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HEAD AND NECK

Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck

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Abstract The TNM classification is not specific for head and neck skin cancer and makes no allowance for disease extent. Studies have shown that the relative number of metastatic-to-examined lymph nodes, termed the Nodal ratio, is a reliable independent prognosticator in several types of cancer. The study was designed as a retrospective analysis in a university affiliated tertiary care center setting. The files of all patients ($n = 71$) with cutaneous head and neck squamous cell carcinoma and regional lymph node metastasis who attended a tertiary medical center between 1990 and 2008 were reviewed for clinical variables and outcome, and Nodal ratio was calculated. Data were analyzed for impact on survival. On multivariate analysis Nodal ratio and age were found to be significant predictors of overall survival. The *N*-ratio was the only significant predictor of disease-specific survival. Age, type of treatment (selective/modified neck dissection), pathologic N stage, and radiotherapy had no effect. The Nodal ratio is a potentially valuable prognostic index in cutaneous squamous cell carcinoma. The minimal number of nodes that need to be excised has to be determined.

Keywords Cutaneous squamous cell carcinoma · Nodal ratio · Lymph node metastasis · Radiotherapy

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Introduction

The skin is the most common site of squamous cell carcinoma (SCC), and the incidence is growing rapidly [1]. Most cutaneous SCC lesions occur on the sun-exposed head and neck, where they have the potential to metastasize from the ear, scalp, temple, and forehead to the parotid and upper cervical lymph nodes [2].

Besides tumor location, risk factors for metastasis include tumor size [3], tumor border status [4], recurrent disease, history of irradiation [5], and immune suppression [6], in addition to pathological features of perineural invasion and degree of differentiation [7]. A high proportion of the mortality and morbidity associated with high-risk cutaneous SCC is a consequence of uncontrolled metastatic nodal disease and, to a lesser extent, distant metastases.

The overall 5-year survival rate in patients with advanced skin cancer is approximately 30 % [8]. Although the clinical staging of the neck is known to be an important prognosticator [9, 10], the current TNM AJCC classification is not specific for the head and neck and makes no allowance for disease extent [11, 12].

Several researchers have proposed that the *N*-ratio, defined as the relative number of metastatic lymph-nodes-to-examined lymph nodes, may serve as an independent prognostic factor in patients with gastric, breast, and pancreatic cancer and stage-III cutaneous malignant melanoma [13–17]. The aim of the present study was to assess the prognostic value of the *N*-ratio in cutaneous SCC of the head and neck.

Materials and methods

A retrospective series design was used. We reviewed the medical charts of all patients with cutaneous SCC of the

head and neck and regional lymph-node metastasis who attended the Department of Otorhinolaryngology and Head and Neck Surgery of Rabin Medical Center between 1990 and 2008. Demographic, clinical, pathologic, and outcome data were collected. Inclusion in the study was limited to patients who were newly diagnosed during the study period, with pathological confirmation, and had not been previously treated. Patients with insufficient data or prior history of other head and neck malignancy were excluded.

At our center, the extent of neck dissection in cutaneous SCC, with or without parotidectomy, is determined by the location and extent of disease, as indicated by the preoperative clinical studies and imaging scans. Patients are staged on the basis of their final pathology results. Postoperative follow-up is performed every 2 months in the first year, every 3 months in the second and third year, and every 6 months for the next 2 years.

For the present study, we calculated the ratio of the positive neck and/or parotid nodes to the total lymph nodes removed during neck dissection and parotidectomy (*N*-ratio), and the cut-off that best correlated with outcome was determined. The clinical and treatment-related variables and the *N*-ratio were analyzed for their impact on outcome.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD). *N*-ratio, age, and positive nodes were treated as continuous variables. Rates of overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were calculated from the date of diagnosis to the date of death or recurrence or last follow-up and analyzed by the Kaplan–Meier method. Univariate analysis with Cox proportional-hazards modeling was used to test the association of the *N*-ratio with OS, DSS, and DFS. Potential covariates were also tested for their association with survival. Multivariate analysis was performed with the Cox proportional-hazards model, with OS, DSS, and DFS as the dependent variables and *N*-ratio, age, and significant variables on univariant analysis as the independent variables. To determine the *N*-ratio cut-off value, we used the log-rank test. All reported p values are two-sided; $p < 0.05$ was considered statistically significant. For statistical analyses, we used SPSS software, version 15.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Background and clinical data

The study group included 71 patients with metastatic cutaneous SCC of the head and neck, 58 (82 %) males and 13 (18 %) females. Mean age was 71 years (range 28–88). Excessive sun exposure was documented in 19 patients (24.6 %), smoking in 8 (11.26 %), and immune-suppressed state in 6 (8.45 %).

The most common primary site of disease was the auricle (14 patients) followed by the cheek (12 patients), and scalp (8 patients). Other sites included the preauricular region (7 patients), forehead (6 patients), temple (4 patients) chin, eyelid, neck, lip (3 patients each), and nose (2 patients).

The type of neck dissection was determined by the extent of disease. Fifty-six patients underwent selective neck dissection of levels 1, 2, 3, and 15 underwent modified radical neck dissection (levels 1–5). The mean (±SD) number of nodes excised during neck dissection was 15.0 ± 2.2 (range 5–42). The mean number of positive metastatic nodes was 2.2 ± 3.2 (range 1–21). Seventeen patients (23.9 %) received adjuvant radiotherapy at a median dose of 60 Gy (range 46–80) to the parotid gland and 50 Gy (range 46–76) to the neck.

Outcome

The mean duration of follow-up was 4.1 ± 4.3 years (range 1–17 years). During the follow-up period, regional recurrence in the parotid gland or neck developed in 24 patients (33 %). Recurrence was noted in 10 patients (59 %) who received radiotherapy and 13 patients (24 %) who did not.

Overall survival

A total of 36 patients died during the study period. The overall 5-year survival rate for the entire cohort was 52 % (Fig. 1). On univariate analysis, the only variables significantly associated with OS were the *N*-ratio (hazards ratio 9.98; 95 % CI 2.03–49.07, $p = 0.005$) and patient age (hazards ratio 1.06; 95 % CI 1.02–1.10, $p = 0.002$). Patient sex, number of positive nodes, number of nodes removed, radiation therapy, and pathological stage showed no association with OS. On multivariate analysis, *N*-ratio and age were found to be significant predictors of OS (*N*-ratio:hazards ratio 7.60, 95 % CI 1.64–35.30, $p = 0.01$; age:hazards ratio 1.06, 95 % CI 1.02–1.10, $p = 0.002$; Table 1).

Disease-specific survival

During the follow-up period, 13 (33 %) patients died of the disease. The 5-year DSS for the entire cohort was 78 % (Fig. 2). On univariate analysis, The *N*-ratio was the only factor significantly associated with DSS (hazards ratio 12.86, 95 % CI 1.64–100.56, $p = 0.015$). Patient age and sex, number of positive nodes, number of nodes removed, radiation therapy, and pathological stage showed no

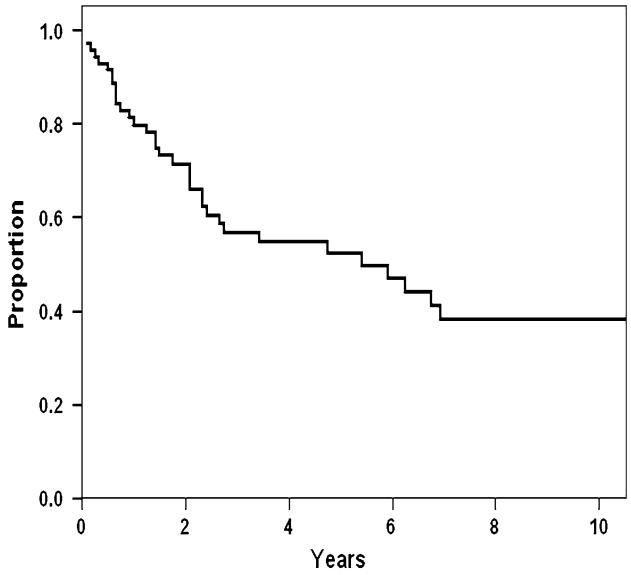

Fig. 1 Overall survival of 71 patients with cutaneous SCC of the head and neck

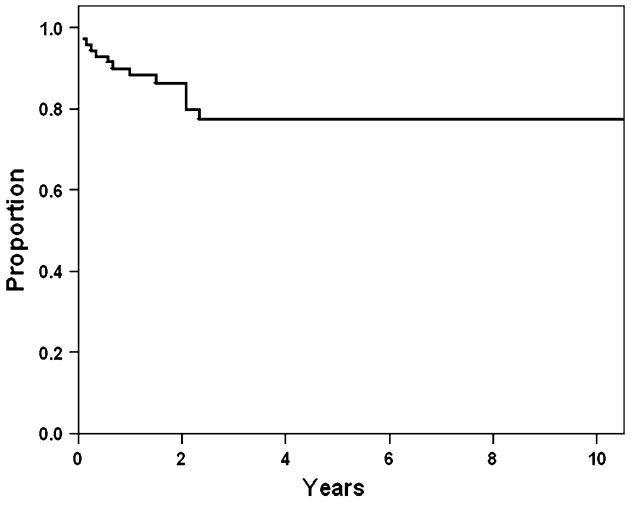

Fig. 2 Disease-specific survival of 71 patients with cutaneous SCC of the head and neck

association with DSS. Multivariate analysis confirmed that the *N*-ratio was the only statistically significant predictor of DSS (hazards ratio 10.47, 95 % CI 1.33–82.31, $p = 0.026$; Table 2).

Disease-free survival

During the follow-up period, recurrence developed in 24 patients (33 %) (Fig. 3). On univariate analysis, pathological stage (poorly differentiated vs. well differentiated) was the only variable significantly associated with DFS (hazards ratio 7.89, 95 % CI 1.02–61.39, $p = 0.048$). *N*-ratio, patient age, number of positive nodes, and number of nodes removed showed no association with DFS. On multivariate analysis, pathological stage (poorly differentiated vs. well differentiated) and radiation therapy were found to be significant predictors of DFS (pathological stage:hazards ratio 8.01, 95 % CI 1.02–61.39, $p = 0.048$; radiation:hazards ratio 2.96, 95 % CI 1.17–7.49, $p = 0.022$; Table 3).

Determination of the *N*-ratio cutoff

The log-rank test was used to determine the appropriate cutoff value for the *N*-ratio. Two subgroups with different survival rates were identified. Patients with an *N*-ratio smaller than 0.1 had a 5-year OS of 66.3 %, and patients with an *N*-ratio to 0.1 or more had a 5-year OS of 43.1 % ($p = 0.058$) (Fig. 4). The 5-year DSS rate was 91.3 % for patients with an *N*-ratio of less than 0.1 and 67.8 % for patients with an *N*-ratio of 0.1 or more ($p = 0.037$) (Fig. 5). Other *N*-ratio cutoff points were also evaluated; however, the highest differences in survival rates were observed only when the 0.1 cutoff was used.

Discussion

This is the first report to describe the potential value of the *N*-ratio in predicting survival in patients with advanced non-melanotic cutaneous SCC of the head and neck.

Table 1 Predictors of overall survival on univariate and multivariate analysis in patients with advanced cutaneous SCC

		Univariate		Multivariate	
Variable		*p* value	HR (95 % CI)	*p* value	HR (95 % CI)
N-ratio	–	0.005	9.98 (2.03–49.07)	0.01	7.60 (1.64–35.30)
Age	–	0.002	1.06 (1.02–1.10)	0.002	1.06 (1.02–1.10)
Sex	Male versus female	0.454	0.74 (0.33–1.64)	–	–
N+	–	0.212	1.05 (0.97–1.14)	–	–
Irradiation	Yes versus no	0.549	0.78 (0.34–1.78)	–	–
Pathological stage	Moderate versus well diff.	0.785	1.13 (0.47–2.74)	–	–
	Poorly versus well diff.	0.362	1.50 (0.63–3.60)	–	–

HR hazards ratio, *N+* total number of positive nodes

Table 2 Predictors of disease-specific survival on univariate and multivariate analysis in patients with advanced cutaneous SCC

Variable		Univariate		Multivariate	
		p value	HR (95 % CI)	*p* value	HR (95 % CI)
N-ratio		0.015	12.86 (1.64–100.56)	0.026	10.47 (1.33–82.31)
Age		0.268	1.03 (0.98–1.09)	0.390	1.024 (0.97–1.08)
Sex	Male versus female	0.258	0.71 (0.26–1.93)	–	–
N+	–	0.462	1.05 (0.93–1.18)	–	–
Irradiation	Yes versus no	0.891	0.914 (0.25–3.33)	–	–
Pathological stage	Moderate versus well diff.	0.317	3 (0.35–25.80)	–	–
	Poorly versus well diff.	0.177	4.24 (0.52–34.53)	–	–

HR hazards ratio, *N+* total number of positive nodes

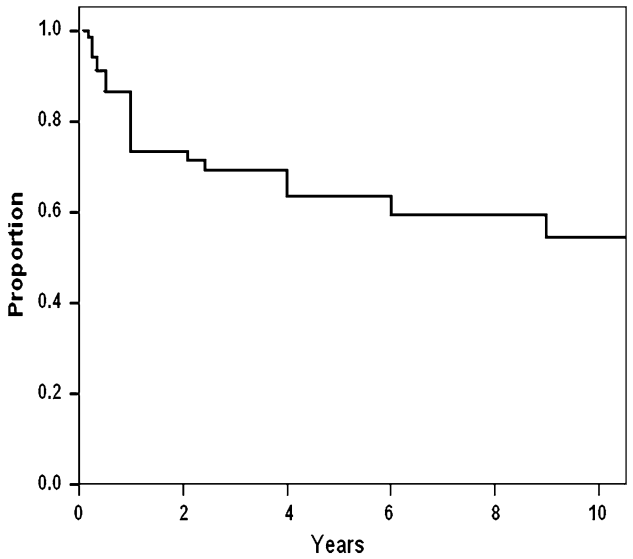

Fig. 3 Disease-free survival of 71 patients with cutaneous SCC of the head and neck

The present TNM staging system fails to accurately predict the outcome of patients with advanced head and neck skin cancer. The pathological N stage takes into consideration only the number, size, and location of the positive neck nodes removed. The *N*-ratio complements TNM staging by taking the extent of neck dissection and lymph-node clearance into consideration as well. It was developed as part of the search for more reliable measures of the significance of the clinical findings in cutaneous SCC in terms of patient outcome. Results indicate that the prognosis is considerably more favorable for patients with a low metastatic burden after comprehensive neck dissection than for patients with a high metastatic volume after selective neck dissection. The findings are in line with earlier studies of other cancers showing that the *N*-ratio may serve as a major prognostic factor in cutaneous melanoma and gastric, breast, and pancreatic cancer [15–20].

The total number of neck nodes excised depends on the extent of the neck dissection, the surgical technique used, and the meticulous analysis of the neck specimen by the pathologist. Bhattacharyya [21] reported a significant difference in the neck yield ($p < 0.05$) between supra-omohyoid neck dissection (9.9 nodes) and both radical dissection (21.8 nodes) and modified radical dissection (26.3 nodes). A significant difference was noted also between functional and modified radical neck dissection. Additionally, the neck yield has been found to be lower when dissection is performed in older patients and after radiotherapy, although this has no significant impact on the number of pathologic/metastatic nodes [21]. All these

Table 3 Predictors of disease-free survival on univariate and multivariate analysis in patients with advanced cutaneous SCC

Variable		Univariate		Multivariate	
		p value	HR (95 % CI)	*p* value	HR (95 % CI)
N-ratio		0.584	2.03 (0.16–25.60)	0.706	1.82 (0.08-40.92)
Age		0.848	1.00 (0.97–1.04	0.320	1.02 (0.98-1.06)
Sex	Male versus female	0.5	0.71 (0.26–1.93)	0.776	0.84 (0.26-2.72)
N+		0.301	0.84 (0.60–1.17)	–	–
Irradiation	Yes versus no	0.052	2.27 (0.99–5.19)	0.022	2.96 (1.17-7.49)
Pathological stage	Moderate versus well	0.073	6.52 (0.84-50.62)	0.117	5.53 (0.65-47.08)
	Poorly versus well	0.048	7.89 (1.02-61.39)	0.048	8.01 (1.02-63.08)

HR hazards ratio, *N+* total number of positive node

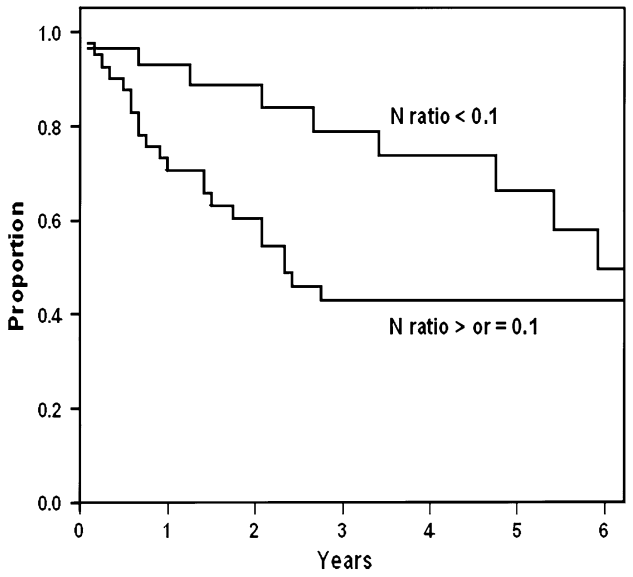

Fig. 4 Overall survival of 71 patients with cutaneous SCC of the head and neck by nodal ratio ($p = 0.05$)

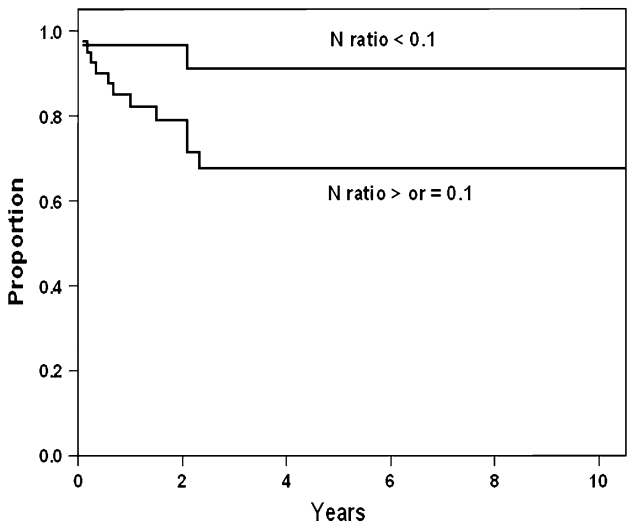

Fig. 5 Disease-specific survival of 71 patients with cutaneous SCC of the head and neck by nodal ratio ($p = 0.037$)

variables can affect the TNM stage and the *N*-ratio. In the present study, the average number of nodes removed (15 nodes) was in accordance with the literature. Although Rossi et al. [13] reported that the total number of excised nodes was not a significant prognostic indicator, Kohler et al. [22] recently found it to be important in oral cancer staging, with a significant association with survival and recurrence in early-stage carcinomas. In the present study, the number of total nodes excised was not found to be a significant predictor of OS, DSS, or DFS.

For the *N*-ratio to serve as a reliable index, the minimal number of lymph nodes that need to be excised during neck dissection must be defined. The TNM classification for gastric cancer suggests that at least 15 lymph nodes should be examined for correct assessment of the N stage [23, 24]; a minimal number of nodes has also been reported for colon cancer [25–27]. As the *N*-ratio comes into more widespread use, it will be possible to determine the necessary minimal number for cutaneous SCC as well. In the present study, we included only patients in whom at least five nodes were dissected. This is in accordance with other head and neck studies in which a minimum of four or six nodes were included in the neck dissection [28, 29]. Although limited lymph-node dissection may weaken the predictive power of the *N*-ratio, Gil et al. [28], in a study of oral cancer, demonstrated that even when fewer than 20 neck lymph nodes were removed, the *N*-ratio remained the only significant outcome predictor. Accordingly, Marchet et al. [19] evaluated patients with gastric cancer and found that the *N*-ratio was valuable even after limited regional lymph-node dissection. Because the *N*-ratio reflects a continuous variable of neck involvement, it is even more important in advanced neck disease (N2–N3) in which the regional tumor burden is not well reflected by the TNM staging system. Therefore, formulation of the *N*-ratio overcomes the inadequate staging of the pathological N stage in cases of selective neck dissections because it takes the proportion of neck clearance into account.

Stage migration refers to the fact that a patient might actually have a more advanced disease than reported at presentation if a more extensive lymph-node dissection had been completed [13, 14, 30]. The phenomenon is expected to occur in cutaneous SCC when an insufficient number of lymph nodes is examined. For example, with better procedures, patients initially staged N0 may be restaged as N+ or N1. Use of the *N*-ratio could limit stage migration because it identifies subgroups with a different prognosis among patients with the same N stage according to the traditional TNM classification [19, 31, 32]. Marchet et al. [14] noted that in patients with gastric cancer, although the excision of a low number of lymph nodes might lead to under-staging when the TNM classification is applied, it did not affect the sensitivity of the *N*-ratio for patient outcome, even in the presence of a small number of nodes. Therefore, the *N*-ratio has a greater prognostic power than the traditional N classification.

The present study has several limitations. Some of our patients underwent selective neck dissection, and the reduced number of lymph nodes removed could have affected the *N*-ratio. The *N*-ratio can be calculated only in patients with positive neck nodes in whom a sufficient number of lymph nodes are removed during neck dissection. Although the predictive power of the *N*-ratio remained significant for DSS and OS in the present study, further investigations of head and neck cancer are needed to establish guidelines for the minimal number of nodes that

should be retrieved. Furthermore, the relatively small sample size might have reduced the statistical power in calculating the predictive value of the *N*-ratio. Larger series from other centers should address this issue.

Conclusions

The *N*-ratio is a potentially valuable prognostic index in cutaneous SCC because it takes into account both the extent of the neck dissection, represented by the number of lymph nodes removed, as well as the regional tumor burden (number of positive nodes in the specimen). The present study found it to be a significant predictor of OS and DSS. The power of the *N*-ratio is derived from the simple way it is calculated and presented, and its use in various types of cancer is supported by a growing body of literature. The *N*-ratio concept enhances the ability of clinicians to accurately evaluate the significance of the pathological findings and thereby improve patient outcome and quality of life. Our study provides additional evidence that favors the *N*-ratio as the standard N-staging system in cutaneous SCC. Further prospective and retrospective studies are needed before it can be integrated into clinical practice.

Conflict of interest None.

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