and treatment on HRQoL and to identify factors associated with this we performed two population based studies, the first focusing on the role of information provision on HRQoL (chapter 5) and the second in relation to treatment (chapter 6).

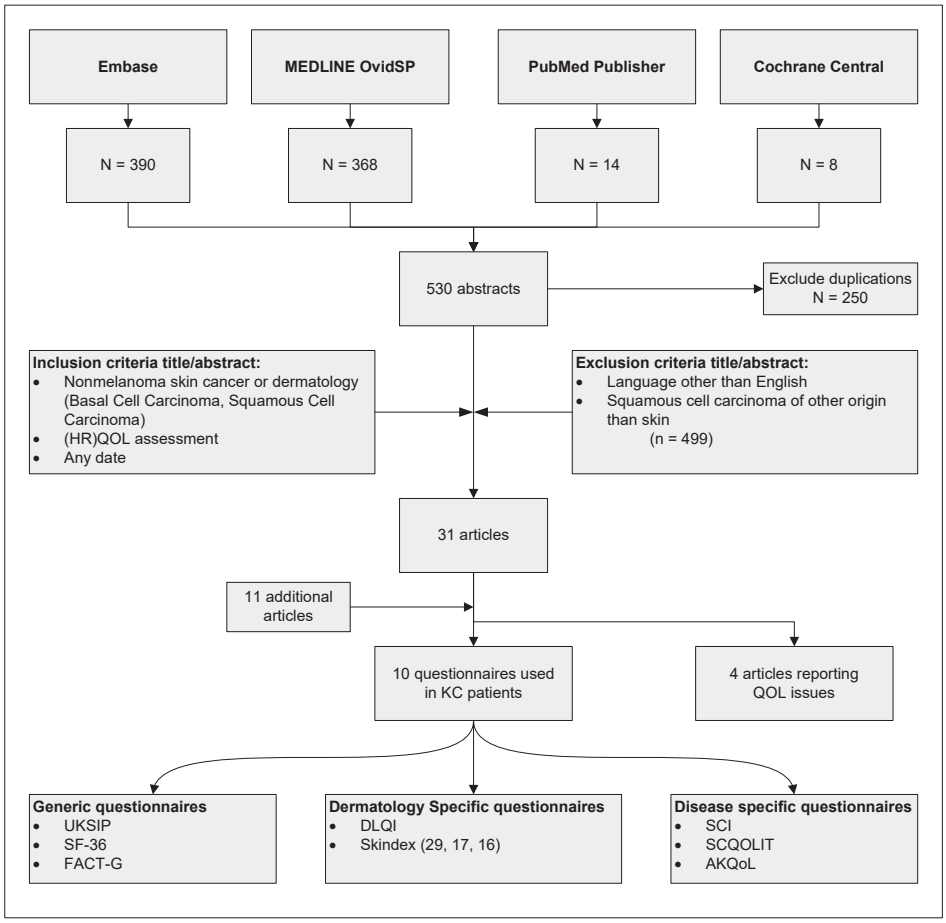

Figure 1. Flowchart systematic search as used in 'A review on quality of life in keratinocyte carcinoma patients' G Ital Dermatol Venereol 2013 Jun;148(3):249-54.

REFERENCES

1. Hollestein LM, de Vries E, Aarts MJ, Schroten C, Nijsten TE. Burden of disease caused by keratinocyte cancer has increased in The Netherlands since 1989. J Am Acad Dermatol. 2014;71(5):896-903.
2. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011;91(1):24-30.
3. (NCR) NCR. Cijfers over kanker [Available from: http://www.cijfersoverkanker.nl.
4. Flohil SC, van der Leest RJ, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. Eur J Cancer. 2013;49(10):2365-75.
5. Wehner MR, Cidre Serrano W, Nosrati A, Schoen PM, Chren MM, Boscardin J, et al. All-cause mortality in patients with basal and squamous cell carcinoma: A systematic review and meta-analysis. J Am Acad Dermatol. 2018;78(4):663-72 e3.
6. Jensen RE, Snyder CF. PRO-cision Medicine: Personalizing Patient Care Using Patient-Reported Outcomes. J Clin Oncol. 2016;34(6):527-9.
7. Nijsten T, de Haas ER, Neumann MH. Question the obvious. Arch Dermatol. 2007;143(11):1429-32.
8. Chen T, Bertenthal D, Sahay A, Sen S, Chren MM. Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Arch Dermatol. 2007;143(11):1386-92.
9. Chren MM. The Skindex Instruments to Measure the Effects of Skin Disease on Quality of Life. Dermatol Clin. 2012;30(2):231-6.
10. Chren MM, Lasek RJ, Quinn LM, Covinsky KE. Convergent and discriminant validity of a generic and a disease-specific instrument to measure quality of life in patients with skin disease. J Invest Dermatol. 1997;108(1):103-7.
11. Chren MM, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol. 2007;127(6):1351-7.
12. Lee KC, Weinstock MA, Veterans Affairs Topical Tretinoin Chemoprevention Trial G. Prospective quality of life impact of keratinocyte carcinomas: observations from the Veterans Affairs Topical Tretinoin Chemoprevention Trial. J Am Acad Dermatol. 2010;63(6):1107-9.
13. Moloney FJ, Keane S, O'Kelly P, Conlon PJ, Murphy GM. The impact of skin disease following renal transplantation on quality of life. Br J Dermatol. 2005;153(3):574-8.
14. Rhee JS, Loberiza FR, Matthews BA, Neuburg M, Smith TL, Burzynski M. Quality of life assessment in nonmelanoma cervicofacial skin cancer. Laryngoscope. 2003;113(2):215-20.
15. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Skin Cancer and Quality of Life: Assessment with the Dermatology Life Quality Index. Dermatol Surg. 2004;30(4 I):525-9.
16. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Quality of Life and Sun-Protective Behavior in Patients with Skin Cancer. Arch Otolaryngol Head Neck Surg. 2004;130(2):141-6.
17. Roberts N, Czajkowska Z, Radiotis G, Korner A. Distress and Coping Strategies Among Patients with Skin Cancer. J Clin Psychol Med Settings. 2012.

18. Sampogna F SA, Di Pietro C, Pagliarello C, Paradisi A, Tabolli S, Abeni D. Field performance of the Skindex-17 quality of life questionnaire: a comparison with the Skindex-29 in a large sample of dermatological outpatients. J Invest Dermatol. 2013;133(1):104-9.

19. Steinbauer J, Koller M, Kohl E, Karrer S, Landthaler M, Szeimies RM. Quality of life in health care of non-melanoma skin cancer - Results of a pilot study. JDDG J German Soc Dermatol. 2011;9(2):129-35.

20. Weinstock MA, Lee KC, Chren MM, Marcolivio K. Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. J Am Acad Dermatol. 2009;61(2):207-15.

21. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. The skin cancer index: Clinical responsiveness and predictors of quality of life. Laryngoscope. 2007;117(3):399-405.

22. Flohil SCS, I.; van Rossum, M.M.; Coebergh, J.W.; de Vries, E.; Nijsten, T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. J Invest Dermatol. 2012.

23. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer. 2012;48(13):2046-53.

24. Cornish D, Holterhues C, van de Poll-Franse LV, Coebergh JW, Nijsten T. A systematic review of health-related quality of life in cutaneous melanoma. Ann Oncol. 2009;20 Suppl 6:vi51-8.

25. van der Geer S, Reijers HA, van Tuijl HF, de Vries H, Krekels GA. Need for a new skin cancer management strategy. Arch Dermatol. 2010;146(3):332-6.

26. Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. Qual Life Res. 1996;5(2):191-4.

27. Rhee JS, Matthews BA, Neuburg M, Burzynski M, Nattinger AB. Creation of a quality of life instrument for nonmelanoma skin cancer patients. Laryngoscope. 2005;115(7):1178-85.

28. Matthews BA, Rhee JS, Neuburg M, Burzynski ML, Nattinger AB. Development of the facial skin care index: a health-related outcomes index for skin cancer patients. Dermatol Surg. 2006;32(7):924-34; discussion 34.

29. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. Validation of a quality-of-life instrument for patients with nonmelanoma skin cancer. Arch Facial Plast Surg. 2006;8(5):314-8.

30. Caddick J, Green L, Stephenson J, Spyrou G. The psycho-social impact of facial skin cancers. J Plast Reconstr Aesthet Surg. 2012;65(9):e257-9.

31. Burdon-Jones D, Thomas P, Baker R. Quality of life issues in nonmetastatic skin cancer. Br J Dermatol. 2010;162(1):147-51.

32. Burdon-Jones D, Gibbons K. The Skin Cancer Quality of Life Impact Tool (SCQOLIT): A validated health-related quality of life questionnaire for non-metastatic skin cancers. J Eur Acad Dermatol Venereol. 2012.

33. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726-39.

34. Esmann S, Vinding, G.R., Christensen, K.B., Jemec, G.B.E. Assessing the influence of Actinic Keratosis on Patients' Quality of Life - The AKQoL Questionnaire. Br J Dermatol. 2013;168(2):277-83.

35. Vis K, Waalboer-Spuij R, Snels D, Hollestein LM. Validity and Reliability of the Dutch Adaptation of the Actinic Keratosis Quality of Life Questionnaire (AKQoL). Dermatology. 2018;234(1-2):60-5.

36. Vinding GR, Christensen KB, Esmann S, Olesen AB, Jemec GB. Quality of life in non-melanoma skin cancer--the skin cancer quality of life (SCQoL) questionnaire. Dermatol Surg. 2013;39(12):1784-93.

37. Vinding GR, Esmann S, Olesen AB, Hansen LB, Christensen KB, Jemec GB. Interpretation of the skin cancer quality of life score: a validated quality of life questionnaire for non-melanoma skin cancer. Dermatology. 2014;229(2):123-9.

Chapter 2

Patient perception of imiquimod treatment for actinic keratosis and superficial basal cell carcinoma in 202 patients

Rick Waalboer-Spuij
Cynthia Holterhues
Simone van Hattem
Marie Louise A. Schuttelaar
Menno T.W. Gaastra
Daniëlle I.M. Kuijpers
Loes M. Hollestein
Tamar E.C. Nijsten

Dermatology. 2015;231(1):56-62.
S.Karger AG, Basel

ABSTRACT

Background/Aims

To document the impact on patient-reported outcomes and health-related quality of life (HRQoL) of treatment with imiquimod cream in patients with actinic keratosis (AK) and superficial basal cell carcinoma (sBCC).

Methods

This open-label, multicenter study included AK and sBCC patients eligible for treatment with imiquimod 5% cream. HRQOL was measured by the Skindex-17 and the Skin Cancer Index (SCI) and treatment satisfaction by the Treatment Satisfaction Questionnaire for Medication.

Results

118 AK patients and 84 with sBCC were included. Low baseline HRQoL impairment was found on both questionnaires, which remained low after treatment, except for a small dip at the end of the application period.

Conclusion

Imiquimod 5% cream treatment has no clinically relevant HRQoL impact in AK and sBCC patients according to the Skindex-17 and SCI. Effect of imiquimod treatment on HRQoL may be limited or these questionnaires do not fully capture relevant issues, such as fear of recurrence.

INTRODUCTION

Actinic keratosis (AK) is regarded as the first clinically relevant sign of sun induced skin damage. This in situ lesion is a precursor lesion for cutaneous squamous cell carcinoma (SCC). It is considered indicative of risk for developing SCC and basal cell carcinoma (BCC), approximately 0.5% per year per lesion progress into SCC.[1, 2] The incidence of cutaneous premalignancies and malignancies is increasing rapidly. Due to the high likelihood of developing multiple lesions during life, it is increasingly being considered as a chronic illness, i.e. “actinic neoplasia syndrome (ANS)”.[3-7]

In chronic diseases, patient reported outcomes (PRO) and health-related quality of life (HRQoL) are increasingly important outcomes in daily patient care. Treatment satisfaction is also a part of the PRO, and more applicable to diseases with multiple treatment options. In AK and sBCC, a variety of treatment options is available, including surgery, locally destructive procedures and non-invasive field therapies such as topical 5-fluorouracil, imiquimod, photodynamic therapy and ingenol mebutate.[8-10]

Imiquimod is available in the Netherlands as 5% cream (Aldara®). It acts as an immunomodulator by activating Toll-like receptor (TLR)-7 which stimulates the epidermal and dermal dendritic cells to produce cytokines and attract natural killer cells, and enhances proliferation of B lymphocytes.[11] Clinical trials have shown complete clearance rates around 70% and partial clearance rates around 80% for AK when treated with two four-week treatment courses of applying the cream 3 days a week.[8, 12] For sBCC the reported clearance rates are around 80% in a six-week treatment course, applying the cream 5 days a week.[9, 13]

Adverse events such as fever-like symptoms and application site reactions are common in imiquimod treatment due to the induced inflammatory response. These possible severe local and systemic reactions may have an impact on treatment response, daily life and treatment satisfaction. The objective of this multicenter open label study was to assess HRQOL and treatment satisfaction in patients with AK or sBCC treated with imiquimod.

MATERIAL AND METHODS

Study design

This open label clinical study was conducted in two university medical centers (Erasmus MC University Medical Center Rotterdam and UMC Groningen) and six other non-university hospitals across the Netherlands (Center Oosterwal Alkmaar, Amphia hospital

Breda, Catharina hospital Eindhoven, Reinier de Graaf hospital Delft, Diaconessen hospital Leiden, St. Antonius hospital Nieuwegein) between January 2009 and September 2011. The primary outcome was defined as the impact of treatment on dermatology-specific and disease-specific HRQoL in daily practice conditions. Secondary outcomes were short-term response rates, adverse events and treatment satisfaction. The study protocol was approved by the medical ethical committee (Erasmus MC, no. NL23594.078.08). All patients provided written informed consent.

Patients

Patients over 18 years of age, clinically diagnosed with one or multiple AK, or sBCC, and eligible for treatment (i.e. capable of performing the treatment correctly) with 5% imiquimod cream were invited to participate. Biopsy was only performed if thought necessary by the participating dermatologist. Patients with inadequate understanding of Dutch language to fill in the questionnaires were excluded.

Questionnaires

The questionnaires used in this study are the Dutch version of both the Skindex-17 and the Treatment Satisfaction Questionnaire for Medication (TSQM).[14, 15] To assess the disease-specific HRQoL, the Skin Cancer Index (SCI) was used. Since there was no Dutch version available, we translated the questionnaire based on forward-backward translation, as recommended.[16] To suit the questionnaire for use in AK patients, we replaced 'skin cancer' by 'actinic keratosis'.

Actinic keratosis

Participants with AK were instructed to apply imiquimod 5% cream once daily in a thin layer to the lesion including 5-10 mm of the surrounding skin, 3 days a week for 4 weeks. They were asked to complete the Skindex-17 and SCI at baseline, before treatment (T=0), directly after 4 weeks of treatment (T_{ak}=1) and 8 weeks after baseline (T_{ak}=2). Questions concerning side effects were administered at T_{ak}=1 and T_{ak}=2, and the TSQM at T_{ak}=2. The treating physician reported on patient history and current dermato-oncological status at baseline and answered questions concerning response at T_{ak}=2 and 16 weeks after baseline (T_{ak}=3). Response rates of the imiquimod therapy were assessed 16 weeks after start of therapy and categorized as 'no response', 'partial response' or 'complete response'. Complete response was defined as clinically observed complete clearance of the lesion, partial response as clinically observed decrease in size and no response as clinically observed no change in the lesion compared to T=0. Retreatment for another four-week course due to insufficient response was allowed if considered necessary by the local dermatologist.

Superficial basal cell carcinoma

Participants with sBCC were instructed to apply imiquimod 5% cream once daily in a thin layer to the lesion including 5-10 mm of the surrounding skin, 5 days a week for 6 weeks. They were also asked to complete the Skindex-17 and SCI at baseline, before treatment (T=0), directly after 6 weeks of treatment (T_{sBCC}=1) and 18 weeks after baseline (T_{sBCC}=2). Questions concerning side effects were administered at T_{sBCC}=1 and T_{sBCC}=2, and the TSQM at T_{sBCC}=2. The treating physician reported on patient history and current dermato-oncological status at baseline and answered questions concerning response at T_{sBCC}=2. Response rates of the imiquimod therapy were assessed at eighteen weeks and categorized as 'no response', 'partial response' or 'complete response'. These categories were defined similarly as in the AK group.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) and categorical variables are described as frequencies and percentages. If the data was not normally distributed, median and interquartile range (IQR) are displayed.

The Friedman test was performed to compare scores of the Skindex-17 and SCI at T0, T1 and T2. Wilcoxon signed rank tests were performed to assess the change compared to baseline (T0). The α-level for these tests was adjusted by using the Bonferroni correction.

The chi-squared test was used for the comparison of response rates and adverse events. Logistic regression was performed to calculate the p-value for trend, using adverse events as dependent variable and response rates as independent variable.

Pearson's (two continues variables) and point biserial (continues and dichotomous variable) correlation coefficients were used to assess correlations. Statistical significance was set at $p < 0.05$ (two-sided). Statistical analyses were performed using IBM SPSS Statistics, version 20 for Windows.

RESULTS

Study population

A total of 202 patients were included in this multicenter open label trial. The study population consisted of 118 patients with AK and 84 with sBCC. The mean age in the AK group was slightly higher than in the sBCC group (67 *vs.* 62 years). In the AK group 58% was male and 37% in de sBCC group. The medical history and previous treatment also differed. All baseline patient and lesion characteristics are shown in Table 1.

Table 1. Patient characteristics

	Actinic Keratosis N (%)	Superficial BCC N (%)
Total number of patients	118	84
Age (years) Mean (SD)	67 (10)	62 (12)
Missing	3 (3)	5 (6)
Gender: Male	68 (58)	31 (37)
Missing	4 (3)	6 (7)
History of cutaneous malignancy or premalignancy:[a]		
• None	25 (21)	26 (31)
• Actinic keratosis	79 (67)	15 (18)
• Melanoma	6 (5)	1 (1)
• Basal cell carcinoma	42 (36)	55 (66)
• Squamous cell carcinoma	13 (11)	4 (5)
• Other skin malignancy	2 (2)	4 (5)
Previous treatment with:[a]		
• None	24 (20)	27 (32)
• Cryotherapy	75 (64)	20 (24)
• Coagulation	2 (2)	1 (1)
• Imiquimod cream	4 (3)	2 (2)
• Surgery	56 (48)	48 (57)
• 5-Fluorouracil cream	22 (18)	7 (8)
• Photodynamic therapy	18 (15)	18 (21)
Missing	1 (1)	1 (1)
Number of lesions:		
• 1	29 (25)	53 (63)
• 2-4	15 (13)	25 (30)
• 5-9	34 (29)	4 (5)
• ≥ 10	36 (31)	-
Missing	4 (3)	2 (2)
Locations of lesions		
• Face / head / neck	78 (66)	14 (17)
• Scalp	23 (20)	1 (1)
• Torso	16 (14)	47 (56)
• Arms	19 (16)	20 (24)
• Legs	3 (3)	25 (30)
Missing	1 (1)	1 (1)

[a] Patients could choose multiple options, therefore the total may add up to >100%

HRQoL

The low baseline HRQoL impairment, as measured by the Skindex-17 and the SCI, did not improve after imiquimod therapy. (Table 2) The impact of AK and sBCC, as measured by the Skindex-17, demonstrated a modest increase (indicating more impairment) in both the scores of the symptom and the psychosocial domains at the end of the application period (e.g. from 26 to 37 on a standardized scale at week 6 for sBCC patients). The change in the SCI was modest for both AK and sBCC (difference < 3 points on a scale from 0 to 100). Almost all the domains and overall standardized scores were above 80 (with 100 indicating no impairment). Except for a small dip at the end of the application period, the SCI standardized scores remained comparable before and after therapy.

There was no correlation between age, gender or educational level and HRQOL scores (p-value >0.05 for age gender and educational level). AK and sBCC patients with adverse events had more HRQoL impairment compared to patients without adverse events ($p<0.05$), which is a consequence of the symptom-related questions in the HRQoL questionnaires. Patients who experience more adverse events (i.e. symptoms), will score higher at the symptom-related questions, leading to higher overall scores, indicating more HRQoL impairment.

Response rates

Retreatment with another four-week course was necessary in 58% of the patients in the AK group due to insufficient response. Overall, complete response was achieved in 46% of the AK patients and 76% of the sBCC patients. Partial response in 35% of the AK patients and 8% of the sBCC patients. (Table 3)

When these response rates of the AK patients are linked to the percentage reporting adverse events, a significant trend is found ($p=0.001$) between the two, showing a high percentage of adverse events in the complete response group (74%) which decreases among patients with a partial response (39%) and without a response (25%). This was not found in the sBCC group.

Adverse events

About half of the patients using imiquimod cream reported at least some itching, redness and pain/burning sensation of which 26% reported it to be severe. A third of patients noted to have vesicles/bullae or swelling. Approximately 10-15% of all patients self-reported to have fever or influenza-like symptoms. The proportion of patients reporting these adverse events was very comparable between the AK and sBCC group. (Table 4) Overall, 6-7% of patients discontinued therapy due to side-effects and 5% would not use imiquimod again due to adverse events (5,1% of AK and 4,8% of sBCC patients).

Table 2. Health-related quality of life for AK and sBCC patients treated with imiquimod

	Actinic Keratosis					Superficial BCC				
	n	Week 0	Week 4	Week 8	p-value	n	Week 0	Week 6	Week 18	p-value
Skindex-17 standardized scores										
median (IQR) range 0-100										
• psychosocial score	93	0 (0-8.3)	0 (0-16.7)*	0 (0-4.2)*	< 0.001	54	0 (0-9.4)	0 (0-16.7)	0 (0-9.4)	0.305
• symptom score	101	30.0 (10.0-40.0)	30.0 (10.0-50.0)*	20.0 (0-40.0)*	< 0.001	58	20.0 (10.0-40.0)	40.0 (10.0-50.0)*	10.0 (0-30.0)*	< 0.001
Skin Cancer Index standardized scores										
median (IQR) range 0-100										
• Total Emotional Subscale	94	85.7 (75.0-92.9)	82.1 (71.4-89.3)*	85.7 (78.6-92.9)	0.003	58	87.5 (75.0-96.4)	82.1 (70.5-92.9)	85.7 (75.0-96.4)	0.066
• Total Social Subscale	102	100 (95.0-100)	95.0 (85.0-100)*	100 (90.0-100)	< 0.001	63	95.0 (90.0-100)	100 (88.6-100)	97.5 (95.0-100)	0.180
• Total Appearance Subscale	105	91.7 (75.00-100)	91.7 (75.0-100)	100 (83.3-100)*	0.002	63	91.7 (81.3-100)	91.7 (75.0-100)	91.7 (75.0-100)	0.185
• Total Skin Cancer Index	91	89,7 (81.7-96.4)	90.1 (78.5-96.0)*	93.6 (84.5-96.4)	< 0.001	58	91.9 (80.8-97.8)	91.0 (77.8-96.4)	91.7 (80.6-97.8)	0.046

*Bonferroni corrected p-value significant compared to baseline score at Week 0.

Table 3. Response rates at T=2[c] to imiquimod therapy

	Actinic Keratosis			Superficial BCC
	1st cycle N=118 (%)	2nd cycle[a,b] N=69 (%)	Overall N=118 (%)	N=84 (%)
• No response	9 (8)	4 (6)	4 (3)	3 (4)
• Partial response	60 (51)	41 (59)	41 (35)	7 (8)
• Complete response	42 (36)	12 (17)	54 (46)	64 (76)
• Cessation of therapy due to side effects	4 (3)	5 (7)	9 (8)	5 (6)

[a] Excluding those with complete response in 1st cycle, those who ceased therapy and missing.
[b] 69 / 118 needed a 2nd cycle
[c] response rate was assessed at 16 weeks for AK and at 18 weeks for superficial BCC
abbreviations: BCC = basal cell carcinoma

Table 4. Adverse events among AK and sBCC patients treated with imiquimod cream at T=1[a]

Type of reaction N (%)	Actinic Keratosis				Superficial BCC			
	Total	Intensity			Total	Intensity		
	Week 4 N=118	Mild	Moderate	Severe	Week 6 N=84	Mild	Moderate	Severe
Itching	58 (49)	19 (33)	24 (41)	15 (26)	38 (45)	16 (42)	14 (37)	8 (21)
Redness	61 (52)	9 (15)	23 (38)	29 (48)	41 (49)	6 (15)	17 (42)	18 (44)
Pain / Burning sensation	49 (42)	13 (27)	20 (41)	16 (33)	34 (41)	9 (27)	14 (41)	11 (32)
Squamae	42 (36)	15 (36)	23 (55)	4 (10)	17 (20)	8 (47)	7 (41)	2 (12)
Vesicles / Bullae	40 (34)	15 (38)	13 (33)	12 (30)	31 (37)	8 (26)	17 (55)	6 (19)
Swelling	37 (31)	14 (38)	16 (43)	7 (19)	23 (27)	9 (39)	14 (61)	-
Other local complaints	9 (8)	2 (22)	3 (33)	4 (44)	3 (4)	-	1 (33)	2 (67)
Influenza-like symptoms	16 (14)	2 (13)	7 (44)	7 (44)	11 (13)	4 (36)	6 (55)	1 (9)
Fever	11 (9)	4 (36)	2 (18)	5 (45)	9 (14)	3 (33)	4 (44)	2 (22)
Other systemic complaints	7 (6)	-	2 (29)	5 (71)	8 (10)	1 (13)	3 (38)	4 (50)

Patients could report multiple reactions, therefore the total may add up to >100%
[a] T=1 was 4 weeks after treatment for AK and 6 weeks after treatment for sBCC.

Treatment satisfaction

Treatment satisfaction, as measured by the TSQM, showed that patients appreciated the convenience of imiquimod use most (>60 on a scale from 0 to 100), but the overall satisfaction scored less than 60. The side effect domain of the TSQM scores were comparable AK and sBCC patients. (Figure 1) No correlation was found between treatment satisfaction and adverse events or previous treatment. Patients with complete response had higher treatment satisfaction (median TSQM overall score 61 for AK and sBCC) than those with partial (median TSQM overall score 54 for AK and 53 for sBCC) or without a response (median TSQM overall score 22 for AK and 40 for sBCC) in both groups ($p<0.05$).

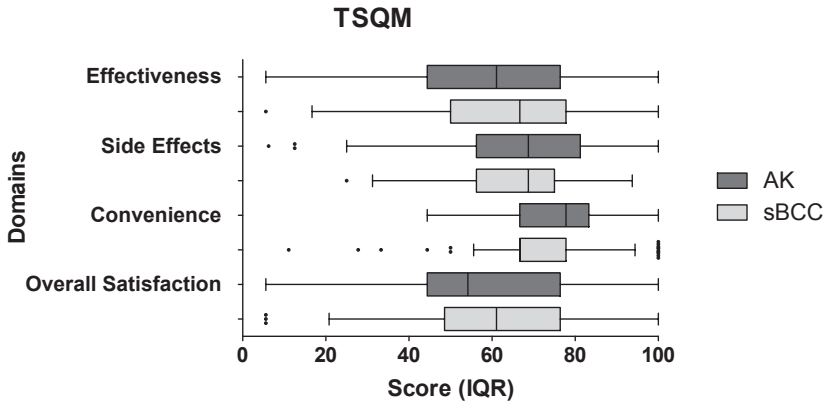

Figure 1. Treatment Satisfaction Questionnaire for Medication (TSQM) scores.
AK = Actinic Keratosis, sBCC = superficial Basal Cell Carcinoma, IQR = Interquartile Range

DISCUSSION

In this study, HRQoL impairment, as measured by the Skindex-17 and SCI, was low prior to treatment and remained low after treatment in both patients with AK and sBCC.

Our results are in line with published data. These results suggests little to moderate impact on HRQoL of AK/BCC treatment or suggest that the available HRQoL instruments are not specific and sensitive enough to record the issues considered important in this large patient population.[17] The Skindex-17 is probably not specific enough to capture specific skin cancer patient concerns. Although the SCI was developed specifically for BCC and SCC patients and demonstrated impairment on the emotional and the appearance subscales in the validation study, in our study standardized scores (0 to 100) were all above 75.[18] This observation implicates that HRQoL impairment in our population (i.e. treated with imiquimod) is less than in patients who will have to be treated surgically, or that the SCI is only suitable for use in patients being treated surgically, since it was developed in a tertiary care Mohs surgery clinic.[19]

Responsiveness, another pivotal feature of HRQoL questionnaires, addressing the effect of treatment, could not be confirmed for the Skindex-17 and the SCI. In the Skindex-17 this can be explained by the more generic aspect of the items in the questionnaire. The SCI however displayed good responsiveness before and after treatment in previous studies. [19, 20] The only treatment assessed however was surgical treatment and the lesions were only located in the head-neck area. Our data suggest only minimal responsiveness in all subscales, but not clinically relevant when considering Norman's "rule of thumb".[21]

We showed that imiquimod scored an overall satisfaction score around 60. It is considered a convenient therapy, but the side effects were scored lower than the overall score by the patients. About half had local side effects and 10-15% systemic reactions. The observed adverse events and response rates were comparable to the large imiquimod RCT.[13]

Application site reactions occurred similarly in both of our groups. The patient reported severity of these reactions are also alike, despite the different treatment regimen in the groups. The intensity was mostly scored as mild or moderate. These findings are in accordance with previous reports.[13, 22-24]

Strengths & Limitations

In our study, we were able to assess HRQoL, treatment satisfaction and short term response rates in daily practice use of imiquimod 5% cream in both AK and sBCC patients. To our knowledge, this is the first study assessing treatment satisfaction using a validated tool. One previous study used a 7-point Likert scale and another an analogue scale [0-10]. [22, 25]

Unfortunately, we have no additional data on all AK and sBCC patients visiting the department. Patient characteristics and reason for non-participation of patients who refused to participate in this study were not available, which hindered the judgment about the presence of a possible selection bias. Selection bias may have occurred if specific patient groups were not included in our study and those patients would have a lower or higher impact on HRQoL or different treatment satisfaction. For example, if older patients refused to participate and the impact of imiquimod on HRQoL among older patients is larger, than the impact of imiquimod in our study on the HRQoL would have been underestimated if only younger patients were included in which the impact was smaller. We deemed selection bias due to age likely because some older patients may not be capable of performing the treatment correctly, and therefore may have refused to participate.

CONCLUSION

In conclusion, this study showed that imiquimod 5% cream treatment has no clinically relevant HRQoL impairment nor improvement after treatment in both AK and sBCC patients according to the Skindex-17 and the SCI. Patients report to tolerate the treatment well, but overall satisfaction is only around 55 to 60% in both groups. The results of this study also suggest that the available HRQoL instruments are not specific and sensitive enough to capture the issues considered important in skin cancer patients.

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REFERENCES

1. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42(1 Pt 2):4-7.
2. Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. J Invest Dermatol. 2013;133(8):1971-8.
3. Traianou A, Ulrich M, Apalla Z, De Vries E, Bakirtzi K, Kalabalikis D, et al. Risk factors for actinic keratosis in eight European centres: a case-control study. Br J Dermatol. 2012;167 Suppl 2:36-42.
4. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011;91(1):24-30.
5. Flohil SCS, I.; van Rossum, M.M.; Coebergh, J.W.; de Vries, E.; Nijsten, T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. J Invest Dermatol. 2012.
6. van der Geer S, Reijers HA, van Tuijl HF, de Vries H, Krekels GA. Need for a new skin cancer management strategy. Arch Dermatol. 2010;146(3):332-6.
7. Weinstock MA, Lee KC, Chren MM, Marcolivio K. Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. J Am Acad Dermatol. 2009;61(2):207-15.
8. Stockfleth E, Terhorst, D., Braathen, L., Cribier, B., Cerio, R., Ferrandiz, C., Giannetti, A., Kemeny, L., Lindelof, B., Neumann, M., Sterry, W., Kerl, H. on behalf of the European Dermatology Forum. Guidelines For the Management of Actinic Keratoses. 2010 8-8-2013.
9. Trakatelli M, Morton, C.A., Nagore, E., Ulrich, C., del Marmol, V., Peris, K., Basset-Seguin, N. on behalf of the European Dermatology Forum. Update of the Guideline on Basal Cell Carcinoma. 2012 8-8-2013.
10. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366(11):1010-9.
11. Schon MP, Schon M. Imiquimod: mode of action. Br J Dermatol. 2007;157 Suppl 2:8-13.
12. Stockfleth E, Sterry W, Carey-Yard M, Bichel J. Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. Br J Dermatol. 2007;157 Suppl 2:41-6.
13. Arits AH, Mosterd K, Essers BA, Spoorenberg E, Sommer A, De Rooij MJ, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncol. 2013;14(7):647-54.
14. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health. 2005;8 Suppl 1:S9-S24.
15. Nijsten TE, Sampogna F, Chren MM, Abeni DD. Testing and reducing skindex-29 using Rasch analysis: Skindex-17. J Invest Dermatol. 2006;126(6):1244-50.
16. Bullinger M, Alonso J, Apolone G, Leplege A, Sullivan M, Wood-Dauphinee S, et al. Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment. J Clin Epidemiol. 1998;51(11):913-23.
17. Waalboer-Spuij R, Nijsten TE. A review on quality of life in keratinocyte carcinoma patients. G Ital Dermatol Venereol. 2013;148(3):249-54.

18. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. Validation of a quality-of-life instrument for patients with nonmelanoma skin cancer. Arch Facial Plast Surg. 2006;8(5):314-8.

19. Rhee JS, Loberiza FR, Matthews BA, Neuburg M, Smith TL, Burzynski M. Quality of life assessment in nonmelanoma cervicofacial skin cancer. Laryngoscope. 2003;113(2):215-20.

20. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. The skin cancer index: Clinical responsiveness and predictors of quality of life. Laryngoscope. 2007;117(3):399-405.

21. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.

22. Dauden E, Group BS. Effectiveness and satisfaction with imiquimod for the treatment of superficial basal cell carcinoma in daily dermatological practice. J Eur Acad Dermatol Venereol. 2011;25(11):1304-10.

23. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2004;50(5):722-33.

24. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. Cochrane Database Syst Rev. 2012;12:CD004415.

25. Serra-Guillen C, Nagore E, Hueso L, Llombart B, Requena C, Sanmartin O, et al. A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. Br J Dermatol. 2011;164(2):429-33.

Chapter 3

Development and validation of the basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire

Rick Waalboer-Spuij
Loes M. Hollestein
Reinier Timman
Lonneke V. van de Poll-Franse
Tamar E.C. Nijsten

on behalf of the BaSQoL Group
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ABSTRACT

Health-related quality of life (HRQoL) is important in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) management. Disease-specific questionnaires exist, but with important shortcomings. Our goal was to develop and validate a questionnaire suitable for use in all BCC and SCC patients. In a four-phase trajectory, a preliminary questionnaire was created and tested population-based (1173 patients). The questionnaire was reduced using exploratory factor analysis and item response theory. Individual item performance was assessed using classical test theory. 721 patients completed the questionnaire. The number of items was reduced to 16, covering five scales. Confirmatory factor analysis showed a good fit. Cronbach's αs (range 0.67 – 0.82) were reasonable to high with good internal consistency. The Basal and Squamous cell carcinoma Quality of Life questionnaire has good face, content and construct validity. It is useful in the wide range of BCC and SCC patients and captures HRQoL impact in different timeframes.

INTRODUCTION

The use of patient-reported outcome measures (PROMs) and more specifically health-related quality of life (HRQoL) in dermatology patients has dramatically increased over the past decades. It is now an essential outcome for clinical studies and in daily practice, especially in chronic inflammatory skin diseases [1, 2]. In skin cancer, the use of PROMs and HRQoL has only been used over the past two decades and most of the focus has been on melanoma [3]. Since the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) is increasing rapidly [4-6], the need for PROMs assessment including HRQoL is warranted to evaluate individual and global disease burden. Generic, cancer or even melanoma specific HRQoL instruments are neither content specific nor sensitive enough to detect the impact of the rarely life-threatening BCCs and SCCs that are most often treated by conventional excision. A specific issue for keratinocytic cancers is that patients are likely to develop multiple carcinomas and also actinic keratosis (AK) (so called actinic neoplasia syndrome) and that they can check their skin constantly [7].

Measurement of HRQoL in BCC patients has occurred in several studies, using generic, cancer related and dermatology specific questionnaires, all reporting little to no impact [7-13].

A few disease specific questionnaires have been developed, but these have several important shortcomings. The Skin Cancer Index (SCI) is developed and tested only in a tertiary care Mohs surgery clinic and therefore only suitable for use in a selected population [14, 15]. The Skin Cancer Quality of Life Impact Tool (SCQOLIT) is developed as a tool for non-metastatic skin cancer patients [16]. A limitation of the SCQOLIT is the addressing of five psychological issues regarding two different aspects in one item. In contrast to the SCI and the SCQOLIT , the Skin Cancer Quality of Life Questionnaire (SCQoL) was developed and validated with modern test theory, namely Rasch analysis [17]. This instrument was however derived from the previously developed Actinic Keratosis Quality of Life questionnaire (AKQoL) and pre-tested in a small sample (18 AK patients, 14 skin cancer patients) with the objective to distinguish the difference between AK and skin cancer patients [18]. From a content validity perspective, we feel that the before mentioned questionnaires do not to capture the psychological issues due to the often required behavioural changes to reduce sun exposure [19].

The objective of this study is to create and validate a HRQoL questionnaire suitable for BCC and SCC patients addressing relevant issues for patients and healthcare providers using different methodological approaches.

METHODS

Study design

The BCC and SCC specific HRQoL questionnaire was prepared and developed following the European Organisation for Research and Treatment of Cancer (EORTC) QOL group guidelines as much as possible [20-22]. However, the questionnaire is not an EORTC QOL group product and was not developed internationally. The development was conducted in four phases.

Phase I:

The main goal of phase I was to generate an extensive list of HRQoL issues relevant to BCC and SCC patients. One focus group meeting to discuss and generate HRQoL issues was facilitated by two independent psychologists with no in-depth skin cancer knowledge. The group consisted of 10 BCC and/or SCC patients with different types and numbers of tumours, treatments, gender and age. The audio recording of the focus group was analysed by RWS to extract as much issues as possible without formal transcribing. Extensive literature searches through PubMed (Table S4) and semi-structured interviews with 5 healthcare providers (HCP) provided additional issues [23].

The issues were discussed in an expert panel including dermatologists, psychologists and epidemiologists to identify the relevant disease-specific domains and issues (figure 1).

The remaining issues were presented to HCP (dermatologists, plastic surgeons, ophthalmologist, head-neck ENT surgeon, general practitioners) and patients for feedback and cognitive debriefing. They were also asked to rate the issues for relevance from 1 (not relevant) to 4 (very relevant) on a Likert scale (relevance rating). Issues with relevance mean score ≥ 1.5 were selected for priority rating. HCP and patients were asked to select 15 core issues to be included in the questionnaire (priority rating). Priority ratings of ≥ 30% were scored in het HCP group and ≥ 20% in the patient group. Issues scoring ≥ 3 criteria were included in the final issue list [20].

Phase II:

The final issue list was rephrased into questions compatible with the EORTC QLQ-C30 in terms of format of response categories [24]. The time frame of the questions was divided into three parts (‘since diagnosis’, ‘time between diagnosis and treatment’ and ‘during the past week’) since the items fitted different timeframes.

Phase III:

The item questionnaire was pretested in 16 patients.

Phase IV:

The questionnaire was field tested in 1,173 patients selected from the Netherlands Cancer Registry, as collected by Comprehensive Cancer Centre Netherlands, location Eindhoven. Patients were selected if they were diagnosed in one of the nine participating hospitals or clinics during the past twelve months before the field testing. The aim of the field testing was to determine scale structure, reliability, validity and to reduce the number of items. The Skindex-17 and the QLQ-C30 were also administered.

Statistical analysis

Descriptive statistics (means and percentages) were used in phase II to calculate relevance and priority ratings of the issue list and in phase IV to describe the patient characteristics. Type of BCC was grouped as multifocal (8091 of the International Classification of Disease for Oncology [ICD-O3]), infiltrating (8092, nodular (8097), other (8090,8093,8094,8095). Aforementioned analyses were performed in IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York: IBM Corporation).

After phase IV, the components were determined using principal component analyses (PCA) with varimax rotation. The number of components was determined with a Monte Carlo PCA for parallel analysis [25]. We ran two PCAs, one with complete cases and one with mean substitution, with one missing at most. Items with loadings of >0.40, were selected for Item Response Theory (IRT) [26]. IRT was used to select a minimum number of the best discriminating items covering the whole range of the latent traits.

For IRT analysis, we applied the two parameter latent trait model (2PL-ltm) [27] of the ltm package in R version 3.0.0. The 2PL-ltm program results in an ordering of the items on a given trait or component and supplies a discrimination value for each item. The 2PL-ltm program needs binary items as input. By collapsing the four answer category to binary items, some loss of information is induced. This method is preferred over multicategory models, because these do not provide an ordering of the items.

The original categories were “not at all”, “a little”, “quite a bit “ and “very much”. For the majority of items the median was between the first and second category, and for this reason we dichotomized between “not at all” and “a little” or more.

The items were selected on basis of their position on the relevant trait or component and their discriminative value. As we postulated an absolute maximum of five items per subscale, we divided the range between the lowest and highest position by five, and we choose from each of these intervals the item with the highest discriminative value. We

checked the unidimensionality of the remaining items with the “unidim” test of the ltm package.

After the item reduction by the 2PL-ltm model, item performance features as used in Classical Test Theory (CTT) were tested. The definitions of the features are presented in Table S5 [28, 29]. Descriptive statistics were used to test item difficulty (missing responses) and response distribution. Spearman’s correlation coefficients were calculated for item-test and item-rest correlation, and also to test item discriminant validity. Internal consistency was tested via Cronbach’s α coefficients. Stepwise regression was performed in order to check the percentage of variance explained by the items in a subscale. The multitrait-multimethod correlation matrix was used to assess convergent and discriminant validity.

The resulting factors were also tested with oblique confirmatory factor analyses. We applied two analyses, a complete cases analysis and a maximum likelihood analysis with missing values. We evaluated the fit indices according to the recommendations of Kline, Hu & Bentler and Brown[30-32]. The correlations between the subscales were reported. The confirmatory factor analyses were performed with STATA version 14.1 (College Station, Texas 77845 USA). All P-values were two sided and considered significant if $\alpha < 0.05$.

RESULTS

Phase I-IV:

The focus group meeting resulted in 63 issues, that were extended to 108 issues after literature searches (Table S4) and HCP interviews (Figure 1). After an expert consensus meeting 51 issues were eliminated from the list due to overlap of the issues, questions concerning information about the disease, cancer generic issues or other problems that were considered outside of the domain of HRQoL.

The remaining 57 issues were rated (mean scores, range, relevance and priority rating) by 42 patients (mean age of 70 years, 1-30 years since diagnosis, 27 BCC, 5 SCC and 10 diagnosis unknown to the patient) and 15 HCP (7 dermatologists, 1 plastic surgeon, 1 head neck ENT-surgeon, 1 ophthalmologist, 1 radiation oncologist and 4 general practitioners) and resulted in the removal of the 24 issues with lowest relevance and priority ratings (Figure 1).

The remaining 33 issues were constructed into a provisional 33 item questionnaire (Table S1)

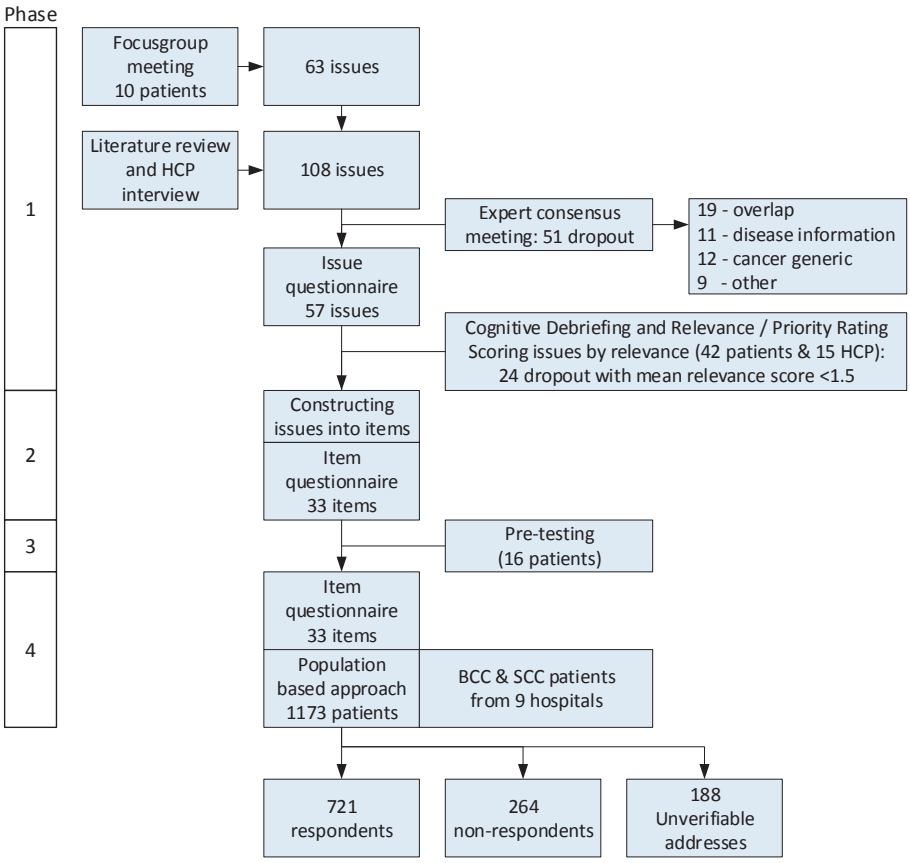

Figure 1. Questionnaire development phases.
HCP = Health Care Professional, BCC = Basal Cell Carcinoma, SCC = Squamous Cell Carcinoma.
Phase number as described by the EORTC QOL group guidelines.

This provisional questionnaire was reviewed by 16 patients for readability, clarity of the items and overlapping of the items and none of the items were excluded or rephrased.

The field testing was performed by selecting 1,173 BCC and SCC patients from 9 hospitals. The response rate was 61% and 721 patients completed the questionnaire. (Table 1) Of all respondents 85% had BCC and 15% had SCC.

The data contained 582 complete cases, 63 cases with one missing value and 76 cases with more missing values.

Table 1. Patient Characteristics

	Respondents	Non-respondents	Unverifiable addresses	p-value
Total number of patients (N)	721	264	188	
Sex	(column%)	(%)	(%)	0.0063
Male	51	37	49	
Female	49	63	51	
Age				
Mean, SD	67.3, 11.8	71.4, 13.5	61.3, 15.1	<0.0001
Median, IQR	68, 15	74.5, 16	61.5, 22.5	
<39	1	2	9	<0.0001
40-49	8	7	16	
50-59	14	9	21	
60-69	31	18	22	
70-79	32	33	18	
80+	14	31	13	
SCC (%)	15	16	9	0.0560
Socioeconomic status				
Low	17	22	13	<0.0001
Intermediate	28	29	20	
High	29	31	18	
Institute	3	4	4	
Unknown	23	13	46	
Location of tumour				
Face	78	78	85	0.1000
Other	22	22	15	
Other skin tumours*				
Multiple BCC	16	19	11	0.1000
Multiple SCC	9	7	6	#
MM	0	0	1	#
Other	0	0	0	#
The following variable is only available for BCC				
BCC (N)	613	222	171	
Type BCC	(column%)	(%)	(%)	
Multifocal	11	8	9	0.070
Infiltrating	18	22	15	
Nodular	64	65	65	
Other	7	4	12	

* patients can have combinations

No statistical test performed due to low numbers

Principal component analyses

The two PCAs (complete cases and with one missing included) both resulted in six components, with the same items loading. Items 23 and 24 formed a separate component, and at face value these items are nearly identical. Leaving out one of them resulted in five components. Item 24 had a higher factor loading than item 23, for this reason item 23 was removed from the analyses. Only item 5 was not eligible, because it had a component loading lower than 0.40.

The five components were labelled as: Worries (8 items, α=0.87), Appearance (7 items, α=0.84), Behaviour (7 items, α=0.85), Diagnosis & Treatment (5 items, α=0.84) and Other people (4 items, α=0.79) (Table 2).

Table 2. Subscales and item characteristics.

	Missing values	Principal component loading	2PL-ltm solution		Selected BaSQoL items	Unidim p-value
			Position	Discrimination		
Worries					α = 0.82	0.0297
19	2	.764	0.013	2.609	10	●
17	1	.724	-0.404	3.056	9	●
25	0	.696	0.249	2.079	12	●
26	0	.665	-0.164	2.206		
21	2	.646	0.827	2.472	11	●
28	0	.630	-0.458	2.357		
18	1	.626	-0.219	2.247		
24	1	.482	-0.115	0.619		
10	2	.401	0.035	1.112		
Appearance					α = 0.71	0.6733
33	0	.787	1.239	5.025	15	●
31	1	.779	1.151	4.414		
29	0	.770	1.144	3.987		
22	2	.725	1.008	3.389	13	●
30	3	.661	1.253	3.06		
15	1	.580	*			
32	9	.459	1.981	2.251	14	●
Behaviour					α = 0.79	0.6931
9	0	.838	0.162	3.985	4	●
4	7	.763	0.212	2.357		
6	1	.760	0.028	2.479		
1	1	.748	-0.099	2.846	1	●
2	2	.741	0.296	2.79	2	●

Table 2. Subscales and item characteristics. (*continued*)

	Missing values	Principal component loading	2PL-ltm solution		Selected BaSQoL items	Unidim p-value
			Position	Discrimination		
3	5	.568	0.748	1.297	3	●
5	1	.349				
Diagnosis & Treatment					α = 0.78	0.7426
12	7	.797	0.34	5.472	7	●
14	2	.745	0.624	2.146		
13	1	.686	0.654	2.381		
11	1	.610	-0.17	1.955	6	●
16	2	.509	-0.942	2.288	8	●
Other People					α = 0.67	1.000
8	2	.809	-0.403	2.362	5	●
7	1	.790	-0.491	2.299		
27	2	.705	0.130	3.624	16	●
20	0	.572	0.048	2.017		

* Item 15 prevented the program to converge, this items also had a high loading on the treatment component (0.371). Preliminary questionnaire item numbers are displayed in the first column (Table S1).

Item response analyses

The position on the components and discrimination values resulting from the 2PL-ltm analyses are presented in Table 2. On basis of these values the item set was reduced from 32 to 16 items. The characteristic curves of the selected items are presented in Figure 2. The "Worries" and "Behaviour" subscales retained 4 items (αs 0.79-0.82), the "Appearance" and "Diagnosis & Treatment" subscales retained three items (αs = 0.71-0.78) and the "Other people" subscale retained 2 items (α = 0.67). The unidim p-value for the 4 selected items of "Worries" was significant (p=0.03), indicating that this subscale was not sufficiently unidimensional. This lack of unidimensionality was caused by item 21. However, the unidim p-value of all 9 items was 0.38 indicating that all 9 items (including 21) belonged to an unidimensional subscale. We decided to include the item in the final questionnaire because we considered it to be a conceptually important aspect and because of the marking of the scale of the highest position on the latent trait. Item 15 in the "Appearance" prevented the program to converge. Inspection of this item showed that it also loaded (0.37) on the "Diagnosis & Treatment" subscale, and thus violated the unidimensionality assumption. It was decided to delete this item from the analyses. After this the unidim test was insignificant for the subscales appearance, behaviour, diagnosis & treatment and other people, indicating that the unidim assumption has been met for these subscales.

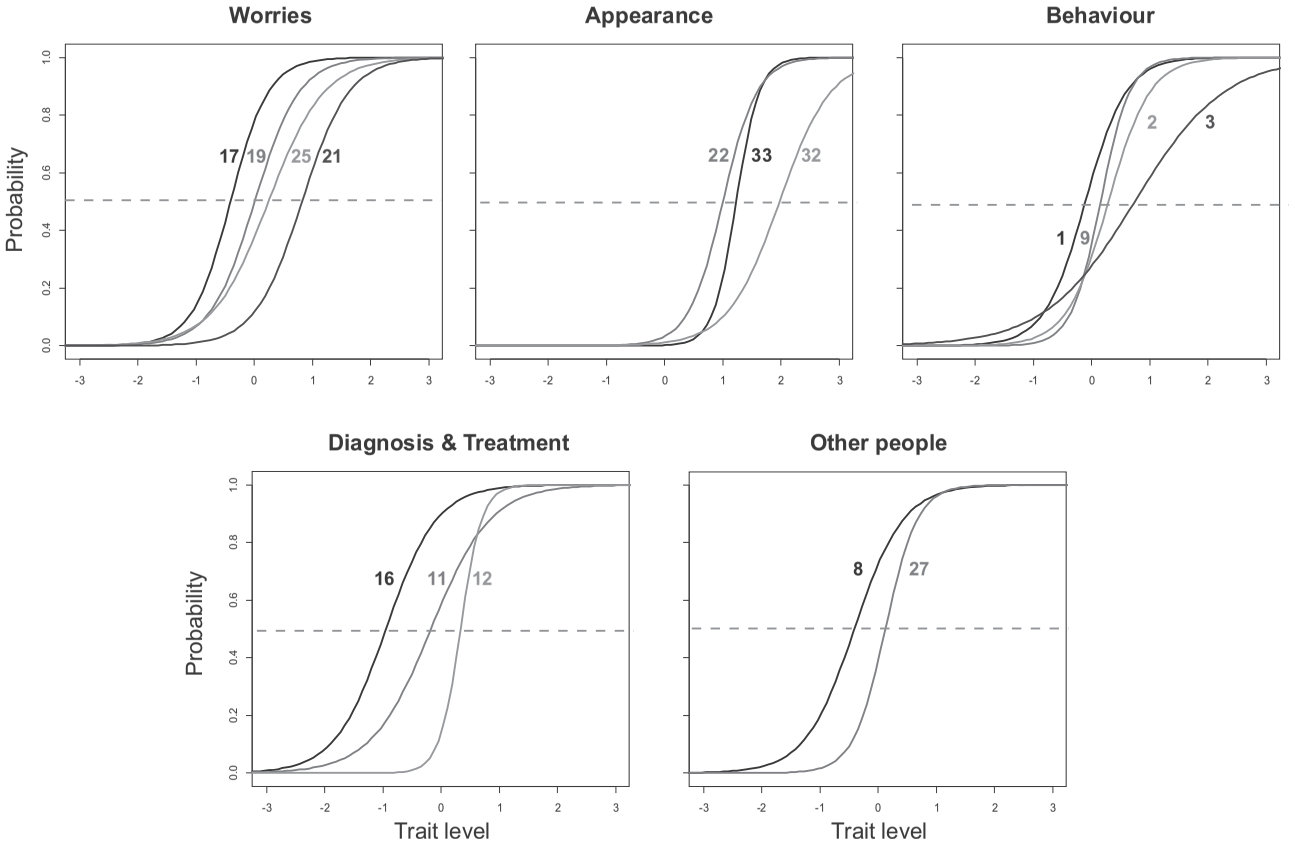

Figure 2. Item characteristic curves of the subscales.
The item characteristic curves depict the placement of the items on a latent ability and its discriminative value. For example, item 3 (provisional item number) discriminates best between patients with a high behavioural score, and item 1 discriminates best in patients with a low score. Additionally, item 9 discriminates better than item 3.

The resulting 16 item questionnaire was named Basal and Squamous cell carcinoma Quality of Life (BaSQoL) questionnaire. (Table S2)

Classical Test Theory

The eight CTT item performance features of the newly constructed questionnaire showed that 7 out of 16 items showed only one suboptimal feature and one showed two suboptimal performance features (Table 3). From a CTT perspective, the overall performance of the BaSQoL is therefore considered as good. There was no significant correlation with the subscales of the Skindex-17 and the QLQ-C30 suggesting different issues were captured.

Table 3. Item performance of the BaSQoL questionnaire

	BaSQoL subscales																
	Behaviour				Other People	Diagnosis & treatment			Worries				Appearance			Other People	
BaSQoL item number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Item performance features																	
Item difficulty																	
Response distribution											•		•		•		
Item-test correlation																	
Item-rest correlation																	
Item discriminant validity																	
Item complexity																	
Internal consistency					•											•	
Stepwise regression		•					•				•			•			
Provisional 33 item questionnaire number	1	2	3	9	8	11	12	16	17	19	21	25	22	32	33	27	

• Indicates suboptimal performance in a given item feature. Definition of suboptimal performance in Table S5. Item numbers displayed are the final BaSQoL item numbers (Table S2)

Confirmatory Factor Analyses

Both the complete cases and the maximum likelihood with missing vales (MLMV) had acceptable to good misfit scores (RMSEA and SRMR) and good goodness of fit (CFI and TLI) (Table 4). The correlations between the subscales were generally low and there were only small differences between the two analyses. (Table S3).

Translation

The original Dutch version of the BaSQoL was translated into English by forward-backward translation [22]. (Table S1)

Table 4. Fit indices Confirmatory Factor Analysis

	Complete cases	MLMV	Recommended Kline	Recommended Hu & Bentler	Recommended Brown
Measures of misfit:					
RMSEA	0.050	0.053	<0.05	± 0.06	<0.05 / <0.08*
SRMR	0.042	--	<0.10	± 0.08	<0.08
Goodness of fit:					
CFI	0.958	0.956	>0.90		>0.95
TLI	0.947	0.944	>0.90	± 0.95	>0.95

MLMV - maximum likelihood with missing values
CFI - comparative fit index
SRMR - standardized root mean squared residual
RMSEA - root mean squared error of approximation
TLI - Tucker-Lewis index
* <0.05 – good, <0.08 reasonable

Scoring

The individual items are scored from 0 to 3, in which 0 represents no impact and 3 very high impact. The mean score per subscale is calculated as a scale score. A minimum of 50% of the questions within the subscale has to be answered to calculate the subscale score.

DISCUSSION

The BaSQoL questionnaire has been developed methodologically by following the EORTC QOL group guidelines as much as possible [20-22] and assesses the relevant dimensions of HRQoL in BCC and SCC patients.

The content of the BaSQoL questionnaire shows some overlap with items from the existing questionnaires for skin cancer, such as cancer recurrence or spreading, concerns about scarring and sun behaviour. But the BaSQoL captures a broader spectrum of the issues relevant in BCC and SCC patients such as treatment and diagnosis related issues and long-term behavioural changes [14, 16, 17]. Since our questionnaire was developed and validated in a large Dutch patient sample by using a population based approach, we consider it to be representative for use in the wide range of BCC and SCC patients.

Since patients were extensively involved in the whole process of the development, the questions are representative and in the terminology as used by the patients.

By combining the use of modern IRT and CTT analyses we aimed to create a questionnaire with optimal psychometric properties. Therefore the BaSQoL has good face, content and construct validity.

The use of the different time frames in our questionnaire is also a unique feature. Patients noted a difference in behaviour before and after the initial diagnosis. Therefore the impact of this behavioural change is measured in the first part of the BaSQoL. The second part of the BaSQoL concerns the period of diagnosis and treatment. This, usually short, timeframe has a high impact on patients HRQoL. This subscale is suitable for assessing the patient's experience of this specific period in order to manage anxiety in the process in case of new tumours and, in general, to optimize patient care. The final part of the questionnaire addresses the impact of the skin cancer during the past week. Since BCC and SCC are being considered as more chronic diseases, addressing the relevant issues at the right moment is important.

The preliminary validation of the BaSQoL has also been established by this study. Cronbach's αs of the reduced subscales remained reasonable, taking into account that a reduction in the number of items generally leads to lower α [33, 34]. The subscales are psychometrically robust, displaying excellent item performance and a good fit in the confirmatory factor analysis. As the BaSQoL measures different aspects of HRQoL, it showed no significant correlation with the subscales of the Skindex-17 and the QLQ-C30 confirming divergent validity. Unfortunately, none of the previously developed BCC or SCC specific questionnaires were included in this study because there are no validated BCC or SCC specific questionnaires available in Dutch and we intended to minimize respondent burden and increase the response rate. A validation study of the English version of the BaSQoL is underway. Construct validity by comparing to the validated SCI, test-retest stability and responsiveness to change will be addressed in this study. Other important features to increase interpretability such as categorization of scores and minimally clinical important difference remain to be determined.

Item 21 (BaSQoL nr 11) 'Were you uncertain about the future?', that violated the unidim assumption of the worries subscale, also had a suboptimal response distribution (Table 3). The confirmatory factor analysis however, showed a good fit. This item reflects a more generic aspect than the other items in the subscale and it had far the highest position on the latent trait for this reason and because of the conceptual general intent of the item we decided to maintain it within the questionnaire.

In summary, the BaSQoL has good face, content and construct validity. The BaSQoL is representative for use in the wide range of BCC and SCC patients and captures HRQoL impact in different time periods. Therefore we consider the BaSQoL as a useful tool to capture HRQoL impact in future studies.

ETHICAL CONSIDERATIONS

This study was approved by the local ethics committee of the Erasmus Medical Centre Rotterdam (Reference number MEC-2013-420)

CONFLICTS OF INTEREST AND FUNDING

The authors state no conflict of interest.

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REFERENCES

1. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726-39.
2. Prinsen CA, de Korte J, Augustin M, Sampogna F, Salek SS, Basra MK, et al. Measurement of health-related quality of life in dermatological research and practice: outcome of the EADV Taskforce on Quality of Life. J Eur Acad Dermatol Venereol. 2013;27(10):1195-203.
3. Livingstone E, Krajewski C, Eigentler TK, Windemuth-Kieselbach C, Benson S, Elsenbruch S, et al. Prospective evaluation of follow-up in melanoma patients in Germany - results of a multicentre and longitudinal study. Eur J Cancer. 2015;51(5):653-67.
4. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011;91(1):24-30.
5. Flohil SCS, I.; van Rossum, M.M.; Coebergh, J.W.; de Vries, E.; Nijsten, T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. J Invest Dermatol. 2012.
6. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer. 2012;48(13):2046-53.
7. Weinstock MA, Lee KC, Chren MM, Marcolivio K. Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. J Am Acad Dermatol. 2009;61(2):207-15.
8. Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. Qual Life Res. 1996;5(2):191-4.
9. Chren MM, Lasek RJ, Quinn LM, Covinsky KE. Convergent and discriminant validity of a generic and a disease-specific instrument to measure quality of life in patients with skin disease. J Invest Dermatol. 1997;108(1):103-7.
10. Roberts N, Czajkowska Z, Radiotis G, Korner A. Distress and Coping Strategies Among Patients with Skin Cancer. J Clin Psychol Med Settings. 2012.
11. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Skin Cancer and Quality of Life: Assessment with the Dermatology Life Quality Index. Dermatol Surg. 2004;30(4 I):525-9.
12. Chren MM, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol. 2007;127(6):1351-7.
13. Sampogna F SA, Di Pietro C, Pagliarello C, Paradisi A, Tabolli S, Abeni D. Field performance of the Skindex-17 quality of life questionnaire: a comparison with the Skindex-29 in a large sample of dermatological outpatients. J Invest Dermatol. 2013;133(1):104-9.
14. Rhee JS, Matthews BA, Neuburg M, Burzynski M, Nattinger AB. Creation of a quality of life instrument for nonmelanoma skin cancer patients. Laryngoscope. 2005;115(7):1178-85.
15. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. The skin cancer index: Clinical responsiveness and predictors of quality of life. Laryngoscope. 2007;117(3):399-405.
16. Burdon-Jones D, Gibbons K. The Skin Cancer Quality of Life Impact Tool (SCQOLIT): A validated health-related quality of life questionnaire for non-metastatic skin cancers. J Eur Acad Dermatol Venereol. 2012.

17. Vinding GR, Christensen KB, Esmann S, Olesen AB, Jemec GB. Quality of life in non-melanoma skin cancer--the skin cancer quality of life (SCQoL) questionnaire. Dermatol Surg. 2013;39(12):1784-93.

18. Esmann S, Vinding, G.R., Christensen, K.B., Jemec, G.B.E. Assessing the influence of Actinic Keratosis on Patients' Quality of Life - The AKQoL Questionnaire. Br J Dermatol. 2013;168(2):277-83.

19. Waalboer-Spuij R, Nijsten TE. A review on quality of life in keratinocyte carcinoma patients. G Ital Dermatol Venereol. 2013;148(3):249-54.

20. Blazeby J, Sprangers MA, Cull A, Groenvold M, Bottomley A. EORTC quality of life group: Guidelines for developing questionnaire modules. Brussels: EORTC; 2002.

21. Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. Qual Life Res. 1993;2(4):287-95.

22. Sprangers MA, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC Quality of Life Study Group. Qual Life Res. 1998;7(4):291-300.

23. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: developing best practices based on science and experience. Qual Life Res. 2009;18(9):1263-78.

24. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

25. Watkins MW. Determining Parallel Analysis Criteria. Journal of Modern Applied Statistical Methods. 2006;5(2):8.

26. Pesudovs K, Burr JM, Harley C, Elliott DB. The development, assessment, and selection of questionnaires. Optometry & Vision Science. 2007;84(8):663-74.

27. Rizopoulos D. Package ltm: Latent trait models under IRT 2012 [Available from: http://rwiki.sciviews.org/doku.php?id=packages:cran:ltm].

28. Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. Arch Dermatol. 1997;133(11):1433-40.

29. Streiner DL, Norman GR. Healt Measurements Scales: a Practical Guide to Their Development and Use. Oxford: Oxford University Press; 2003.

30. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal. 1999;6(1):1-55.

31. Kline RB. Principles and practices of structural equation modeling. New York: Guilford Press; 1998.

32. Brown TA. Confirmatory factor analysis for applied research. New York: The Guilford Pres; 2006.

33. Massof RW. The measurement of vision disability. Optometry & Vision Science. 2002;79(8):516-52.

34. Guilford JP. Psychometric Methods. New York, London: McGraw-Hill; 1936.

Table S1. Provisional item list

Number	Item	
1	Does it bother you to be careful about your behaviour in the sun?	●
2	Does it bother you to use more sunscreen (cream, spray, etc.)?	●
3	Does it bother you to check your skin for skin cancer?	●
4	Does it bother you to adjust your vacation to avoid the sun?	
5	Do you feel that you have to avoid direct sunlight?	
6	Does it bother you to wear certain clothing or a hat to protect you from the sun?	
7	Do you feel that you should warn others for the sun?	
8	Do you feel that you have to encourage others to get their skin checked?	●
9	Does it bother you to have to protect your skin from the sun?	●
10	Did you have the feeling having no control over your skin cancer?	
11	Were you worried about the period between diagnosis and treatment?	●
12	Were you afraid of the treatment?	●
13	Were you worried about (possible) side-effects of the treatment?	
14	Were you worried about the anaesthetic injections?	
15	Were you worried about scarring?	
16	Were you frightened by the word cancer?	●
17	Were you afraid to get skin cancer on multiple body sites?	●
18	Were you worried that the skin cancer would come back at the treated area?	
19	Were you worried about skin cancer spreading to other parts of the body?	●
20	Were you worried about family members getting skin cancer?	
21	Were you uncertain about the future?	●
22	Were you worried that you would be less attractive?	●
23	Was your skin itching at the skin cancer area?	
24	Was your skin sensitive at the skin cancer area?	
25	Were you worried about other skin disorders?	●
26	Were you insecure about not being able to recognise the signals of skin cancer?	
27	Were you worried about other people's skin?	●
28	Were you worried about the severity of skin cancer?	
29	Were you ashamed of the scar(s)?	
30	Did the questions by others about your scar(s) bother you?	
31	Were you worried about whether your scar(s) could be covered?	
32	Did it bother you to adjust your clothing in order to cover your scars and spots?	●
33	Did you feel less attractive?	●

● These items were translated from Dutch through forward/backward translating and are included in the final questionnaire.

Table S2. Basal and Squamous cell carcinoma Quality of Life questionnaire

The following questions are about the influence of skin cancer on your daily life

	Since the skin cancer diagnosis,	Not at all	A little	Quite a bit	Very much
1.	Does it bother you to be careful about your behaviour in the sun?	☐	☐	☐	☐
2.	Does it bother you to use more sunscreen (cream, spray, etc.)?	☐	☐	☐	☐
3.	Does it bother you to check your skin for skin cancer?	☐	☐	☐	☐
4.	Does it bother you to have to protect your skin from the sun?	☐	☐	☐	☐
5.	Do you feel that you have to encourage others to get their skin checked?	☐	☐	☐	☐
	When you think back to the time of diagnosis and treatment,	**Not at all**	**A little**	**Quite a bit**	**Very much**
6.	Were you worried about the period between diagnosis and treatment?	☐	☐	☐	☐
7.	Were you afraid of the treatment?	☐	☐	☐	☐
8.	Were you frightened by the word cancer?	☐	☐	☐	☐
	During the past week,	**Not at all**	**A little**	**Quite a bit**	**Very much**
9.	Were you afraid to get skin cancer on multiple body sites?	☐	☐	☐	☐
10.	Were you worried about skin cancer spreading to other parts of the body?	☐	☐	☐	☐
11.	Were you uncertain about the future?	☐	☐	☐	☐
12.	Were you worried about other skin disorders?	☐	☐	☐	☐
13.	Were you worried that you would be less attractive?	☐	☐	☐	☐
14.	Did it bother you to adjust your clothing in order to cover your scars and spots?	☐	☐	☐	☐
15.	Did you feel less attractive?	☐	☐	☐	☐
16.	Were you worried about other people's skin?	☐	☐	☐	☐
	Scoring of the items	**0**	**1**	**2**	**3**

Table S3. Correlations between subscales.

	Worries	Appearance	Behaviour	Diagnosis & Treatment	Other People
Worries		0.11	0.15	0.33	0.20
Appearance	0.14		0.08	0.13	0.04
Behaviour	0.15	0.09		0.16	0.09
Diagnosis & Treatment	0.33	0.16	0.15		0.17
Other People	0.20	0.06	0.09	0.17	

Lower triangle complete cases, upper triangle maximum likelihood with missing values (MLMV).

Table S4. Keywords used in PubMed searches

quality of life
health-related quality of life
basal cell carcinoma
squamous cell carcinoma
non-melanoma skin cancer

Table S5. Definitions of item performance features used in classical test theory

Item	Item performance feature	Definition
1	**Item difficulty**	Proportion of missing scores among the 721 respondents. Item difficulty was considered high if 10% or more of scores were missing.
2	**Response distribution**	The proportion of patients who responded to each item with the same response was determined. An item was described as having a poor distribution if > 70% of patients had chosen the same response.
3	**Item–test correlation**	The Spearman's correlation coefficients (r) of each item with its subscale were calculated. If the r of an item differed > 0,1 with the r of the other items in the subscale[a], it was considered suboptimal.
4	**Item–rest correlation**	The Spearman's correlation coefficients (r) of each item with the sum of the other items in that subscale[a] were calculated. Suboptimal item–rest correlation was defined as r < 0,20
5	**Item discriminant validity**	We compared the item–rest correlation coefficients with the correlation coefficients of an item with the other subscales[a]. If the former equalled or was smaller than the latter, an item was defined as having poor discriminant validity.
6	**Item complexity**	We investigated the factor loadings in a factor analysis for each item. Suboptimal complexity was said to exist if the highest loading of an item was < 0,40 or if the difference between the loadings on different factors was < 0,10.
7	**Internal consistency**	For each subscale, the Cronbach's α was calculated. If α < 0,70, the internal consistency was considered suboptimal for each subscale's item.
8	**Stepwise regression**	For each subscale, a forward stepwise regression analysis was performed. If an item entered the model after 90% or more of the variance of that subscale was explained it was considered suboptimal.

[a] Subscales derived from the principal component analysis were used.

Chapter 4

Validation of the English basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire

Wesley Y. Yu*
Rick Waalboer-Spuij*
Rebecca Bremer
Brian Lu
Christine Aroyan
Lauren Crow
Roy Grekin
Isaac Neuhaus
Siegrid Yu
Sarah T. Arron
Loes M. Hollestein

**contributed equally to this paper.*
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ABSTRACT

Background: Keratinocyte carcinomas (KC) impact patient quality of life (QoL). There is a need for validated QoL instruments specific to KC. The Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) questionnaire was developed to comprehensively measure issues of importance to patients with KC.

Objective: To validate and characterize the BaSQoL questionnaire for QoL measurement following diagnosis and treatment of KC.

Methods: This was a prospective, observational study. Patients with basal or squamous cell carcinoma were asked to fill out BaSQoL, Skin Cancer Index (SCI), and Hospital Anxiety and Depression Scale (HADS) questionnaires. Descriptive statistics and classical test theory were used to assess validity.

Results: 187 subjects enrolled in this study: 122 with BCC and 65 with SCC. 171 subjects (91.4%) completed questionnaires at all three time points; 16 patients (8.6%) were lost to follow up. Overall performance using classical test theory was good, with good internal consistency (Cronbach's s 0.63-0.80). BaSQoL subscales were strongly correlated with subscales of the SCI, demonstrating convergent validity, and weakly correlated with HADS, showing divergent validity.

Conclusion: The English language version of BaSQoL has good face, content, and construct validity. This study validates BaSQoL for use in English-speaking patients with BCC and SCC.

INTRODUCTION

The keratinocyte carcinomas (KC), basal and squamous cell carcinoma (BCC, SCC), severely impact patient quality of life (QoL). [1] Patients may suffer from pain, bleeding, social embarrassment, and anxiety surrounding the diagnosis of cancer. Objective and accurate tools to measure these experiences and document the impact of KC are necessary. [2] General QoL tools, such as the Hospital Anxiety and Depression Scale, are not targeted towards skin disease. Within the field of dermatology, the patient experience of skin cancer is different from that of inflammatory skin disease. Skin-targeted quality of life questionnaires such as the Dermatology Life Quality Index (DLQI) are not specific enough to demonstrate significant quality of life impairment in patients with skin cancer, and show little to no improvement in quality of life after treatment. [3,4] Skindex, another general dermatologic questionnaire, is not specific enough to measure the impact of KC on quality of life. [5] More targeted questionnaires such as the Skin Cancer Index (SCI) and the Skin Cancer Quality of Life Impact Tool (SCQOLIT) have advanced the field but have limitations. [6,7] For example, neither captures one of the most reported issues in skin cancer patients—the necessary behavioral changes regarding sun exposure. [8] In addition, the SCI does not capture anxiety about the treatment itself, other than scarring. [6] Finally, neither tool addresses the full spectrum of dermatologic issues such as the burden of frequent skin checks, triggering worries about other skin diseases, and the behavior change necessary to prevent future skin cancers. [4, 6-9]

The Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) questionnaire was developed through a rigorous multi-phase process to comprehensively measure problems specific to patients with keratinocyte carcinomas, such as fear of scars and coping mechanisms, worries about subsequent skin tumors, and the burden of sun protective behavior. [8,10] As described previously, topics in the questionnaire were generated through exhaustive patient focus groups led by independent psychologists and semi-structured interviews with healthcare providers. These items were then reviewed by an interdisciplinary expert panel (including dermatologists, dermatologic surgeons, plastic surgeons, general practitioners, ophthalmologists, and head-neck ear nose and throat (ENT) surgeons) then presented to patients for feedback. Patients and physicians were asked to rate items for inclusion in the study. Finally, the questionnaire was field tested in 1,173 patients selected from the Netherlands Cancer Registry and the questionnaire was reduced using exploratory factor analysis and item response theory. In this study, we validate the English translation of the BaSQoL, compare its performance to the SCI and HADS, and demonstrate the utility of BaSQoL in measuring quality of life in patients with skin cancer before and after surgical treatment.

METHODS

The study was conducted from July 1, 2017 to June 30, 2018. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at University of California, San Francisco (UCSF). [11] A consecutive sample of patients with the diagnosis of SCC or BCC and scheduled for treatment in the UCSF Dermatologic Surgery center were approached for voluntary participation. Demographic and clinical information, including age, sex, contact information, tumor type, tumor size, tumor location, history of skin cancer, and treatment plan were collected. Participants were not compensated. The UCSF Institutional Review Board approved the study and all participants provided written informed consent.

The original BaSQoL questionnaire consisting of 16 questions written in Dutch was translated to English using forward-backward translation. [12,13] The BaSQoL consists of 5 subscales (behavior, diagnosis & treatment, worries, appearance and other people) scored from 0 to 3, with higher scores indicating poorer QoL. Participants were asked to fill out this questionnaire one week before their treatment (T0), four weeks after treatment (T1), and five weeks after treatment (T2). Additionally, participants were asked to complete the Skin Cancer Index (SCI) and the Hospital Anxiety and Depression Scale (HADS) one week before treatment (T0). The SCI consists of three subscales (emotional, social, appearance) with standardized score ranges from 0 to 100, with higher scores indicating higher QoL. We hypothesized high correlations between comparable subscales of the SCI and the BaSQoL (convergent validity). The HADS consists of two subscales (anxiety and depression) with scores ranging from 0 to 21, with higher scores indicating poorer QoL. The HADS was included to demonstrate divergent validity.

We aimed to include at least 100 patients with BCC and 50 with SCC in order to include sufficiently large samples of both types of KC, recognizing that BCC is the more common tumor. A formal sample size calculation was not performed. Classical test theory is a framework for evaluating the reliability of items in a questionnaire. Eight performance features (item difficulty, response distribution, item-test correlation, item-rest correlation, discriminant validity, item complexity, internal consistency, stepwise regression) were tested for each item on the BaSQoL (Table S1). Descriptive statistics were used to test item difficulty (missing responses) and response distribution. Spearman's correlation coefficients were calculated for item-test and item-rest correlation, and to test item discriminant validity. Internal consistency was tested via Cronbach's α coefficients. A forward stepwise regression was performed for each subscale in order to check the percentage of variance explained by the items in a subscale. The multitrait-multimethod correlation matrix was used to assess convergent and discriminant validity. We accounted for multiple

hypothesis testing where appropriate by correcting p-values using the false discovery rate (FDR) calculated by the Benjamini-Hochberg procedure. [14] In order to test the stability of BaSQoL responses over time, T1 and T2 responses were compared using a two-way mixed effect model to calculate the intraclass correlation coefficients. Analyses were performed in IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York: IBM Corporation).

RESULTS

A total of 187 subjects enrolled in this study: 122 with BCC and 65 with SCC. 171 subjects (91.4%) completed questionnaires at all three time points; 16 patients (8.6%) were lost to follow up (Figure 1). The mean age of respondents was 67 and 59% were male (Table 1). Tumors were more likely to be located on the head and neck (84%). Most patients had a previous history of skin cancer (63%).

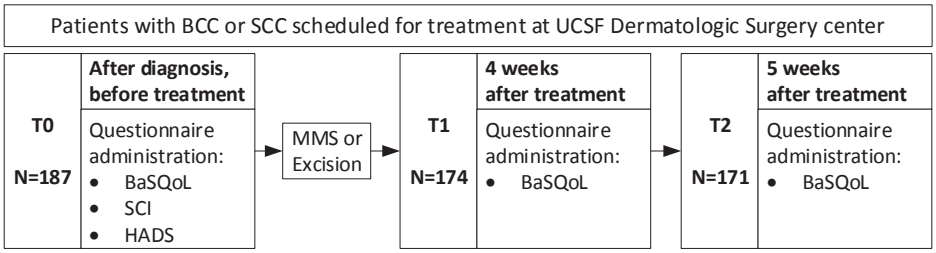

Figure 1. Study Design and Patient Flow Diagram. Patients with the diagnosis of SCC or BCC and scheduled for treatment in the UCSF Dermatologic Surgery center were approached for voluntary participation. Participants were asked to fill out BaSQoL, HADS, and SCI one week before their treatment (T0). They were then asked to complete BaSQoL four weeks after treatment (T1), and five weeks after treatment (T2).

Table 1. Patient characteristics

N participants T0	187
N participants T1	174
N participants T2	171
N= 187	**N (%)**
Gender	
• Male	111 (59)
• Female	75 (41)
Age mean (SD)	67 (13.9)

Table 1. Patient characteristics (*continued*)

Age groups	
• < 60	46 (25)
• 60-69	53 (28)
• 70-79	59 (32)
• ≥ 80	29 (16)
First skin cancer?	
• No	118 (63)
• Yes	49 (26)
• Unknown	20 (11)
Tumor site	
• 1	162 (87)
• multiple	25 (13)
Tumor site	
• scalp	14 (8)
• forehead	19 (10)
• nose	39 (21)
• eyelids	5 (3)
• cheeks	31 (17)
• lips	6 (3)
• other face	36 (19)
• neck	7 (4)
• trunk	14 (8)
• hands or feet	2 (1)
• extremity (not hands or feet)	14 (8)
Tumor type	
• BCC	122 (65)
- superficial	- 9 (5)
- nodular	- 71 (38)
- infiltrative	- 17 (9)
- morpheaform	- 3 (2)
- micronodulair	- 12 (6)
- infundibulocystic	- 2 (1)
- unknown	- 8 (4)
• SCC	65 (35)

Table 1. Patient characteristics (*continued*)

Treatment	
• Mohs surgery	170 (91)
• Conventional excision	17 (9)
Mohs rounds	
• 1	88 (47)
• 2	51 (27)
• 3	14 (8)
• ≥ 4	16 (9)

Overall scores for BaSQoL subscales were generally low, demonstrating a moderate impact on QoL. Patients with SCC tended to demonstrate higher levels of anxiety about their cancer than patients with BCC as measured by the Worries subscale (median score 0.9 [IQR: 0.5-1.2] for BCC and median score 1.0 [IQR 0.5-1.4] for SCC, p=0.013). The SCI similarly measured moderate overall impact on quality of life and higher impact on the Emotional subscale for SCC patients. HADS scores were almost uniformly low, except for a few patients who indicated anxiety. Table 2 summarizes scores for the various instruments before treatment (T0).

Table 2. HRQoL measurement T0

N = 187	BCC		SCC		p-value
BaSQoL (range 0-3)[#]	**N**	**Median score (IQR)**	**N**	**Median score (IQR)**	
• Behaviour	122	1.0 (0.5-1.3)	63	0.5 (0-1.3)	0.281
• Diagnosis & Treatment	122	1.0 (0.3-1.3)	65	1.0 (0.3-1.3)	0.987
• Worries	120	0.9 (0.5-1.2)	61	1.0 (0.5-1.4)	0.013
• Appearance	118	0.3 (0-1.0)	64	0.3 (0-1.0)	0.344
• Other People	120	1.0 (0.5-1.5)	64	0.5 (0.5-1.5)	0.913
SCI (range 0-100)[$]					
• Emotional	120	73.2 (57.1-82.1)	64	60.7 (39.3-81.3)	0.035
• Social	118	90.0 (80.0-95.0)	64	85.0 (71.3-98.8)	0.641
• Appearance	121	75.0 (50.0-92.0)	64	75.0 (50.0-100.0)	0.527
HADS (range 0-21)[#]					
• Anxiety	122	4.0 (2.0-7.0)	65	4.0 (2.0-7.0)	0.659
• Depression	121	1.0 (0-3.5)	63	2.0 (0-4.0)	0.865

[#] Higher score indicates higher impact on HRQoL

[$] Higher score indicates lower impact on HRQoL

Each item on the BaSQoL was tested using eight performance features (Table 3). Poor performance is defined as suboptimal performance on 3 or more features. None of the BaSQoL items met criteria for poor performance. Five out of 16 BaSQoL items showed one suboptimal feature, and three out of the 16 BaSQoL items showed 2 suboptimal performance features. Internal consistency was good with Cronbach's αs ranging from 0.63-0.80 for the different subscales (Behavior 0.80; Diagnosis & treatment 0.72; Worries 0.74; Appearance 0.76; Other people 0.63).

Table 3. Item performance of the BaSQoL questionnaire

N = 187	BaSQoL item number															
	Behavior				Other People	Diagnosis & treatment			Worries				Appearance			Other People
Item performance features	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Item difficulty																
Response distribution																
Item-test correlation			•		•						•					•
Item-rest correlation																
Item discriminant validity								•								
Item complexity											•					
Internal consistency					•											•
Stepwise regression		•								•					•	

• Indicates suboptimal performance in a given item feature. Definition of suboptimal performance in Supplementary Table 1.

The ICC between T1 and T2 was high (≥0.75) for nearly all subscales, indicating a stable response of the BaSQoL over time. Only the Worries subscale had moderate reliability (ICC 0.64, 95% CI: 0.53 – 0.72) (Table 4).

BaSQoL subscales were strongly correlated with subscales of the SCI, demonstrating convergent validity, but were weakly correlated with HADS, indicating divergent validity (Table 5).

We observed a trend towards improvement in 3 subscales (behavior, diagnosis & treatment and worries) and a trend towards deterioration in 2 subscales (appearance and other people) when comparing scores from before treatment (T0) to after treatment (T1). However, these changes did not reach statistical significance (Table 6).

Table 4. Test-retest reliability BaSQoL subscales T1 and T2
N = 171

Subscale	Mean (SD) score test	Mean (SD) score retest	Intraclass correlation coefficient*	95% CI	p-value
Behavior	0.87 (0.62)	0.83 (0.66)	0.795	0.731 – 0.845	<0.001
Diagnosis & Treatment	0.86 (0.63)	0.84 (0.62)	0.801	0.740 – 0.849	<0.001
Worries	0.80 (0.60)	0.75 (0.59)	0.635	0.533 – 0.719	<0.001
Appearance	0.55 (0.66)	0.52 (0.69)	0.745	0.668 – 0.807	<0.001
Other People	0.94 (0.70)	0.93 (0.70)	0.754	0.680 – 0.813	<0.001

* Two-way mixed effect model

Table 5. Convergent and divergent validity

N = 187	Multitrait-Multimethod correlation matrix using Spearman correlation coefficient				
	BaSQoL				
	Behavior	Diagnosis & Treatment	Worries	Appearance	Other People
Convergent validity: Skin Cancer Index					
Emotional	-0.247*	-0.532*	-0.721*	-0.369*	-0.361*
95% CI	-0.404/-0.091	-0.644/-0.402	-0.800/-0.623	-0.497/-0.231	-0.494/-0.213
Social	-0.810	-0.424*	-0.471*	-0.562*	-0.190*
95% CI	-0.244/0.078	-0.550/-0.282	-0.586/-0.340	-0.668/-0.445	-0.327/-0.046
Appearance	-0.201*	-0.441*	-0.288*	-0.670*	-0.134
95% CI	-0.372/-0.059	-0.569/-0.309	-0.424/-0.131	-0.757/-0.573	-0.279/0.013
Divergent validity: Hospital Anxiety and Depression Scale					
Anxiety	0.163*	0.402*	0.355*	0.394*	0.057
95% CI	0.020/0.315	0.260/0.525	0.205/0.492	0.247/0.518	-0.094/0.214
Depression	0.272*	0.235*	0.282*	0.376*	-0.020
95% CI	0.119/0.409	0.079/0.369	0.134/0.413	0.239/0.504	-0.177/0.131

* Correlation is significant at the 0.042 level (2-tailed) (FDR corrected).

are hypothesized high correlations

Table 6. BaSQoL subscale scores before and (4 weeks) after treatment

N = 174	Mean (SD)		Mean difference*	95% CI of the difference	p-value
BaSQoL subscale	T0	T1			
• Behavior	0.91 (0.71)	0.87 (0.62)	0.04	-0.05 – 0.13	0.44
• Diagnosis & Treatment	0.94 (0.67)	0.87 (0.65)	0.07	-0.21 – 0.15	0.14
• Worries	0.88 (0.58)	0.82 (0.61)	0.06	-0.02 – 0.14	0.16
• Appearance	0.53 (0.59)	0.58 (0.67)	-0.05	-0.15 – 0.05	0.34
• Other People	0.90 (0.71)	0.93 (0.71)	-0.04	-0.13 – 0.06	0.48

* Paired samples T-test

DISCUSSION

Health-related QoL has emerged as an essential outcome measure in dermatology. Therefore, disease-specific tools for measuring the impact of KC on QoL are needed. The BaSQoL questionnaire was developed following European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL) group guidelines to comprehensively measure problems specific to patients with KC, such as fear of scars, coping mechanisms, worries about subsequent skin tumors, and the burden of sun protective behavior.

We have validated the English language translation of BaSQoL and demonstrated its utility in assessing an English-speaking American population. Using classical test theory, we have shown that BaSQoL performs well on all test features. Cronbach's αs were reasonable to high and demonstrated good internal consistency.

As hypothesized, BaSQoL correlated very well to SCI in our study population. However, BaSQoL also has several advantages over existing quality of life tools for KC. BaSQoL measures sun protective behavioral changes due to skin cancer, measures worries about treatment, and measures the QoL impact reliably over time. Three different sections of the questionnaire measure QoL impact since diagnosis, between diagnosis and treatment, and during the past week. This division of the questionnaire allows measurement of changing patient perceptions over time. In addition, BaSQoL addresses the impact of behavior change on patient QoL. The daily need for sun protection can be quite bothersome to patients with a new diagnosis of skin cancer, but is also one of the most important interventions to prevent further keratinocyte carcinomas. Measuring the impact of sun protection on patient QoL may give us insight into best practices to encourage behavior change.

Health-related QoL scores measured by both BaSQoL and SCI in this study indicated a modest impact compared to prior studies. [3,8] Our study population may have reported lower impact on QoL because the majority had a prior history of KC and may have been inured to the diagnosis. At least 63% had been treated for skin cancer previously and all of them were currently being treated at a tertiary referral center. Despite these low pre-treatment scores, the BaSQoL questionnaire was still able to detect a trend toward improvement in scores on 3 subscales (behavior, diagnosis & treatment and worries) and deterioration in 2 subscales (appearance and other people) after treatment. This demonstrates that this questionnaire is sensitive to change and could be used to compare treatment modalities for KC. Although the changes detected in this study did not reach statistical significance, as mentioned before, our study population was drawn from a tertiary referral center, had more experience with skin cancer and thus may have been less impacted by this diagnosis,

all of which would bias scores towards a smaller impact. Another reason for the small difference in BaSQoL scores before and after treatment may be the short time span between T0 and T1. Surgical scars may still be healing at 4 weeks postoperatively. Longer follow up may be needed to detect differences in HRQoL as measured by BaSQoL.

Strengths of this study include the comparison of the BaSQoL to two other HRQoL instruments, measurement of the BaSQoL at different time points, a sufficiently large sample of both BCC and SCC patients to test validity in both types of KC and excellent study completion with 91% of respondents completing the entire study. Limitations of this study include lack of a formal sample size calculation to measure sensitivity to change. As this is the first study measuring the BaSQoL before and after treatment, the anticipated difference was unknown before the start of the study and thus a formal calculation was not possible. The observed differences in the mean scores before and after treatment were very small, requiring at least more than 1,000 patients to show a statistical significant difference. As indicated before, larger differences may be observed within other patient populations or if longer periods of time are allowed between BaSQoL measurements.

In summary, the English language version of the BaSQoL has good face, content, and construct validity given its ability to measure moderate quality of life decrement in patients with keratinocyte carcinomas, its broad range of content drawn from patients and subject experts, and its convergence with SCI, and divergence with HADS. This study validates BaSQoL as a QoL measure for BCC and SCC patients over time. BaSQoL may be a useful tool in future studies to compare treatment modalities, interventions for sun protective behavior, or to identify patients in clinical practice with a substantial impact on their HRQoL who may benefit from additional clinical attention.

REFERENCES

1. Chren M-M, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol*. 2007;127:1351-1357. doi:10.1038/sj.jid.5700740.
2. Lee EH. Patient expectations and performance measures in dermatologic surgery. *Clin Dermatol*. 2016;34(1):111-113. doi:10.1016/j.clindermatol.2015.07.002.
3. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski ML, Nattinger AB. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. *Dermatol Surg*. 2004;30(4 Pt 1):525-529. doi:10.1111/j.1524-4725.2004.30169.x.
4. Lee EH, Klassen AF, Nehal KS, Cano SJ, Waters J, Pusic AL. A systematic review of patient-reported outcome instruments of nonmelanoma skin cancer in the dermatologic population. *J Am Acad Dermatol*. 2013;69(2). doi:10.1016/j.jaad.2012.09.017.
5. Lee K, Weinstock M. Prospective quality of life impact of keratinocyte carcinomas: Observations from the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *JAAD*. 2010;63(6):1107–1109.
6. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. The skin cancer index: clinical responsiveness and predictors of quality of life. *Laryngoscope*. 2007;117(3):399-405. doi:10.1097/MLG.0b013e31802e2d88.
7. Burdon-Jones D, Gibbons K. The Skin Cancer Quality of Life Impact Tool (SCQOLIT): A validated health-related quality of life questionnaire for non-metastatic skin cancers. *J Eur Acad Dermatology Venereol*. 2013;27(9):1109-1113. doi:10.1111/j.1468-3083.2012.04669.x.
8. Waalboer-Spuij R, Nijsten T. A review on quality of life in keratinocyte carcinoma patients. *G Ital Dermatol Venereol*. 2013;148:249-254.
9. Gibbons E, Casañas I Comabella C, Fitzpatrick R. A structured review of patient-reported outcome measures for patients with skin cancer, 2013. *Br J Dermatol*. 2013. doi:10.1111/bjd.12310.
10. Waalboer-Spuij R, Hollestein LM, Timman R, van de Poll-Franse L V, Nijsten TE. Development and Validation of the Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) Questionnaire. *Acta Derm Venereol*. 2018;98(2):234-239. doi:10.2340/00015555-2806.
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009. doi:10.1016/j.jbi.2008.08.010.
12. Sprangers MAG, Cull A, Groenvold M, Bjordal K, Blazeby J, Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: An update and overview. *Qual Life Res*. 1998. doi:10.1023/A:1008890401133.
13. Bullinger M, Alonso J, Apolone G, et al. Translating health status questionnaires and evaluating their quality: The IQOLA Project approach. *J Clin Epidemiol*. 1998. doi:10.1016/S0895-4356(98)00082-1.
14. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol*. 2014. doi:10.1016/j.jclinepi.2014.03.012.

Supplementary Table 1. Definitions of item performance features used in classical test theory

Item	Item performance feature	Definition
1	Item difficulty	Proportion of missing scores among the 187 respondents. Item difficulty was considered high if 10% or more of scores were missing.
2	Response distribution	The proportion of patients who responded to each item with the same response was determined. An item was described as having a poor distribution if > 70% of patients had chosen the same response.
3	Item–test correlation	The Spearman's correlation coefficients (r) of each item with its subscale were calculated. If the r of an item differed > 0.1 with the r of the other items in the subscale, it was considered suboptimal.
4	Item–rest correlation	The Spearman's correlation coefficients (r) of each item with the sum of the other items in that subscale were calculated. Suboptimal item–rest correlation was defined as $r < 0.20$
5	Item discriminant validity	We compared the item–rest correlation coefficients with the correlation coefficients of an item with the other subscales. If the former equalled or was smaller than the latter, an item was defined as having poor discriminant validity.
6	Item complexity	We investigated the factor loadings in a factor analysis for each item. Suboptimal complexity was said to exist if the highest loading of an item was < 0.40 or if the difference between the loadings on different factors was < 0.10.
7	Internal consistency	For each subscale, the Cronbach's α was calculated. If $\alpha < 0.70$, the internal consistency was considered suboptimal for each subscale's item.
8	Stepwise regression	For each subscale, a forward stepwise regression analysis was performed. If an item entered the model after 90% or more of the variance of that subscale was explained it was considered suboptimal.

Chapter 5

Satisfaction with information provision and health-related quality of life in basal and squamous cell carcinoma patients: a cross-sectional population-based study

Rick Waalboer-Spuij
Loes M. Hollestein
Tamar E.C. Nijsten
Lonneke V. van de Poll-Franse

on behalf of the BaSQoL Group
Based on: Acta Derm Venereol. 2019 May 23. [Epub ahead of print]

ABSTRACT

This study aims to determine the satisfaction with information provision received by basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) patients and associations with health-related quality of life (HRQoL). 1,173 patients from the Netherlands Cancer Registry, received questionnaires on BCC/SCC-specific HRQoL (BaSQoL), cancer-specific HRQoL (EORTC QLQ-C30), information provision (EORTC QLQ-INFO25) and general satisfaction (EORTC INPATSAT-32). 721 (61%) patients participated. The HRQoL impact (BaSQoL) was higher among female and younger patients. One third (N=237) of all patients indicated to be dissatisfied with the information provision. Dissatisfaction with information provision was associated with younger age, facial tumour, not having a partner and multiple comorbidities. HRQoL was worse in patients dissatisfied with information provision (e.g. BaSQoL-worries mean score satisfied patients: 0.54 (95%CI:0.48–0.59), dissatisfied patients: 0.77 (95%CI:0.67–0.87), p=0.001). Dissatisfaction with provided information was associated with an impact on HRQoL. Possibly, HRQoL could be improved by improving the information provision.

INTRODUCTION

Patient reported outcome measures (PROMs) and more specifically health-related quality of life (HRQoL) are increasingly being used in dermatology over the past decades. It is an essential and established outcome for clinical studies and in daily practice in inflammatory skin diseases and is increasingly used in skin cancer.[1-3] Patients with keratinocytic carcinomas (KC), which include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are likely to develop multiple lesions including actinic keratosis (AK) (so called 'actinic neoplasia syndrome').[4] Since the incidence of BCC and SCC continues to rise rapidly, it is important to identify patients with high disease burden in order to intervene appropriately.[5-7] Recently, the basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire was developed to measure disease specific HRQoL in BCC and SCC patients.[8]

An important factor associated with HRQoL is information provision. A systematic review in head and neck, breast, lung, gastro-intestinal, genitourinary and haematological cancer patients showed a positive association between information provision and HRQoL.[9] Information provision is considered as one of the most important aspects of supportive care, as an increase in knowledge about the disease and treatment leads to better illness perception, which could lead to a better HRQoL[10, 11]. However, this relation has not been described in BCC and SCC patients, and may differ from the aforementioned cancers, because the mortality is very low and treatment may have less impact. This study aims to assess current level of satisfaction with received information and the association with HRQoL in a large population-based sample of KC patients in the Netherlands. We hypothesized that patients who were more satisfied with the received information reported a better HRQoL.

METHODS

Setting and participants

A cross-sectional study was performed among 1,173 patients, selected from the Southern region of the population-based Netherlands Cancer Registry (NCR), because during the study period, the NCR did not register all BCC and SCC nationwide yet. Patients were selected if they were diagnosed in one of the nine participating hospitals or clinics during the past twelve months before sending the questionnaire. Data was collected during the validation phase of the BaSQoL questionnaire.[8]

Data collection

Participating patients completed a web-based questionnaire, or paper based on request. Patients were invited to participate through their dermatologist by a postal letter explaining the study. When no reply was received, patients were sent a reminder several weeks later. Informed consent was obtained for the questionnaire and obtaining the clinical disease history data as registered by the NCR.

The questionnaire is part of the PROFILES (Patient Reported Outcomes Following Initial treatment and Long Term Evaluation of Survivorship) registry. PROFILES is a registry studying physical and psychosocial impact of cancer and its treatment. It is linked directly to the data from the NCR[12].

Disease and patient characteristics

Socio-demographic data (age, education, occupation, partnership) was collected using standardized questionnaires. Disease specific data such as tumour type, location, treatment and date of treatment were gathered from NCR.

Questionnaires

Information provision

Satisfaction with information provision was measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire INFO25 (EORTC QLQ-INFO25) [13, 14]. This is a 25-item questionnaire to evaluate the provided information received by cancer patients. The questionnaire consists of 4 subscales: information about the disease, medical tests, treatment, other services and additional single items. Responses are given in a 4-point Likert scale (‘not at all’, ‘a little’, ‘quite a bit’ and ‘very much’), except four items with a dichotomous yes or no response. All scales (excluding the satisfaction with information provision item) were converted to a 0-100 scale with higher scores meaning higher level of information received or higher wishes on information.

For this study, the 4-point Likert scale of the item ‘satisfaction with information provision’ was dichotomized into satisfied (‘quite a bit’ – ‘very much’) and dissatisfied (‘not at all’ – ‘a little’).

Health-related quality of life

Cancer-specific quality of life was measured by the EORTC QLQ-Core 30 (EORTC QLQ-C30), which is a 30 item questionnaire, divided in several scales: functional scales (physical, role, emotional, social and cognitive functioning), symptom scales (fatigue, pain and nausea/vomiting) and single items concerning global health and quality of life, financial impact

and symptoms [15, 16]. All scales were converted to a 0-100 scale with higher scores meaning higher quality of life in the functional scales and more impact in the symptom scales.

The BaSQoL questionnaire was used to assess disease specific quality of life [8]. The BaSQoL is a 16 item questionnaire in which responses are given in a 4-point Likert scale ('not at all', 'a little', 'quite a bit' and 'very much'). The questionnaire is divided into 5 subscales ('behavior', 'worries', 'appearance', 'diagnosis and treatment' and 'other people'). All subscale scores are converted to a 0-3 scale with higher scores implicating higher impact on HRQoL.

Patient satisfaction

The EORTC satisfaction with in-patient cancer care (INPATSAT-32) questionnaire addresses patient satisfaction with aspects of care, relevant to oncological disease [17]. It consists of several domains assessing doctors' skills, nurses' skills, information provision and availability, hospital personnel and the hospital generally, leading to 11 multi item scales and three single item scales. Responses are given in a 5-point Likert scale ranging from 'poor' to 'excellent'. All scales were converted to a 0-100 scale with higher scores representing higher satisfaction with care. In the current study, the domain of INPATSAT-32 addressing nurses' skills was not administered since the participants were predominantly outpatients and were generally not treated by nurses.

Comorbidity

Comorbidity was measured by the self-reported comorbidity questionnaire.[18]

Statistical analyses

Mean values of different scales were compared with independent samples T-tests between patients who were satisfied and dissatisfied with information. KC were studied collectively, but separate descriptive analyses for BCC and SCC were performed. Bar charts were created to display the different values of the BaSQoL and EORTC QLQ-C30 subscales, stratified by satisfaction with information provision. Multivariable linear regression analysis was used to assess the association between the HRQoL as outcome measure (i.e., each subscale of the BaSQoL) and satisfaction with information (i.e., satisfaction item of the EORTC QLQ-INFO25) as covariate. In order to take missing data into account in the regression analyses, we applied multiple imputation (25 imputations). In the imputation models we included all covariates and outcomes of the regression models. The model was adjusted for age at time of the questionnaire, time since diagnosis, sex, education, occupation, partnership, location of tumour, type of tumour and comorbidity. The selection of these variables was done a priori. The assumptions of multiple linear regression (no multicollinearity, normality of the residual values, homoscedascity) were met. A bar chart was

plotted to display the possible differences in satisfaction with information between the participating centres. As a secondary analysis, two multivariable logistic regression models were used to test if hospitals/clinics were independently associated with satisfaction with information provision or HRQoL, regardless of any of the aforementioned tumour and patient characteristics.

P-values <0.05 (two-sided) obtained from regression models were considered statistically significant. All other p-values were corrected for the false discovery rate proportion of true null hypothesis among significant results (Benjamini-Hochberg procedure) [19]. Corrected p-values < 0.033 (two-sided) were considered statistically significant. All analyses were performed in IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York: IBM Corporation).

RESULTS

721 of the 1,173 patients completed the questionnaire (response rate of 61%). Of all respondents 85% had BCC and 15% had SCC. One third (N=237) indicated to be dissatisfied with the information provision as measured by the dichotomized item 'satisfaction with information provision' within the EORTC QLQ-INFO25 questionnaire. Dissatisfied patients were a few years older than satisfied patients (75 vs 71 years of age; table 1). Of all patients, 16% (N=116) indicated that they had wanted to receive more information about skin cancer in general, but also about causes, treatment and follow-up plan and how to recognize new lesions. This corresponds to 37% (84/225) of all dissatisfied patients and 7% (28/416) of the satisfied patients. Three percent (N=24) wanted to have had received less information. The information received was considered helpful in 68% (N=417) of all patients. There was no difference in satisfaction about the information in the tumour type (BCC vs SCC) or BCC subtype (Table 1). Facial location of the tumour, not having a partner and having more comorbidities did show a statistical significant increase in dissatisfaction (Table 1). Patients who were dissatisfied with the information provision also scored statistically significantly lower on the general satisfaction with in patient care (as measured by the EORTC INPATSAT-32 questionnaire) and also on all other subscales of the EORTC INFO-25 (data not shown).

HRQoL, as measured by the BaSQoL and EORTC QLQ-C30 was statistically significantly lower among patients who were dissatisfied with information provision (figure 1a and 1b).

The distribution of satisfied versus dissatisfied with the information provision differed substantially between the 9 participating hospitals or clinics (Figure 2, Suppl. Table 1).

Table 1. Basal cell carcinoma and squamous cell carcinoma patient characteristics according to satisfaction with information provision*

	Dissatisfied patients# N=237	Satisfied patient# N=422	P-value
Age at time of survey in years, median (IQR)	75 (16)	71 (15)	0.015
Years since diagnosis , median (IQR)	4 (0.6)	4 (0.5)	0.363
Sex			0.148
• Male (%)	113 (33)	226 (67)	
• Female (%)	124 (39)	196 (61)	
Education			0.051
• Low	74 (41)	104 (58)	
• Medium	142 (34)	279 (66)	
• High	15 (30)	35 (70)	
Current occupation			0.094
• (Self-) Employed	48 (30)	114 (70)	
• Unemployed	168 (37)	289 (63)	
Partnership			0.002
• Partner	163 (33)	339 (67)	
• No partner	70 (47)	78 (53)	
Tumour type			0.548
• BCC	203 (36)	358 (64)	
• SCC	18 (32)	38 (68)	
Location of tumour			0.004
• Face	197 (39)	311 (61)	
• Other	40 (26)	111 (74)	
Type BCC			0.633
• Multifocal superficial	14 (23)	48 (77)	
• Infiltrating	51 (50)	51 (50)	
• Nodular	124 (34)	238 (66)	
• Other	14 (40)	21 (60)	
Comorbidity			< 0.001
• No	100 (28)	260 (72)	
• 1	33 (40)	50 (60)	
• ≥2	95 (49)	100 (51)	

* Because of missing values numbers do not always add up to 721.

Measured by the dichotomized item 'satisfaction with information provision' of the EORTC QLQ-INFO25 questionnaire.

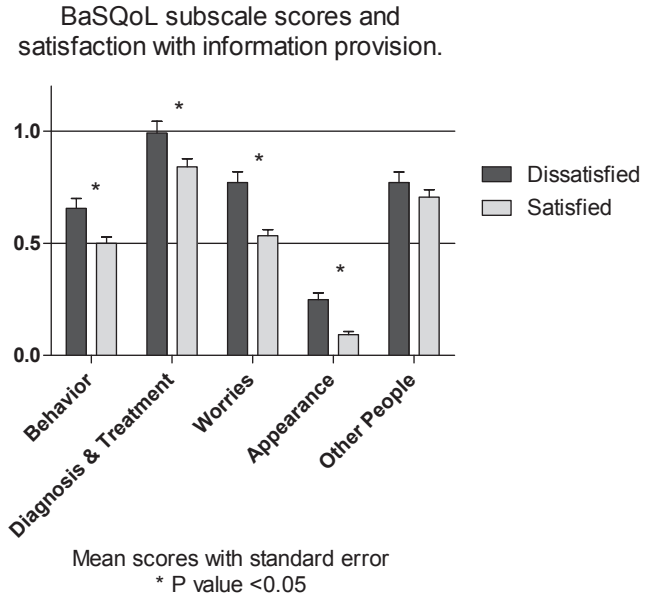

Figure 1a. BaSQoL subscale scores and satisfaction with information provision.

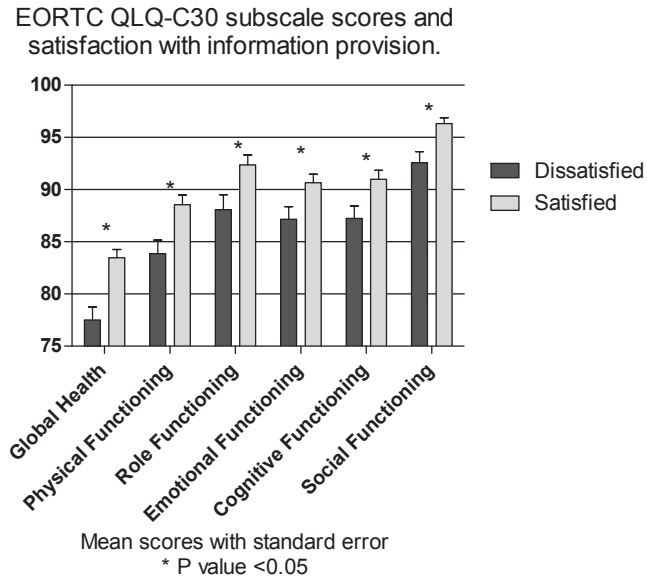

Figure 1b. EORTC QLQ-C30 subscale scores and satisfaction with information provision.

Figure 1a and 1b. Mean BaSQoL And EORTC QLQ-C30 subscale scores and satisfaction with information provision.
Mean scores with standard error
* p value < 0.033 (FDR corrected)

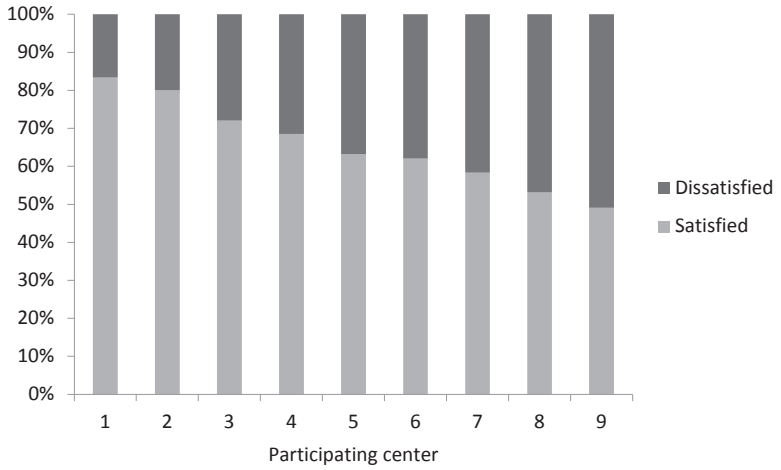

Figure 2. Percentage of patients satisfied and dissatisfied with information provision per hospital / clinic. Ranked descending in percentage of satisfaction.

However, after adjustment for patient and tumour characteristics, participating centre was no longer associated with satisfaction with information provision (Suppl. Table 1). Also, participating centre was not statistically significantly associated with any BaSQoL subscale in a multivariable regression model (data not shown).

Satisfaction with information provision was associated with the behavior, diagnosis & treatment, worries and appearance subscales of the BaSQoL questionnaire with negative Beta's (-0.3 to -0.1), indicating that satisfied patients had a 0.3 to 0.1 lower BaSQoL subscale score, thus lower impact on HRQoL (table 2).

Other factors associated with worse HRQoL scores were younger age (all BaSQoL subscales), recent time since diagnosis (on diagnosis & treatment, worries and appearance subscales of the BaSQoL questionnaire, indicating higher HRQoL impact if diagnosis and treatment was more recent) and being female (on diagnosis & treatment, worries and other people BaSQoL subscales). Facial location of the tumour was also associated with more HRQoL impact in the behavior, diagnosis and treatment and appearance subscales. Having a SCC led to a higher score than a BCC in the worries and other people subscales. No consistent effect on BaSQoL subscales was observed among different categories of patient' education.

Table 2. Multiple linear regression analysis evaluating the association between BaSQoL subscales and satisfaction with information
*** p < 0.05**

	Behavior		Diagnosis & Treatment		Worries		Appearance		Other People	
	Beta	95 % CI	Beta	95 % CI	Beta	95 % CI	Beta	95 % CI	Beta	95 % CI
Satisfaction with information (dissatisfied = ref)										
• Satisfied	***-0.15****	-0.25 / -0.05	***-0.12****	-0.25 / -0.00	***-0.25****	-0.35 / -0.15	***-0.14****	-0.20 / -0.08	-0.07	-0.18 / 0.05
Age at time of questionnaire	***-0.01****	-0.01 / - 0.00	***-0.01****	-0.02 / -0.00	***-0.01****	-0.02 / -0.00	***-0.01****	-0.01 / -0.01	***-0.01****	-0.01 / -0.00
Time since diagnosis	-0.01	-0.04 / 0.03	***0.07****	0.02 / 0.12	***0.07****	0.02 / 0.12	***0.06****	0.02 / 0.09	- 0.02	-0.5 / 0.08
Seks (male = ref)										
• Female	0.07	-0.02 / 0.16	***0.29****	0.17 / 0.40	***0.12****	0.02 / 0.21	0.02	-0.04 / 0.07	***0.20****	0.09 / 0.30
Education (low = ref)										
• Medium	***-0.14****	-0.24 / -0.04	-0.03	-0.16 / 0.10	-0.04	-0.14 / 0.06	-0.04	-0.10 / 0.02	***0.13****	0.01 / 0.25
• High	***0.20****	0.02 / 0.38	-0.15	-0.38 / 0.08	-0.15	-0.33 / 0.03	-0.08	-0.19 / 0.02	-0.06	-0.16 / 0.28
Occupation ((self-)employed = ref)										
• Unemployed	-0.08	-0.22 / 0.06	-0.14	-0.32 / 0.03	-0.05	-0.19 / 0.09	0.08	-0.00 / 0.16	-0.02	-0.18 / 0.15
Partnership										
• No partner (partner = ref)	0.08	-0.03/ 0.19	0.12	-0.02 / 0.26	-0.07	-0.18 / 0.04	0.05	-0.01 / 0.12	-0.00	-0.13 / 0.13
Location of tumour (face = ref)										
• Other	***-0.11****	-0.21 / -0.01	***-0.14****	-0.26 / -0.01	0.02	-0.09 / 0.12	***-0.09****	-0.15 / -0.03	0.07	-0.05 / 0.20
Type tumor (BCC= ref)										
• SCC	0.04	-0.11 / 0.18	0.14	-0.05 / 0.32	***0.29****	0.14 / 0.44	0.05	-0.04 / 0.13	***0.25****	0.07 / 0.43
Comorbidity (no = ref)										
• 1	-0.08	-0.22 / 0.06	0.09	-0.09 / 0.27	0.01	-0.13 / 0.15	0.07	-0.01 / 0.15	0.03	-0.14 / 0.20
• ≥2	-0.02	-0.13 / 0.08	0.11	-0.02 / 0.25	0.04	-0.07 / 0.15	***0.07****	0.00 / 0.13	0.13	0.00 / 0.25

DISCUSSION

In this cross-sectional population based study we demonstrated that patients who were dissatisfied with information provision had statistically significant higher impact on four of the five subscales of the BaSQoL and all of the EORTC QLQ-C30 subscales. There are two possible explanations for this correlation. First, patients dissatisfied with provided information may not have sufficient knowledge about the disease and treatment and therefore have inadequate illness perception which causes more impact on HRQoL. Second, patients who reported a more negative impact of their disease on HRQoL are generally more dissatisfied with care, thus also with information provision. Since our study had a cross-sectional design, satisfaction with information and HRQoL were assessed at a single time point, so we cannot differentiate on which explanation is correct. Worse HRQoL on all BaSQoL subscales was found in younger patients. This is similar to the results of a pooled analysis studying the relation between age and HRQoL in cancer patients which showed that social functioning (as measured by the EORTC QLQ-C30) is better in older patients in comparison to younger cancer patients. [20]

In contrast to our hypothesis, being female did not show a significant association on the appearance subscale whilst it was associated with the diagnosis & treatment, worries and other people subscales. To improve the HRQoL impact in BCC and SCC patients, the BaSQoL could be used to identify patients with higher impact and provide supportive care accordingly. Further research is necessary to identify which scores require additional attention.

This study also showed that one third of Dutch BCC and SCC patients were dissatisfied with the received information provision. These dissatisfied patients showed substantially lower scores on all subscales of provided information provision (EORTC INFO-25) in comparison to satisfied patients. Comparable results have been described earlier in patients with prostate cancer, multiple myeloma, lymphoma, endometrial cancer, colorectal cancer and thyroid cancer. In these studies the perceived receipt of disease-specific information was associated with better understanding of the disease and more personal and treatment control. [10, 11, 21] Especially in the dissatisfied with information provision group there is a wish for receiving more information. By taking into account the role of information provision in understanding, coping with the disease and choosing treatment, meeting the patients' needs for more information is desirable. [9, 22] In this study factors associated with dissatisfaction with information provision were younger age, facial location of the tumour, not having a partner and having more comorbidities. Another study described lower income and education, female, unmarried status and type of cancer with good prognosis associated with patients' perception of inadequate information provision. [23] In comparison to our study the role of having no partner is similar. Lower education

level was not significant (p= 0.051) but did show a similar trend. No difference was seen between SCC and BCC.

We observed a large difference in how patients scored their satisfaction with information provision per hospital or clinic. These differences can partially be explained by the patient and tumour characteristics. But there is still room for improvement. These demonstrated differences underline the need for optimizing and standardizing the way to inform patients about their KC and possibly other diseases. The Dutch Society for Dermatology and Venerology has developed several disease specific patient leaflets with general information about the disease and treatment. The results of our study suggest that the BCC and SCC information leaflets of the Dutch Society for Dermatology and Venerology (NVDV) are not fully satisfactory to all patients, that the leaflet may not always have been provided to the patient upon diagnosing BCC or SCC, or that certain subgroups of KC patients may require more detailed information (e.g., patients with facial tumours). Unfortunately, no specific questions about the general patient leaflet were included in our questionnaire. A recent discrete choice experiment (DCE), regarding patient preferences among patients with BCC in the Netherlands, indicated that patients prefer personalized information, rather than general information. [24]

Strengths & Limitations

Strengths of this study include, that it was a population-based disease-specific HRQoL assessment of BCC and SCC patients, a validated questionnaire was used and a large sample was included. Therefore, the results can be generalized to the general population with BCC and SCC. A limitation of this study was the cross-sectional design and thus satisfaction with information and HRQoL were assessed at a single time point, therefore we cannot differentiate if dissatisfaction with information provision leads to more HRQoL impact or vice versa. In addition, the time since diagnosis is different for patients within our sample and it would be informative to follow the BaSQoL scores at several time points after diagnosis within the same patient. For example, the scarring shortly after (surgical) treatment is more present so the appearance subscale score could decrease over time. The behaviour subscale score on the other hand could fluctuate over time with the changing of the weather and therefor the necessity to protect the skin against sunlight.

CONCLUSION

There is room for improvement in providing satisfactory information to BCC and SCC patients, especially in younger patients, patients with a facial location of the tumour, those who do not have a partner and have more comorbidities. Dissatisfaction with provided

information is associated with an impact on HRQoL which may be improved by improving the satisfaction in information provision. In addition to satisfaction with information, females and younger patients experienced a higher impact on several subscales of the BaSQoL. Possibly, these subgroups may require more supportive care, but further research is necessary to identify these patients based on their BaSQoL scores.

ETHICAL CONSIDERATIONS

This study was approved by the local ethics committee of the Erasmus Medical Centre Rotterdam (Reference number MEC-2013-420)

CONFLICTS OF INTEREST AND FUNDING

The authors state no conflict of interest.

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REFERENCES

1. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726-39.
2. Prinsen CA, de Korte J, Augustin M, Sampogna F, Salek SS, Basra MK, et al. Measurement of health-related quality of life in dermatological research and practice: outcome of the EADV Taskforce on Quality of Life. J Eur Acad Dermatol Venereol. 2013;27(10):1195-203.
3. Waalboer-Spuij R, Nijsten TE. A review on quality of life in keratinocyte carcinoma patients. G Ital Dermatol Venereol. 2013;148(3):249-54.
4. Weinstock MA, Lee KC, Chren MM, Marcolivio K. Quality of life in the actinic neoplasia syndrome: The VA Topical Tretinoin Chemoprevention (VATTC) Trial. J Am Acad Dermatol. 2009;61(2):207-15.
5. Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011;91(1):24-30.
6. Flohil SCS, I.; van Rossum, M.M.; Coebergh, J.W.; de Vries, E.; Nijsten, T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. J Invest Dermatol. 2012.
7. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer. 2012;48(13):2046-53.
8. Waalboer-Spuij R, Hollestein LM, Timman R, van de Poll-Franse LV, Nijsten TE. Development and Validation of the Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) Questionnaire. Acta Derm Venereol. 2018;98(2):234-9.
9. Husson O, Mols F, van de Poll-Franse LV. The relation between information provision and health-related quality of life, anxiety and depression among cancer survivors: a systematic review. Annals of Oncology. 2011;22(4):761-72.
10. Husson O, Thong MS, Mols F, Oerlemans S, Kaptein AA, van de Poll-Franse LV. Illness perceptions in cancer survivors: what is the role of information provision? Psychooncology. 2013;22(3):490-8.
11. Lamers RE, Cuypers M, Husson O, de Vries M, Kil PJ, Ruud Bosch JL, et al. Patients are dissatisfied with information provision: perceived information provision and quality of life in prostate cancer patients. Psychooncology. 2016;25(6):633-40.
12. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, Denollet J, Roukema JA, Aaronson NK, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer. 2011;47(14):2188-94.
13. Arraras JI, Greimel E, Chie WC, Sezer O, Bergenmar M, Costantini A, et al. Information disclosure to cancer patients: EORTC QLQ-INFO25 questionnaire. Expert Rev Pharmacoecon Outcomes Res. 2011;11(3):281-6.
14. Arraras JI, Greimel E, Sezer O, Chie WC, Bergenmar M, Costantini A, et al. An international validation study of the EORTC QLQ-INFO25 questionnaire: an instrument to assess the information given to cancer patients. Eur J Cancer. 2010;46(15):2726-38.
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

16. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2002;38:125-33.

17. Brédart A, Bottomley A, Blazeby JM, Conroy T, Coens C, D'Haese S, et al. An international prospective study of the EORTC cancer in-patient satisfaction with care measure (EORTC IN-PATSAT32). European Journal of Cancer. 2005;41(14):2120-31.

18. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003;49(2):156-63.

19. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol. 2014;67(8):850-7.

20. Quinten C, Coens C, Ghislain I, Zikos E, Sprangers MA, Ringash J, et al. The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients. Eur J Cancer. 2015;51(18):2808-19.

21. Husson O, Mols F, Oranje WA, Haak HR, Nieuwlaat WA, Netea-Maier RT, et al. Unmet information needs and impact of cancer in (long-term) thyroid cancer survivors: results of the PROFILES registry. Psycho-Oncology. 2014;23(8):946-52.

22. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. Br J Cancer. 2001;84(1):48-51.

23. Sim JA, Shin JS, Park SM, Chang YJ, Shin A, Noh DY, et al. Association between information provision and decisional conflict in cancer patients. Ann Oncol. 2015;26(9):1974-80.

24. Misirli Y, De Vries E, Hollestein LM, Bastiaens MT, De Roos KP, Kuijpers DI, et al. Patients' preferences for basal cell carcinoma follow-up: a discrete choice experiment. in preparation 2018.

Supplementary Table 1. Satisfaction with information across participating centres.

	Satisfied	Dissatisfied	Univariable		Multivariable *	
	N	N	OR (95%CI)	p-value	OR (95%CI)	p-value
Participating centre						
A	74	34	Ref.		Ref.	
B	48	12	1.84 (0.87 – 3.90)	0.11	2.02 (0.93 – 4.40)	0.08
C	36	14	1.18 (0.56 – 2.47)	0.66	1.39 (0.64 – 3.05)	0.41
D	20	4	2.30 (0.73 – 7.24)	0.16	1.89 (0.58 – 6.16)	0.29
E	34	30	0.52 (0.28 – 0.99)	0.05	0.53 (0.27 – 1.04)	0.07
F	49	35	0.64 (0.36 -1.17)	0.15	0.70 (0.37 – 1.32)	0.27
G	67	41	0.75 (0.43 – 1.32)	0.32	0.81 (0.45 – 1.74)	0.49
H	67	39	0.79 (0.45 – 1.39)	0.41	0.89 (0.49 – 1.62)	0.69
I	27	28	0.44 (0.23 – 0.86)	0.02	0.49 (0.24 – 1.00)	0.05

* The multivariable model was adjusted for HRQoL (Global subscale of the EORTC QLQ-C30) age at time of the questionnaire, time since diagnosis, sex, education, occupation, partnership, location of tumour, type of tumour and comorbidity

Chapter 6

Health-related quality of life, satisfaction with care and cosmetic results in relation to treatment among patients with keratinocyte cancer in the head and neck area: results from the PROFILES-registry

Lindy P.J. Arts
Rick Waalboer-Spuij
Kees-Peter de Roos
Monique R.T.M. Thissen
Luc J. Scheijmans
Mieke J. Aarts
Simone Oerlemans
Marnix L.M. Lybeert
Marieke W.J. Louwman

Accepted Dermatology.
S. Karger AG, Basel

ABSTRACT

Background

Little is known about the impact of keratinocyte cancer (KC) and its treatment on health-related quality of life (HRQoL). The aims of the present study were to [1] evaluate HRQoL among patients with KC in a population-based setting and compare this with an age- and sex-matched norm population, and [2] compare HRQoL, satisfaction with care and cosmetic results for patients who underwent conventional excision, Mohs' micrographic surgery, or radiotherapy.

Methods

A random sample of 347 patients diagnosed with cutaneous basal cell (BCC) or squamous cell carcinoma (SCC) in the head and neck area between January 1, 2010 and December 31, 2014 were selected from the Netherlands Cancer Registry (NCR) and were invited to complete a questionnaire on HRQoL, satisfaction with care, and cosmetic results. Data were collected within Patient-Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship (PROFILES). Outcomes were compared to an age- and sex-matched normative population.

Results

Two hundred fifteen patients with KC returned a completed questionnaire (62% response). Patients with KC reported better global quality of life (79.6 versus 73.3; $p<0.01$) and less pain ($p<0.01$) compared to the norm population. No statistically significant differences in HRQoL, satisfaction with care, and cosmetic results were found between patients with KC who underwent conventional excision, Mohs' micrographic surgery, or radiotherapy.

Conclusion

The impact of KC and its treatment seems relatively low and more positive than negative as patients reported better HRQoL compared to an age- and sex-matched norm population probably due to adaptation. No statistically significant differences between treatment types were found concerning HRQoL, patients satisfaction and cosmetic results. This information could be used by healthcare professionals involved in KC care to improve patients' knowledge about different aspects of disease as patient's preference is an important factor for treatment choice.

INTRODUCTION

Keratinocyte cancer (KC) is the most common cancer in the Western world [1, 2]. Basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) account for respectively 80% and 20% of cases of KC [2-4]. These cancers are called KC because they share lineage with keratinocytes and histologically resemble epidermal keratinocytes [3]. Keratinocytes are vulnerable to damage from sun exposure and therefore KCs usually develop on sun-exposed areas, especially the head and neck [5-8]. BCCs are slow-growing cancers that are nearly always asymptomatic, while SCCs may grow faster and may induce tenderness or pain, but are also mostly asymptomatic [3]. However, SCCs are more aggressive cancers with tendency to metastasis, especially the larger ones located on lips and ears [9].

KC is typically treated with surgical excision. However, less invasive options exist, such as radiotherapy, cryotherapy or topical therapy [3, 4, 10]. Choice of treatment depends on various factors, both clinical and personal. Important clinical factors are aggressiveness of the cancer, size and localization of the lesion, and especially for BCC, histological subtype [4, 11]. In addition, elderly patients and those with comorbid conditions are less suitable for surgical excision and are more likely to receive a less invasive treatment option. Furthermore, cosmetic aspects and patients' preferences may also have impact on the choice of treatment, since treatment of KC can cause substantial facial cosmetic and functional disturbances [11]. Previous research showed that most prevalent concerns of patients with KC include worries about tumor recurrence, as well as the potential size and conspicuousness of the scar [12].

Patient-reported outcomes and health-related quality of life (HRQoL) are increasingly important outcomes in daily patient care [8, 13, 14]. HRQoL refers to an individual's physical, psychological and social well-being, which may be affected by disease and treatment [15]. Since patients with KC are likely to develop multiple cancers during lifetime, KC and its treatment may be associated with impaired health-related quality of life (HRQoL) [16]. Despite the high incidence rates of KC and the importance of incorporating patient values into evidence-based medicine, little is known about the impact of specific treatment options for KC on HRQoL [13, 17]. In addition, the attention for perspectives of patients with KC is increasing over the past two decades, since previous research focused mainly on patients with melanoma [14, 18]. Satisfaction with care is also a part of the patient-reported outcomes and more applicable to diseases with multiple treatment options, such as KC [19]. As patients with KC strongly expressed the need for a shared decision making process [20, 21], in which they are actively engaged and value detailed information regarding their disease and treatment options, healthcare professionals that are working with

patients with KC need to understand their psychosocial concerns and needs in order to offer appropriate care services [22].

The aims of the present study were to [1] evaluate HRQoL among patients with KC in a population-based setting and compare this with an age- end sex-matched normative population, and [2] compare HRQoL, satisfaction with care and cosmetic results between patients who underwent conventional excision, Mohs' micrographic surgery, or radiotherapy.

METHODS

Setting and population

A cross-sectional cohort study was performed among patients with KC registered within the Netherlands Cancer Registry (NCR). Data from the NCR Eindhoven area were used to select a random sample of patients who were diagnosed with KC. The NCR Eindhoven area comprises an area with 2.4 million inhabitants (almost 15% of the Dutch population) in the South-Eastern part of the Netherlands. Patients diagnosed with at least one BCC or SCC in the head and neck area between January 1, 2010 and December 31, 2014 were eligible for participation. Patients with unverifiable addresses, with cognitive impairment, who died prior to the start of the study or were terminally ill and those with *in situ* lesions or who were already included in another study were excluded.

The NCR Eindhoven area is one of the few cancer registries that records data on BCC. The available data in the Netherlands Cancer Registry (NCR) does not include data on treatment – only histological diagnosis of first BCC [23]. If there is no histological information concerning BCC (neither biopsy nor excision), patients are not registered in the NCR. This may especially be the case for patients who received radiotherapy, as not all carcinomas are histologically confirmed. We have opted for an oversampling of patients who received radiotherapy as primary treatment to enable a better comparison between treatment groups. Thus, we invited all eligible patients who received radiotherapy from two radiotherapy institutions.

Study measures

The Dutch-validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) was used to assess generic HRQoL [24]. Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single items measures range in score from 0 to 100. A higher

score on functioning scores implies better health-related quality of life, whereas higher symptom scores refer to more symptoms [24].

The 16-item Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) questionnaire was used to capture impact of KC on HRQoL [14]. It assesses the relevant dimensions of HRQoL in patients with BCC and those with SCC. The individual items are scored from 0 to 3, where 0 represents no impact and 3 very high impact. The mean score per subscale was calculated. A minimum of 50% of the questions within the subscale has to be answered in order to calculate the subscale score. No total score was calculated.

The Dutch version of the European Organization for Research and Treatment of Cancer In-Patient Satisfaction with care Questionnaire (EORTC IN-PATSAT32) was used to assess patient satisfaction [25]. Items were assigned a score from one (poor) to five (excellent). After linear transformation, all scales and single items measures range in score from 0 to 100. Higher scale scores represent better satisfaction with care. Since the EORTC IN-PATSAT32 was designed for in-patients, items about nurses and information provision at hospitalization and discharge were excluded from our questionnaire.

One single item was used to assess the cosmetic results of the treatment. This item was assigned a score from 1 to 10. A higher score reflects a higher level of satisfaction with the cosmetic result.

Comorbidity was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ) [26]. Patients were asked to identify comorbid conditions present in the past 12 months. Positive responses were summed to obtain a total score (range 0-13).

Sociodemographic characteristics and clinical information were available from the NCR that routinely collects data on patients' age and sex, date of diagnosis, cancer type, and treatment. As for BCCs only the first histologically confirmed carcinoma is registered, from the eligible BCC patients additional data on treatment, tumor size and morphology was manually collected by reviewing the patient records. Information on marital status, educational level, and employment status were assessed in the questionnaire.

Data collection

Data were collected within Patient-Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship (PROFILES). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short- and long-term cancer survivors [27]. PROFILES is linked directly to clinical data from the NCR. In 2016, a survey was conducted among 345

individuals with BCC or SCC in the head and neck area. Eligible patients were informed about the study via a from their (former) dermatologist or radiotherapist. Patients were asked to complete and return the enclosed paper-and-pencil questionnaire. Patients were assured that refusing to participate in the study had no consequences for their follow-up care. If the questionnaire was not completed within 4 weeks, a reminder letter and a questionnaire was sent. More information about PROFILES and the data collection has been published previously [27]. (figure 1) All respondents have given written informed consent. This study was approved by the Medical Research Ethics Committees United (M15-0341).

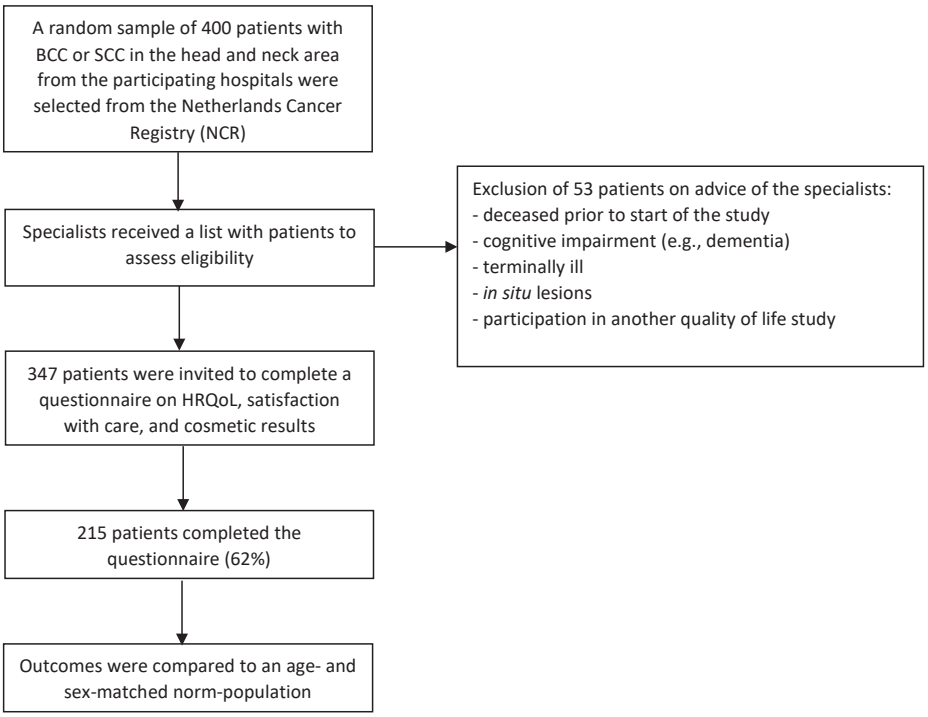

Figure 1. Flowchart of data collection process

Normative population

The normative population was selected from a reference cohort of 2,040 individuals from the general Dutch population (CentER panel). This cohort is representative for the Dutch population [28]. The set of questionnaires completed by this normative population in November 2011 included the EORTC QLQ-C30, SCQ, and data on sociodemographics. From this normative population, an age- and sex-matched selection was made to compare HRQoL with patients with KC. For matching, ten strata were formed using sex and age

(five categories). Within each stratum a maximum number of persons from the reference were randomly matched according to the strata frequency distribution of the patients. This resulted in 277 matched cancer-free individuals for the 215 KC patients.

Statistical analyses

Differences in sociodemographic and clinical characteristics between patients with KC and an age- and sex-matched normative population were assessed with a Chi-square for categorical variables and t-tests for continuous variables. Differences in sociodemographic and clinical characteristics between patients with KC according to treatment regime were also assessed with a Chi-square and t-tests, where appropriate.

Mean EORTC QLQ-C30 scores from the patients with KC were compared with the mean scores of an age- and sex-matched normative population using independent sample t-tests. To compare HRQoL scores between patients with one versus multiple skin cancer, we used analyses of covariance (ANCOVA) adjusting for age. To compare mean scores between patients with KC who underwent conventional excision, Mohs' micrographic surgery, or radiotherapy on QLQ-C30 scales, symptoms, BaSQoL scales, IN-PATSAT32 scales, general satisfaction with care, and cosmetic results, we used analyses of covariance (ANCOVA) adjusting for age. Age was calculated at the time of administering the questionnaire.

All statistical analyses were performed using SAS (version 9.4 for Windows; SAS Institute Inc., Cary, NC). *P* values of <0.05 were considered statistically significant. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups [29].

RESULTS

Patient characteristics

Two hundred fifteen patients with KC returned a completed questionnaire (62% response). Respondents were younger compared to non-respondents ($p<0.001$) and had a more recent diagnosis of KC ($p=0.004$; Table 1). No differences between responding and non-responding patients were found according to type of cancer or localization.

The mean age at completion of the questionnaire was 71.3 years with a mean time since diagnosis of 3.3 years. Most patients were diagnosed with BCC (81%) and almost half of all patients reported they have had more than one skin cancer. Medium educational level was most common (60%). Comorbid conditions were reported by 75% of patients. In the normative population, mean age at questionnaire completion was 69.3 years with

Table 1. Sociodemographic and clinical characteristics of responding and non-responding patients with keratinocyte cancer (KC), and an age- and sex-matched normative population

	Respondents N=215 N (%)	Non-respondents N=130 N (%)	Norm population N=255 N (%)
Sex			
Male	116 (54)	66 (51)	137 (54)
Female	99 (46)	64 (49)	118 (46)
Age at time of survey: mean (SD)	71.3 (11.9)	76.6 (14.1)*	69.3 (12.8)
<50	14 (7)	6 (5)	16 (6)
50-59	24 (11)	13 (10)	27 (11)
60-69	38 (18)	13 (10)	45 (18)
70-79	89 (41)	31 (24)	105 (41)
80+	50 (23)	67 (52)	62 (24)
Years since diagnosis: mean (SD)	3.3 (1.4)	3.7 (1.5)*	
Educational level[#]			
Low	34 (17)		95 (37)*
Medium	120 (60)		62 (24)*
High	47 (23)		98 (38)*
Partner			
Yes	66 (31)		83 (33)
No	149 (69)		172 (67)
Self-reported comorbidities: mean (SD)	1.5 (1.5)		1.4 (1.3)
Most frequent comorbid conditions			
Hypertension	64 (32)		92 (36)
Arthritis	65 (32)		81 (32)

[*] Significantly different from respondents ($p<0.05$); [#] Educational levels were low = none/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/ high level vocational training/university.

a comorbidity percentage of 70%. In our sample, 49% of patients with KC underwent conventional excision, 26% radiotherapy and Mohs' micrographic surgery was received by 9% of patients with KC. The remaining patients received a variety of treatments, such as photodynamic therapy, cryotherapy or topical chemotherapy. This group, however, is too small to be further outlined. Patients who received radiotherapy were significantly older (75.9 years) than patients with KC who underwent conventional excision or Mohs' micrographic surgery (68.2 and 67.4 years, respectively; $p<0.001$). In addition, patients who received radiotherapy had more often cancer located on the nose (60%) compared to patients treated with conventional excision or Mohs' micrographic surgery (25 and 32%, respectively; $p<0.001$) (Table 2).

Table 2. Sociodemographic and clinical characteristics of questionnaire respondents who were treated with radiotherapy (n=55), conventional excision (n=106), and Mohs micrographic surgery (n=19).

	Conventional excision	Mohs' micrographic surgery	Radiotherapy	p-value
	N=106	N=19	N=55	
	N(%)	N(%)	N(%)	
Sex				0.34
Male	54 (51)	8 (42)	33 (60)	
Female	52 (49)	11 (58)	22 (40)	
Age at time of survey: mean (SD)	68.2 (11.9)	67.4 (13.2)	75.9 (9.7)	
<50	9 (8)	4 (21)	0 (0)	≤0.001
50-59	17 (16)	1 (5)	4 (7)	
60-69	24 (23)	4 (21)	6 (11)	
70-79	39 (37)	6 (32)	28 (51)	
80+	17 (16)	4 (21)	17 (31)	
Education level[1]				0.37
Low	14 (14)	1 (5)	10 (20)	
Medium	59 (60)	11 (58)	32 (63)	
High	26 (26)	7 (37)	9 (18)	
Partner (yes)	77 (73)	17 (89)	36 (65)	0.13
Type of cancer				0.30
BCC	86 (81)	18 (95)	48 (87)	
SCC	15 (14)	1 (5)	7 (12)	
Unknown	5 (5)	0 (0)	(0)	
Number of skin cancers				0.04
One skin cancer	44 (42)	9 (50)	33 (63)	
More than one skin cancer	60 (58)	9 (50)	19 (37)	
Localization				≤0.001
Forehead	16 (15)	1 (5)	4 (7)	
Scalp	23 (22)	1 (5)	3 (5)	
Nose	26 (25)	6 (32)	33 (60)	
Ear	9 (8)	3 (16)	6 (11)	
Lip	3 (3)	3 (16)	2 (4)	
Other parts of head and neck	29 (28)	5 (26)	7 (13)	
Number of comorbidities: mean (SD)	1.2 (1.2)	1.4 (1.7)	1.6 (1.2)	0.22
Most frequent comorbid conditions				
Hypertension	21 (21)	8 (42)	20 (41)	0.02
Arthritis	26 (26)	6 (32)	16 (33)	0.67

[1] Education levels were low = none/primary school; medium = lower general secondary education/ vocational training; or high = pre-university education/ high level vocational training/university.

Comparison between patients with multiple skin cancers and one skin cancer

Patients with multiple skin cancers were less satisfied with the cosmetic results compared to patients with one skin cancer (8.3 versus 7.7, p<0.01) (Figure 2), and were more concerned about their appearance (0.18 versus 0.32, p=0.04). No significant differences were found on HRQoL (as measured with the EORTC QLQ-C30 and BaSQoL) between patients with one or multiple skin cancers (all p>0.05). No differences between patients with infiltrative and non-infiltrative BCC were found in HRQoL scores, general satisfaction with care and cosmetic results (all p>0.05).

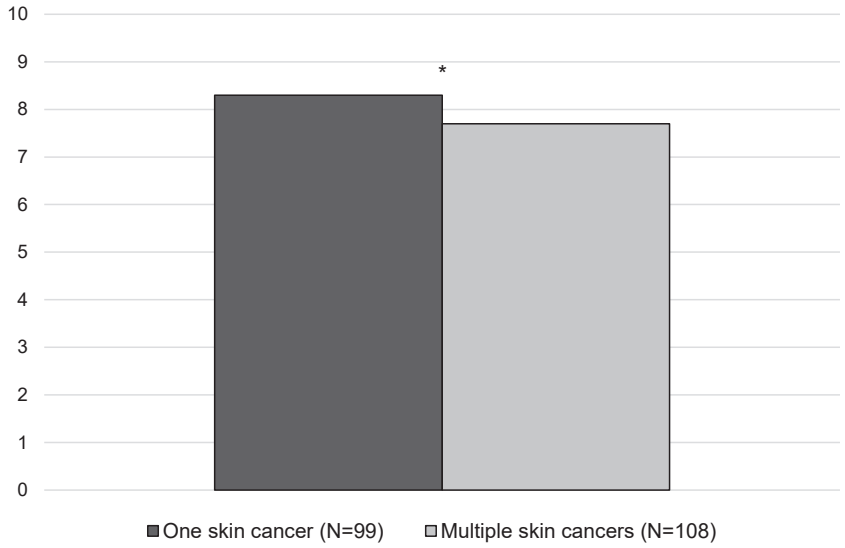

Figure 2. Differences in cosmetic results between patients who have had one skin cancer (N=99) and patients who have had multiple skin cancers (N=108).
* P < 0.001

Comparison between patients with KC and an age- and sex-matched normative population

No statistically significant differences were observed between patients with KC and an age- and sex-matched norm population on physical, emotional, cognitive, social, and role functioning (EORTC QLQ-C30) (all p>0.05). However, patients with KC reported statistically significant better scores on global quality of life (79.6 versus 73.3; p<0.01) and they reported less pain (p<0.01) compared to a normative population (Figure 3a and 3b). These represented small clinically important differences. Other symptoms were comparable (p>0.05).

Comparison between treatment groups

No differences in global quality of life, functioning scores (both EORTC QLQ-C30) or BaSQoL mean scores were found between patients treated with conventional excision, Mohs' micrographic surgery and radiotherapy (all p>0.05, Figure 4a and 4b, Table 3).

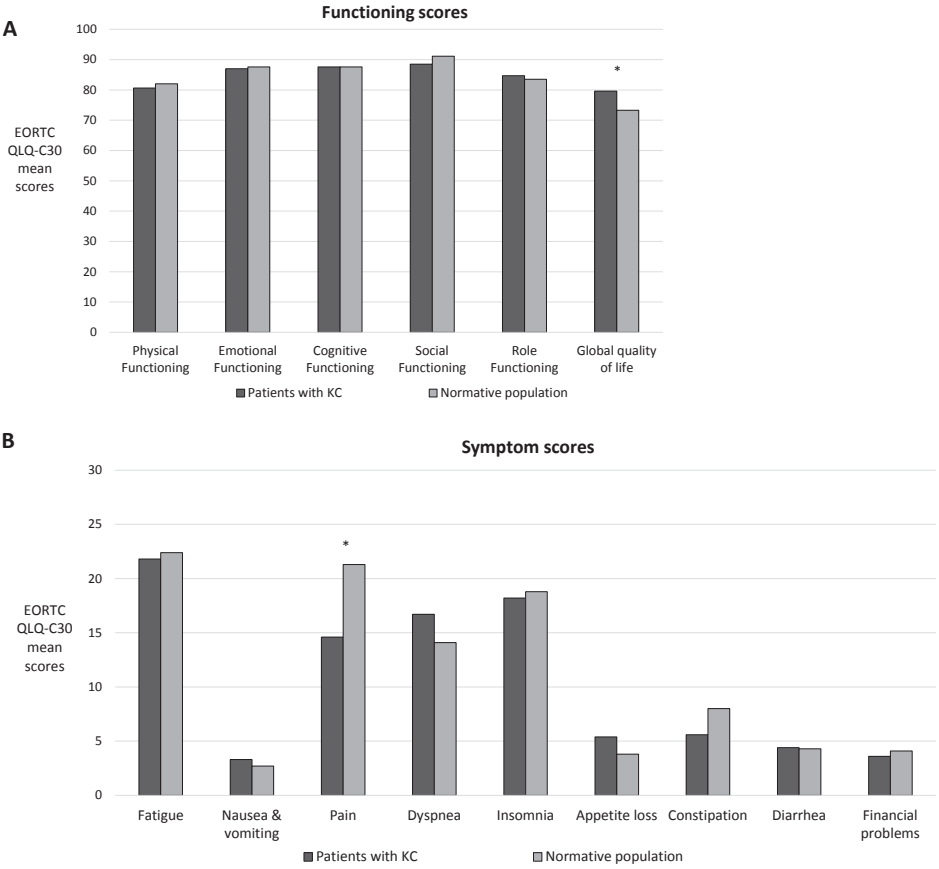

Figure 3a and 3b. Differences on EORTC QLQ-C30 mean functioning and global quality of life (a) and symptom scores (b) between patients with KC (N=215) and an age- and sex-matched normative population (N=255).
* $p < 0.05$ and small clinically important difference; A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Patients with KC who underwent radiotherapy were more satisfied with the cosmetic results than patients who underwent conventional excision or Mohs' micrographic surgery (8.5 versus 7.8 and 7.9, respectively), but this difference was not statistically significant (p=0.06) nor clinically relevant. Patients who underwent radiotherapy reported better scores for hospital comfort/cleanness (72.1 versus 62.9, p=0.03) compared to patients treated with conventional excision. No other statistically significant differences were found

between treatment groups. In all treatment groups, approximately half of the patients rated their general satisfaction with care as “very good” or “excellent”.

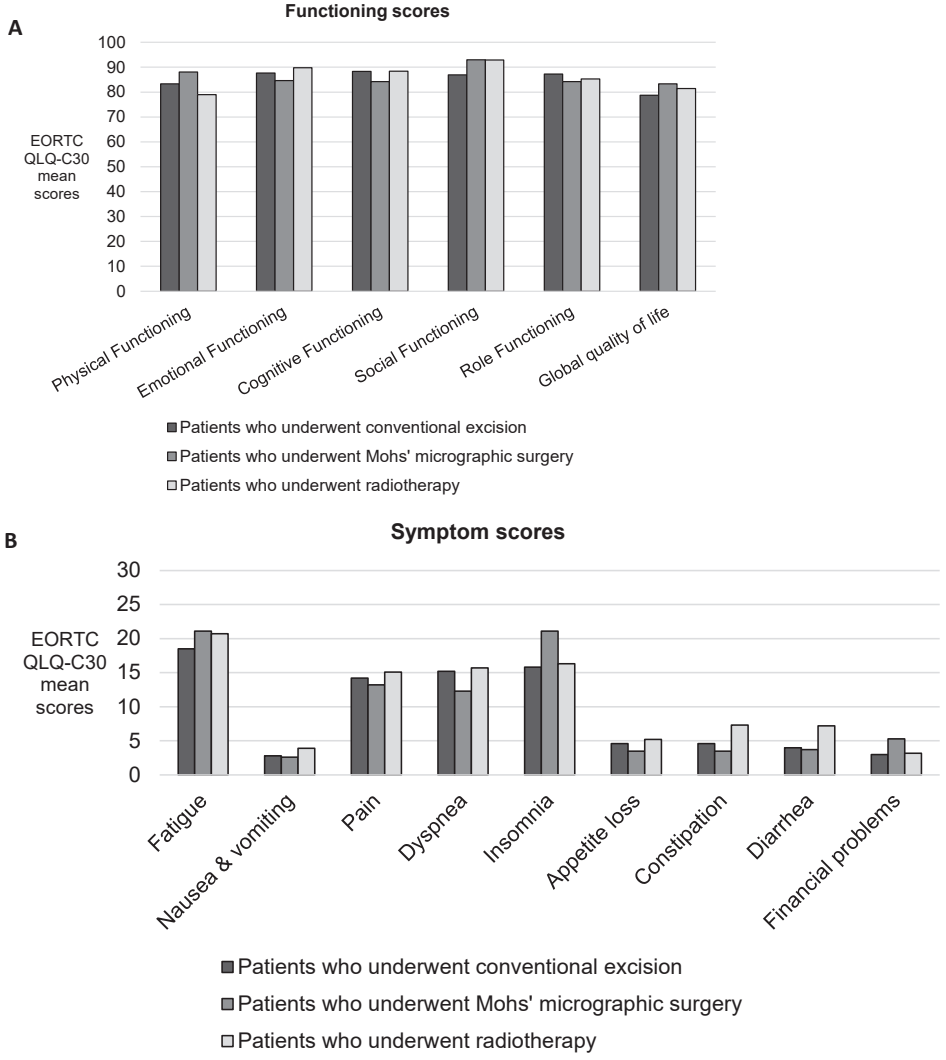

Figure 4a and 4b. Differences on EORTC QLQ-C30 mean functioning and global quality of life (a) and symptom scores (b) between patients with KC who underwent conventional excision (N=106), Mohs’ micrographic surgery (N=19), or radiotherapy (N=55).

A higher score on functioning scores implies a better health-related quality of life, whereas a higher score on symptom scores refers to more symptoms. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Table 3. Differences between patients treated with radiotherapy, conventional excision, and Mohs' micrographic surgery on mean EORTC IN-PATSAT32 scores and cosmetic result, adjusted for age.

	Conventional excision N=106 Mean (SD)	Mohs' micrographic surgery N=19 Mean (SD)	Radiotherapy N=55 Mean (SD)	p-value
BaSQoL (0-3)[1]				
Behaviour	0.7 (0.7)	0.5 (0.5)	0.6 (0.7)	0.27
Diagnosis and treatment	0.9 (0.7)	1.0 (1.0)	1.1 (0.7)	0.39
Worries	0.7 (0.6)	0.7 (0.7)	0.9 (0.7)	0.44
Appearance	0.3 (0.5)	0.2 (0.5)	0.3 (0.4)	0.19
Other people	0.7 (0.7)	0.5 (0.6)	0.6 (0.7)	0.28
EORTC IN-PATSAT32 (0-100)[2]				
Doctors' technical skills	65.4 (19.4)	68.9 (14.4)	66.6 (22.0)	0.77
Doctors' interpersonal skills	58.2 (22.2)	67.1 (20.1)	63.0 (22.9)	0.19
Doctors' information provision	64.5 (21.4)	71.9 (22.1)	69.3 (22.0)	0.24
Doctors' availability	55.5 (24.3)	65.3 (19.0)	59.7 (25.2)	0.23
Other hospital staff interpersonal skills and information provision	66.9 (20.0)	64.5 (20.9)	73.6 (22.9)	0.12
Exchange of information between caregivers	56.1 (21.2)	53.9 (28.0)	58.8 (21.7)	0.66
Waiting time	61.4 (18.2)	54.6 (25.4)	64.9 (22.6)	0.17
Hospital access	60.5 (18.3)	64.5 (21.4)	66.6 (23.2)	0.20
Hospital comfort/cleanness	62.9 (19.2)	68.4 (18.3)	72.1 (23.6)	**0.03**
General satisfaction	64.4 (19.6)	68.1 (18.8)	68.8 (21.6)	0.43
Cosmetic results (0-10)[3]				
Cosmetic results	7.9 (1.5)	7.8 (1.5)	8.5 (1.1)	0.06

Results in bold are statistically significant different. [1] A higher score implies more impact of the disease; [2] A higher score implies more satisfaction; [3] A higher score represents more satisfaction with the cosmetic result.

DISCUSSION

In this study, patients with KC reported better global quality of life and less pain compared to an age- and sex-matched norm population. Similar results have previously been observed among patients with other types of cancer [30, 31], and among patients with melanoma [32]. A possible explanation is that patients score better because they adapt the new situation of having a skin cancer diagnosis, assessing their quality of life better than before the diagnosis, the so-called response shift [33].

Although different treatment options may lead to different HRQoL scores, we found similar scores on functioning and global quality of life among patients with KC who underwent conventional excision, Mohs' micrographic surgery or radiotherapy. This is in line with research among patients with KC that showed similar HRQoL after excision and Mohs' micrographic surgery [13]. It was expected that patients who underwent radiotherapy might experience their treatment as more severe, as they need to visit the hospital several days in a row for therapy. Irradiation can also result in complaints about 'burning' of the skin [34, 35]. We found that patients who underwent radiotherapy were more satisfied with the cosmetic results, however this was not statistically relevant. The mean time since diagnosis was more than 3 years, so it might be that complaints about burning of the skin are not relevant anymore after few years, while scars as a result of conventional excision or Mohs' micrographic surgery might remain more visible, especially when patients have had multiple skin cancers. It is likely that adverse aspects of different treatment options are of greater impact on HRQoL when patients are closer to diagnosis [13]. In this study, we included only patients with KC who have been diagnosed at least one year before questionnaire completion. More complaints might be expected when patients are closer to treatment.

Patients who had multiple skin cancers reported lower cosmetic results and more concerns about their appearance compared to patients who had only one skin cancer. Previous research showed that potential disfigurement and scarring is a concern for many patients [11, 12, 36], especially multiple scars from multiple skin cancers.

Approximately half of the patients with KC rated their general satisfaction with care as "very good" or "excellent". High cure rates of both excision and radiotherapy (>90%) might therefore be an explanation for high satisfaction scores [37].

The current study has some limitations, such as the small sample size, which may limit statistical significance of our findings. The sample size is especially small for patients treated with Mohs' micrographic surgery. At the time patients included in this study were treated, the benefits of Mohs' micrographic surgery in the treatment of BCC and SCC had not yet been sufficiently demonstrated [38, 39]. Therefore, Mohs' micrographic surgery was not a standard of treatment for KC yet and as a result of which it was used less frequently. The availability of Mohs' micrographic surgery in the NCR Eindhoven area has increased since 2014. The study should be replicated with a larger sample of KC patients to get more conclusive results. In addition, we did not have detailed information on radiotherapy schedules of KC. Therefore, we are not aware whether the frequency of radiotherapy appointments has impact on HRQoL and satisfaction with care. Furthermore, we did not have detailed information of non-responding patients. Previous research reported that

patients not participating in observational PRO research may systematically have lower HRQoL scores compared to participants [40]. Therefore, observed outcomes might represent the healthier patient with better outcomes.

In conclusion, despite the cross-sectional design of this study, this population-based study give an overview of the HRQoL that patients with KC experience after their disease and treatment. The impact of KC and its treatment seems relatively low and more positive than negative as patients reported better HRQoL compared to an age- and sex-matched norm population probably due to adaptation. No statistically significant differences between treatment types were found concerning HRQoL, patients satisfaction and cosmetic results. This information could be used by healthcare professionals involved in KC care to improve patients' knowledge about different aspects of disease as patient's preference is an important factor for treatment choice.

REFERENCES

1. Kim RH, Armstrong AW. Nonmelanoma skin cancer. Dermatologic clinics. 2012;30(1):125-39, ix.
2. Dubas LE, Ingraffea A. Nonmelanoma skin cancer. Facial plastic surgery clinics of North America. 2013;21(1):43-53.
3. Albert MR, Weinstock MA. Keratinocyte carcinoma. CA: a cancer journal for clinicians. 2003;53(5):292-302.
4. Griffin LL, Ali FR, Lear JT. Non-melanoma skin cancer. Clin Med (Lond). 2016;16(1):62-5.
5. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. The British journal of dermatology. 2012;166(5):1069-80.
6. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. The Journal of investigative dermatology. 2004;123(4):634-8.
7. Smith V, Walton S. Treatment of facial Basal cell carcinoma: a review. Journal of skin cancer. 2011;2011.
8. Rhee JS, Matthews BA, Neuburg M, Burzynski M, Nattinger AB. Creation of a quality of life instrument for nonmelanoma skin cancer patients. Laryngoscope. 2005;115(7):1178-85.
9. Jennings L, Schmults CD. Management of high-risk cutaneous squamous cell carcinoma. J Clin Aesthet Dermatol. 2010;3(4):39-48.
10. Fleming ID, Amonette R, Monaghan T, Fleming MD. Principles of management of basal and squamous cell carcinoma of the skin. Cancer. 1995;75(2 Suppl):699-704.
11. Garcovich S, Colloca G, Sollena P, Andrea B, Balducci L, Cho WC, et al. Skin Cancer Epidemics in the Elderly as An Emerging Issue in Geriatric Oncology. Aging Dis. 2017;8(5):643-61.
12. Radiotis G, Roberts N, Czajkowska Z, Khanna M, Korner A. Nonmelanoma skin cancer: disease-specific quality-of-life concerns and distress. Oncology nursing forum. 2014;41(1):57-65.
13. Chen T, Bertenthal D, Sahay A, Sen S, Chren MM. Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Arch Dermatol. 2007;143(11):1386-92.
14. Waalboer-Spuij R, Hollestein LM, Timman R, van de Poll-Franse LV, Nijsten TE. Development and Validation of the Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) Questionnaire. Acta dermato-venereologica. 2018;98(2):234-9.
15. Bottomley A. The cancer patient and quality of life. The oncologist. 2002;7(2):120-5.
16. Waalboer-Spuij R, Nijsten TE. A review on quality of life in keratinocyte carcinoma patients. G Ital Dermatol Venereol. 2013;148(3):249-54.
17. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Quality of Life and Sun-Protective Behavior in Patients with Skin Cancer. Arch Otolaryngol Head Neck Surg. 2004;130(2):141-6.
18. van Egmond S, Wakkee M, Droger M, Bastiaens MT, van Rengen A, de Roos KP, et al. Needs and preferences of patients regarding basal cell carcinoma and cutaneous squamous cell carcinoma care: a qualitative focus group study. The British journal of dermatology. 2019;180(1):122-9.

19. Waalboer-Spuij R, Holterhues C, van Hattem S, Schuttelaar ML, Gaastra MT, Kuijpers DI, et al. Patient Perception of Imiquimod Treatment for Actinic Keratosis and Superficial Basal Cell Carcinoma in 202 Patients. Dermatology. 2015;231(1):56-62.

20. Magin P. Patient preferences and patient-centredness in skin cancer care: implications for clinicians and patient management. The British journal of dermatology. 2019;180(1):22-3.

21. Cartee TV, Alam M, Armbrecht ES, Behera A, Lawrence N, Bordeaux JS, et al. Patient-Centered Outcomes for Skin Cancer Management: Utilization of a Patient Delphi Process to Identify Important Treatment Themes. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2019;45(2):246-53.

22. Bath-Hextall F, Nalubega S, Evans C. The needs and experiences of patients with skin cancer: a qualitative systematic review with metasynthesis. The British journal of dermatology. 2017;177(3):666-87.

23. Waalboer-Spuij R, Hollestein LM, van de Poll-Franse LV, Nijsten TEC. Histological diagnosis of basal cell carcinoma is not associated with life expectancy in elderly Dutch people: a population-based cohort study. Br J Dermatol. 2017;177(4):e88-e9.

24. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

25. Bredart A, Bottomley A, Blazeby JM, Conroy T, Coens C, D'Haese S, et al. An international prospective study of the EORTC cancer in-patient satisfaction with care measure (EORTC IN-PATSAT32). European journal of cancer. 2005;41(14):2120-31.

26. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis and rheumatism. 2003;49(2):156-63.

27. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, Denollet J, Roukema JA, Aaronson NK, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer. 2011;47(14):2188-94.

28. van de Poll-Franse LV, Mols F, Gundy CM, Creutzberg CL, Nout RA, Verdonck-de Leeuw IM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. European journal of cancer. 2011;47(5):667-75.

29. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(1):89-96.

30. Joly F, Heron JF, Kalusinski L, Bottet P, Brune D, Allouache N, et al. Quality of life in long-term survivors of testicular cancer: a population-based case-control study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(1):73-80.

31. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. Journal of the National Cancer Institute. 2002;94(1):39-49.

32. de Vries M, Hoekstra HJ, Hoekstra-Weebers JE. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. Ann Surg Oncol. 2009;16(10):2840-7.

33. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med. 1999;48(11):1531-48.

34. Rong Y, Zuo L, Shang L, Bazan JG. Radiotherapy treatment for nonmelanoma skin cancer. Expert Rev Anticancer Ther. 2015;15(7):765-76.

35. Skiveren J, Mikkelsen MR, Daugbjerg H, Wulf HC. Skin reactions and quality of life after x-ray therapy of Basal cell carcinoma. J Skin Cancer. 2012;2012:825095.

36. Bath-Hextall F, Jenkinson C, Kumar A, Leonardi-Bee J, Perkins W, Cox K, et al. Longitudinal, mixed method study to look at the experiences and knowledge of non melanoma skin cancer from diagnosis to one year. BMC Dermatol. 2013;13:13.

37. Connolly KL, Nehal KS, Disa JJ. Evidence-Based Medicine: Cutaneous Facial Malignancies: Nonmelanoma Skin Cancer. Plastic and reconstructive surgery. 2017;139(1):181e-90e.

38. van Lee CB, Roorda BM, Wakkee M, Voorham Q, Mooyaart AL, de Vijlder HC, et al. Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study. The British journal of dermatology. 2018.

39. Flohil SC, van Dorst AM, Nijsten T, Martino Neumann HA, Munte K. Mohs micrographic surgery for basal cell carcinomas: appropriateness of 'Rotterdam' criteria and predictive factors for three or more stages. Journal of the European Academy of Dermatology and Venereology : JEADV. 2013;27(10):1228-35.

40. de Rooij BH, Ezendam NPM, Mols F, Vissers PAJ, Thong MSY, Vlooswijk CCP, et al. Cancer survivors not participating in observational patient-reported outcome studies have a lower survival compared to participants: the population-based PROFILES registry. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2018;27(12):3313-24.

Chapter 7

Discussion

The aims of this thesis were to develop and validate a disease-specific health-related quality of life (HRQoL) questionnaire and assess HRQoL and patient perception on disease, treatment and provided information in keratinocyte carcinoma (KC) patients. This final chapter reflects on the main findings and limitations, and concludes with a discussion on future perspectives.

Health

In order to discuss HRQoL, it is important to discuss the definition of health. The definition used until 2011 was formulated by the World Health Organization (WHO) in 1948 and describes health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] This definition has been criticized but was never adapted. In 2011, Hubert et al proposed a new definition; "health is the ability to adapt and self-manage", which has been accepted since.[2]

(Health-Related) Quality of life

Since the introduction of 'quality of life' in medicine, it is being used increasingly as an outcome of care in studies. Unfortunately, there is no consensus on a definition for 'quality of life' and it may appear as health status, physical functioning, perceived health status, subjective health, health perceptions, symptoms, need satisfaction, individual cognition, functional disability, psychiatric disturbance, well-being and -quite often- several of these at the same time. In order to clarify these issues, the term 'health-related quality of life' was defined as the value of a life affected by illness and disease. It is a multidomain concept representing the general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. [3]

It has been stated that in reality it is impossible to separate effects due to health and other effects which are a consequence of changing patterns such as finance, friendship, occupation and ageing.[4-6] It does however add value to the patient's perspective and the clinicians perspective in the evaluation of treatment outcomes. And aiming for the best possible physical and emotional state compatible with the medical condition has the best chance of achieving a high quality of life.[7] The European Organization for Research and Treatment of Cancer (EORTC) Quality Of Life Group uses the following definition: HRQoL covers the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment. [8] When incorporating HRQoL measurement into clinical practice, it is recommended to evaluate the usefulness of the questionnaires as experienced by the patient. [9] An example of HRQoL use in clinical practice is in patients with chronic idiopathic urticaria. The guideline of the Dutch Society of Dermatology recommends that measurement with a disease specific and a dermatol-

ogy specific HRQoL instrument, and a specific minimal score, is necessary before starting omalizumab treatment. [10]

In oncology, the aforementioned EORTC Quality Of Life Group started to develop the EORTC quality of life core questionnaire (QLQ-C30) in 1986. The main goal was to develop an instrument suitable for standardized HRQoL measurement in international clinical trials in oncology. [11] In the following decades, the majority of clinical trials in oncology reported HRQoL assessment, especially in systemic treatments for metastasized cancer with or without radiotherapy since there are substantial disease and treatment effects on the short and long term. The tendency to investigate HRQoL in cancer therefore was mainly in metastasized cancer. Non-metastasized cancer and KC were only studied sparsely during this period.

In dermato-oncology, specifically in KC patients, the first sparse attention for HRQoL was in the late 90's, suggesting little to no HRQoL impact in BCC patients, measured with generic and dermatology specific HRQoL questionnaires. [12] This is most likely due to the often straightforward surgical treatment and lack of severe and lasting side effects of treatments. Measuring HRQoL with both a generic and a specific HRQoL instrument is preferable over only using a generic HRQoL instrument to assess impact and responsiveness.[13] Unfortunately, existing HRQoL questionnaires for KC were not suitable for use, because of methodological flaws, such as the use of multiple issues and questions combined in one item. They also failed to capture one of the most reported issues in skin cancer patients; the often required behavioral changes (and related psychological issues) to reduce sun exposure.[14] A previous study by Holterhues et al. showed that Dutch melanoma survivors reported a better quality of life than the general population, but nevertheless, reported substantial impact on 'melanoma specific' items suggesting that their diagnosis did affect their quality of life.[15] In this thesis we identified the HRQoL issues in KC patients (chapter 3) and tested the impact of these issues in population based samples (chapter 5 and 6). The identified issues have some overlap with issues in existing HRQoL questionnaires used in skin cancer patients, such as concerns about appearance and scarring, sun behavior and fear of cancer recurrence or spreading.[16-18] The BaSQoL questionnaire however also captures treatment and diagnosis related issues and issues related to long-term behavioral changes.

Another unique feature of the BaSQoL questionnaire is the use of different time-frames within the questionnaire. This was created since patients mentioned a distinct difference in behavior before and after the initial skin cancer diagnosis. The first part of the BaSQoL captures the impact of these changes. The second part of the questionnaire assesses the usually short period between diagnosis and treatment. This is a known stressful period for

patients with cancer with a high impact on the HRQoL and measurement helps to assess the patient's experience of this period. Patients with high HRQoL impact may benefit from additional care, especially in case of first tumours. The final part of the BaSQoL is more classic in the way that it concerns the HRQoL impact of the skin cancer in the past week. By using this three time periods concept, the questionnaire addresses the several issues in the right context. The downside to this is that it requires more thought and therefore may be more difficult to complete.

The validation of the English version of the BaSQoL and the simultaneous assessment of the construct validity by comparison with the Skin Cancer Index, test-retest stability and responsiveness to change completed the validation of the newly created questionnaire (chapter 4).

The measurement of the HRQoL impact in KC patients in chapter 5 and 6 showed a higher impact in younger patients and patients who were dissatisfied with provided information about the disease. Female patients had higher impact in some of the subscales, but surprisingly not on the appearance subscale. In comparison to an age- and sex-matched normative population, patients with KC reported statistically significant better scores on global quality of life as measured by the EORTC QLQ-C30 questionnaire. This is also seen in melanoma and may be explained by the so-called response shift; adaptation to the new situation of having a skin cancer diagnosis and better assessment of their QoL than before diagnosis.[19, 20] Patients with BCC even have a lower all-cause mortality in comparison to the general population. [21]

When comparing BaSQoL scores of patients who have had different treatments for their KC (conventional excision, Mohs' micrographic surgery or radiotherapy), no differences were found. In general, the impact of KC and its treatment seems relatively low in different treatment groups. These findings are similar to the findings of Chren et al. in 2007, comparing conventional excision, Mohs' micrographic surgery and electrodessication and curettage. [22]

The use of the BaSQoL in KC still needs further investigation. Especially to determine the optimal timing of questionnaire administration and clinical implications of scores. The BaSQoL seems to be a useful tool to assess the impact of KC diagnosis in order to identify these patients at risk for major HRQoL impact.

A problem in the current way of measuring HRQoL in oncology is the extensive and lengthy course of the development of a questionnaire. The development of the BaSQoL, from phase 1 to the final acceptance of the manuscript took 5 years (Figure 1), similar to many

other HRQoL questionnaire developments in oncology. Especially in questionnaires for cancer addressing symptoms due to systemic therapy, by the time the questionnaire is ready for use, it is already outdated due to the rapid development and implementation of new cancer therapies. [23, 24] Another approach in this field, to monitor symptoms during systemic cancer treatment, is the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). It is a questionnaire which is customizable for use in cancer trials, measuring symptomatic adverse events. The specific items which are needed for a study can be selected from the item bank (which is a database of previously studied and validated items).[25] In this way, a new questionnaire can be assembled rather quickly, fitted for the new therapy, without the time consuming process of developing a completely new questionnaire. Fortunately, symptoms are not much of an issue in KC or KC treatment options and are thus not included in the BaSQoL.

Patient Reported Outcomes

Patient Reported Outcomes (PROs) are outcomes about a disease, health or treatment directly from patients without interpretation. It includes HRQoL, but also other outcomes such as severity and frequency of symptoms, treatment satisfaction, functional status and well-being but in general, it reflects how patients feel.[26] It includes for example symptom checklists such as pain and itch, which are also being used in chronic idiopathic urticaria [10]. By collecting PRO's, the caregivers are able to understand the impact of disease and treatment better and therefore able to intervene and thus optimize how patients feel. [27] In cancer, PRO monitoring has shown improvements in patient-care-provider communication. [28] It also helps to identify issues patients might not have raised and that clinicians would therefore assume were not of concern, on which tailored care can be provided. In oncology, the web-based self-management application "Oncokompas" is being integrated in routine cancer-care, monitoring health-related quality of life and support cancer survivors in finding and obtaining optimal supportive care. [29] It assesses a wide range of outcomes, covering the following domains: physical, psychological, social, healthy lifestyle and existential issues. Completing PROs might also make patients feel cared for, and therefore improving emotional functioning.[30] It was shown, that improved physician-patient communication resulted in better HRQoL and emotional functioning for a proportion of patients. [31] In research it can be used to identify the benefits and harms of treatments and interventions.[32] This all will improve outcomes and also patient-centeredness, as is demonstrated in a study using the PRO-CTCAE, even improving survival when using web-based symptom monitoring versus routine surveillance following treatment for lung cancer. [33]

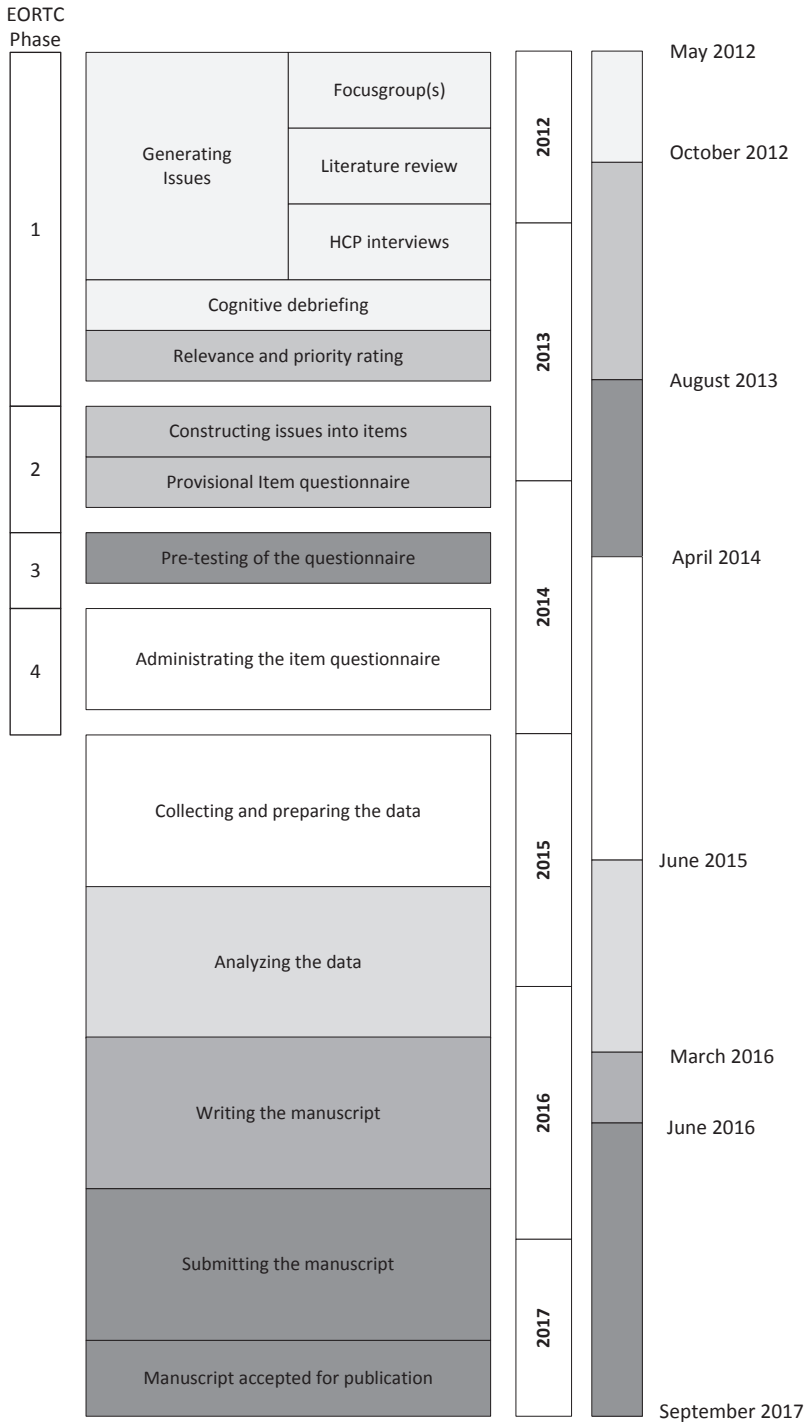

Figure 1. Timeline of the development of the BaSQoL questionnaire.

By routinely monitoring PROs, care can be tailored to match the patients' needs. [26, 28, 34] By providing feedback about the PRO, patients have their own responsibility to discuss issues with their treating physician or their general practitioner.

Another use for PRO is to monitor the patient post-treatment. The time between the (surgical) treatment and the first follow-up visit may be used to proactively address and manage symptoms and following problems (e.g. complications, urgent care evaluations). [35]

Patient centered care

The National Academy of Medicine (formerly known as Institute of Medicine) formulated six dimensions of patient-centered care, which stated that care must be: 1) respectful to patients' values, preferences, and expressed needs; 2) coordinated and integrated; 3) provide information, communication, and education; 4) ensure physical comfort; 5) provide emotional support – relieving fear and anxiety; and 6) involve family and friends.[36, 37] To measure these dimensions the use of PROs is needed. HRQoL measurement can help to identify needs and preferences, assess satisfaction on information and help to optimize physical and emotional needs. A recent qualitative study in BCC and SCC patients showed the wish for investing in the patient–physician relationship and personalizing the type and form of information and the follow-up schedules.[38] The BaSQoL can help to identify if there are any issues bothering the individual patient. The behavior subscale for example helps to evaluate if the patient can fit the often required behavioral changes after the first skin cancer diagnosis into his/her daily life whilst not interfering with patients' values and preferences. The worries and also the diagnosis & treatment subscales address fear and anxiety. On the other hand is the BaSQoL useful for assessment on group level and these results may be used to compare individual scores to group scores.

Specifically in cancer care, a more holistic approach to the patient is desirable, also assessing supportive care, encompassing clinical, ethical/existential and spiritual dimensions. [39] To measure the needs of supportive care, questionnaires exist. [40, 41] Existing HRQoL questionnaires may even be used to identify a change in patients' supportive care needs.[42] The BaSQoL may also be used for this purpose since it is specific enough to identify the patients with high impact of the diagnosis and treatment. In daily practice, we notice that additional (supportive) care is helpful in managing anxiety in patients. Detailed and personalized information provided by the doctor or the nurse helps to cope with the disease and manage it in daily life. Further research should assess how to use and interpret the BaSQoL for this purpose.

Another way to center the patient in the care process is to empower them to own their PRO results. A current study in lymphoma patients evaluates the impact of providing patients PRO with feedback. [43] Results of a pilot study suggest that a high number of patients wished to receive PRO feedback and that they would find the comparison of their scores versus a disease specific reference cohort most valuable. [44] This current ongoing study will provide information about the usefulness of providing feedback to the patient on PRO. Whatever the outcomes of this study will be, providing individual PRO results to the patient can help to address the deviant outcomes or subscales with their treating physician. But with empowerment also comes responsibility for the patient creating a bilateral perspective on the concept of 'shared decision making'.

Strengths and limitations of the studies in this thesis

The impact of KC on HRQoL seems to be limited in most patients, but the smaller proportion of patients on which KC has a larger impact on HRQoL need to be identified in order to provide additional care. Since the total number of KC patients is high, even a small proportion of patients with high HRQoL impact means that a high absolute number of patients might suffer.

The development of the BaSQoL questionnaire has been thorough in all aspects of the development in comparison to other skin cancer specific HRQoL questionnaires. The development phase was designed and executed mostly following EORTC questionnaire development guidelines. The patient sample was population-based with a generous sample size and the analyses were not only the state of the art Item Response Theory analyses, but also included conventional classical test theory principles. The population based approach which we used in chapter 3, 5 and 6 helps to study a large group of patients over several hospitals and clinics. However, information about treatment was also based on patients' self-report and therefore may be less accurate.

Interpretation of the BaSQoL subscale scores may be time-consuming in daily clinical practice since it concerns several subscales and a minimal clinically important difference or any other cut-off scores to help interpret the scores do not yet exist.

Development was done in one country and cross cultural difference may exist, but in the validation study of the English version of the BaSQoL in chapter 4 no indications for this were found.

The questionnaire is developed as an instrument to assess the impact of KC on patients' lives and not so much to evaluate the effect of (different) treatments.

A major limitation in the study described in chapter 3, the development and validation of the BaSQoL questionnaire, was that we did not compare the newly developed questionnaire to an existing one. In order to overcome this issue, we compared the BaSQoL to the Skin Cancer Index in the additional validation study of the English version of the BaSQoL in chapter 4.

Future perspective

The BaSQoL may be used in two different contexts. First it may be used on a group level, in a population based setting or a larger group of patients, for example in a hospital of clinic, to evaluate the impact of disease and care in general. It helps to assess which problems arise in KC patients, to help the physician address these items in outpatient consultations or to provide care and more extensive explanation by dermatology nurses. Furthermore, it can be used to measure before and after changes in care plans to assess the impact on group level (e.g. before and after reducing follow-up regimens for low risk KC patients or before and after implementation of new treatments). Variation between hospitals can also be assessed to identify and evaluate differences in order to improve care and learn from each other.

Second, the BaSQoL may be used on an individual patient level to assess the impact of the disease, diagnosis and the treatment. Although it was not developed for this purpose, it makes sense to use it as such. This has happened in the past with the EORTC QLQ-C30 questionnaire and which has been commented on frequently. Determination of minimal clinically important differences or cut-off scores would help to guide the clinician in which patient is at risk for high impact and therefore requires additional attention and care. Also the way the scores are presented back to the patient or the physician may lead to easier interpretation; further research is necessary to optimize this aspect. Using the BaSQoL as an instrument to assess the level of distress in patients, identifying distressed patients and providing supportive care may also help to reduce healthcare costs overall, as it has been shown that distressed patients use more healthcare services in comparison to non-distressed patients or a normative population. [45] Additional studies are needed to identify patients who may need psychological care and to assess if psychosocial interventions could reduce the frequency of medical contacts.

The data generated with studies from the first group (group-level data) can help to monitor the patient's PROs (individual-level data) and to compare individual-level data with mean group level outcomes. Knowledge about the patients individual PRO may even help in decision making in choosing the best suitable treatment. For example, a patient with a superficial BCC with high impact on the worries subscale might be better off treated with surgical excision with histopathological examination of the specimen instead of topical

treatment with 5-fluorouracil cream or imiquimod cream without the histopathological confirmation of the excision.

One of the greatest challenges is how to integrate routinely measurement of HRQoL instruments such as the BaSQoL in daily practice. The BaSQoL is short and therefore quick and easy to complete for patients, but calculation and interpretation of the scores is still time consuming. Creation of a web-based form can help to display the scores immediate. How this data is displayed to optimize interpretability is also an important aspect to consider. Mean scores for example can be presented next to the individual score. It can be displayed as a number, but also in a graph such as a bar chart, pie chart or a line chart. Deviant scores can be displayed in a different color to simplify interpretation. One study demonstrated that the best way to display individual PRO scores is to use a line chart with high scores meaning better HRQoL and a threshold line within the chart to identify the scores below which are possibly concerning. [46]

It also has to be assessed what the optimal moment in time is for questionnaire administration (e.g. 1 month after treatment, 3 months after treatment). The clinical meaning or interpretation of the subscale scores is another area of attention for future research. It can be assessed on an individual patient level using anchor-based methodology, which examines the relationship between scores on an HRQoL instrument and an independent measure (anchor), or on a population level by statistical analysis appointing a score of 1 or 2 SD above the mean as deviant. [47]

The use of modern technology such as questionnaire administration through apps and automated feedback to the patient and his/her electronic medical file about the PRO outcomes with practical advice when to act, what to do and whom to discuss the results with may help to empower patients and to use the questionnaire in daily practice. This is also stated in the directives agreement (‘hoofdlijnen akkoord’) on speciality care 2019-2022 as stated by the current Dutch government. [48]

Conclusion

The perception of KC patients on their disease and treatment and the related HRQoL impact is captured in the newly developed BaSQoL questionnaire. This thesis presents studies on the development and validation of this questionnaire and factors influencing the HRQoL in KC patients. More research is needed to optimize the use and interpretation of the BaSQoL questionnaire in order to confirm and sustain the KC patient empowerment.

REFERENCES

1. WHO. Constitution of the World Health Organization. 2006.
2. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, et al. How should we define health? BMJ. 2011;343:d4163.
3. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-9.
4. Hunt SM. The problem of quality of life. Qual Life Res. 1997;6(3):205-12.
5. Ferrans CE. Quality of life: conceptual issues. Semin Oncol Nurs. 1990;6(4):248-54.
6. Flannery M. Conceptual Issues Surrounding Quality of Life in Oncology Nursing. Oncol Nurs Forum. 2017;44(3):285-7.
7. Leplege A, Hunt S. The problem of quality of life in medicine. JAMA. 1997;278(1):47-50.
8. Group QoL. Quality of Life: EORTC; 2018 [Available from: https://qol.eortc.org/quality-of-life/.
9. Snyder CF, Herman JM, White SM, Luber BS, Blackford AL, Carducci MA, et al. When using patient-reported outcomes in clinical practice, the measure matters: a randomized controlled trial. J Oncol Pract. 2014;10(5):e299-306.
10. Urgert MC, Knulst AC. Samenvatting Richtlijn chronische spontane urticaria. Ned Tijdschr Dermatol Venereol. 2016;26(1):10-3.
11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
12. Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. Qual Life Res. 1996;5(2):191-4.
13. Wiebe S, Guyatt G, Weaver B, Matijevic S, Sidwell C. Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol. 2003;56(1):52-60.
14. Waalboer-Spuij R, Nijsten TE. A review on quality of life in keratinocyte carcinoma patients. G Ital Dermatol Venereol. 2013;148(3):249-54.
15. Holterhues C, Cornish D, van de Poll-Franse LV, Krekels G, Koedijk F, Kuijpers D, et al. Impact of melanoma on patients' lives among 562 survivors: a Dutch population-based study. Arch Dermatol. 2011;147(2):177-85.
16. Rhee JS, Matthews BA, Neuburg M, Burzynski M, Nattinger AB. Creation of a quality of life instrument for nonmelanoma skin cancer patients. Laryngoscope. 2005;115(7):1178-85.
17. Burdon-Jones D, Gibbons K. The Skin Cancer Quality of Life Impact Tool (SCQOLIT): A validated health-related quality of life questionnaire for non-metastatic skin cancers. J Eur Acad Dermatol Venereol. 2012.
18. Vinding GR, Christensen KB, Esmann S, Olesen AB, Jemec GB. Quality of life in non-melanoma skin cancer--the skin cancer quality of life (SCQoL) questionnaire. Dermatol Surg. 2013;39(12):1784-93.
19. de Vries M, Hoekstra HJ, Hoekstra-Weebers JE. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. Ann Surg Oncol. 2009;16(10):2840-7.

20. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med. 1999;48(11):1531-48.

21. Wehner MR, Cidre Serrano W, Nosrati A, Schoen PM, Chren MM, Boscardin J, et al. All-cause mortality in patients with basal and squamous cell carcinoma: A systematic review and meta-analysis. J Am Acad Dermatol. 2018;78(4):663-72 e3.

22. Chren MM, Sahay AP, Bertenthal DS, Sen S, Landefeld CS. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol. 2007;127(6):1351-7.

23. Kluetz PG, Slagle A, Papadopoulos EJ, Johnson LL, Donoghue M, Kwitkowski VE, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms. Clin Cancer Res. 2016;22(7):1553-8.

24. Groenvold M, Aaronson NK, Darlington AE, Fitzsimmons D, Greimel E, Holzner B, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials-Letter. Clin Cancer Res. 2016;22(22):5617.

25. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book. 2016;35:67-73.

26. Jensen RE, Snyder CF. PRO-cision Medicine: Personalizing Patient Care Using Patient-Reported Outcomes. J Clin Oncol. 2016;34(6):527-9.

27. Basch E, Snyder C, McNiff K, Brown R, Maddux S, Smith ML, et al. Patient-reported outcome performance measures in oncology. J Oncol Pract. 2014;10(3):209-11.

28. Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014;32(14):1480-501.

29. Matthijs de Wit L, van Uden-Kraan CF, Lissenberg-Witte BI, Melissant HC, Fleuren MAH, Cuijpers P, et al. Adoption and implementation of a web-based self-management application "Oncokompas" in routine cancer care: a national pilot study. Support Care Cancer. 2019;27(8):2911-20

30. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. Lancet. 2009;374(9687):369-70.

31. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol. 2004;22(4):714-24.

32. Snyder CF, Jensen RE, Segal JB, Wu AW. Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Med Care. 2013;51(8 Suppl 3):S73-9.

33. Denis F, Basch E, Septans AL, Bennouna J, Urban T, Dueck AC, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. JAMA. 2019;321(3):306-7.

34. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol. 2016;34(6):557-65.

35. Smith AB, Basch E. Role of Patient-Reported Outcomes in Postsurgical Monitoring in Oncology. J Oncol Pract. 2017;13(8):535-8.

36. Tzelepis F, Sanson-Fisher RW, Zucca AC, Fradgley EA. Measuring the quality of patient-centered care: why patient-reported measures are critical to reliable assessment. Patient Prefer Adherence. 2015;9:831-5.

37. Medicine. Io. Crossing The Quality Chasm: A New Health System for the 21st Century. Washington DC: National Academy Press; 2001.

38. van Egmond S, Wakkee M, Droger M, Bastiaens MT, van Rengen A, de Roos KP, et al. Needs and preferences of patients regarding basal cell carcinoma and cutaneous squamous cell carcinoma care: a qualitative focus group study. Br J Dermatol. 2019;180(1):122-9.

39. Carrieri D, Peccatori FA, Boniolo G. Supporting Supportive Care in Cancer: The ethical importance of promoting a holistic conception of quality of life. Crit Rev Oncol Hematol. 2018;131:90-5.

40. Jansen F, Eerenstein SEJ, Lissenberg-Witte BI, Uden-Kraan CFV, Leemans CR, Leeuw IMV. Unmet supportive care needs in patients treated with total laryngectomy and its associated factors. Head Neck. 2018;40(12):2633-41.

41. Jansen F, Witte BI, van Uden-Kraan CF, Braspenning AM, Leemans CR, Verdonck-de Leeuw IM. The need for supportive care among head and neck cancer patients: psychometric assessment of the Dutch version of the Supportive Care Needs Survey Short-Form (SCNS-SF34) and the newly developed head and neck cancer module (SCNS-HNC). Support Care Cancer. 2016;24(11):4639-49.

42. Snyder CF, Blackford AL, Sussman J, Bainbridge D, Howell D, Seow HY, et al. Identifying changes in scores on the EORTC-QLQ-C30 representing a change in patients' supportive care needs. Qual Life Res. 2015;24(5):1207-16.

43. Arts LPJ, van de Poll-Franse LV, van den Berg SW, Prins JB, Husson O, Mols F, et al. Lymphoma InterVEntion (LIVE) - patient-reported outcome feedback and a web-based self-management intervention for patients with lymphoma: study protocol for a randomised controlled trial. Trials. 2017;18(1):199.

44. Oerlemans S, Arts LP, Horevoorts NJ, van de Poll-Franse LV. "Am I normal?" The Wishes of Patients With Lymphoma to Compare Their Patient-Reported Outcomes With Those of Their Peers. J Med Internet Res. 2017;19(8):e288.

45. Arts LPJ, Oerlemans S, Tick L, Koster A, Roerdink HTJ, van de Poll-Franse LV. More frequent use of health care services among distressed compared with nondistressed survivors of lymphoma and chronic lymphocytic leukemia: Results from the population-based PROFILES registry. Cancer. 2018;124(14):3016-24.

46. Snyder CF, Smith KC, Bantug ET, Tolbert EE, Blackford AL, Brundage MD, et al. What do these scores mean? Presenting patient-reported outcomes data to patients and clinicians to improve interpretability. Cancer. 2017;123(10):1848-59.

47. Prinsen CA, Lindeboom R, Sprangers MA, Legierse CM, de Korte J. Health-related quality of life assessment in dermatology: interpretation of Skindex-29 scores using patient-based anchors. J Invest Dermatol. 2010;130(5):1318-22.

48. Bestuurlijk akkoord medisch-specialistische zorg 2019 t/m 2022. In: VWS, editor. www.rijksoverheid.nl.

Chapter 8

Summary / Samenvatting

SUMMARY

Chapter 1 is the general introduction to this thesis. Keratinocyte carcinoma (KC) is a common health problem affecting a great number of patients. The different studies on health-related quality of life (HRQoL) instruments in KC published previous to this thesis are described. The first studies used generic and cancer specific HRQoL questionnaires. In these studies the relevance of many items was questioned by study participants. It may be concluded that affected domains of HRQoL in KC patients are not captured by generic and cancer specific questionnaires. Dermatology specific HRQoL questionnaires created for use in skin disease patients, in particular inflammatory skin disease. Measurement with these questionnaires in KC patients display some differences when comparing different treatment modalities, but still lack face validity and fail to capture the KC patients concerns in detail. The previous developed skin cancer specific HRQoL questionnaires do assess some important and relevant issues, but fail to capture the important behavioral changes of KC patients, interpretability is questionable due to multiple items in 1 question and face and content validity are lacking. Therefore the aims of this thesis were to develop and validate a disease-specific HRQoL questionnaire and assess HRQoL and patient perception of disease, treatment and provided information in KC patients.

In **chapter 2** we used the dermatology specific Skindex-17 questionnaire and the skin cancer specific Skin Cancer Index (SCI) in an open-label, multicenter study (2 university medical centers and 6 hospitals) in which patients with actinic keratosis (AK) and superficial basal cell carcinoma (sBCC) eligible for treatment with imiquimod 5% cream were included. Treatment satisfaction was measured by the Treatment Satisfaction Questionnaire for Medication (TSQM). 118 AK and 84 sBCC patients were included and asked to complete the HRQoL questionnaires at baseline (before treatment), directly after treatment and 8-16 weeks after treatment. TSQM was measured at the final measure point. Low baseline HRQoL impairment was found on the Skindex-17 and the SCI, which remained low after treatment, except for a small dip at the end of the application period. Imiquimod 5% cream treatment has no clinically relevant HRQoL improvement nor impairment in both AK and sBCC as measured by the Skindex-17 and the SCI. Treatment is well tolerated, but overall treatment satisfaction (as measured by the TSQM) is only around 55-60% in both groups. We concluded that the results of this study also suggest that the used HRQoL instruments are not specific and sensitive enough to capture the issues important in KC patients.

Chapter 3 describes the development and validation of the Basal and Squamous cell carcinoma Quality of Life (BaSQoL) questionnaire. This was primarily done in a 4 phase development, mostly following guidelines of the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL) group (phase 1: generating issues; phase

2: reduction of items; phase 3: pre-testing; phase 4: field testing). The first phase consisted of generating an extensive list of HRQoL issues relevant to KC patients. A focus group meeting, semi-structured interviews with healthcare professionals and a literature search led to 57 issues which were presented to patients and healthcare professionals for relevance and priority rating. This led to a reduced 33 issues which were converted into items which were pre-tested in a 16 patients (phase 2 and 3). The provisional 33 item questionnaire was field-tested in 1,173 patients selected from the Netherlands Cancer Registry (phase 4). 721 patients responded (61%) of which 85% had basal cell carcinoma (BCC) and 15% squamous cell carcinoma (SCC). Principal component analyses were performed to determine the 5 components, which were labelled as Worries, Appearance, Behaviour, Diagnosis & Treatment and Other people. Item response analyses were used to reduce the number of items to 16. The performance of the new questionnaire was assessed by eight classical test theory features and with a confirmatory factor analysis, showing a good face, content and construct validity.

Chapter 4 describes the additional validation of the English translation of the BaSQoL. In this prospective, observational study, 122 BCC and 65 SCC patients were enrolled who were scheduled for treatment in the University of California, San Francisco. They were asked to fill in the BaSQoL questionnaire before treatment (T0), four weeks after treatment (T1) and one week thereafter (5 weeks after treatment; T2). Additionally, participants were asked to complete the SCI and the Hospital Anxiety and Depression Scale (HADS) one week before treatment. Mean scores for BaSQoL subscales were generally low, demonstrating a moderate impact on HRQoL for most patients. Patients with SCC had higher levels of anxiety as measured by the Worries subscale in comparison to BCC patients. The SCI measured higher impact in SCC patients in the Emotional subscale. HADS scores were low, except for a few patients who indicated anxiety. The eight classical test theory features showed good performance. Internal consistency was good with Cronbach's αs ranging from 0.63-0.80 for the different subscales. The intra-class correlation coefficient (ICC) between T1 and T2 was high (≥0.75) for nearly all subscales, indicating a stable response of the BaSQoL over time. BaSQoL subscales were strongly correlated with subscales of the SCI, demonstrating convergent validity, but were weakly correlated with HADS, indicating divergent validity. The English language version of the BaSQoL therefore has good face, content, and construct validity. This study validates the English translation of the BaSQoL for use in a wide range of BCC and SCC patients.

In **chapter 5** the BaSQoL questionnaire is used to measure HRQoL impact in BCC and SCC patients in a large population based sample from the Netherlands Cancer Registry. Additional questionnaires regarding cancer-specific HRQoL (EORTC QLQ-C30), information provision (EORTC QLQ-INFO25) and general satisfaction with care (EORTC IN-PATSAT32)

were administered. 721 of 1,173 (61%) patients participated. HRQoL impact as measured by the BaSQoL was higher among female and younger patients. One third (N=237) of all patients indicated to be dissatisfied with the information provision as measured by the dichotomized item 'satisfaction with information provision' within the EORTC QLQ-INFO25 questionnaire. Of all patients, 16% (N=116) indicated that they had wanted to receive more information about skin cancer in general, but also about causes, treatment and follow-up plan and how to recognize new lesions. This corresponds to 37% (84/225) of all dissatisfied patients and 7% (28/416) of the satisfied patients. Dissatisfaction with information provision was associated with younger age, facial tumour, not having a partner and multiple comorbidities. HRQoL was worse in patients dissatisfied with information provision (e.g. BaSQoL-worries mean score satisfied patients: 0.54 (95%CI:0.48–0.59), dissatisfied patients: 0.77 (95%CI:0.67–0.87), p=0.001). The distribution of satisfied versus dissatisfied with the information provision differed substantially between the 9 participating hospitals or clinics. However, after adjustment for patient and tumour characteristics, participating centre was no longer associated with satisfaction with information provision. Dissatisfaction with provided information was associated with an impact on HRQoL. Possibly, HRQoL could be improved by improving the information provision.

In **chapter 6** the BaSQoL questionnaire is used to measure impact of diagnosis and treatment of KC in the head and neck area in a random population based sample of 347 patients, independent to the sample of the validation study. Additional questionnaires concerning cancer-specific HRQoL (EORTC QLQ-C30) and patient satisfaction with care (EORTC IN-PATSAT32) were administered. One single item was used to assess the cosmetic results of the treatment. HRQoL was also compared to an age- and sex-matched norm population. 215 patients (62%) participated. Patients with KC reported better global quality of life and less pain in comparison to the norm population. No statistically significant differences in HRQoL, satisfaction with care, and cosmetic results were found between patients with KC who underwent conventional excision, Mohs' micrographic surgery, or radiotherapy. The impact of KC and its treatment is low and more positive than negative as patients reported better quality of life compared to a normative population. This information could be used by specialists involved in KC care to improve patients' knowledge about different aspects of disease as patient's preference is an important factor for treatment choice.

SAMENVATTING

Hoofdstuk 1 is de algemene introductie van dit proefschrift. Keratinocyt kanker (KC) is een veelvoorkomend gezondheidsprobleem wat bij veel patiënten voorkomt. De verschillende studies op het gebied van gezondheid gerelateerde kwaliteit van leven (HRQoL) instrumenten bij patiënten met KC worden beschreven. De eerste studies gebruikten generieke en kanker specifieke HRQoL vragenlijsten. In deze studies gaven veel deelnemers aan de gestelde vragen niet zo relevant te vinden. Er mag geconcludeerd worden dat de aangedane domeinen van HRQoL bij KC patiënten niet voldoende gemeten worden in generieke en kanker specifieke vragenlijsten. Dermatologie specifieke HRQoL vragenlijsten zijn ontwikkeld om te gebruiken in patiënten met huidziekten, voornamelijk inflammatoire huidziekten. Metingen met deze vragenlijsten bij KC patiënten geven enkele verschillen weer wanneer verschillende behandelingen vergeleken worden, maar hebben onvoldoende indruksvaliditeit en vangen de zorgen van KC patiënten onvoldoende nauwkeurig. De eerder ontwikkelde huidkanker specifieke HRQoL vragenlijsten meten wel enkele belangrijke en relevante zorgen, maar niet de belangrijke gedragsveranderingen bij KC patiënten. De interpretatie is twijfelachtig doordat één vraag verschillende items bevat en de indruks- en inhoudsvaliditeit zijn onvoldoende. Daarom was de doelstelling van dit proefschrift om een ziektespecifieke HRQoL vragenlijst te ontwikkelen en te valideren en om de HRQoL en de perceptie van patiënten over ziekte, behandeling en informatie bij KC patiënten te beoordelen.

In **hoofdstuk 2** hebben we de dermatologie specifieke Skindex-17 vragenlijst en de huidkanker specifieke Skin Cancer Index (SCI) gebruikt in een open-label multicenter studie (2 universitaire medische centra en 6 perifere ziekenhuizen). Hierbij zijn patiënten met actinische keratosen (AK) en superficiële basaalcelcarcinomen (sBCC) geïncludeerd als ze geschikt waren voor behandeling met imiquimod 5% crème. De behandeltevredenheid werd gemeten met de Treatment Satisfaction Questionnaire for Medication (TSQM). 118 AK en 84 sBCC patiënten werden geïncludeerd en gevraagd om de HRQoL vragenlijsten in te vullen bij aanvang van de studie (voorafgaand aan behandeling), direct na de behandeling en 8-16 weken na de behandeling. De TSQM is alleen afgenomen op het laatste meetpunt. Lage HRQoL uitgangsscores werden gevonden op de Skindex-17 en de SCI, welke laag bleven na behandeling, wat een lage impact op de HRQoL aangeeft, met uitzondering van een korte verslechtering aan het einde van de applicatieperiode. Imiquimod 5% crème gaf geen klinisch relevante HRQoL verbetering of verslechtering bij zowel AK en sBCC zoals gemeten met de Skindex-17 en SCI. De behandeling werd goed verdragen, maar globale behandeltevredenheid (zoals gemeten met de TSQM) is slechts rond de 55-60% in beide groepen. Wij concludeerden dat de resultaten van deze studie ook suggereren dat de

gebruikte HRQoL instrumenten niet specifiek en sensitief genoeg zijn om de belangrijkste zorgen die van belang zijn in KC patiënten te ondervangen.

Hoofdstuk 3 beschrijft de ontwikkeling en validatie van de Basal and Squamous cell carcinoma Quality of Life (BaSQoL) vragenlijst. De ontwikkeling van de vragenlijst vond in eerste instantie plaats in 4 fasen, waarbij we de richtlijnen van de European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL) groep zo goed als mogelijk gevolgd hebben (fase 1: genereren van HRQoL punten; fase 2: reductie van items; fase 3: pre-testen; fase 4: veldtesten). De eerste fase bestond uit het genereren van een uitgebreide lijst met HRQoL punten welke relevant zijn voor KC patiënten. Een focusgroep bijeenkomst, semigestructureerde interviews met zorgverleners en een literatuuronderzoek leidde tot een lijst van 57 punten welke voorgelegd werden aan patiënten en zorgverleners ter beoordeling van de relevantie en ter prioritering. Hierdoor werd de lijst gereduceerd tot 33 punten welke omgezet werden naar items. Deze werden voorafgaand aan het verdere onderzoek getest door 16 patiënten (fase 2 en 3). De voorlopige vragenlijst met 33 items werd in de praktijk getest in 1,173 patiënten welke geselecteerd werden uit de Nederlandse Kankerregistratie (fase 4). 721 patiënten reageerden (61%) waarvan 85% basaalcelcarcinoom (BCC) had en 15% plaveiselcelcarcinoom (PCC). Principale componenten analyse werd uitgevoerd om uiteindelijk 5 componenten vast te stellen, welke zijn bestempeld als Zorgen, Uiterlijk, Gedrag, Diagnose & Behandeling en Andere mensen. Item response analyses werden gebruikt om het aantal items terug te brengen naar 16. Het presteren van de nieuwe vragenlijst werd beoordeeld met acht criteria volgens de klassieke test theorie en met een bevestigende factoranalyse en toonde een goede indruks- en inhouds- en begripsvaliditeit.

Hoofdstuk 4 beschrijft de aanvullende validatie van de Engelse vertaling van de BaSQoL. In deze prospectieve, observationele studie werden 122 BCC en 65 PCC patiënten geïncludeerd welke gepland stonden voor behandeling in het ziekenhuis van de universiteit van California, San Francisco. Aan hen werd gevraagd om de BaSQoL vragenlijst in te vullen voorafgaand aan behandeling (T0), vier weken na behandeling (T1) en één week daarna (5 weken na behandeling; T2). Aanvullend werd aan de deelnemers gevraagd om de SCI en de Hospital Anxiety and Depression Scale (HADS) in te vullen één week voor de behandeling. In het algemeen waren de gemiddelde BaSQoL subschaal scores laag, wat een matige impact op de HRQoL aangeeft voor de meeste patiënten. Patiënten met PCC rapporteerden meer angst (gemeten met de Zorgen subschaal) in vergelijking met de BCC patiënten. De SCI toonde een hogere impact bij PCC patiënten in de Emoties subschaal. HADS scores waren laag, met uitzondering van enkele patiënten welke angst aangaven. De acht criteria volgens de klassieke test theorie toonden dat de lijst goed presteert. Interne validiteit was goed met Cronbach's α's tussen 0.63-0.80 voor de verschillende subschalen.

De intraklasse correlatie coëfficiënt (ICC) tussen T1 en T2 was hoog (≥0.75) voor vrijwel alle subschalen, wat een stabiele weergave van de BaSQoL over de tijd weergeeft. De BaSQoL subschalen hadden een hoge correlatie met de subschalen van de SCI, wat een goede convergente validiteit betekent. De correlatie met de HADS was laag, wat een goede divergente validiteit betekent. De Engelse versie van de BaSQoL heeft dus een goede indruks-, inhouds- en begripsvaliditeit. Deze studie valideert de Engelse vertaling van de BaSQoL voor gebruik in het gehele spectrum van BCC en PCC patiënten.

In **hoofdstuk 5** is de BaSQoL gebruikt om HRQoL impact te meten bij BCC en PCC patiënten in een grote steekproef van de bevolking vanuit de Nederlandse Kankerregistratie. Aanvullende vragenlijsten over kanker-specifieke HRQoL (EORTC QLQ-C30), informatievoorziening (EORTC QLQ-INFO25) en algemene tevredenheid met zorg (EORTC IN-PATSAT32) zijn afgenomen. 721 van de 1.173 (61%) patiënten namen deel aan de studie. HRQoL impact zoals gemeten met de BaSQoL was hoger bij vrouwelijke en jongere patiënten. Eén derde (N=237) van alle patiënten gaf aan ontevreden te zijn over de gegeven informatie zoals gemeten met het gedichotomiseerde item 'tevredenheid met informatievoorziening' binnen de EORTC QLQ-INFO25 vragenlijst. Van alle patiënten gaf 16% (N=116) aan dat ze meer informatie hadden willen ontvangen over huidkanker in het algemeen, maar ook over oorzaken, behandelingen en follow-up en hoe nieuwe plekken te herkennen. Dit verhoud zich tot 37% (84/225) van alle ontevreden patiënten en 7% (28/416) van de tevreden patiënten. Ontevredenheid met de ontvangen informatie was geassocieerd met jongere leeftijd, tumorlokalisatie in het gezicht, geen partner hebben en het hebben van meerdere comorbiditeiten. HRQoL was slechter bij patiënten die ontevreden waren over de ontvangen informatie (bijvoorbeeld: de BaSQoL Zorgen gemiddelde score bij tevreden patiënten: 0.54 (95% CI: 0.48-0.59), ontevreden patiënten: 0.77 (95% CI: 0.67-0.87), p= 0.001). De verdeling van tevreden versus ontevreden patiënten over de ontvangen informatie verschilde wezenlijk tussen de 9 deelnemende ziekenhuizen en zelfstandige behandelcentra. Echter, na correctie voor patiënt en tumorkarakteristieken was de variabele 'deelnemend centrum' niet langer geassocieerd met tevredenheid over de ontvangen informatie. Ontevredenheid over de ontvangen informatie was geassocieerd met een impact op de HRQoL. Mogelijk kan de HRQoL verbeterd worden door de informatievoorziening te verbeteren.

In **hoofdstuk 6** is de BaSQoL vragenlijst gebruikt om de impact te meten van diagnose en behandeling van KC in het hoofdhals gebied in een willekeurige steekproef van 347 patiënten, onafhankelijk van de steekproef van de validatie studie. Aanvullende vragenlijsten over kanker-specifieke HRQoL (EORTC QLQ-C30) en algemene tevredenheid met zorg (EORTC IN-PATSAT32) zijn afgenomen. Eén item is gebruikt om het cosmetische resultaat van de behandeling vast te stellen. HRQoL is ook vergeleken met een aan leeftijd en geslacht gekoppelde norm populatie. 215 patiënten (62%) namen deel aan de studie.

Patiënten met KC rapporteerden een betere algehele kwaliteit van leven en minder pijn in vergelijking met de normpopulatie. Geen statistisch significante verschillen werden gevonden met betrekking tot HRQoL, tevredenheid met zorg en cosmetisch resultaat tussen KC patiënten die behandeld werden met conventionele excisie, Mohs' micrografische chirurgie en radiotherapie. De impact van KC en de behandeling bleek laag en meer positief dan negatief, aangezien de KC patiënten een betere kwaliteit van leven rapporteerden in vergelijking met de norm populatie. Deze informatie kan gebruikt worden door specialisten die betrokken zijn bij KC behandeling om de kennis van patiënten over verschillende aspecten van ziekte te verbeteren, aangezien patiëntenvoorkeur een belangrijke factor speelt bij keuze voor een behandeling.

Chapter 9

BaSQoL questionnaire NL and EN
Abbrevations
List of co-authors
List of publications
Dankwoord
Curriculum vitae
PhD portfolio

BaSQoL-NL

De volgende vragen gaan over de invloed van de huidkanker op uw dagelijks leven

Sinds de diagnose huidkanker,	Helemaal niet	Een beetje	Nogal	Heel erg
1. Vindt u het vervelend dat u moet letten op uw zongedrag?	☐	☐	☐	☐
2. Vindt u het vervelend dat u meer zonnebrandproduct (crème, spray, etc.) moet gebruiken?	☐	☐	☐	☐
3. Vindt u het vervelend dat u uw huid moet controleren op huidkanker?	☐	☐	☐	☐
4. Vindt u het vervelend uw huid beter te moeten beschermen tegen de zon?	☐	☐	☐	☐
5. Heeft u het gevoel anderen te moeten aanmoedigen om hun huid te laten controleren?	☐	☐	☐	☐

Als u terugdenkt aan de periode van diagnose en behandeling,	Helemaal niet	Een beetje	Nogal	Heel erg
6. Maakte u zich zorgen over de periode tussen diagnose en behandeling?	☐	☐	☐	☐
7. Was u bang voor de behandeling?	☐	☐	☐	☐
8. Was u geschrokken van het woord kanker?	☐	☐	☐	☐

Gedurende de afgelopen week,	Helemaal niet	Een beetje	Nogal	Heel erg
9. Was u bang om op meerdere plaatsen huidkanker te krijgen?	☐	☐	☐	☐
10. Maakte u zich zorgen over uitzaaiingen?	☐	☐	☐	☐
11. Was u onzeker over de toekomst?	☐	☐	☐	☐
12. Maakte u zich zorgen over andere huidafwijkingen?	☐	☐	☐	☐
13. Maakte u zich zorgen verminderd aantrekkelijk te zijn?	☐	☐	☐	☐
14. Vond u het vervelend om uw kleding aan te passen om littekens en plekken te bedekken?	☐	☐	☐	☐
15. Voelde u zich minder aantrekkelijk?	☐	☐	☐	☐
16. Maakte u zich zorgen over de huid van anderen?	☐	☐	☐	☐

BaSQoL-EN

The following questions are about the influence of skin cancer on your daily life

	Since the skin cancer diagnosis,	Not at all	A little	Quite a bit	Very much
17.	Does it bother you to be careful about your behavior in the sun?	☐	☐	☐	☐
18.	Does it bother you to use more suncreen (cream, spray, etc.)?	☐	☐	☐	☐
19.	Does it bother you to check your skin for skin cancer?	☐	☐	☐	☐
20.	Does it bother you to have to protect your skin from the sun?	☐	☐	☐	☐
21.	Do you feel that you have to encourage others to get their skin checked?	☐	☐	☐	☐

	When you think back to the time of diagnosis and treatment,	Not at all	A little	Quite a bit	Very much
22.	Were you worried about the period between diagnosis and treatment?	☐	☐	☐	☐
23.	Were you afraid of the treatment?	☐	☐	☐	☐
24.	Were you frightened by the word cancer?	☐	☐	☐	☐

	During the past week,	Not at all	A little	Quite a bit	Very much
25.	Were you afraid to get skin cancer on multiple body sites?	☐	☐	☐	☐
26.	Were you worried about skin cancer spreading to other parts of the body?	☐	☐	☐	☐
27.	Were you uncertain about the future?	☐	☐	☐	☐
28.	Were you worried about other skin disorders?	☐	☐	☐	☐
29.	Were you worried that you would be less attractive?	☐	☐	☐	☐
30.	Did it bother you to adjust your clothing in order to cover your scars and spots?	☐	☐	☐	☐
31.	Did you feel less attractive?	☐	☐	☐	☐
32.	Were you worried about other people's skin?	☐	☐	☐	☐

ABBREVATIONS

2PL-ltm	2-Parameter latent trait model
5-FU	5-fluorouracil
AK	Actinic Keratosis
AKQoL	Actinic Keratosis Quality of Life
ANS	Actinic Neoplasia Syndrome
BaSQoL	Basal and Squamous cell carcinoma Quality of Life
BCC	Basal Cell Carcinoma
CFI	Comparative Fit Index
CoRPS	Centre of Research on Psychology in Somatic diseases
CTT	Classical Test Theory
DCE	Discrete Choice Experiment
DLQI	Dermatology Life Quality Index
ENT	Ear Nose and Throat
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
FDR	False Discovery Rate
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Provider
HRQoL	Health-Related Quality of Life
ICC	Intra-class Correlation Coefficient
ICD-O3	International Classification of Disease for Oncology
IKNL	Netherlands Comprehensive Cancer Organization
INPATSAT-32	Satisfaction with in-patient cancer care-32
IQR	Interquartile Range
IRT	Item Response Theory
KC	Keratinocyte Carcinoma
MLMV	Maximum Likelihood with Missing Values
MM	Malignant Melanoma
NCR	Netherlands Cancer Registry
NMSC	Non Melanoma Skin Cancer
NVDV	Dutch Society for Dermatology and Venerology
PCA	Principal Component Analyses
PRO	Patient Reported Outcomes
PROFILES	Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship
PROMS	Patient-Reported Outcome Measures
QLQ-C30	Quality of Life Questionnaire Core 30

QOL	Quality Of Life
REDCap	Research Electronic Data Capture
RMSEA	Root Mean Squared Error of Approximation
sBCC	Superficial Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
SCI	Skin Cancer Index
SCQoL	Skin Cancer Quality of Life
SCQOLIT	Skin Cancer Quality Of Life Impact Tool
SD	Standard Deviation
SF-36	Short Form 36-item health survey
SRMR	Standardized Root Mean squared Residual
TLI	Tucker-Lewis Index
TSQM	Treatment Satisfaction Questionnaire for Medication
UKSIP	United Kingdom Sickness Impact Profile
WHO	World Health Organization
WOC-CA	Ways Of Coping questionnaire Cancer version

LIST OF CO-AUTHORS

Affiliations at the time at which the research was conducted.

Mieke J. Aarts
Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands.

Christine Aroyan
Department of Dermatology, University of California, San Francisco, USA

Sarah Arron
Department of Dermatology, University of California, San Francisco, USA

Lindy P.J. Arts
Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands.

Rebecca Bremer
Department of Dermatology, University of California, San Francisco, USA

Lauren Crow
Department of Dermatology, University of California, San Francisco, USA

Menno T.W. Gaastra
Department of Dermatology, Center Oosterwal, Alkmaar , the Netherlands

Roy Grekin
Department of Dermatology, University of California, San Francisco, USA

Simone van Hattem
Department of Dermatology , University Medical Center, Groningen, the Netherlands

Loes M. Hollestein
Department of Dermatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands
Netherlands Comprehensive Cancer Organization (IKNL), Netherlands Cancer Registry, Eindhoven, The Netherlands

Cynthia Holterhues
Department of Dermatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands

Daniëlle I.M. Kuijpers
Department of Dermatology, Amphia Hospital, Breda , the Netherlands

Marieke W.J. Louwman
Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands.

Brian Lu
Department of Dermatology, University of California, San Francisco, USA

Marnix L.M. Lybeert
Department of Radiation Oncology, Catharina Hospital, Eindhoven, the Netherlands

Isaac Neuhaus
Department of Dermatology, University of California, San Francisco, USA

Tamar E.C. Nijsten
Department of Dermatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands

Simone Oerlemans
Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands

Lonneke V. van de Poll-Franse
Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands
CoRPS - Centre of Research on Psychology in Somatic diseases, Department of Medical and Clinical Psychology, Tilburg University, Tilburg, the Netherlands
Division of Psychosocial research and epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands

Kees-Peter de Roos
Department of Dermatology, DermaPark, Uden, the Netherlands

Luc J. Scheijmans
Department of Radiation Oncology, Dr. Bernard Verbeeten Institute, Tilburg, the Netherlands

Marie Louise A. Schuttelaar
Department of Dermatology , University Medical Center, Groningen, the Netherlands

Reinier Timman
Department of Psychiatry, Section of Medical Psychology and Psychotherapy, Erasmus MC University Medical Centre, Rotterdam, the Netherlands

Monique R.T.M. Thissen
Department of Dermatology, Catharina Hospital, Eindhoven, the Netherlands
Department of Dermatology, Maastricht University Medical Centre, Netherlands
GROW, School for Oncology and Developmental Biology, University Maastricht, Netherlands

Siegrid Yu
Department of Dermatology, University of California, San Francisco, USA

Wesley Y. Yu
Department of Dermatology, University of California, San Francisco, USA

LIST OF PUBLICATIONS

Health-related quality of life, satisfaction with care and cosmetic results in relation to treatment among patients with keratinocyte cancer in the head and neck area: results from the PROFILES-registry.
Arts LPJ, **Waalboer-Spuij R**, de Roos K-P, Thissen MRTM, Scheijmans LJ, Aarts MJ, Oerlemans S, Lybeert M, Louwman MWJ
Accepted Dermatology.

Satisfaction with information provision and health-related quality of life in basal and squamous cell carcinoma patients: a cross-sectional population-based study.
Waalboer-Spuij R, Hollestein LM, Nijsten TEC, van de Poll-Franse LV
Acta Derm Venereol 2019 May 23. [Epub ahead of print]

Validation of the English basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire.
Yu WY*, **Waalboer-Spuij R***, Bremer R, Lu B, Aroyan C, Crow L, Grekin R, Neuhaus I, Yu S, Arron ST, Hollestein LM
Accepted Dermatol Surg.
* contibuted equally to this paper

Psychodermatologie in de 21ste eeuw: multidisciplinair?
Waalboer-Spuij R, Tan MBM, Dieleman S
Ned Tijdschr Dermatol Venereol 2018, nr 10.

Multidisciplinaire huidkankerzorg.
van den Bos RR, **Waalboer-Spuij R**, Wakkee M
Ned Tijdschr Dermatol Venereol 2018, nr 10.

Validity and reliability of the Dutch adaptation of the actinic keratosis quality of life questionnaire (AKQoL).
Vis K, **Waalboer-Spuij R**, Snels DGCTM, Hollestein LM
Dermatology 2018;234(1-2):60-65.

Development and validation of the basal and squamous cell carcinoma quality of life (BaSQoL) questionnaire.
Waalboer-Spuij R, Hollestein LM, Timman R, van de Poll-Franse LV, Nijsten TEC
Acta Derm Venereol 2018 Feb 7;98(2):234-239.

Histological diagnosis of basal cell carcinoma is not associated with life expectancy in elderly Dutch people; a population-based cohort study.
Waalboer-Spuij R, Hollestein LM, van de Poll-Franse LV, Nijsten TEC
Br J Dermatol 2017 Oct;177(4):e88-e89.

Zorg voor niet-melanoom huidkankerpatiënt in de praktijk.
Verwoert R, **Waalboer-Spuij R**
Cutis Cura 2015, nr 3.

Psychodermatologie in het Erasmus MC: een overzicht van vijf jaar.
Ferket IS, Tan MBM, **Waalboer-Spuij R**
Nederlands Tijdschrift voor Dermatologie en Venereologie 2015;25(09): 492-494.

Psychodermatology outpatient clinic in Rotterdam, the Netherlands: overview of a five-year experience.
Waalboer-Spuij R, Tan MBM, Ferket IS, Nijsten TEC
Acta Derm Venereol 2015;95:4. 16th Congress of the European Society for Dermatology and Psychiatry, Saint-Petersburg, Russia, 25-27 June 2015.

Patient perception of imiquimod treatment for actinic keratosis and superficial basal cell carcinoma in 202 patients.
Waalboer-Spuij R, Holterhues C, van Hattem S, Schuttelaar MLA, Gaastra MTW, Kuijpers DIM, Nijsten TEC
Dermatology 2015;231(1):56-62.

Psychodermatologie in onderzoek en praktijk - Ontwikkelingen in academische centra in Nederland.
Spillekom-van Koulil S, **Waalboer-Spuij R**, Boonstra HE, Casteelen G, Evers AWM, de Korte J, Kemperman P, van der Veen JPW, Vulink NC, Crijns MB
Ned Tijdschr Dermatol Venereol 2013, nr 10.

A review on quality of life in keratinocyte carcinoma patients.
Waalboer-Spuij R, Nijsten T
G Ital Dermatol Venereol 2013 Jun;148(3):249-54. Review.

Enteric-coated mycophenolate sodium in psoriasis vulgaris: an open pilot study.
Fallah-Arani S, **Waalboer-Spuij R**, Nijsten T, Neumann HAM, Thio HB
J Dermatolog Treat 2014 Feb;25(1): 46-9.

Psoriasis en atopisch eczeem.
Waalboer-Spuij R, Balak D, Thio HB
Ned Tijdschr Dermatol Venereol 2012, nr 12.

Patiënt met een vreemde navel.
Waalboer-Spuij R, West RL, van Praag MCG
Ned Tijdschr Dermatol Venereol 2011, nr 9.

Een man met huidafwijkingen op de handrug.
Waalboer-Spuij R, Loots MAM
Ned Tijdschr Geneeskd 2011;155(18):A2546.

Botryomycose; goed reagerend op antibiotica.
Biemans AAM, **Waalboer-Spuij R**, Koljenovic S, Thio HB
Ned Tijdschr Dermatol Venereol 2010, nr 9.

Cutane scedosporiose.
Waalboer-Spuij R, de Steenwinkel JEM, Biemans AAM, Thio HB
Ned Tijdschr Dermatol Venereol 2010, nr 9.

Analysis of rectal Chlamydia trachomatis serovar distribution including L2 (lymphogranuloma venereum) at the Erasmus MC STI clinic, Rotterdam.
Waalboer R, van der Snoek EM, van der Meijden WI, Mulder PG, Ossewaarde JM
Sexually Transmitted Infections 2006;82:207-11.

DANKWOORD

Het is af! Het is gelukt om mijn proefschrift te voltooien. Al die jaren werken op 'tussendoor-momenten', maar vooral op mijn vrije woensdag (lekker thuis SPSS'en op de laptop) zitten erop. Ondanks dat het een langdurig traject was heb ik genoten van de reis en niet alleen van de bestemming. Ik heb mij ontwikkeld op een manier welke ik mij van te voren niet had kunnen bedenken. In dit laatste hoofdstuk van dit proefschrift wil ik een aantal mensen bedanken die mij hebben gesteund of geholpen gedurende deze jaren.

Om te beginnen mijn 1e promotor, Tamar Nijsten. Beste Tamar, de eerste vragen die je mij stelde over onderzoek en promoveren hebben mij (letterlijk) op pad gestuurd langs allerlei interne en externe collega's. Dit heb ik later weten te ontwikkelen tot een van mijn sterkste eigenschappen; het maken en onderhouden van connecties, verbanden en relaties. Ook heb je mij geholpen om mijn twee dermatologische voorliefdes; de psychodermatologie en de dermato-oncologie, samen te brengen in dit proefschrift. Tijdens dit hele promotietraject heb je me gestimuleerd en intellectueel geprikkeld en de kans gegeven om dit als staflid op onze afdeling te doen. Dank je wel.

Mijn 2e promotor, Lonneke van de Poll-Franse. Beste Lonneke, tijdens onze afspraken wist jij me altijd te enthousiasmeren om buiten de lijntjes van de dermatologie te kijken. Na elk overleg dat we hadden, zei ik steevast dat ik vaker met je zou moeten afspreken én zat ik boordevol inspiratie om er verder mee aan de slag te gaan. Je frisse blik als niet-dokter op de projecten hebben mij enorm geholpen om een goede lijn te vinden, vast te houden en af te ronden. Bedankt voor je beschikbaarheid en bereidwilligheid om deze dokter-promovendus mede te begeleiden.

Mijn copromotor, Loes Zandwijk-Hollestein. Lieve Loes, zonder jou was dit proefschrift er nooit geweest. Ik ben de eerste promovendus waarbij je vrijwel het gehele traject betrokken bent geweest. En betrokken was je. Ik kon bij je terecht met welke vraag dan ook, methodologisch, statistisch, praktisch, taalkundig of wat dan ook. Ik kon altijd rekenen op een snel en deskundig antwoord van je of een moment samen achter SPSS om weer een nieuwe statistische analyse te proberen. Door je aanstekelijke enthousiasme over statistiek zat ik te genieten van het programmeren en syntaxen schrijven. Al mijn domme vragen durfde ik aan jou te stellen. En boven alles ben je een heerlijk mens, dank je wel!

Ik wil de leden van zowel de kleine als de grote promotiecommissie, prof. dr. Cees Verhoef, prof. dr. Jan van Busschbach, prof. dr. Irma Verdonck-de Leeuw, dr. Marc Mureau, dr. Klara Mosterd en dr. Marlies Wakkee hartelijk danken voor de tijd en moeite die u allen heeft genomen voor de beoordeling van dit proefschrift en het plaatsnemen in deze commissie.

De overige co-auteurs van mijn manuscripten wil ik graag bedanken voor de betrokkenheid en de inbreng. De leden van de BaSQoL groep wil ik bedanken voor hun bijdrage, enerzijds door te helpen bij het ontwerpen van de BaSQoL vragenlijst en anderzijds door deelname om patiënten te includeren. Reinier Timman, hartelijk dank voor je hulp met de IRT analyses en om dit dusdanig te vertalen dat deze dermatoloog begrijpt wat er gedaan is. Lindy Arts, dank voor de fijne samenwerking en heel veel succes bij het afronden van je eigen proefschrift.

Sarah Arron and team UCSF, thank you so much for collaborating with us in translating and validating the English version of the BaSQoL. Wesley Yu, thank you for the great collaboration in finalizing the study and co-writing the manuscript.

Alle patiënten welke hebben deelgenomen aan de studies wil ik van harte bedanken voor hun hulp.

Beste collega dermatologen (Anke, Maarten, Otto, Frans, Theo, Marloes), verpleegkundigen, verpleegkundig specialisten, analisten, secretaresses en poli-assistentes van de polikliniek dermatologie van het ETZ in Tilburg en Waalwijk, bedankt voor jullie aanhoudende steun en interesse in mijn promotieonderzoek, ondanks dat dit soms letterlijk ver van jullie bed was.

Beste collega dermatologen, ex-AIOS, AIOS, ANIOS, onderzoekers, verpleegkundigen, doktersassistenten en secretaresses van de afdeling dermatologie van het Erasmus MC. Hartelijk dank voor al jullie hulp, steun, interesse en afleiding tijdens mijn promotietraject. In het bijzonder wil ik Renate, Marlies, Ellen, Armanda, Michelle, Annemarie, Suzan, Emöke, Bing, Barbera en prof. Neumann bedanken.

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The New Life Singers in Schiedam, dank voor de muzikale ontspanning op de dinsdagavonden en excuses voor de keren dat ik repetitie moest overslaan.

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Mijn paranimfen. Lieve Anke, sinds het begin van mijn opleiding was jij mijn maatje. Ons beider zuidelijke afkomst zorgde direct voor de eerste klik en dit hebben we in de loop der jaren uitgebouwd tot een fijne vriendschap. Jij stond altijd klaar om even lekker samen te

klagen, met een relativerende blik en vooral met je volledige aandacht. Op 25 september 2013 mocht ik je bijstaan als paranimf en nu sta je mij bij. Ik ben blij dat we ook nog een paar jaar samen in een vakgroep hebben gewerkt in Tilburg. Dank je wel dat je zo'n fijne collega en vriendin bent.

Lieve Michelle, tijdens mijn perifere stage in het SFG in 2010, waar jij toen als ANIOS werkte, hebben wij elkaar leren kennen. Wij hebben sindsdien een enorme klik wat betreft onze "niet lullen maar poetsen" instelling en behoefte aan gezelligheid. Jij was er altijd voor begrip, relativering en een knuffel. Dank je wel voor je hartelijkheid, interesse, vriendschap en je humor.

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Lieve Andre, door jou ben ik de beste versie van mijzelf. Dank je wel. Ik hou van jou!

CURRICULUM VITAE

Rick Waalboer is geboren op 1 april 1982 te Geleen waar hij ook opgegroeid is. Na het afronden van het atheneum op scholengemeenschap Sint Michiel, startte hij in 2001 met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens zijn tweede studiejaar startte hij met een bijbaan op het ROHOCO-studie avondspreekuur van dermatoloog in opleiding Eric van der Snoek. Hier werd zijn interesse gewekt voor de dermato-venereologie. De wetenschappelijke stage bij prof. dr. Arnold Oranje, een keuze co-schap bij prof. John Harper in het Great Ormond Street ziekenhuis in Londen, Verenigd Koninkrijk, en uiteindelijk zijn oudste co-schap dermatologie in het Erasmus MC bevestigden zijn enthousiasme voor de dermatologie. Na 4 maanden werkervaring opgedaan te hebben op de spoedeisende hulp van het toenmalige Ruwaard van Putten ziekenhuis te Spijkenisse, is hij op 1 januari 2009 gestart met zijn opleiding tot dermatoloog in het Erasmus MC. Tijdens zijn opleiding is hij in 2012 gestart met zijn promotieonderzoek onder begeleiding van prof. dr. Tamar Nijsten, prof. dr. Lonneke van de Poll en dr. Loes Hollestein. Gedurende zijn opleiding was hij eerst als secretaris en later als voorzitter actief binnen de Vereniging AIOS Dermatologie en Venereologie (VADV) en tevens lid van het Consilium Dermatologicum. Binnen de afdeling Dermatologie van het Erasmus MC was hij in AIOS lid van het management team. Op 16 november 2014 rondde hij zijn opleiding tot dermatoloog af waarna hij voor 0,5 FTE toetrad tot de vakgroep dermatologie van het TweeSteden ziekenhuis (het huidige ETZ) te Tilburg en Waalwijk, alwaar hij de tumorwerkgroep en het bijbehorende multidisciplinaire overleg dermato-oncologie heeft opgericht. Daarnaast werkte hij voor 0,4 FTE als staflid dermatologie in het Erasmus MC met als aandachtsgebieden dermato-oncologie, dermato-chirurgie en psychodermatologie. Per 1 januari 2019 is hij volledig werkzaam in het Erasmus MC.

Hij is op 2 oktober 2009 getrouwd met Andre Spuij en zij wonen in Rotterdam.

PHD PORTFOLIO

Name PhD student:	R. Waalboer-Spuij
Erasmus MC Department:	Dermatology
Research School:	NIHES
PhD period:	2012 - 2019
Promotors:	Prof. dr. T.E.C. Nijsten
	Prof. dr. L.V. van de Poll
Supervisor:	dr. L.M. Hollestein

	Year	Workload (Hours/ECTS)
1. PhD training		
General Courses		
Teach the Teacher II	2012	0.5 ECTS
Basic Introduction Course on SPSS, MolMed	2013	1.0 ECTS
Quality of Life Measurement, NIHES	2013	0.9 ECTS
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2013	1.0 ECTS
Teach the Teacher III	2016	0.5 ECTS
Teach the Teacher EPA	2018	2 hours
Seminars and Workshops		
Endnote, Medical Library	2012	3 hours
CPO Minicourse	2013	7 hours
Oral Presentations		
'Quality of life in NMSC patients' Dermatologie Immunologie Stichting (DIS) symposium, Amsterdam	2012	1.0 ECTS
'The importance of PRO and personalized dermatology' Fagron Group, Rotterdam	2013	1.0 ECTS
'Is there a rationale for QoL in the treatment of NMSC?' ZonMW symposium dermatology, Radboudumc, Nijmegen	2013	1.0 ECTS
'The role of QoL in the treatment of actinic keratosis' Dermatologie Immunologie Stichting (DIS) symposium, Amsterdam	2014	1.0 ECTS
'Quality of life in nonmelanoma skin cancer' International Society of Dermatologic Surgery (ISDS) congress, Amsterdam	2016	1.0 ECTS
'Quality of life in AK and NMSC patients' EuroPDT congress, Munich, Germany	2017	1.0 ECTS

	Year	Workload (Hours/ECTS)
'Development and validation of the BaSQoL questionnaire' European Dermato-Epidemiology Network (EDEN) meeting, Madrid, Spain	2017	1.0 ECTS
'Dermatologic surgery in elderly patients' Continuüm Dermatologie, Utrecht	2018	1.0 ECTS
Poster Presentation		
'Development and validation of the BaSQoL questionnaire' International Dermato-Epidemiology Association -Keratinocyte Carcinoma Consortium (IDEA-KeraCon) meeting, Denver, USA	2016	1.0 ECTS
Conferences (attending)		
Dermatologendagen, Papendal	2013	1.0 ECTS
Symposium Nazorg, nacontrole en revalidatie bij kanker (IKNL), Utrecht	2013	1.0 ECTS
International Psycho-Oncology Society (IPOS) 15th World Congress of Psycho-Oncology, Rotterdam	2013	1.0 ECTS
Partner Class Prevention, Diagnosis and Treatment of Skin Cancer, European Skin Cancer Foundation, Charité, Berlin, Germany	2013	1.0 ECTS
European Academy of Dermatology and Venereology (EADV) Congress, Amsterdam	2014	1.0 ECTS
American Academy of Dermatology (AAD) annual meeting, Washington, USA	2016	1.0 ECTS
International Society of Dermatologic Surgery (ISDS) annual meeting, Amsterdam	2016	0.7 ECTS
International Dermato-Epidemiology Association -Keratinocyte Carcinoma Consortium (IDEA-KeraCon) meeting, Denver, USA	2016	1.0 ECTS
EuroPDT meeting, Munich, Germany	2017	1.0 ECTS
European Dermato-Epidemiology Network (EDEN) meeting, Madrid, Spain	2017	1.0 ECTS
Cells to Surgery, Rotterdam	2017	1.0 ECTS
Dermatologendagen, Amsterdam	2018	1.0 ECTS
Cells to Surgery, Rotterdam	2019	1.0 ECTS
Dermatologendagen, Utrecht	2019	0.5 ECTS
Scientific Award		
Herman Musaph literature prize	2018	

	Year	Workload (Hours/ECTS)
2. Teaching		
Lecturing		
Dermato-oncology for physiotherapists	2012 2013 2014	9 hours
Skin tumors for medical students	2013	9 hours
Skin tumors for residents radiotherapy	2013	2 hours
Oncological ulcers for wound nurses	2014	2 hours
Dermato-oncology for general practitioners	2014 2016 2018	6 hours
Epidemiology and treatment of skin cancer for medical students	2016	6 hours
Metastasized melanoma for medical students	2016 2018	2 hours
Reconstruction of skin defects for residents dermatology	2017	2 hours
Supervising master's thesis		
'Aspects of Quality of Life in eldery with Actinic Keratosis' Rianne Elling, medical student Universitair Medisch Centrum Groningen / Deventer hospital	2013- 2014	1.0 ECTS
Supervising research project		
'Validity and Reliability of the Dutch Adaptation of the Actinic Keratosis Quality of Life Questionnaire (AKQoL)' Kelly Vis	2014- 2017	1.0 ECST

The cover photograph is part of the artwork Second-wind by James Turrell and was taken in 2018 at the NMAC Foundation in Vejer de la Frontera, Spain. It is one of many Skyspaces; specifically proportioned chambers with an aperture in the ceiling open to the sky. The construction guides the viewer's experience and transforms light into an object of art.

By focusing the attention we are able to observe more features and details, similar as in dermatology and disease specific quality of life.

This thesis describes several studies on aspects of health-related quality of life and the development and validation of a disease specific quality of life questionnaire for keratinocyte cancer patients.

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