

Supplementary

The Stratified Odds Ratio of N1 and N2 Stages

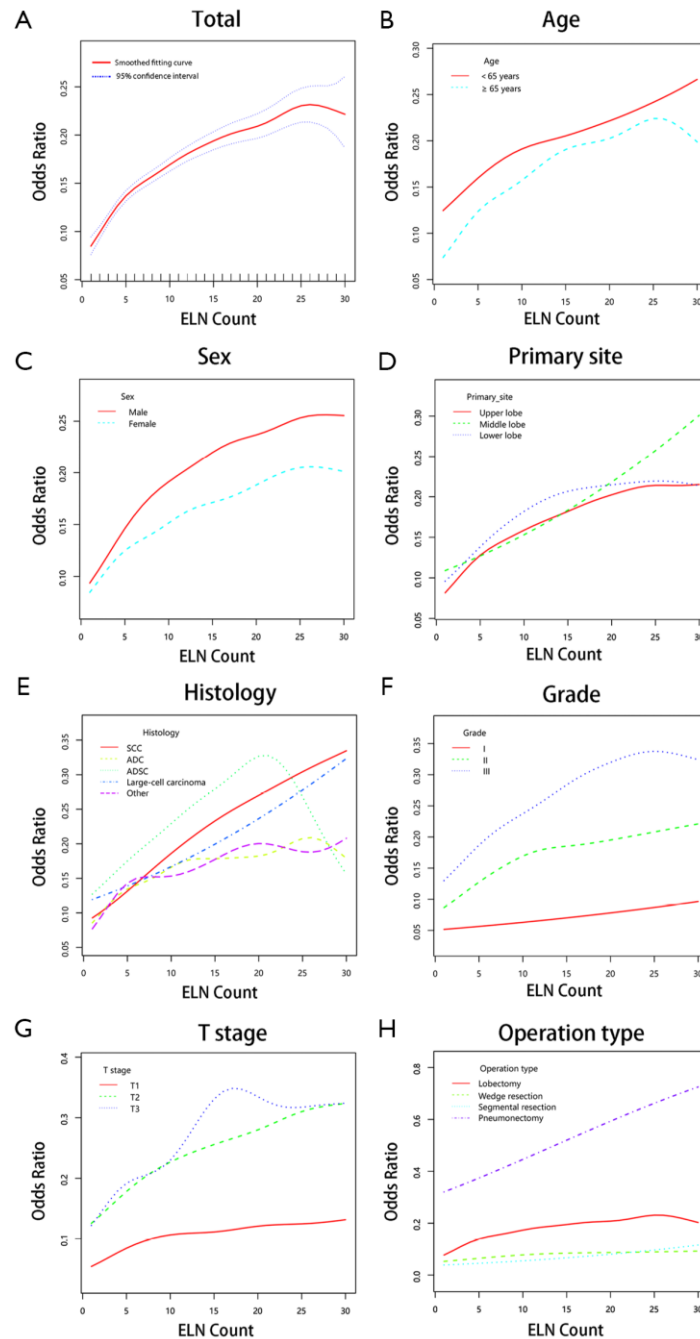


Figure S1 Proportion of node-positive cases according to examined lymph node count, by subgroup. (A) Total population. (B) Age. (C) Sex. (D) Primary site. (E) Histology. (F) Grade. (G) T stage. (H) Operation type. Subgroups with fewer than 400 patients are not displayed because estimates were unstable. Adjusted for age, sex, primary site, grade, histology, T stage, N stage, operation type, radiotherapy and chemotherapy, except for the stratifying variable itself. ELN, examined lymph node.

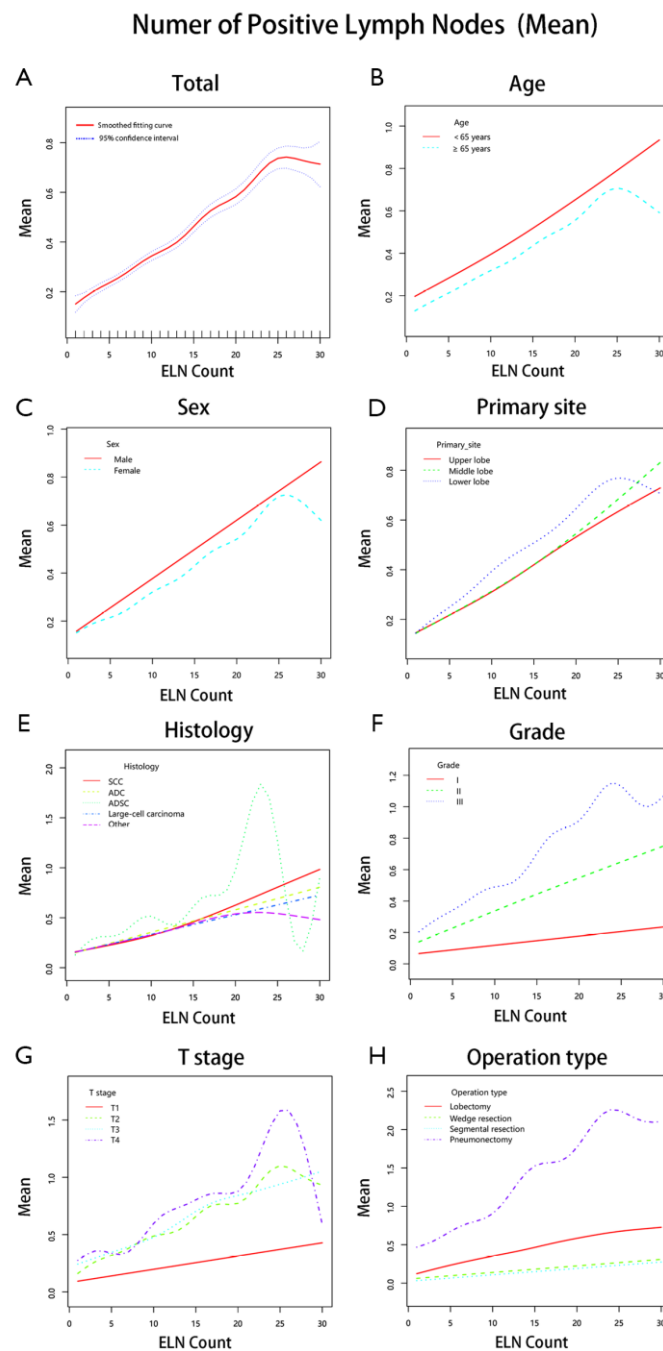


Figure S2 Mean number of positive lymph nodes according to examined lymph node count, by subgroup. (A) Total population. (B) Age. (C) Sex. (D) Primary site. (E) Histology. (F) Grade. (G) T stage. (H) Operation type. Subgroups with fewer than 400 patients are not displayed because estimates were unstable. Adjusted for age, sex, primary site, grade, histology, T stage, N stage, operation type, radiotherapy and chemotherapy. except for the stratifying variable itself. ELN, examined lymph node.

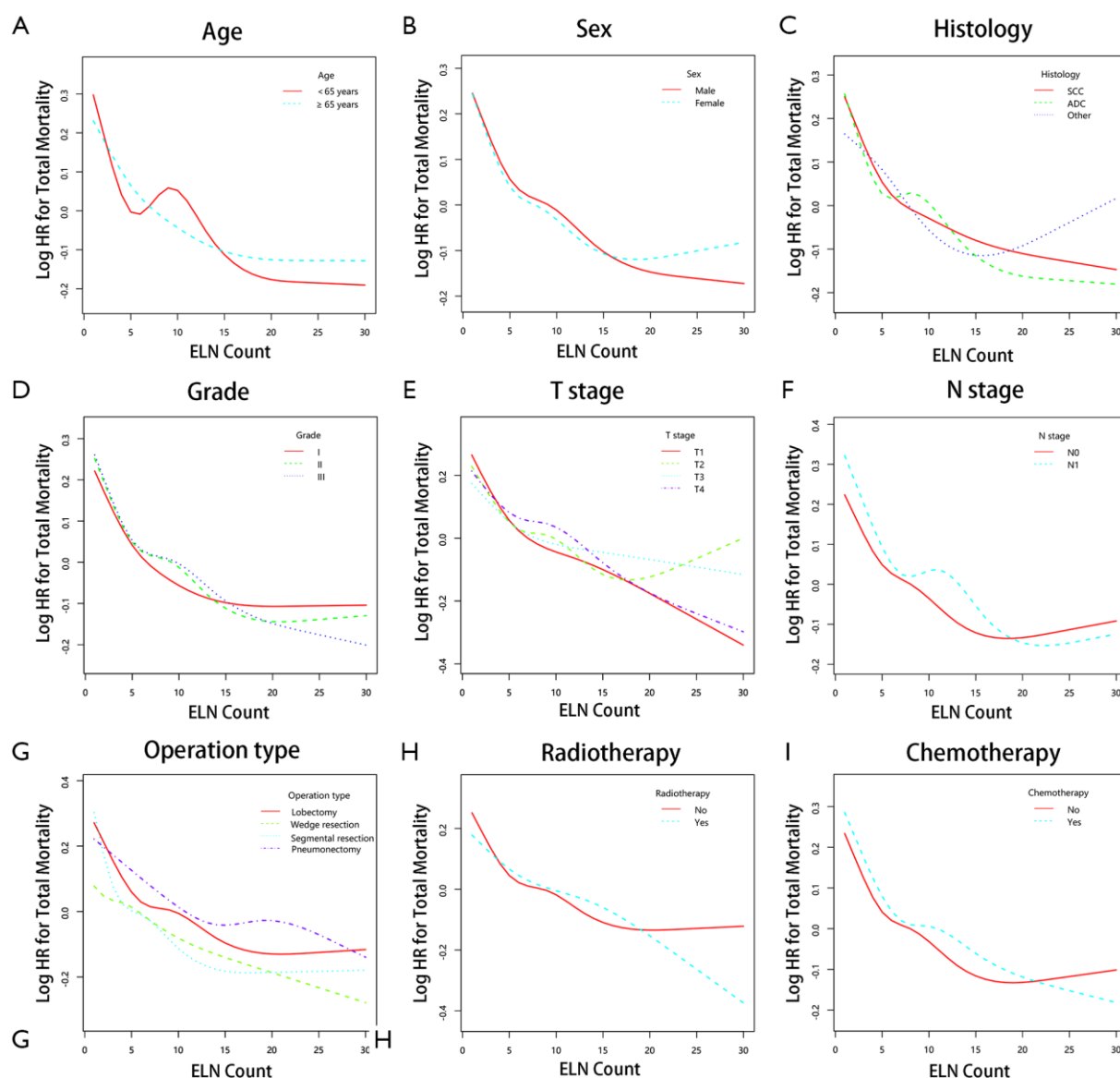


Figure S3 Log hazard ratio for overall mortality according to examined lymph node count, by subgroup. (A) Age. (B) Sex. (C) Histology. (D) Grade. (E) T stage. (F) N stage. (G) Operation type. (H) Radiotherapy. (I) Chemotherapy. Subgroups with fewer than 400 patients are not displayed because estimates were unstable. Adjusted for age, sex, primary site, grade, histology, T stage, N stage, operation type, radiotherapy and chemotherapy. except for the stratifying variable itself. ELN, examined lymph node; HR, hazard ratio.

Table S1 Trend test of the association between examined lymph node count and the detection of nodal metastasis (stratified by histology)

ELN number	Histology					
	SCC	ADC	ADSC	Large-cell carcinoma	BAC	Other
	OR (95% CI) <i>P</i> value	OR (95% CI) <i>P</i> value	OR (95% CI) <i>P</i> value	OR (95% CI) <i>P</i> value	OR (95% CI) <i>P</i> value	OR (95% CI) <i>P</i> value
Model I						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	1.98 (1.72, 2.28) <0.0001	1.64 (1.50, 1.79) <0.0001	1.64 (1.12, 2.40) 0.0114	1.63 (0.69, 3.85) 0.2611	0.00 (0.00, Inf) 0.9976	1.70 (1.46, 1.96) <0.0001
11-15	3.04 (2.63, 3.51) <0.0001	2.22 (2.02, 2.43) <0.0001	2.74 (1.83, 4.11) <0.0001	1.56 (0.59, 4.10) 0.3664	0.00 (0.00, Inf) 0.9986	2.09 (1.79, 2.44) <0.0001
16-20	3.91 (3.34, 4.56) <0.0001	2.37 (2.12, 2.64) <0.0001	3.18 (2.00, 5.04) <0.0001	3.50 (1.42, 8.64) 0.0066	0.00 (0.00, Inf) 0.9990	2.77 (2.33, 3.28) <0.0001
21-25	5.09 (4.26, 6.10) <0.0001	2.79 (2.45, 3.19) <0.0001	3.89 (2.23, 6.79) <0.0001	2.12 (0.65, 6.91) 0.2101	0.00 (0.00, Inf) 0.9991	2.73 (2.21, 3.37) <0.0001
26-30	5.74 (4.63, 7.12) <0.0001	3.06 (2.59, 3.62) <0.0001	1.22 (0.49, 3.06) 0.6694	4.25 (0.92, 19.69) 0.0643	0.00 (0.00, Inf) 0.9995	2.91 (2.22, 3.83) <0.0001
<i>P</i> for trend	<0.0001	<0.0001	<0.0001	0.0089	0.9970	<0.0001
Increase of per level	1.43 (1.39, 1.48)	1.27 (1.24, 1.30)	1.29 (1.17, 1.42)	1.31 (1.07, 1.60)	0.00 (0.00, Inf)	1.27 (1.23, 1.32)
Model II						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	1.94 (1.68, 2.23) <0.0001	1.63 (1.49, 1.78) <0.0001	1.65 (1.12, 2.42) 0.0105	1.65 (0.70, 3.89) 0.2559	0.00 (0.00, Inf) 0.9989	1.68 (1.45, 1.95) <0.0001
11-15	2.92 (2.53, 3.37) <0.0001	2.22 (2.02, 2.43) <0.0001	2.77 (1.85, 4.16) <0.0001	1.55 (0.59, 4.09) 0.3728	0.00 (0.00, Inf) 0.9993	2.07 (1.77, 2.42) <0.0001
16-20	3.82 (3.27, 4.47) <0.0001	2.37 (2.12, 2.64) <0.0001	3.25 (2.05, 5.16) <0.0001	3.48 (1.41, 8.61) 0.0069	0.00 (0.00, Inf) 0.9995	2.75 (2.32, 3.27) <0.0001

21-25	4.83 (4.03, 5.79) <0.0001	2.80 (2.45, 3.19) <0.0001	3.96 (2.26, 6.92) <0.0001	2.12 (0.65, 6.89) 0.2119	0.00 (0.00, Inf) 0.9996	2.73 (2.21, 3.38) <0.0001
26-30	5.56 (4.48, 6.91) <0.0001	3.06 (2.59, 3.62) <0.0001	1.28 (0.51, 3.22) 0.5951	4.24 (0.91, 19.64) 0.0650	0.00 (0.00, Inf) 0.9998	2.90 (2.20, 3.80) <0.0001
<i>P</i> for trend	<0.0001	<0.0001	<0.0001	0.0096	0.9978	<0.0001
Increase of per level	1.42 (1.38, 1.47)	1.27 (1.24, 1.30)	1.30 (1.18, 1.43)	1.30 (1.07, 1.59)	0.00 (0.00, Inf)	1.27 (1.23, 1.32)
Model III						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	1.54 (1.32, 1.81) <0.0001	1.38 (1.24, 1.54) <0.0001	1.37 (0.88, 2.12) 0.1622	1.38 (0.49, 3.88) 0.5386	0.00 (0.00, Inf) 0.9990	1.35 (1.15, 1.60) 0.0004
11-15	2.13 (1.81, 2.51) <0.0001	1.67 (1.50, 1.87) <0.0001	2.04 (1.28, 3.24) 0.0027	1.25 (0.42, 3.73) 0.6934	0.14 (0.00, Inf) 1.0000	1.56 (1.30, 1.86) <0.0001
16-20	2.53 (2.11, 3.02) <0.0001	1.68 (1.47, 1.92) <0.0001	2.14 (1.26, 3.65) 0.0050	3.61 (1.18, 11.00) 0.0241	1.29 (0.00, Inf) 1.0000	2.00 (1.64, 2.43) <0.0001
21-25	2.88 (2.33, 3.55) <0.0001	1.81 (1.54, 2.13) <0.0001	2.79 (1.45, 5.38) 0.0021	2.05 (0.52, 7.98) 0.3022	4.35 (0.00, Inf) 1.0000	1.86 (1.45, 2.37) <0.0001
26-30	3.29 (2.55, 4.24) <0.0001	2.04 (1.66, 2.51) <0.0001	0.68 (0.23, 2.04) 0.4931	2.50 (0.39, 15.81) 0.3316	0.15 (0.00, Inf) 1.0000	1.98 (1.44, 2.71) <0.0001
<i>P</i> for trend	<0.0001	<0.0001	0.0049	0.0541	0.9983	<0.0001
Increase of per level	1.28 (1.23, 1.33)	1.15 (1.12, 1.19)	1.18 (1.05, 1.32)	1.27 (1.00, 1.61)	0.00 (0.00, Inf)	1.17 (1.12, 1.22)

Model I: unadjusted. Model II: adjusted for age and sex. Model III: adjusted for age, sex, primary site, grade, T stage, operation type, radiotherapy and chemotherapy. ELN, examined lymph nodes; OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchoalveolar carcinoma.

Table S2 Trend test of the association between examined lymph node count and overall mortality (stratified by histology)

ELN number	Histology					
	SCC	ADC	ADSC	Large-cell carcinoma	BAC	Other
	HR (95% CI) <i>P</i> value	HR (95% CI) <i>P</i> value	HR (95% CI) <i>P</i> value	HR (95% CI) <i>P</i> value	HR (95% CI) <i>P</i> value	HR (95% CI) <i>P</i> value
Model I						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	0.89 (0.84, 0.95) 0.0006	0.91 (0.87, 0.96) 0.0005	0.84 (0.70, 1.02) 0.0777	1.16 (0.79, 1.70) 0.4566	0.48 (0.26, 0.89) 0.0196	0.92 (0.84, 1.01) 0.0805
11-15	0.85 (0.79, 0.91) <0.0001	0.90 (0.85, 0.96) 0.0008	0.81 (0.64, 1.02) 0.0703	0.72 (0.44, 1.18) 0.1959	0.26 (0.08, 0.84) 0.0248	0.88 (0.79, 0.97) 0.0128
16-20	0.91 (0.84, 1.00) 0.0400	0.85 (0.79, 0.92) <0.0001	0.74 (0.55, 0.99) 0.0412	1.24 (0.77, 2.02) 0.3737	0.64 (0.23, 1.82) 0.4031	0.96 (0.84, 1.08) 0.4925
21-25	0.81 (0.72, 0.91) 0.0005	0.84 (0.76, 0.94) 0.0016	0.70 (0.47, 1.05) 0.0848	0.73 (0.36, 1.49) 0.3852	0.43 (0.10, 1.81) 0.2506	1.06 (0.91, 1.24) 0.4469
26-30	0.88 (0.76, 1.02) 0.0817	0.93 (0.81, 1.07) 0.3039	0.58 (0.34, 0.99) 0.0478	2.67 (1.20, 5.90) 0.0156	2.31 (0.55, 9.66) 0.2524	1.05 (0.85, 1.30) 0.6447
<i>P</i> for trend	<0.001	<0.001	0.003	0.718	0.135	0.968
Decrease of per level	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	0.9 (0.9, 1.0)	1.0 (0.9, 1.1)	0.8 (0.7, 1.1)	1.0 (1.0, 1.0)
Model II						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	0.89 (0.84, 0.95) 0.0006	0.92 (0.87, 0.97) 0.0009	0.84 (0.70, 1.02) 0.0762	1.16 (0.79, 1.71) 0.4551	0.53 (0.29, 0.97) 0.0410	0.93 (0.85, 1.02) 0.1318
11-15	0.85 (0.79, 0.91) <0.0001	0.90 (0.85, 0.96) 0.0010	0.82 (0.65, 1.04) 0.0963	0.71 (0.43, 1.15) 0.1650	0.31 (0.09, 1.01) 0.0514	0.87 (0.78, 0.97) 0.0091

16-20	0.92 (0.84, 1.00) 0.0522	0.85 (0.79, 0.92) <0.0001	0.76 (0.57, 1.02) 0.0692	1.22 (0.75, 1.99) 0.4123	0.77 (0.27, 2.18) 0.6198	0.94 (0.83, 1.07) 0.3707
21-25	0.80 (0.71, 0.90) 0.0002	0.82 (0.74, 0.91) 0.0002	0.68 (0.45, 1.02) 0.0609	0.72 (0.35, 1.46) 0.3603	0.48 (0.11, 2.03) 0.3200	1.03 (0.88, 1.20) 0.6991
26-30	0.86 (0.74, 1.00) 0.0438	0.88 (0.77, 1.02) 0.0807	0.56 (0.33, 0.96) 0.0357	2.85 (1.28, 6.33) 0.0101	2.42 (0.57, 10.25) 0.2312	1.01 (0.82, 1.25) 0.9203
<i>P</i> for trend	<0.001	<0.001	<0.003	0.761	0.280	0.623
Decrease of per level	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	0.9 (0.9, 1.0)	1.0 (0.9, 1.1)	0.9 (0.7, 1.1)	1.0 (1.0, 1.0)
Model III						
1-5	Reference	Reference	Reference	Reference	Reference	Reference
6-10	0.88 (0.82, 0.94) 0.0002	0.90 (0.86, 0.95) 0.0001	0.82 (0.67, 1.00) 0.0525	0.78 (0.49, 1.24) 0.2906	0.55 (0.30, 0.99) 0.0460	0.91 (0.83, 1.00) 0.0392
11-15	0.81 (0.75, 0.87) <0.0001	0.84 (0.79, 0.90) <0.0001	0.80 (0.63, 1.02) 0.0778	0.51 (0.30, 0.88) 0.0158	0.29 (0.09, 0.92) 0.0360	0.79 (0.71, 0.88) <0.0001
16-20	0.84 (0.77, 0.92) 0.0003	0.78 (0.72, 0.85) <0.0001	0.67 (0.49, 0.91) 0.0097	0.83 (0.48, 1.45) 0.5150	0.92 (0.33, 2.57) 0.8665	0.83 (0.73, 0.94) 0.0045
21-25	0.73 (0.64, 0.82) <0.0001	0.74 (0.66, 0.82) <0.0001	0.66 (0.44, 1.01) 0.0559	0.52 (0.24, 1.11) 0.0909	0.60 (0.15, 2.45) 0.4737	0.89 (0.76, 1.04) 0.1388
26-30	0.76 (0.66, 0.89) 0.0005	0.77 (0.67, 0.88) 0.0002	0.44 (0.25, 0.76) 0.0038	1.40 (0.56, 3.50) 0.4762	1.63 (0.40, 6.72) 0.4967	0.84 (0.68, 1.03) 0.1001
<i>P</i> for trend	<0.001	<0.001	<0.001	0.314	0.395	<0.001
Decrease of per level	0.9 (0.9, 1.0)	0.9 (0.9, 0.9)	0.9 (0.8, 0.9)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)	1.0 (0.9, 1.0)

Model I: unadjusted. Model II: adjusted for age and sex. Model III: adjusted for age, sex, primary site, grade, T stage, operation type, radiotherapy and chemotherapy. ELN, examined lymph nodes; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchoalveolar carcinoma.

Table S3 Sensitivity analysis across alternative pre-specified breakpoints

Breakpoint K	HR below K (95% CI)	HR above K (95% CI)	P above K
10	0.972 (0.967, 0.978)	0.994 (0.990, 0.998)	0.002
11	0.974 (0.969, 0.979)	0.995 (0.991, 0.999)	0.013
12	0.975 (0.971, 0.980)	0.996 (0.991, 1.000)	0.080
13	0.976 (0.972, 0.981)	0.997 (0.992, 1.002)	0.283
14	0.977 (0.973, 0.981)	0.999 (0.993, 1.004)	0.594
15	0.978 (0.975, 0.982)	1.000 (0.994, 1.006)	0.898
16	0.979 (0.976, 0.983)	1.001 (0.994, 1.007)	0.880
17	0.980 (0.977, 0.984)	1.001 (0.994, 1.009)	0.719
18	0.981 (0.978, 0.984)	1.003 (0.994, 1.011)	0.513
19	0.982 (0.979, 0.985)	1.005 (0.995, 1.015)	0.316
20	0.982 (0.979, 0.985)	1.008 (0.996, 1.019)	0.190
21	0.982 (0.980, 0.985)	1.011 (0.998, 1.024)	0.104
22	0.983 (0.980, 0.986)	1.014 (0.999, 1.030)	0.069
23	0.983 (0.981, 0.986)	1.018 (0.999, 1.037)	0.067

Hazard ratios represent the change in mortality risk per one-node increase in examined lymph nodes below and above each candidate breakpoint. Across all breakpoints from 12 to 23, no significant association was detected above the breakpoint, indicating that the attenuation of marginal benefit is not contingent on the specific value of 16. Adjustment as in Table 3.

Table S4 Sensitivity analysis with and without adjustment for pathological N stage

Model term	Adjusted for N stage (primary)	Not adjusted for N stage
Single linear model	0.986 (0.983, 0.988)	0.989 (0.986, 0.991)
ELN < 16	0.979 (0.976, 0.983)	0.983 (0.980, 0.987)
ELN > 16	1.001 (0.994, 1.007)	1.002 (0.995, 1.009)

P for LRT	<0.0001	<0.0001
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Hazard ratios per one-node increase in examined lymph nodes. Nodal upstaging is a plausible mediator of the association between ELN count and survival; the primary model therefore yields a conservative estimate. Conclusions were unchanged when N stage was omitted, with a significant association below the breakpoint and no association above it in both specifications.

Table S5 Internal validation of the pre-specified breakpoint

Sample	N	Deaths	HR below 16 (95% CI)	HR above 16 (95% CI)	P for LRT
Full cohort	59,961	18,849	0.979 (0.976, 0.983)*	1.001 (0.994, 1.007)	<0.0001
Random split — set A	29,980	9,392	0.981 (0.976, 0.986)*	1.002 (0.993, 1.012)	0.001
Random split — set B	29,981	9,457	0.978 (0.973, 0.982)*	0.999 (0.989, 1.008)	0.001
Bootstrap (200 resamples)†	59,961	18,849	0.979 (0.976, 0.983)	1.000 (0.994, 1.007)	—

* $P < 0.0001$. † Median hazard ratio with 2.5th–97.5th percentile interval across resamples. The association below the breakpoint was directionally consistent (HR <1) in 100% of resamples, whereas above the breakpoint the hazard ratio exceeded unity in 51.5% of resamples, consistent with a null association. Covariate adjustment as in Table 3.

Table S6 Kaplan-Meier survival estimates by examined lymph node count and pathological N stage

Stratum	Group	N	Deaths	1-year	3-year	5-year	10- year	Log- rank P
Total	ELN < 16	48,007	15,483	91.9%	76.7%	64.5%	42.3%	0.890

	ELN $\geq$ 16	13,987	4,017	90.9%	76.1%	65.0%	44.7%	
pN0	ELN < 16	41,423	12,555	92.9%	79.2%	67.2%	44.4%	0.0008
	ELN $\geq$ 16	10,551	2,690	92.7%	80.2%	69.3%	47.5%	
pN1	ELN < 16	5,202	2,538	84.9%	60.6%	46.5%	28.9%	0.0023
	ELN $\geq$ 16	2,709	1,129	84.9%	64.0%	51.5%	36.4%	
pN2‡	ELN < 16	1,382	390	87.2%	63.4%	—	—	0.983
	ELN $\geq$ 16	727	198	87.1%	63.2%	—	—	

Analysis population: full eligible cohort (n = 61,994). Survival advantage favoured ELN $\geq$ 16 within every N stratum in which follow-up was adequate. ‡ Estimates beyond 3 years are not reported for pN2. Ninety-nine per cent of pN2 patients were diagnosed in 2015–2019 (median follow-up 23 months, versus 39 and 30 months for pN0 and pN1), and only 1.2% were followed beyond 48 months. This imbalance reflects differences in the assignment of N2 disease to stage IIIA across successive staging editions, and renders the pN2 subgroup underpowered for long-term survival comparison. In the overall cohort the difference between groups was not significant, whereas a significant advantage for ELN $\geq$ 16 was evident within both the pN0 and pN1 strata. This pattern is consistent with stage migration: patients with more nodes examined are more frequently classified as node-positive, and the resulting shift in case-mix offsets the within-stratum survival advantage in the pooled comparison.