

General introduction

Based on:

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

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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).

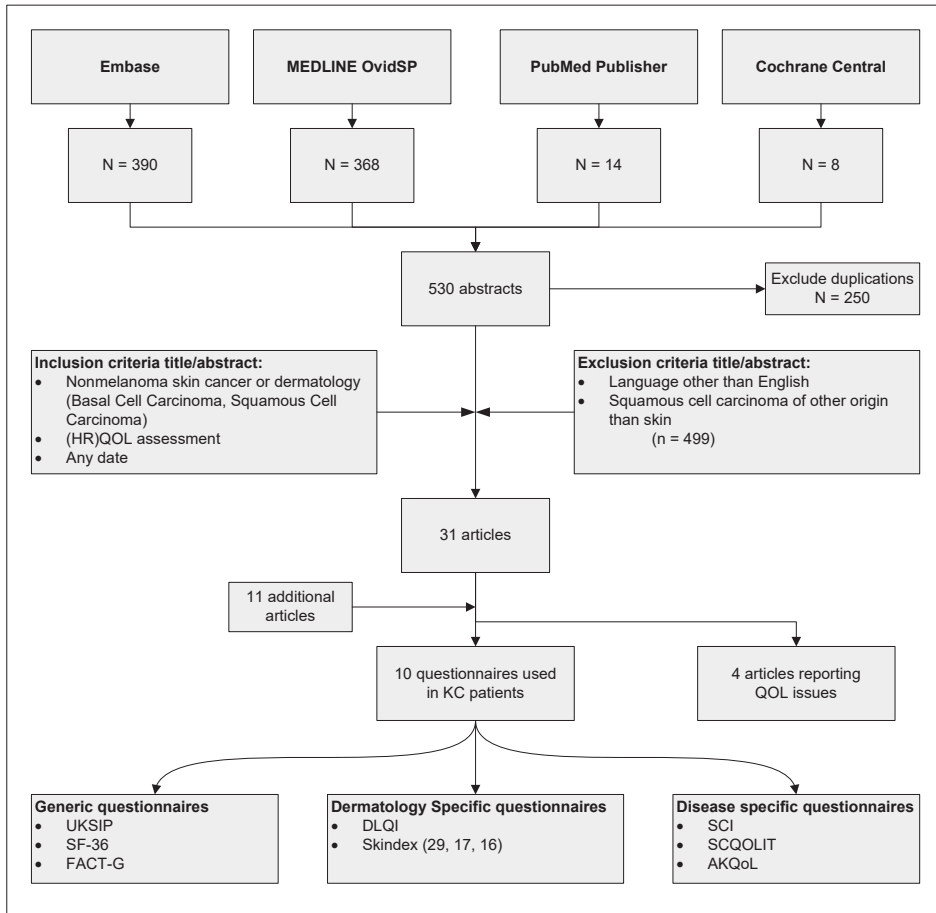


Figure 1. Flowchart systematic search as used in 'A review on quality of life in keratinocyte carcinoma patients' G Ital Dermatol Venereol 2013 Jun;148(3):249-54.

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