

Lymphadenectomy after neoadjuvant chemoradiation for esophageal adenocarcinoma: what is the optimal lymph nodes dissection?

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Abstract

Background

The optimal lymph nodes dissection (LND) for esophageal adenocarcinoma (EAC) patients who underwent neoadjuvant chemoradiotherapy (NCRT) is controversial.

Methods

Patients were selected from Surveillance Epidemiology and End Results database. Multivariable Cox analysis was used to identify predictors of overall survival (OS). Restricted Cubic Splines (RCS) was used to examine the relationship between the number of LND and OS.

Result

2,019 patients with non-metastatic EAC underwent NCRT were stratified into three groups according to LND using X-tile software: group 1: 1–8, group 2: 9–14, group 3: ≥ 15 . In Multivariable Cox Regression analysis, the death risk was reduced by 22% ($P = 0.001$), 43% ($P < 0.001$) respectively, for patients in groups 2, 3 compared with those in group 1. The results were similar for patients with pathological lymph node-negative (ypN0) EAC patients. But for pathological lymph node-positive (ypN+) patients, a significantly reduced hazard was present only in group 3 ($P < 0.001$). RCS exhibited a nonlinear relationship between the number of lymph nodes removed and OS for ypN0 EAC ($P = 0.002$). The risk of death sharply dropped until around 24 nodes removed and then started to steadily increase afterward. However, for ypN + EAC, it showed a linear relationship between LND and OS ($P = 0.205$), with a better OS when an increase in the number of lymph nodes removed.

Conclusions

For ypN0 patients, the optimal LND was approximately 24 lymph nodes, with the number of lymph nodes removed beyond 24 nodes did not provide additional benefit. However, for ypN + patients, a more extensive lymphadenectomy could favor survival.

1. Introduction

Esophageal cancer is still the leading cause of cancer mortality in the world. It is reported that more than 572,000 are newly diagnosed per year, causing more than 508,000 deaths globally.(1) Neoadjuvant chemoradiation followed by surgery become a standard treatment for esophageal cancer, which dramatically improved the 5-year overall survival.(2–5) However, it remains controversial whether increasing the number of lymph nodes removed could enhance patient survival for EAC patients after NCRT. Although it is recommended to dissect at least 15 lymph nodes during esophagectomy based on

National Comprehensive Cancer Network guidelines,(2) the optimum number of lymph nodes harvested is unknown for patients after NCRT.

Previous studies had investigated the association of the number of lymph nodes removed and survival, but the results showed conflicting.(6, 7) Hanna et al. and Susanna et al. reported that patients with a higher number of lymph nodes removed had better survival.(8, 9) However, the study of Talsma et al. enrolled 161 patients with surgery alone and 159 patients with NCRT followed by surgery, demonstrated that the number of lymph nodes removed was a prognostic impact for patients who underwent surgery alone, but not in patients who underwent NCRT.(10) Shridhar et al. identified 358 patients had also concluded that the number of lymph nodes removed did not improve survival after NCRT.(11)

To date, the number of lymph nodes removed for EAC patients after NCRT has not yet been standardized in the guidelines. Therefore, the focus of this present study based on multi-institution data from the SEER database aimed to evaluate the correlation between lymph node numbers removed and survival in EAC patients suffering NCRT and explore the optimal extent of lymphadenectomy as well.

2. Methods

2.1 SEER database and Patients Selection

The SEER database collected cancer incidence data from population-based cancer registries covering approximately 34.6 percent of the United States (<http://seer.cancer.gov/>). The National Cancer Institute's SEER*Stat software (version 8.3.6) was used for data of patients. We included 2,019 patients with non-metastatic EAC who underwent NCRT followed by surgery between 1988 and 2016. The covariates were collected as follows: age, gender, primary tumor site, grade, cT stage, cN stage, ypN stage, and LND. The 8th edition of the TNM staging system for esophageal cancer as a reference was used in the study. The exclusion criteria included (1) patients who did not underwent neoadjuvant chemoradiation and esophagectomy (2) patients who had metastatic disease (3) patients with a histological type other than adenocarcinoma. The ICD-O3 code for EAC patients were as followed: adenocarcinoma (8140–8144), adenocarcinoma in an adenomatous polyp (8210), tubular adenocarcinoma (8211), adenocarcinoma with mixed subtypes (8255), papillary adenocarcinoma (8260), mixed cell adenocarcinoma (8323), mucinous adenocarcinoma (8480–8481) (4) patients with unknown data such as age at diagnosis, gender, primary tumor location, cT stage, cN stage, ypN stage, and the number of lymph nodes dissection (5) patients with survival time less than one month after NCRT followed by surgery (Fig. 1). In addition, the endpoint of this study was overall survival (OS), which was calculated as the time from the date of the surgery to the date of death from any cause or the date of the last follow-up.

2.2 Statistical Analysis

All statistical calculations were analyzed using SPSS (version 25.0, IBM, Armonk, NY, USA) and R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). The best cutoff values

for LND were calculated using X-tile software (version 3.6.1), which is a valuable tool to generate the optimal cut-point with minimum p values.(12) First, we divided the patients into three groups according to the optimal cut-off value generating by X-tile program (Fig. 2). Then Chi-Square test was utilized to identify differences among these groups. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. In Univariate analysis, all factors with p value < 0.10 were entered into Multivariate Cox Regression analysis to determine independent prognostic factors. Finally, the relationship between LND and OS was evaluated using restricted cubic splines (RCS), which could reveal the true nature and complexity of relationships between continuous variables.(13) In addition, RCS could recognize the hazard function inflexion point (ie, threshold).(14) The threshold was considered as the optimal LND with the lowest risk of death. All statistical analyses were two-sided analysis, and significance is defined as $P < 0.05$.

3. Result

3.1 Patients Characteristics

A total of 2,019 EAC patients who underwent NCRT followed by surgery met inclusion criteria. The median LND was 12 (range 1 to 83). As showed in Table 1, the majority of patients were male (89.1%), cT3-4 stage (72.0%), and cN + stage (64.8%). 93.3% of tumors were located in the lower third of esophagus. Patients were stratified by LND using X-tile software (group 1: 1–8, group 2: 9–14, group 3: ≥ 15). There were 696 patients in group 1, 544 patients in group 2, and 779 patients in group 3. The significant difference among these groups were tumor site, cT and cN stage: patients with ≥ 15 LNs were more likely to have cT stage ($P = 0.03$) and cN + stage ($P < 0.001$).

Table 1
Distribution of patient's characteristics for three categories by the number of lymph nodes removed.

Variables	Overall cohort n = 2019	1 to 8 LND n = 696	9 to 14 LND n = 544	≥ 15 LND n = 779	P
Age					0.410
< 65	1274(58.1)	417(59.9)	317(58.3)	440(56.5)	
≥ 65	845(41.9)	279(40.1)	227(41.7)	339(43.5)	
Gender					0.391
male	1798(89.1)	625(89.8)	476(87.5)	697(89.5)	
female	221(10.9)	71(10.2)	68(12.5)	82(10.5)	
Tumor site					0.006
upper/middle	136(6.7)	60(8.6)	22(4.0)	54(6.9)	
lower	1883(93.3)	636(91.4)	522(96.0)	725(93.1)	
Grade					0.769
I/II	856(42.4)	304(43.7)	224(41.2)	328(42.1)	
III/IV	908(45.0)	304(43.7)	256(47.1)	348(44.7)	
unknown	255(12.6)	88(12.6)	64(11.8)	103(13.2)	
cT stage					0.030
T1-2	566(28.0)	205(29.5)	168(30.9)	193(24.8)	
T3-4	1453(72.0)	491(70.5)	376(69.1)	586(75.2)	
cN stage					< 0.001
N0	711(35.2)	295(42.4)	177(32.5)	239(30.7)	
N+	1308(64.8)	401(57.6)	367(67.5)	540(69.3)	
ypN stage					0.064
ypN0	1477(73.2)	524(75.3)	378(69.5)	575(73.8)	
ypN+	542(26.8)	172(24.7)	166(30.5)	204(26.2)	

3.2 Survival analysis for OS in the whole cohort

Median survival time was 24 months (range 1 to 224). On Univariate Cox Regression analysis (Table 2), the prognostic factors for OS included age, gender, grade, cT stage, cN stage, LND and ypN stage (P <

0.005 for all). On Multivariate Cox Regression analysis, the number of lymph nodes removed was an independent prognosticator for OS. (1–8 vs 9–14: HR: 0.78, 95% CI: 0.673–0.904; P = 0.001; 1–8 vs \geq 15: HR: 0.572, 95% CI: 0.494–0.661, P < 0.001). Besides, the factors included age (HR: 1.369, 95% CI: 1.211–1.547; P = < 0.001), gender (HR: 1.409, 95% CI: 1.136–1.746, P = 0.002), grade III/IV (HR: 1.198, 95% CI: 1.053–1.363, P = 0.006), cT stage (HR: 1.292, 95% CI: 1.124–1.486, P < 0.001) and ypN stage (HR: 1.830, 95%CI: 1.572–2.129, P < 0.001) were independently associated with OS. Figure 3 showed that patients in group 3 had a better OS than in other groups. The 5-year OS were 33.9% in group 1, 42.3% in group 2, and 52.0% in group 3 respectively (P < 0.001).

Table 2
Predictors of overall survival in esophageal adenocarcinoma patients after neoadjuvant chemoradiotherapy and surgery.

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P	HR(95% CI)	P
Age				
< 65 vs \geq 65	1.283(1.136–1.449)	< 0.001	1.369(1.211–1.547)	< 0.001
Gender				
female vs male	1.332(1.075–1.649)	0.009	1.409(1.136–1.746)	0.002
Primary Site				
upper/middle vs lower	0.934(0.736–1.185)	0.574		
Grade				
I/II vs III/IV	1.264(1.112–1.437)	< 0.001	1.198(1.053–1.363)	0.006
I/II vs unknown	0.912(0.754–1.116)	0.371	0.912(0.745–1.117)	0.375
T stage				
T1–2 vs T3–4	1.353(1.180–1.551)	< 0.001	1.292(1.124–1.486)	< 0.001
N stage				
N0 vs N+	1.240(1.092–1.407)	0.001	0.960(0.825–1.117)	0.597
LND				
1 to 8 vs 9 to 14	0.791(0.683–0.917)	0.002	0.780(0.673–0.904)	0.001
1 to 8 vs \geq 15	0.601(0.520–0.694)	< 0.001	0.572(0.494–0.661)	< 0.001
ypN stage				
ypN0 vs ypN+	1.775(1.563–2.016)	< 0.001	1.830(1.572–2.129)	< 0.001

3.3 Survival analysis for OS stratified by ypN stage

We conducted stratification analyses on OS according to the ypN stage. On Univariate Cox Regression analysis, age, gender, grade, cT stage, and LND ($P < 0.05$ for all) were the prognostic factors of OS for ypN0 EAC (Table 3), while only grade and LND ($P < 0.05$ for both) were the prognostic factors for ypN+ EAC (Table 4). In Multivariable Cox Regression analysis, the number of lymph nodes removed was an independent prognosticator of OS for both ypN0 and ypN+ patients. For ypN0 EAC patients, the death hazard was reduced by 30% ($P < 0.001$), 44% ($P < 0.001$) respectively, for patients in groups 2, 3 compared with those in group 1. Figure 4A showed the 5-year OS were 39.2% in group 1, 51.1% in group 2, 58.6% in group 3 respectively (group1 vs group 2: $P < 0.001$; group1 vs group 3: $P < 0.001$; group2 vs group 3: $P = 0.094$) for ypN0 patients. There was no significant difference between group 2 and group 3 on OS. ($P = 0.094$). However, for ypN+ patients, a significantly reduced hazard was present only in group 3 (HR = 0.589, $P < 0.001$). Figure 4B showed the 5-year OS were 18.3% in group 1, 23.0% in group 2, 34.3% in group 3 respectively (group1 vs group 2: $P = 0.282$; group1 vs group 3: $P < 0.001$; group2 vs group 3: $P < 0.001$) for ypN+ patients.

Table 3
Predictors of overall survival in patients with ypN0 esophageal adenocarcinoma after neoadjuvant chemoradiotherapy and surgery.

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P	HR(95% CI)	P
Age				
< 65 vs \geq 65	1.390(1.198–1.614)	< 0.001	1.415(1.218–1.643)	< 0.001
Gender				
female vs male	1.355(1.040–1.766)	0.024	1.347(1.033–1.757)	0.028
Primary Site				
upper/middle vs lower	0.911(0.690–1.203)	0.511		
Grade				
I/II vs III/IV	1.196(1.021–1.402)	0.027	1.166(0.994–1.367)	0.059
I/II vs unknown	0.946(0.746–1.200)	0.646	0.933(0.735–1.185)	0.571
cT stage				
T1–2 vs T3–4	1.336(1.135–1.573)	< 0.001	1.369(1.162–1.613)	< 0.001
LND				
1 to 8 vs 9 to 14	0.700(0.581–0.843)	< 0.001	0.704(0.584–0.847)	< 0.001
1 to 8 vs \geq 15	0.588(0.493–0.702)	< 0.001	0.565(0.474–0.675)	< 0.001

Table 4
Predictors of overall survival in patients with ypN + esophageal adenocarcinoma after neoadjuvant chemoradiotherapy and surgery.

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P	HR(95% CI)	P
Age				
< 65 vs ≥ 65	1.229(0.992–1.523)	0.060	1.264(1.019–1.567)	0.033
Gender				
female vs male	1.262(0.877–1.815)	0.210		
Primary Site				
upper/middle vs lower	0.766(0.483–1.217)	0.259		
Grade				
I/II vs III/IV	1.287(1.032–1.604)	0.025	1.250(1.001–1.561)	0.049
I/II vs unknown	0.883(0.599–1.300)	0.527	0.887(0.602–1.306)	0.542
T stage				
T1–2 vs T3–4	1.154(0.894–1.488)	0.271		
LND				
1 to 8 vs 9 to 14	0.879(0.686–1.125)	0.305	0.894(0.697–1.145)	0.374
1 to 8 vs ≥ 15	0.575(0.447–0.739)	< 0.001	0.589(0.457–0.759)	< 0.001

3.4 The relationship between LND and survival

Restricted cubic spline (RCS) analysis with adjusted for age, gender, tumor site, grade, cT stage was used to classify the association between the number of LND and survival. Figure 5A demonstrated a nonlinear relationship between LND and OS for patients with ypN0 EAC. The death hazard sharply decreased until around 24 lymph nodes removed and then started to steadily increase afterward (P = 0.002 for non-linearity). The lowest risk of death was approximately 24 lymph nodes removed. However, for ypN + patients, it presented a linear relationship between LND and OS (P = 0.205 for non-linearity), with a better OS when an increase in the number of lymph nodes removed (Fig. 5B). But the incremental reduction in the probability of death was not evident when LND was over 24 nodes.

4. Discussion

Nowadays, neoadjuvant chemoradiotherapy followed by surgery has been regarded as a standard treatment for EAC.(3, 4, 15) It reported that approximately 20–51% of EAC patients could achieve

pathological complete response (pCR) after NCRT.(16, 17) Based on the frequency of pCR, we hypothesize that it is unnecessary to extend lymph node dissection for patients who underwent NCRT. Although previous several studies have explored the effect of the number of lymph nodes removed for prognosis in patients with neoadjuvant therapy. It remains controversial the optimal LND for patients after NCRT.(8–11, 18–21) Furthermore, few studies have used RCS to explore the linear relationship between LND and survival. Therefore, in this study, we aimed to investigate the survival effect of total number of lymph nodes removed and further determined the optimal LND in EAC patients receiving NCRT.

In our study, we based on a large sample analysis from the SEER database to examine the relationship between LND and survival. The median number of lymph nodes removed in our study was 12 (range 1 to 83). Patients were stratified by LND using X-tile software (group 1: 1–8, group 2: 9–14, group 3: ≥ 15). Multivariate Cox Regression analysis demonstrated the number of lymph nodes removed was an independent prognosticator for OS. (1–8 vs 9–14: HR: 0.78, 95% CI: 0.673–0.904; $P = 0.001$; 1–8 vs ≥ 15 : HR: 0.572, 95% CI: 0.494–0.661, $P < 0.001$). The 5-year OS in group 1 (33.9%) was lower than in group 2 (42.3%), 3 (52.0%) ($P < 0.001$). Groth et al. included 4882 patients demonstrated that the risk of death was lower when more than 12 lymph nodes were removed.(19) Hanna et al. and Susanna et al. also reported that patients with a higher number of lymph nodes removed had better survival.(8, 9) In addition, a larger cohort of 2698 patients from the Netherlands Cancer Registry, Visser et al. demonstrated that the number of lymph nodes removed was independently associated with survival following trimodality therapy.(21) These data and our study result, support that lower lymph nodes removed may result in worse survival. One possible explanation is that when the number of lymph nodes removed was not enough, potential metastatic lymph nodes may be undetected, resulting in poor prognosis. It reported that micro-metastases had been found in up to 50% of patients with histology-negative nodes.(22) Extensive the number of LND that may eliminate occult metastasis of lymph nodes, decrease local recurrence rates, and then improved survival.(23–25)

Could a more extensive lymphadenectomy improve survival for patients with ypN0 stage after NCRT? At present, there is a lack of study to discuss this issue deeply. Therefore, in this study, stratification analyses were conducted on OS according to the ypN stage. Interestingly, we found that for ypN0 EAC patients, the death hazard decreased by 30% ($P < 0.001$), 44% ($P < 0.001$) respectively, for patients in groups 2, 3 compared with those in group 1. The 5-year OS were 39.2%, 51.1%, 58.6% in group 1, 2, and 3 respectively (group1 vs group 2: $P < 0.001$; group1 vs group 3: $P < 0.001$; group2 vs group 3: $P = 0.094$). There was no significant difference between group 2 and group 3 on OS ($P = 0.094$). It meant that LND at least 8 lymph nodes for ypN0 stage EAC patient could achieve better survival. Although Rizk et al. demonstrated that the optimum lymphadenectomy was at least 10 lymph nodes removed for pN0 EAC, they only enrolled patients with surgery alone.(24) Their conclusion may not apply to patients who undergoing NCRT. A population-based cohort study by Els Visser et al. showed that a high lymphadenectomy was associated with favorable survival in both ypN0 and ypN + patients after NCRT. (21) Our results were similar to their research. In our study, for ypN + patients, a significantly reduced hazard was present in group 3 (HR = 0.589, $P < 0.001$). The 5-year OS were 18.3%, 23.0%, 34.3% in group 1, 2, and 3 respectively (group1 vs group 2: $P < 0.001$; group1 vs group 3: $P < 0.001$; group2 vs group 3: $P <$

0.001), which demonstrated less than 14 nodes removed were not enough, more lymph nodes removed were needed to improve survival.

What is the optimal lymph node dissection? National Comprehensive Cancer Network guidelines recommend at least 15 lymph nodes should be dissected during esophagectomy.(2) But for patients after NCRT, the optimal LND is unknown. In our study, we used the restricted cubic spline to determine the optimal number of lymph nodes removed. Interestingly, we found a nonlinear relationship between LND and OS for patients with ypN0 EAC. The death hazard sharply decreased until around 24 lymph nodes removed and then started to steadily increasing afterward ($P = 0.002$ for non-linearity). The lowest risk of death was approximately 24 lymph nodes removed. The optimal LND is approximately 24 nodes for ypN0 stage EAC. Limited lymph node dissection may lead to underestimation of pathological stage since positive nodes can be missed, whereas extensive lymphadenectomy might bring unexpected complications, including anastomotic leakage, recurrent nerve palsy, respiratory complications. The result was similar to a recent study by Sihag S et al. that demonstrated that around 25 lymph nodes removed was optimal to enhance both staging and survival for patients with EAC after NCRT.(26) Likewise, Raja S et al. included 3859 patients with EAC concluded that for patients with ypN0 stage, the potential benefit increase incrementally when the number of lymph nodes removed up to 25, and decreased when more than 25 lymph nodes dissection was performed.(27)

However, the result was different for ypN + patients. Our study presented a linear relationship between LND and OS ($P = 0.205$ for non-linearity) by adjusted RCS, with a better OS when an increase in the number of LND. But when the number of lymph nodes removed was above 24 nodes, the incremental decrease of the risk of death became not obvious. In the study of Sihag S et al, OS tended to be maximized at 20 to 25 resected lymph nodes for patients with a higher risk of ypN + disease.(26) Raja S et al also showed a better survival when up to about 30 nodes were removed for ypN + patients and worse survival with more extensive lymphadenectomy beyond about 30 nodes. The underlying mechanism is unknown. The ypN + was a significant adverse prognostic factor that has been confirmed in several studies.(28, 29) Extensive lymph node dissection allows for more complete removal of positive lymph nodes and avoidance of potential metastatic lymph nodes. In our analysis, the optimal number of lymph nodes removed was not given a specific value for ypN + patients, but our result confirmed that more extensive lymph node dissection was necessary and at least 24 lymph nodes could favor survival for ypN + patients.

Our study represents one of the largest analyses of EAC patients to evaluate the relationship between the number of LND and survival using the SEER database, which may reduce the potential for selection biases. Furthermore, our research only included adenocarcinomas to reduce the confounding effect of other histologies on our results. However, there are several limitations in our study. First of all, this study is a retrospective study with an underlying weakness. Secondly, the SEER database did not provide specific description on radiation methods, chemotherapy regimen and esophagectomy skills. Further prospective studies are needed to validate these results.

5. Conclusion

In conclusion, the extent of lymph nodes resected was an independent prognostic factor for EAC patients after NCRT. The optimal LND is maybe approximately 24 lymph nodes for ypN0 patients, with the number of lymph nodes removed beyond 24 nodes did not provide additional benefit. However, for ypN + patients, a more extensive lymphadenectomy could favor survival. These results need confirmation in further research.

Declarations

Ethics statement

This retrospective study analyzed data from the publicly accessible SEER database. Before the study, we obtained an official permit for the research purpose (ID: 19895-Nov2019). Informed consent or ethical approval was not required for this study.

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Guideline statement

All methods were carried out in accordance with relevant guidelines and regulations.

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Declaration of Competing Interest

None declared.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions statement

W.Y.H., L.M.Q, and Z.M.Y. conceived and designed the study. L.T.X. and W.Z.P. collected the data. W.Y.H. and L.M.T. analyzed the data. L.J.C. supervised the study. W.Y.H. wrote the manuscript and L.M.Q. prepared Figs. 1, 2, 3, 4, and 5. All authors read and approved the final manuscript prior to submission.

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Figures

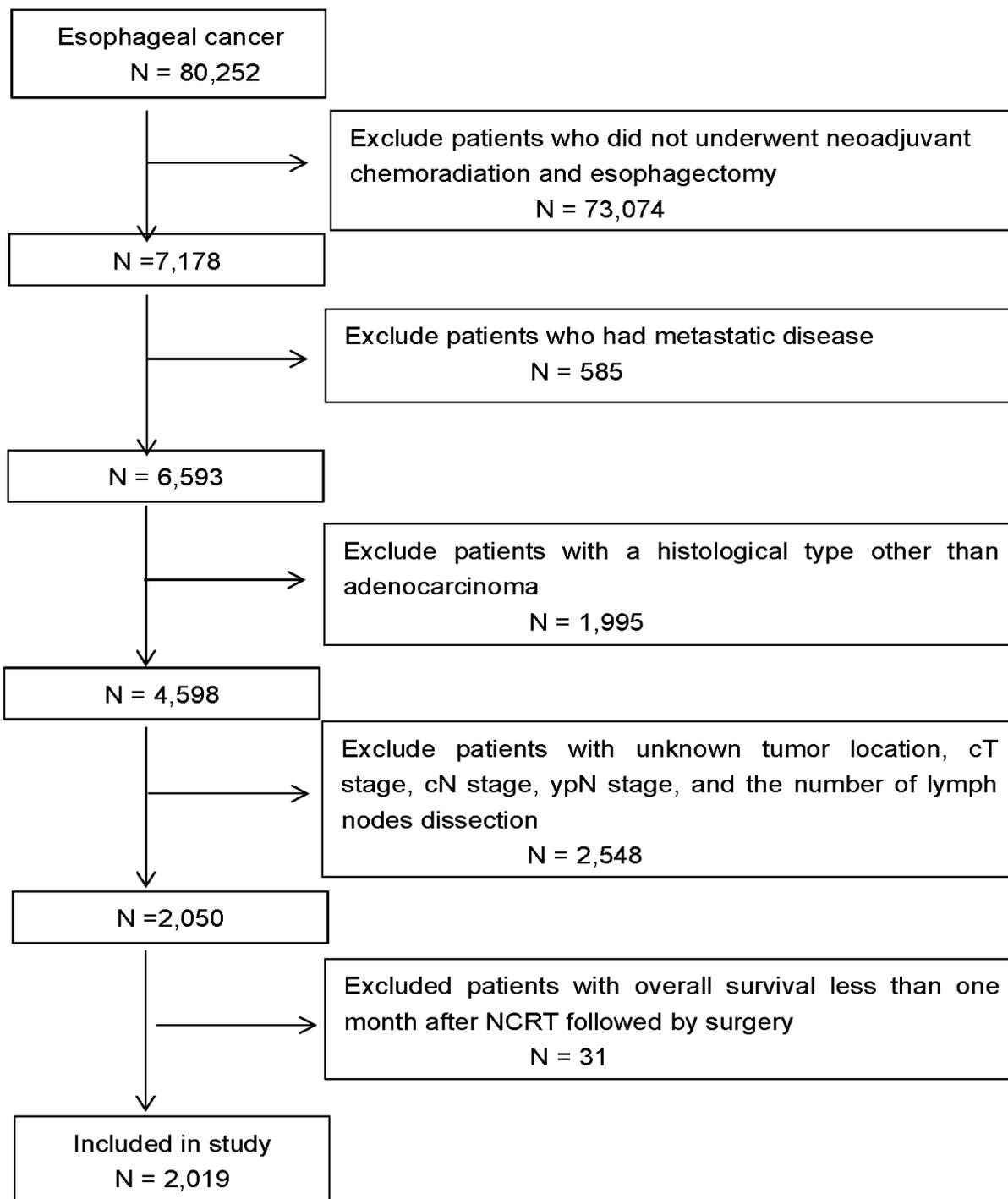


Figure 1

Patients included in and excluded from study.

Statistics						Chi-Sq Hi/Mid/Lo		
Pt No	% Total	Events	Rate	Rank	Range	Lo vs Mid	Mid vs Hi	Lo vs Hi
696	34.47	481	69.11	0 to 7	1.00 thru 8.00	48.5352	9.7667	10.8252
544	26.94	281	51.65	8 to 13	9.00 thru 14.00	47.8626	1.78	1.33
779	38.58	302	38.77	14 to 57	15.00 thru 83.00			
2019	100.00	1064	52.70	0 to 57	1.00 thru 83.00			

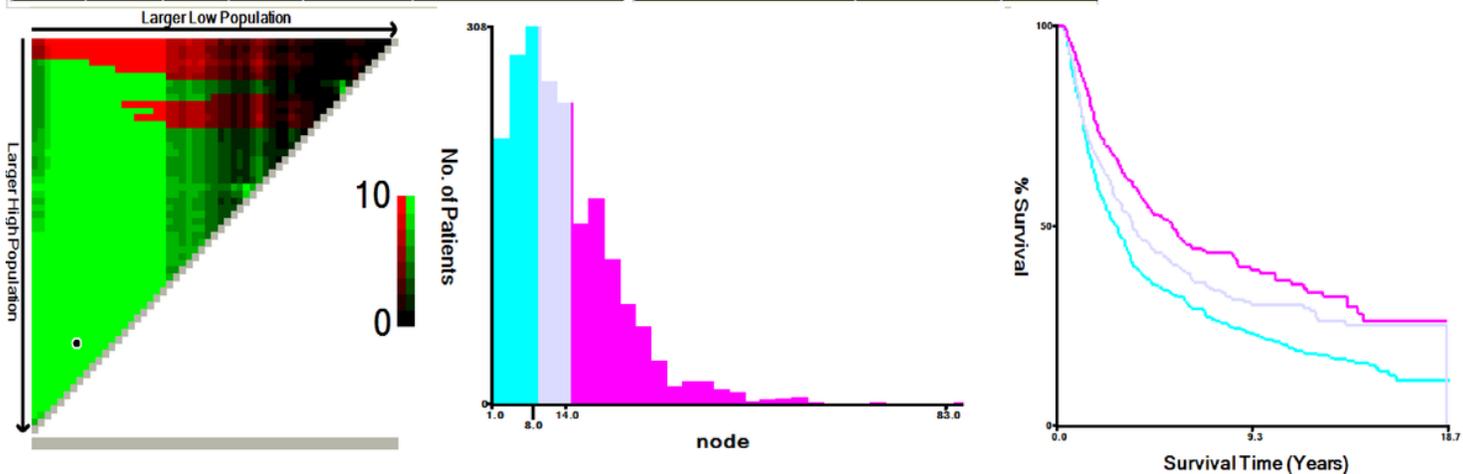


Figure 2

X-tile analysis for best cut-off value of the number of lymph nodes dissection.

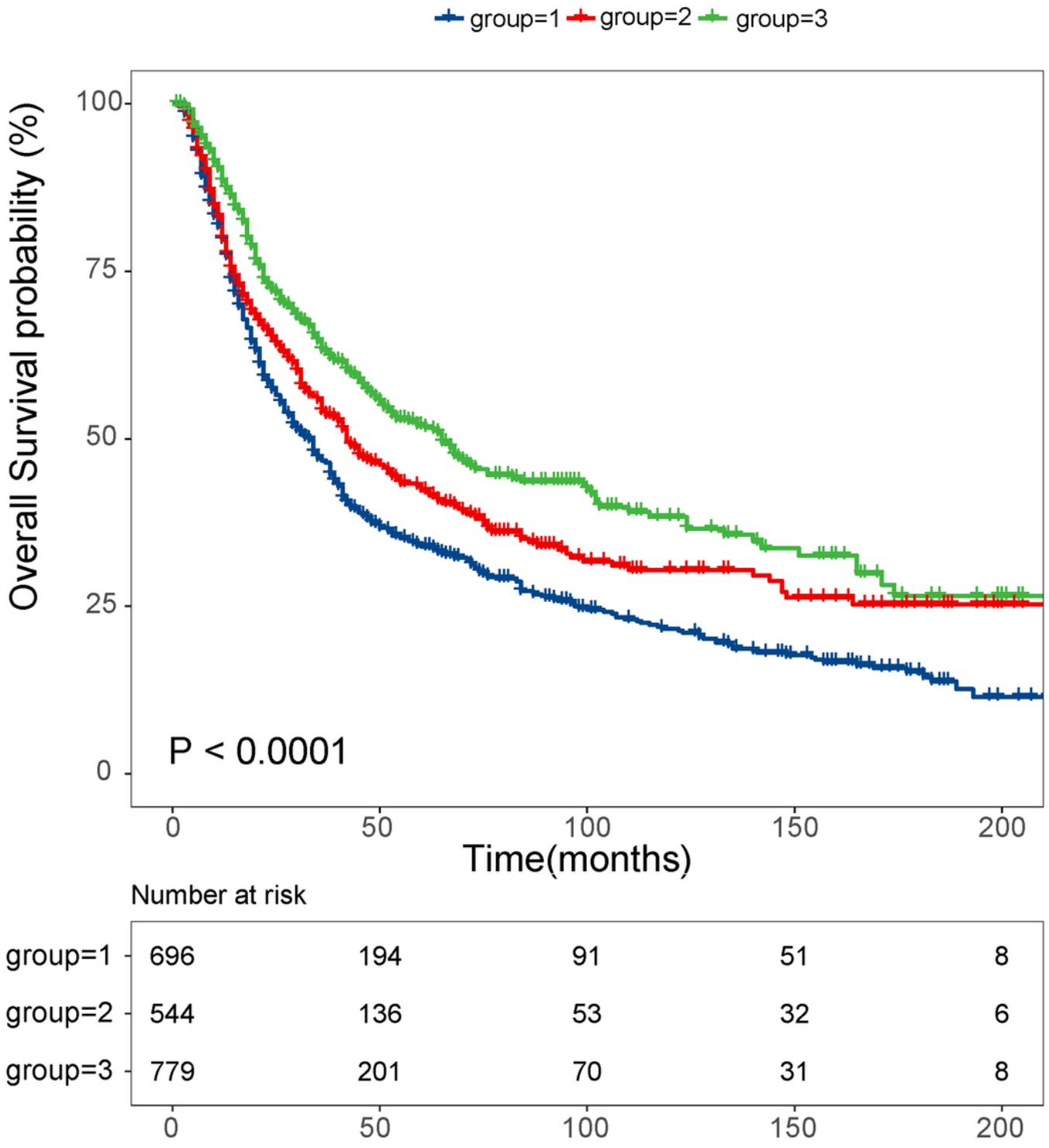


Figure 3

The overall survival with stratification for the number of lymph nodes dissection in whole cohort.

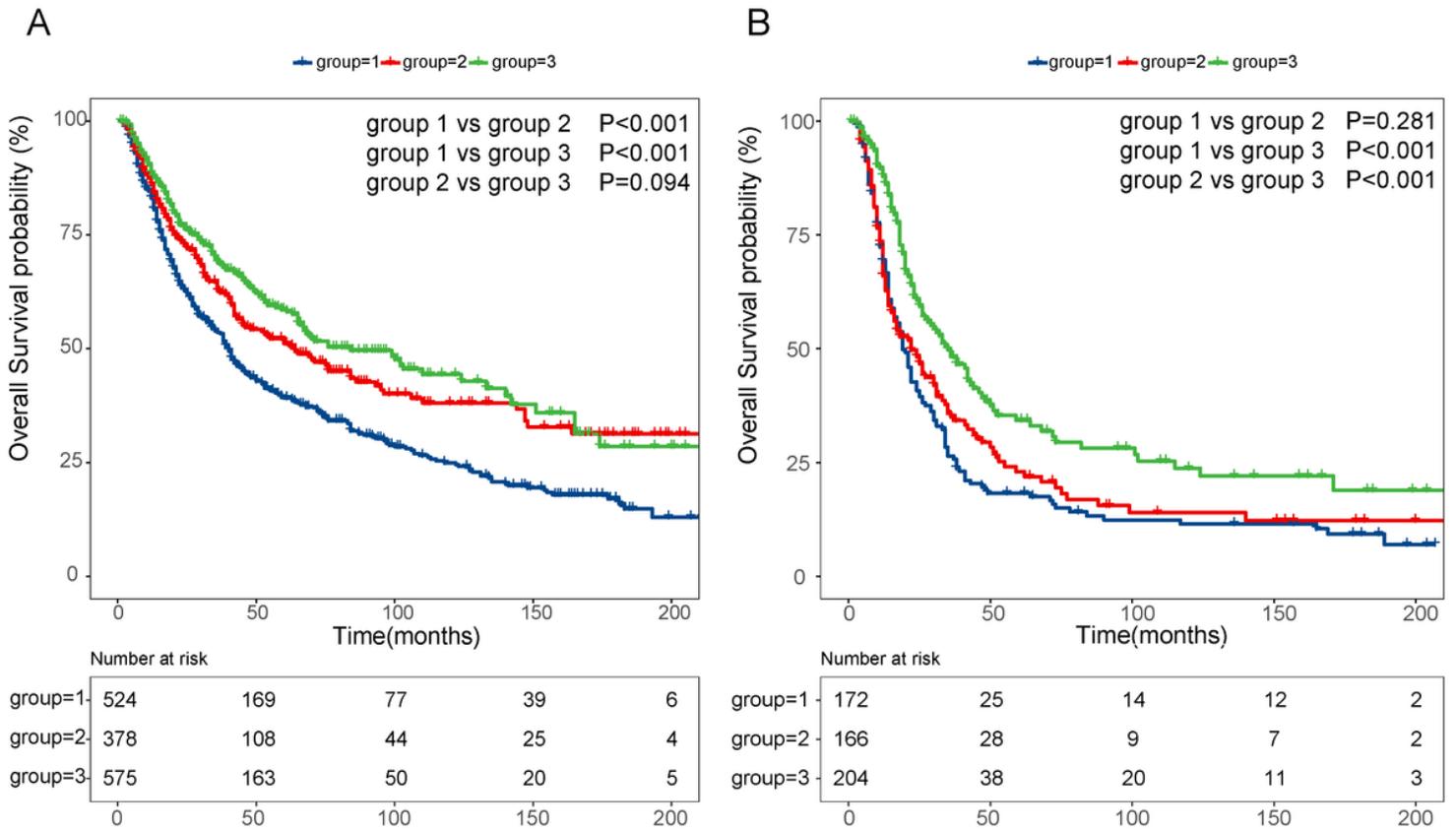


Figure 4

The overall survival with stratification for the number of lymph nodes dissection in ypN0 (A) and ypN+(B) patients.

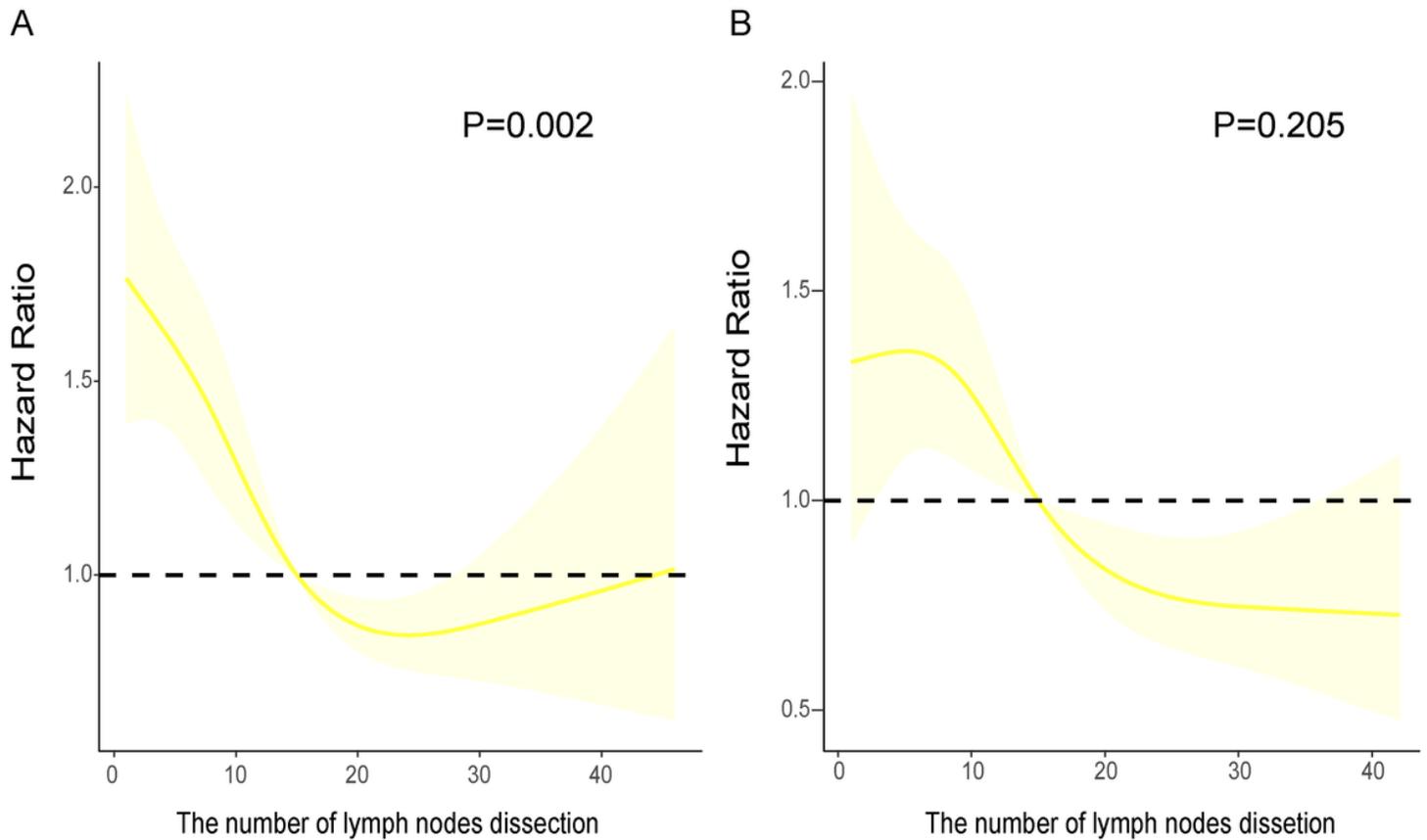


Figure 5

Restricted Cubic Spline analysis was used to classify the association between the number of lymph nodes dissection and overall survival in ypN0 (A) and ypN+ (B) patients. The hazard ratio derived from a Multivariate Cox model is shown on the y-axis. The 95% CI of the adjusted hazard ratio are represented by the shaded area. 15 lymph nodes are the reference (HR=1).