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Actinic keratosis area and severity index (AKASI) is associated with the incidence of squamous cell carcinoma

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ABSTRACT

Background Actinic keratoses (AKs) are commonly diagnosed clinically. Actinic keratosis area and severity index (AKASI) is a new easy-to-use tool to assess the severity of AK on the head.

Objective. To determine the association between chronically UV-induced tumours such as basal cell carcinomas (BCC) or squamous cell carcinomas (SCC) and AKASI.

Methods We performed a retrospective analysis of patients who had undergone oncological surgery due to UV-induced tumours and who were assessed for AKASI and Physician's Global Assessment (PGA) prior to surgery. Statistical analysis was performed to evaluate correlation between AKASI, PGA and invasive carcinomas.

Results Of the 210 patients included, 26 patients had histologically diagnosed SCCs and presented with a median (range) AKASI of 6.9 (0 – 13.0) and PGA of 2 (0 - 4). In contrast, the 82 patients with BCCs showed a median (range) AKASI of 3.3 (0 -15.2)

and PGA of 1 (0 - 4). The Mann-Whitney U test showed significant differences (p= 0.0018) between AKASI of patients with SCC and BCC. In addition, we found a significantly higher AKASI in patients with SCC compared to patients with non-invasive lesions like AK and Bowen disease (BD) (p= 0.0275). Spearman's coefficient of rank correlation between AKASI and PGA indicates that these measures of AK severity were strongly correlated (p< 0.0001; r = 0.90; 95%CI 0,865 to 0,920).

Conclusions Patients with SCC show significantly higher AKASI than patients with BCC or patients without invasive tumours. Hence, AKASI may be used to stratify risk for developing invasive SCC.

INTRODUCTION

Actinic keratoses (AK) are commonly seen in dermatological practice[1, 2] They are regarded as early in situ carcinomas and bear the potential to progress into an invasive squamous cell carcinoma (SCC), which may subsequently metastasize. AKs are mainly induced by chronic exposure to UV-radiation and located on sun-exposed sites such as the scalp/face, décolletage, forearms, back of the hands and lower legs.[3-6] As the entire area of sun-exposed skin is affected by both clinical and subclinical disease resulting in field cancerisation, treatment approaches ideally need to address all AK lesions and the entire affected field.[7]

Due to a change in leisure activities in the past few decades and a demographic change in industrial countries, increasing incidence of non-melanoma skin cancer (NMSC) and AKs in particular, have been observed.[2] AKs are regarded as chronic disease and as the prevalence continues to rise, this has led to an increasing number of episodes of treatment and the options available, resulting in increasing

costs to the health service. Commonly, AKs are diagnosed clinically and their severity is graded according to a classification scheme introduced by Olsen et al.[8] The main limitation of this scoring system is that it only grades discrete AK lesions according to their overall thickness and does not take into account the entire area affected by AK. To overcome this problem a new assessment tool was recently introduced. The "actinic keratosis area and severity index" (AKASI) quantitatively evaluates the severity of AKs across the entire affected area of the head.[9]

Thus, AKASI is a new grading tool which provides the possibility to objectively monitor and compare disease progression. It is analogous to established scoring systems of other chronic diseases i.e. the psoriasis area and severity index (PASI). To assess AKASI, the head is divided into four areas and each area is evaluated to its approximate relative size and the severity of three characteristic clinical signs of AK (distribution, erythema, thickness).

Currently clinical and histological classification schemes lack the predictive power to determine carcinoma risk of single AKs.[2, 7] It would therefore be valuable to have a scoring system which assesses the overall risk of an individual patient developing invasive carcinoma, but thus far, no clinical classification scheme has been reported which stratifies the severity of AKs and the risk of developing invasive carcinomas such as SCC or BCC.

The aim of this study was to analyse patients who have undergone oncological surgery due to UV-induced tumours on the head. All patients were assessed using the PGA and AKASI prior to surgery. This is the first study to show a correlation between AKASI and PGA in clinical dermatological practice.

MATERIALS AND METHODS

Study population

This retrospective study was conducted according to the Declaration of Helsinki and performed at the Skin Cancer Centre of the Ruhr-University Bochum (Bochum, Germany). The study was approved by the ethics review board of the Ruhr-University Bochum. We searched our database consecutively from January 2017 to May 2017 for all patients who had undergone oncological surgery (surgical and shave excisions) due to UV-induced tumours (AK, BD, SCC and BCC) located on the head and had an existing AKASI and PGA. Patients under immunosuppressive therapy were excluded from this study.

Data assessment

Prior to surgery for UV-induced tumours on the head, AKASI and PGA were evaluated in all patients. These assessments were performed by one investigator (LS). AKASI is part of our AK management and determined routinely. For area assessment of the AKASI, the head was divided into four areas: scalp, forehead, left cheek, ear, nose, and chin as well as right cheek, ear, nose and chin. Each area on the head affected by AKs was given a weighting with 40% to the scalp and 20% each to the other three areas. The severity of each area was evaluated by three characteristic clinical signs of AKs (distribution, erythema, thickness) using a quantitative scale from 0 (none) to 4 (severe). Finally, all sub scores for each area of the head were added to give a total AKASI of the head, which ranged from 0 to 18. For PGA scoring, the following categories were used: ‘None’ (0), ‘Light’ (1), ‘Moderate’ (2), ‘Severe’ (3) and ‘Very severe’ (4).

Statistical analysis

Data analysis was performed using the statistical package MedCalc software version 17.4.4 (Ostend, Belgium). Distribution of data was assessed by the D`Agostino-Pearson test. In the case of normal distribution, data were expressed as mean and standard deviation (SD), otherwise as median and range. Data were analyzed using the Spearman's coefficient of rank correlation and Mann-Whitney U test for independent sample analysis. P-values less than 0.05 were considered statistically significant.

.RESULTS

210 patients with a median (range) age of 77 (42-95) years were included in this study. Two thirds of patients were male (66.2%) and most patients had Fitzpatrick skin type II (61.9%). More than half of the study group had a positive history of invasive skin cancer (52.4%) and increased UV-exposure (57.1%). Further demographic and clinical characteristics are shown in **table 1**.

Overall, 636 lesions on the head were surgically treated. Histological evaluation revealed AKs in 298 (46.9%), BD in 88 (13.8%), SCC in 32 (5.0%), BCC in 118 (18.6%) and other tumours such as seborrhoeic keratosis in 104 (16.4%) cases (**Table 1**). Further characteristics of the 32 SCCs are shown in **table 2**. Highly significant differences between AKASI in male and female patients were observed ($p < 0.0001$) (**Fig 1**).

Patients (n = 26) with SCC showed median (range) AKASI of 6.9 (0 – 13.2) and PGA of 2.0 (0 - 4). In contrast, patients exclusively presenting AKs (n = 106) showed a median (range) AKASI of 4.6 (0-15.5) and PGA of 2.0 (0-4.0), whereas patients (n = 82) with BCC had an AKASI of 3.3 (0 – 15.2) and a PGA of 1.0 (0 – 4.0). The Mann-

Whitney U test showed significant differences (p = 0.0018) between AKASI of patients with SCC and BCC (**Fig. 2**). The Spearman's coefficient of correlation shows a strong association between the AKASI and the number of lesions on the head having been indicated to receive surgery due to suspicion of invasiveness (P < 0.0001; r = 0.55; 95% CI 0.44 to 0.63) (Table 1).

Subgroup analysis of patients with BCC or SCC and AKASI > 0 showed that patients with SCC (n = 24) had a higher median (range) AKASI of 7.1 (1.4 – 13.2) and PGA of 2.5 (1.0 – 4.0) compared to patients with BCC (n = 59) who had an AKASI of 4.8 (1.0 – 15.2) and PGA of 2.0 (1.0 – 4.0). The Mann-Whitney U test showed significant differences (p = 0.0304) between AKASI in patients with SCC and BCC (**Fig. 3**). Patients with solely non-invasive tumours (n = 43) such as AKs and BD had a median (range) AKASI of 5.0 (0.6 – 11.2). A significant difference (p = 0.0275) between AKASI of patients with AKs/ BD and SCC was observed (**Fig. 3**).

The Spearman's coefficient of rank correlation between AKASI and PGA indicated that these measures of AK severity were strongly correlated (P < 0.0001; r = 0.90; 95% CI 0.87 to 0.92). Moreover, AKASI clearly discriminated between different PGA categories (**Fig. 4**). In 36 patients without any AKs a PGA rating of `none´ and a median (range) AKASI of 0 (0 - 3.6) were observed. The median (range) AKASI increased from 2.8 (0.6 - 8.0) for a PGA classification of 'light' to 5.8 (1.8 – 10.2) for a PGA classification of 'moderate', 8.4 (5.0 -13.2) for a PGA classification of 'severe', and 11.5 (6.8 – 15.8) for a PGA classification of 'very severe'.

DISCUSSION

AKs are located on chronically sun-exposed areas and are regarded as major predictors for actinically damaged skin.[10] The “actinic keratosis area and severity index” has recently been reported and can be used to assess the entire sun-damaged field on the head. It is based on the evaluation of clinical signs of AK and is assessed in each of 4 areas of the head. Thus, individual AK lesions, as well as field cancerisation, can be measured objectively and AKASI can provide inter- and intraindividual comparable indices of disease severity.[9] To our knowledge, this is the first study which compares AKASI to NMSC occurring on the head in clinical practice.

The majority of studies and clinical trials for AKs have been based on AK lesion counts or Olsen`s lesion classification.[11] The main limitation of these scoring systems is that they assess only the severity of individual lesions and do not consider the entire area affected by AK.[9] To our knowledge, our study is the first to demonstrate AKASI cut off thresholds with respect to the incidence of invasive NMSC. As most SCC lesions (between 82% and 97%) arise from AK or in proximity of AK, AKASI can become a powerful tool for risk stratification in individual patients.[12, 13] Our data indicate that patients with an AKASI between 6.9 and 7.1 or higher may have an increased risk of an invasive SCC. Therefore, we propose that AKASI of over 7 may suggest an increased risk of SCC transformation and thus greater vigilance may be required in these patients. Conversely patients with in situ lesions (AK and BD) had significantly lower AKASI than patients with SCC. A “typical” AK patient is described to have 6 to 8 AK lesions and the annual risk of developing SCC ranges from 0.15% to 80%, accordingly.[5, 13-16] In patients with multiple AK lesions (more than 15), the risk of SCC is 10 to 15 times higher than in

people with no AKs.[17] As AKs are one of the strongest predictors of SCC development, further larger studies using AKASI are required to ascertain more robust thresholds and the risk of developing SCC.[18]

AKs are indicative of photodamage and thus associated with an increased risk of BCC,[19] which is lower than the risk of developing a SCC.[20] Our study shows that only 59.3% of the patients with BCC presented with AKs (AKASI > 0) compared to 93.8% of patients affected by SCC. Moreover, the comparison of AKASI showed significant differences between patients with BCC and SCC in the full cohort and when patients with AKASI of zero were excluded. Our study shows that AKASI is significantly higher in patients with SCC than those with AK/BD and BCC, and could therefore be used in future risk stratification systems. Furthermore, our data confirm for the first time the well-known association between AKs and SCC as demonstrated by AKASI. Until now, existing data have been evaluated by aforementioned lesion based counts and classifications.[8]

Our study has confirmed that AKASI was clearly able to discriminate between different PGA categories in a much larger cohort than in the pivotal study.[9] The PGA categories none, mild, moderate and severe showed similar correlation with AKASI as the pivotal study. The PGA category “very severe”, however, exhibited a higher AKASI than the pivotal study. This might be related to a larger study population and inclusion of more severely affected patients who were admitted for surgery. After reviewing the pivotal study and our current study data, we would propose that scores around 3, 5.5, 8.5 and > 11 correspond to mild, moderate, severe and very severe disease, respectively.[9] In comparison to psoriasis, a PASI higher than 10 is regarded as moderate to severe disease.[21] Hence, we would suggest an AKASI higher than

8.5 to indicate severely affected AK patients. In the future, AKASI scores may have an application in determining treatment options and regimens.

On the one hand, limitations of this study include that the scores (AKASI and PGA) have been evaluated by only one investigator. This might have led to an overestimation of the correlation between AKASI and PGA. On the other hand, there was no risk of inter-rater variability. Another limitation of this study might be that patients with more lesions being suspicious for invasiveness received more surgical interventions than patients with less noticeable lesions. A strong correlation between the number of lesions with intervention per patient and AKASI has been shown in this study. Hence, there might have been a higher risk to detect invasive tumours in patients with higher AKASIs due to more frequently performed excisions. Nevertheless, people with more severe sun-damaged skin and thus high AKASIs may just have more invasive NMSC such as SCC as a matter of fact.

In conclusion, our study shows that AKASI is a reliable objective tool which can be used to assess field damage in clinical practice. The scores are associated with known epidemiological data with higher scores in men and those with SCC. Our study delineates thresholds for disease severity and the risk of developing invasive carcinomas, especially SCC. Further longitudinal studies are required to investigate the correlation between AKASI and SCC risk. This may in the future lead to risk stratified therapy.

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TABLE LEGEND

Table1. Demographic and clinical characteristics (N=210)

Characteristic	n (%)
Sex	
Male	139 (66.19)
Female	71 (33.81)
Age, years	77 (42-95)[a]
Skin Type (Fitzpatrick)	
I	77 (36.7)
II	130 (61.9)
III	3 (1.4)
IV+V	0 (0)
UV Exposure (increased)	120 (57.1)
leisure activities	92 (76.7)[b]
occupational	37 (30.8)[b]
artificial	4 (3.3)[b]
AK History	
no AK	33 (15.7)
first diagnosed at admission for surgery	79 (37.6)
previously diagnosed AK	98 (46.7)
mean time since first diagnosed	6.3 (years)
Skin cancer history (invasive)	110 (52.4)
BCC	87 (79.1)[b]
SCC	30 (27.3)[b]

KA	3 (2.7)[b]
Other (e.g. malignant Melanoma)	31 (28.2)[b]
Surgical sites on head (mean sites per patient)	636 (3.03)
patients with > 1 surgical site	119 (56.7)
Of these 636 lesions, histologically diagnosed as	
AK	298 (46.9)
BD	88 (13.8)
SCC	32 (5.0)
BCC	118 (18.6)
Other (e.g. seborrhoeic keratosis, scar)	104 (16.4)
Correlation between lesions with intervention and AKASI	
patients (n = 90) with 1 lesion	1.9 (0-11.4)[a]
patients (n = 41) with 2 lesions	5.2 (0-13.2)[a]
patients (n = 79) with 3 or more lesions	7.7 (0-15.8)[a]

AK, actinic keratosis; AKASI, actinic keratosis area and severity index; BCC, basal cell carcinoma; BD, Bowen disease; KA, keratoacanthoma; SCC, squamous cell carcinoma

[a]Data are median (range); [b]% referring to absolute value of the headline in this row

Table 2. Clinical characteristics of SCC (N=32) and patients´ characteristics (N=26)

Characteristic	n (%)
SCC lesions total	32 (5.0)*
patients with SCC	26 (12.4)[#]
patients with 1 SCC	22 (10.5) [#]
patients with >1 SCC	4 (1.9) [#]
Tumour thickness	2.55 (0.4–14.4)[a]
Tumour thickness < 4 mm	20 (62.5)
mean tumour thickness < 4 mm	1.45 (0.4-3.1)[a]
Tumour thickness ≥ 4 mm	12 (37.5)
mean tumour thickness ≥ 4 mm	5.5 (4.12-14.4)[a]
Invasion depth´s (Clark´s level)	
into the papillary dermis (I+II)	0 (0)
to the junction of papillary and reticular dermis (III)	2 (6.3)
into the reticular dermis (IV)	24 (75.0)
into the subcutaneous fat (V)	6 (18.8)
Histological differentiation (grading)	
well differentiated (1)	28 (87.5)
moderately differentiated (2)	3 (9.4)
poorly differentiated (3)	1 (3.1)
undifferentiated (4)	0 (0)
Perineural invasion	1 (3.1)
Tumour sites	
parietal	9 (28.1)
ear	6 (18.8)
scalp	5 (15.6)
cheek	5 (15.6)
forehead	5 (15.6)
nose	1 (3.1)
lip	1 (3.1)

*referring to overall lesions (636); [#]referring to overall patients (210); [a] Data are median (range) in mm