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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Clinical Nodal Stage is a Significant Predictor of Outcome in Patients with Oral Cavity Squamous Cell Carcinoma and Pathologically Negative Neck Metastases: Results of the International Consortium for Outcome Research

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ABSTRACT

Background. We aimed to study the importance of clinical N classification (cN) in a subgroup of patients with oral cavity squamous cell carcinoma (OSCC) and pathologically negative neck nodes (pN−).

Methods. A total of 2,258 patients from 11 cancer centers who underwent neck dissection for OSCC (1990–2011) had pN− disease. The median follow-up was 44 months. 5-year overall survival (OS), disease-specific survival (DSS), disease free survival, local control, locoregional control, and distant metastasis rates were calculated by the Kaplan–Meier method. cN classification and tumor, node, metastasis classification system staging variables were subjected to multivariate analysis.

Results. A total of 345 patients were preoperatively classified as cN+ and 1,913 were classified as cN−. The 5-year OS and DSS of cN− patients were 73.6 and 82.2 %, respectively. The 5-year OS and DSS of cN+ patients were 64.9 and 76.9 %, respectively ($p < 0.0001$ each). A cN+ classification was a significant predictor of worse OS ($p = 0.03$) and DSS ($p = 0.016$), regardless of treatment, depth of invasion, or extent of neck dissection. cN classification was associated with recurrence-free survival ($p = 0.01$) and locoregional (neck and primary tumor) control ($p = 0.004$), but not with local ($p = 0.19$) and distant ($p = 0.06$) recurrence rates.

Conclusions. Clinical evidence of neck metastases is an independent predictor of outcome, even in patients with pN− nodes.

The management of oral cavity squamous cell carcinoma (OSCC) generally includes surgical resection of the primary tumor and elective neck dissection for clinically

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negative neck nodes (cN−) or therapeutic neck dissection for clinically positive neck nodes (cN+).[1] Adjuvant radiotherapy or chemoradiotherapy are indicated only if there are adverse pathological features that increase the risk of tumor recurrence.[2,3] Because pathological evidence of lymph node metastases was demonstrated to be associated with poor outcome, it most often requires adjuvant therapy in the form of neck radiotherapy.[4–6] In contrast, the absence of pathological evidence of nodal metastases usually rules out the need for radiotherapy.

Both clinical and pathological stage are significant predictors of outcome.[7] Clinical nodal stage was demonstrated to be an independent risk factor in laryngeal cancer, yet its role in OSCC still remains to be proven.[8] However, although histological analysis is considered the gold standard for staging, insufficient lymph node dissection and inaccurate histopathological evaluation can potentially result in understaging of cancer.[9] In such settings, it is possible that the combination of imaging and physical examination will result in accurate detection of nodal metastases that the surgical clearance and pathological evaluation have missed.

In this multicenter international study, we studied the importance of cN classification in a selected group of patients with pathologically negative neck nodes (pN−). We hypothesized that the clinical evidence of nodal disease would reflect the true presence of neck metastases in some of those patients. We tested this hypothesis by analyzing the outcome of patients by Kaplan–Meier plots and multivariate analyses. We were able to demonstrate, for the first time, that clinical evidence of neck metastases reflects an independent risk of poor outcome in patients with a pN− classification.

PATIENTS AND METHODS

Our study cohort included anonymized data on 4,259 patients from 11 cancer centers worldwide between 1990 and 2011. The study was approved by the local institutional review board committees of the participating centers. Data were collected retrospectively on all patients by using uniform database templates to ensure consistent data collection. Eligible patients were preoperatively staged by the anatomical extent of the disease as found on physical examination and computed tomography. Staging was done before first definitive treatment was given according to the current tumor, node, metastasis (TNM) classification system. Patients were treated for OSCC with primary surgery with or without adjuvant radiotherapy or chemoradiotherapy. All patients underwent unilateral or bilateral neck dissection involving levels I–III, I–IV, or I–V as described by the American Head and Neck Society.[10] The type of neck dissection was planned beforehand in all patients before the operation. Median follow-up was 41 months (range 2–322 months).

Histopathological Analysis

All the lymph nodes were evaluated for metastasis by local pathologists at each institute. A total of 144,719 lymph nodes were evaluated, of which 138,285 (95.5 %) were defined as pN−. Specimen dissection and tissue sampling of the primary tumor was in accordance with the guidelines for the histopathological assessment of head and neck cancer.[11]

Statistical Analysis

Five-year overall survival (OS), disease-specific survival (DSS), and local control, locoregional control, and distant metastasis rates were calculated by the Kaplan–Meier method. The differences in survival rate were assessed by the log-rank test. The 5-year distant metastasis rate was calculated using failure plots, and the differences in metastasis rates were assessed by the log rank test. OS was measured from the date of surgery to the date of death or last follow-up. For DSS, the patients who died from causes other than OSCC were censored at the time of their death. Lymph node dissection yield cutoff was determined to 18.[12] The variables that had prognostic potential as suggested by the univariate analysis were subjected to multivariate analysis by the Cox proportional hazard regression model. Analysis was performed by JMP software (SAS Institute, Cary, NC) and confirmed by independent statisticians (E.S. and C.R.) by the IBM SPSS Statistics package (IBM, Armonk, NY). A two-sided p value of <0.05 was considered to indicate statistical significance. The sixth edition of the TNM system for oral cavity SCC was used for staging.[13]

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies.[14]

RESULTS

We aimed to study the importance of cN classification in a subgroup of patients who had no evidence of nodal metastases on pathological examination (pN− classification). Table 1 shows the clinical and pathological characteristics of those patients. Out of a total of 4,259 patients diagnosed as having OSCC, 2,424 (57 %) patients had a cN− classification. Of the cN− patients, 1,913 (79 %) had negative nodes on pathological examination

and 511 (21 %) had positive neck nodes (Fig. 1). Among the cN+ patients, 345 (19 %) had a pN− classification and 1,491 (81 %) had pathological evidence of neck metastases. The number of neck metastases varied from 1 to 34 (mean 3.1 ± 4.6). The sensitivity, specificity, and accuracy of the clinical evaluation of the neck were 81, 79, and 80 %, respectively.

Further analysis of the 2,258 patients with a pN− classification revealed that 1,913 (79 %) underwent elective neck dissection (cN−), while therapeutic neck dissection (cN+) was performed in the remaining 345 patients (21 %). Kaplan–Meier estimates of 5-year OS and DSS in this group were 81 and 72 %, respectively (Fig. 1b). At 5 years after surgery, 567 patients (25.1 %) had experienced locoregional recurrence and 82 patients (3.6 %) had distant metastasis.

Next, the outcome of patients with cN− or cN+ and pN− was compared by Kaplan–Meier analysis. The 5-year OS of patients staged as cN− was 73.6 %, whereas it was 64.9 % in those staged as cN+ ($p < 0.0001$). Similarly, the 5-year DSS of patients staged as cN− was 82.2 % compared to 76.9 % for those staged as cN+ ($p = 0.007$). The Kaplan–Meier graphs of the patients with cN+ and cN− classification are provided in Fig. 2.

In order to identify predictors of outcome in this group, we initially performed a univariate analysis for each of the following variables: depth of invasion (DOI, ≤4 mm vs. >4 mm), margin status (positive, close <5 mm, or negative), total number of nodes resected (≤18 vs. >18), treatment group (surgery alone, surgery and radiotherapy, or surgery and chemoradiotherapy), pathological T stage, clinical N stage, age (≤70 years vs. >70 years), and gender.[12] The results of these analyses demonstrated that age, pathological T stage, DOI, margin status, clinical N stage, and treatment group were significant predictors of both 5-year OS and DSS among patients with a pN− neck (Table 2). Interestingly, treatment group and number of nodes resected were a significant predictor of 5-year OS but not DSS.

The prognostic importance of these variables among patients with a pN− classification was next evaluated by a multivariate model. Age, margin status, DOI, and clinical N stage remained significant independent predictors for both OS and DSS on multivariate analysis (Table 2). For OS, the treatment group lost statistical significance, and interestingly, pathological T stage lost significance for DSS. Clinical nodal status was associated with recurrence-free survival ($p = 0.01$) and locoregional (neck and primary tumor) control ($p = 0.004$), but not with local ($p = 0.19$) and distant ($p = 0.06$) recurrence rates (Fig. 3). To assess noncontemporaneous control bias, we analyzed the prognostic importance of clinical N stage in two time periods, 1990–2000 and 2000–2011.[15] The results of these analyses demonstrated that clinical N stage remained significant predictors of both 5-year OS and DSS among patients with a pN − neck during both time periods ($p = 0.03$ and $p = 0.04$, respectively).

TABLE 1 Clinical data of patients with a pN− classification

Characteristic	Variable	Value
Patients	Total no.	2,258 (100 %)
Age (year)	Mean ± SD (range)	55 ± 12 (26–93)
Gender	Male	1,516 (67 %)
	Female	742 (33 %)
Treatment	Surgery	1,115 (49 %)
	Surgery + RT	987 (44 %)
	Surgery + CRT	93 (4 %)
	Surgery + RT + cetuximab	63 (3 %)
Type of neck dissection	Elective	1,913 (85 %)
	Therapeutic	345 (15 %)
Extent of neck dissection (by level)	I–III/IV	1,512 (67 %)
	I–V	273 (12 %)
	Radical	179 (8 %)
	Bilateral	294 (13 %)
Pathological T classification	1	461 (20 %)
	2	798 (35 %)
	3	280 (13 %)
	4	719 (32 %)
Follow-up, all patients (month)	Mean	57 ± 48
	Median	44
	Range	1–302

pN− negative pathological nodal stage, *SD* standard deviation, *RT* radiotherapy, *CRT* chemoradiotherapy

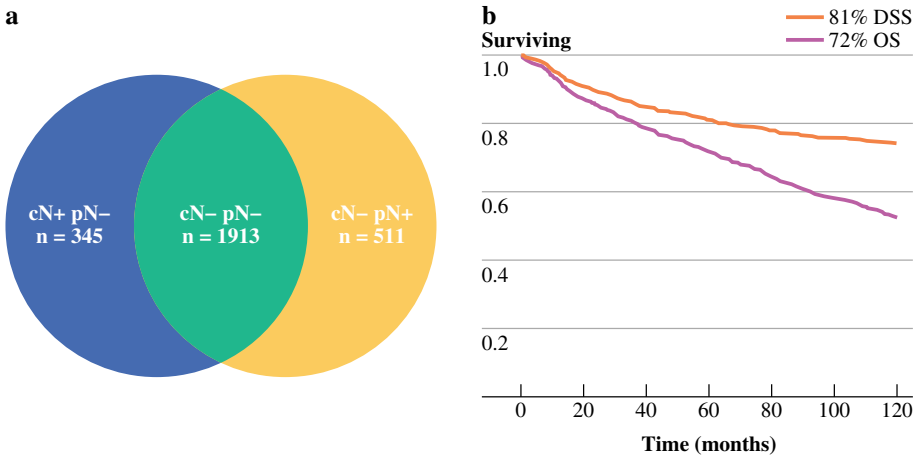

FIG. 1 **a** Venn diagram showing the relationship between clinical and pathological staging. Distribution of clinical and pathological analyzes of all patients in this cohort. *cN* clinical node status (− or +), *pN* pathological node status (− or +). **b** 5-year overall survival (*purple line*) and disease-specific survival (*red line*) calculated by Kaplan–Meier analysis of all patients in this cohort

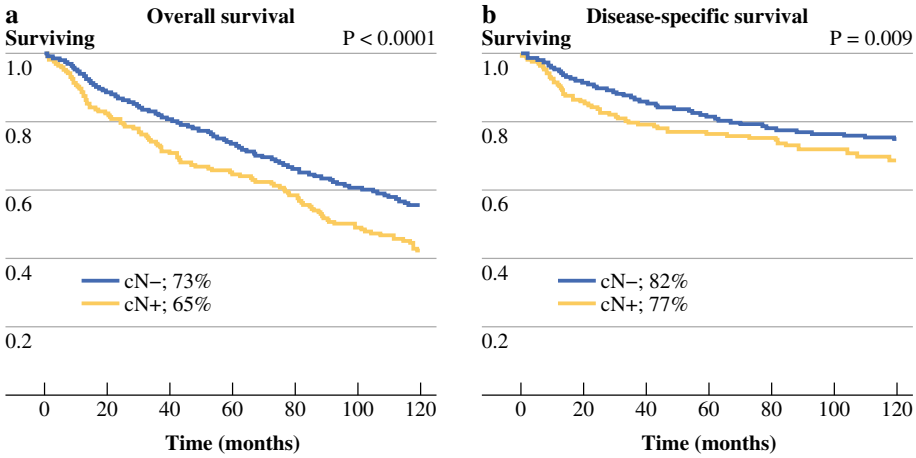

FIG. 2 Clinical neck classification and outcome. **a** 5-year overall survival and **b** disease-specific survival calculated using the Kaplan–Meier analysis in patients with pathologically negative neck nodes. *cN−* clinically node negative patients (*blue line*), *cN+* clinically node positive patients (*yellow line*)

Adjuvant therapy in OCSS may include radiotherapy or chemoradiotherapy. We next investigated whether the type of adjuvant treatment improved the outcome of patients with cN+/pN− (high risk group). To answer this question, we performed a multivariate analysis for the outcome of patients with cN+/pN− according to the type of adjuvant treatment. This analysis revealed that chemoradiotherapy treatment is an independent prognostic factor for better OS and DSS in this population ($p = 0.04$, hazard ratio 0.74, 95 % CI 0.67–0.97, and $p = 0.002$, hazard ratio 0.81, 95 % CI 0.66–0.94, respectively) (Supplemental Fig. 1).

To confirm our results, we repeated the multivariate analysis on the 219 pathologically N0 patients who were treated in a single institution (Memorial Sloan-Kettering Cancer Center, New York, NY). Statistical analyses of this single institution cohort found that better OS and DSS was achieved in cN− patients compared to cN+ patients ($p = 0.006$ and $p = 0.02$, respectively).

DISCUSSION

Analysis of the patterns of treatment failure in patients with OSCC reveals that approximately one-third of them will experience treatment failure as a result of regional metastases.[16–19] Pathological staging is the gold standard analysis by which risk stratification is made and treatment is tailored. However, the pN classification, which depends on the extent of neck dissection (the surgical technique) and on the sampling procedure (the level of histopathologic scrutiny), is not error free. We hypothesized that there may be situations in which neck metastases that were discovered in the clinical/radiological examinations were missed by the pathological study. This research aimed to investigate the importance of a cN+ finding vis-à-vis a pN− finding. Our results demonstrated that clinical evidence of neck metastases is associated with reduced OS and DSS, even when the pathological analyses revealed no evidence of neck metastases. Multivariate analysis indicated that the cN classification is an independent predictor of outcome among patients with a pathologically N0 classification, regardless of other clinical or pathological variables. Our finding that a cN+ classification is associated with neck recurrence but not with local recurrence or distant metastases further strengthens the possibility of missed nodal metastases in this population.

TABLE 2 Univariate and multivariate analysis of outcome

Variable	Univariate analysis		Multivariate analysis	
	OS (*p*)	DSS (*p*)	OS (*p*) or HR (95 % CI)	DSS (*p*) or HR (95 % CI)
Gender	0.87	0.29	NA	NA
Age	<0.0001	<0.0001	<0.0001	<0.0001
≤70 year			1	1
>70 year			3.1 (1.9–6.3)	1.7 (1.22–2.98)
Treatment	0.02	0.34	0.28	NA
Surgery			1	
SRT			1.31 (0.73–1.55)	
SCRT			1.22 (0.76–1.42)	
pT stage	<0.0001	0.02	0.001 (2.6)	0.08
1			1	1
2			1.4 (1.03–2.1)	1.22 (0.41–1.9)
3			2.1 (1.46–4.2)	1.5 (0.53–2.6)
4			2.6 (1.68–5.3)	2.05 (0.88–3.98)
cN stage	<0.0001	0.009	0.03 (1.47)	0.016 (1.52)
Negative			1	1
Positive			1.47 (1.1–3.1)	1.52 (1.2–4.3)
Total no. of LN	0.049	0.1	0.02	NA
≤18			1	
>18			1.36 (1.06–1.87)	
DOI	<0.0001	<0.0001	0.003	<0.0001
≤4 mm			1	1
>4 mm			1.7 (1.22–3.6)	2.2 (1.76–4.65)
Margins	<0.0001	<0.0001	<0.0001	<0.0001
Negative			1	1
Positive			1.9 (1.3–5.56)	2.8 (1.6–6.78)

OS overall survival, *DSS* disease-specific survival, *HR* hazard ratio, *CI* confidence interval, *NA* not applicable, *S* surgery, *SRT* surgery and radiotherapy, *SCRT* surgery and chemoradiotherapy, *LN* lymph node, *DOI* depth of invasion

The relationship between preoperative clinical nodal status and survival in pN− patients has not been examined systematically in a large cohort of patients with OSCC. Preoperative clinical nodal staging is primarily based on physical examination, combined with radiographic features as revealed by computerized tomography (CT), positron emission tomography (PET), or ultrasound.[20] The size and shape of lymph nodes, loss of fatty hilum, central necrosis, increased vascularity, and high FDG uptake on PET are suggestive of malignant nodal spread.[21] It was demonstrated that physical examination can identify 75 % of pathologic cervical adenopathy, and that this detection rate increases to 91 % with the addition of CT studies.[22] Recent reports revealed that clinical staging has a 15 % false-positive and a 44 % false-negative rate, and demonstrated 53 % concordance between clinical and pathological nodal staging.[23]

Metastatic tumor cells may be present in lymph nodes, even in patients without histological evidence of nodal metastases by conventional methods. Indeed, previous reports have indicated that standard pathologic staging underestimates the true presence of nodal metastases.[24,25] Furthermore, serial sectioning, immunohistochemical staining, and RT-PCR can detect lymph node metastases that were missed by conventional staining with hematoxylin and eosin.[26–28] In this respect, our finding further strengthen the possibility that pathological analysis or surgical sampling may miss small volume nodal disease.

One of the factors inherent to the design of the current study is variability in the processing of the pathological specimens. In our patient population, the mean number (±SD) of lymph nodes that were removed was 29 ± 20 (range 1–154). However, fewer than 20 lymph nodes were found only in 550 (24.2 %) patients, and 91 % of them had selective neck dissection. The previously reported mean lymph nodes yield in a unilateral radical neck dissection was 21–50, and therefore, the variations in the number of lymph nodes retrieved from our specimens are similar to other studies.[29–31] Another limitation of this study is the lack of information on how clinical staging was performed and the fact that with the long study period it may not be generalizable to current clinical staging with modern imaging techniques.[32] Yet the significance of cN stage as a predictor of outcomes in our heterogenous cohort across

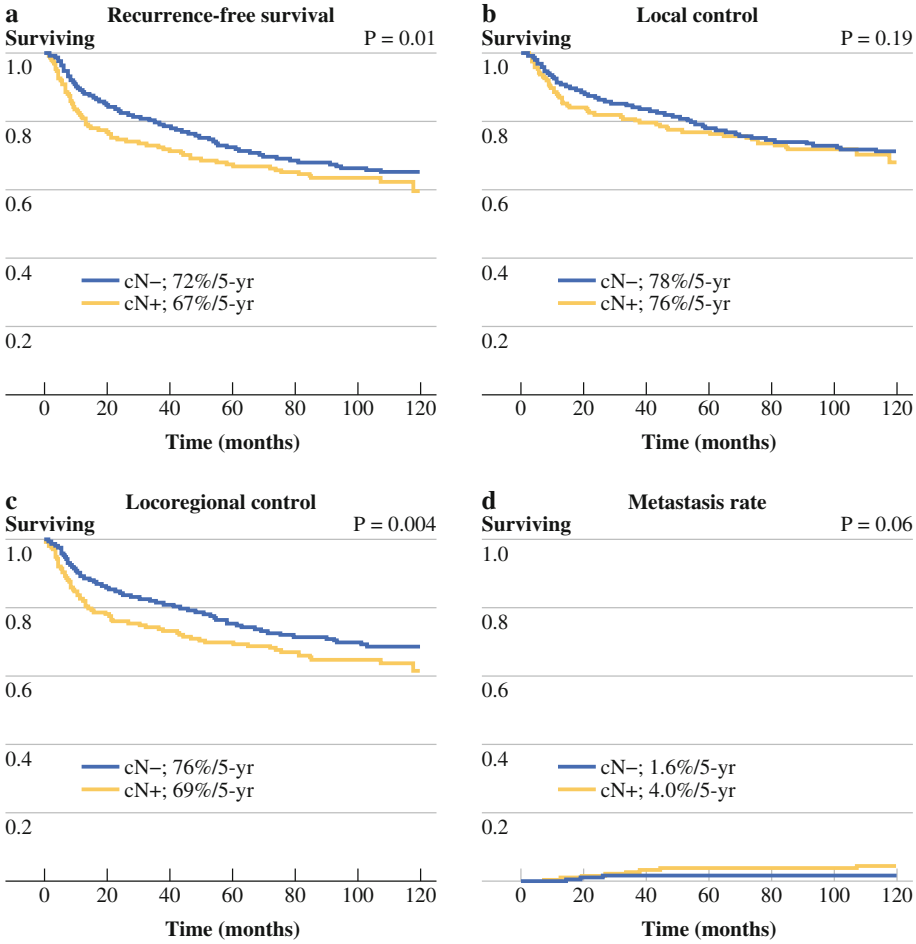

FIG. 3 Patterns of failure in patients with cN− and cN+ nodes. **a** 5-year local recurrence-free survival (at the primary site). **b** 5-year regional recurrence-free survival (in the neck region). **c** 5-year locoregional recurrence-free survival (at the primary site and neck). **d** Distant metastasis failure rate. *cN−* clinically node negative patients (*blue line*), *cN+* clinically node positive patients (*yellow line*)

multiple countries assure the broad applicability of research finding worldwide and might facilitate the uptake of LND as a prognosticator into standard practice in diverse patient populations.[33]

Recent studies have demonstrated slight improvement in 5-year survival rates after adjuvant concurrent chemoradiotherapy compared to radiotherapy alone for advanced head and neck squamous cell carcinoma.[2] However, as a result of the significant morbidity associated with intensification of adjuvant treatment, i.e., adding chemotherapy to radiotherapy, there is still considerable controversy over the pathological characteristics of the tumor that predict the need for more aggressive adjuvant treatment.[34] On the basis of our findings in a high-risk patient group (cN+/pN−), we hypothesize that clinical nodal staging can potentially assist in identifying patients with poor outcomes and therefore for whom more aggressive adjuvant treatment is needed. Further studies are required to determine whether patients with cN+/pN− staging will benefit from concurrent chemoradiotherapy. Our findings are based on data retrieved from 11 different centers, a factor that bestows considerable power on this study. Although our findings indicate that patients with cN+ classifications are at higher risk for recurrence, the conventional system of pathological classification should remain in standard use until the value of clinical staging is validated by other studies.

In conclusion, in this study, we investigated a selected group of patients with a pN− neck classification. We demonstrated that clinical evidence of neck metastases is associated with a high risk of regional recurrence regardless of the pathological N classification. According to our results, clinical evidence of nodal metastases is an independent prognostic factor of OS and DSS. Further studies are warranted in order to decide whether these patients would benefit from adjuvant treatment.

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DISCLOSURE The authors declare no conflict of interest.

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