Patient-reported health outcomes in patients with non-melanoma skin cancer and actinic keratosis: results from a large-scale observational study analysing effects of diagnoses and disease progression

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Abstract

Background Non-melanoma skin cancer (NMSC) and actinic keratosis (AK) are very common among fair-skinned individuals. A disease continuum from AK to squamous cell carcinoma (SCC) has been frequently postulated. AK and NMSC may influence quality of life (QL) of patients, and it can be suspected that disease progression entails a QL reduction. The purpose of this study was to document QL in patients with NMSC and AK using the health-outcome questionnaire EQ-5D-5L.

Methods The study was designed as a non-interventional, prospective, cross-sectional study. Patients with AK, SCC, basal cell carcinoma (BCC) or multiple diagnoses were enrolled in this study in 29 dermatological centres across Germany. Patients were asked to complete the EQ-5D-5L (compromising EQ Index and EQ VAS), and the dermatologists provided diagnosis, disease history and treatment data.

Results A total of 1184 patients were enrolled and diagnosed as follows: 73% AK, 49% BCC and 17% SCC. 66% had a single diagnosis, 28% two different diagnoses and 6% three different diagnoses. QL was strongly associated with patients’ diagnosis. Patients with a single AK diagnosis had significantly higher mean EQ VAS (78) than patients with BCC (74), SCC (72), and BCC plus SCC (69), P < 0.050. When the effects of disease progression were calculated, patients with AK plus SCC reported significantly less mean EQ VAS (71) than patients with a single AK diagnosis (78), P < 0.011.

Conclusions While rarely being imminently life-threatening, NMSC and AK have an impact on QL as quantified by the EQ-5D-5L. This impact is associated with diagnosis (AK vs. NMSC) and clinical progression (AK vs. AK plus SCC). Both lead to a clear decline in QL. This shows that disease progression is perceived and judged as detrimental by patients and that AK and NMSC should be diligently treated to preserve and restore QL.

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Conflicts of interest disclosure

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**Introduction**

Non-melanoma skin cancer (NMSC) is a collective term that describes several forms of cutaneous neoplasia that do not stem from melanocytes. Among these neoplasia, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common forms that are considered the most common malignancies in the Western world.\(^1\) Thus, these cancers represent a major healthcare problem due to the large group of affected patients. In Germany, the incidence was 119 of 100,000 for women and 145 of 100,000 for men in a recent screening period, which makes NMSC 6.5 times more common than malignant melanoma.\(^2\) Among the affected patients, 53% are male, and the age-standardised incidence is as high as 108.2 per 100,000 (European standard) and thus in the incidence range of prostate cancer.\(^3\) In women, the incidence rate is 77.8 per 100,000 (European standard), which ranks between breast cancer (123.8 per 100,000) and colorectal cancer (38.0 per 100,000).\(^3\) Identified risk factors for the development of NMSC are age (strong increase in male patients over 60), fair skin phototype (Fitzpatrick I and II) and patients over 60), fair skin phototype (Fitzpatrick I and II) and (cumulative) UV-exposure.

A further risk factor, particularly for SCC, is the presence of actinic keratosis (AK). These epidermal neoplastic lesions have been described as epidermal *carcinoma-in-situ*.\(^4,5\) A large cohort analysis revealed that 65% of all primary SCCs occurred in lesions previously clinically diagnosed as AKs.\(^6\) Thus, it is reasonable to include AK in the wider scope of NMSC, whenever prognostic or epidemiological considerations are made. AK is, just as both SCC and BCC, an ultraviolet-light-induced lesion of the skin that may progress to invasive carcinoma.\(^7,8\) It is the most common lesion with malignant potential. AK is mostly seen in Caucasians on skin areas of long-term sun exposure.\(^9\) Epidemiological data show a high occurrence rate of AK, which is even higher in regions with higher ultraviolet exposure. For the United States, the prevalence ranges from 11% to 26%,\(^7\) while in Australia, it ranges from 40% to 60%.\(^10\) In Europe, a prevalence of 15% in men and 6% in women has been documented.\(^11\) Over the age of 70 years, 34% of men and 18% of women were found to have AK.\(^11\) While this represents a massive disease burden on society, NMSC and AK tend to involve lower morbidity and mortality than malignant melanoma\(^12\) and can be treated or managed successfully in many cases. Still, treatment of BCC and SCC routinely involves surgery and –given the predominant occurrence of these cancers in sun-exposed areas such as the face and scalp –surgical measures can be gruelling, stressful and cosmetically unfavourable for the patients.\(^13\)

The numerous therapeutic options available for the treatment of AK\(^14\) are regarded as a valuable approach to SCC prevention.\(^15\) There is reason to assume that NMSC goes along with a reduction in health-related quality of life (QL), and various studies have tried to quantify this reduction with various patient-reported outcome measures (PROMs).\(^13\) Still, no robust data set is available for German-speaking countries. So far, some groups have used standard dermatological instruments such as DLQI\(^16–18\) or Skindex-16,\(^19,20\) others developed specialised instruments for patients with NMSC\(^21\) and AK\(^22,23\) and validated them in different populations.\(^24,25\) While such an approach may be useful for assessing the disease burden of individual NMSC subtypes, AK and NMSC represent a clinical continuum. It is thus worthwhile investigating, how QL is affected in a cross-sectional selection of patients with different stages of epidermal neoplasia in the sense of disease progression. Additionally, in their recent structured review on PROMs, authors from the United Kingdom expressed the need to analyse NMSC QL using a common standardised instrument and recommended the implementation of EQ-5D in this disease spectrum.\(^26,27\) The EQ Index in particular represents a very robust outcome measure\(^28\) that can also be implemented in the calculation of quality-adjusted life years (QALYs) in future health economic evaluations of NMSC treatments.\(^29\)

This study included patients with NMSC and AK and was designed to elucidate whether the proposed disease continuum is also accompanied by impairment in QL.

**Methods**

**Study design**

This prospective, cross-sectional, German-wide, multicentre study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Regensburg (Institutional Review Board Number 15-160-0036). Between October 2015 and February 2016, 1194 consecutive patients with NMSC and AK treated at 29 local medical practices or hospitals were recruited. Inclusion criteria were as follows: age ≥18 years, current diagnosis of NMSC (BCC or SCC) and/or AK, and informed consent. Ten patients did not meet the inclusion criteria and were excluded from the analyses, which resulted in a total number of 1184 patients.

**Documentation and procedure**

Patients filled in the EQ-5D-5L (EuroQol 5 dimensions 5 levels) to report their degree of QL. The EQ-5D-5L is a reliable and valid tool used in patient and general population groups in various countries.\(^30,31\) The questionnaire consists of a descriptive system including five dimensions (mobility, self-care, usual activities, pain and anxiety), each rated on five levels (no problem, slight problems, moderate problems, severe problems and extreme problems), and a visual analogue scale (VAS) assessing the current health status on a scale ranging from 0 (worst) to 100 (best).\(^32\) The developers of the EQ-5D-5L emphasise the need to use both parts of the questionnaire.\(^32\) According to the guidelines of the EuroQol Group,\(^32\) the five dimensions were transformed into individual health status profiles.
Patients were asked to provide information regarding basic demographic variables (age, sex, marital status and number of children, educational level and current professional activity). Educational level was classified as low, medium or high according to the International Standard Classification of Education (ISCED).34 Clinicians in charge of treating patients provided information on diagnosis, number of lesions, treatment period (in months) and current and past treatments. The treatments were recorded as follows: physical (excision, excision with histographic control of resection margin, curettage and/or electrodesiccation, laser therapy, radiotherapy and cryosurgery), drug (5% 5-FU, imiquimod, 0.5% 5-FU/10% salicylic acid-lacquer, 3% diclofenac-sodium/hyaluronic acid gel and ingenol mebutate), photodynamic therapy as well as watch and wait.

Statistical analyses

Descriptive analyses (frequencies \([n]\), percentages \([\%]\), mean \([m]\), standard deviation \([SD]\), 95% confidence interval \([95\% CI]\), median \([med]\) and quartiles \([Q1/Q3]\)) were used to describe sociodemographic, clinical and QL data. Normal distribution of continuous variables was examined with the Shapiro-Wilk test.

Spearman’s rank correlation was used to assess the correlation between EQ Index and EQ VAS. To examine whether a proposed disease continuum is also accompanied by impairment in QL (EQ Index and EQ VAS), two-way ANCOVAs (analyses of covariance) were conducted. Age and sex were included in the model as both factors were consistently found to be related with QL (EQ Index and EQ VAS), two-way ANCOVAs (analyses of covariance-based ranks of QL data),36 which yielded comparable results (results not reported, but available upon request).

The programme IBM SPSS Statistics 24 was used for all statistical analyses. The significance level was set at \(P_{(two-sided)} \leq 0.050\).

Results

Patient characteristics

Sociodemographic data (Table 1). The median age was 74 years (Q1/Q3 = 66/79 years, range = 32 to 95 years). The majority of the patients were male (61%), had a low educational level (64%), and were retired (73%).

Clinical data

The diagnoses were documented as follows (multiple answers were permissible): 73% AK, 49% BCC and 17% SCC. 66% had a single diagnosis, 28% two different diagnoses and 6% three different diagnoses. The majority of the lesions were located on the head (86%). Table 2 presents detailed
clinical data. The median treatment period was 49 months (Q1/Q3 = 16/101 months, range = 0 to 308 months, \( n = 1105 \)). Table 3 presents treatments broken down by diagnoses.

**Table 2** Clinical data

| Diagnosis (multiple answers) | n   | %   |
|-----------------------------|-----|-----|
| Actinic keratosis           | 869 | 73.4|
| Basal cell carcinoma        | 578 | 48.8|
| Superficial                 | 282 | 23.6|
| Nodular                     | 231 | 19.5|
| Other                       | 82  | 6.9 |
| Missing value               | 64  | 5.4 |
| Squamous cell carcinoma     | 204 | 17.2|

**Number of diagnosis**

| Diagnosis      | n   | %   |
|----------------|-----|-----|
|                | 1   | 825 | 66.3|
|                | 2   | 331 | 28.0|
|                | 3   | 68  | 5.7 |

**Number of lesions**

| Diagnosis            | n   | %   |
|----------------------|-----|-----|
| Actinic keratosis    | 869 | 73.9|
| 1-3                  | 329 | 37.9|
| 4-6                  | 232 | 26.7|
| >6/field             | 271 | 31.2|
| Missing value        | 37  | 4.3 |
| Basal cell carcinoma | 578 | 85.6|
| 1-3                  | 429 | 74.2|
| 4-6                  | 34  | 5.9 |
| >6                   | 28  | 4.8 |
| Missing value        | 87  | 15.1|
| Squamous cell carcinoma | 204 | 83.8|
| 1-3                  | 171 | 83.8|
| 4-6                  | 9   | 4.4 |
| >6                   | 4   | 2.0 |
| Missing value        | 20  | 9.8 |

**Localisation of lesions** (multiple answers)

| Diagnosis      | n   | %   |
|----------------|-----|-----|
| Head           | 1014| 85.6|
| Trunk          | 180 | 15.2|
| Extremities    | 218 | 18.4|
| Missing value  | 42  | 3.5 |
| Actinic keratosis | 869 | 780 | 89.8|
| Head           | 780 | 89.8|
| Trunk          | 40  | 4.6 |
| Extremities    | 93  | 10.7|
| Missing value  | 53  | 6.1 |
| Basal cell carcinoma | 578 | 405 | 70.1|
| Head           | 405 | 70.1|
| Trunk          | 146 | 25.3|
| Extremities    | 111 | 19.2|
| Missing value  | 19  | 3.3 |
| Squamous cell carcinoma | 204 | 155 | 76.0|
| Head           | 155 | 76.0|
| Trunk          | 9   | 4.4 |
| Extremities    | 44  | 21.6|
| Missing value  | 10  | 4.9 |

**QL data** Four hundred and forty-three (38%) of the patients reported no problems in any of the five dimensions of the EQ-5D-5L. Table 4 presents the distribution of the EQ-5D-5L dimensions by levels. The median EQ Index was 0.91 (Q1/Q3 = 0.83/1.00, \( m = 0.87, \ SD = 0.18, \) range = -0.21 to 1.00, \( n = 1162 \)) and the median EQ VAS was 90 (Q1/Q3 = 65/90, \( m = 75, \ SD = 19, \) range = 3 to 100, \( n = 1175 \)). There exists a strong and positive association between EQ Index and EQ VAS (\( r_{(1134)} = 0.65, P < 0.001 \)).

**Association between quality of life and diagnosis**

**Model 1** To assess QL differences between patients with different NMSC diagnoses and AK, model 1 made the following comparisons: AK vs. BCC vs. SCC vs. BCC plus SCC.

Using the EQ Index as a dependent variable, model 1 was statistically significant (\( F_{(8/1134)} = 18.322, P < 0.001 \)). Main effects were found for diagnosis (\( F_{(1/1134)} = 5.687, P = 0.001 \)), sex (\( F_{(1/1134)} = 13.985, P < 0.001 \)) and age (\( F_{(1/1134)} = 102.743, P < 0.001 \)). Patients with SCC plus BCC reported significantly less QL than patients with AK (\( P = 0.002, 9\% \)) (Fig. 1a). Men (\( m = 0.88, 95\% CI = 0.86/0.90 \)) had a significantly higher mean EQ Index than women (\( m = 0.82, 95\% CI = 0.80/0.85, P < 0.001 \)). There was no interaction effect between diagnosis and sex (\( F_{(3/1134)} = 2.469, P = 0.061 \)).

Using EQ VAS as a dependent variable, model 1 was also statistically significant (\( F_{(8/1148)} = 14.402, P < 0.001 \)). Main effects were found for diagnosis (\( F_{(3/1134)} = 6.496, P < 0.001 \)) and age (\( F_{(1/1148)} = 74.510, P < 0.001 \)). Patients with a single AK diagnosis had significantly higher mean EQ VAS than patients with BCC (\( P = 0.013, 4\% \)), SCC (\( P = 0.040, 6\% \)) and BCC plus SCC (\( P = 0.004, 9\% \)) (Fig. 1b). There was no main effect for sex (\( F_{(1/1148)} = 0.377, P = 0.539 \)), and no interaction effect between diagnosis and sex (\( F_{(3/1148)} = 0.047, P = 0.986 \)).
There was no main effect for sex ($F_{(1/589)} = 0.025, P = 0.874$), and no interaction between diagnosis and sex ($F_{(2/589)} = 0.081, P = 0.922$).

Table 5 presents medians and quartiles of QL values (not adjusted for age) separated for the fixed factors of both models.

**Table 3 Treatment types (multiple answers)**

| Current treatment | All $n = 1184$ | Actinic keratosis $n = 869$ | Basal cell carcinoma $n = 578$ | Squamous cell carcinoma $n = 204$ |
|-------------------|---------------|-----------------------------|-------------------------------|-------------------------------|
| No/no information | 114 9.6       | 88 10.1                     | 188 32.5                      | 92 45.1                      |
| Yes               | 1070 90.4     | 781 89.9                    | 390 67.5                      | 112 54.9                     |
| Physical therapy  | 661 55.8      | 351 40.4                    | 329 56.9                      | 92 45.1                      |
| Excision          | 246 20.8      | 49 5.6                      | 179 31.0                      | 50 24.5                      |
| Excision with histographic control of resection margin | 188 15.9 | 16 1.8 | 149 25.8 | 42 20.6 |
| Curettage         | 84 7.1        | 78 9.0                      | 12 2.1                       | 1 0.5                       |
| Laser             | 53 4.5        | 50 5.8                      | 3 0.5                        | 0 0                         |
| Radiotherapy      | 2 0.2         | 2 0.2                       | 0 0                          | 0 0                         |
| Cryosurgery       | 226 19.1      | 219 25.2                    | 13 2.2                       | 1 0.5                       |
| Drug therapy      | 251 21.2      | 245 28.2                    | 5 0.9                        | 2 1.0                       |
| 5-FU              | 61 5.2        | 60 6.9                      | 0 0                          | 1 0.5                       |
| Imiquimod         | 29 2.4        | 26 3.0                      | 3 0.5                        | 0 0                         |
| 5-FU/salicylic acid-lacquer | 49 4.1 | 48 5.5 | 1 0.2 | 0 0 |
| Diclofenac-sodium/hyaluronic acid gel | 114 9.6 | 111 12.8 | 2 0.3 | 1 0.5 |
| Ingenol mebutate  | 27 2.3        | 27 3.1                      | 0 0                          | 0 0                         |
| Photodynamic therapy | 342 28.9 | 315 36.2 | 41 7.1 | 2 1.0 |
| Watch and wait    | 101 8.5       | 54 6.2                      | 42 7.3                       | 18 8.8                      |

| Past treatment | All $n = 1184$ | Actinic keratosis $n = 869$ | Basal cell carcinoma $n = 578$ | Squamous cell carcinoma $n = 204$ |
|----------------|---------------|-----------------------------|-------------------------------|-------------------------------|
| No/no information | 389 32.9       | 231 26.6                    | 269 46.5                      | 88 43.1                      |
| Yes             | 795 67.1       | 638 73.4                    | 309 53.5                      | 116 56.9                     |
| Physical therapy | 599 50.6       | 397 45.7                    | 288 49.8                      | 112 54.9                     |
| Excision        | 257 21.7       | 99 11.4                     | 154 26.6                      | 54 26.5                      |
| Excision with histographic control of resection margin | 183 15.5 | 26 3.0 | 136 23.5 | 58 28.4 |
| Curettage       | 140 11.8       | 125 14.4                    | 20 3.5                       | 7 3.4                        |
| Laser           | 63 5.3         | 58 6.7                      | 4 0.7                        | 1 0.5                        |
| Radiotherapy    | 5 0.4          | 2 0.2                       | 0 0                          | 3 1.5                        |
| Cryosurgery     | 246 20.8       | 226 26.0                    | 26 4.5                       | 10 4.9                       |
| Drug therapy    | 298 25.2       | 283 32.6                    | 14 2.4                       | 3 1.5                        |
| 5-FU            | 78 6.6         | 76 8.7                      | 1 0.2                        | 1 0.5                        |
| Imiquimod       | 81 6.8         | 70 8.1                      | 11 1.9                       | 1 0.5                        |
| 5-FU/salicylic acid-lacquer | 52 4.4 | 52 6.0 | 0 0 | 0 0 |
| Diclofenac-sodium/hyaluronic acid gel | 201 17.0 | 196 22.6 | 4 0.7 | 2 1.0 |
| Ingenol mebutate | 47 4.0         | 46 5.3                      | 2 0.3                        | 1 0.5                        |
| Photodynamic therapy | 274 23.1 | 255 29.3 | 33 5.7 | 6 2.9 |
| Watch and wait  | 53 4.5         | 43 4.9                      | 14 2.4                       | 1 0.5                        |

Table 5 presents medians and quartiles of QL values (not adjusted for age) separated for the fixed factors of both models.

Discussion

Only in recent years have PROMs received increasing recognition in the assessment of the burden of benign and malignant cutaneous tumours.\(^{37}\) NMSC in all their different manifestations affect a substantial proportion of the general public, especially in the second half of life.\(^{8,38}\) Mortality with these conditions is generally low, except for invasive SCC, which has a disease-specific death risk of 2%.\(^{39}\) Still, the different forms of NMSC may impact patient well-being by being cosmetically unfavourable or even disfiguring and by showing locally destructive growth patterns. In addition to that, there is a continuum from AK to invasive disease (SCC).\(^{7,8,40,41}\) Thus, part of the perceived burden may be patient insecurity about their prognosis and its progression. However, in the absence of comparable data and representative studies, it is difficult to determine how far a diagnosis of NMSC and/or AK might influence the life of patients. Thus, we have designed such a study as a non-interventional, prospective, cross-sectional study in the context of healthcare research in...
patients with NMSC and AK in Germany. The EQ-5D-5L questionnaire was chosen for its robustness and cross-cultural applicability and its further use for pharmacoeconomic analyses. The population-based EQ Index is used for these pharmacoeconomic analyses, whereas the EQ VAS represents patient–individual self-assessment. In the present study, the EQ-5D-5L proved its sensitivity to discern between groups of patients with different levels of disease progression. Nevertheless, some absolute values

| Description of the EQ-5D-5L |
|----------------------------|
| **n = 1162**               |
| **Mobility**               |
| **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| No problem | 759 | 65.3 | 966 | 83.1 | 834 | 71.8 | 590 | 50.8 | 819 | 70.5 |
| Slight problems | 215 | 18.5 | 107 | 9.2 | 201 | 17.3 | 341 | 29.3 | 228 | 19.6 |
| Moderate problems | 112 | 9.6 | 58 | 5.0 | 76 | 6.5 | 151 | 13.3 | 76 | 6.5 |
| Severe problems | 112 | 9.6 | 58 | 5.0 | 76 | 6.5 | 151 | 13.3 | 76 | 6.5 |
| Extreme problems | 67 | 5.8 | 24 | 2.1 | 41 | 3.5 | 59 | 5.1 | 35 | 3.0 |

*Missing values for n = 22 (1.9%).

Figure 1  Quality of life differences (adjusted for age) between diagnoses. QL was measured by EQ Index and EQ VAS of the EQ-5D-5L. ANCOVA model 1 compares QL between patients with AK and NMSC diagnoses; Model 2 compares in detail QL differences between patients with AK and SCC to estimate whether disease progression results in higher QL impairment. All corrected ANCOVA models were significant: 1a $F_{(8/1134)} = 18.322, P < 0.001$, 1b $F_{(8/1148)} = 14.402, P < 0.001$, 1c $F_{(6/580)} = 11.931, P < 0.001$, and 1d $F_{(6/589)} = 7.227, P < 0.001$. Based on the estimated marginal means of QL (adjusted for age) of patients with AK, QL decrease (in percentage) for patients with NMSC diagnoses is presented along with significant levels: * $P \leq 0.050$, ** $P \leq 0.010$, *** $P \leq 0.001$. © 2017 The Authors. Journal of the European Academy of Dermatology and Venereology published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology.
obtained in the present study population (e.g. med = 0.91 for the EQ Index, med = 90 for the EQ VAS, perfect health status profile of 11 111 in 38% of the patients) indicate that the EQ-SD-5L is still prone to ceiling effects.

So far, very few studies exist that report utilities for NMSC. However, patient groups in these studies were small (n = 8 to 41)19,42,43 and the used tools were heterogeneous (for a review see13). In the present study, the average, age-adjusted EQ Index was 0.87 for patients with BCC (n = 472) and 0.84 for patients with SCC (n = 112). Especially for AK, data on utilities are sparse. Pharmacoeconomic calculations (e.g.29,44,45) using either standard gamble or TTO methodology resulted in utilities of 0.99 and 0.98.46,47 However, these two studies included a total number of 312 patients with relatively benign AK to those having developed SCC and multiple diagnoses.

In addition, the present study has the benefit that several forms of NMSC and multiple diagnoses were assessed along with AK although a larger subgroup size might have been desirable, especially for the smallest subgroup of n = 31 patients with SCC only. A further limitation of the present study is its cross-sectional design, which does not allow for longitudinal QL reassessment. The data are restricted to Germany, but the country-specific EQ Index allows comparisons across countries. QL reference values for several European countries including Germany are available.49,50

ANCOVAs significantly showed that QL is correlated with age and differs between diagnoses. Older patients reported significantly lower QL than younger patients. The analyses showed a clear reduction in QL, when patients with tumour diagnoses (SCC, BCC, or SCC plus BCC) are compared to those with AK only (4–9%). More importantly, the comparison of patients with AK to those with AK plus SCC demonstrates a significant decline in QL (7%). This may serve as initial evidence that progression from AK to SCC is accompanied by a decrease in QL. This is not automatically evident, because progression to SCC does not immediately mean gross functional impairment, but patients still perceive it as meaningful and detrimental. Therefore, dermatologists are advised to pay full attention to AK and initiate treatments with highest clearance probabilities as early as possible. Treatment of AK should be performed with both, the intention to prevent SCC and to preserve and restore QL in patients. To observe these effects in more detail, a longitudinal study is warranted, following up patients with AK progressing to SCC over time. Moreover, further analyses are planned within the present data set focusing on the predictors of QL, such as lesion site (especially sites of high cosmetic importance), number of lesions

Table 5  Unadjusted descriptive statistics of QL measures broken down by diagnosis and sex

| Groups                   | EQ INDEX | Male                      | Female                  | EQ VAS | Male                      | Female                  |
|--------------------------|----------|---------------------------|-------------------------|--------|---------------------------|-------------------------|
|                           | n        | Med Q1/Q3                 | Med Q1/Q3               | n      | Med Q1/Q3                 | Med Q1/Q3               |
| ANCOVA model 1           |          |                           |                         |        |                           |                         |
| AK                       | 468      | 1.00 (0.83/1.00)          | 0.92 (0.83/1.00)        | 477    | 80 (70/90)                | 80 (70/90)              |
| BCC                      | 472      | 0.91 (0.83/1.00)          | 0.91 (0.83/1.00)        | 477    | 80 (65/90)                | 80 (65/90)              |
| SCC                      | 112      | 0.91 (0.72/1.00)          | 0.86 (0.68/1.00)        | 112    | 75 (51/90)                | 77 (55/90)              |
| BCC + SCC                | 82       | 0.89 (0.72/1.00)          | 0.81 (0.54/0.98)        | 82     | 70 (50/82)                | 70 (50/81)              |
| ANCOVA model 2           |          |                           |                         |        |                           |                         |
| AK                       | 468      | 1.00 (0.83/1.00)          | 0.92 (0.83/1.00)        | 477    | 80 (70/90)                | 80 (70/90)              |
| SCC                      | 32       | 0.91 (0.84/1.00)          | 0.91 (0.83/1.00)        | 31     | 80 (60/90)                | 80 (58/90)              |
| AK                      | 80       | 0.91 (0.70/1.00)          | 0.74 (0.55/0.92)        | 81     | 75 (50/90)                | 75 (54/90)              |

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and treatment types. Another important research question for the future is a thorough comparison between NMSC/AK patients with reference data from the general population and from other patient groups.\footnote{51–54}

In conclusion, we analysed QL data from 1184 patients with NMSC and AK, which makes this study one of the largest reported PROM studies in the field of dermatology. Our results suggest that disease progression from AK to SCC is associated with a significant reduction in QL. This finding should be interpreted as a valid reason to treat AK with due diligence and to acknowledge the fact that NMSC, albeit seldom life-threatening, has considerable impact on patients’ health and well-being.

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