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Lymph node ratio and capsule penetration as independent risk factors in head and neck squamous cell carcinoma

M Lanzer[1]*, A Kruse[1], HT Lübbers[1], W Zemann[1], S Reinisch[2]

Abstract

Introduction

Knowledge of independent prognostic factors in patients with head and neck squamous cell carcinoma is important for appropriate treatment decisions. Given the availability of aggressive therapeutic options with known side effects and burdens for the patient, choosing the correct treatment option is vital.

Materials and methods

Using a retrospective database of patients treated over a 10-year period, independent prognostic factors for disease-free survival and overall survival were assessed. Univariate analysis was used to identify significant variables, and multivariate Cox regression analysis was used to determine independent prognostic factors.

Results

Between 1 January 1999 and 31 December 2009, 291 patients with head and neck squamous cell carcinomas were analysed to identify prognostic factors for disease-free survival and overall survival. Although univariate analysis identified several significant factors, multivariate Cox regression analysis showed that capsule penetration and lymph node ratio were the only significant factors for disease-free survival and overall survival.

Conclusion

Lymph node ratio is an independent predictor of survival and should be examined in every patient undergoing neck dissection. Capsule penetration of lymph nodes was another independent prognostic factor. In cases of capsule penetration or inappropriate lymph node ratio, adjuvant therapies are necessary.

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Introduction

The importance of tumour stage in disease-free survival (DFS) and overall survival (OS) in patients with head and neck squamous cell carcinoma (SCC) is well known[1–3]. Tumour location[4,5], grade[6] and histological aspects such as perineural invasion[7] and capsule penetration[8] have been associated with poorer DFS and OS. Nevertheless, some aspects of tumour biology and patient survival remain unclear. Given the availability of aggressive therapies and their known side effects, selection of patients who require aggressive treatment has become important.

In this study, we evaluated independent prognostic risk factors for DFS and OS in patients with SCC of the head and neck. We hypothesise that certain attributes lead to a poorer prognosis, whereas other attributes are unimportant.

Materials and methods

Study design

We developed a retrospective patient database.

Study sample

The study population was derived from patients who presented at the Department of Otorhinolaryngology and Head and Neck (ENT) at the Medical University Hospital Graz for treatment of head and neck SCC between 1 January 1999 and 31 December 2009. The study was approved by the institutional ethics committee.

Inclusion criteria included the diagnosis of SCC in the head and neck region and operative treatment at the primary tumour site with/without adjacent adjuvant radiotherapy or radiochemotherapy. Subjects were excluded if they had histological findings other than SCC, distant metastasis before neck dissection (ND) or were treated primarily outside the ENT department.

Study variables

Variables examined were age and sex; tumour location, stage, size and grade; neck lymph node status; histological factors [blood vessel invasion (hemangiosis), lymph vessel invasion (lymphangiosis), capsule penetration, perineural invasion and conglomerate lymph nodes]; resection margin; number of positive lymph nodes; lymph node ratio and adjuvant therapy (postoperative chemotherapy and/or adjuvant radiotherapy). Treatment algorithm was defined (Table 1).

Point of interest

- Bivariate analysis to identify factors significantly affecting DFS and OS.
- Multivariate analyses of significant factors to identify independent prognostic factors.

Data collection, management and analyses

Data were collected and processed by building a database of information about the patient (sex, age), tumour (location, size and lymph node status), operation (date, type of resection, resection margin, type of ND, number of levels excised, number of lymph nodes excised, number of positive lymph nodes, excision of non-lymphatic structures), histopathological diagnostic findings (hemangiosis,

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Table 1 Treatment algorithm

	Procedure	Dosage/agent
Tumour staging	By the Interdisciplinary Tumour Board including: – clinical examination – ultrasound (2 examiners) – CT-scan (if contraindication → MRI) – X-ray of the lungs and ultrasound of abdomen – PET-CT in some patients	-
Operation	Intention of complete resection of tumor in all patients	-
Adjuvant radiotherapy if	Positive resection margin of primary tumour Positive lymph node atatus Tumour size T3 or T4	66 Gy dosage if positive resection margin All others recived 60 Gy Neck was radiated bilaterally 50 Gy
Adjuvant radio-chemotherapy if	Perineural invasion Capsule penetration Lymph node status higher than pN2a	Cisplation 100 mg/m^2 on day 1, 22, 43 If Cisplation was not possible (kidney malfunction or high age) Calais-Scheme[9] was used (Carboplation/5 FU)
Follow-up	First 2 years every 3 month, next 3 years every 6 month After 5 years follow-up was conducted yearly CT/MRI, ultrasound and X-ray was conducted yearly	-

CT, computed tomography; MRI, magnetic resonance imaging

lymphangiosis, capsule penetration and perineural invasion), post-operative therapy, second primary tumours, location and time of recurrence and OS. Patient data were analysed using SPSS software (SPSS Inc., Chicago, IL, USA).

Descriptive statistics were computed for each variable. Bivariate Cox regression analysis was used for each variable and odds ratios (OR) and p values were calculated. Multivariate Cox regression analysis was used for each predictor variable ($p < 0.05$) identified as significant in univariate analysis. We used a forward step-wise (likelihood ratio) procedure.

For the analysis of cut-off points for lymph node ratio, the 'maximally selected rank statistic' method of Lausen and Schumacher[10] was used. Cut-off points with the highest diversity of groups were calculated.

Results

In total, 291 patients were included (Table 2). The mean age was 64 (range, 27–87) years. Most (82.8%) patients were men. The mean follow-up duration was 38 months (maximum, 128 months). Most patients had a tumour in the oropharyngeal region (32%), followed by the oral cavity (25.4%), hypopharynx (16.8%), larynx (15.1%), unknown primary location (8.6%) and nasopharynx (2.1%). Most patients presented with a stage IV tumour (56%), followed by stage III (19.6%), stage II (13.7%) and stage I (10.7%). Regarding T-status, most patients presented with a T2 tumour (29.4%). Lymph node status was pN0 in 37.5% of patients, followed by pN2b in nearly 31% of patients. Because patients with distant metastasis at diagnosis were excluded, all patients were in the M0 state.

Tumour grade was dominated by patients with moderately (43.6%) or poorly (51.2%) differentiated tumours. Only a few patients presented with well-differentiated or undifferentiated tumours. Perineural invasion was seen in 7.9% of patients; the percentage of lymphangiosis, hemangiosis, capsule penetration and conglomerate lymph nodes was 7.2%, 2.4%, 18.6% and 10.3%, respectively.

Operative success, defined as a negative resection margin (R0 resection), was achieved in 78.4% of patients. R1 resection was achieved in 19.9% of patients and tumour resection was macroscopically positive (R2 resection) in five (1.7%) patients. Forty-one (14.1%) patients underwent radical ND on the ipsilateral side. The largest proportion of patients was treated with modified radical ND (28.9%), followed by posterolateral (25.1%), selective (8.2%), supraomohyoidal (8.9%), expanded supraomohyoidal (8.2%), lateral selective (4.8%), suprahyoidal (1.0%) and expanded lateral selective (0.7%) NDs. At least five levels were examined and dissected in 35.1% of patients. Given the small number of patients who underwent bilateral ND, only a minority (16.8%) of patients underwent more than five levels of ND.

Results of neck dissections demonstrated a pN0 situation in 37.5% of patients. One or 2–5 lymph nodes were positive in 26.5% and 26.5% of patients, respectively. In 9.6% of patients, more than five lymph nodes were affected. Nearly two thirds of patients had lymph node ratios (number of negative lymph nodes/total number of excised lymph nodes)

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Table 2 Descriptive statistics of 291 patients

	Attribute	Number (%)	Mean	SD	Median	Minimum	Maximum
Age (yr)	-	291	64.08	10.6	64	27	97
Follow-up (mo)	-	291	38.39	32.6	27.2	0.1	128.3
Sex	Male	241 (82.8)	-	-	-	-	-
Localisation	Oral cavity Oropharynx Nasopharynx Hyopharynx Larynx Unknown primary	74 (25.4) 93 (32.0) 6 (2.1) 49 (16.8) 44 (15.1) 25 (8.6)	-	-	-	-	-
TNM stage	Stage I–II Stage III–IV	71 (24.4) 220 (75.6)	-	-	-	-	-
Tumor stage	T1–2 T3–4 Tx	150 (51.6) 116 (39.9) 25 (8.6)	-	-	-	-	-
Lymph node status	N0 N1 N2a N2b N2c N3	109 (37.5) 38 (13.1) 28 (9.6) 90 (30.9) 15 (5.2) 11 (3.8)	-	-	-	-	-
Tumour grade	Well/moderately-differentiated Poorly/un-differentiated	137 (47.0) 154 (52.9)	-	-	-	-	-
Perineural invasion	No Yes	268 (92.1) 23 (7.9)	-	-	-	-	-
Lymphangiosis	No Yes	270 (92.8) 21 (7.2)	-	-	-	-	-
Hemangiosis	No Yes	284 (97.6) 7 (2.4)	-	-	-	-	-
Capsule penetration	No Yes	237 (81.4) 54 (18.6)	-	-	-	-	-
Conglomerate lymph nodes	No Yes	261 (89.7) 30 (10.3)	-	-	-	-	-
Resection margin	Negative Positive	228 (78.4) 63 (21.6)	-	-	-	-	-
Number of positive lymph nodes	0 1 2–5 >5	109 (37.5) 77 (26.5) 77 (26.5) 28 (9.6)	-	-	-	-	-
Lymph nodes ratio	100%-94% 93%-87% <87%	187 (64.3) 48 (16.5) 56 (19.2)	-	-	-	-	-
Lymph nodes ratio (neg/exc)[%]	-	291	91.96	13.0	96.3	0	100
Adjuvant therapy	No Radiotherapy Chemotherapy Radiochemotheraphy	113 (38.8) 140 (48.1) 1 (0.3) 37 (12.7)	-			-	

SD, standard deviation

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exceeding 94%. In total, 113 (39.2%) patients received no adjuvant therapy, 140 (48.1%) patients received radiotherapy, 12.7% received combined radiochemotherapy and one received chemotherapy alone.

Two-thirds of patients experienced no recurrence during follow-up. Recurrence was observed in 98 (33.7%) cases; distant metastasis occurred in 34 of these patients. In total, 155 (53.3%) patients were disease free after follow-up, 13.7% of patients suffered recurrence but survived follow-up, 19.9% of patients died after recurrence and 13.1% died of other causes. In total, 195 patients survived follow-up.

Univariate analysis identified the following factors as significantly affecting DFS: age, tumour location, stage, pT status, pN status, perineural invasion, lymphangiosis, hemangiosis, capsule penetration, conglomerate lymph nodes, resection margin, number of positive excised lymph nodes and lymph node ratio (Table 3). The highest level of significance was found for capsule penetration and lymph node ratio ($p < 0.001$), followed by conglomerate lymph nodes, lymphangiosis and positive resection margin.

Univariate analysis identified the following factors as significantly affecting OS: age, tumour location, stage, pT status, pN status, perineural invasion, lymphangiosis, hemangiosis, capsule penetration, conglomerate lymph nodes, resection margin, number of positive excised lymph node, and lymph node ratio (Table 4). OS also significantly differed according to the use of adjuvant radiotherapy. The highest level of significance was obtained for capsule penetration, conglomerate lymph nodes, pN status and lymph node ratio ($p < 0.001$), followed by hypopharyngeal location and overall staging.

Multivariate analysis revealed two independent predictor variables for DFS: lymph node ratio and capsule penetration (Table 3). Lymph node ratio was divided into three groups: 100–94% (reference), 93–87% and <87%. The OR for a lymph node ratio of <94% was 1.698 ($p = 0.023$) and that for a ratio of <87% was 2.271 ($p < 0.001$). The OR for an event was 1.693-fold higher when capsule penetration was evident than when the capsule was intact ($p = 0.014$).

Multivariate analysis for OS (Table 4) identified the same independent predictors as for DFS. The ORs for lymph node ratio were 2.269 and 2.904 for 93–87% and <87%, respectively, compared with the reference (100–94%). The OR for capsule penetration was 1.886 ($p = 0.009$).

Discussion

In the data analysis of 291 patients with head and neck SCC, two variables were found to be independent prognostic factors in multivariate analyses: lymph node ratio and capsule penetration. The impact of capsule penetration on locoregional DFS and OS is well known[8,11,12]. Even in patients with clinically negative necks, occult metastases with capsule penetration occur[13], putting the patient at high-risk of undertreatment. This finding also disproves the former idea that extracapsular spread was associated with larger lymph node metastases and fixed lymph nodes[14].

In an investigation of 266 patients with SCC of the tongue, Myers et al.[15] reported 5-year OS rates for patients with pathological node-negative necks, node-positive necks without extracapsular spread and node-positive necks with extracapsular spread of 75%, 50% and 30%, respectively. Despite postoperative radiotherapy in 89% of patients with extracapsular spread, the regional failure rate was 29%. Thus, the authors concluded that further adjuvant therapy was necessary for regional and distant control and improved survival.

Our data suggests the importance of extracapsular spread for DFS and OS. Of seven patients with extracapsular spread who received no adjuvant therapy, six (85.7%) died during follow-up. Adjuvant therapy significantly increased OS in patients with extracapsular spread to 50% (27/54 patients died during follow-up).

Perineural invasion, another histological aspect discussed as an independent prognostic factor, was not found to be significant in this multivariate analysis. Previous reports have indicated that perineural invasion is a strong predictor for local and locoregional recurrence, and thus should be included in pathological examinations[7] and treated with adjuvant therapy[2]. In cutaneous cancer of the head and neck, perineural invasion is also a predictive factor for survival. In our study, perineural invasion was identified as significant in univariate analyses ($p = 0.031$ for DFS and $p = 0.034$ for OS), but it was not an independent prognostic factor in multivariate analysis. These findings are important because most data supporting associations between perineural invasion and outcome have been derived from univariate analyses[7].

Lymph node ratio was the second independent prognostic factor. Previous studies have demonstrated that this variable is an important diagnostic tool in certain tumours, such as gastric[16–18], endometrial[19], colorectal[20–22] and pancreatic[23,24] cancers. To our knowledge, only three reports have investigated lymph node ratio as a prognostic tool in head and neck cancer. Shrime et al.[25] suggested that the ratio between the number of excised and that of positive lymph nodes was a predictive factor for outcome. In an investigation of 386 patients with oral SCCs, Gil et al.[26] reached the same conclusion. Shrime et al.[24] used two cut-off points (6%, 13%), whereas Gil et al.[25] used only 6%. Both studies obtained similar results and demonstrated significant effects of lymph node ratio on DFS and OS. Suslu et al.[27] reached the same conclusion about the importance of lymph node ratio, using 4% as the cut-off value for a significant difference in outcome.

The present study used a method for calculating cut-off points (the

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Table 3 Disease-free survival (bivariate and multivariate analyses)

Variable	Reference category	n Reference	Risk for	n Risk	OR	95% CI LB	95% CI UB	p values
Age	-	-	Increase of 1 year		1.018	1.002	1.035	0.031
Oral cavity/oropharynx	Other tumor sites	124	Oral cavity/ oropharnyx	167	0.709	0.506	0.992	0.046
Hypopharyngeal cancer	Other tumor sites	242	Hypopharyngeal cancer	49	1.554	1.036	2.333	0.333
Stage	-	-	-	-	-	-	-	0.010
	Stage I	31	Stage II	40	1.198	0.512	2.806	0.677
	Stage I	31	Stage III	57	2.341	1.107	4.951	0.026
	Stage I	31	Stage IV	163	2.476	1.240	4.946	0.010
pT status	-	-	-	-	-	-	-	0.007
	T1	64	T2	86	1.446	0.857	2.440	0.168
	T1	64	T3	68	1.836	1.059	3.183	0.030
	T1	64	T4	48	2.546	1.472	4.403	0.001
	T1	64	Tx	25	2.516	1.259	5.027	0.009
pN status	-	-	-	-	-	-	-	0.009
	N0	109	N1	38	1.890	1.141	3.132	0.013
	N0	109	N2a	28	0.863	0.419	1.779	0.690
	N0	109	N2b	90	1.840	1.203	2.813	0.005
	N0	109	N2c	15	2.134	1.034	4.404	0.040
	N0	109	N3	11	2.555	1.139	5.730	0.023
Perineural invasion	No	268	Yes	23	1.842	1.057	3.210	0.031
Lymphangiosis	No	270	Yes	21	2.212	1.290	3.793	0.004
Hemangiosis	No	284	Yes	7	2.559	1.042	6.286	0.040
Capsule penetration	No	237	Yes	54	2.290	1.554	3.375	<0.001
Conglomerate lymph nodes	No	261	Yes	30	2.253	1.425	3.563	0.001
Resection margin	-	-	-	-	-	-	-	0.004
	R0	228	R1	58	1.713	1.162	2.525	0.007
	R0	228	R2	5	3.098	1.132	8.479	0.028
Positive lymph nodes	pN0	109	pN+	182	1.720	1.189	2.487	0.004
Positive lymph nodes	All (Range 0–40)	n = 291	Increase of 1 positive lymph node		1.038	1.011	1.066	0.005
Positive lymph nodes	-	-	-	-	-	-	-	0.005
	0	109	1	77	1.395	0.890	2.185	0.147
	0	109	2–5	77	1.885	1.218	2.916	0.004
	0	109	>5	28	2.375	1.361	4.144	0.002
Lymph node ratio [%]		Decrease of 1%			1.022	1.012	1.031	<0.001
Lymph node ratio	-	-	-	-	-	-	-	<0.001
	100%-94%	187	93%-87%	48	1.926	1.241	2.991	0.003
	100%-94%	187	<87%	56	2.678	1.795	3.996	<0.001

(*Contd*)

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Model: Multivariate Cox regression					
All significant variables from univariate analysis included	**Risk for**	**OR**	**95% CI LB**	**95% CI UB**	**p values**
Lymph node ratio	- 93%-87% vs 100%-94% <87% vs 100%-94%	- 1.698 2.271	- 1.077 1.482	- 2.678 3.482	0.001 0.023 <0.001
Capsule penetration	Yes vs No	1.693	1.114	2.572	0.014

CI, confidence interval; LB, lower bound; n, number (patients); R1, microscopically positive resection margin; R2, macroscopically positive resection margin; Reference, patients referred to; Risk, patients at risk; UB, upper bound

Table 4 Overall survival (bivariate and multivariate Cox regression analyses)

Variable	Reference category	n Reference	Risk for	n Risk	OR	95% CI LB	95% CI UB	p values
Age			Increase of 1 year		1.020	1.000	1.040	0.046
Oral cavity/oropharynx	Other tumour sites	124	Oral cavity/ oropharynx	167	0.637	0.426	0.951	0.027
Hypopharyngeal cancer	Other tumour sites	242	Hypopharyngeal cancer	49	2.142	1.371	3.347	0.001
Localisation	- Oral cavity Oral cavity Oral cavity Oral cavity Oral cavity	- 74 74 74 74 74	- Oropharynx Nasopharynx Hypopharynx Larynx Unknown primary	- 93 6 49 44 25	- 1.040 0.985 2.298 1.249 1.126	- 0.578 0.229 1.276 0.634 0.449	- 1.873 4.236 4.137 2.459 2.821	0.041 0.896 0.984 0.006 0.520 0.801
Staging	- Stage I Stage I Stage I	- 31 31 31	- Stage II Stage III Stage IV	- 40 57 163	- 1.608 3.336 4.408	- 0.484 1.132 1.601	- 5.345 9.829 12.138	0.002 0.438 0.029 0.004
Staging T	- T1 T1 T1 T1	- 64 64 64 64	- T2 T3 T4 Tx	- 86 68 48 25	- 1.313 1.573 2.509 1.304	- 0.72 0.82 1.345 0.512	- 2.392 3.017 4.681 3.321	0.045 0.374 0.173 0.004 0.578
Staging N	- N0 N0 N0 N0 N0	- 109 109 109 109 109	- N1 N2a N2b N2c N3	- 38 28 90 15 11	- 2.104 0.608 2.216 2.697 4.756	- 1.140 0.212 1.329 1.167 2.041	- 3.884 1.748 3.696 6.232 11.083	<0.001 0.017 0.356 0.002 0.020 <0.001
Perineural invasion	No	268	Yes	23	1.984	1.054	3.734	0.034
Lymphangiosis	No	270	Yes	21	2.602	1.415	4.784	0.002
Hemangiosis	No	284	Yes	7	3.422	1.241	9.433	0.017
Capsule penetration	No	237	Yes	54	2.821	1.810	4.396	<0.001
Conglomerate lymph nodes	No	261	Yes	30	2.938	1.771	4.874	<0.001

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Table 4 Continued

Variable	Reference category	n Reference	Risk for	n Risk	OR	95% CI LB	95% CI UB	p values
Resection margin	- R0 R0	- 228 228	- R1 R2	- 58 5	- 1.987 5.468	- 1.259 1.960	- 3.138 15.254	<0.001 0.003 0.001
Positive lymph nodes	All (Range 0–40)	n = 291	Increase of 1 LKpos		1.055	1.026	1.084	<0.001
Positive lymph nodes	w/o 0 (Range 1–40)	n = 182	Increase of 1 LKpos		1.041	1.009	1.075	0.013
Positive lymph nodes	- 0 = 0 0 = 0 0 = 0	- 109 109 109	- 1 2–5 >5	- 77 77 28	- 1.336 2.405 3.361	- 0.755 1.428 1.796	- 2.361 4.052 6.287	<0.001 0.320 0.001 <0.001
Lymph node ratio (%)			Increase of 1%		1.024	1.014	1.035	<0.001
Lymph nodes	Negative	109	Positive	182	2.021	1.285	3.180	0.002
Lymph node ratio	- 100%-94% 100%-94%	- 187 187	- 93%-87% <87%	- 48 56	- 2.617 3.561	- 1.561 2.232	- 4.387 5.682	<0.001 <0.001 <0.001
Adjuvant radiotherapy	No	114	Yes	177	1.548	1.010	2.374	0.045

Model: Multivariate Cox regression					
All significant variables from univariate analysis included	Risk for	OR	95% CI LB	95% CI UB	p values
Lymph node ratio	- 93%-87% vs 100%-94% <87% vs 100%-94%	- 2.269 2.904	- 1.331 1.761	- 3.867 4.789	<0.001 0.003 <0.001
Capsule penetration	Yes vs No	1.886	1.169	3.043	0.009

CI, confidence interval; LB, lower bound; n, number (patients); R1, microscopically positive resection margin; R2, macroscopically positive resection margin; Reference, patients referred to; Risk, patients at risk; UB, upper bound

'maximally selected rank statistic' method) as described by Lausen and Schumacher[10] and applied by Shrime et al.[24]. However, instead of defining lymph node ratio as positive lymph nodes/all excised lymph nodes, we used the percentage of negative lymph nodes/all excised lymph nodes. This technique allowed us to include all patients with negative lymph node status. This method was used for two reasons. First, our lymph node status data demonstrated no significant difference between pN0 and pN1 status. In particular, patients who underwent extensive ND and excision of a large number of lymph nodes had good prognostic outcomes if only one lymph node was positive. DFS and OS in these patients were similar to those in patients with a negative neck. In contrast, the recurrence rate was high in patients who underwent selective ND procedures, especially those who were thought to have negative neck status. Another reason for our calculation of negative instead of positive lymph nodes was the likelihood that 'the next excised lymph node' would also be negative; thus, this type of calculation is more accurate.

Ebrahimi et al.[28] also described the importance of adequate ND, demonstrating that nodal yield was an independent prognostic factor in patients with oral SCC undergoing elective ND. The combined use of nodal yield and lymph node ratio should inform the surgeon about the risk of encountering additional positive lymph nodes and may be a useful prognostic tool in the treatment of head and neck SCC.

Abbreviations list

DFS, disease-free survival; ND, neck dissection; OS, overall survival; SCC, squamous cell carcinoma.

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