Supplementary Online Content

Ho AS, Kim S, Tighiouart M, et al. Association of quantitative metastatic lymph node burden with survival in hypopharyngeal and laryngeal cancer. JAMA Oncol. Published online November 30, 2017. doi:10.1001/jamaoncol.2017.3852

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eFigure 2. Kaplan-Meier estimates of overall survival in hypopharyngeal and laryngeal cancer, stratified by number of positive metastatic lymph nodes in (a). all cases, (b). N2b cases, and (c). N2c cases.

eFigure 3. Adjusted hazard ratio (HR) with increasing number of lymph nodes (LN) examined in hypopharyngeal and laryngeal cancers. Gray dashed lines represent estimated 95% CIs of the predicted HRs. Black solid line represents predicted adjusted HR versus the number of LN examined on multivariable analysis, with reference value of 10. As there was no evidence of non-linear association with OS, this was linearly modeled.

eFigure 4. Novel proposed nodal staging system developed by recursive partitioning analysis in hypopharyngeal and laryngeal cancer patients with determinable AJCC 8th Edition stage. Bonferroni adjusted p-values are given in the inner nodes. Given similar OS rates, 1 LN+/ENE(+) and 2-3 LN+ categories were merged to N2 status.

TABLE LEGENDS

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SUPPLEMENTARY REFERENCES

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SUPPLEMENTARY METHODS

Data Source

Data were acquired from the National Cancer Data Base (NCDB), a tumor registry maintained by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB records data from more than 1500 hospitals, capturing roughly 70% of all cancer cases treated in the United States. All current NCDB head and neck participant user files were evaluated, covering from 2004 to 2013. This study was deemed exempt by the Cedars-Sinai institutional review board.

Statistical analysis

Data patterns for the variables with missing values were examined using the method proposed by Little.[1] Missing rates were 31.6% for extranodal extension (ENE), 12.7% for LN size, 7.4% for lower neck LN involvement, and 0.1%-3.6% for other covariates. The data was found to be not missing completely at random (MCAR). To mitigate the possibility of bias related to missing data, missing values were imputed using fully conditional specification using the multivariate imputation by chained equations (MICE) algorithm under the missing at random (MAR) assumption.[2,3] Thirty complete data sets were generated and analyzed separately. Results were combined using the formula given in Rubin.[4]

The study's primary endpoint was overall survival (OS), defined as the time from diagnosis to death. Patients not experiencing an event were censored at the time of last follow-up. Baseline patient characteristics were compared between nodal status (N0 vs. N+) with Wilcoxon rank-sum test or chi-squared test, where appropriate. Median follow-up was calculated via the reverse Kaplan-Meier method.[5] Survival curves were calculated using the Kaplan-Meier method and compared with a log-rank test.[6] Univariate and multivariable survival analyses were performed with Cox proportional hazards models.[7] Multivariable models were constructed using a stepwise variable selection procedure based on Akaike Information Criterion (AIC).[8] Final multivariable models were chosen based on the lowest AIC value. In multivariable analyses, the possibility of multicollinearity was assessed by examining tolerance and the variance inflation factor (VIF). Two-way interaction effects between variables in relation to OS were examined. The proportional hazards assumption was assessed with scaled Schoenfeld residuals.[9] Stratified Cox regression models were used to account for covariates violating the proportional hazards assumption. The set S of covariates included in the multivariable model in **eTable 2** were common to all models fitted to the 30 imputed data sets. Each multivariable model from the 30 imputed data sets had between 0 and 3 additional covariates to the list in the set S. Likelihood ratio tests were carried out to compare each full model to the reduced model that has the set S of covariates and the results were not statistically significant.

Given the non-linear relationship between number of positive LNs and OS, a restricted cubic spline function was employed to model this relationship. The optimal number of knots was chosen based on the lowest AIC.[10] Three knots were placed at 1, 3, and 9 positive metastatic LN corresponding to 55th, 75th and 95th percentiles, respectively, due to their right-skewed distribution. Hazard ratios were estimated with Cox proportional hazards models stratified on postoperative radiation and adjusted for age, gender, tumor site, insurance status, income, Charlson/Deyo comorbidity index, T-

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classification, number of positive metastatic LN with three knots, number of LN examined, extranodal extension (ENE), margins, and postoperative chemotherapy. A change point in the number of positive metastatic LN was estimated with a piecewise linear regression model.[25]

Recursive partitioning analysis (RPA)[11,12] with independent nodal predictors of mortality (i.e., number of positive LN and ENE) was used to create a novel nodal classification system in patients with a determinable AJCC 8E stage. A conditional inference tree was estimated by the optimized binary recursive partitioning based on a permutation test with a quadratic form of the standardized log-rank statistic with Bonferroni-adjusted p-values for multiple comparisons. The performance of the multivariable models with the proposed N-classification system derived from RPA and AJCC 8E N-classification were assessed with c-indices.[10] Internal validation was performed by estimating and correcting possible optimism in c-indices using the bootstrap method with 1000 replicates. [13,14]

Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) and R package version 3.3.2 (*mice*, *rms*, s*urvival*, *SiZer, party* libraries)[15], with two-sided tests and a significance level of 0.05.

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SUPPLEMENTARY RESULTS

In multivariable analyses, no evidence of multicollinearity was found. We also examined all possible two-way interaction effects between covariates included in the multivariable model (total 66 interaction terms). Three of these interaction terms were found to be statistically significant, including the interaction between (1) number of positive metastatic LN and tumor site, (2) number of LN examined and margins, and (3) gender and tumor site.

Because of the significant interaction between anatomic site and number of positive LN, we analyzed the larynx and hypopharynx subgroups separately. Although both sites had a change points identified at 5 LN, the impact of number of positive LN was stronger for larynx cancer (HR 1.21, 95% CI 1.17-1.25, p<0.001) than for hypopharynx cancers (HR 1.10, 95% CI 1.17-1.25, p<0.001) for each LN ≤5 (**eTable 4**). The reverse pattern was seen for each positive LN >5 when comparing larynx (HR 1.01, 95% CI 1.00-1.02, p=0.046) and hypopharynx cancer (HR 1.03, 95% CI 1.01-1.05, p<0.001).

Similarly, we analyzed the impact of number of LN examined separately for subgroups of patients with negative versus positive margins. Although there was a significant benefit from increased number of LN examined without evidence of change point in both groups of patients, the impact was greater in patients with positive margins (HR 0.92 per 10 LN, 95% CI 0.88-0.95, p<0.001) than in those with negative margins (HR 0.98 per 10 LN, 95% CI 0.97-1.00, p=0.023). Gender was also associated with an improved OS in larynx cancer female patients (HR 0.75, 95% CI 0.69-0.82; p<0.001) while there was no difference in OS between male and female in hypopharynx cancer patients (**eTable 5**).

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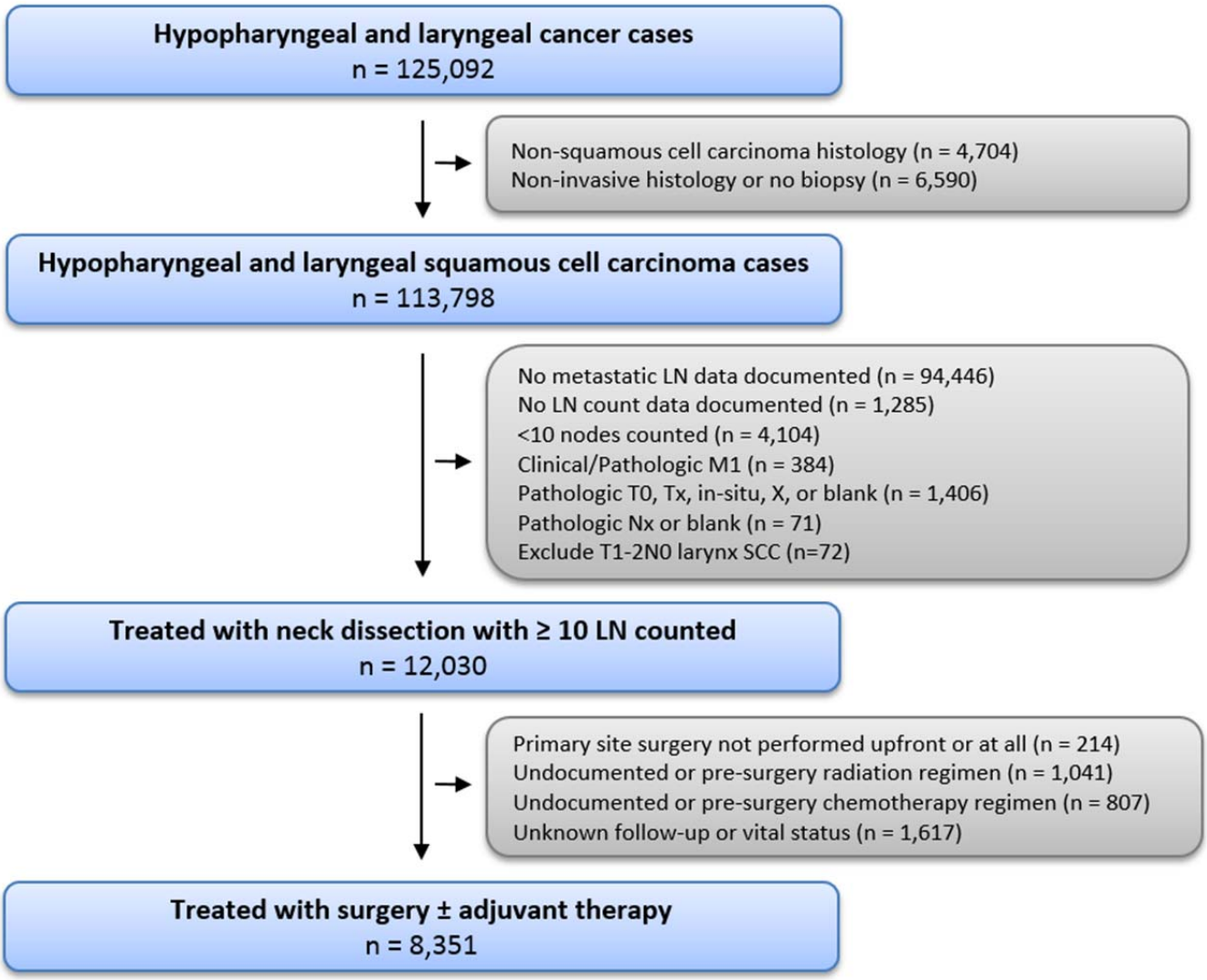
eFigure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.



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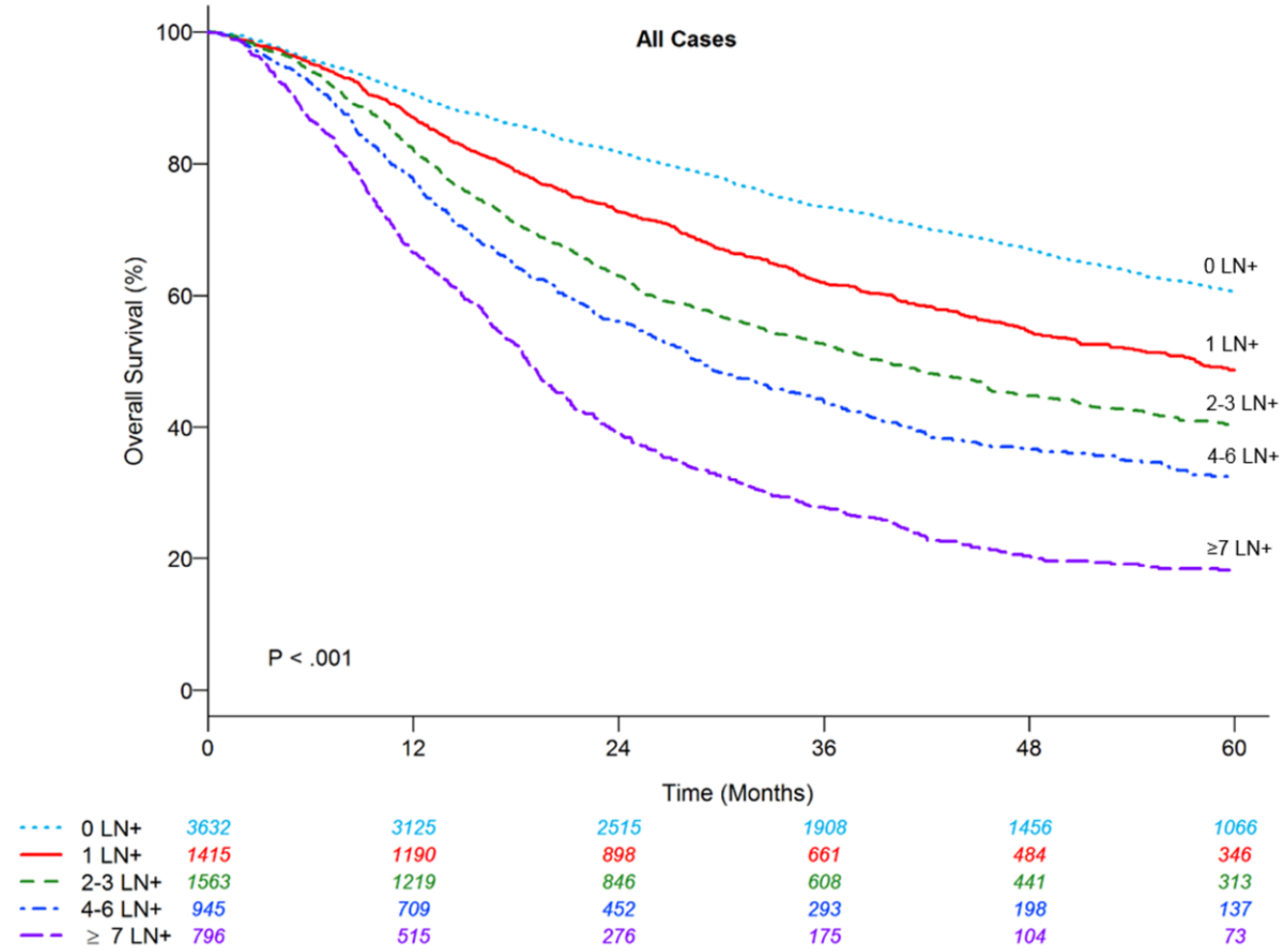
eFigure 2. Kaplan-Meier estimates of overall survival in hypopharyngeal and laryngeal cancer, stratified by number of positive metastatic lymph nodes in (a). all cases, (b). N2b cases, and (c). N2c cases.

(A)



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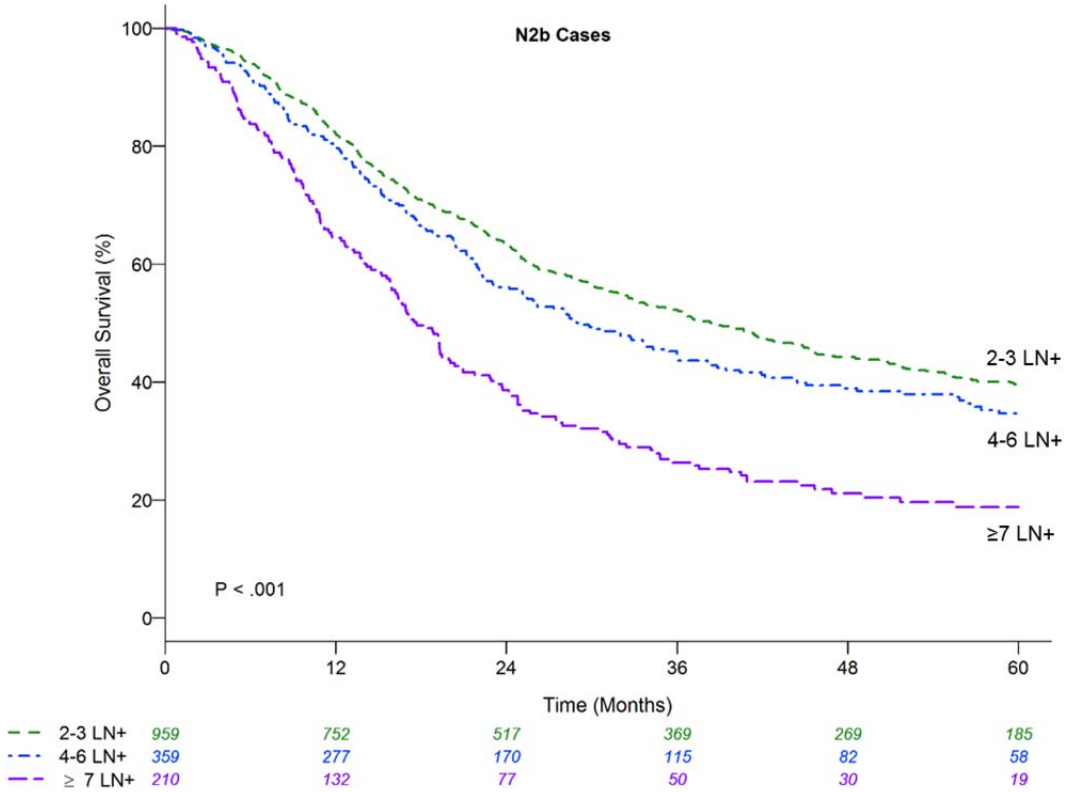
(B)



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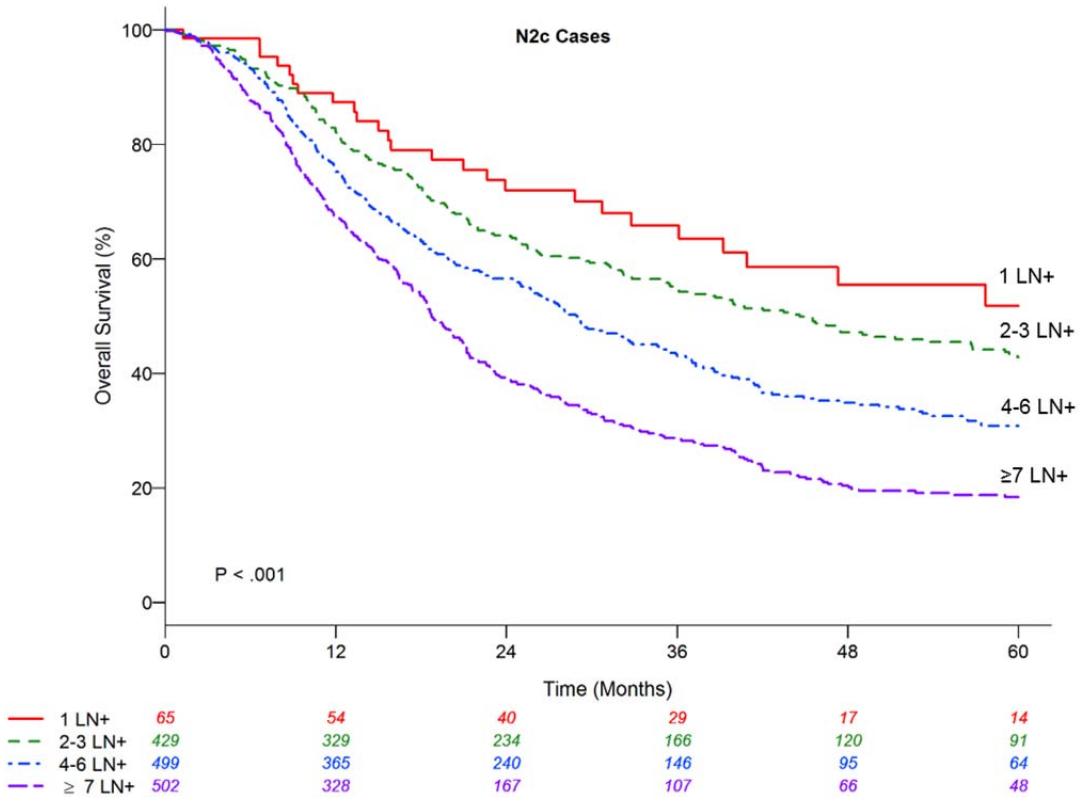

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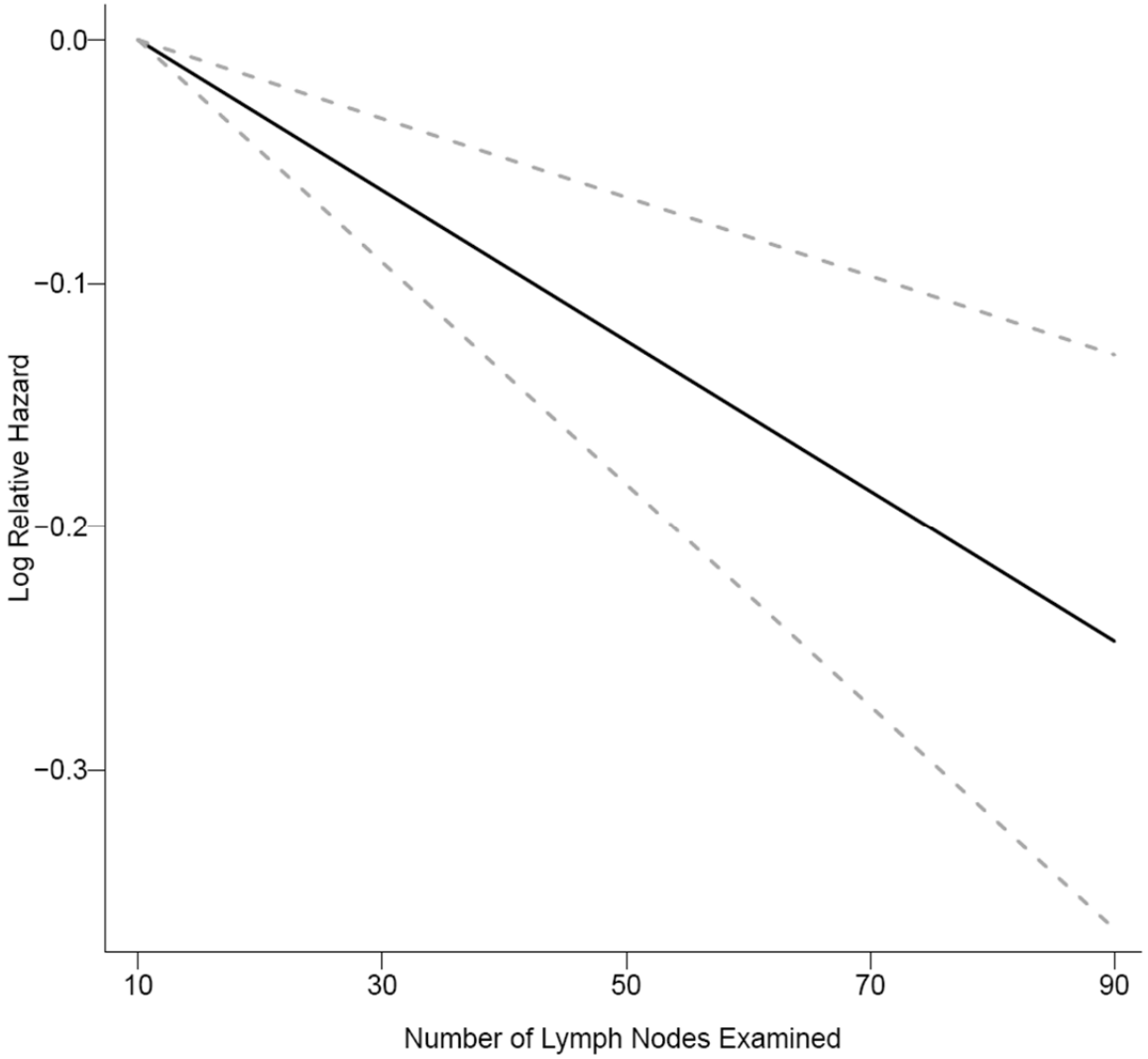

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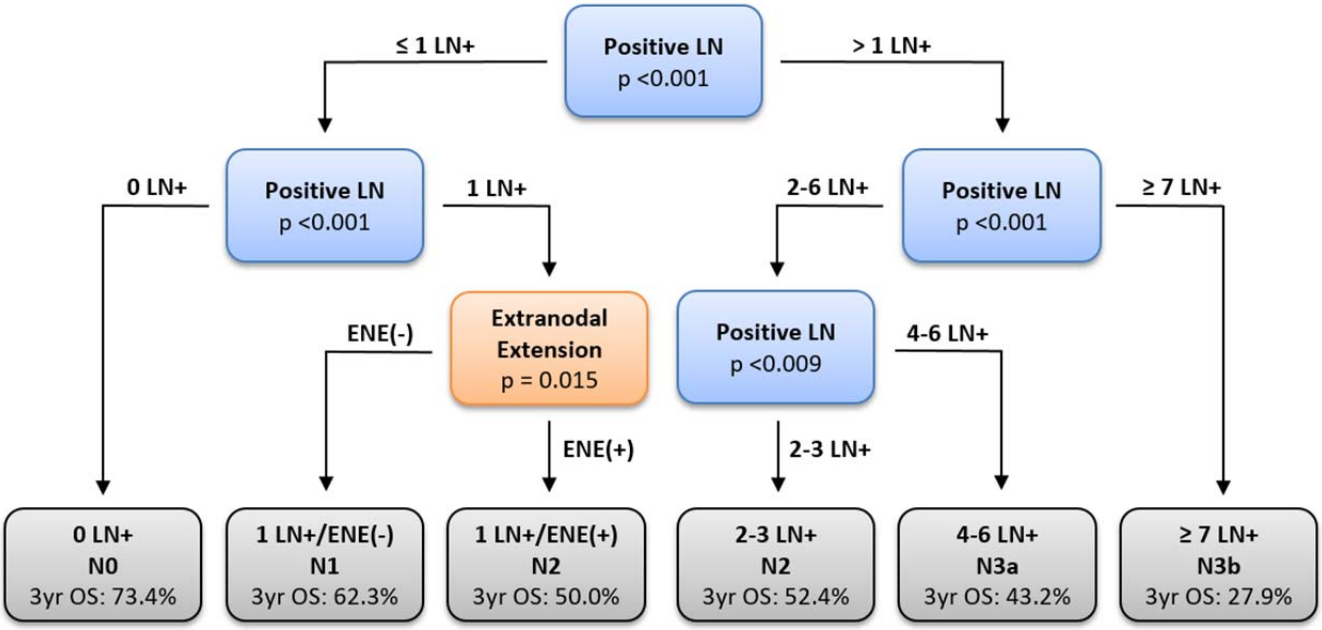
eFigure 4. Novel proposed nodal staging system developed by recursive partitioning analysis in hypopharyngeal and laryngeal cancer patients with determinable AJCC 8th Edition stage. Bonferroni adjusted p-values are given in the inner nodes. Given similar OS rates, 1 LN+/ENE(+) and 2-3 LN+ categories were merged to N2 status.



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eTable 1. Baseline patient demographics stratified by nodal status.

Variable	All patients (N=8,351)	N0 (N=3,641)	N+ (N=4,710)	P-value
Age (Years)				0.155
Median (IQR)	60 (54 - 68)	61 (54 - 68)	60 (54 - 68)	
Mean (± SD)	61 (± 10.13)	61.13 (± 10.41)	60.85 (± 9.91)	
Gender				
Male	6499 (77.82)	2822 (77.53)	3526 (78.03)	0.590
Female	1852 (22.18)	818 (22.47)	993 (21.97)	
Race *				
Other	179 (2.14)	68 (1.86)	111 (2.37)	0.123
White	6742 (80.74)	2970 (81.58)	3772 (80.08)	
Black	1430 (17.12)	603 (16.56)	827 (17.55)	
Tumor site				
Hypopharynx	1332 (15.95)	370 (10.16)	933 (20.65)	<.001
Larynx	7019 (84.05)	3270 (89.84)	3586 (79.35)	
Facility type				
Non-Academic	2986 (35.76)	1215 (33.38)	1683 (37.24)	<.001
Academic	5365 (64.24)	2425 (66.62)	2836 (62.76)	
Facility volume				
Low volume <= 75th percentile	6303 (75.48)	2700 (74.18)	3446 (76.26)	0.030
High volume > 75th percentile	2048 (24.52)	940 (25.82)	1073 (23.74)	
Region				
East	1352 (16.19)	599 (16.46)	733 (16.22)	0.398
Midwest	2711 (32.46)	1146 (31.48)	1502 (33.24)	
South	3370 (40.35)	1486 (40.82)	1799 (39.81)	
West	918 (10.99)	409 (11.24)	485 (10.73)	
Insurance status *				
Private	2600 (31.13)	1152 (31.64)	1448 (30.74)	<.001
Medicaid	1613 (19.32)	640 (17.58)	973 (20.66)	
Medicare	3306 (39.59)	1482 (40.71)	1824 (38.73)	
Other government	151 (1.80)	49 (1.34)	102 (2.16)	
Uninsured	681 (8.16)	318 (8.74)	363 (7.71)	
Income *				
< $38K	2377 (28.46)	1001 (27.49)	1376 (29.21)	0.201
$38K-$63K	4483 (53.68)	1973 (54.18)	2510 (53.29)	
> $63K	1491 (17.86)	667 (18.33)	824 (17.50)	
Charlson/Deyo comorbidity index				
0	5466 (65.45)	2332 (64.07)	3005 (66.5)	0.026
1	2187 (26.19)	1009 (27.72)	1133 (25.07)	
>= 2	698 (8.36)	299 (8.21)	381 (8.43)	
AJCC T stage *				
T1	515 (6.16)	269 (7.40)	245 (5.21)	<.001
T2	1330 (15.93)	661 (18.14)	670 (14.22)	
T3	2549 (30.53)	1141 (31.34)	1408 (29.90)	
T4	3957 (47.38)	1570 (43.12)	2387 (50.68)	
Number of positive metastatic LN				
Median (IQR)	1 (0 - 3)	0 (0 - 0)	2 (0 - 3)	<.001
Mean (± SD)	2.3 (± 4.3)	0.0 (± 0.0)	4.1 (± 5.1)	
Number of LN examined				
Median (IQR)	40 (25 - 57)	38 (25 - 57)	41 (25 - 57)	<.001
Mean (± SD)	42.8 (± 21.8)	41.5 (± 21.7)	43.8 (± 21.8)	
Metastatic LN size *				

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Variable	All patients (N=8,351)	N0 (N=3,641)	N+ (N=4,710)	P-value
0-1cm	4558 (54.58)	3641 (100.0)	971 (20.62)	<.001
1-2cm	1265 (15.15)	0 (0.0)	1245 (26.45)	
2-3cm	1128 (13.51)	0 (0.0)	1114 (23.64)	
3-4cm	511 (6.12)	0 (0.0)	506 (10.74)	
4-5cm	289 (3.47)	0 (0.0)	287 (6.10)	
5-6cm	405 (4.84)	0 (0.0)	398 (8.45)	
>= 6cm	195 (2.34)	0 (0.0)	189 (4.00)	
Lower LN (Level 4-5) involvement *				
No	6735 (80.65)	3641 (100.0)	3118 (66.19)	<.001
Yes	1616 (19.35)	0 (0.0)	1592 (33.81)	
Contralateral (N2c) LN involvement *				
No	6843 (81.94)	3641 (100.0)	3202 (68.00)	<.001
Yes	1508 (18.06)	0 (0.0)	1508 (32.00)	
Extranodal extension (ENE) *				
ENE(-)	6177 (73.97)	3641 (100.0)	2536 (53.85)	<.001
ENE(+)	2174 (26.03)	0 (0)	2174 (46.15)	
Margins *				
Negative	7194 (86.15)	3341 (91.77)	3853 (81.81)	<.001
Positive	1157 (13.85)	300 (8.23)	857 (18.19)	
Postoperative radiation				
No	3465 (41.49)	2102 (57.75)	1305 (28.88)	<.001
Yes	4886 (58.51)	1538 (42.25)	3214 (71.12)	
Postoperative chemotherapy				
No	6088 (72.9)	3260 (89.56)	2713 (60.04)	<.001
Yes	2263 (27.1)	380 (10.44)	1806 (39.96)	
Year of diagnosis				
Median (IQR)	2009 (2007 - 2011)	2009 (2007 - 2011)	2009 (2007 - 2011)	0.605
Mean (± SD)	2009.0 (± 2.8)	2009.1 (± 2.9)	2009.0 (± 2.8)	

Data are presented as number of patients (column %), mean (± SD) or median (IQR, interquartile range).
* Missing data were imputed by multiple imputation.

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eTable 2. Univariate and multivariable analyses of overall survival in hypopharyngeal and laryngeal cancer.

Variable	N	Univariate		Multivariable	
		Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Number of positive metastatic LN [a]		-	<.001	-	<.001
Age	8351	1.03 (1.02-1.03)	<.001	1.02 (1.02-1.02)	<.001
Gender					
Male	6499	1 (Reference)		1 (Reference)	
Female	1852	0.81 (0.75-0.87)	<.001	0.79 (0.73-0.86)	0.034
Race [b]			0.563*		
White	6742	1 (Reference)			
Black	1430	1.01 (0.93-1.10)	0.768	†	
Other	179	1.12 (0.91-1.39)	0.293		
Tumor site					
Larynx	7019	1 (Reference)		1 (Reference)	
Hypopharynx	1332	1.38 (1.27-1.49)	<.001	1.10 (1.02-1.20)	0.020
Facility type					
Non-Academic	2986	1 (Reference)			
Academic	5365	0.94 (0.88-1.00)	0.039	†	
Facility volume					
Low volume ≤ 75th percentile	6303	1 (Reference)			
High volume > 75th percentile	2048	1.00 (0.93-1.07)	1.000	†	
Region			0.275*		
East	1352	1 (Reference)			
South	3370	1.05 (0.96-1.15)	0.304	†	
Midwest	2711	1.10 (1.00-1.20)	0.059		
West	918	1.08 (0.95-1.21)	0.232		
Insurance status [b]			<.001*		<.001*
Private	2600	1 (Reference)		1 (Reference)	
Uninsured	681	1.00 (0.88-1.15)	0.955	1.10 (0.96-1.25)	0.190
Medicaid	1613	1.21 (1.10-1.33)	<.001	1.22 (1.11-1.35)	<.001
Medicare	3306	1.64 (1.52-1.77)	<.001	1.26 (1.15-1.37)	<.001
Other government	146	1.35 (1.07-1.70)	0.012	1.10 (0.86-1.40)	0.442
Income [b]			0.019*		0.006*
< $38K	2377	1 (Reference)		1 (Reference)	
$38K-$63K	4483	0.96 (0.89-1.03)	0.212	0.99 (0.92-1.06)	0.704
> $63K	1491	0.87 (0.80-0.96)	0.005	0.87 (0.79-0.95)	0.003
Charlson/Deyo comorbidity index			<.001*		<.001*
0	5466	1 (Reference)		1 (Reference)	
1	2187	1.14 (1.06-1.22)	<.001	1.09 (1.02-1.17)	0.016
≥ 2	698	1.55 (1.40-1.72)	<.001	1.42 (1.28-1.58)	<.001
AJCC 7th Edition T-Classification *			<.001*		<.001*
T1	515	1 (Reference)		1 (Reference)	
T2	1330	1.17 (1.00-1.38)	0.056	1.19 (1.01-1.40)	0.041
T3	2549	1.35 (1.15-1.57)	<.001	1.35 (1.16-1.58)	<.001
T4	3957	1.66 (1.43-1.92)	<.001	1.65 (1.42-1.93)	<.001
Number of LN examined (10 units)	8351	0.98 (0.97-0.98)	0.001	0.97 (0.96-0.98)	<.001
LN size [b]			<.001*		
0.0-1.0cm	4558	1 (Reference)			
1.1-2.0cm	1265	1.72 (1.57-1.88)	<.001	†	
2.1-3.0cm	1128	1.73 (1.57-1.91)	<.001		

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Variable	N	Univariate		Multivariable	
		Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
3.1-4.0cm	511	1.77 (1.55-2.02)	<.001		
4.1-5.0cm	289	2.21 (1.87-2.60)	<.001		
5.1-6.0cm	405	1.99 (1.73-2.30)	<.001		
> 6.0cm	195	2.23 (1.85-2.70)	<.001		
Lower LN (Level 4-5) involvement [b]					
No	6735	1 (Reference)			
Yes	1616	1.90 (1.77-2.05)	<.001	†	
Contralateral (N2c) LN involvement [b]					
No	6843	1 (Reference)			
Yes	1508	1.78 (1.65-1.91)	<.001	†	
Extranodal extension (ENE) [b]					
ENE(–)	6177	1 (Reference)		1 (Reference)	
ENE(+)	2174	2.10 (1.86-2.37)	<.001	1.34 (1.13-1.59)	0.001
Margins [b]					
Negative	7194	1 (Reference)		1 (Reference)	
Positive	1157	1.57 (1.45-1.70)	<.001	1.26 (1.16-1.37)	<.001
Postoperative radiation ‡					
No	3465	1 (Reference)			
Yes	4886	0.94 (0.88-1.00)	0.045	‡	
Postoperative chemotherapy					
No	6088	1 (Reference)		1 (Reference)	
Yes	2263	1.12 (1.04-1.19)	0.002	0.85 (0.78-0.93)	<.001
Year of diagnosis	8351	1.00 (0.98-1.01)	0.479	†	

[a] Number of positive metastatic LN was modeled using a restricted cubic spline function with three knots at 1, 3 and 9.
[b] Missing data were imputed by multiple imputation.
* Overall p-value for categorical variables with more than two levels.
† Variables dropped out of the model.
‡ Multivariable model was stratified on postoperative radiation due to non-proportional hazards.

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eTable 3. Summary of hazard ratios for positive metastatic lymph nodes and number of lymph nodes examined in hypopharyngeal and laryngeal cancer, stratified by change point. LN, lymph nodes

Variable	Univariate		Multivariable	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Number of positive metastatic LN (per 1 LN) [a]				
> 5 LN+	1.02 (1.01-1.03)	<.001	1.01 (1.01-1.02)	0.001
≤ 5 LN+	1.21 (1.18-1.23)	<.001	1.19 (1.16-1.23)	<.001
Number of LN examined (per 10 LN) [b]	0.98 (0.97-0.98)	0.001	0.97 (0.96-0.98)	<.001

Missing data were imputed by multiple imputation.

[a] Multivariable models were stratified on postoperative radiation and adjusted for age, gender, tumor site, insurance status, income, Charlson/Deyo comorbidity index, AJCC T-Classification, number of LN examined, extranodal extension, margins, and postoperative chemotherapy.

[b] Multivariable model was stratified on postoperative radiation and adjusted for age, gender, tumor site, insurance status, income, Charlson/Deyo comorbidity index, AJCC T-Classification, number of positive LN with three knots at 1, 3, and 9 LN corresponding to 55^{th}, 75^{th} and 95^{th} percentiles, respectively, extranodal extension, margins, and postoperative chemotherapy.

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eTable 4. Summary of hazard ratios for positive metastatic lymph nodes, stratified by hypopharyngeal or laryngeal cancer site and change point. LN, lymph nodes

Variable	Univariate		Multivariable	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Number of positive metastatic LN (per 1 LN)				
In larynx patients (N=7,019)				
> 5 LN+	1.01 (1.00-1.02)	0.011	1.01 (1.00-1.02)	0.046
≤ 5 LN+	1.22 (1.19-1.25)	<.001	1.21 (1.17-1.25)	<.001
In hypopharynx patients (N=1,332)				
> 5 LN+	1.03 (1.01-1.04)	<.001	1.03 (1.01-1.05)	<.001
≤ 5 LN+	1.11 (1.05-1.16)	<.001	1.10 (1.03-1.18)	0.005

Missing data were imputed by multiple imputation.
Multivariable models were stratified on postoperative radiation and adjusted for age, gender, insurance status, income, Charlson/Deyo comorbidity index, AJCC T-Classification, number of LN examined, extranodal extension, margins, postoperative chemotherapy, and interaction term between number of LN examined and margins.

eTable 5. Summary of hazard ratios for number of lymph nodes examined stratified by margin status, and for gender stratified by hypopharynx or larynx cancer site. LN, lymph nodes

Variable	Multivariable	
	Hazard Ratio (95% CI)	P-value
Interaction between number of LN examined and margins		
Number of LN examined (10 units) in negative margins	0.98 (0.97-1.00)	0.023
Number of LN examined (10 units) in positive margins	0.92 (0.88-0.95)	<.001
Interaction between gender and cancer site		
Female vs. male in larynx	0.75 (0.69-0.82)	<.001
Female vs. male in hypopharynx	1.07 (0.89-1.28)	0.502

Missing data were imputed by multiple imputation.
Multivariable models were stratified on postoperative radiation and adjusted for age, gender, insurance status, income, Charlson/Deyo comorbidity index, AJCC T-Classification, number of LN examined, extranodal extension, margins, postoperative chemotherapy, and three interaction terms between number of positive metastatic LN and tumor site, gender and tumor site, and number of LN examined and margins.

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eTable 6. Multivariable analyses with proposed N-Classification system and AJCC 8th Edition N-Classification system in hypopharyngeal and laryngeal cancer.

Variable	Proposed N-Classification		AJCC 8th Edition N-Classification	
	Hazard Ratio (95% CI)	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
Proposed N-Classification		<.001 *		
N0 (0 LN+)	1 (Reference)		Not Included	
N1 (1 LN+/ENE(–))	1.51 (1.28-1.77)	<.001		
N2 (2-3 LN+ or 1 LN+/ENE(+))	2.18 (1.92-2.48)	<.001		
N3a (4-6 LN+)	2.88 (2.47-3.35)	<.001		
N3b (≥ 7 LN+)	4.66 (3.97-5.46)	<.001		
AJCC 8th Edition N-Classification				<.001 *
N0	Not Included		1 (Reference)	
N1			1.45 (1.22-1.72)	<.001
N2a			1.95 (1.54-2.47)	<.001
N2b			1.82 (1.51-2.20)	<.001
N2c			2.22 (1.83-2.70)	<.001
N3a			9.62 (3.91-23.63)	<.001
N3b			2.90 (2.52-3.34)	<.001
Age	1.02 (1.02-1.03)	<.001	1.02 (1.02-1.03)	<.001
Gender				
Male	1 (Reference)		1 (Reference)	
Female	0.84 (0.76-0.93)	<.001	0.85 (0.77-0.94)	0.002
Race [a]				
White				
Black	†		†	
Other				
Tumor site				
Larynx	1 (Reference)		1 (Reference)	
Hypopharynx	1.26 (1.13-1.41)	<.001	1.25 (1.12-1.40)	<.001
Facility type				
Non-Academic				
Academic	†		†	
Facility volume				
Low volume ≤ 75th percentile				
High volume > 75th percentile	†		†	
Region				
East				
South	†		†	
Midwest				
West				

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Variable	Proposed N-Classification		AJCC 8th Edition N-Classification	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Insurance status [a]		<.001*		<.001*
Private	1 (Reference)		1 (Reference)	
Uninsured	1.08 (0.90-1.29)	0.392	1.07 (0.89-1.28)	0.467
Medicaid	1.27 (1.11-1.44)	<.001	1.28 (1.12-1.46)	<.001
Medicare	1.32 (1.18-1.48)	<.001	1.32 (1.18-1.48)	<.001
Other government	0.83 (0.58-1.19)	0.312	0.88 (0.61-1.27)	0.482
Income [a]		0.016*		0.021*
< $38K	1 (Reference)		1 (Reference)	
$38K-$63K	0.97 (0.88-1.06)	0.472	0.97 (0.88-1.06)	0.505
> $63K	0.84 (0.74-0.95)	0.006	0.84 (0.74-0.96)	0.008
Charlson/Deyo comorbidity index		0.001*		0.001*
0	1 (Reference)		1 (Reference)	
1	1.08 (0.98-1.19)	0.101	1.08 (0.98-1.18)	0.114
≥ 2	1.50 (1.31-1.72)	<.001	1.50 (1.31-1.72)	<.001
AJCC T-Classification (8th Edition)		<.001*		<.001*
T1	1 (Reference)		1 (Reference)	
T2	1.21 (0.98-1.49)	0.080	1.20 (0.97-1.48)	0.090
T3	1.40 (1.15-1.70)	<.001	1.40 (1.14-1.70)	0.001
T4	1.72 (1.42-2.10)	<.001	1.74 (1.43-2.12)	<.001
Number of LN examined (10 units)	0.97 (0.96-0.99)	0.009	0.98 (0.96-0.99)	0.013
Metastatic LN size [a]				
0.0-1.0cm	†		Not Included	
1.1-2.0cm				
2.1-3.0cm				
3.1-4.0cm				
4.1-5.0cm				
5.1-6.0cm				
> 6.0cm				
Lower LN (Level 4-5) involvement [a]				
No			1 (Reference)	
Yes	†		1.27 (1.11-1.46)	<.001
Contralateral (N2c) LN involvement				
No				
Yes	†		Not Included	
Margins [a]				
Negative	1 (Reference)		1 (Reference)	
Positive	1.30 (1.16-1.46)	<.001	1.33 (1.19-1.50)	<.001
Postoperative radiation ‡				
No				
Yes	‡		‡	
Postoperative chemotherapy				
No	1 (Reference)		1 (Reference)	
Yes	0.89 (0.79-1.00)	0.045	0.88 (0.78-0.99)	0.033

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Variable	Proposed N-Classification		AJCC 8th Edition N-Classification	
	Hazard Ratio (95% CI)	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
Year of diagnosis	†		†	
C-index at 3-year (95% CI)	0.678 (0.665-0.690)		0. 675 (0.663-0.688)	
Optimism-corrected c-index at 3-year (95% CI)	0.674 (0.661-0.687)		0.671 (0.658-0.684)	

[a] Missing data were imputed by multiple imputation.
* Overall p-value for categorical variables with more than two levels.
† Variables dropped out of the model.
‡ Multivariable models were stratified on postoperative radiation due to nonproportional hazards.

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SUPPLEMENTARY REFERENCES

1. Little RJ. A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association.* 1988;83(404):1198-1202.

2. van Buuren S, Groothuis-Oudshoorn, K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software.* 2011;15(3):1-67.

3. van Buuren S. Multiple imputation of discrete and contnuous data by fully conditional specification. *Statistical Methods in Medical Research.* 2007;16:219-242.

4. Rubin DB. *Multiple imputation for nonresponse in surveys.* New York: John Wiley & Sons; 1987.

5. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Controlled clinical trials.* Aug 1996;17(4):343-346.

6. Kalbfleisch JD PR. *The statistical analysis of failure time data.* New York: John Wiley & Sons; 1980.

7. Cox DR. Regression Models and Life Tables. *J Royal Stat Society.* 1972;B34:187-220.

8. Yamashita T, Yamashita K, Kamimura R. A Stepwise AIC Method for Variable Selection in Linear Regression. *Communications In Statistics - Theory And Methods.* 2007;36(13).

9. Grambsch P.M. TTM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81:515-526.

10. Toms JD, Lesperance ML. Piecewise regression: a tool for identifying ecological thresholds. *Ecology.* 2003;84:2034-2041.

11. Hothorn T HK, Zeileis A. Unbiased Recursive Partitioning: A Conditional Inference Framework. Journal of Computational and Graphical Statistics. 2006;15(3):651–674.

12. Segal MR. Regression Trees for Censored Data. *Biometrics.* 1998;44:35-47.

13. Harrell F. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. *Springer Series in Statistics.* 2001.

14. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in medicine.* Feb 28 1996;15(4):361-387.

15. R Core Team. R: A language and environment for statistical computing. 2016; http://www.R-project.org/.

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