Original Article

Establishing Quality Indicators for Neck Dissection: Correlating the Number of Lymph Nodes With Oncologic Outcomes (NRG Oncology RTOG 9501 and RTOG 0234)

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BACKGROUND: Prospective quality metrics for neck dissection have not been established for patients with head and neck squamous cell carcinoma. The purpose of this study was to investigate the association between lymph node counts from neck dissection, local-regional recurrence, and overall survival. **METHODS:** The number of lymph nodes counted from neck dissection in patients treated in 2 NRG Oncology trials (Radiation Therapy Oncology Group [RTOG] 9501 and RTOG 0234) was evaluated for its prognostic impact on overall survival with a multivariate Cox model adjusted for demographic, tumor, and lymph node data and stratified by the postoperative treatment group. **RESULTS:** Five hundred seventy-two patients were analyzed at a median follow-up of 8 years. Ninety-eight percent of the patients were pathologically N+. The median numbers of lymph nodes recorded on the left and right sides were 24 and 25, respectively. The identification of fewer than 18 nodes was associated with worse overall survival in comparison with 18 or more nodes (hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.09-1.74; $P = .007$). The difference appeared to be driven by local-regional failure (HR, 1.46; 95% CI, 1.02-2.08; $P = .04$) but not by distant metastases (HR, 1.08; 95% CI, 0.77-1.53; $P = .65$). When the analysis was limited to NRG Oncology RTOG 0234 patients, adding the p16 status to the model did not affect the HR for dissected nodes, and the effect of nodes did not differ with the p16 status. **CONCLUSIONS:** The removal and identification of 18 or more lymph nodes was associated with improved overall survival and lower rates of local-regional failure, and this should be further evaluated as a measure of quality in neck dissections for mucosal squamous cell carcinoma. ***Cancer*** **2016;122:3464-71.** © *2016 American Cancer Society.*

KEYWORDS: head and neck cancer, neck dissection, quality indicators, surgery, survival.

INTRODUCTION

Neck dissection is the cornerstone of modern head and neck surgery. After Crile[1] proposed the systematic management of regional lymphatics of the neck in 1906, the procedure became widely practiced and adopted as an integral aspect of managing head and neck cancer. Beginning in 1951, Hates Martin promoted radical neck dissection as an en bloc ipsilateral resection of all lymphatic tissues of the neck as well as the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve (cranial nerve XI).[2] However, over time, neck dissection evolved. In 1984, Byers introduced the more conservative modified radical neck dissection,[3] which preserved the sternocleidomastoid muscle, internal jugular vein, and cranial nerve XI, and eventually advocated selective neck dissection, which removed fewer than all 5 levels of the neck.[4]

Despite efforts to standardize and classify techniques,[5] the practice of neck dissection now varies widely across centers and from surgeon to surgeon. As such, there may be significant variability in the quality of cervical lymphadenectomy. For other solid malignancies such as colorectal cancer, prospective studies have demonstrated the impact of the quality and extent of surgery on survival and, in particular, the number of lymph nodes retrieved during regional nodal dissection. For patients with stage II or III colorectal cancer, the removal of 12 or more lymph nodes is associated with increased overall

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survival.[6-9] This quality metric was adopted for patients with colorectal cancer in the 2009 National Voluntary Consensus Standards for Quality of Cancer Care.[10]

In the head and neck surgical oncology literature, retrospective single and multicenter studies have attempted to address surgical quality in neck dissection.[11,12] However, to our knowledge, no prospective data have been examined to determine relations between the number of nodes removed in neck dissection and oncologic outcomes such as locoregional recurrence and survival.

Here we investigate whether or not the number of lymph nodes reported after neck dissection for node-positive mucosal squamous cell carcinoma correlates with overall survival in prospective NRG Oncology Radiation Therapy Oncology Group (RTOG) clinical trials. Our hypothesis is that higher lymph node counts for neck dissections are correlated with improved survival. We aim to identify a cut point that would be a proxy for quality when one is measuring lymph nodes retrieved during neck dissection.

MATERIALS AND METHODS

This study included patients treated in 2 postoperative NRG Oncology trials: RTOG 9501[13] and RTOG 0234.[14] NRG Oncology RTOG 9501 was a phase 3 trial comparing radiation alone with radiation with concurrent cisplatin. NRG Oncology RTOG 0234 was a randomized phase 2 trial comparing 2 experimental regimens, radiation with concurrent cisplatin and cetuximab and radiation with concurrent docetaxel and cetuximab, with the historical control NRG Oncology RTOG 9501 chemoradiation arm. Protocol approval was received from the institutional review board at each study site, and informed consent was obtained from each patient before participation.

The analysis was limited to patients with complete data for the following potential covariates: age, sex, race, Zubrod performance status, smoking history, primary site, pathologic T stage, pathologic N stage, type of neck dissection (unilateral or bilateral), extracapsular nodal extension, positive margin, number of lymph nodes counted, and number of positive lymph nodes. For patients with bilateral neck dissection, the mean of the 2 sides was used for the number of counted lymph nodes. Possible differences in the distributions of patient characteristics were tested as follows: continuous or ordinal variables, Wilcoxon rank-sum test; categorical variables (for 2 groups and 2 levels), Fisher's exact test; and other categorical variables, Pearson chi-square test.

The number of lymph nodes counted from neck dissection was evaluated for its prognostic impact on overall survival, local-regional failure, and distant metastasis with a multivariate Cox model adjusted for demographic, tumor, and lymph node data and stratified by the postoperative treatment group. Overall survival was defined as the time from randomization to death (event) or last follow-up. Rates were estimated with the Kaplan-Meier method.[15] Local-regional failure was defined as the time from randomization to local or regional relapse (event), death (competing risk), or last follow-up. Distant metastasis was defined as the time from randomization to distant metastasis (event), death (competing risk), or last follow-up. Rates were estimated with the cumulative incidence method.[16] Hazard ratios (HRs) were estimated via Cox modeling.[17]

All analyses that included both trials were stratified by the treatment group: 1) radiation (NRG Oncology RTOG 9501), 2) chemoradiation (NRG Oncology RTOG 9501), and 3) chemoradiation and cetuximab (NRG Oncology RTOG 0234). Models were compared with the Akaike information criterion (AIC). The initial model with all covariates was reduced by minimization of AIC. Then, the number of lymph nodes dissected was added as a categorical variable. An initial cut point of 18 lymph nodes was used on the basis of previously published analyses for node-negative patients.[11] The following sensitivity analyses were performed: 1) an analysis limited to unilateral neck dissections, 2) an analysis censoring patients at 5 years, 3) an analysis of NRG Oncology RTOG 9501 with the assigned treatment (chemoradiation vs radiation) added to the model, and 4) an analysis of NRG Oncology RTOG 0234 with the p16 status (p16-negative vs p16-positive) added to the model.

RESULTS

Patient Demographics and Tumor Characteristics

Six-hundred ninety-seven patients were enrolled in NRG Oncology RTOG 9501 (n = 459) and NRG Oncology RTOG 0234 (n = 238), and 613 of these patients (410 in NRG Oncology RTOG 9501 and 203 in NRG Oncology RTOG 0234) were eligible and were included in an analysis of protocol endpoints. Five hundred seventy-two of these patients (93.3%) were included in this secondary analysis (Fig. 1). The median follow-up for surviving patients was 8.0 years (range, 0.2-14.0 years).

Patient and tumor characteristics by the number of lymph nodes dissected (<18 and ≥ 18) are shown in Table 1. Overall, 35% percent had a bilateral neck dissection. The median number of positive lymph nodes was 3. The median number of counted lymph nodes on the left and right sides were 24 and 25, respectively. Ninety-eight

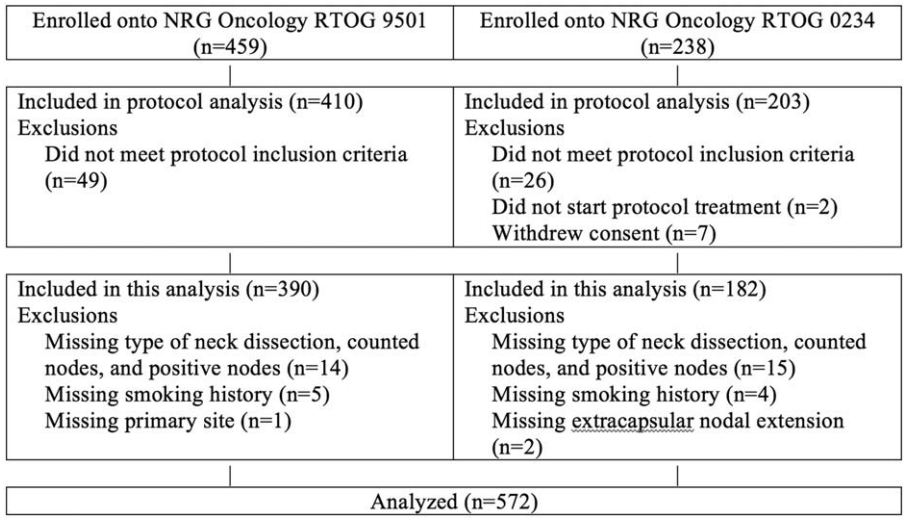

Figure 1. Consolidated Standards of Reporting Trials diagram. RTOG indicates Radiation Therapy Oncology Group.

percent of the patients were N+. Prospective data collection for RTOG 9501 and RTOG 0234 did not include notation about the level of each harvested node or which lymph node levels were dissected. Distributions of the N stage ($P < .001$), type of neck dissection ($P < .001$), lymph node density ($P < .001$), and margin status ($P = .05$) differed significantly between the 2 groups. The distribution of counted lymph nodes is shown in Figure 2 and has a shape very similar to that for the Surveillance, Epidemiology, and End Results data from Agrama et al.[18] The median lymph node density (positive nodes/total nodes) between the 2 groups was 0.23 (<18 nodes) versus 0.09 (≥18 nodes; $P < .001$).

Among 130 patients in NRG Oncology RTOG 0234 for whom the p16 status was known, 57 were p16-positive (43.8%). Distributions of the primary site ($P < .001$), T stage ($P < .001$), and margin status ($P < .001$) differed between the p16-positive and p16-negative groups. The median number of resected nodes was 27 for the p16-positive group and 23 for the p16-negative group ($P = .14$). The median lymph node densities (positive nodes/total nodes) for the 2 groups were 0.12 (p16-positive) and 0.11 (p16-negative; $P = .70$.).

Cutpoint Threshold

Table 2 shows the full and reduced models (minimum AIC) for overall survival before the addition of counted lymph nodes. The reduced model was created by the removal of variables that did not contribute to a better model fit (AIC) to achieve a more parsimonious model. In the third model, counted lymph nodes were added with a single cut-point threshold to differentiate 2 separate groups of patients. Having fewer than 18 counted lymph nodes was significantly associated with worse overall survival (HR, 1.38; 95% confidence interval [CI], 1.09-1.74; $P = .007$) after adjustments for age, race, Zubrod performance status, smoking history, primary site, pathologic T stage, extracapsular nodal extension, and number of positive nodes. Including the additional variables that were left out of our final model (sex, N stage, unilateral/bilateral dissection, and margin status) did not change the results appreciably (HR, 1.37; 95% CI, 1.08-1.74; $P = .009$). Figure 3 demonstrates overall survival curves for <18 lymph nodes versus ≥ 18 lymph nodes. The model using 18 lymph nodes as a cut point had a maximum effect size (largest HR) and minimum AIC among all possible models with a lymph node cutoff ranging from 10 to 46 (10th to 90th percentiles).

Sensitivity Analysis

Sensitivity analyses were performed for the effect of <18 counted nodes versus ≥ 18 counted nodes on overall survival. When the analysis was limited to patients with unilateral neck dissection, the HR was 1.43 (95% CI, 1.05-1.95). Censoring all patients at 5 years yielded an HR of 1.30 (95% CI, 1.01-1.68). Limiting the analysis to NRG Oncology RTOG 9501 and adding the assigned treatment (chemoradiation vs radiation) to the model did not change the HR for counted nodes: 1.29 (95% CI, 0.99-1.69) with treatment in the model and 1.28 (95% CI, 0.98-1.67) without treatment. Including an interaction term in the NRG Oncology RTOG 9501 model (assigned treatment × counted nodes) yielded an interaction P value

TABLE 1. Patient and Tumor Characteristics by the Number of Resected Nodes (Mean)

	<18 Nodes (n = 162)	≥18 Nodes (n = 410)	Total (n = 572)
Treatment group, No. (%), $P = .25$[a]			
RT	47 (29.0)	149 (36.3)	196 (34.3)
RT + CT	59 (36.4)	135 (32.9)	194 (33.9)
RT + CT + cetuximab	56 (34.6)	126 (30.7)	182 (31.8)
Age, y, $P = .26$[b]			
Mean (standard deviation)	56.4 (9.43)	55.6 (9.58)	55.8 (9.53)
Median (range)	58 (27-79)	55 (21-80)	56 (21-80)
Sex, No. (%), $P = 1.00$[c]			
Male	134 (82.7)	339 (82.7)	473 (82.7)
Female	28 (17.3)	71 (17.3)	99 (17.3)
Race, No. (%), $P = .72$[c]			
White	129 (79.6)	333 (81.2)	462 (80.8)
Nonwhite	33 (20.4)	77 (18.8)	110 (19.2)
Zubrod performance status, No. (%), $P = .30$[c]			
0	84 (51.9)	233 (56.8)	317 (55.4)
1	76 (46.9)	173 (42.2)	249 (43.5)
2	2 (1.2)	4 (1.0)	6 (1.0)
Smoking history, No. (%), $P = .50$[a]			
Never	21 (13.0)	67 (16.3)	88 (15.4)
Former	81 (50.0)	187 (45.6)	268 (46.9)
Current	60 (37.0)	156 (38.0)	216 (37.8)
Primary site, No. (%), $P = .16$[a]			
Oral cavity	56 (34.6)	137 (33.4)	193 (33.7)
Oropharynx	56 (34.6)	173 (42.2)	229 (40.0)
Hypopharynx	20 (12.3)	30 (7.3)	50 (8.7)
Larynx	30 (18.5)	70 (17.1)	100 (17.5)
T stage (surgical-pathological), No. (%), $P = .88$[b]			
T1	30 (18.5)	55 (13.4)	85 (14.9)
T2	36 (22.2)	125 (30.5)	161 (28.1)
T3	42 (25.9)	92 (22.4)	134 (23.4)
T4	54 (33.3)	138 (33.7)	192 (33.6)
N stage (surgical-pathological), No. (%), $P < .001$[b]			
N0	4 (2.5)	7 (1.7)	11 (1.9)
N1	5 (3.1)	23 (5.6)	28 (4.9)
N2a	8 (4.9)	26 (6.3)	34 (5.9)
N2b	86 (53.1)	276 (67.3)	362 (63.3)
N2c	57 (35.2)	68 (16.6)	125 (21.9)
N3	2 (1.2)	10 (2.4)	12 (2.1)
AJCC stage (surgical-pathological), No. (%), $P = .98$[b]			
I	0 (0.0)	1 (0.2)	1 (0.2)
III	6 (3.7)	14 (3.4)	20 (3.5)
IV	156 (96.3)	395 (96.3)	551 (96.3)
Type of neck dissection, No. (%), $P < .001$[c]			
Unilateral	88 (54.3)	284 (69.3)	372 (65.0)
Bilateral	74 (45.7)	126 (30.7)	200 (35.0)
Counted lymph nodes (left)	(n = 116)	(n = 254)	(n = 370)
Mean (standard deviation)	11.9 (6.10)	32.8 (14.38)	26.3 (15.76)
Median (range)	12 (1-32)	31 (1-89)	24 (1-89)
Counted lymph nodes (right)	(n = 120)	(n = 282)	(n = 402)
Mean (standard deviation)	11.6 (5.74)	32.7 (13.50)	26.4 (15.20)
Median (range)	11 (2-32)	31 (1-78)	25 (1-78)
Counted lymph nodes (mean)[d]			
Mean (standard deviation)	11.7 (4.10)	34.1 (13.06)	27.7 (15.13)
Median (range)	12 (2-17)	32 (18-89)	26 (2-89)
Lymph nodes with pathologically confirmed metastasis (total), $P = .10$[b]			
Mean (standard deviation)	4.1 (3.23)	5.2 (5.13)	4.9 (4.69)
Median (range)	3 (0-19)	3 (0-34)	3 (0-34)
<2, No. (%),	18 (11.1)	47 (11.5)	65 (11.4)
≥2, No. (%),	144 (88.9)	363 (88.5)	507 (88.6)
Lymph node density (positive/counted), $P < .001$[b]			
Mean (standard deviation)	0.28 (0.21)	0.13 (0.13)	0.17 (0.17)
Median (range)	0.23 (0.00-1.00)	0.09 (0.00-0.83)	0.12 (0.00-1.00)
Extracapsular nodal extension, No. (%), $P = .40$[c]			
No	76 (46.9)	176 (42.9)	252 (44.1)
Yes	86 (53.)	234 (57.1)	320 (55.9)
Positive margin, No. (%), $P = .05$[c]			
No	122 (75.3)	339 (82.7)	461 (80.6)
Yes	40 (24.7)	71 (17.3)	111 (19.4)

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiation therapy.

[a] Pearson chi-square test.

[b] Wilcoxon rank-sum test.

[c] Fisher's exact test. Zubrod 1 and Zubrod 2 were combined.

[d] If there was bilateral neck dissection, the mean of the left and right sides was used; if there was unilateral neck dissection, the number counted was used.

of.27, so it does not appear that the effect of counted nodes differs with the treatment. Limiting the analysis to patients in NRG Oncology RTOG 0234 with a known p16 status and adding p16 to the model did not affect the HR for counted nodes: 1.51 (95% CI, 0.87-2.63) with p16 in the model and 1.54 (95% CI, 0.88-2.67) without p16. Including an interaction term in the NRG Oncology RTOG 0234 model (p16 status × counted nodes) yielded an interaction *P* value of .99, so it does not appear that the effect of counted nodes differs with the p16 status.

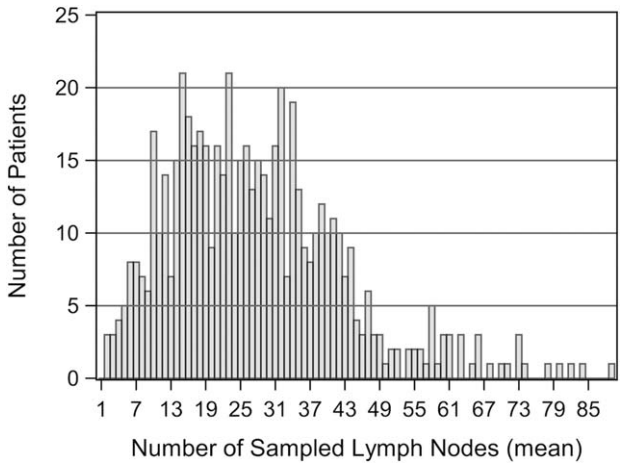

Figure 2. Distribution of the number of counted lymph nodes (mean).

Patterns of Failure

Patterns of failure are shown in Figures 4 and 5. Patients with fewer than 18 nodes had significantly more local-regional failure (HR, 1.46; 95% CI, 1.02-2.08; $P = .04$; Fig. 4) but not distant metastasis (HR, 1.08; 95% CI, 0.77-1.53; $P = .65$; Fig. 5).

DISCUSSION

Using data from prospective clinical trials, we found that lymph node counts ≥ 18 in patients with node-positive mucosal squamous cell carcinoma were associated with improved survival and decreased rates of local-regional recurrence. The effect was similar for p16-positive and p16-negative patients. To our knowledge, this study is the first to show this effect in node-positive patients with head and neck cancer, and it offers a potential quality metric for neck dissection.

Furthermore, to our knowledge, this study is the first to query prospective data to identify a correlation between lymph node counts and oncologic outcomes. Several teams have previously investigated this potential relation with single or multi-institutional retrospective data sets. Gil et al[10] used a cut point of 30 lymph nodes, Ryu et al[20] used a cut point of 52 lymph nodes, and Shrime et al[21] used the lymph node count as a continuous variable. These values were considerably higher than our cut point, and this is possibly why they did not demonstrate a survival difference. Patel el al[22] evaluated the impact of lymph node density, not counts, on overall survival for more than 4200 patients. As part of their secondary analysis, a

TABLE 2. Overall Survival: Multivariate Analysis (572 Patients, 352 Events)

	Model 1: Full Model		Model 2: Reduced Model (Minimum AIC)		Model 3: Reduced Model With Counted Nodes Added	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (>55 vs ≤ 55 y)	1.25 (1.01-1.56)	.04	1.25 (1.00-1.55)	.05	1.24 (0.99-1.54)	.06
Sex (male vs female)	1.20 (0.89-1.63)	.24				
Race (nonwhite vs white)	1.35 (1·05-1.75)	.02	1.36 (1.05-1.75)	.02	1.33 (1.03-1.72)	.03
Zubrod PS (1-2 vs 0)	1.55 (1.25-1.92)	<.001	1.53 (1.23-1.89)	<.001	1.53 (1.23-1.90)	<.001
Smoking history (current vs former/never)	1.39 (1.09-1.76)	.007	1.38 (1.09-1.74)	.007	1.34 (1.06-1.69)	.01
Primary site (other vs oropharynx)	1.76 (1.38-2.25)	<.001	1.74 (1.38-2.20)	<.001	1.69 (1.33-2.14)	<.001
T stage (T2-T4 vs T1)	2.10 (1.40-3.15)	<.001	2.10 (1.40-3.13)	<.001	2.22 (1.48-3.33)	<.001
N stage (N2c-N3 vs N0-N2b)	1.19 (0.88-1.60)	.26				
Neck dissection (bilateral vs unilateral)	0.88 (0.66-1.15)	.34				
ECE (yes vs no)	1.76 (1.40-2.20)	<.001	1.77 (1.41-2.20)	<.001	1.77 (1.42-2.21)	<.001
Positive margin (yes vs no)	1.08 (0.80-1.47)	.62				
Positive nodes (≥2 vs 0-1)	1.68 (1.15-2.46)	.008	1.67 (1.15-2.43)	.007	1.68 (1.16-2.45)	.007
Counted nodes (<18 vs ≥ 18)					1.38 (1.09-1.74)	.007
AIC	3197.221		3192.466		3187.367	

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; ECE, extracapsular nodal extension; HR, hazard ratio; PS, performance status.
Cox models were stratified by the treatment group (radiation therapy; radiation therapy and chemotherapy; and radiation therapy, chemotherapy, and cetuximab).

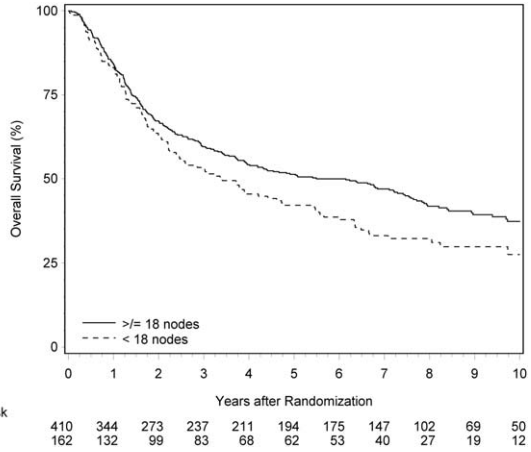

Figure 3. Kaplan-Meier estimates of overall survival by the number of counted nodes (572 patients, 352 events). Patients with fewer than 18 counted lymph nodes had worse survival than patients with 18 or more nodes (univariate hazard ratio stratified by treatment group, 1.40; 95% confidence interval, 1.11-1.76; $P = .005$); the 5-year survival rates were 42.1% (95% confidence interval, 34.3%-49.9%) and 51.3% (95% confidence interval, 46.4%-56.2%), respectively.

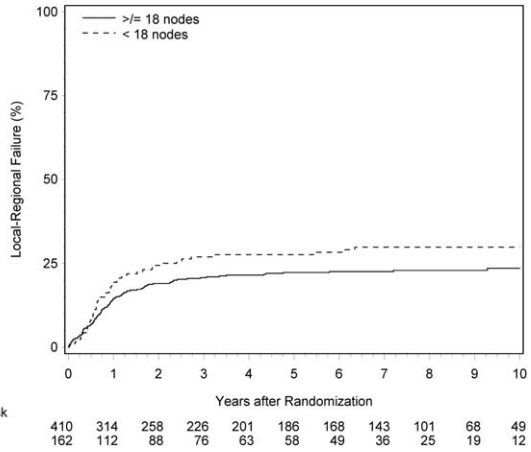

Figure 4. Cumulative incidence of local-regional failure by the number of sampled nodes (572 patients, 141 events). Patients with fewer than 18 sampled lymph nodes had more local-regional failure than patients with 18 or more nodes (univariate hazard ratio stratified by treatment group, 1.46; 95% confidence interval, 1.02-2.08; $P = .04$). The 5-year local-regional failure rates were 27.7% (95% confidence interval, 20.9%-34.8%) and 22.1% (95% confidence interval, 18.4%-26.5%), respectively.

single cut point of 20 was tested but did not demonstrate significance, although it is unclear whether other cut points would have shown a difference in survival. Ebrahimi et al[11] studied 225 patients with N0 squamous cell carcinoma of the oral cavity from the Sydney Head and Neck Institute, and they found that patients with lymph node counts < 18 had an increased risk of mortality (HR, 2.0; 95% CI, 1.1-3.6; $P = .020$). A pooled, multi-institutional, retrospective review of 1567 N0 squamous cell carcinoma oral cancer patients from 9 cancer centers found that a nodal yield < 18 was associated with decreased overall survival (HR, 1.69; 95% CI, 1.22-2.34; $P = .002$) and an increased risk of locoregional recurrence (HR, 1.53; 95% CI, 1.04-2.26; $P = .032$).[12] This also supports the theory that more thorough neck dissections removing more than 18 nodes may improve outcomes.

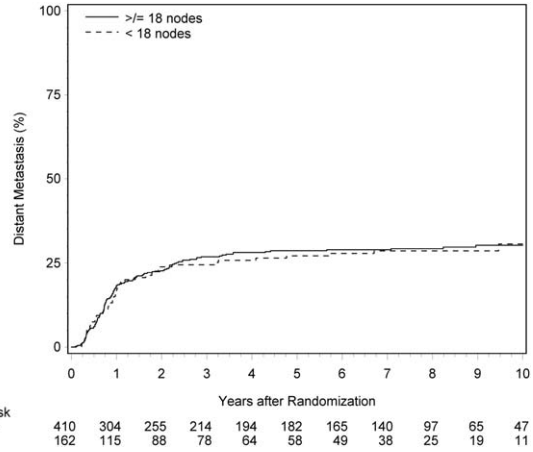

Figure 5. Cumulative incidence of distant metastasis by the number of sampled nodes (572 patients, 167 events). Patients with fewer than 18 sampled lymph nodes had rates of distant metastasis similar to those of patients with 18 or more nodes (univariate hazard ratio stratified by treatment group, 1.08; 95% confidence interval, 0.77-1.53; $P = .65$). The 5-year distant metastasis rates were 27.2% (95% confidence interval, 20.5%-34.3%) and 28.7% (95% confidence interval, 24.4%-33.2%), respectively.

The use of lymph node counts fits a larger national trend toward using specific numbers to address the quality of care. Recent efforts have shown that for clinicians to begin to improve cancer care, multidisciplinary teams must first have a way to measure quality. However, devising measurement tools can be challenging and frequently controversial. To do so, the complexity of medical care, patient presentations (natural history and variability of disease), and tumor heterogeneity must be distilled into a clinically robust metric that is easily compared across physicians and institutions. These metrics will always have exceptions; however, when multiple metrics are used to evaluate the care of a larger group of patients, a clearer picture of quality should emerge. These metrics should ideally represent intermediate points of care that can be directly affected by providers to improve long-term outcomes. The lymph node count from neck dissection is one such potential metric and, on the basis of the findings in this study, may deserve further evaluation.

Because of the additional factors that might affect the nodal count, it is possible that this metric may be able to be reached only in a significant number of patients—not in all patients—even in an optimal setting. In this case, implementation would have to be considered at a hospital level or a surgeon level across many cases as opposed to the individual patient level. Further studies of the impact of such a metric used in this fashion need to be first evaluated before any recommendation can be made.

The relation of lymph node counts and survival is an association but may not necessarily equate with causality. There are multiple aspects of patient care that may be the ultimate cause of the improved survival in patients with higher node counts. Lymph node counts are dependent on the technique of both the surgeon and the pathologist. Although the technical skill of a surgeon may lead to the removal of more lymphatic tissue, ultimately the pathologist is responsible for identifying and evaluating the lymph nodes. Differences in the numbers of lymph nodes retrieved in the pathology laboratory from a neck dissection may vary because of several factors. Surgeons with less experience may have more difficulty in identifying lymph nodes than those with more experience.[23] The degree of tissue fixation can result in different lymph node yields. A longer duration of formalin fixation has been shown to yield increased lymph node counts.[24] Prior radiation therapy to the neck has also been shown to result in decreased lymph node yield from lymph node dissections.[25]

Higher lymph node counts in patients cannot be separated from the structural and process-related aspects of a patient's care. Patients who have higher lymph node counts may receive care in higher volume institutions, have better perioperative care, be treated by more experienced radiation oncologists and medical oncologists, or be treated at more integrated academic medical centers. Although we have likely minimized some of these effects because of the greater consistency of patients entered into prospective clinical trials (NRG Oncology RTOG 9501 and NRG Oncology RTOG 0234), we cannot totally eliminate any potential influence of the type of institution or experience of the treating physicians. A study by Wuthrick et al[26] looked at patients treated at high-accruing centers versus low-accruing centers on the basis of accrual to 21 RTOG head and neck carcinoma trials. Patients at high-accruing centers had fewer protocol deviations (6% vs 18%, $P < .001$) and better overall survival (69.1% vs 51.0%, $P = .002$). Therefore, although lymph node counts are associated with improved survival, we cannot determine what component of that is due to direct removal of cancer cells within the regional lymphatics and other factors that might positively correlate with higher lymph node counts.

Finally, this report is a post hoc study of prospectively collected data from clinical trials designed to evaluate adjuvant therapy in node-positive patients. We were unable to control for system-level factors and unmeasured process measures that may have influenced outcomes.[26] Further studies should be performed on larger data sets with standardized treatment protocols to better isolate the effect of the lymph node count on survival.

Neck dissections with 18 or more lymph nodes are associated with improved survival and lower rates of local-regional failure in node-positive patients. On the basis of the current literature and this secondary analysis from prospective clinical trials, lymph node counts should be further evaluated as a potential measure of quality in head and neck surgery.

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CONFLICT OF INTEREST DISCLOSURES

Anthony J. Cmelak declares honoraria from a speakers' bureau and a consulting or advisory role for Merck. David Raben declares honoraria, travel expenses, accommodations, or other expenses from Astra Zeneca, Merck, and Ferring. Robert L. Foote declares a pending patent with the Mayo Clinic (licensed to Bionix) and royalties from UpToDate and Elsevier. Wade L. Thorstad has an immediate family member who is employed by and receives travel, accommodations, or other expenses from Elekta. Qiang (Ed) Zhang has an immediate family member who is employed by and has stock or other ownership in Pfizer. Quynh Thu Le declares stock or other ownership in Aldea, and her institution receives research funding from Amgen.

AUTHOR CONTRIBUTIONS

Vasu Divi: Literature search, figures, study design, data interpretation, writing, and approval of the final manuscript. Jonathan Harris: Data analysis, data interpretation, writing, and approval of the final manuscript. Paul M. Harari: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Jay S. Cooper: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Jonathan McHugh: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Diana Bell: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Erich M. Sturgis: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Anthony J. Cmelak: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Mohan Suntharalingam:

Study design, data collection, data interpretation, writing, and approval of the final manuscript. David Raben: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Harold Kim: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Sharon A. Spencer: Study design, data collection, data interpretation, writing, and approval of the final manuscript. George E. Laramore: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Andy Trotti: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Robert L. Foote: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Christopher Schultz: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Wade L. Thorstad: Study design, data collection, data interpretation, writing, and approval of the final manuscript. Qiang (Ed) Zhang: Figures, data analysis, data interpretation, writing, and approval of the final manuscript. Quynh Thu Le: Study design, data collection, data interpretation, writing, and approval of the final manuscript. F. Christopher Holsinger: Literature search, figures, study design, data interpretation, writing, and approval of the final manuscript.

REFERENCES

1. Crile G. III. On the technique of operations upon the head and neck. *Ann Surg*. 1906;44:842-850.
2. Martin H, Del Valle B, Ehrlich H, et al. Neck dissection. *Cancer*. 1951;4:441-499.
3. Byers RM. Modified neck dissection. A study of 967 cases from 1970 to 1980. *Am J Surg*. 1985;150:414-421.
4. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. *Head Neck Surg*. 1988;10:160-167.
5. Robbins KT, Medina JE, Wolfe GT, et al. Standardizing neck dissection terminology. Official report of the Academy's Committee for Head and Neck Surgery and Oncology. *Arch Otolaryngol Head Neck Surg*. 1991;117:601-605.
6. Swanson RS, Compton CC, Stewart AK, et al. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol*. 2003;10:65-71.
7. Prandi M, Lionetto R, Bini A, et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. *Ann Surg*. 2002;235:458-463.
8. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol*. 2003; 21:2912-2919.
9. Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007;99:433-441.
10. National Quality Forum. National Voluntary Consensus Standards for Quality of Cancer Care. http://www.qualityforum.org/pdf/cancer/txAppA-Specifications_web.pdf. Accessed January 5, 2016.
11. Ebrahimi A, Zhang WJ, Gao K, et al. Nodal yield and survival in oral squamous cancer: defining the standard of care. *Cancer*. 2011; 117:2917-2925.
12. Ebrahimi A, Clark JR, Amit M, et al. Minimum nodal yield in oral squamous cell carcinoma: defining the standard of care in a multicenter international pooled validation study. *Ann Surg Oncol*. 2014;21:3049-3055.
13. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937-1944.
14. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. 2014;32:2486-2495.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
16. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: Wiley; 1980.
17. Cox DR. Regression models and life tables. *J R Stat Soc Ser B*. 1972;34:187-229.
18. Agrama MT, Reiter D, Topham AK, et al. Node counts in neck dissection: are they useful in outcomes research? *Otolaryngol Head Neck Surg*. 2001;124:433-435.
19. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer*. 2009;115:5700-5710.
20. Ryu IS, Roh JL, Cho KJ, et al. Lymph node density as an independent predictor of cancer-specific mortality in patients with lymph node–positive laryngeal squamous cell carcinoma after laryngectomy. *Head Neck*. 2014;37:1319-1325.
21. Shrime MG, Bachar G, Lea J, et al. Nodal ratio as an independent predictor of survival in squamous cell carcinoma of the oral cavity. *Head Neck*. 2009;31:1482-1488.
22. Patel SG, Amit M, Yen TC, et al. Lymph node density in oral cavity cancer: results of the International Consortium for Outcomes Research. *Br J Cancer*. 2013;109:2087-2095.
23. Ostadi MA, Harnish JL, Stegienko S, et al. Factors affecting the number of lymph nodes retrieved in colorectal cancer specimens. *Surg Endosc*. 2007;21:2142-2146.
24. Lemmens VE, van Lijnschoten I, Janssen-Heijnen ML, et al. Pathology practice patterns affect lymph node evaluation and outcome of colon cancer: a population-based study. *Ann Oncol*. 2006;17:1803-1809.
25. Wong SL. Lymph node counts and survival rates after resection for colon and rectal cancer. *Gastrointest Cancer Res*. 2009;3:S33-S35.
26. Wuthrick EJ, Zhang Q, Machtay M, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol*. 2015;33:156-164.