Impact of High Age and Comorbidity on Management Decisions and Adherence to Guidelines in Patients with Keratinocyte Skin Cancer

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Appropriate medical decision-making in patients with keratinocyte skin cancer (KSC) can be challenging, especially in those with a limited life expectancy (LEx). Treatment should be beneficial for the individual patient, the risk of both over- and under-treatment should be carefully considered, and deviation from guideline recommendations may be necessary. In this study retrospective analysis was performed to determine the influence of age and comorbidity, both factors strongly related to limited LEx, on KSC management in daily practice. After analysis of 401 patients it was found that management in patients with KSC is not influenced, or is only minimally influenced, by high age and comorbidity. Better integration of aspects related to a limited LEx in KSC management might optimize care and prevent overtreatment. Future research on the general prognostication, prediction of the patient burden caused by tumour and treatment, and time-to-benefit in KSC management is strongly recommended.

Key words: keratinocyte skin cancer; limited life expectancy; frail older adults; geriatric dermatology; skin cancer management; clinical practice guideline.

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Dermatologists are increasingly likely to be confronted with older adults with multiple comorbidities who have keratinocyte skin cancer (KSC), considering: (*i*) the increasing incidence rates of KSC in general; (*ii*) the rising incidence rates of KSC with increasing age; (*iii*) and the ageing world population (1, 2). In general, the majority of KSC has a relatively low malignant potential compared with many other types of cancer. However, potential morbidity and mortality should not be underestimated (1). Adequate medical decision-making in patients with KSC requires physicians to be aware of several important aspects, including patient and tumour characteristics (e.g. tumour subtype, comorbidity, and life expectancy), treatment goals, and the availability of diagnostic and treatment options. Treatment should be beneficial for the individual patient, and the risks of both over- and under-treatment should be carefully weighed. Consequently, management decisions in patients with KSC may be challenging, especially in the growing population of frail older adults with a limited life expectancy (LEx) (3, 4).

The main purpose of clinical practice guidelines (CPGs) is to assist physicians in medical decision-making, based on the best evidence available, thereby optimizing healthcare (5). However, CPG recommendations might not be applicable to every individual, and CPG guidance for older adult patients and patients with multiple comorbidities is limited (6–8). Therefore, properly reasoned deviation from CPG recommendations may be in the best interest of a patient and should be considered in some situations.

Estimating a patient's LEx is difficult. In addition to age, a patient's LEx may be influenced by several factors, of which comorbidity is considered the strongest and best-studied predictor (9–13). It might be expected that a limited LEx and influencing factors might contribute to the extent of deviation from CPG in KSC, but little is known regarding these decisions from daily practice. Hence, the aim of this study was to determine the influence of high age and comorbidity on management in patients with KSC in daily clinical practice.

METHODS

Setting and patient selection

Patients with KSC seen in the outpatient dermatology department of Radboud University Medical Centre, Nijmegen, the Netherlands, were analysed retrospectively. Selection of histologically proven basal cell carcinomas (BCCs) or squamous cell carcinomas (SCCs) diagnosed in 2012 or 2013 took place using the national pathology database (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief; PALGA) combined with patient charts. Patients were sorted into 2 age groups (<80 or ≥ 80 years), based on the United Nations (UN) age stratification (2) and the Dutch LEx data by Statistics Netherlands (mean residual LEx of 4.5 years at an age of 80 years) (14, 15). Since every lesion suspicious for KSC is histopathologically confirmed in our hospital, it is assumed that no cases were missed. In case multiple tumours per patient were found, only the first tumour was included. Exclusion criteria were: (*i*) tumours other than BCC or SCC (including basosquamous carcinoma); (*ii*) non-cutaneous tumours (e.g. mucosal); (*iii*) patients using chronic immunosuppressive medication; (*iv*) patients having a genetic disorder resulting in an increased risk of developing KSC (e.g. basal cell naevus syndrome, oculocutaneous albinism, and epidermodysplasia verruciformis); (*v*) clinical trial subjects; and (*vi*) patients in whom diagnosis and/or treatment was not performed within our hospital.

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Data collection and quality control

Data for all included patients were independently collected by 2 data collectors (SL and CM) using a standardized form. Discrepancies between the 2 data collectors were discussed and, in case no consensus could be reached, a third author was consulted (RB or MJG). A pilot study of 20 patients was initially performed as a data-collection training (to test the standardized form, to discuss doubtful cases, and to increase inter-observer agreement). A data-collector manual was created to document all definitions and agreements.

Patient and tumour characteristics

Several patient and tumour characteristics were collected (**Table I**). Comorbidity was classified using the Deyo adaptation of the Charlson Comorbidity Index (CCI; ICD-10 version), which is the most commonly used tool to assess comorbidity, validated in several populations. This includes assigning a weighted score to 17 groups of comorbid conditions when present in a patient (resulting in a score ranging from 0 to 30). Weights are based on their relative risk on 1-year mortality (12, 13, 16–18). When tumour characteristics were reported inconsistently, the pathology report after surgical excision overruled the biopsy report.

Management decision

Data regarding management decisions and adherence to guidelines, including reasons for non-adherence, were collected. Adherence to guidelines was based on 2 AUDIT-checklists for BCC and SCC, respectively (Appendices S1 and S2[1]). The 16-item checklist for BCC was based on a previously developed and tested checklist (19). The 21-item checklist used for SCC was newly developed using the same principles as the BCC checklist. Both checklists included items related to risk factors, diagnosis, staging, treatment, prevention, and follow-up. All included items were directly based on recommendations from the Dutch guidelines (20, 21). Adherence to guidelines was calculated by dividing the number of items fulfilled by the total number of items. Only items applicable for that specific patient were included in the calculation (e.g. in case a tumour was treated solely with radiotherapy the items regarding surgical excision were not included).

Statistical analysis

The primary outcome of this study was adherence to guidelines (which included data regarding management decisions). Age and comorbidity are the main factors of influence studied regarding adherence to guidelines. Interobserver agreement was measured using Cohen's κ for each relevant variable. Since the amount of missing data was small, no imputation of missing data was performed and only the available data per variable was analysed. For a detailed description of the univariate and multivariable logistic regression models used in this study see Appendix S3[1]. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient and tumour characteristics

A total of 401 patients were included in the study, of which 128 patients were aged ≥80 years. Interobserver agreement was substantial to excellent for all variables (median κ=0,971; range 0.646–1.000). All discrepancies could be solved during consensus-meetings between the 2 data collectors. Comparison between the 2 age groups showed that more patients within the older age group had a positive history for KSC and a higher CCI. Furthermore, tumours within the older age group were more often SCC, less often superficial BCC, more often located within the head-and-neck area and had a larger

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Table I. Patient and tumour characteristics

Characteristic	Overall population (*n* = 401)	Patients aged <80 years (*n* = 273)	Patients aged ≥80 years (*n* = 128)	*p*-value
Patient				
Age, years, median (range)	71.0 (30–97)	64.0 (30–79)	83.0 (80–97)	**<0.001***
Male sex, *n* (%)	203 (50.6)	133 (48.7)	70 (54.7)	0.265
Positive history for KSC, *n* (%)[a]	222 (55.5)	131 (48.0)	91 (71.7)	**<0.001***
Charlson comorbidity index, median (range)	1 (0–7)	0 (0–7)	2 (0–7)	**<0.001***
Tumour-related complaints[b], *n* (%):				
Yes	138 (34.4)	96 (35.2)	42 (32.8)	0.897
No	235 (58.6)	158 (57.9)	77 (60.2)	
Unknown	28 (7.0)	19 (7.0)	9 (7.0)	
Tumour				
Histopathological subtype, *n* (%):				
SCC	75 (18.7)	34 (12.5)	41 (32.0)	**<0.001***
Nodular BCC	81 (20.2)	59 (21.6)	22 (17.2)	
Superficial BCC	89 (22.2)	77 (28.2)	12 (9.4)	
Infiltrative BCC	47 (11.7)	30 (11.0)	17 (13.3)	
Micronodular BCC	40 (10.0)	31 (11.4)	9 (7.0)	
Mixed type BCC	69 (17.2)	42 (15.4)	27 (21.1)	
Location, *n* (%):				
Head-and-neck area	215 (53.6)	126 (46.2)	89 (69.5)	**<0.001***
Trunk	121 (30.2)	101 (37.0)	20 (15.6)	
Upper limbs	27 (6.7)	18 (6.6)	9 (7.0)	
Lower limbs	38 (9.5)	28 (10.3)	10 (7.8)	
High-risk location, *n* (%):				
H-zone[c]	129 (39.6)	82 (34.3)	47 (54.0)	**0.001***
Lip or ear[d]	4 (5.3)	2 (5.9)	2 (4.9)	1.000
Largest diameter in mm, median (range)[e]	9.0 (2–45)	8.0 (2–30)	10.0 (2–45)	**0.027***
Tumour depth in mm[4], median (range)[f]	2.0 (1–9)	2.0 (1–8)	2.5 (1–9)	0.267
Degree of histological differentiation[d], *n* (%):				
Well-differentiated	26 (34.7)	17 (50.0)	9 (22.0)	0.029*
Moderately-differentiated	43 (57.3)	15 (44.1)	28 (68.3)	
Poorly-differentiated	2 (2.7)	0 (0)	2 (4.9)	
Perineural invasion[d,g], *n* (%)	6 (8.5)	1 (3.2)	5 (12.5)	0.222
Vascular and/or lymphatic invasion[d,g], *n* (%)	1 (1.4)	0 (0)	1 (2.5)	NA
Previously treated (recurrence), *n* (%)	24 (6.0)	15 (5.5)	9 (7.0)	0.545
TNM-stage[d,h], *n* (%)				
Stage I	58 (77.3)	28 (82.4)	30 (73.2)	0.344
Stage II or higher	17 (22.7)	6 (17.6)	11 (26.8)	

[a]1 missing; [b]Tumour-related complaints mentioned were bleeding, itch, pain and/or ulceration; [c]Basal cell carcinoma (BCC) only; [d] Squamous cell carcinoma (SCC) only; [e]33 missing; [f]2 missing: [g]4 missing. [h]Staging based on the classification of the American Joint Commission on Cancer (AJCC) tumor/node/metastasis (TNM) system (26); *$p \leq 0.05$ (shown in bold). Values may not add up due to missing data and rounding.
KSC: keratinocyte skin cancer; NA: not applicable.

diameter. A full overview of patient and tumour characteristics is given in Table I.

Management decisions

Univariate analysis. In both SCC and BCC, conventional surgical excision was the treatment option performed most frequently (Tables SI and SII[1]). Comparison between both age groups in BCC showed that Mohs micrographic surgery (MMS) was performed less often (8.4% vs. 1.1%, overall $p=0.004$), and radiotherapy (RT) was performed more often in the older age group (2.5% vs. 10.3%, overall $p=0.004$). In SCC, no differences regarding treatment options were found comparing both age groups.

Multivariate analyses. Secondary multivariate logistic regression analyses were performed to study the management differences found in the univariate analysis in more detail. As the number of treatments with MMS and RT were performed in BCC was rather small (21 and 15 times, respectively), a large logistic regression model was not possible. Hence, 3 consecutive analyses were performed for each treatment option, each with age and one important confounder (location, previous treatment, and CCI, respectively). Inclusion of BCC subtype in the model was not possible due to: (*i*) the relatively low number of BCC treated by MMS and RT; and (*ii*) the extent of variance found in different BCC subtypes treated by both treatment options. MMS was less often performed in BCC in the older age group compared with the younger patients (1.1% vs. 8.4%; $p=0.019$). This finding persisted after consecutive correction for previous treatment (primary vs. recurrent BCC ($p=0.042$)) and location (within or without the H-zone; $p=0.014$). After correction for CCI the model failed to show a statistical significant difference in treatment of BCC by MMS between the 2 age groups, although a trend could be seen ($p=0.056$). The opposite was observed for RT in BCC, which was more frequently performed in the older patient group compared with the younger (10.3% vs. 2.5%; $p=0.003$), also after consecutive correction for previous treatment ($p=0.007$), location ($p=0.033$) and CCI ($p=0.011$).

Adherence to guidelines

Univariate analyses. Overall adherence to guidelines was high (88% vs. 90% for SCC and BCC, respectively) and did not differ between the 2 age groups ($p=0.898$ and $p=0.301$, respectively), as also shown in Tables SI and SII[1]. When focusing more specifically on the individual guideline recommendations advice on appropriate sun protection was less frequently provided in the older age group with BCC (77.4% vs. 51.7%, $p<0.001$), while the primary care physician was more frequently informed about the diagnosis and management in the older age group with BCC (87.4% vs. 96.6%, $p=0.016$). All other guideline recommendations showed no difference in adherence between both age groups. In 4.5% ($n=25$) of the deviations from guideline recommendations, the reason was extractable from the patient chart. The most frequently mentioned reasons for deviation from guidelines were: (*i*) a limited LEx; (*ii*) severe impaired mobility; and (*iii*) patient's refusal.

Multivariate analyses. Adherence to guidelines below 90% was considered as "low" adherence to guidelines (cut-off based on approximate median). The multivariate logistic regression model for this dependent variable is presented in **Table II**. The results of this model show that adherence to guidelines is not influenced by age (odds ratio (OR) = 0.834; 95% confidence interval (95% CI) 0.508–1.371; $p=0.475$) or comorbidity (OR 0.919; 95% CI 0.764–1.106; $p=0.373$), after correction for the other variables. Of the other variables in the model, the effect of tumour type is by far the most clear ($p=0.026$). Much better adherence to guidelines in patients with a superficial BCC, as opposed to patients with a SCC, (OR 5.309; 95% CI 2.042–13.804; $p=0.001$) was noted.

DISCUSSION

This study shows that management decisions in BCC are influenced by high age to some extent, while the influence of comorbidity seems only minimal to absent.

Table II. Multivariate logistic regression model of the correlation of different factors in adherence to guidelines with at least 90% as dependent variable

Variable	Odds ratio	95% CI	*p*-value
Age (<80 vs. ≥80 years)	0.834	0.508–1.371	0.475
Charlson comorbidity index (0–30)	0.919	0.764–1.106	0.373
Previous treatment (yes vs. no)	0.608	0.241–1.536	0.293
Treatment method			0.754
Conventional SE	Reference		
Photodynamic therapy	0.985	0.371–2.616	0.976
Topical imiquimod	0.558	0.164–1.902	0.351
Mohs micrographic surgery	2.020	0.669–6.094	0.212
Radiotherapy	1.085	0.381–3.095	0.878
Other	0.867	0.049–15.208	0.922
Tumour type			**0.026***
SCC	Reference		
Nodular BCC	1.950	0.878–4.331	0.101
Superficial BCC	5.309	2.042–13.804	**0.001***
Infiltrative BCC	1.875	0.791–4.448	0.154
Micronodular BCC	1.419	0.577–3.489	0.445
Mixed type BCC	1.540	0.710–3.342	0.274
Location			0.227
Head-and-neck area	Reference		
Trunk	0.684	0.350–1.336	0.266
Upper limbs	0.563	0.215–1.477	0.243
Lower limbs	0.397	0.160–0.984	**0.046***
Location (high vs. low risk)[a]	1.402	0.728–2.700	0.312
Complaints			0.280
No	Reference		
Yes	1.449	0.915–2.294	0.114
Unknown	1.045	0.452–2.419	0.918

[a]A basal cell carcinoma (BCC) located in the H-zone or a squamous cell carcinoma (SCC) located on an ear or lip. *$p \leq 0.05$ (shown in bold).
CI: confidence interval; SE: surgical excision.

Furthermore, high age and comorbidity did not have a significant influence on management decisions in SCC, or on overall guideline-adherence in both BCC and SCC. The possibility to draw direct conclusions from the results found in this study with respect to quality of care is limited and the definition of optimal skin cancer care remains open for discussion. One might expect deviation from regular treatment protocols and guideline recommendations in KSC to be more common among frail older adults with a limited LEx; however, this was not shown by the results of this study.

Studies on the impact of high age and comorbidity on treatment decisions in KSC patients are scarce. Two studies from the USA showed that a limited LEx did not influence treatment decisions in patients with KSC, including treatment with MMS (22, 23). These studies show important agreement with our findings that high age and comorbidity do not have a significant influence on treatment choice in SCC and the decision not to treat KSC is rare. On the other hand, our finding that MMS is less frequently performed in patients $\geq$80 years with BCC, while RT is more frequently used in this population, seems to contradict these studies, which might be explained by differences in healthcare systems and guidelines between countries.

It should be pointed out that medical decision-making solely based on age might be a pitfall, since age alone is just one factor influencing life expectancy and the population of older adults is heterogeneous. For instance, on the one hand, MMS is a treatment option, which might lead to a significant patient burden and overtreatment in some (frail) older patients, especially in case a patient will not live long enough to benefit from this treatment (time-to-benefit principle) (22, 23). On the other hand, MMS is a suitable treatment option in some (less frail) older adults and exclusion solely based on age seems to be an insufficient selection method (24). We believe (more extensive) inclusion of patient characteristics related to frailty and a limited LEx in medical decision-making in older adults optimizes KSC care. Examples of these characteristics are: comorbidity, cognition, and functional status. Clinicians may be stimulated to act on this in a greater extent through education, more cooperation with elderly care specialists, and further inclusion of these considerations within clinical practice guidelines (8). Furthermore, we believe that watchful waiting is a suitable alternative for treatment in some patients with an asymptomatic low-risk KSC, which should be considered more frequently in patients with a limited LEx. Instruments to determine (the extent of) frailty and a patient's general prognosis can assist in these management decisions; however, currently these are not validated for patients with KSC (25). Consequently, since reliable and validated methods for general prognostication, prediction of the patient burden caused by tumour and treatment, and time-to-benefit data are lacking in current KSC literature, management decisions in daily practice might remain complex. We strongly recommend focussing future research on these aspects in order to provide guidance for clinicians.

Study limitations

Generalization of the results in this single-centre study from one university hospital in the Netherlands should be performed with care, since population and management differences can exist between different healthcare institutions and countries. Since patient records were retrospectively studied, non-reporting bias might have occurred, which could have influenced data on adherence to guidelines. However, it is unlikely that this potential non-reporting bias differed among the compared patient groups, and therefore its influence on the main outcomes in this study is expected to be limited.

Conclusion

In contradiction with our expectations, the present study shows that management in patients with KSC is not, or is only minimally, influenced by high age and comorbidity. We believe that better integration of aspects related to a limited LEx in KSC management might optimize care and prevent overtreatment. Future research on general prognostication, prediction of the patient burden caused by tumour and treatment, and time-to-benefit in KSC management is strongly recommended.

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