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Minimum Nodal Yield in Oral Squamous Cell Carcinoma: Defining the Standard of Care in a Multicenter International Pooled Validation Study

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ABSTRACT

Purpose. There is evidence to suggest that a nodal yield <18 is an independent prognostic factor in patients with clinically node negative (cN0) oral squamous cell carcinoma (SCC) treated with elective neck dissection (END). We sought to evaluate this hypothesis with external validation and to investigate for heterogeneity between institutions.

Patients and Methods. We analyzed pooled individual data from 1,567 patients treated at nine comprehensive cancer centers worldwide between 1970 and 2011. Nodal yield was assessed with Cox proportional hazard models, stratified by study center, and adjusted for age, sex, pathological T and N stage, margin status, extracapsular nodal spread, time period of primary treatment, and adjuvant therapy. Two-stage random-effects meta-analyses were used to investigate for heterogeneity between institutions.

Results. In multivariable analyses of patients undergoing selective neck dissection, nodal yield <18 was associated with reduced overall survival [hazard ratio (HR) 1.69; 95 % confidence interval (CI) 1.22–2.34; $p = 0.002$] and disease-specific survival (HR 1.88; 95 % CI 1.21–2.91; $p = 0.005$), and increased risk of locoregional recurrence (HR 1.53; 95 % CI 1.04–2.26; $p = 0.032$). Despite significant differences between institutions in terms of patient clinicopathological factors, nodal yield, and outcomes, random-effects meta-analysis demonstrated no evidence of heterogeneity between centers in regards to the impact of nodal yield on disease-specific survival ($p = 0.663$; I^2 statistic $= 0$).

Conclusion. Our data confirm that nodal yield is a robust independent prognostic factor in patients undergoing END for cN0 oral SCC, and may be applied irrespective of the underlying patient population and treating institution. A minimum adequate lymphadenectomy in this setting should include at least 18 nodes.

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Each year an estimated 263,000 cases of oral cavity squamous cell carcinoma (SCC) occur worldwide, and over

127,000 patients die from the disease.[1] In most institutions, treatment comprises primary surgical resection with administration of adjuvant therapy tailored to the individual risk profile.[2,3] In view of the substantial risk of occult nodal metastases,[4,5] elective neck dissection (END) is performed in the majority of patients who are clinically and radiologically lymph node negative (cN0), with the exception of selected thin early-stage tumors.[2,3,6] In addition to the therapeutic benefits, END facilitates histopathological staging of the neck, which provides critical prognostic information that also guides decisions regarding adjuvant therapy.[2,3]

The extent of regional lymph node dissection, as defined by the nodal yield, has been shown to be an important prognostic factor in a number of cancers, including bladder,[7,8] breast,[9] colorectal,[10,11] gastric,[12] and esophageal.[13,14] A previous single-institution analysis demonstrated that retrieval of less than 18 nodes after END is an independent adverse prognostic factor in patients with oral SCC.[15] However, several important questions remain unanswered due to the limited statistical power of that study. First, the prognostic value of nodal yield in the subgroup of patients with pathologically node-negative disease (pN0) could not be definitively established. Second, it is unclear if low nodal yields are associated with increased regional failure rates, suggesting that undertreatment of occult neck disease is responsible for the adverse survival outcomes. Finally, there may be substantial variability in nodal yield after END between different surgeons, pathologists, and institutions. Hence, it remains uncertain whether the minimum standard of care for adequate lymphadenectomy in this setting may be defined by the retrieval of at least 18 nodes irrespective of the treating institution.

The primary aim of this study was to validate the nodal yield as an independent prognostic factor after END for oral SCC in an analysis of pooled data from multiple international comprehensive cancer centers. Our secondary aims were threefold. First, to determine if nodal yield is prognostic in the subgroup of patients with pN0 disease. Second, to establish whether low nodal yields are associated with increased rates of locoregional recurrence. Third, we aimed to investigate for sources of heterogeneity between centers in terms of the prognostic impact of nodal yield.

MATERIALS AND METHODS

Study Population

This multicenter validation study included pooled individual patient data from nine comprehensive cancer centers worldwide. Ethics approval was obtained from local Institutional Review Board committees of participating centers. We identified 2,221 patients with cN0 oral SCC undergoing surgical resection of the primary tumor and END with curative intent as candidates for inclusion. After excluding cases with neoadjuvant therapy, perioperative mortality, lack of follow-up data, age <20 years, or inadequate information to determine nodal yield, the final study population consisted of 1,567 patients treated between 1970 and 2011.

Histopathological Analysis

Nodal evaluation was performed by pathologists experienced in the examination of head and neck tumors. The original pathology reports were reviewed to determine nodal yield. In patients where a bilateral neck dissection was performed ($n = 192$), the average of the two sides was used. We assumed some heterogeneity in specimen dissection and tissue handling in view of the extended time period of the study as well as the number of involved institutions, surgeons, and pathologists.

Statistical Analysis

Statistical analysis was performed using Stata version 12.0 SE (StataCorp LP, College Station, TX, USA). All statistics were two-sided and a p value of <0.05 was considered statistically significant. Overall survival was calculated from the date of surgery to the date of death or last follow-up. For disease-specific survival, patients who died from causes other than oral SCC were censored at the time of death. Locoregional recurrence was defined as pathologically proven tumor relapse in the primary site or neck. Differences in survival and locoregional failure rates were determined using univariate Cox regression analysis, and survival curves generated using the Kaplan–Meier method when appropriate. Nodal yield was analyzed as a binary variable (<18, ≥18) based on previous findings.[15] Other covariates of interest included age at diagnosis (continuous), sex, pathological T (pT) stage (T1–4), pathological N (pN) stage (N1–3), surgical margin status [clear, close (<5 mm), involved], extracapsular nodal spread (absent, present), time period of primary treatment (1970–1979, 1980–1989, 1990–1999, 2000–2011), and adjuvant therapy [nil, radiotherapy (RT) alone, chemoradiotherapy (CRT), RT + cetuximab]. A Cox proportional hazards model, stratified by study center and adjusted for the effect of these covariates was used to determine if nodal yield is an independent prognostic factor. Model diagnostics were performed to check for linearity of continuous predictors and the proportional hazards assumption.

Several sensitivity analyses were performed to assess the robustness of our findings. First, we limited the analysis to patients treated from the year 2000 onwards in whom preoperative staging, surgical and pathological techniques, and adjuvant therapy are likely to better reflect contemporary practice. Second, in view of the large differences in nodal yield observed between institutions, we repeated the analysis based on a binary nodal yield variable with a cutoff at the 25th percentile specific to each center. This percentile was used by the authors of the original study to arrive at a cutoff of 18 nodes.[15] Finally, we performed an analysis restricted to patients undergoing selective neck dissection, SND (levels I–III or I–IV) since this reflects the current surgical approach to the cN0 neck.

Next, we used a two-stage random-effects modeling approach to investigate for the presence and sources of heterogeneity between centers in terms of the prognostic impact of nodal yield.[16] At the first stage, the effect of nodal yield on disease-specific survival was determined for each center using Cox proportional hazards models adjusting for age (continuous), pT stage (T1–2, T3–4), pN stage, extracapsular spread (ECS), postoperative RT, and year of primary treatment. At the second stage of analysis, the center-specific estimates were introduced into the random-effects model of DerSimonian and Laird,[17] which allows for unexplained sources of heterogeneity between centers. Heterogeneity across centers was assessed using Cochran's Q test ($p < 0.1$ was considered statistically significant given the test has limited power) and quantified using the I^2 measure (the percentage of total variation across centers attributable to heterogeneity rather than chance).[18]

RESULTS

Patient Demographics

The study cohort consisted of 1,567 patients with oral SCC, including 1,263 men and 304 women, with a median age of 55 years (range 22.0–93.2 years) and median follow-up of 67 months. Adjuvant therapy was administered to 740 (47.3 %) patients. Relevant demographic and clinicopathological details are summarized in Table 1. A total of 1,759 neck dissections were performed, including 275 comprehensive and 1,484 SNDs. The majority of SNDs included levels I–III ± IV. The rate of pathological cervical lymph node involvement was 27.1 %, and 7.7 % of patients had ECS.

TABLE 1 Patient clinicopathological data

Variables	*N*	%
Age (years)		
≤45	365	23.3
46–55	439	28.0
56–65	390	24.9
≥66	373	23.8
Sex		
Male	1,263	80.6
Female	304	19.4
Nodal yield		
<18	345	22.0
≥18	1,222	78.0
Pathological T stages		
T1	368	23.5
T2	675	43.1
T3	257	16.4
T4	266	17.0
Pathological N stages		
N0	1,143	73.0
N1	220	14.0
N2	204	13.0
TNM stages		
I	283	18.1
II	517	33.0
III	382	24.4
IV	357	22.8
Extracapsular nodal spread		
Absent	1,377	92.3
Present	115	7.7
Surgical excision margin		
Clear	1,300	83.1
Close (<5 mm)	183	11.7
Involved	81	5.2
Adjuvant therapy		
No	767	49.0
Radiotherapy	598	38.2
Chemoradiotherapy	136	8.7
Radiotherapy + cetuximab	64	4.1
Year of primary treatment		
1970–1979	50	3.2
1980–1989	121	7.7
1990–1999	284	18.1
2000–2011	1,112	71.0

Nodal Yield

The mean and median nodal yield per neck dissection were 31.3 and 30.0, respectively. The mean nodal yield was higher in younger patients ($p < 0.001$) and those ultimately staged as pN+ ($p = 0.067$). Significant differences were also noted based on decade of primary treatment ($p < 0.001$). The higher nodal yields in the first two decades of the study reflect the high rate of

TABLE 2 Multivariable analyses: baseline and sensitivity analyses of the association of nodal yield with survival and locoregional failure

Multivariable analysis	Overall survival		Disease-specific survival		Locoregional failure	
	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value
Baseline analysis	1.25 (0.98–1.60)	0.069	1.54 (1.10–2.17)	0.012	1.24 (0.91–1.68)	0.179
Treatment year ≥2000	1.48 (1.05–2.08)	0.024	1.84 (1.16–2.93)	0.010	1.29 (0.86–1.95)	0.215
Center-specific nodal yield[a]	1.33 (1.09–1.64)	0.006	1.49 (1.10–2.01)	0.010	1.19 (0.90–1.55)	0.217
SND patients only	1.69 (1.22–2.34)	0.002	1.88 (1.21–2.91)	0.005	1.53 (1.04–2.26)	0.032

Multivariable analyses performed with multivariable Cox regression models adjusting for age in years (age^2 also included in models for overall survival), sex, pathological T stage (T1–4), pathological N stage (N0–2), surgical margin status [clear, close (<5 mm), involved], extracapsular nodal spread (absent, present), time period of primary treatment (1970–1979, 1980–1989, 1990–1999, 2000–2011), and adjuvant therapy (nil, radiotherapy alone, chemoradiotherapy, radiotherapy + cetuximab)

HR hazard ratio, *CI* confidence interval, *SND* selective neck dissection

[a] Center-specific nodal yields were based on a binary variable with a cutoff at the 25th percentile for each institution, ranging from 9 to 29 nodes

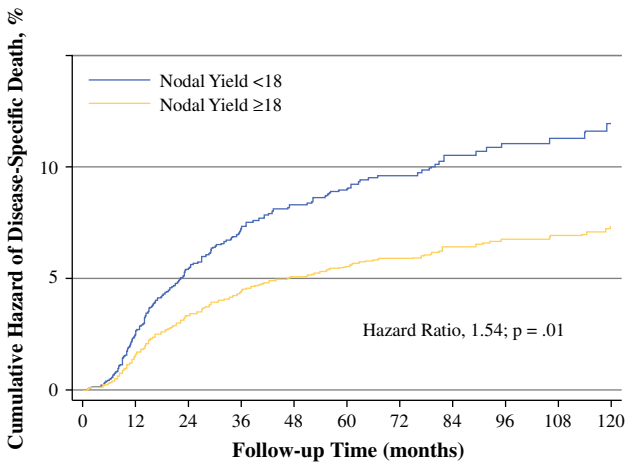

FIG. 1 Cumulative hazard plot demonstrating association between nodal yield and death due to oral SCC in multivariable Cox regression analysis, adjusted for age, sex, pathological T stage (T1–4), pathological N stage (N0–2), surgical margin status [clear, close (<5 mm), involved], extracapsular nodal spread (absent, present), time period of primary treatment (1970–1979, 1980–1989, 1990–1999, 2000–2011), and adjuvant therapy (nil, radiotherapy alone, chemoradiotherapy, radiotherapy + cetuximab). Patients with nodal yield <18 had an approximate 54 % increased risk of death from oral SCC compared with those with ≥18 nodes harvested. *SCC* squamous cell carcinoma

comprehensive neck dissections, consistent with surgical practice at the time. Finally, the mean nodal yield differed substantially by study center, ranging from 17 to 39.6 nodes ($p < 0.001$).

Survival and Locoregional Failure Analyses

The median overall survival was 139 months with 560 deaths, 269 of which were due to oral SCC. Documented locoregional recurrence occurred in 309 patients. There was no significant difference in overall survival ($p = 0.556$), disease-specific survival ($p = 0.280$), or locoregional recurrence ($p = 0.638$) based on nodal yield (<18 vs. ≥18) in univariate analyses. The results of multivariable Cox proportional hazards regression models stratified by study center are shown in the 'baseline'-adjusted analyses of Table 2. Low nodal yield was an independent predictor of disease-specific survival [hazard ratio (HR) 1.54; 95 % confidence interval (CI) 1.10–2.17; $p = 0.012$] and of borderline significance for overall survival (HR 1.25; 95 % CI 0.98–1.60; $p = 0.069$). There was no statistically significant association between nodal yield and locoregional recurrence (HR 1.24; 95 % CI 0.91–1.68; $p = 0.179$). As demonstrated in Fig. 1, patients with nodal yield <18 had a 54 % increased risk of death from oral SCC compared with those with at least 18 nodes harvested.

Sensitivity Analyses

The fully-adjusted multivariable Cox proportional hazards models were used to perform several sensitivity analyses for the prognostic significance of nodal yield (Table 2). First, we assessed nodal yield limiting the analysis to patients treated from the year 2000 onwards ($N = 1{,}112$). Nodal yield (<18 vs. ≥18) was a significant predictor of overall survival (HR 1.48; 95 % CI 1.05–2.08; $p = 0.024$) and disease-specific survival (HR 1.84; 95 % CI 1.16–2.93; $p = 0.010$) but not locoregional failure (HR 1.29; 95 % CI 0.86–1.95; $p = 0.215$). Next, we repeated the analyses using a new binary nodal yield variable, using a cutoff at the 25th percentile specific to each center, which ranged from 9 to 29 nodes. Again, nodal yield (lowest quartile vs. upper three quartiles in each center) was a significant predictor of overall survival (HR 1.33; 95 % CI 1.09–1.64; $p = 0.006$) and disease-specific survival (HR 1.49; 95 % CI 1.10–2.01; $p = 0.010$) but not locoregional control (HR 1.19; 95 % CI 1.19–1.55; $p = 0.217$). Finally, analysis limited to patients undergoing SND showed a significant association with overall survival (HR 1.69; 95 % CI 1.22–2.34; $p = 0.002$) and disease-specific

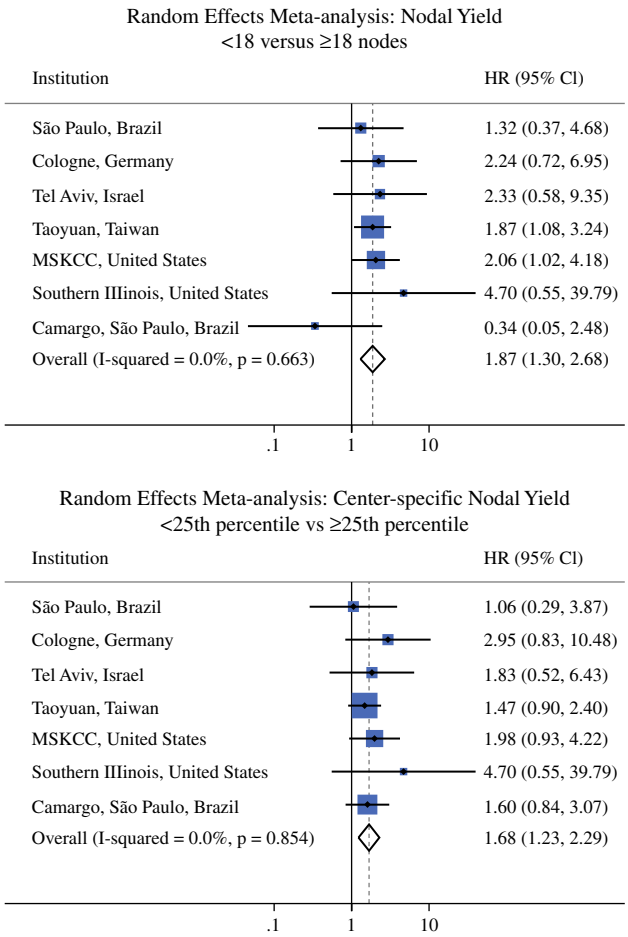

FIG. 2 Adjusted HR of death due to oral SCC according to nodal yield based on **a** a cutoff of 18 nodes, and **b** a cutoff at the 25th percentile for each institution. The summary estimates were obtained using a random-effects model. The *data markers* indicate the adjusted HRs in patients with nodal yield <18 versus ≥18. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The *diamond data marker* indicates the pooled HR. *HR* hazard ratio, *CI* confidence interval, *MSKCC* Memorial Sloan-Kettering Cancer Center

survival (HR 1.88; 95 % CI 1.21–2.91; $p = 0.005$) as well as locoregional recurrence (HR 1.53; 95 % CI 1.04–2.26; $p = 0.032$).

Investigation of Between-Center Heterogeneity

A two-stage random-effects modeling approach was then used to investigate for the presence and sources of heterogeneity between centers specifically in terms of the prognostic impact of nodal yield on disease-specific survival. Patients from Brescia, Italy, and Petach Tikva, Israel, were excluded from this analysis since they had few participants and disease-specific deaths. Figure 2 shows the forest plot from a random-effects meta-analysis demonstrating a statistically significant summary effect of nodal yield on disease-specific survival (HR 1.87; 95 % CI 1.30–2.68; $p = 0.001$) consistent with our earlier results. Importantly, there was no evidence of heterogeneity between centers with a non-significant Cochran's Q test ($p = 0.663$) and I^2 statistic of 0. Influence analysis was performed confirming that exclusion of any single-center data had minimal impact on the summary effect estimate. Similar results were obtained when the analysis focused on nodal yields with institution-specific cutoffs at the 25th percentile.

DISCUSSION

Occult nodal metastases are a critical determinant of prognosis in cN0 oral SCC.[19] In view of the trend toward increasingly SND in these patients, it is important to determine the minimum extent of regional lymphadenectomy, as defined by the nodal yield, to ensure the neck is accurately staged and adequately treated. Based on a single-institution experience from the Sydney Head and Neck Cancer Institute, it was proposed that an adequate lymphadenectomy in this setting should include at least 18 nodes.[19] In the current study, we were able to validate the nodal yield as an independent prognostic factor after END for oral SCC, using pooled individual patient data from nine comprehensive cancer centers worldwide.

In baseline multivariable analyses, nodal yield <18 was an independent predictor of reduced disease-specific survival (HR 1.54; 95 % CI 1.10–2.17; $p = 0.012$), borderline significant for overall survival (HR 1.25; 95 % CI 0.98–1.60; $p = 0.069$), and not associated with locoregional recurrence (HR 1.24; 95 % CI 0.91–1.68; $p = 0.179$). In view of the substantial heterogeneity in nodal yield between centers, we repeated the analyses with nodal yield dichotomized using a cutoff at the 25th percentile for each study center, with values ranging from 9 to 29. However, multivariable analyses yielded similar results to the baseline analysis, suggesting that a single cutoff at 18 nodes is reasonable.

Sensitivity analyses limiting the study population to patients treated from the year 2000 onwards, and also to those undergoing SND, provided strong evidence that nodal yield provides valid prognostic information in the context of contemporary clinical practice. Importantly, in patients who underwent SND there was a significant association between nodal yield and overall survival (HR 1.69; 95 % CI 1.22–2.34; $p = 0.002$), disease-specific survival (HR 1.88; 95 % CI 1.21–2.91; $p = 0.005$), and locoregional failure (HR 1.53; 95 % CI 1.04–2.26; $p = 0.032$). Furthermore, we found no evidence of interaction between nodal yield and pN stage (data not shown), suggesting the results may be applied to both pathologically node negative and positive patients. The fact that we

found no evidence of heterogeneity between centers with regards to the prognostic impact of nodal yield provides reassurance that it is a robust prognostic factor that may be applied in diverse clinical settings.

The fact that patients with nodal yield <18 after SND had an 88 % increased risk of death from oral SCC compared with those with ≥18 nodes is a cause for concern. This raises the issue of whether nodal yield information should be incorporated into decisions regarding adjuvant therapy. Lending some support to this possibility is the fact that we were able to demonstrate a significant 53 % increased risk of locoregional failure in the context of low nodal yield after SND. However, it remains unclear if the benefits of escalating adjuvant therapy in this setting are justified, and future prospective studies are needed before recommendations for clinical practice can be made.

The prognostic value of nodal yield may be modified by adjuvant therapy since administration of postoperative RT should ameliorate the excess risk associated with low nodal yield if the issue is undertreatment of occult neck disease resulting in regional failure. However, there was no evidence to support this, with a non-significant interaction between nodal yield and adjuvant therapy (data not shown). Although this may be due to inadequate power, an alternative explanation is that low nodal yield is a surrogate marker of compromised surgical and pathological quality of care,[20] or reflects underlying patient factors such as immunologic response,[21,22] rather than purely a risk factor for residual microscopic nodal disease.

Among the strengths of this study are the large sample size, the availability of pooled individual patient data, the diverse study populations included, and the number of participating institutions. However, there are also several limitations that must be acknowledged. First, the data are observational and residual confounding cannot be excluded. Second, we were unable to standardize factors such as patient selection, preoperative imaging, and surgical and pathological technique between institutions.

CONCLUSIONS

In this international multicenter analysis of pooled individual patient data, we confirmed that the nodal yield is a robust independent prognostic factor in patients undergoing SND for cN0 oral SCC. We further demonstrated that the prognostic significance of nodal yield applies to contemporary clinical practice in a diverse range of settings and study populations, providing reassurance that the results may be generalized irrespective of the treating institution. Not only does the nodal yield provide additional prognostic information for the clinician, it may also reflect the adequacy of treatment and staging of the neck, with potential therapeutic implications that require further study. On the basis of our results, a minimum adequate lymphadenectomy in this setting should include at least 18 nodes, although institution-specific cutoffs appear equally reasonable.

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