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Influence of Frailty and Life Expectancy on Guideline Adherence and Outcomes in Cutaneous Squamous Cell Carcinoma of the Head and Neck: A Prospective Pilot Study

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Keywords
Cutaneous squamous cell carcinoma · Frailty · Guideline adherence · Life expectancy · Quality of life

Abstract
Background: Cutaneous squamous cell carcinoma is the second most common malignancy of the skin, often occurring in older patients and in the head and neck area (cSCCHN). Age, life expectancy, and frailty are not taken into consideration by current guidelines. ***Objectives:*** The objective of this study was to evaluate the influence of frailty and life expectancy on guideline deviation, treatment outcomes, and quality of life (QoL) after treatment in patients with cSCCHN. ***Methods:*** Patients with cSCCHN were prospectively included. A geriatric assessment was performed, including the Geriatric 8 (G8), Groningen Frailty Indicator, and Timed Up and Go test (TUG). The Lee index was used to predict a limited life expectancy, and the Adult Comorbidity Evaluation-27 was used as a comorbidity index. QoL was assessed by the Basal and Squamous cell carcinoma Quality of Life (BaSQoL) questionnaire at three time points. ***Results:*** Seventy-seven patients with cSCCHN were included. Frail patients had significantly more high-risk tumours. Guideline deviation occurred in 7.8% and was more common in patients who were frail (G8), with high-risk tumours (≥T2), with a limited life expectancy or an increased TUG. Guideline deviation did not lead more often to progression of disease in our study. No predictors for post-operative complications were found. BaSQoL subscores were very low at each time point and did not change significantly with time in the total group. Frail patients reported more fear of recurrence or new tumours 3 months after treatment, and less concern about other people's skin 6 months after treatment, compared to non-frail patients. Complication rate, gender, or guideline deviation did not affect any subscale scores. ***Conclusions:*** Assessment of frailty and life expectancy can guide physicians and patients in treatment decisions. Deviation from guidelines towards less aggressive treatment schedules can be consid-

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ered in frail patients with a limited life expectancy, since it did not negatively affect short-term outcomes or QoL in patients with cSCCHN in our study. However, these results should be confirmed by other, larger prospective studies with a longer follow-up period.

Introduction

As cumulative ultraviolet damage to the skin is a main driving factor of cutaneous squamous cell carcinoma (cSCC) development, it is an increasing problem in the elderly population, where the majority of tumours occur in the head and neck area (cSCCHN) [1–3]. Although the overall prognosis after surgical excision is good, patients with advanced cSCC have a poor long-term prognosis [4–6].

In current treatment guidelines, cSCCs are divided into low-risk and high-risk cSCC based on prognostic factors for progression of disease (POD), with the recommendation to treat and follow patients with a high-risk cSCC more extensively [2, 7, 8]. Age, life expectancy, and frailty are currently not considered but are desired to be integrated into clinical practice guidelines [9]. Frail and older patients may be more likely to develop complications after skin cancer surgery compared to younger patients and may not live long enough to benefit from (over) treatment [10–12]. Therefore, it is important to weigh the risks and benefits from under- and over-treatment, which can lead to deviation from the guidelines in individual cases.

Frailty is a predictor of morbidity and mortality in older patients [13]. There are several tools to assess frailty. A comprehensive geriatric assessment (CGA) is the current gold standard for detecting frailty in older patients [14]. However, shorter frailty screening instruments, such as the Geriatric 8 (G8) and Groningen Frailty Indicator (GFI) are also available [12, 15–17].

Since the majority of cSCCs are located in the often visible head and neck region, surgical treatment of cSCCHN can have impact on the patients' appearance and quality of life (QoL) [18]. Little is known about the influence of cSCC treatment on QoL, which has not yet been evaluated in older patients specifically (aged ≥75 years) [19–21]. The aim of this prospective study in patients with cSCCHN was to evaluate the influence of frailty and life expectancy on guideline deviation, clinical outcome (i.e., complications, POD, and death), and QoL after treatment.

Patients and Methods

Consecutive patients with primary cSCCHN treated in the University Medical Center Groningen (UMCG) between April 2018 and April 2019 who were willing to participate in the study were prospectively included. Diagnostic and treatment policy conformed to current clinical practice and was not influenced by the study. Patient, tumour, and treatment characteristics were extracted from hospital records. The occurrence of complications was also extracted from hospital records, which are consistently registered at our hospital. Geographical distance to treatment was defined as the total amount of kilometres between the house address and the hospital and was included because of the possible influence on patient delay.

Poor outcome was defined as POD, comprising local recurrence, nodal metastases, distant metastases, and death-of-disease. To assess physical fitness and frailty, patients filled in questionnaires and underwent tests on the day of treatment, 3 and 6 months after primary treatment. All questionnaires were administered by the same researcher (A.L.). Questionnaires and tests comprised the G8, Groningen Frailty Indicator (GFI), and Timed Up and Go test (TUG). QoL was assessed by the Basal and Squamous cell carcinoma Quality of Life (BaSQoL) questionnaire. All questionnaires are displayed in the online supplementary Material (for all online suppl. material, see www.karger.com/doi/10.1159/000525974).

Patients were divided into two age groups; patients aged <75 years and patients aged ≥75 years, based on the classification of "middle-old" by the National Institute on Aging [21]. Patients were indexed as frail according to the G8 in case the total score was ≤14 and were indexed as frail according to the GFI in case the total score was ≥4 [17]. Patients were indexed as having limited functional mobility by the TUG when the mean time of 3 consecutive tests exceeded 13.5 s [22, 23].

The Lee index, a prognostic index for risk of mortality, was used as a predictor of life expectancy. A score of ≥13 was considered as limited life expectancy [24]. The Adult Comorbidity Evaluation-27 (ACE-27) was used as a comorbidity index with scores of 0 = no comorbidities, 1 = mild, 2 = moderate, and 3 = severe comorbidities. Information about comorbidities was extracted from the patient records.

The BaSQoL consists of 16 items and comprises 5 subscales: *Behavior* (displeasure about preventive measures), *Other People* (concerns about the skin of others), *Diagnosis and Treatment* (concerns about the skin cancer diagnosis and treatment), *Worries* (fear of recurrence or new tumours), and *Appearance* (concerns about attractiveness). Higher scores per subscale implicate a higher impact on health-related QoL [25].

Guideline deviation was defined as deviation from regular treatment as indicated by the Dutch treatment guideline for cSCC [2]. For example, it is recommended to treat patients with T1 tumours with a surgical margin of 5 mm and to treat ≥T2 tumours with a surgical margin of 10 mm. Additional treatment is recommended for patients with ≥T2 tumours with close (<2 mm) or positive margins, and radiation therapy should be considered in case of perineural invasion.

This study was reviewed and approved by the Institutional Review Board of the UMCG, approval number 2018/137. The Medical Ethical Committee of the UMCG confirmed that this study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). In 2018, when the study was registered, it

Table 1. Patient and tumour characteristics in the total group and categorized into frail and non-frail patients

	Total group (*N* = 77)	Frail G8 (*N* = 40)	Non-frail G8 (*N* = 37)	*p* value[a]
Median age (*N* = 77), years (IQR)	78 (70–85)	83 (71–87)	73 (70–79)	**0.003**[b]
Gender (*N* = 77), *n* (%)				
Men	55 (71.4)	27 (67.5)	28 (75.7)	0.43
Women	22 (28.6)	13 (32.5)	9 (24.3)	
Median follow-up, months (IQR)	24 (11–30)	21 (5–29)	27 (21–30)	**0.004**[b]
Comorbidities ACE-27				
0	9 (11.7)	0 (0)	9 (24.3)	
1	31 (40.3)	15 (37.5)	16 (43.2)	**0.003**
2	20 (26.0)	14 (35.0)	6 (16.2)	
3	17 (22.1)	11 (27.5)	6 (16.2)	
Lee index (*N* = 77), *n* (%)				
<13	72 (93.5)	35 (87.5)	37 (100)	0.055
≥13	5 (6.5)	5 (12.5)	0 (0.0)	
TUG (*N* = 77), *n* (%)				
<13.5 s	59 (76.6)	23 (57.5)	36 (97.3)	
≥13.5 s	12 (15.6)	11 (27.5)	1 (2.7)	**0.001**
Unknown	6 (7.8)	6 (15.0)	–	
Distance from the hospital, *n* (%)				
<50 km	60	30 (75)	30 (81.1)	0.52
≥50 km	17	10 (25)	7 (18.9)	
T-stage AJCC-8 (*N* = 77), *n* (%)				
T1	55 (71.4)	24 (60.0)	31 (83.8)	**0.021**
T2	12 (15.6)	7 (17.5)	5 (13.5)	0.63
T3	10 (13.0)	9 (22.5)	1 (2.7)	**0.015**
T4	–	–	–	–
Treatment (*N* = 77), *n* (%)				
Surgery	73 (94.8)	38 (95.0)	35 (94.6)	1.00
Surgery + radiation therapy	3 (3.9)	1 (2.5)	2 (5.4)	0.605
Curettage	1 (1.3)	1 (2.5)	0 (0)	1.00
Radiation monotherapy	–	–	–	–
None	–	–	–	–

ACE-27, Adult Comorbidity Evaluation-27; AJCC-8, American Joint Committee on Cancer 8th edition; G8, Geriatric 8; IQR, interquartile range; km, kilometre; T-stage, tumour stage; TUG, Timed Up and Go test. [a] 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). [b] Age and follow-up were not normally divided and therefore the median was compared with the Mann-Whitney U test.

was not necessary for participants to sign informed consent in the case of a non-WMO study in our centre. Therefore, our population did not sign a consent form but gave their oral consent.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. IBM Corp, Armonk, NY, USA. All analyses were performed per patient rather than per individual tumour. In patients with multiple tumours, the tumour with the highest tumour stage or with the most aggressive tumour characteristics was included in the analyses. χ^2 or Fisher's exact tests were used to compare patient and tumour characteristics between different subgroups. Median age at diagnosis and follow-up time were compared by the Mann-Whitney U test.

Differences in BaSQoL subscores between different time moments were compared using the Wilcoxon matched-pair signed-rank test. BaSQoL subscores of different subpopulations based on age, gender, complications, frailty, and guideline deviation were compared using the Mann-Whitney U test. Possible prognostic factors for higher subscores were assessed using negative binomial regression analysis with the negative binomial set at 1 [26]. Baseline subscores were included in the binomial regression models for the subscores at $t = 3$ and $t = 6$ to assess the effect of treatment on QoL. A p value of <0.05 was considered statistically significant for all analyses.

Results

Patient and Tumour Characteristics

A total of 77 patients with 82 cSCCHNs were included. Patient and tumour characteristics are shown in Table 1 for

Table 2. Associations among all predictors and outcomes

	Treatment according to guideline			Complications[a]			POD			Death		
	yes $N = 71$	no $N = 6$	p value[b]	yes $N = 16$	no $N = 57$	p value[b]	yes $N = 3$	no $N = 74$	p value[b]	yes $N = 15$	no $N = 62$	p value[b]
Age, years, *n* (%)												
<75	29 (40.8)	2 (33.3)	1.00	5 (31.3)	24 (42.1)	0.43	1 (33.3)	30 (40.5)	1.00	5 (33.3)	26 (41.9)	0.54
≥75	42 (59.2)	4 (66.7)		11 (68.7)	33 (57.9)		2 (66.7)	44 (59.5)		10 (66.7)	36 (58.1)	
Comorbidity ACE-27												
0–1	39 (54.9)	1 (16.7)	0.100	8 (50.0)	29 (50.9)	1.00	2 (66.7)	38 (51.4)	1.00	2 (13.3)	38 (61.3)	**0.001**
2–3	32 (45.1)	5 (83.3)		8 (50.0)	28 (49.1)		1 (33.3)	36 (48.6)		13 (86.7)	24 (38.7)	
Frailty G8, *n* (%)												
Yes	34 (47.9)	6 (100)	**0.026**	8 (50)	31 (54.4)	0.76	1 (33.3)	39 (52.7)	0.61	13 (86.7)	27 (43.5)	**0.003**
No	37 (52.1)	0 (0)		8 (50)	26 (45.6)		2 (66.7)	35 (47.3)		2 (13.3)	35 (56.5)	
Frailty GFI, *n* (%)												
Yes	20 (28.2)	2 (33.3)	1.00	2 (12.5)	20 (35.1)	0.12	0 (0)	22 (29.7)	0.55	8 (53.3)	14 (22.6)	**0.027**
No	51 (71.8)	4 (66.6)		14 (87.5)	37 (64.9)		3 (100)	52 (70.3)		7 (46.7)	48 (77.4)	
T-stage AJCC-8, *n* (%)												
T1	54 (76.1)	1 (16.7)	**0.006**	10 (62.5)	43 (75.4)	0.35	0 (0)	55 (74.3)	**0.021**	8 (53.3)	47 (75.8)	0.11
T2–T3	17 (23.9)	5 (83.3)		6 (37.5)	14 (24.6)		3 (100)	19 (25.7)		7 (46.7)	15 (24.2)	
Lee index, *n* (%)												
<13	68 (95.8)	4 (66.7)	**0.046**	14 (87.5)	54 (94.7)	0.30	3 (100)	69 (93.2)	1.00	11 (73.3)	61 (98.4)	**0.004**
≥13	3 (4.2)	2 (33.3)		2 (12.5)	3 (5.3)		0 (0)	5 (6.8)		4 (26.7)	1 (1.6)	
TUG,[a] *n* (%)												
<13.5 s	57 (80.3)	2 (33.3)	**0.031**	10 (62.5)	45 (79.0)	0.12	2 (66.7)	57 (77.0)	0.43	9 (60.0)	50 (80.7)	1.00
≥13.5 s	9 (12.7)	3 (50.0)		5 (31.3)	7 (12.3)		1 (33.3)	11 (14.9)		2 (13.3)	10 (16.1)	
Distance to hospital, *n* (%)												
<50 km	56 (78.9)	4 (66.7)	0.61	n/a	n/a	n/a	2 (66.7)	58 (78.4)	0.53	10 (66.7)	50 (80.6)	0.30
≥50 km	15 (21.1)	2 (33.3)					1 (33.3)	16 (21.6)		5 (33.3)	12 (19.4)	
Treatment according to guideline, *n* (%)												
Yes	n/a	n/a	n/a	13 (81.3)	55 (96.5)	0.067	2 (66.6)	69 (93.2)	0.22	10 (66.6)	61 (98.4)	**0.001**
No				3 (18.7)	2 (3.5)		1 (33.3)	5 (7.8)		5 (33.3)	1 (1.6)	

ACE-27, Adult Comorbidity Evaluation-27; AJCC-8, American Joint Committee on Cancer 8th edition; G8, Geriatric 8; GFI, Groningen Frailty Indicator; km, kilometre; n/a, not applicable; POD, progression of disease; T-stage, tumour stage; TUG, Timed Up and Go test. [a] "Unknown" was excluded from analyses due to low numbers. [b] χ^2 or Fisher's exact test in the case of an expected count less than 5 in 20% of the cells or more.

all patients and for the frail and non-frail subgroup separately, defined by the G8. At baseline, 40 patients (51.9%) were frail. The median age was 78 years (interquartile range [IQR] 70–85) for the total group and was significantly higher in frail patients (83 years, IQR 71–87) compared to non-frail patients (73 years, IQR 70–79, $p = 0.003$). Most patients were men ($n = 55$, 71.4%). Median follow-up time was 24 months (IQR 11–30), with a significantly shorter follow-up time in frail patients (21 months, IQR 5–29), compared to non-frail patients (27 months, IQR 21–30, $p = 0.004$). Comorbidity scores of 2 (moderate) and 3 (severe) according to the ACE-27 were more frequent in frail patients compared to non-frail patients ($n = 14$, 35.0% vs. $n = 6$, 16.2% and $n = 11$, 27.5% vs. $n = 6$, 16.2%, respectively, $p = 0.003$). Limited life expectancy, reflected by a Lee index ≥13, was only present in frail patients, but this difference was not significant. An increased TUG was significantly more common in frail patients ($n = 11$, 27.5% vs. $n = 1$, 2.7%, $p = 0.001$). Geographical distance to treatment did not differ between both groups.

Tumours were mostly located on visible sites such as the cheek ($n = 15$, 19.5%), scalp ($n = 14$, 18.2%), and ear ($n = 12$, 15.6%). Most tumours were classified as T1 according to the American Joint Committee on Cancer 8th edition classification system in the total group, which was significantly more common in non-frail patients ($n = 31$, 83.8% vs. $n = 24$, 60.0% in frail patients, $p = 0.021$). T3 tumours were significantly more common in frail patients ($n = 9$, 22.5% vs. $n = 1$, 2.7% in non-frail patients, $p = 0.015$). There were no T4 tumours in our cohort. Most patients were treated with surgical monotherapy in both groups (95%).

Deviation from the Guideline

Six patients (7.8%) were not treated according to current guidelines. Documented reasons for guideline deviation were mainly patients' preferences, comorbidities, and estimated limited life expectancy based on age and/or comorbidities ("eyeballing" of the physician), resulting in less aggressive treatments such as curettage and coagulation instead of surgical excision, acceptation of close or positive surgical margins without further treatment, and refraining from post-operative radiation of cSCC with perineural invasion. No patients were untreated in our study, and no patients underwent geriatric assessment before treatment decision. Guideline deviation was significantly more common in patients who were frail according to the G8 ($p = 0.026$), in patients with a limited life expectancy ($p = 0.046$), impaired mobility ($p = 0.031$), and in patients with T2 or T3 tumours ($p = 0.006$, Table 2).

Complications

Sixteen patients (20.8%) developed complications, of which wound infection was the most common ($n = 8$, 10.4%). Furthermore, full-thickness graft failure ($n = 5$, 6.5%), post-radiation ectropion ($n = 1$, 1.3%), delirium ($n = 1$, 1.3%), and post-operative bleeding ($n = 1$, 1.3%) were documented. Wound dehiscence occurred in 2 patients who also developed wound infection and full-thickness graft failure. No factors significantly influenced the development of complications (Table 2).

POD and Death

Three patients developed lymph node metastases, of which 1 patient also developed local recurrence and distant metastasis. No further local recurrences and distant metastases were reported.

Patients with tumour stage ≥T2 were significantly more likely to develop POD ($p = 0.021$). No other factors were associated with POD (Table 2).

During follow-up, 15 patients (19.5%) died. None of the patients died due to their cSCCHN in the study, so we had no cases of "death-of-disease." However, 2 patients died due to another cSCC, which developed after the inclusion period (tumours with more high-risk features and at a different location, closer to the metastasis, making these tumours more likely to be the culprit of metastasis than the included tumours). Frailty according to both the G8 and GFI was significantly associated with all-cause mortality ($p = 0.003$ and 0.027, respectively). Mortality was also significantly associated with moderate to severe comorbidities (ACE-27 score 2–3, $p = 0.001$), limited life expectancy ($p = 0.004$), and with guideline deviation ($p = 0.001$, Table 2).

Table 3. Mean and median subscores of the BaSQoL questionnaire per subscale at 3 time points in the total group and categorized into frail and non-frail patients

BaSQoL subscales	Baseline, mean ± SD/median (IQR)			3 months, mean ± SD/median (IQR)			6 months, mean ± SD/median (IQR)		
	total group ($N = 76$)	frail group ($N = 40$)	non-frail group ($N = 36$)	total group ($N = 68$)	frail group ($N = 32$)	non-frail group ($N = 36$)	total group ($N = 63$)	frail group ($N = 34$)	non-frail group ($N = 29$)
Behavior (range 0–3)	0.27±0.41/ 0.00 (0.31)	0.29±0.46/ 0.00 (0.25)	0.26±0.36/ 0.00 (0.50)	0.29±0.43/ 0.00 (0.75)	0.27±0.40/ 0.00 (0.38)	0.32±0.47/ 0.25 (0.75)	0.27±0.43/ 0.00 (050)	0.13±0.23/ 0.00 (0.50)	0.44±0.54/ 0.00 (0.25)
Other people (range 0–3)	0.45±0.54/ 0.50 (1.00)	0.38±0.56/ 0.00 (0.50)	0.54±0.51/ 0.00 (1.00)	0.35±0.47/ 0.00 (0.50)	0.30±0.49/ 0.00 (0.50)	0.40±0.46/ 0.50 (0.50)	0.48±0.53/ 0.50 (1.00)	**0.26±0.39/ 0.00 (0.50)**[a]	0.72±0.58/ 0.50 (1.00)
Diagnosis and treatment (range 0–3)	0.42±0.59/ 0.00 (0.67)	0.45±0.62/ 0.00 (0.83)	0.39±0.57/ 0.00 (0.67)	0.43±0.57/ 0.33 (0.67)	0.46±0.60/ 0.33 (1.00)	0.41±0.55/ 0.33 (0.67)	0.39±0.52/ 0.17 (0.67)	0.37±0.50/ 0.33 (0.67)	0.40±0.56/ 0.00 (0.67)
Worries (range 0–3)	0.28±0.40/ 0.00 (0.50)	0.31±0.45/ 0.00 (0.50)	0.24±0.32/ 0.00 (0.38)	0.19±0.34/ 0.00 (0.25)	**0.29±0.39/ 0.25 (0.50)**[a]	0.10±0.27/ 0.00 (0.00)	0.19±0.33/ 0.00 (0.25)	0.16±0.26/ 0.00 (0.50)	0.22±0.40/ 0.00 (0.25)
Appearance (range 0–3)	0.04±0.13/ 0.00 (0.00)	0.04±0.15/ 0.00 (0.00)	0.04±0.11/ 0.00 (0.00)	0.04±0.18/ 0.00 (0.00)	0.09±0.26/ 0.00 (0.00)	0.00±0.00/ 0.00 (0.00)	0.05±0.27/ 0.00 (0.00)	0.08±0.36/ 0.00 (0.00)	0.01±0.06/ 0.00 (0.00)

Frailty was assessed by the G8. BaSQoL, Basal and Squamous Cell Carcinoma Quality of Life; IQR, interquartile range. [a] p value <0.05 with Mann-Whitney U test compared to non-frail group.

Quality of Life

The mean and median subscores of the BaSQoL per subscale are described in Table 3 for all three time points for the total patient group and the frail patients according to the G8. Overall, we found that the tumour itself had little impact on QoL. This is reflected by low BaSQoL scores in all five subscales at the three time points (Table 3). BasQoL subscores did not change significantly between time points in the total group. Frail patients reported more fear of recurrence or new tumours when compared to non-frail patients 3 months after treatment (mean 0.29 [SD = 0.39] and median 0.25 [IQR = 0.50] in frail patients vs. mean 0.10 [SD = 0.27] and median 0.00 [IQR = 0.00] in non-frail patients, $p = 0.015$, Table 3). After 6 months of treatment, frail patients reported less concerns about the skin of others when compared to non-frail patients (mean 0.26 [SD = 0.39] and median 0.00 [IQR = 0.50] in frail patients vs. mean 0.72 [SD = 0.58] and median 0.50 [IQR = 1.00] in non-frail patients, $p = 0.014$).

The fear of recurrence or new tumours decreased in the older group 6 months after treatment (from a mean of 0.26 [SD = 0.38] and median of 0.00 [IQR = 0.50] at baseline to a mean of 0.13 [SD = 0.23] and median of 0.00 [IQR = 0.25] at $t = 6$, $p = 0.018$). Additionally, younger patients reported more displeasure about preventive measures at baseline (mean = 0.37 [SD = 0.46], median = 0.25 [IQR = 0.75]) compared to older patients (mean = 0.21 [SD = 0.37], median = 0.00 [IQR = 0.50], $p = 0.042$). This difference remained significant after 3 months. Additionally, younger patients reported more worries about diagnosis and treatment compared to older patients after 3 months (mean = 0.58 [SD = 0.62], median = 0.33 [IQR = 1.00] vs. mean = 0.34 [SD = 0.52], median = 0.00 [IQR = 0.67], $p = 0.033$, respectively).

Gender, guideline deviation, and the occurrence of complications after treatment did not affect subscale scores at any time points in our cohort. Negative binomial regression analysis showed no significant predictors for BaSQoL baseline subscores or change in BaSQoL subscores after treatment.

Discussion

In this prospective observational study in 77 patients with cSCCHN, guideline deviation was observed in 7.8% of the patients and was more common in patients who were frail (according to the G8), in patients with shorter life expectancy (predicted by the Lee index), impaired mobility (measured by TUG), and higher tumour stage (≥T2). Although 20% of the patients developed post-operative complication, no significant predictors for these events were found. Little effect of diagnosis and treatment of cSCCHN on QoL was observed in this mostly elderly group.

Frailty

Just over half of the patients in our study population were frail according to the G8 (51.9%). Frail patients with alternative treatments did not more often develop complications or POD compared to non-frail patients and patients treated according to current treatment guidelines in our study. Therefore, frailty screening could help to select patients who are eligible for adjusted treatment. The G8 seems most suitable for predicting frailty in patients with skin cancer [15] and was therefore most frequently used in our analyses. However, the G8 can select patients who may benefit from a CGA, but cannot replace CGA. On the other hand, the G8 is easier to implement since it is less time-consuming and has proven its value in multiple studies [12, 15–17].

The shorter follow-up time in frail patients can be explained by the higher risk of dying in frail patients, and the possible burden of visiting a hospital due to limited physical and cognitive reserve [27]. This burden could lead to a patient's and doctor's delay and may also explain why high-risk tumours were more common in frail patients compared to non-frail patients.

Guideline Deviation

As mentioned before, guideline deviation was more common in patients who were frail, with impaired mobility, with high-risk tumours, shorter life expectancy, and who died during follow-up. Documented reasons for guideline deviation in our study were mainly comorbidities, estimated limited life expectancy, and patients' preferences. The study of Lubeek et al. [28] also found high adherence to guidelines (88–90%) in patients with keratinocyte carcinoma (KC) and found no significant influence of age or comorbidities on adherence to guidelines, comparable to our study. They did not evaluate frailty status and both basal cell carcinoma (BCC) and cSCC were included.

Extensive treatment of KC can lead to complications and a reduced QoL in frail and older patients [10, 11]. In our study, the small group of patients with guideline deviation did not develop more complications or POD. This suggests that deviation from the guideline, selecting the most appropriate and patient-centred strategy, can some-

times be justified and can be necessary in the best interest of a patient. Shared decision-making with discussing the risks and benefits of (withdrawing from) extensive treatment is important (preventing over-treatment [29]), especially in patients with a limited life expectancy because they may not live long enough to benefit from extensive treatment.

No patients were untreated in our cohort, so we were unable to evaluate the effect of "watchful waiting" on clinical outcomes. In another study, significantly more patients did not receive any treatment above 85 years (13%) and in only 21% of cases, age or comorbidities were documented as reasons for not treating. However, that study included mostly BCC [30].

Outcomes

Complications

The frequency of complications after treatment of skin malignancies is variable in current literature (5.8–26%) [11, 31, 32]. In our study, 16 patients (20.8%) developed complications. No predictors for post-operative complications were found.

Age also had no significant influence on the development of post-operative complications in our study, which has been variably reported as a predictor for post-operative complications in the literature after skin cancer treatment [33]. Furthermore, we found no influence of frailty or comorbidities on post-operative complications. A study by de Vries et al. [12] found that the G8 was an independent predictor for post-operative complications in patients with cutaneous head and neck malignancies. However, this study comprised other head and neck skin malignancies as well, indicating more extensive treatment. Studies are contradictory regarding the risk of complications after skin cancer treatment in patients with comorbidities. One study found that the presence of at least one comorbidity was significantly associated with post-operative complications after surgical treatment of BCC in patients aged >75 years. Another study found that "endocrine" and "neurologic" comorbidities according to ACE-27 significantly predicted grade of complication in patients with head and neck malignancies [34]. It was not clear whether and how much skin malignancies were included [35]. Several other studies found that comorbidities did not influence (wound) complication rate after treatment of KC [32, 36, 37].

Progression of Disease

Three patients (3.9%) developed lymph node metastases. This percentage is comparable to the lymph node metastatic rate of approximately 2–4% reported in the literature [4, 38, 39].

Advanced tumour stage (≥T2) was significantly associated with POD. The association between tumour stage and POD has been extensively described in the literature [38–41]. Frailty and age were not associated with POD in our study. The recent study by our group [42] also found that advanced age was not an independent risk factor for POD. These findings were confirmed by multiple other studies [38, 43, 44].

Guideline deviation did not increase the risk of POD. However, guideline deviation was significantly more common in patients who died during follow-up, and consequently, these patients are likely to die before the potential development of locoregional recurrences.

Mortality

As expected, frailty, moderate-severe comorbidities, and limited life expectancy were significantly associated with all-cause mortality. As a possible consequence, death during follow-up was also significantly associated with guideline deviation, since guideline deviation was associated with frailty and limited life expectancy. All patients in our cohort died due to another cause than their cSCCHN included in our study, and therefore, guideline deviation did not lead to death.

Quality of Life

As many patients develop more than one skin malignancy in their lifetime, assessment of QoL is becoming an important part of treatment, especially if tumours are located in the visible parts of the head and neck region [18]. Furthermore, in older or frail patients, extensive cancer treatment is more often refrained because of the wish to maintain QoL [45–47].

Patients reported little effect of their diagnosis and treatment on QoL, with lower BaSQoL subscores than described previously [48–50]. Other studies that used different methods to assess QoL reported more influence of skin cancer on QoL [51, 52]. Furthermore, frailty was reported to be associated with a reduced QoL in a recent study in patients with head and neck cancer [53]. A possible explanation for the low impact on QoL in our cohort might be the high amount of low-risk tumours. In addition, the BaSQoL was not specifically validated for frail and older patients and may be less suitable for this specific group [25].

Strengths and Limitations

A strength of our study is the prospective nature and that all questionnaires were administered by the same researcher, minimizing inter-researcher bias. A limitation of this study is the small sample size and the relatively short follow-up time, especially in the frail population. With a longer follow-up period, potentially more cases of POD could be identified.

Conclusion

We found that most patients in our study were treated according to current guidelines. Guideline deviation (resulting in less intensive treatments) was more common in patients with high-risk tumours, who were frail, with impaired mobility, and with a limited life expectancy; however, it did not increase the short-term risk of complication or POD. Therefore, our results suggest that guideline deviation, selecting the most appropriate and patient-centred strategy, can be considered in frail patients with a limited life expectancy because they may not live long enough to benefit from extensive treatment in case of high-risk tumours, and potentially die before POD. The assessment of frailty using the G8 and life expectancy using the Lee index can guide physicians in their treatment decisions. Furthermore, skin cancer-related QoL scores were very low at each time point, indicating little impact of cSCCHN diagnosis and treatment on QoL. However, these results should be interpreted with care, and larger prospective studies are needed to confirm our results, to assess the predictive value of the G8 and Lee index, and to evaluate the long-term outcomes of guideline deviation, including a follow-up period of at least 5 years.

Key Message

Assessment of frailty and life expectancy can guide physicians and patients in treatment decisions.

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of the University Medical Center Groningen, approval number 2018/137. The Medical Ethical Committee (METc) of the UMCG confirmed that this study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). In 2018, when the study was registered, it was not necessary for participants to sign informed consent in the case of a non-WMO study in our centre. Therefore, our population did not sign a consent form but gave their oral consent.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Alet J.G. Leus: collecting data, conceptualization and methodology, formal analysis and validation, and writing of original draft. Marjolijn S. Haisma: conceptualization and methodology, formal analysis and validation, and writing of original draft. Jorrit B. Terra and Suzzane Festen: conceptualization and methodology and writing – review and editing. Grigory Sidorenkov: formal analysis and validation and writing – review and editing. Boudewijn E.C. Plaat: writing – review and editing. György B. Halmos and Emoke Racz: supervision and writing – review and editing.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Marjolijn S. Haisma upon reasonable request.

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