Establishing quality indicators for neck dissection: correlating the number of lymph nodes with oncologic outcomes, NRG Oncology RTOG 9501 and 0234

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This project was supported by grants U10CA21661, U10CA180868, U10CA180822, U10CA37422, and UG1CA189867 from the National Cancer Institute (NCI) and Bristol-Myers Squibb/Aventis Pharmaceuticals.

Running title: Neck dissection lymph node count and survival

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Conflicts of Interest: Dr. Cmelak declares honoraria from, speakers' bureau and consulting or advisory role for Merck. Dr. Raben declares honoraria, travel, accommodations, or other expenses from Astra Zeneca, Merck, and Ferring. Dr. Foote declares patent other intellectual property with Mayo Clinic and another relationship with Up-to-Date. Dr. Thorstad has an immediate family member employed by and who receives travel, accommodations or other expenses from Elekta. Dr. Zhang has an immediate family member employed by and who has stock or other ownership of Pfizer. Dr. Le declares stock or other ownership of Aldea and her institution receives research funding from Amgen.

Author contributions: Drs. Divi and Holsinger contributed to the literature search, figures, study design, data interpretation, writing, and approval of the final manuscript. Mr. Harris contributed to the data analysis, data interpretation, writing, and approval of the final manuscript. Drs. Harari, Cooper, McHugh, Bell, Sturgis, Cmelak, Suntharalingam, Raben, Kim, Spencer, Laramore, Trotti, Foote, Schultz, Thorstad, and Le contributed to the study design, data collection, data interpretation, writing, and approval of the final manuscript. Dr. Zhang contributed to the figures, data analysis, data interpretation, writing, and approval of the final manuscript.

Number of text pages: 16

Number of tables: 2

Number of figures: 5

Neck dissection lymph node count and survival

Precis: The removal and evaluation of 18 or more lymph nodes was associated with improved overall survival in node-positive mucosal head and neck cancer. This threshold should be further evaluated as a potential measure of quality in neck dissections.

Neck dissection lymph node count and survival

Abstract

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 is 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 on NRG Oncology RTOG trials 9501 and 0234 was evaluated for its prognostic impact on overall survival using a multivariate Cox model adjusted for demographic, tumor, and lymph node data, and stratified by postoperative treatment group.

Results: 572 patients were analyzed at median follow-up of eight years. 98% of patients were pathologically N+. Median number of lymph nodes recorded on the left and right sides were 24 and 25. Fewer than 18 nodes identified was associated with worse overall survival relative to ≥18 nodes (hazard ratio 1.38, 95%CI 1.09-1.74, p=0.007). The difference appeared to be driven by local-regional failure (HR 1.46, 95%CI 1.02-2.08, p=0.04) but not distant metastases (HR 1.08, 95%CI 0.77-1.53, p=0.65). When analysis was limited to NRG Oncology RTOG 0234 patients, adding p16 status to the model did not affect the hazard ratio for dissected nodes and the effect of nodes was not different by p16 status.

Conclusion: The removal and identification of 18 or more lymph nodes was associated with improved overall survival and lower rates of local-regional failure, and should be further evaluated as a measure of quality in neck dissections for mucosal squamous cell carcinoma.

Keywords: Quality indicators, head and neck cancer, neck dissection, survival, surgery

Introduction

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

Despite efforts to standardize and classify technique,[5] the practice of neck dissection now varies widely across centers and from surgeon to surgeon. As such, there may be significant variability in 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 and III colorectal cancer, removing 12 lymph nodes or more is associated with increased overall 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 multi-center studies have attempted to address surgical quality in neck dissection. [11,12] However, to our knowledge, no prospective data has been examined to determine relationships between the number of nodes removed in neck dissection and oncologic outcomes such as locoregional recurrence or survival.

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

Methods

This study included patients treated on postoperative trials NRG Oncology RTOG 9501[13]and NRG Oncology RTOG 0234.[14] NRG Oncology RTOG 9501 was a phase III trial comparing radiation alone to radiation with concurrent cisplatin. NRG Oncology RTOG 0234 was a randomized phase II trial comparing two experimental regimens (1) radiation with concurrent cisplatin and cetuximab and (2) radiation with concurrent docetaxel and cetuximab to 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 prior to participation.

The analysis was limited to patients with complete data for the following potential covariates: age, gender, 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 two sides was used for the number of counted lymph nodes. Possible differences in distributions of patient characteristics were tested as follows: continuous or ordinal variable, Wilcoxon rank-sum test;

categorical variable (for two groups and two levels), Fisher's exact test; other categorical variable, 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 using a multivariate Cox model adjusted for demographic, tumor, and lymph node data, and stratified by postoperative treatment group. Overall survival was defined as the time from randomization to death (event) or last follow-up. Rates were estimated by the Kaplan-Meier method.[15] Local-regional failure is defined as the time from randomization to local or regional relapse (event), death (competing risk), or last follow-up. Distant metastasis is defined as the time from randomization to distant metastasis (event), death (competing risk), or last follow-up. Rates were estimated by the cumulative incidence method.[16] Hazard ratios were estimated by Cox modeling.[17]

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

Results

Patient Demographics and Tumor Characteristics

Six-hundred ninety-seven patients were enrolled to NRG Oncology RTOG 9501 (n=459) or NRG Oncology RTOG 0234 (n=238) of whom 613 (NRG Oncology RTOG 9501: 410; NRG Oncology RTOG 0234: 203) were eligible and included in analysis of protocol endpoints. Of these, 572 (93.3%) were included in this secondary analysis (Figure 1). Median follow-up for surviving patients was 8.0 years (range 0.2 to 14.0).

Patient and tumor characteristics by 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 three. The median number of counted lymph nodes on the left and right sides were 24 and 25, respectively. 98% of patients were N+. Prospective data collection for RTOG 9501 and 0234 did not include notation about the level of each harvested node and which lymph node levels were dissected. Distributions of N stage (p<0.001), type of neck dissection (p<0.001), lymph node density (p<0.001), and margin status (p=0.05) differ significantly between the two groups. The distribution of counted lymph nodes is shown in Figure 2 and shows a very similar shape as the SEER data from Agrama.[18] The median lymph node density (positive nodes/total nodes) between the two groups was 0.23 (<18) verses 0.09 (≥18) (p<0.001).

In 130 patients on NRG Oncology RTOG 0234 for whom p16 status was known, 57 were p16-positive (43.8%). Distributions of primary site (p<0.001), T stage (p<0.001), and margin status (p<0.001) differ between the p16-positive and p16-negative groups. Median number of resected nodes was 27 for the p16-positive group and 23 for the p16-negative group (p=0.14).

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The median lymph node density (positive nodes/total nodes) between the two groups was 0.12 (p16-positive) verses 0.11 (p16-negative) (p=0.70.).

Cut point Threshold

Table 2 shows the full and reduced models (minimum AIC) for overall survival prior to adding counted lymph nodes. The reduced model was created by removing variables that did not contribute to better model fit (AIC) to achieve a more parsimonious model. In the third model, counted lymph nodes were added using a single cut point threshold to differentiate two separate groups of patients. Having < 18 counted lymph nodes significantly associated with worse overall survival [hazard ratio 1.38, 95% confidence interval (CI) 1.09 to 1.74, p=0.007] after adjustment for age, race, Zubrod, smoking history, primary site, pathologic T stage, ECE, and number of positive nodes. Including the additional variables that were left out of our final model (gender, N stage, unilateral/bilateral, margin status) does not change the results appreciably [hazard ratio 1.37, 95% confidence interval 1.08 to 1.74, p=0.009]. Figure 3 demonstrates overall survival curves for < 18 vs. ≥ 18 lymph nodes. The model using 18 lymph nodes as a cut point has maximum effect size (largest hazard ratio) and minimum AIC among all possible models with a lymph node cut off ranging from *10 – 46 (10^{th} to 90^{th} percentiles).*

Sensitivity Analysis

Sensitivity analyses were performed for the effect of < 18 vs. ≥ 18 counted nodes on overall survival. Limited to patients with unilateral neck dissection, the hazard ratio is 1.43 (95% CI 1.05 to 1.95). Censoring all patients at five years yields a hazard ratio of 1.30 (95% CI 1.01 to 1.68). Limited to NRG Oncology RTOG 9501, adding assigned treatment (chemoradiation vs. radiation) to the model does not change the hazard ratio for counted nodes: 1.29 (95% CI 0.99-1.69) with treatment in the model, 1.28 (95% CI 0.98-1.67) without. Including an interaction term in the NRG Oncology RTOG 9501 model (assigned treatment X counted nodes) yields an interaction p-value of 0.27, so it does not appear that the effect of counted nodes differs by treatment. Limited to patients in NRG Oncology RTOG 0234 with known p16 status, adding p16 to the model does not affect the hazard ratio for counted nodes: 1.51 (95% CI 0.87-2.63) with p16 in the model, 1.54 (95% CI 0.88-2.67) without. Including an interaction term in the NRG Oncology RTOG 0234 model (p16 status X counted nodes) yields an interaction p-value of 0.99, so it does not appear that the effect of counted nodes differs by p16 status.

Patterns of Failure

Patterns of failure are shown in Figures 4 and 5. Patients with < 18 nodes had significantly more local-regional failure (hazard ratio 1.46, 95% confidence interval 1.02 to 2.08, p=0.04; Figure 4) but not distant metastasis (hazard ratio 1.08, 95% confidence interval 0.77 to 1.53, p=0.65; Figure 5).

Discussion

Using data from prospective clinical trials, we found that lymph node counts ≥ 18 in patients with node-positive mucosal squamous cell carcinoma are associated with improved survival and decreased rates of local-regional recurrence. The effect is 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 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 relationship using single or multi-institutional retrospective data sets. Gil *et al* used a cut point of 30 lymph nodes, Ryu *et al* used a cut point of 52 lymph nodes, and Shrime *et al* used lymph node count as a continuous variable.[19-21] These values were considerably higher than our cut point which is possibly why they did not demonstrate a survival difference. Patel *el al* evaluated the impact of lymph node density, not counts, on overall survival on over 4200 patients. As part of their secondary analysis, a single cut point of 20 was tested but did not demonstrate significance, though it is unclear if other cut points would have shown a difference in survival.[22] Ebrahimi and colleagues studied 225 patients with N0 SCC of the oral cavity from the Sydney Head and Neck Institute, finding that patients with lymph node counts < 18 had an increased risk of mortality (HR 2.0; 95% CI, 1.1-3.6; P=0.020).[11] A pooled multi-institutional retrospective review of 1,567 N0 SCC oral cancer patients from nine cancer centers found that a nodal yield < 18 was associated with decreased overall survival (HR 1.69; 95% CI 1.22–2.34; p = 0.002) and increased risk of locoregional recurrence (HR 1.53; 95% CI 1.04–2.26; p = 0.032).[12] It also supports the theory that more thorough neck dissections removing greater than 18 nodes may improve outcomes.

The use of lymph node counts fits in with a larger national trend towards 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. In order 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. Lymph node counts from neck dissection is one such potential metric and based on the findings in this study, may deserve further evaluation.

Given the additional factors that might impact the nodal count, it is possible that this metric may only be able to be reached in a significant number of, but not 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 at 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 could be made.

The relationship 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 pathologist. While the technical skill of a surgeon may remove 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 due to several factors. Surgeons with less experience may have more difficulty in identifying lymph nodes as compared to those with more experience.[23] Degree of tissue fixation can result in different lymph node yields. 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 be cared for 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. While we have likely minimized some of these effects given 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. looked at patients treated at high-accruing versus low-accruing centers based on accrual to 21 RTOG HNC trials.[26] Patients at high-accruing centers had fewer protocol deviations (6% v 18%; $P < .001$) and better overall survival (69.1% v 51.0%; $P = .002$). Therefore, while lymph node counts are associated with improved survival, we cannot determine what component of that is from 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 datasets with standardized treatment protocols to better isolate the effect of lymph node count on survival.

Neck dissections with 18 or greater lymph nodes are associated with improved survival and lower rates of local-regional failure in node-positive patients. Based on 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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Figure Legends

Figure 1. CONSORT diagram

Figure 2. Distribution of Number of Counted Lymph Nodes (mean)

Figure 3. Kaplan-Meier estimates of overall survival by the number of counted nodes (n=572; 352 events). Patients with < 18 counted lymph nodes have worse survival compared to those with ≥ 18 nodes (univariate hazard ratio stratified by treatment group 1.40, 95% confidence interval 1.11 to 1.76, p=0.005) with five-year survival rates of 42.1% (95% confidence interval 34.3 to 49.9) and 51.3% (95% confidence interval 46.4 to 56.2).

Figure 4. Cumulative incidence of local-regional failure by the number of sampled nodes (n=572; 141 events). Patients with < 18 sampled lymph nodes have more local-regional failure compared to those with ≥ 18 nodes (univariate hazard ratio stratified by treatment group 1.46, 95% confidence interval 1.02 to 2.08, p=0.04) with 5-year local-regional failure rates of 27.7% (95% confidence interval 20.9 to 34.8) and 22.1% (95% confidence interval 18.4 to 26.5).

Figure 5. Cumulative incidence of distant metastasis by the number of sampled nodes (n=572; 167 events). Patients with < 18 sampled lymph nodes have similar rates of distant metastasis compared to those with ≥ 18 nodes (univariate hazard ratio stratified by treatment group 1.08, 95% confidence interval 0.77 to 1.53, p=0.65) with 5-year distant metastasis rates of 27.2% (95% confidence interval 20.5 to 34.3) and 28.7% (95% confidence interval 24.4 to 33.2).

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Table 1. Patient and Tumor Characteristics by Number of Resected Nodes (mean)

	< 18 (n=162)	≥ 18 (n=410)	Total (n=572)
Treatment group, p=0.25 [1]			
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 (years), p=0.26 [2]			
Mean (standard deviation)	56.4 (9.43)	55.6 (9.58)	55.8 (9.53)
Median (min-max)	58 (27-79)	55 (21-80)	56 (21-80)
Gender, p=1.00 [3]			
Male	134 (82.7%)	339 (82.7%)	473 (82.7%)
Female	28 (17.3%)	71 (17.3%)	99 (17.3%)
Race, p=0.72 [3]			
White	129 (79.6%)	333 (81.2%)	462 (80.8%)
Non-white	33 (20.4%)	77 (18.8%)	110 (19.2%)
Zubrod performance status, p=0.30 [3]			
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, p=0.50 [1]			
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, p=0.16 [1]			
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), p=0.88 [2]			
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%)

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	< 18 (n=162)	≥ 18 (n=410)	Total (n=572)
T4	54 (33.3%)	138 (33.7%)	192 (33.6%)
N stage (surgical-pathological), p<0.001 [2]			
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), p=0.98 [2]			
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, p<0.001 [3]			
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 (min-max)	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 (min-max)	11 (2-32)	31 (1-78)	25 (1-78)
Counted lymph nodes (mean) [4]			
Mean (standard deviation)	11.7 (4.10)	34.1 (13.06)	27.7 (15.13)
Median (min-max)	12 (2-17)	32 (18-89)	26 (2-89)
Lymph nodes with pathologically confirmed metastasis (total), p=0.10 [2]			
Mean (standard deviation)	4.1 (3.23)	5.2 (5.13)	4.9 (4.69)
Median (min-max)	3 (0-19)	3 (0-34)	3 (0-34)
< 2	18 (11.1%)	47 (11.5%)	65 (11.4%)
>/= 2	144 (88.9%)	363 (88.5%)	507 (88.6%)

Neck dissection lymph node count and survival

	< 18 (n=162)	≥ 18 (n=410)	Total (n=572)
Lymph node density (positive/counted), p<0.001 [2]			
Mean (standard deviation)	0.28 (0.21)	0.13 (0.13)	0.17 (0.17)
Median (min-max)	0.23 (0.00-1.00)	0.09 (0.00-0.83)	0.12 (0.00-1.00)
Extracapsular nodal extension, p=0.40 [3]			
No	76 (46.9%)	176 (42.9%)	252 (44.1%)
Yes	86 (53.%)	234 (57.1%)	320 (55.9%)
Positive margin, p=0.05 [3]			
No	122 (75.3%)	339 (82.7%)	461 (80.6%)
Yes	40 (24.7%)	71 (17.3%)	111 (19.4%)

[1] Pearson chi-square test.
[2] Wilcoxon rank-sum test.
[3] Fisher's exact test. Zubrod 1 and 2 were combined.
[4] If bilateral neck dissection mean of left and right sides; if unilateral, the number counted.

Neck dissection lymph node count and survival

Table 2. Overall Survival: multivariate analysis (n=572; 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-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (>55 vs. </=55)	1.25 (1.01-1.56)	0.04	1.25 (1.00-1.55)	0.05	1.24 (0.99-1.54)	0.06
Gender (male vs. female)	1.20 (0.89-1.63)	0.24				
Race (non-white vs. white)	1.35 (1·05-1.75)	0.02	1.36 (1.05-1.75)	0.02	1.33 (1.03-1.72)	0.03
Zubrod PS (1-2 vs. 0)	1.55 (1.25-1.92)	<0.001	1.53 (1.23-1.89)	<0.001	1.53 (1.23-1.90)	<0.001
Smoking history (current vs. former/never)	1.39 (1.09-1.76)	0.007	1.38 (1.09-1.74)	0.007	1.34 (1.06-1.69)	0.01
Primary site (other vs. oropharynx)	1.76 (1.38-2.25)	<0.001	1.74 (1.38-2.20)	<0.001	1.69 (1.33-2.14)	<0.001
T stage (T2-4 vs. T1)	2.10 (1.40-3.15)	<0.001	2.10 (1.40-3.13)	<0.001	2.22 (1.48-3.33)	<0.001
N stage (N2c-3 vs. N0-2b)	1.19 (0.88-1.60)	0.26				
Neck dissection (bilateral vs. unilateral)	0.88 (0.66-1.15)	0.34				
ECE (yes vs. no)	1.76 (1.40-2.20)	<0.001	1.77 (1.41-2.20)	<0.001	1.77 (1.42-2.21)	<0.001
Positive margin (yes vs. no)	1.08 (0.80-1.47)	0.62				
Positive nodes (>/=2 vs. 0-1)	1.68 (1.15-2.46)	0.008	1.67 (1.15-2.43)	0.007	1.68 (1.16-2.45)	0.007
Counted nodes (<18 vs. >/=18)					1.38 (1.09-1.74)	0.007
AIC	3197.221		3192.466		3187.367	

Cox models were stratified by treatment group (RT, RT+CT, RT+CT+cetuximab).
RT: radiation therapy; CT: chemotherapy; HR: hazard ratio; CI: confidence interval; PS: performance s tatus;
ECE: extracapsular nodal extension; AIC: Akaike information criterion.

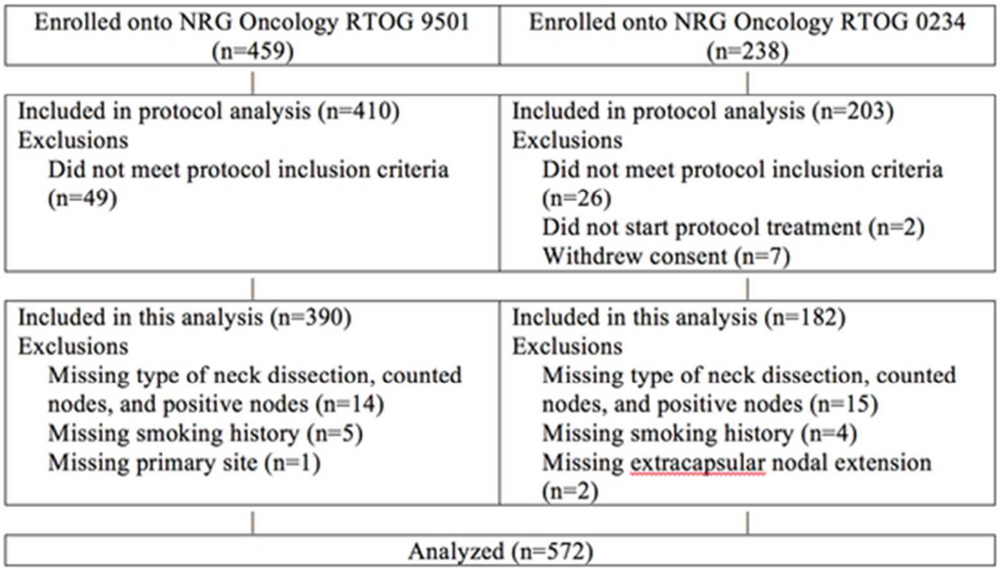


Figure 1
23x13mm (600 x 600 DPI)

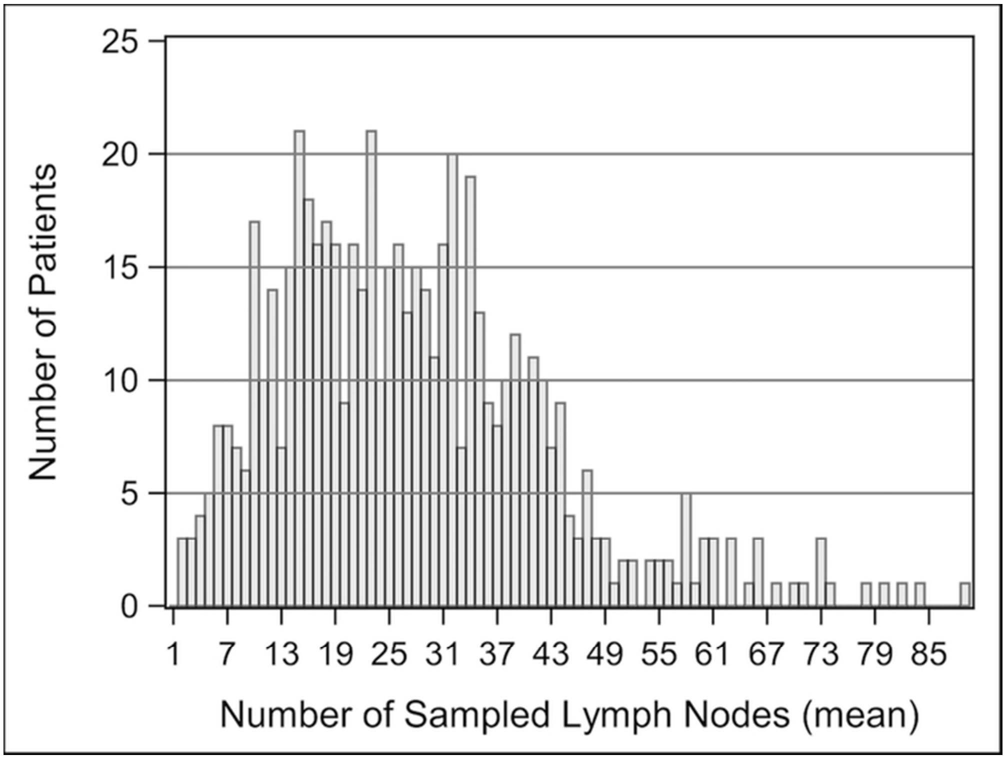
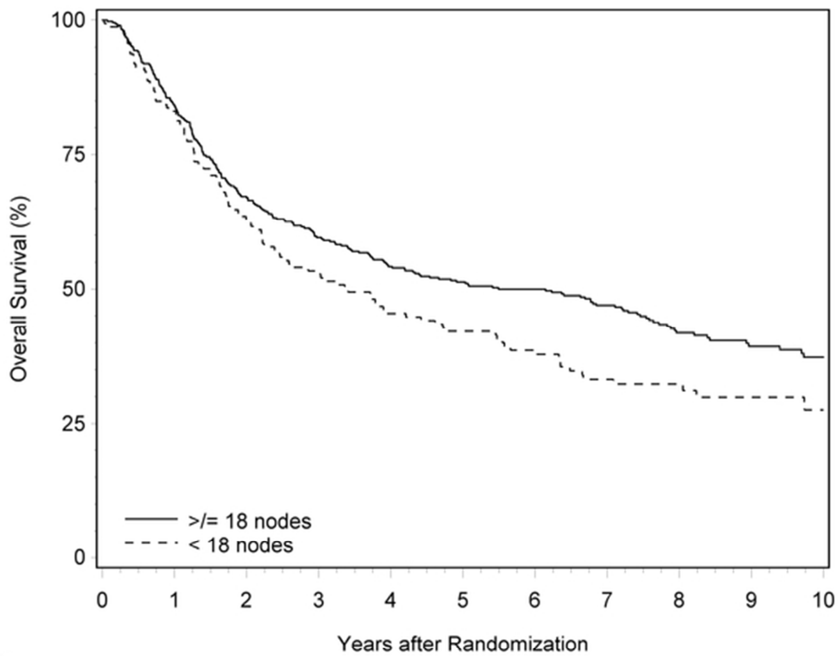


Figure 2
30x22mm (600 x 600 DPI)



Patients at Risk											
>/= 18 nodes	410	344	273	237	211	194	175	147	102	69	50
< 18 nodes	162	132	99	83	68	62	53	40	27	19	12

Figure 3
30x22mm (600 x 600 DPI)

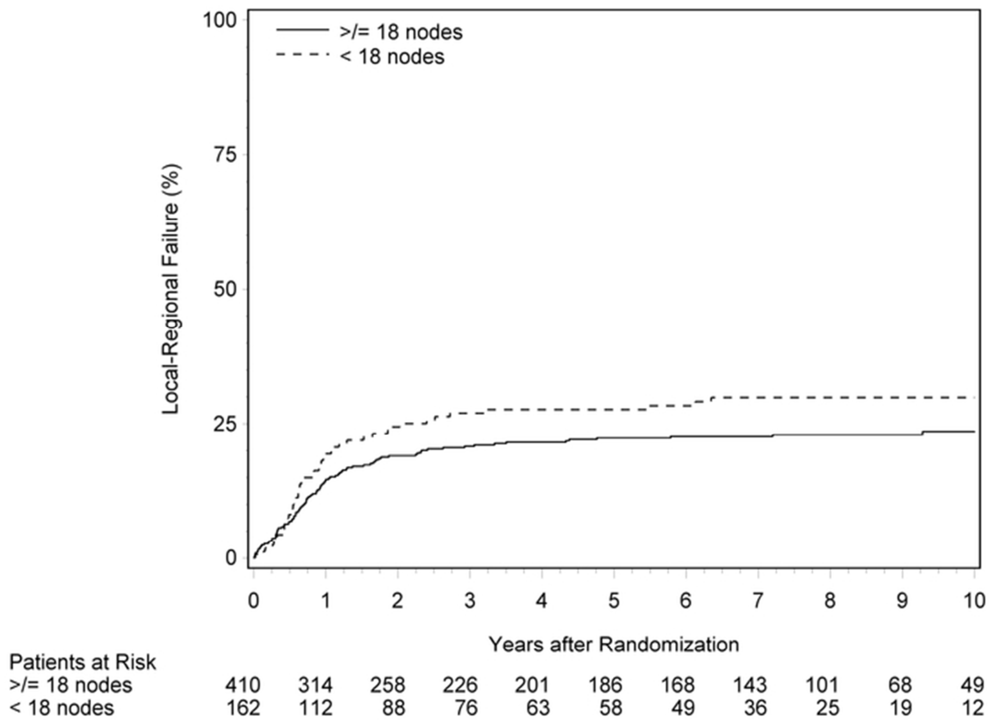


Figure 4
30x22mm (600 x 600 DPI)

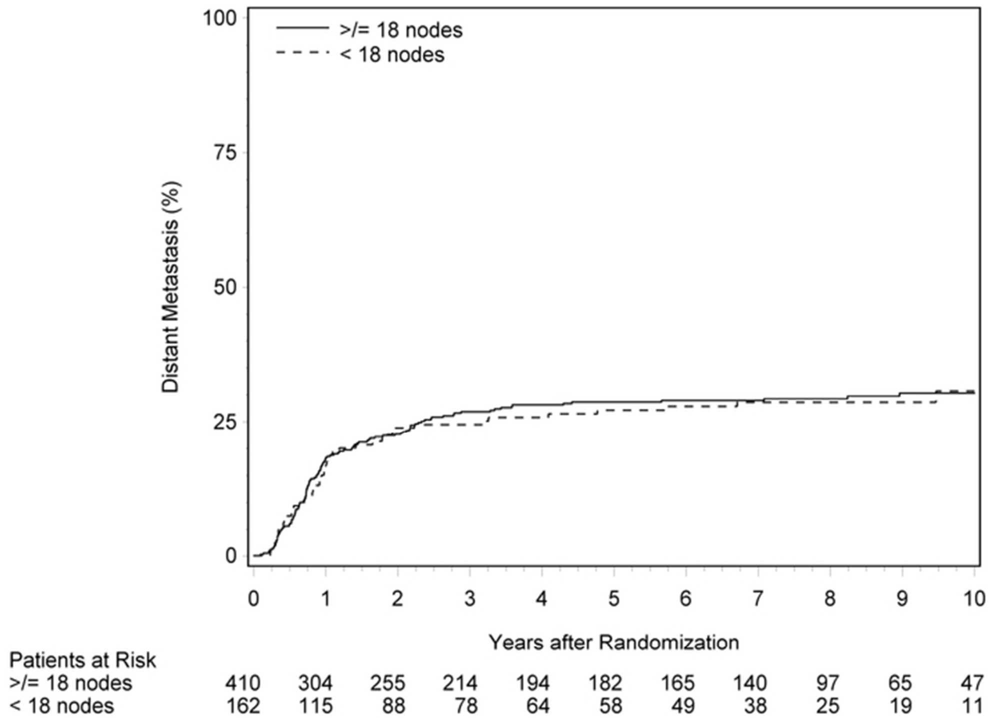


Figure 5
30x22mm (600 x 600 DPI)