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Cutaneous squamous cell carcinoma (SCC) of the head and neck: Risk factors of overall and recurrence-free survival

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ABSTRACT

Background: Head and neck cutaneous squamous cell carcinoma (HNCSCC) although rarely fatal has significant adverse public health effects due to high medical costs, compromised quality of life, functional impairment and other serious consequences. The present longitudinal cohort study of HNCSCC was designed to determine whether certain clinical–pathologic features of HNCSCC are associated with reduced overall and recurrence-free survival, as suggested by previous data.

Patients: The cohort sample consisted of 315 consecutive patients presenting with primary HNCSCC of the head and neck. Life-table analysis and Kaplan–Meier survival analysis were performed. Multivariate Cox's proportional hazards regression models were used to assess the effects of covariates on the length of the interval.

Results: There were 145 male and 170 female Caucasian patients. At the time of analysis, 222 patients were alive. The mean follow-up time of a patient after enrolment has been 46.7 months (range, 12–124 months). Broder's differentiation grade, perineural involvement, the presence of inflammation and T-stage were independent adjusted predictors for overall survival. pT and N-stage, inflammation and perineural involvement were significant predictors for recurrence-free survival while adjuvant irradiation was associated with a 92% reduced risk for recurrence. Life-table analysis showed that 87% and 69% study patients were free from recurrence at years 3 and 5, respectively.

Conclusions: Certain clinico-pathological predictors can be used to discriminate subsets of high-risk patients that could benefit from long-term follow-up. After excision in negative margins, patients with HNCSCC should be referred to specialised multidisciplinary oncology clinics for counselling on adjuvant radiotherapy and follow-up.

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1. Introduction

Non-melanoma skin cancer (NMSC) is the commonest cancer in Caucasians. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) constitute nearly all NMSC; the incidence of these tumours is rising.[1–4] Cutaneous SCC has an incidence of 16/100,000 people in Europe and of 356/100,000 sun-exposed Caucasians in the US.[5] At least 75% of cutaneous SCC arises in the head and neck.[5,6] Head and neck cutaneous squamous cell carcinoma (HNCSCC) although rarely fatal has significant adverse public health effects due to high medical costs and, in advanced or aggressive cases, compromised quality of life from devastating aesthetic and psychosocial sequelae, functional impairment and other serious consequences.[1,7,8] Histological diagnosis (tumour differentiation, depth of invasion, perineural involvement, size (horizontal dimension/diameter)) and immune status of the patients all have a role in predicting the risk of recurrence and metastasis. Other parameters such as the presence of inflammation are not well studied.[8] Most patients are at low risk (<5%) of developing metastasis to regional lymph nodes. Clinicians often underappreciate patients with unfavourable clinico-pathological factors such as the ones mentioned above but these patients remain at high risk of developing metastatic lymph node disease and dying.[6,9] Standard treatment modalities include wide local excision (WLE) with, or without regional control (neck dissection, ND), radiotherapy (XRT) and chemotherapy (CHT).[6,10,11] These modalities may be combined to treat aggressive tumours.[7,11] The present longitudinal cohort study of HNCSCC was designed to determine whether certain clinical–pathologic features of HNCSCC are associated with reduced overall and recurrence-free survival, as suggested by previous data.

2. Patients

The cohort sample consisted of 387 consecutive patients presenting with primary HNCSCC of the head and neck between January 1996 and December 2006 in a tertiary referral cancer hospital. Institutional Review Board approval was waived due to the observational nature of the study. According to the Unit protocol follow-up was on a monthly basis for the first year, on a bimonthly basis for the second year, on a quarterly basis for the third year, a 6-monthly basis for the fourth and fifth year and on a yearly basis ever after. Detailed description of clinical appearance of the excision area as well as prompt charting of any new skin lesions is routinely documented pre-operatively and on follow-up visits while histopathological evaluations are ordered only as indicated for new or recurrent cancers, symptoms or signs. All patients had either head and neck CT or neck ultrasonography performed annually.

All patients with primary cutaneous HNCSCC were included in the study. Exclusion criteria were referral for the treatment of recurrent HNCSCC tumours, T-*in situ* stage and follow-up duration shorter than 1 year. In patients who developed more than one HNCSCC lesion during the follow-up period, the first lesion only was documented as index-lesion. Any other HNCSCC lesion was considered to be a second-primary HNCSCC lesion (SPT) if, (i) the lesion developed in a longer than 5 cm distance from the index-lesion or, (ii) the lesion did not develop within the irradiated skin in those patients who received XRT. Lesions that did not fulfil these criteria were characterised as local-failures. Recurrent lesions were separated in three distinct categories: local-failure (already explained), regional-failure (recurrence in the neck lymph nodes) and distant-metastasis (recurrence metastatic in distant parts of the body-M1). Baseline for follow-up documentation was defined as the operation-date, in which the tumour was excised in at least 5 mm free of tumour (negative) margins. Survival was estimated as the time between treatment of the index-tumour and either death or last follow-up. The survival analysis censored patients at the time of last follow-up for patients still alive at that time.

Pre-surgical diagnosis of HNCSCC was based on clinical assessment, while pre-treatment biopsy was available only in cases where amputating surgery or systematic patient condition necessitated pre-surgical Head and Neck Tumour Board counselling. Medical consultation was performed in every patient before surgery. Most excisions were performed under local anaesthesia without sedation, while general anaesthesia was used for larger tumours. Haematoxylin and eosin-stained sections from all patients were reviewed in a blinded fashion for different histopathologic features and recorded by one of four experienced histopathologists. Histopathological diagnosis was confirmed to be HNCSCC in all cases. In all patients treated with WLE, completely tumour-free margins were achieved. The Head and Neck Tumour Board of our Hospital advised on administration of adjuvant treatment modalities after assessment of each case. Patients with HNCSCC were the units of analysis for this prospective study.

Dichotomous variables introduced in the current study are sex, living status (dead or alive), recurrence, status of cervical lymph nodes at baseline (N, cN or pN where available, TNM staging), the presence of inflammation, perineural involvement of superficial dermal nerves and deep beyond subcutaneous invasion.

Categorical variables included anatomical location of the lesion (forehead, eyelid, auricle, cheek, nasal and neck), Broder's differentiation grade,[12] combination of treatment modalities, tumour stage (pT, pN, cN and M staging). Patients with HNCSCC of the lips were not included in this study since lips are oral cavity and not cutaneous mucosa.[13]

Quantitative variables included age (years), overall survival (months), recurrence-free survival (months), tumour size (cm) and negative margin excised (cm).

Most variables were used as independent cohort exposures, while living status (primary end-point) and recurrence (secondary end-point) were used as dependent outcome variables. An independent investigator collected data from administration, medical and histology records and uploaded into the database. Selection bias was minimised by including all verified cases treated within the study period. Differential misclassification and informational bias were not possible due to the definite histopathological diagnosis and detailed record maintenance.

The statistical methods and life-table analysis of the cohort are described in the necessary additional data along with figures demonstrating characteristic presence of inflammation.

3. Results

3.1. Demographics

Between January 1996 and December 2006, 387 patients presented with cutaneous HNCSCC of the head and neck. Forty-seven of these patients were ineligible for the study because they presented with recurrent tumours, *in situ* disease or did not receive treatment in our department, and 25 patients were excluded due to an inadequate follow-up. This left 315 patients with at least one HNCSCC lesion on presentation, definite treatment with curative intent and a minimum of 12 months of follow-up who were eligible and were enrolled in the present study. The mean age at presentation was 71.9 years (range, 26–95). There were 145 male and 170 female Caucasian patients. At the time of analysis, 222 patients were alive. The mean follow-up time of a patient after enrolment has been 46.7 months (range, 12–124). Confirmed living status data were available for the 315 patients and confirmed recurrence data were available for 291 of those patients.

All patients had histologically verified HNCSCC on presentation. Among those included, 85 patients have been previously treated in our department for BCC. Two hundred and seventy-five patients presented with a primary single HNCSCC, 28 patients presented with multiple baseline HNCSCC tumours and 12 patients presented with concurrent clinically evident (cN1 or higher) disease in neck lymph nodes.

3.2. Lesion characteristics at presentation

Of the 315 index-lesions documented in the present study, 55 occurred in the forehead and temple, 41 in the eyelids and periocular skin, 75 occurred in the auricle and the periauricular skin, 103 occurred in the cheek, 28 occurred in the nasal area while 13 occurred in the neck (log-rank test for overall survival, $p = 0.058$).

Pathologic estimates of size were available for 307 of 315 index-tumours. Overall, the mean diameter of a HNCSCC at presentation was 2.2 cm (range = 0.5–8.0 cm). Tumour thickness was available for 104 index-tumours. Mean tumour thickness was 0.50 cm (range = 0.04–1.76). Locally recurrent lesions were statistically significantly smaller (mean = 1.5 cm; range = 0.5–7.5 cm) than were primary lesions (mean = 2.2 cm; range = 0.5–8.0 cm; Mann–Whitney *U*-test, $p < 0001$). This finding is inconsistent with the present literature[1] and is discussed below.

3.3. Perineural involvement

Of the 315 initial tumours, 62 featured perineural involvement. The rates of perineural involvement in baseline lesions that recurred versus those that did not recur were 56% (31/55) versus 11% (24/236, RR = 11.4; 95% confidence intervals (CI): 5.8–22.5, $p < 0.001$). Increment of tumour size correlated with the incidence of perineural involvement (Pearson's $r = 0.35$, $p < 0.001$).

3.4. Deep invasion (beyond subcutaneous tissues)

86/315 patients had baseline lesions that invaded deeply into one or more of the adjacent tissues. The percentage of deep invasion was significantly higher for tumours that recurred (52%, 29/55) versus those that did not (21%, 45/236; RR = 4.7; 95% CI: 2.5–8.8, $p < 0.001$). Increment of tumour size correlated with the incidence of deep invasion (Pearson's $r = 0.39$, $p < 0.001$).

3.5. Presence of inflammation

It is established knowledge that there may be a mild to moderate chronic inflammatory cell infiltrate at the periphery of the tumours.[14] In the present cohort of patients, a dense infiltrate of lymphocytes was identified in the dermis in 84/315 index-tumours (Supplementary data, Figs. 3 and 4). The presence of this inflammatory infiltrate correlated with perineural involvement (Pearson's $r = 0.55$, $p < 0.001$) but not with deep invasion or tumour differentiation grade. Notably, the proportion of the presence of this infiltrate was significantly higher in those tumours that recurred (43%, 23/55) versus those that did not (23%, 55/236; RR = 2.4; 95% CI: 1.3–4.4, $p = 0.005$).

3.6. Treatment

Surgery, including WLE, ND or both, was part of treatment for 93.7% of all patients (295/315 patients, Tables 1 and 2). Based on AJCC staging at diagnosis, stage-I patients received WLE ($n = 160$) or XRT alone ($n = 1$). Stage-II patients received WLE ($n = 2$), WLE + XRT ($n = 52$) and XRT alone ($n = 10$). Stage-III patients received WLE ($n = 4$), WLE + ND ($n = 13$), WLE + ND + XRT ($n = 5$), WLE + XRT ($n = 57$), XRT alone ($n = 9$) and WLE + ND + XRT + CHT ($n = 2$). The mean radiotherapy dose to the site of surgical excision was 58 Grey (Gy; range, 45–68 Gy) in 2 Gy fractions. Patients only received XRT alone if they were medically unfit for surgery or had advanced inoperable disease (skull base or carotid artery invasion). From the 315 index-tumours treated with WLE, data on the extent of negative margin excised from the pathology reports were available for 307. Mean extent of negative margin excised was 12, 7 ± 5.4 mm.

3.7. Cutaneous HNCSCC second-primary tumours (SPTs)

Histology reports for a total of 405 HNCSCC tumours which are reported in the present study are available. A total of 90 SPTs occurred during the follow-up in 49 patients. Twenty-eight of those patients, presented to the Unit with multiple HNCSCC. Presenting with multiple HNCSCC was not associated with increased risk of recurrence (2/28 versus 53/263; RR = 0.31; 95% CI: 0.1–1.32, $p = 0.113$). Interestingly, these patients survived for a longer period of time (median survival 108 versus 82 months, $p = 0.042$).

Table 1 – Five-year overall survival as a function of selected clinical and histopathologic features. From 315 patients with cutaneous squamous cell carcinoma of the head and neck.

	Predictor	Number of patients[a]	5-year overall survival (%)	*p*
Sex	Male	145	71	0.106
	Female	167	66	
Age	<70	124	90	<0.001
	⩾70	187	53	
AJCC[b] stage	I	159	86	<0.001
	II	63	55	
	III	90	47	
Deep invasion beyond subcutaneous tissues	No	226	76	<0.001
	Yes	86	47	
Presence of inflammation	No	228	73	0.002
	Yes	84	56	
Perineural involvement	No	250	76	<0.001
	Yes	62	45	
Differentiation Grade	Good	88	71	0.026
	Good–moderate	28	60	
	Moderate	90	65	
	Moderate–poor	14	37	
	Poor	30	52	
Recurrence at any time during follow-up	No	**252**	**87**	**<0.001**
	Yes	**55**	**31**	
At least one SPT	No	263	69	0.605
	Yes	49	67	
Combination of treatment modalities[c]	WLE	160	83	<0.001
	WLE + ND	13	9	
	WLE + ND + XRT	5	0	
	WLE + XRT	112	66	
	XRT	20	40	
	WLE + ND + XRT + CHT	2	0	

[a] Number of patients summary may not be 315 in all cases due to missing values.
[b] American Joint Committee on Cancer Staging.
[c] WLE: wide local excision, ND: neck dissection, XRT: radiotherapy therapy, CHT: adjuvant chemotherapy.

3.8. *Predictors for regional-failure*

In a multivariate logistic regression model in which concurrent or recurrent regional-failure was set as dependent variable, we included histopathological predictors, namely perineural involvement, deep invasion, the presence of inflammation and tumour differentiation grade. A subset of two variables was able to predict regional-failure: deep invasion (OR = 16.6; 95% CI: 4.7–59.0; $p < 0.001$) and the presence of inflammation (OR = 4.0; 95% CI: 1.5–10.6; $p = 0.005$).

3.9. *Overall survival*

Ninety-three patients were deceased at the time follow-up was closed. Three and 5-year overall survival was 82% and 69%, respectively (Supplementary data Table 5). Survival estimates were based on the complete follow-up on the 93 deceased patients and a median follow-up of 48.5 (range 15–124) months in the 222 patients still alive at the time of analysis.

Mortality was associated with recurrence at any time during follow-up. 89% (49/55) of the patients who experienced a recurrence died versus 12% (28/236, RR = 60.7; 95% CI: 23.8–154.5, $p < 0.001$, Fig. 1) of those who did not.

3.10. *Recurrence and recurrence-free survival*

After primary HNCSCC treatment, 55 patients developed recurrent disease during the study period. Twenty-three of these patients were among the 49 patients who developed at least one SPT (RR = 5.8; 95% CI: 3.0–11.4, $p < 0.001$). Thirty-five patients had local-failure only. Nineteen patients had regional-failure (nine patients had regional-failure alone, three patients had regional and local-failure and seven patients had regional-failure and parotid recurrence). During follow-up five patients were diagnosed with distant-metastasis, of whom one with distant-metastasis alone and four with local ($n = 1$) or regional ($n = 3$) failure concurrent with distant-metastasis. Life-table analysis showed that 87% and 69% study patients were free from recurrence

at years 3 and 5, respectively. During the follow-up period, the hazard-rates for recurrence appeared to be stable (9-year recurrence-free survival 51%, Supplementary data Table 6, Fig. 2).

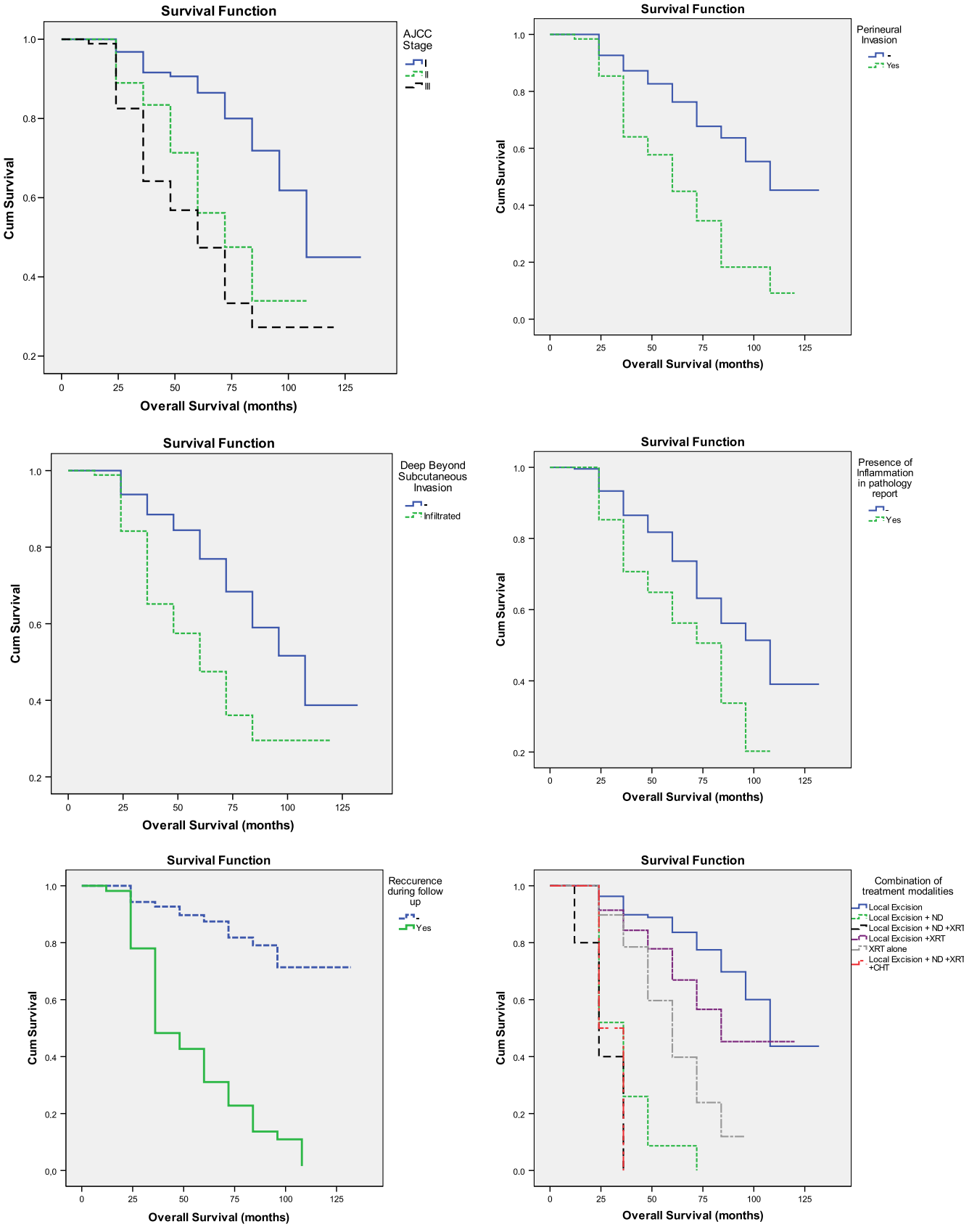

Fig. 1 – Life-table analysis: predictors of overall survival. For *p* values see Table 1.

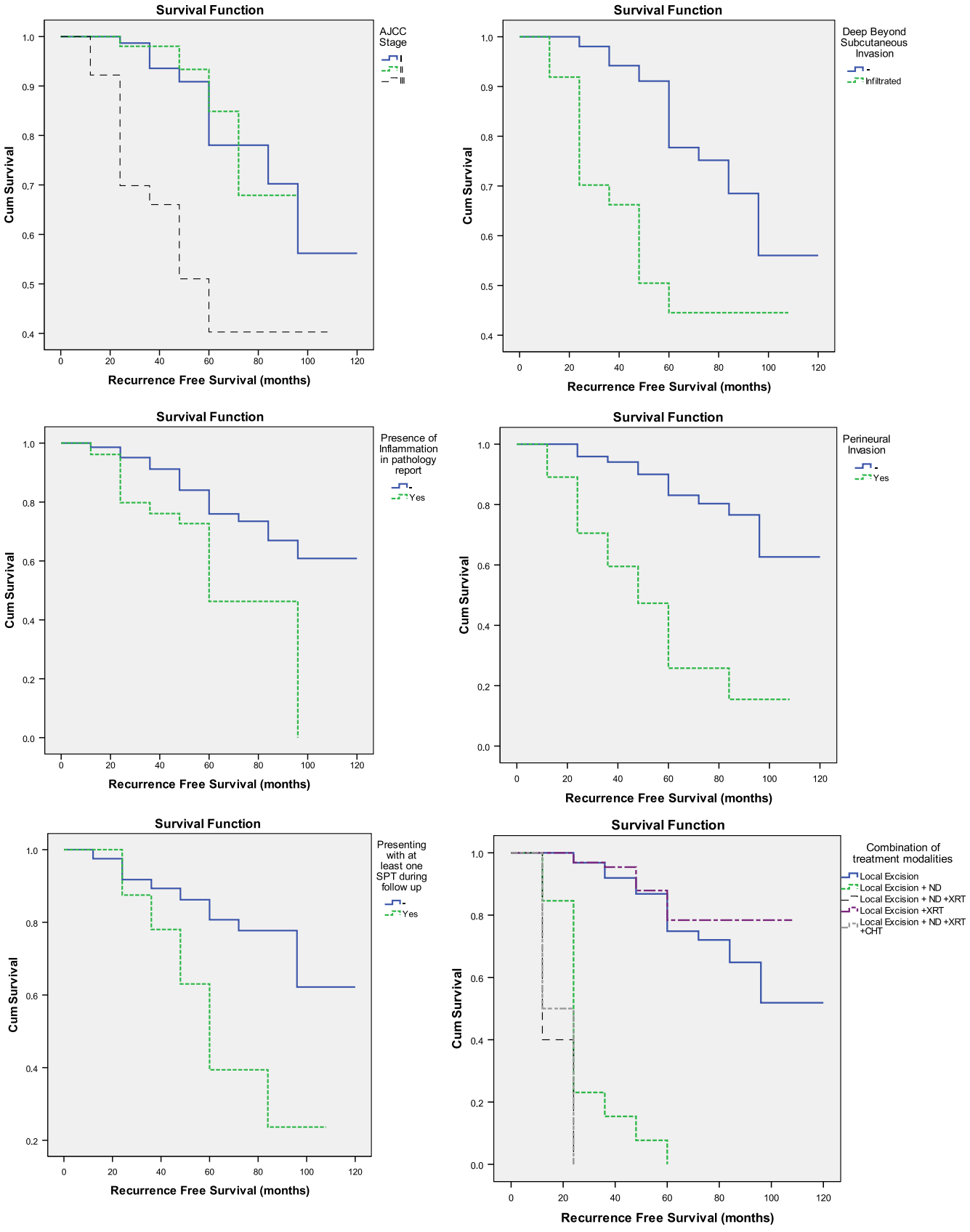

Fig. 2 – Life-table analysis: predictors of recurrence-free survival. For *p* values see Table 2.

Table 2 – Five-year recurrence-free survival as a function of selected clinical and histopathologic features. From 291 patients with cutaneous squamous cell carcinoma of the head and neck.

	Predictor	Number of patients[a]	5-year recurrence-free survival (%)	*p*
Sex	Male	136	67	0.805
	Female	152	70	
Age	<70	124	76	0.013
	⩾70	163	60	
AJCC[b] stage	I	158	77	<0.001
	II	53	84	
	III	77	40	
Deep invasion beyond subcutaneous tissues	No	214	77	<0.001
	Yes	74	45	
Presence of inflammation	No	228	75	<0.001
	Yes	79	46	
Perineural involvement	No	233	82	<0.001
	Yes	55	26	
Differentiation Grade	Good	81	83	0.013
	Good–moderate	24	76	
	Moderate	82	57	
	Moderate–poor	13	21	
	Poor	28	54	
At least one SPT	No	258	80	0.007
	Yes	49	39	
Combination of treatment modalities[c]	WLE	164	74	<0.001
	WLE + ND	13	0	
	WLE + ND + XRT	5	0	
	WLE + XRT	104	78	
	WLE + ND + XRT + CHT	2	0	

For recurrence-free survival, the XRT alone category is not included since recurrence cannot be defined according to the study criteria for tumours that only received XRT.

[a] Number of patients summary may not be 291 in all cases due to missing values.

[b] American Joint Committee on Cancer Staging.

[c] WLE: wide local excision, ND: neck dissection, XRT: radiotherapy therapy, CHT: adjuvant chemotherapy.

3.11. *Risk factors associated with overall and recurrence-free survival*

Clinico-pathological factors were investigated for their associations with overall and recurrence-free survival (Tables 1 and 2). Univariate logistic regression analysis determined that the following factors were statistically significantly associated with increased probability of dying: recurrent disease (OR = 43.9, 95% CI: 17.6–109.4, $p = 0.001$), deep invasion beyond subcutaneous tissues (OR = 2.5, 95% CI: 1.5–4.2, $p = 0.001$), perineural involvement (OR = 5.2, 95% CI: 2.9–9.4, $p < 0.001$) and the presence of inflammation (OR = 1.7, 95% CI: 1.1–2.9, $p = 0.046$). T-stage (OR = 43.9, 95% CI: 17.6–109.4, $p < 0.001$), N-stage (OR = 64.5, 95% CI: 8.5–487.6, $p < 0.001$) and AJCC-stage (OR = 2.0, 95% CI: 1.5–2.6, $p < 0.001$) were expectedly associated with increased probability of dying.

Twelve patients with lymph node involvement on presentation (pN1 or cN1) had 5-year overall survival of 10% versus 71% without involvement ($p < 0.001$). HNCSCC recurrence significantly reduced survival: patients who developed recurrence had 5-year overall survival of 31% versus 87% without a recurrence ($p < 0.001$). Perineural involvement was also found to be a significant predictor for 5-year survival: 76% versus 47% (Fig. 1).

3.12. *Multivariate survival analysis*

Statistically significant two-way interactions are reported: lesion size was associated with deep invasion beyond subcutaneous tissues (Pearson's $r = 0.39$, $p < 0.001$), perineural involvement (Pearson's $r = 0.34$, $p < 0.001$) and lymph node involvement (Pearson's $r = 0.42$, $p < 0.001$). These predictors remain independent risk factors for overall and recurrence-free survival in the multivariate Cox-model analysis. In a comprehensive Cox-multivariate-model, we included AJCC-stage, T- and N-stage, histology differentiation grade, combination of treatment modalities, deep beyond subcutaneous invasion, perineural involvement and the presence of inflammation. This model showed that differentiation grade, perineural involvement, the presence of inflammation and T-stage are independent adjusted predictors for overall survival (Table 3).

The same variables were included in a second model to determine predictors for recurrence of HNCSCC following

Table 3 – Adjusted predictors of overall survival. Multivariate cox regression analysis from 315 patients with cutaneous squamous cell carcinoma of the head and neck.

Predictor	Adjusted HR	95% confidence intervals*		p Value#
		Lower	Upper	
Combination of treatment modalities (logit = WLE)				<0.001
WLE + ND	2.2	0.5	8.8	0.276
WLE + ND + XRT	**6.6**	**1.5**	**28.5**	**0.011**
WLE + XRT	0.6	0.2	1.5	0.274
XRT	1.5	0.5	4.6	0.434
WLE + ND + XRT + CHT	4.0	0.4	36.2	0.218
Inflammation	**2.6**	**1.5**	**4.4**	**0.001**
Differentiation grade (logit = good)				**0.012**
Good–moderate	**3.9**	**1.8**	**8.3**	**0.001**
Moderate	**1.9**	**1.2**	**3.4**	**0.045**
Moderate–poor	1.1	0.4	3.4	0.871
Poor	1.2	0.5	2.6	0.677
Perineural	**2.0**	**1.1**	**3.8**	**0.046**
T-stage (logit = T1)				**0.001**
T-stage 2	3.5	1.2	10.9	0.029
T-stage 3	18.5	5.5	62.8	<0.001
T-stage 4	2.6	0.8	8.1	0.099
N-stage	3.7	1.0	13.8	0.052

Cox-model variables; categorical: T-stage (logit = T1), AJCC-stage (logit = I), treatment modality (logit = WLE), histology differentiation grade (logit = good); dichotomous: N-stage, deep beyond subcutaneous invasion, perineural involvement, presence of inflammation. Logit = no for all dichotomous variables in the model.

Multivariate cox regression analysis, forward stepwise inclusion with likelihood ratio criteria.

*,# values printed in bold denote statistical significance.

treatment with curative intent. pT and N-stage, inflammation and perineural involvement were significant predictors for recurrence-free survival. Of note, WLE followed by XRT is associated with a 92% reduced risk for recurrence (Table 4).

4. Discussion

Cause of death was not specifically recorded in this study. However, the high association between mortality and recurrence observed in the study imply that most deaths in the cohort could be attributed to HNCSCC and its sequelae.

Known risk factors for the recurrence of cutaneous SCCs are treatment modality, tumour size >2 cm, depth of invasion >4 mm, poor histological differentiation, location on the ear, perineural involvement, location within scars or chronic inflammation, treatment failure and immunosuppression.[15] Multivariate analysis of the studied population showed age, AJCC-stage, deep invasion beyond subcutaneous tissues,

Table 4 – Adjusted predictors of recurrence-free survival. Multivariate cox regression analysis from 291 patients with cutaneous squamous cell carcinoma of the head and neck.

Predictor	Adjusted HR	95% confidence intervals*		p Value#
		Lower	Upper	
Combination of treatment modalities (logit = WLE)				<0.001
WLE + ND	1.8	0.6	5.6	0.278
WLE + ND + XRT	2.3	0.6	9.2	0.238
WLE + XRT	**0.08**	**0.03**	**0.26**	**<0.001**
XRT	4.5	0.8	27.2	0.099
Inflammation	**2.3**	**1.3**	**4.5**	**0.019**
Perineural	**3.3**	**1.5**	**7.4**	**0.004**
T-stage (logit = T1)				**0.012**
T-stage 2	4.7	0.9	24.3	0.065
T-stage 3	**11.3**	**2.0**	**62.8**	**0.006**
T-stage 4	**9.7**	**2.8**	**34.2**	**<0.001**
N-stage	**2.3**	**1.2**	**4.5**	**0.019**

Cox-model variables; categorical: T-stage (logit = T1), AJCC-stage (logit = I), treatment modality (logit = WLE), histology differentiation grade (logit = good); dichotomous: N-stage, deep beyond subcutaneous invasion, Perineural involvement, presence of inflammation. Logit = no for all dichotomous variables in the model.

Multivariate cox regression analysis, forward stepwise inclusion with likelihood ratio criteria.

*,# values printed in bold denote statistical significance.

presence of inflammation, perineural involvement, histology differentiation grade and combination of treatment modalities as independent parameters determining mortality in patients with HNCSCC. Development of any SPT was not found to be a predictor of overall survival but it was statistically associated with reduced recurrence-free survival.

Previous longitudinal studies reported on a 37/210 (Clayman and colleagues[1]), a 40/615 (Brantsch and colleagues[5]) and a 70/250 (Oddone[4]–Veness[16] and colleagues) recurrence rate, respectively. The earlier study by Veness and colleagues[11] only included patients with concurrent or subsequent regional-failure and compared outcome of different treatment strategies. Our recurrence rate of 55/315 is more comparable to the results reported by Clayman and colleagues[1] and Brantsch and colleagues.[5] This study and the studies by Oddone–Veness and colleagues[4,11] refer to HNCSCC only.

We performed multivariate Cox-regression to control for any advantage of certain treatment modalities applied. It appears that patients who receive adjuvant radiotherapy after local excision are at lower risk for developing recurrent HNCSCCs. Veness and colleagues also reported a beneficial outcome with adjuvant radiotherapy in HNCSCC patients, however their series included only patients who had metastatic HNCSCC to regional lymph nodes.[4,11] Although this cohort includes patients with diverse disease AJCC-stages and not uniform treatment modalities across AJCC-stage groups, we demonstrate that all HNCSCC patients benefit from adjuvant radiotherapy through a Cox-multivariate-model in which we control for AJCC-stage and a series of possible confounders. The objective of adjuvant radiotherapy is to decrease the risk of regional[4] but also local recurrence by eradicating microscopic HNCSCC. These evidence justify referral to a head and neck multidisciplinary clinic for every HNCSCC excised in negative margins for possible adjuvant radiotherapy and dictate new clinical trial research; future data from randomised-controlled clinical-trials are expected to further support this argument.[4]

Brantsch and colleagues, in a recent publication[5] reported that tumour thickness is a predictor for regional recurrence. More specifically, tumour thickness >6 mm is associated with increased risk for regional recurrence. The latter is in accordance with our finding that deep beyond subcutaneous invasion is associated with increased risk for recurrence. Since facial skin thickness varies significantly (i.e. eyelids versus forehead), it may be more time-efficient for dermatopathologists to report on invasion beyond the subcutaneous level instead of reporting tumour thickness. Still, direct comparison of the usefulness of the two is yet to be performed. Previous well-conducted studies have also reported on deep invasion.[1]

Opposite to previous findings,[1] we report smaller tumour dimensions for recurrent HNCSCCs. We attribute this difference to our follow-up programme which is uniform for all head and neck cancer patients. Patients who developed a SPT during follow-up did not exhibit higher mortality rates (Table 1 and Fig. 1). Subsets of high-risk patients, categorised through certain histopathological and clinical predictors (Tables 2 and 4) could be benefited from long-term follow-up accompanied with an annual neck CT scan or ultrasonography. Since recurrence was the most potent predictor of overall survival in our cohort (Table 1), we believe a structured follow-up will allow for timely treatment of recurrences and will prolong the overall survival of these patients.

Two types of perineural involvement are reported in the literature, both with distinct outcomes. Those with major perineural involvement (deep larger nerves) and those where incidental small nerve perineural involvement (superficial dermal nerves) is seen histologically.[17,18] A retrospective cohort study of 48 patients reported that small nerve invasion may not adversely affect outcomes.[17] In the present study which is of greater statistical power, we found superficial perineural involvement to be statistical significantly associated with both higher mortality (Table 3) and risk for recurrence (Table 4).

The presence of inflammation in the histology report has not been previously studied as a predictor of outcome.[19,20] The significance of inflammation in regard to HNCSCC is reported to be controversial.[8] However, inflammation and its relation to cancer have been redefined since the hierarchical cancer-stem model appeared.[21–23] Inflammation in the tumour microenvironment is reported to play diverse roles in the maintenance of cancer-stem-cells and to promote the seeding of cancer cells at metastatic sites.[24,25] Associations between the presence of inflammation and carcinogenesis have been reported for alimentary tract cancers.[26,27] Thus, formal reporting of lymphocyte inflammatory infiltration in the dermis from HNCSCC samples by dermatopathologists might present new research opportunities and a potential predictor.

Several pathological predictors for HNCSCC treatment outcome have been reported.[1,5,11] AJCC-staging may need to be revised.[4,5] Further to other well-conducted observational studies[1,4,5,16], the present study adds the presence of inflammation as a possible predictor. Appropriate follow-up strategy for head and neck NMSC patients should also be established. Patients with BCC may be followed up less frequently[2,3] while subsets of patients with cutaneous SCC should be enrolled in a follow-up protocol. After excision in negative margins, patients with HNCSCC should be referred to specialised multidisciplinary oncology clinics for counselling on adjuvant radiotherapy and follow-up.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.02.046.

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