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Age-related Differences in Tumour Characteristics and Prognostic Factors for Disease Progression in Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Guidelines for cutaneous squamous cell carcinoma of the head and neck do not take the age of the patient into account, but instead assume equal tumour characteristics and prognostic factors for poor outcome in younger and elderly patients. The aim of this study was to compare tumour characteristics of younger (<75 years) and elderly (≥75 years) patients and identify age-specific risk factors for progression of disease, comprising local recurrence, nodal metastasis and distant metastasis. Patient and tumour characteristics were compared using χ^2 or Fisher's exact tests. Multivariable competing risk analyses were performed to compare risk factors for progression of disease, incorporating the risk of dying before developing progression of disease. A total of 672 patients with primary cutaneous squamous cell carcinoma of the head and neck were retrospectively included. Larger tumour diameter, worse differentiation grade and deeper invasion were observed in older patients. In elderly patients, but not in younger patients, tumour diameter ≥40 mm, moderate differentiation grade and an invasion depth ≥2 mm were independent risk factors for progression of disease.

Key words: cutaneous squamous cell carcinoma of the head and neck; ageing; metastasis; recurrence; disease progression; elderly.

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Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy of the skin associated with metastatic disease, and the incidence is increasing (1–3). The most contributing risk factor for the development of cSCC is cumulative ultraviolet (UV) damage (4, 5). Therefore, cSCC is an increasing problem in the elderly population: the incidence of cSCC increases strongly with age worldwide (6, 7). The majority (80–90%) of cSCCs is located in the head and neck region (cSCCHN) (8, 9). In most cases, the prognosis is excellent after excision of the primary tumour. However,

SIGNIFICANCE

Although the age of the patient is not taken into account in guidelines for cutaneous squamous cell carcinoma of the head and neck, the diagnosis and treatment of elderly patients can be challenging. Elderly patients often present with large tumours and, due to comorbidities or frailty, do not tolerate all treatment options. This study observed that characteristics of cutaneous squamous cell carcinoma of the head and neck might be age-specific and could influence treatment outcome. Therefore, the implementation of age in the guidelines for cutaneous squamous cell carcinoma of the head and neck could help treating physicians to identify patients with high-risk tumours and provide a more personalized treatment to prevent over- or under-treatment.

in patients with metastatic disease the long-term prognosis is poor (3, 10–13).

Guidelines for cSCC mention several prognostic factors for poor outcome, based on literature (8, 9). Based on these prognostic factors, cSCCs are divided into low-risk and high-risk tumours, which translates to a higher intensity of treatment and follow-up for patients with a high-risk cSCC. Age of the patient at diagnosis is not taken into account in these guidelines, instead they assume equal tumour properties in younger and elderly patients. Treatment choice and prognosis are not only determined by treatment guidelines and tumour characteristics, but also by patient factors (14). Since older patients often have comorbidities and are often frail, repeated or extensive surgical treatment should be considered carefully in these patients (14–16). This raises the question of whether existing treatment guidelines, based on tumour characteristics but lacking patients' characteristics, are equally applicable in both younger and older patients. Little is known about differences in prognostic tumour characteristics between younger and elderly patients.

This large retrospective study aimed to evaluate age-specific tumour characteristics in patients with cSCCHNs. A further aim was to identify age-specific prognostic factors for progression of disease. This could help treating physicians to adjust treatment and follow-up of cSCCHNs to the age of patients.

Table I. Patient and tumour characteristics divided into age groups

	Total group (n = 672)	Patients < 75 years (n = 316)	Patients ≥ 75 years (n = 356)	p-value*
Age, years, median (range)	75 (25–105)	66 (25–74)	82 (75–105)	<0.001
Sex, n (%)				0.959
Men	443 (65.9)	208 (65.8)	235 (66.0)	
Women	229 (34.1)	108 (34.2)	121 (34.0)	
Comorbidities ^a , n (%)				<0.001
None	157 (23.4)	108 (34.2)	49 (13.8)	
Mild	214 (31.8)	102 (32.3)	112 (31.5)	
Moderate	202 (30.1)	61 (19.3)	141 (39.6)	
Severe	91 (13.5)	44 (13.9)	47 (13.2)	
Unknown	8 (1.2)	1 (0.3)	7 (2.0)	
Immunosuppression, n (%)	63 (9.4)	34 (10.8)	29 (8.1)	0.256
ECOG performance score, n (%)				<0.001
0–1	466 (69.4)	259 (82)	207 (58.1)	
2–4	64 (9.5)	7 (2.2)	57 (16.0)	
Unknown	142 (21.1)	50 (15.8)	92 (25.8)	
Number of cSCCs, median (range), mean	1 (1–16), 1.27	1 (1–16), 1.30	1 (1–6), 1.24	0.118
Tumour location, n (%)				
Forehead	59 (8.8)	24 (7.6)	35 (9.8)	0.307
Temples	71 (10.6)	25 (7.9)	46 (12.9)	0.035
Periocular	30 (4.5)	16 (5.1)	14 (3.9)	0.479
Cheek	100 (14.9)	43 (13.6)	57 (16.0)	0.382
Nose bridge/tip	58 (8.6)	38 (12.0)	20 (5.6)	0.003
Nostril	19 (2.8)	16 (5.1)	3 (0.8)	0.001
Cutaneous upper lip	2 (0.3)	0	2 (0.6)	0.501
Vermillion	83 (12.4)	54 (17.1)	29 (8.1)	<0.001
Cutaneous lower lip and chin	3 (0.4)	2 (0.6)	1 (0.3)	0.603
Neck	18 (2.7)	10 (3.2)	8 (2.2)	0.462
Ear	133 (19.8)	49 (15.5)	84 (23.6)	0.009
Scalp	83 (12.4)	29 (9.2)	54 (15.2)	0.018
Vestibulum nasi	7 (1.0)	6 (1.9)	1 (0.3)	0.056
Ear canal	6 (0.9)	4 (1.3)	2 (0.6)	0.428
Tumour diameter, mm, n (%)				<0.001
< 20	517 (76.9)	270 (85.4)	247 (69.4)	
20–39	117 (17.4)	33 (10.4)	84 (23.6)	
≥ 40	34 (5.1)	12 (3.8)	22 (6.2)	
Unknown	4 (0.6)	1 (0.3)	3 (0.8)	
Tumour differentiation, n (%)				0.063
Well	288 (42.9)	150 (47.5)	138 (38.8)	0.025
Moderate	329 (49.0)	145 (45.9)	184 (51.7)	0.124
Poor	54 (8.0)	21 (6.6)	33 (9.3)	0.208
Unknown	1 (0.1)	0	1 (0.3)	–
Invasion depth, mm, n (%)				0.017
< 2	284 (42.3)	151 (47.8)	133 (37.4)	
2–6	313 (46.6)	130 (41.1)	183 (51.4)	
> 6	70 (10.4)	32 (10.1)	38 (10.7)	
Unknown	5 (0.7)	3 (0.9)	2 (0.6)	
Perineural invasion, n (%)	60 (8.9)	26 (8.2)	34 (9.6)	0.548
Vascular invasion, n (%)	15 (2.2)	6 (1.9)	9 (2.5)	0.581
Extradermal invasion, n (%)				
Invasion in muscle	27 (4.0)	15 (4.7)	12 (3.4)	0.365
Invasion in cartilage	19 (2.8)	6 (1.9)	13 (3.7)	0.171
Invasion in bone	3 (0.4)	3 (0.9)	0	0.103
Invasion in parotid	1 (0.1)	0	1 (0.3)	>0.999
Unknown	8 (1.2)	2 (0.6)	6 (1.7)	0.293
T-stage (AJCC 8), n (%)				
T1	457 (68.0)	239 (75.6)	218 (61.2)	<0.001
T2	75 (11.2)	21 (6.6)	54 (15.2)	<0.001
T3	133 (19.8)	52 (16.5)	81 (22.8)	0.041
T4a	3 (0.4)	3 (0.9)	0	0.103
Unknown	4 (0.6)	1 (0.3)	3 (0.8)	0.627
Treatment modality, n (%)				
Surgical monotherapy	525 (78.1)	253 (80.1)	272 (76.4)	0.252
Radiation monotherapy	61 (9.1)	24 (7.6)	37 (10.4)	0.208
Surgery and radiotherapy	73 (10.9)	35 (11.1)	38 (10.7)	0.867
None/palliative/other/unknown	13 (1.9)	4 (1.3)	9 (2.5)	0.236
Surgical margin, mm, n (%)				0.597
< 2	262 (39.0)	116 (36.7)	146 (41.0)	
2–5	183 (27.2)	77 (24.4)	106 (29.8)	
> 5	82 (12.2)	40 (12.7)	42 (11.8)	
Not treated surgically/no tumour found after biopsy/unknown	145 (21.6)	83 (26.3)	62 (17.4)	
Local recurrence, n (%)	53 (7.9)	23 (7.3)	30 (8.4)	0.581
Lymph node metastasis, n (%)	44 (6.5)	11 (3.5)	33 (9.3)	0.002
Distant metastasis, n (%)	6 (0.9)	0	6 (1.7)	0.032
Progression of disease, n (%) ^b	83 (12.4)	30 (9.5)	53 (14.9)	0.034

^aT4a (n = 2) and T4b (n = 1) were analysed as 1 category. ^bProgression of disease comprises local recurrence, nodal metastasis and distant metastasis.

*p-value of χ^2 test (or Fisher's exact test in the case of an expected count less than 5 in 20% of the cells or more) between age < 75 and age ≥ 75 years. Age at diagnosis and number of cSCCHNs per patient did not have a normal distribution and were compared with a Mann-Whitney U test.

The category "unknown" was not included in the analyses, except for the variables Eastern Cooperative Oncology Group performance score, extradermal invasion, American Joint Committee on Cancer 8th edition (AJCC 8) tumour stage and treatment modality.

Perineural invasion was ≥ 0.1 mm in calibre in all cases.

cSCC: cutaneous squamous cell carcinoma; NS: not significant. Significant p-values are shown in bold.

MATERIALS AND METHODS

This retrospective study included patients with histologically proven primary cSCCHN, diagnosed or treated in the University Medical Center Groningen (UMCG), a tertiary care academic hospital in the Netherlands, from 1 January 2000 until 1 January 2014. Patients with a history of organ transplant or chronic lymphatic leukaemia (CLL) were excluded from analysis, in order to prevent overestimation of number and aggressiveness of tumours. Poor outcome was defined as progression of disease (POD), comprising local recurrence, nodal metastases and distant metastases. Patients with POD within 1 month or death within 1 month were not included for analysis, in order to prevent residual disease being interpreted as disease progression. Patients were divided into 2 age groups; patients < 75 and patients ≥ 75 years of age, based on the median age in our cohort and the classification of "middle-old" by the National Institute on Aging (17).

Patient, tumour and treatment characteristics were extracted from the medical records. Patient-related data included sex, age at the time of histological diagnosis, comorbidities indexed by the Adult Comorbidity Evaluation-27 (ACE-27), performance score indexed by the Eastern Cooperative Oncology Group (ECOG) and presence of immunocompromise. Histopathological characteristics were derived from pathology reports, and included tumour differentiation, invasion depth, presence of perineural or vascular invasion and histopathological excision margins. Re-assessment of the histopathology was performed by a dermatopathologist (GD) if data were missing. Tumours were restaged according to the 8th edition of the American Joint Committee on Cancer Staging Manual (AJCC8) (18). The number of cSCCs was defined as the total number of primary cSCCs including the current one. Follow-up time was defined as the time between diagnosis and last follow-up visit or death.

Statistical analyses were performed using SPSS (v.22.0; SPSS Inc., Chicago, IL, USA) and STATA (v. 14.2; StataCorp). Patient and tumour characteristics were summarized using descriptive statistics and compared using a χ^2 or Fisher's exact test. Correlation analyses were performed using Pearson correlation for continuous variables and Spearman correlation for categorical variables. Due to our elderly population, competing risk analyses were performed to account for the risk of dying before developing poor outcome, and visualized with cumulative incidence function (CIF) curves for POD per age group. Univariable and multivariable competing risk analyses were performed to compare prognostic factors for POD between the 2 age groups. Death was defined as a competing event. Due to small numbers, the category "unknown" in categorical variables was not selected for analysis. In the AJCC8 variable, stages T4a and T4b were analysed as 1 group. The proportional hazard assumption was assessed by adding a time-varying covariate to check whether each variable interacted with time. The Wald test was used to test the significance of categorical variables in the case of heterogeneity in significance of covariates. Only significant variables were included in the multivariable model. All analyses were performed at the level of the patient; in the case of multiple tumours per patient the tumour with the highest stage was selected, in the case of equal stages the tumour that developed first within the inclusion period was selected. *p*-values < 0.05 were considered statistically significant.

RESULTS

A total of 770 patients with 1,116 cSCCHNs could be identified. Exclusion of patients

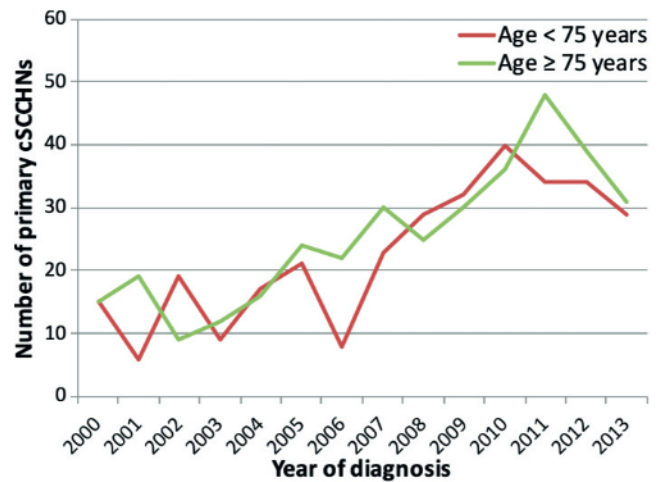


Fig. 1. Number of primary cutaneous squamous cell carcinoma of the head and neck (cSCCHN) per year, by age group.

with a history of organ transplant ($n = 65$), CLL ($n = 17$) and progression of disease or death within 1 month after tumour diagnosis ($n = 16$) left a total of 672 patients with 845 tumours to be analysed. Patient and tumour characteristics for the total patient group and the age groups below 75 years old and 75 years or older are shown in Table I. The median age of the patients was 75 years (range 25–105 years), and 65.9% of patients were men. Most tumours were staged as T1 (68.0%) and the most frequent treatment was surgery as monotherapy (78.1%). The number of patients with cSCCHN increased over the years for both younger and elderly patients, with an

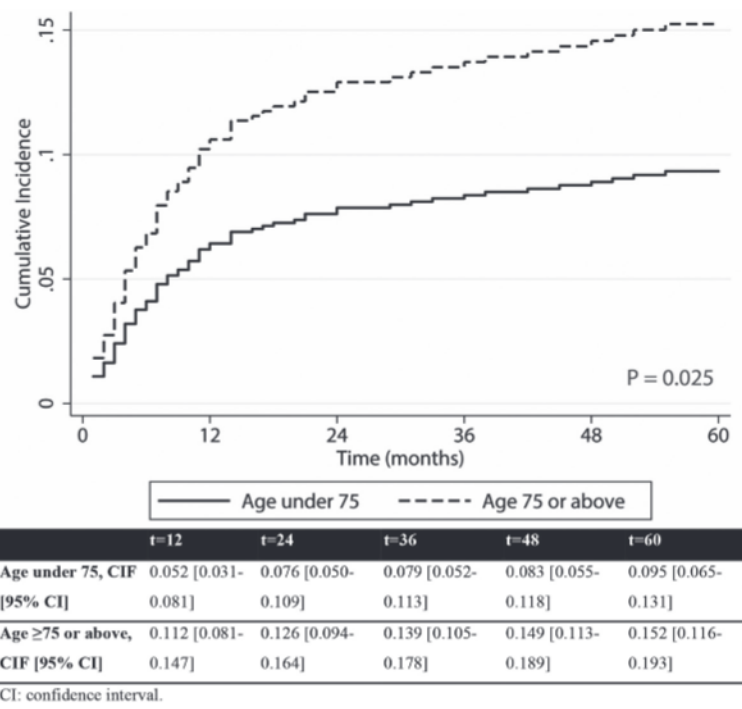


Fig. 2. Cumulative incidence function (CIF) curves of progression of disease (POD), comprising local recurrence, nodal metastasis and distant metastasis within 60 months per age group with death as competing risk.

	t=12	t=24	t=36	t=48	t=60
Age under 75, CIF	0.052 [0.031-	0.076 [0.050-	0.079 [0.052-	0.083 [0.055-	0.095 [0.065-
[95% CI]	0.081]	0.109]	0.113]	0.118]	0.131]
Age ≥75 or above, CIF	0.112 [0.081-	0.126 [0.094-	0.139 [0.105-	0.149 [0.113-	0.152 [0.116-
[95% CI]	0.147]	0.164]	0.178]	0.189]	0.193]

CI: confidence interval.

increase from 2000 to 2013 of 200% in the total group, 193% in the younger group, and 207% in the elderly group (Fig. 1). Elderly patients had tumours with more high-risk characteristics, such as larger tumour diameter ($p < 0.001$), worse differentiation grade ($p = 0.011$) and deeper tumour invasion ($p = 0.034$), compared with younger patients. Furthermore, tumour location was different between the 2 age groups ($p < 0.001$) with more tumours on the scalp ($p < 0.001$) and ear ($p = 0.018$) in the elderly patients, and more tumours on the nose ($p < 0.001$) in the younger patients. Lymph node metastasis ($p = 0.020$) and POD ($p = 0.038$) were observed more frequently in the elderly patients.

A correlation was found between age and tumour diameter ($p < 0.001$), age and differentiation grade ($p = 0.047$) and between comorbidity and performance score ($p < 0.001$). No correlation was found between age and invasion depth, age and localization of the tumour, age and perineural invasion, and age and surgical margin.

Competing risk analysis for POD showed a total of 80 patients with the event POD and 201 patients with

the competing event death at 60 months. Three patients developed POD after 60 months. Fig. 2 shows the CIF curves for POD with death as competing event for both age groups, including 95% confidence intervals (95% CI) per time-point. Patients aged 75 years or above showed a higher incidence of POD within 60 months compared with the younger group ($p = 0.025$). Results of the univariable and multivariable competing risk analyses for the total patient group are shown in Table II. Independent risk factors for POD within 60 months for the total patient group were moderate or poor differentiation grade, invasion depth of 2 mm or more, and a closer surgical margin. Age was not found to be an independent risk factor for POD.

Univariable and multivariable competing risk analyses were also performed for the 2 age groups separately (Tables III and IV). An independent risk factor for POD for both age groups was poor differentiation grade. A closer surgical margin was an independent risk factor in the younger group, but not in patients older than 75 years. In elderly patients, but not in younger patients, tumour diameter ≥ 40 mm, moderate differentiation grade and an invasion depth of ≥ 2 mm were independent prognostic factors for POD.

Table II. Univariable and multivariable competing risk analysis for POD within 60 months with death as a competing event in the total patient group ($n = 672$)

Characteristics	Univariable model		Multivariable model	
	SHR [95% CI]	<i>p</i> -value	SHR (95% CI)	<i>p</i> -value
Age				
< 75 years	1 (reference)		1 (reference)	
≥ 75 years	1.69 [1.07–2.67]	0.025	1.58 [0.86–2.88]	0.139
Sex				
Men	1 (reference)			
Women	0.64 [0.38–1.06]	0.080		
Immunosuppression				
Yes	0.61 [0.25–1.50]	0.286		
No	1 (reference)			
Comorbidities ^a				
None	1 (reference)			
Mild	0.85 [0.45–1.62]	0.620		
Moderate	1.16 [0.63–2.13]	0.624		
Severe	1.53 [0.77–3.07]	0.228		
Tumour diameter				
< 20 mm	1 (reference)		1 (reference)	
20–39 mm	3.14 [1.93–5.10]	< 0.001	1.13 [0.54–2.35]	0.751
≥ 40 mm	3.76 [1.82–7.76]	< 0.001	2.19 [0.92–5.24]	0.078
Tumour differentiation				
Well	1 (reference)		1 (reference)	
Moderate	1.99 [1.17–3.37]	0.011	2.89 [1.41–5.96]	0.004
Poor	5.42 [2.86–10.25]	< 0.001	6.01 [2.56–14.10]	< 0.001
Invasion depth				
< 2 mm	1 (reference)		1 (reference)	
2–6 mm	4.11 [2.14–7.91]	< 0.001	2.91 [1.26–6.74]	0.012
> 6 mm	9.15 [4.43–18.93]	< 0.001	5.49 [1.97–15.31]	0.001
Perineural invasion				
Yes	3.91 [2.36–6.48]	< 0.001	1.47 [0.72–3.02]	0.291
No	1 (reference)		1 (reference)	
Vascular invasion				
Yes	2.52 [0.89–7.10]	0.081		
No	1 (reference)			
Surgical margin				
< 2 mm	1 (reference)		1 (reference)	
≥ 2 mm	0.26 [0.15–0.47]	< 0.001	0.51 [0.28–0.93]	0.027

^aComorbidities were indexed by the Adult Comorbidity Evaluation-27 (ACE-27). *p*-value calculated by Wald test. 95% CI: 95% confidence interval; POD: progression of disease, comprising local recurrence, nodal metastasis and distant metastasis; SHR: subhazard ratio. Significant *p*-values are shown in bold.

Table III. Univariable and multivariable competing risk analysis for POD within 60 months in the patient group aged < 75 years ($n = 316$)

Characteristics	Univariable model		Multivariable model	
	SHR [95% CI]	<i>p</i> -value	SHR [95% CI]	<i>p</i> -value
Sex				
Men	1 (reference)			
Women	0.51 [0.21–1.24]	0.138		
Immunosuppression				
Yes	0.28 [0.04–2.07]	0.214		
No	1 (reference)			
Comorbidities ^a				
None	1 (reference)			
Mild	1.05 [0.42–2.63]	0.923		
Moderate	0.75 [0.23–2.42]	0.629		
Severe	1.29 [0.43–3.84]	0.647		
Tumour diameter		0.030^b		
< 20 mm	1 (reference)		1 (reference)	
20–39 mm	3.28 [1.29–8.29]	0.012	0.91 [0.19–4.44]	0.906
≥ 40 mm	2.42 [0.56–10.37]	0.235	1.25 [0.18–8.84]	0.822
Tumour differentiation		0.003^b		
Well	1 (reference)		1 (reference)	
Moderate	1.28 [0.56–2.94]	0.563	2.27 [0.63–8.11]	0.209
Poor	5.39 [1.95–14.90]	0.001	6.71 [1.28–35.21]	0.024
Invasion depth				
< 2 mm	1 (reference)		1 (reference)	
2–6 mm	5.27 [1.77–15.68]	0.003	1.79 [0.44–7.33]	0.416
> 6 mm	7.90 [2.23–28.02]	0.001	1.75 [0.24–13.03]	0.583
Perineural invasion				
Yes	5.58 [2.35–12.34]	< 0.001	1.90 [0.39–9.15]	0.426
No	1 (reference)		1 (reference)	
Vascular invasion				
Yes	4.44 [1.03–19.06]	0.045	2.18 [0.37–12.72]	0.386
No	1 (reference)			
Surgical margin				
< 2 mm	1 (reference)		1 (reference)	
≥ 2 mm	0.07 [0.02–0.30]	< 0.001	0.11 [0.02–0.50]	0.004

^aComorbidities were indexed by the Adult Comorbidity Evaluation-27 (ACE-27). ^b*p*-value calculated by Wald test. 95% CI: 95% confidence interval; POD: progression of disease, comprising local recurrence, nodal metastasis and distant metastasis; SHR: subhazard ratio. Significant *p*-values are shown in bold.

Table IV. Univariable and multivariable competing risk analysis for POD within 60 months in the patient group aged ≥ 75 (n=356)

Characteristics	Univariable model		Multivariable model	
	SHR [95% CI]	p-value	SHR [95% CI]	p-value
Sex				
Men	1 (reference)			
Women	0.72 [0.39–1.33]	0.296		
Immunosuppression				
Yes	0.93 [0.34–2.51]	0.884		
No	1 (reference)			
Comorbidities ^a				
None	1 (reference)			
Mild	0.58 [0.24–1.43]	0.239		
Moderate	0.93 [0.42–2.06]	0.867		
Severe	1.38 [0.55–3.46]	0.498		
Tumour diameter				
< 20 mm	1 (reference)		1 (reference)	
20–39 mm	2.77 [1.54–4.99]	0.001	1.16 [0.51–2.65]	0.721
≥ 40 mm	4.17 [1.79–9.72]	0.001	2.90 [1.08–7.76]	0.034
Tumour differentiation				
Well	1 (reference)		1 (reference)	
Moderate	2.50 [1.23–5.11]	0.012	3.38 [1.34–8.57]	0.010
Poor	5.28 [2.28–12.21]	< 0.001	6.72 [2.39–18.92]	< 0.001
Invasion depth				
< 2 mm	1 (reference)		1 (reference)	
2–6 mm	3.31 [1.46–7.49]	0.004	3.22 [1.11–9.35]	0.032
> 6 mm	9.25 [3.82–22.43]	< 0.001	7.39 [2.16–25.25]	0.001
Perineural invasion				
Yes	3.13 [1.66–5.91]	< 0.001	1.31 [0.60–2.85]	0.501
No	1 (reference)		1 (reference)	
Vascular invasion				
Yes	1.65 [0.38–7.18]	0.504		
No	1 (reference)			
Surgical margin				
< 2 mm	1 (reference)		1 (reference)	
≥ 2 mm	0.44 [0.23–0.85]	0.014	0.79 [0.41–1.52]	0.472

^aComorbidities were indexed by the Adult Comorbidity Evaluation-27 (ACE-27). 95% CI: 95% confidence interval; POD: progression of disease, comprising local recurrence, nodal metastasis and distant metastasis; SHR: subhazard ratio. Significant p-values are shown in bold.

DISCUSSION

This large retrospective study observed more high-risk tumour characteristics in elderly patients. Furthermore, POD was observed more often in the elderly group, but the multivariable competing risk analysis showed that higher age itself was not an independent risk factor for POD. When analysing both age groups separately, poor differentiation grade was an independent risk factor in both groups, while a closer surgical margin was only statistically significant in patients under 75 years old, and moderate differentiation grade, tumour diameter ≥ 40 mm and invasion depth ≥ 2 mm were risk factors for patients 75 years old or older.

Studies comparing tumour characteristics of different age groups are limited. The results of the current study confirm an increase in the number of patients with cSCCHN over time and with age (19). Larger tumours were observed in elderly patients, in line with earlier studies (15, 20). The observed age-specific difference in tumour localization, with tumours in elderly patients arising more often on the temples, ears and scalp, and tumours in younger patients arising more often on the nose and vermillion, has not been found previously (20). A closer

surgical margin was more common in the elderly group, as reported previously (21).

The current results show differences in tumour characteristics and oncological progression in elderly patients compared with their younger counterparts. This difference could be explained by a diagnostic delay leading to more advanced tumours, or it could indicate a difference in pathogenesis, which deserves further tumour biological and clinical research. The observed difference in tumour diameter, differentiation grade, invasion depth, and metastasis, to the disadvantage of the elderly patients, might indicate that cSCCHNs in elderly patients have a different tumour biology for oncological progression compared with younger patients. Since cSCC development and progression is more common in immunosuppressed patients, immunological senescence could play a role, leading to more aggressive tumours in elderly patients (22, 23). The role of the ageing immune microenvironment in cSCC has not been studied, but is described for other tumour types. Age-related cellular changes in the microenvironment may stimulate slow-growing tumour cells to transform into aggressive and metastatic disease. In younger patients fibroblasts are providing a growth-restrictive environment for malignant cells through secretion of cytokines, growth factors and other proteins. Effector immune cells are cytotoxic towards malignant cells in healthy tissue. With age, the renewal rate of healthy fibroblast decreases, and immunosenescence leads to a decreased immune cell function. This might enable malignant cells to grow and multiply (24). A study in elderly patients with colorectal cancer shows that a high percentage of senescent cytotoxic T cells negatively impacts disease outcome (25). In patients with breast cancer, age-related differences in tumour immune response were described, with decreased lymphocytic infiltration in the older group (26). Another possible explanation for more frequent tumour progression in elderly patients related to tumour biology could be the metabolic alterations that occur with age and decreasing telomere length (27–31). The observed larger tumour diameter, deeper invasion and more frequent tumour progression in elderly patients might also be a result of patient or physician delay. Treatment delay is described in the literature to lead to larger cSCCs (32, 33). Moreover, elderly patients were found to be more likely to wait to seek care compared with younger patients (34).

Multiple studies assessed age as a possible risk factor for POD; however, none of these studies performed a competing risk analysis to take into account the higher age of cSCC patients. A retrospective study in 6,164 patients with 8,997 cSCCs (median age 74, range 21–108 years) found that age was not an independent risk factor for metastasis (35). Another retrospective study in 43 patients (mean age 74.7, standard deviation 10.2 years) with advanced cSCCHN (AJCC 8 T3/T4) found that age

did not affect observed survival or recurrence rate (36). Kounoike et al. (21) did not find a significant difference in rates of recurrence and nodal metastasis between younger (<85 years) and elderly patients (≥85 years). A systematic review and meta-analysis with 21 included articles found age to be a significant risk factor for overall survival, but not for locoregional control (37). Summarizing, in the literature age itself is found not to be an independent risk factor for POD in patients with cSCC.

Using a competing risk analysis to account for the risk of dying in an ageing population, we showed that age was not an independent risk factor for POD. However, POD was significantly more common in the elderly patient group with the competing risk of death taken into account. Furthermore, independent risk factors are identified for the separate age groups, although these findings should be confirmed by larger studies. Interestingly, a larger tumour size did not seem to be prognostic for disease progression in younger patients. A possible explanation could be the small sample size of only 12 patients in the younger group with a tumour diameter ≥4 cm. Furthermore, most elderly patients with large tumours were treated with surgical monotherapy, while the younger patients with large tumours were mostly treated with surgery and postoperative radiotherapy. This could be related to patient compliance: patients with endometrial cancer or breast cancer declining postoperative radiotherapy were more likely to be older (38, 39).

In daily clinical practice, knowledge about age-dependent tumour biology could lead to a more personalized treatment or follow-up schedule. A possible adaptation could be a more intensive follow-up schedule in elderly patients with independent risk factors for POD, regardless of tumour stage. Elderly patients have a higher chance to develop postoperative complications (40), larger defects after surgery and more wound-healing disorders (15). Our analyses showed surgical margin not to be an independent risk factor for POD in elderly patients. If this result is confirmed by future studies, then a wait-and-see policy after close surgical margins with more intensive follow-up instead of re-excision might be justifiable for elderly patients; however, randomized controlled trials are needed to give such recommendations. In contrast, frail elderly patients might encounter difficulties with an intensive follow-up schedule, due to mobility problems. In these cases a re-excision might be preferable to avoid frequent hospital visits. Should diagnostic delay be the main reason for the differences in tumour characteristics between younger and elderly patients, raising consciousness on skin cancer recognition amongst the elderly patients, as well as amongst (para)medics treating elderly patients might be important to improve disease outcomes.

A limitation of this study is the monocentre setup in a tertiary centre, which might lead to a selection of patients with more complex tumours. Furthermore, due

to its retrospective nature, diagnostic delay could not be assessed in this study. The major strengths of this study are that all missing histopathological data were reassessed by a dermatopathologist, and the use of competing risk analyses, which is a novelty in this research area.

In conclusion, tumour characteristics in elderly and younger patients with cSCCHN differ, with more high-risk characteristics in elderly patients. POD is significantly more common in elderly patients, and different independent risk factors are identified for younger and elderly patients. This suggests that a more personalized treatment and follow-up with attention to the age of the patient can be beneficial. Patients might rather benefit from management based on the age-specific risk factors for progression and performance score, than treatment based purely on tumour stage. Further research is necessary to confirm these results and give clear recommendations on age-specific tailored treatment and follow-up in patients with cSCCHN.

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