Original Investigation

The Origin of Regional Failure in Oral Cavity Squamous Cell Carcinoma With Pathologically Negative Neck Metastases

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IMPORTANCE Squamous cell carcinoma of the oral cavity (OSCC) is a common malignant tumor worldwide.

OBJECTIVE To determine if regional failure in patients with OSCC and pathologically negative neck nodes (pN–) is due to an incomplete sampling procedure during surgery.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively reviewed the medical records of 2258 patients from 11 cancer centers worldwide who underwent neck dissection for OSCC (1990-2011) and who were pN–. Of those, 345 had clinical evidence of nodal metastases (cN+) on radiologic workup. The neck specimens were available for reanalysis in 193 patients. Survival rates were calculated using the Kaplan-Meier graphs and analyzed by multivariable analysis.

MAIN OUTCOMES AND MEASURES Five-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS).

RESULTS Resectioning and analysis of the neck dissection specimens in the cN+/pN– subgroup revealed false-negative results in 29 (15%) of 193 patients. The negative predictive value of the initial pathologic examination was 85%. The 5-year OS and DSS in the cN–/pN– group were 77.6% and 87.2%, respectively. The 5-year OS and DSS of the cN+/pN– group were 62.6% and 78.5%, respectively ($P < .001$). In multivariable analysis, cN+ classification was significantly associated with poor OS (hazard ratio [HR], 1.7; 95% CI, 1.1-3.8; $P = .03$) and poor DSS (HR, 1.46; 95% CI, 1.1-4.1; $P = .04$). A cN+ classification was associated with lower DFS (66.3% vs 76.2%; $P = .05$) and lower regional recurrence–free survival (68.6% vs 78.8%; $P = .02$) but not with local ($P = .20$) or distant recurrence ($P = .80$).

CONCLUSIONS AND RELEVANCE Pathologic staging underestimates the incidence of nodal metastases in cN+ disease. After correction for pathologically missed nodal metastases, radiologic evidence of neck nodes is an independent predictor of outcome, suggesting that traditional sampling during surgery might miss metastases, and this fact might explain the origin of treatment failure in these patients.

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With an estimated 263 900 new cases annually and 128 000 deaths per year worldwide, squamous cell carcinoma of the oral cavity (OSCC) represents a common malignant lesion and a significant cause of morbidity.[1] Although the incidence of OSCC has decreased in most developed countries over the past decades, it remains a prevalent cancer for both men and women in south central Asia and in central and eastern Europe.[2] The AJCC/UICC (American Joint Cancer Committee/Union Internationale Contre le Cancer) TNM staging system for OSCC is based on primary tumor classification (T); quantification of nodal metastases according to size, number, and distribution (N); and the presence of distant metastases (M).[3] The management of OSCC generally includes surgical resection of the primary tumor and elective neck dissection for clinically negative neck nodes (cN−) or therapeutic neck dissection for clinically positive neck nodes (cN+).[1] Adjuvant radiotherapy and/or chemoradiation are indicated only if there are adverse pathologic features that increase the risk of tumor recurrence.[4,5] Positive lymph nodes are identified by a thorough clinical examination, imaging studies, and a properly performed neck dissection with appropriate pathologic analysis of its contents. Since any therapeutic decision is based on histopathologic analysis, sampling problems like low nodal yield with insufficient lymph node dissection can potentially result in inaccurate diagnosis of cancer.[6-8] It was previously shown that routine histopathologic tissue sampling and processing had a false-negative results, which led to understaging, in 45% of patients.[9] As such, the probability of identifying metastasis in lymph nodes relies on the technical performance of both surgeons and pathologists. Hence it is possible that the combination of imaging and physical examination will result in accurate detection of nodal metastases that the surgical clearance and pathologic evaluation have missed.[10,11]

Recently, our research group[12] has shown that clinical evidence of nodal metastases is an independent predictor of outcome even in patients with pathologically negative neck disease. In the present study, we seek to investigate the rate of missed nodal metastases in patients with cN+/pN− disease by reanalysis of the pathologic neck specimens in this population. We also aim to reevaluate whether these missed nodal metastases may account for the poorer outcome of this group of patients.

Methods

Our study cohort included anonymized data on 4259 patients from 11 cancer centers worldwide treated 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 according to the results of the physical examination and the radiology workup (computed tomography and ultrasonography). Neck nodes were considered positive according to standard criteria.[3] Staging was performed according to the TNM system before definitive treatment. Patients were treated for OSCC with primary surgery with or without adjuvant radiotherapy or chemoradiotherapy. All patients underwent an ipsilateral or bilateral neck dissection involving either levels I to III, I to IV, or I to V, the boundaries of which have been defined by the American Head and Neck Society.[13] The type of neck dissection was determined in all patients before the operation. Median follow-up was 68 months (range, 6-302 months).

Histopathologic Analysis

A total of 144 719 lymph nodes were evaluated, of which 138 285 (95.5%) were defined as being pN−. The neck specimens of patients with cN+/pN− disease were reevaluated for metastasis at each center by a certified head and neck pathologist. Specimen dissection, tissue sampling, fixing, cutting, and microscopic examination of the primary tumor were carried out in a similar way according to the guidelines for histopathologic assessment.[14] For revision, all nodes identified by the pathologist and available for analysis were submitted for analysis. Lymph node paraffin blocks were sampled at 5-µm sections with 150- to 200-µm intervals. Seven to 12 sections per lymph node were assigned for hematoxylin-eosin staining and histopathologic assessment.

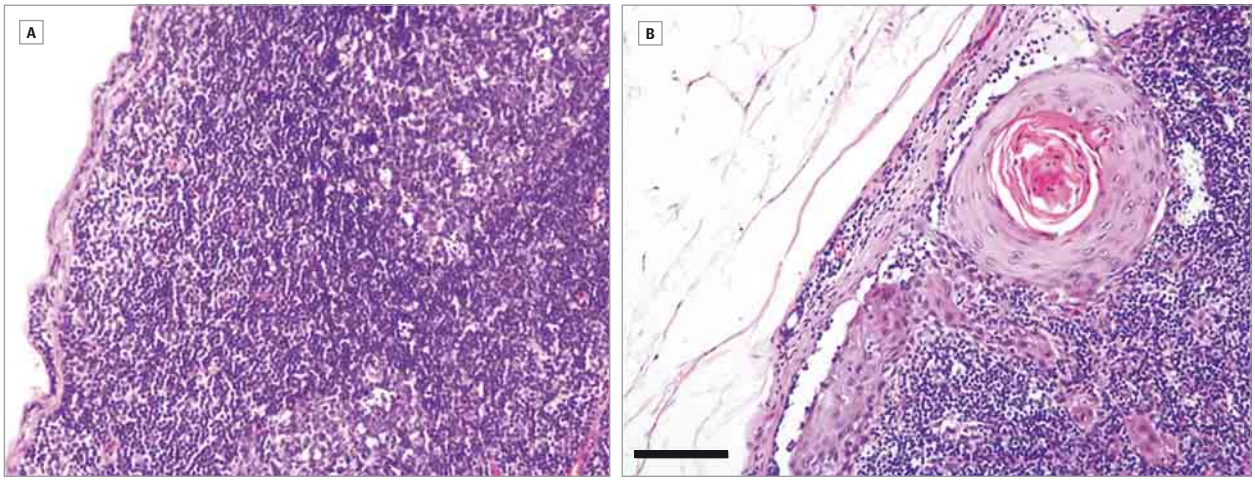
Statistical Analysis

Five-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS); local control; regional control; and distant metastasis rates were calculated using the Kaplan-Meier method. The differences in survival rates were assessed by the log-rank test. Overall survival 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 death. To identify predictors of outcome, we performed a univariable analysis for each of the following variables: depth of invasion (DOI, ≤4 mm vs >4 mm), margin status (positive or negative), treatment group (surgery alone, surgery and radiotherapy, or surgery and chemoradiation), pathologic T stage, clinical N stage, age (≤70 years vs >70 years) and sex.[15] The variables that had prognostic potential as suggested by the univariable analysis were subjected to multivariable analysis with the Cox proportional hazards regression model. Analysis was performed using JMP software, version 9 (SAS Institute Inc) and confirmed by an independent statistician using the 2010 release of the IBM SPSS Statistics package (IBM). A 2-sided *P* value of <.05 was considered to indicate statistical significance. The sixth edition of the AJCC/UICC TNM staging system for OSCC was used for TNM staging.[3]

Results

There were 2258 total patients with pN− disease: 1913 (84%) with cN− disease and 345 (16%) with cN+ disease. Among the 345 neck specimens that were cN+/pN−, 193 (56%) were reprocessed for pathologic evaluation. The number of nodes per neck dissection obtained at each institution summarized in the eTable in the Supplement. Of these, pathologic evidence of nodal metastases was found in 29 patients. Sample patho-

Figure 1. Pathologic Images From a Representative Case of Revised Pathology



A, Pathologic sample originally read as negative for metastasis. B, Pathologic sample after resectioning prompted a change in reading to positive for metastasis. Original magnification ×20 and hematoxylin-eosin stain for both panels.

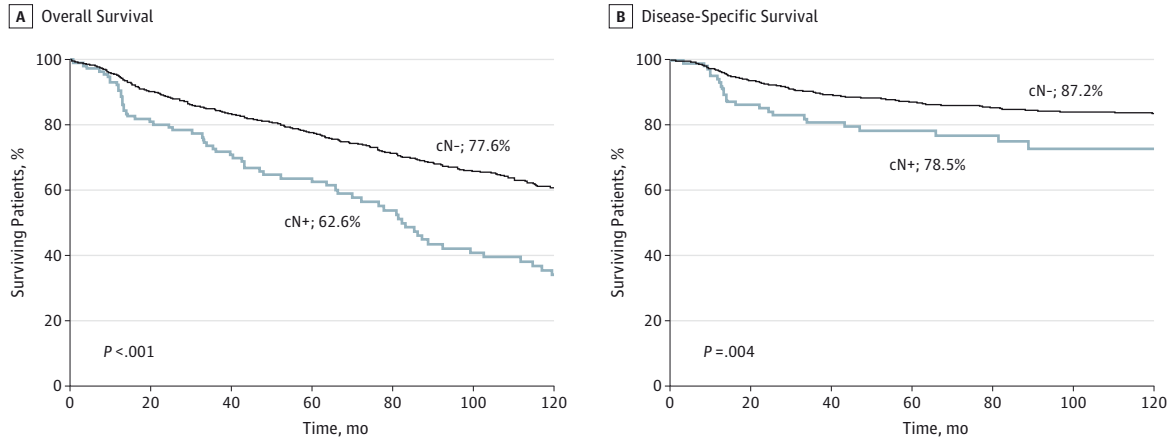
Table 1. Clinical Nodal Status of Patients With pN− Disease After Pathology Revision

Characteristic	Patients, No. (%) (n = 2077)		*P* Value
	cN− (n = 1913)	cN+ (n = 164)	
Age, mean (SD), y	55 (13)	54 (11)	.80
Sex			
Male	1243 (65)	100 (61)	.40
Female	670 (35)	64 (39)	
Treatment			
Surgery	937 (49)	92 (56)	.10
Surgery + RT	842 (44)	62 (38)	
Surgery + CRT	134 (7)	10 (6)	
Extent of neck dissection (by levels)			
I-III/IV	1492 (78)	31 (19)	.01
I-V	153 (8)	23 (14)	
Radical	76 (4)	66 (40)	
Bilateral	192 (10)	44 (27)	
Total excised nodes, median (range), No.	25 (15-120)	44 (16-142)	.008
Pathologic T classification			
1-2	1090 (57)	97 (59)	.12
3-4	823 (43)	67 (41)	
Depth of invasion, mm			
≤4	1447 (76)	113 (69)	.07
>4	466 (24)	51 (31)	
Margin status			
Negative	1702 (89)	137 (84)	.40
Positive	211 (11)	27 (16)	
Follow-up, median (range), mo	66 (6-302)	72 (6-277)	.18

Abbreviations: cN+, clinically positive neck nodes ; cN−, clinically negative neck nodes; CRT, chemoradiotherapy; pN−, pathologically negative neck nodes; RT, radiotherapy.

logic images from a case of revised diagnosis are provided in **Figure 1**. The mean (SD) number of missed nodes with metastasis was 1.13 (1.35) (1 node in 25 patients upstaged to N1 and 2 nodes in 4 patients upstaged to N2). Hence, revision of the pathologic analysis of cN+/pN− revealed a false-negative value of 15% for routine pathology. Analysis of variance between institutions revealed no difference in sampling errors. Clinical and pathologic characteristics of the patients with cN+/pN− (n = 164) and cN−/pN− (n = 1913) disease included in the analysis are listed in **Table 1**. Kaplan-Meier estimates of 5-year OS and DSS in the pN− group (**Figure 2**) were 76.5% and 86.6%, respectively.

Figure 2. Kaplan-Meier Survival Graphs in Patients With Pathologically Negative Neck Nodes by Clinical Nodal Status



A, Five-year overall survival. B, Five-year disease-specific survival. Both graphs are calculated using Kaplan-Meier analysis of patients with pathologically negative neck nodes after revision of the pathology. cN+ indicates patient with clinically positive neck nodes (n = 164); cN−, clinically negative neck nodes (n = 1913).

Table 2. Univariable Analysis of Outcomes[a]

Variable	Survival			Regional Recurrence
	Overall	Disease-Specific	Disease-Free	
Sex	.20	.36	.40	.70
Age, y				
≤70	<.001	.001	.18	.08
>70				
Treatment				
Surgery	.01	.02	.06	.72
Surgery + RT				
Surgery + CRT				
pT stage				
1	<.001	<.001	.006	.06
2				
3				
4				
cN stage				
Negative	<.001	.009	.04	.03
Positive				
DOI, mm				
≤4	.003	.001	.08	.16
>4				
Margins				
Negative	<.001	<.001	<.001	<.001
Positive				

Abbreviations: CRT, chemoradiotherapy; DOI, depth of invasion; HR, hazard ratio; LN, lymph node; NA, not applicable; pT, pathologic T stage; RT, radiotherapy.

[a] Data are given as *P* values.

Next we compared the outcome of patients with pN− disease according to their clinical nodal classification after revision of the pathology (the 29 patients with disease upstaged to pN+ following reexamination were classified with the pN+ group). The 5-year OS of patients with cN− disease was 77.6%, whereas it was 62.6% in those staged with cN+ disease ($P < .001$). The 5-year DSS of patients with cN− disease was 87.2% compared with 78.5% for those staged with cN+ disease ($P = .004$). Kaplan-Meier graphs presenting the OS and DSS in patients with pN− disease according to their clinical nodal classification are shown in Figure 2. Kaplan-Meier graphs comparing patients with cN+/pN− disease that stayed within classification and those with cN+/pN− disease that converted from cN+/pN− to cN+/pN+ during reanalysis (n = 29) revealed that both OS and DSS were lower for those with the true cN+/pN+ disease ($P = .002$ and $P < .001$, respectively; eFigure 1 in the Supplement).

Table 3. Multivariable Analysis of Outcomes

	Survival							
	Overall		Disease-Specific		Disease-Free		Regional Recurrence	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex	NA	NA	NA	NA	NA	NA	NA	NA
Age, y								
≤70	1 [Reference]	<.001	1 [Reference]	.02	NA	NA	NA	NA
>70	2.3 (1.2-5.5)		1.9 (1.1-2.8)		NA		NA	
Treatment								
Surgery	1 [Reference]	.73	1 [Reference]	.70	NA	NA	NA	NA
Surgery+RT	1.14 (0.5-1.2)		1.1 (0.4-1.9)		NA		NA	
Surgery+CRT	1.2 (0.7-1.5)		1.16 (0.7-1.9)		NA		NA	
pT stage								
1	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	.04	NA	NA
2	1.18 (1.02-3.1)		1.19 (0.58-1.9)		1.4 (1.1-2.8)		NA	
3	1.88 (1.26-5.3)		1.98 (1.06-3.68)		1.9 (1.2-3.6)		NA	
4	2.9 (1.28-10.4)		2.7 (1.3-6.21)		2.12 (1.1-4.46)		NA	
cN stage								
Negative	1 [Reference]	.003	1 [Reference]	.04	1 [Reference]	.05	1 [Reference]	.03
Positive	1.7 (1.1-3.8)		1.46 (1.1-4.1)		1.6 (1.02-3.2)		2.4 (1.4-4.16)	
DOI, mm								
≤4	1 [Reference]	.32	1 [Reference]	.06	NA	NA	NA	NA
>4	1.5 (0.79-3.2)		1.4 (1.2-4.01)		NA		NA	
Margins								
Negative	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	.01
Positive	2.56 (1.3-6.9)		2.1 (1.3-5.3)		2.33 (1.7-3.1)		1.8 (1.1-4.2)	

Abbreviations: CRT, chemoradiotherapy; DOI, depth of invasion; HR, hazard ratio; LN, lymph node; NA, not applicable; RT, radiotherapy.

Univariable analysis demonstrated that age, pathologic T stage, DOI, margin status, clinical N stage, and treatment group were significant predictors of both 5-year OS and DSS among patients with pN– disease of the neck (**Table 2**). In a multivariable model, age, margin status, pathologic T stage, and clinical N stage remained significant independent predictors for both OS and DSS (**Table 3**). Most importantly, the multivariable analysis reveals that clinical nodal status was significantly associated with DFS (*P* = .05) and regional-free survival (*P* = .03) but not with local (*P* = .20) or distant metastases-free survival (*P* = .80). Kaplan-Meier graphs presenting the DFS, local- and regional-free survival, and distant metastasis-free survival are shown in **Figure 3**.

To assess noncontemporaneous control bias, we analyzed the prognostic significance of clinical N stage in 2 periods, 1990 to 2000 and 2000 to 2011.[16] The results of these analyses demonstrated that clinical N stage remained a significant predictor of 5-year OS, DSS, and DFS for both time intervals.

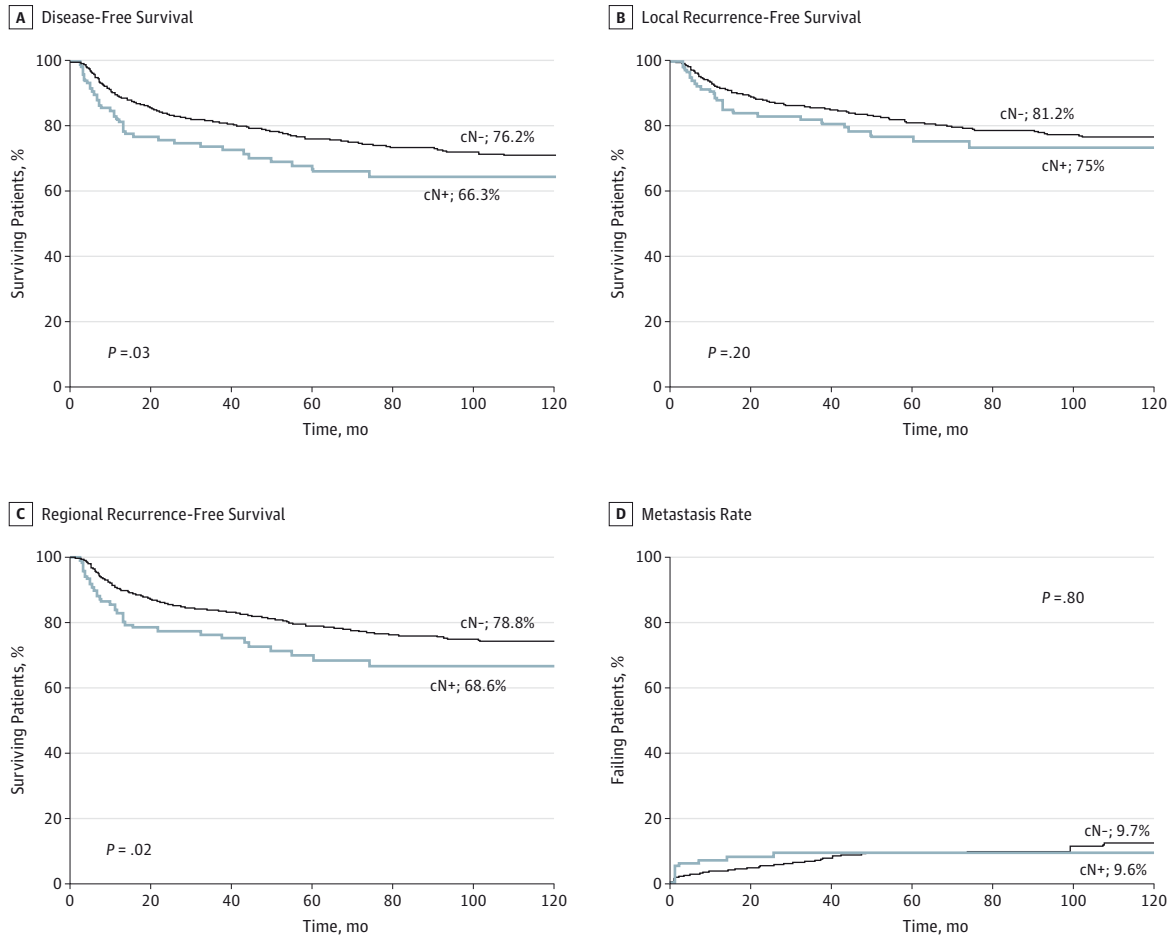
Discussion

Pathologic staging is the gold standard by which risk is stratified and treatment is tailored. However, the pN classification depends on the extent of neck dissection (the surgical technique) and the sampling procedure (the level of histopathologic scrutiny) and so is not error free. Our research group[12] has shown that cN+ classification is an independent predictor of poor outcome in patients with pN– disease. We hypothesized that there might be situations in which neck metastases discovered during physical or radiologic examinations were missed by either the sampling procedure (ie, the surgery) of in the pathologic analysis. The present research aims to elucidate the origin of treatment failure in this specific group of patients.

To explore this issue, we revised the neck specimens of the patients who had clinical evidence of nodal metastases and found that the false negative rate was 15%. The mean (SD) number of missed nodes per patient was 1.13 (0.35) (range, 1-2 nodes). After correction for the missed pathologic neck metastases, we found that clinical neck classification remained an independent risk factor, even when the pN classification was negative. Most importantly, the clinical neck status was predictive of regional recurrence but not of distance or local failure.

Published data indicate that treatment will fail for approximately one-third of patients with OSCC due to regional recurrence.[17-20] Our finding that a cN+ classification is associated with neck recurrence but not with local recurrence or distant metastases further strengthens the possibility that nodal metastases are overlooked in this population. The nodal disease may be missed if positive nodes are left in the neck as a result of incomplete neck dissection. Alternatively, missed microscopic disease can lead to a failure to administer adjuvant therapy in patients who would benefit from such treatment. Although a multivariable analysis repeatedly showed the validity of our

Figure 3. Kaplan-Meier Patterns of Survival and Failure Rates in Patients With Pathologically Negative Neck Nodes by Clinical Nodal Status



A, Five-year disease-free survival. B, Five-year local recurrence-free survival. C, Five-year regional recurrence-free survival. D, Distant metastasis failure rate calculated using the Kaplan-Meier analysis. cN+ indicates patient with clinically positive neck nodes (n = 164); cN−, clinically negative neck nodes (n = 1913).

data, we cannot ignore the possibility that our findings may represent failure to adjust for a hidden confounding factor.

Preoperative clinical nodal staging is primarily based on physical examination combined with imaging studies such as computed tomography (CT), positron emission tomography (PET), or ultrasonography.[21] The size and shape of lymph nodes, loss of fatty hilum, central necrosis, increased vascularity, and high fluorodeoxyglucose uptake on PET are suggestive of malignant nodal spread.[22] It has been shown that the sensitivity of physical examination in detection of pathologic cervical lymph nodes is 75% and that this rate increases to 91% with the addition of CT studies.[23] Recent reports have revealed that clinical staging has a 44% false negative rate and have demonstrated a 53% concordance between clinical and pathologic nodal staging.[24]

Metastatic tumor cells may be present in lymph nodes and can go undetected using standard pathologic staging.[9,25] Furthermore, previous reports have shown that conventional pathology revision and advanced techniques such as serial sectioning, immunohistochemical staining, and reverse transcriptase-polymerase chain reaction analysis can detect lymph node metastases that were missed by conventional staining with hematoxylin-eosin.[26-28] In this respect, one of the limitations of the present study is lack of data regarding immunohistochemical staining and confirmation of positive nodal metastases. Nevertheless, our finding of a 15% false negative pN classification further strengthens the possibility that conventional pathologic analysis may miss microscopic nodal disease.[9]

Patients were preoperatively staged by the anatomic extent of the disease as found on physical examination and CT or neck ultrasonography. Nevertheless, one of the limitations of the current study is the lack of uniformity in how clinical staging was performed; another is the long study period and multiple international institutions, which may restrict generalizability to current clinical staging with modern imaging techniques.[29] Yet the significance of cN stage as a predictor of outcomes in our heterogeneous cohort across multiple centers from several countries assures the validity of our findings worldwide.

Owing to the retrospective nature of the study, data regarding ethnicity, primary tumor site, smoking status, and al-

cohol exposure were not available. As well, the tissues were reevaluated for metastasis at each center by a certified head and neck pathologist. We realize that one of the limitations of this study is the potential for interobserver error owing to the inconsistency in the surgical technique and processing of the pathologic specimens. Yet 2-stage random effects analysis revealed minimal heterogeneity between centers, and even after we excluded cases with fewer than 18 lymph nodes from our analysis, cN staging remained the only significant independent predictor of outcome.

Regardless of the results of the revised pathologic report, patients with cN+ disease have worse outcomes than those with cN− disease, even when the pathologic study shows no evidence of nodal metastases, since these patients are likely to succumb to regional recurrence of their disease. Patients with cN+/pN− disease are at more risk than patients with cN−/pN− disease, and such knowledge should be used by the oncologist when deciding about adjuvant treatment. Our results suggest that adjuvant treatment should be considered in this scenario.[30]

Further studies are required to determine whether patients with the clinically positive neck metastases will benefit from adjuvant therapy regardless of the pathologic neck status.

Conclusions

Our study revealed that 15% of patients with cN+/pN− disease had occult nodal metastases that were missed during the initial pathologic workup. Even after correction for these missed neck metastases, we showed that clinical evidence of neck metastases is an independent predictor of OS, DSS, and regional recurrence. Our data suggest that traditional sampling during surgery might miss metastases in accordance with tumors of other sites, and this fact might explain the origin of treatment failure in these patients. The high risk of failure in patients with clinical evidence of nodal metastases suggests that in selected cases, adjuvant neck irradiation should be considered.

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