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ORIGINAL ARTICLE

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Proposed revision of N categories to the 8th edition of the AJCC-TNM staging system for non-surgical esophageal squamous cell cancer

Kai Hu[1,2,3] | Ning Kang[2] | Yang Liu[3,4] | Dong Guo[3,5] | Wang Jing[3] | Jiamei Lu[2] | Tianmeng Tan[6] | Caitiao Lv[6] | Yuyan Deng[6] | Jianxiong Long[7] | Rensheng Wang[2] | Jinming Yu[1,3]

[1]School of Medicine, Shandong University, Jinan, Shandong, China

[2]Department of Radiation Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

[3]Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, Shandong, China

[4]School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, Shandong, China

[5]Weifang Medical University, Weifang, Shandong, China

[6]Pre-Clinical Faculty of Guangxi Medical University, Nanning, Guangxi, China

[7]School of Public Health of Guangxi Medical University, Nanning, Guangxi, China

Correspondence
Rensheng Wang, Department of Radiation Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.
Email: 13807806008@163.com
Jinming Yu, Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, Shandong, China.
Email: sdyujinming@163.com

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The 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC-TNM) staging system for esophageal cancer (EC) retained the definition of N categories based on the number of metastatic lymph nodes (LN). However, it is difficult to accurately determine the number of metastatic LN without surgery. This study aimed to propose a revision to the N categories of the 8th edition AJCC-TNM staging system that makes staging easier to perform and better represents the prognosis of non-surgical esophageal squamous cell cancer (ESCC). We retrospectively reviewed the data of 336 patients with ESCC. The revised N categories were based on the anatomic regions of LN metastasis (cervix, thorax and abdomen). Survival was analyzed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses were performed using the Cox proportional hazard model. Survival differences were adequately discriminated when the revised N categories were used. Subgroup analyses by T stage showed significant difference in overall survival between the revised N categories. Multivariate analyses demonstrated that T stage, revised N category, age, sex and treatment modality were independent risk factors, with the revised N category being the most significant variable. The revised N categories determined in this study can be used to fill gaps in the staging system for patients with non-surgical ESCC, which can help clinicians to make better treatment decisions and more effectively predict patient prognoses. Future large-scale studies are required to validate these results.

KEYWORDS
AJCC-TNM staging system, esophageal squamous cell cancer, N category, non-surgical, prognosis

1 | INTRODUCTION

Esophageal cancer (EC) is one of the most common highly aggressive malignancies worldwide, including in China, and it has a dismal prognosis.[1,2] In 2015, approximately 477 900 new cases of esophageal cancer and 375 000 esophageal cancer-related deaths were reported in China.[3] These new cases of EC and EC-related deaths in China account for the majority of EC cases worldwide.[2-4] In addition, an estimated 90% of patients with EC in China were diagnosed with squamous cell cancer.[5,6] Accordingly, esophageal squamous cell cancer (ESCC) is sometimes considered to be a characteristic disease epidemic in China. Nevertheless, the 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC-TNM) staging system for EC launched on January 2018 was based on the Worldwide Esophageal Cancer Collaboration database, which includes only 19.4% (4401/22 654) of Asian patients.[7-10] Thus, the accumulation of more data from Asian patients, particularly Chinese patients with ESCC, is essential to establish a more accurate staging system for EC.

Moreover, the main drawback of the 8th edition of the AJCC-TNM staging system is that it is generally not applicable for patients with non-surgical EC because it is difficult to accurately evaluate lymph node (LN) metastasis without surgery. Therefore, an easy-to-perform and effective pre-therapeutic prognostic clinical staging system for non-surgical EC needs to be established. In a study performed by An et al,[11] patients with EC who underwent 3-field lymphadenectomy were divided into 4 groups according to the fields of LN involved (no LN metastasis; 1-field LN metastasis; 2-field LN metastasis; and 3-field LN metastasis); a significant difference in 5-year survival was reported among the 4 groups. Shimada et al[12] also found a significant decrease in the 5-year survival rates of patients with EC who underwent 3-field lymphadenectomy as the number of fields with LN metastasis increased.

In this retrospective study, using data from a cohort of Chinese patients treated in 2 institutions, we propose a revision of the N categories in the 8th edition of the AJCC-TNM staging system based on the anatomic regions of LN metastasis (cervix, thorax and abdomen) that makes staging easier to perform and better represents the prognosis of non-surgical ESCC.

2 | MATERIALS AND METHODS

2.1 | Patients

We recruited patients with ESCC who underwent radiotherapy alone or chemoradiotherapy from The First Affiliated Hospital of Guangxi Medical University and Shandong Cancer Hospital Affiliated to Shandong University between January 2010 and April 2013. The inclusion criteria for patients were as follows: (i) diagnosed with pathologically confirmed ESCC; (ii) received radiotherapy or chemoradiotherapy initially and without surgery or any prior treatments; (iii) had complete information for stage grouping; (iv) had no combined malignancy or distant metastasis (M0); (v) had completed the treatment plan; and (vii) had an Eastern Cooperative Oncology Group performance status of 0-2. This study was carried out in accordance with the Declaration of Helsinki of 1975, revised in 2008, and was approved by the medical ethics committees of both hospitals. The requirement for written informed consent from all participants was waived due to the retrospective nature of this study.

TABLE 1 Regional lymph node stations for staging esophageal cancer

LN station NO.	LN name	LN region
1R/1L	Right/left lower cervical paratracheal nodes	Cervical region[a]
2R/2L	Right/left upper paratracheal nodes	Thoracic region
4R/4L	Right/left paratracheal nodes	
7	Subcarinal nodes	
8U	Upper thoracic paraesophageal nodes	
8M	Middle thoracic paraesophageal nodes	
8Lo	Lower thoracic paraesophageal nodes	
9R/9L	Right/left pulmonary ligament nodes	
15	Diaphragmatic nodes	
16	Paracardial nodes	Abdominal region
17	Left gastric nodes	
18	Common hepatic nodes	
19	Splenic nodes	
20	Celiac nodes	

LN, lymph node.

[a]In the lymph node maps for esophageal cancer, NO.1 LN station was defined as lower cervical paratracheal nodes between the supraclavicular paratracheal space and apex of the lung. Therefore, the supraclavicular lymph nodes were included in the cervical region.

TABLE 2 Clinicopathological characteristics of patients and results of univariate analysis for 3-y overall survival

Variables	Number of patients (%)	Median survival (m)	3-y survival (%)	*P*
Age				
≤60	140 (41.7)	32	41.3	.031
>60	196 (58.3)	31	38.6	
Sex				
Male	263 (78.3)	30	37.3	.021
Female	73 (21.7)	36	50.7	
Tumor location				
Upper	125 (37.2)	32	42.4	.596
Middle	128 (38.1)	31	37.5	
Lower	83 (24.7)	32	41.0	
T stage				
T1	3 (.9)	53	66.7	<.001
T2	66 (19.6)	46	72.7	
T3	181 (53.9)	33	40.3	
T4	86 (25.6)	19	14.0	
Revised N category				
N0	93 (27.7)	42	67.7	<.001
N1	138 (41.1)	33	44.2	
N2	74 (22.0)	25	13.5	
N3	31 (9.2)	16	3.2	
Modified staging				
I	3 (.9)	53	66.7	<.001
II	106 (31.5)	45	70.8	
III	130 (38.7)	32	35.4	
IVA	97 (28.9)	19	12.4	
Treatment modality				
RT alone	101 (30.1)	30	34.7	.014
CRT	235 (69.9)	33	42.6	

CRT, chemoradiotherapy; RT, radiotherapy.

2.2 | Staging

After histological confirmation was obtained, staging modalities included upper gastrointestinal endoscopy, barium esophagography and computed tomography (CT) scans of the cervix, thorax and abdomen with intravenous contrast. Endoscopic ultrasound (EUS), ^{18}F-fluorodeoxyglucose positron emission tomography-CT and bronchoscopy were used for a portion of patients. EUS-guided fine-needle aspiration or ultrasound-guided biopsy was performed if necessary.

Tumor staging was performed according to the 8th edition of the AJCC staging system for ESCC. We divided the esophageal lymphatic drainage into 3 groups based on the anatomic regions: cervical, thoracic or abdominal LN (Table 1). We then classified the patients into 4 categories: N0 (no region involved), N1 (1 region involved), N2 (2 regions involved) and N3 (3 regions involved). Subsequently, we used the revised N categories instead of the N stages in the 8th edition of the AJCC-TNM clinical staging system to determine the modified TNM stage, which was also classified into 5 homogeneous groups as I, II, III, IVA and IVB.

TABLE 3 Multivariate cox regression analyses of the prognostic factors for overall survival in patients with esophageal squamous cell cancer

Variables	Hazard ratio	95% CI	*P*
Age			
>60 vs ≤60	1.801	1.357-2.389	<.001
Sex			
Male vs female	1.494	1.123-1.986	.006
T stage (baseline, T4)			
T1	.087	.021-.365	.001
T2	.116	.077-.175	<.001
T3	.340	.252-.460	<.001
Revised N category (baseline, N3)			
N0	.064	.039-.106	<.001
N1	.147	.091-.236	<.001
N2	.532	.333-.850	.008
Treatment modality			
RT alone vs CRT	1.865	1.394-2.495	<.001

CI, confidence interval; CRT, chemoradiotherapy; RT, radiotherapy.

According to the Clinical Staging Criteria for Esophageal Cancer Treated with Non-surgical Methods proposed by an expert panel on behalf of the Non-surgical Esophageal Cancer Clinical Staging Group in China,[13] we mainly used CT for the diagnosis of metastatic lymph nodes. Lymphadenectasis is the criterion for cancerous metastasis. The general criterion is that the short-axis diameter of LN is more than 10 mm on the CT images, but if the long-axis diameter of the paraesophageal, tracheoesophageal sulcus, pericardial angle or abdominal LN is more than 5 mm, cancerous metastasis is also considered to be positive.

2.3 | Treatment protocols

External beam radiotherapy was performed with intensity-modulated radiation therapy or 3-D conformal radiotherapy in all patients. The primary esophageal gross tumor volume (GTV) and the involved LN (GTVnd) were defined according to imaging examinations and endoscopic findings. The clinical target volume (CTV) was created with a 2-4 cm margin in the superoinferior direction and 5-15 mm margins in the anteroposterior and lateral directions around the primary GTV. The planning target volume (PTV) was generated by adding a 5 mm margin to the CTV. The radiation dose delivered to PTV was 50-64 Gy in 25-32 fractions of 1.8-2.0 Gy per fraction. Radiotherapy was performed 5 times a week. Platinum-based chemotherapy with 5-fluorouracil was administered to patients in this study, with a focus on its integration with radiotherapy.

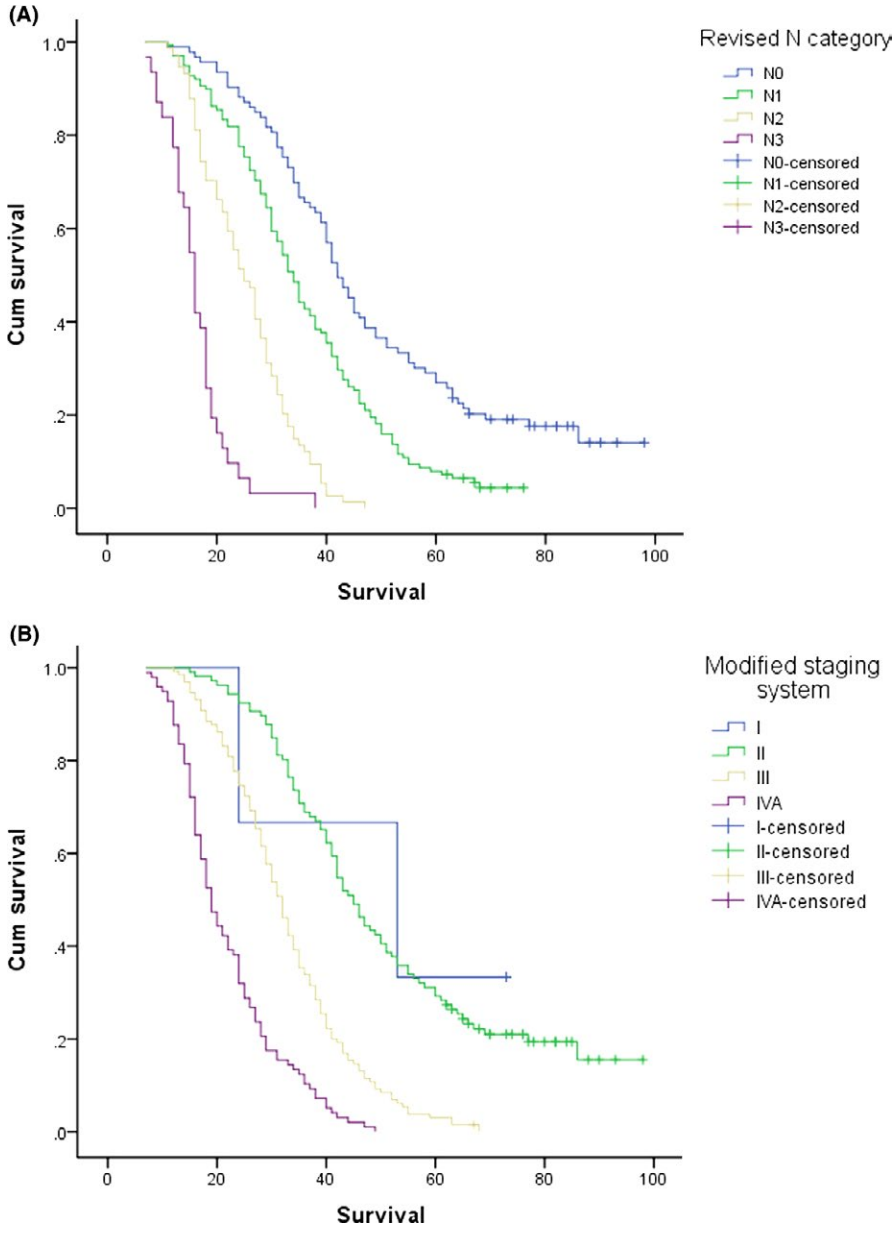

FIGURE 1 Kaplan-Meier survival curves for patients stratified on the basis of the revised N categories (A) and the modified staging system (B)

2.4 | Follow-up

In our study, all patients were followed up every 3 months for the first 2 years, every 6 months until 5 years, and then annually thereafter. The regular follow-up protocol included physical, laboratory, imaging and endoscopic examination for assessing recurrence or metastasis. Overall survival (OS) was defined as the time between the date of the beginning of radiotherapy and date of death or last follow-up. All patients were followed up by phone calls until the end of May 2018. Data of surviving patients were censored on the day of the last contact.

2.5 | Statistical analysis

The survival rate was calculated using the Kaplan-Meier method, and the log-rank test was used to assess the survival differences between groups. All variables that achieved significance ($P < .1$) in univariate analyses were enrolled in a multivariate Cox proportional hazards regression model. A 2-sided probability value of <.05 was considered significant. All statistical analyses were performed using SPSS 17.0 software (SPSS, Chicago, IL, USA).

3 | RESULTS

3.1 | Demographic and clinicopathological characteristics

A total of 336 patients (263 men and 73 women) with a median age of 63 years (range: 38-79 years) were enrolled in this study. Of these, 243 patients (72.3%) had LN metastasis. The median survival time was 32 months (range: 7-98 months), and the 3-year and 5-year OS rates were 40.2% and 11.3%, respectively. There were 23

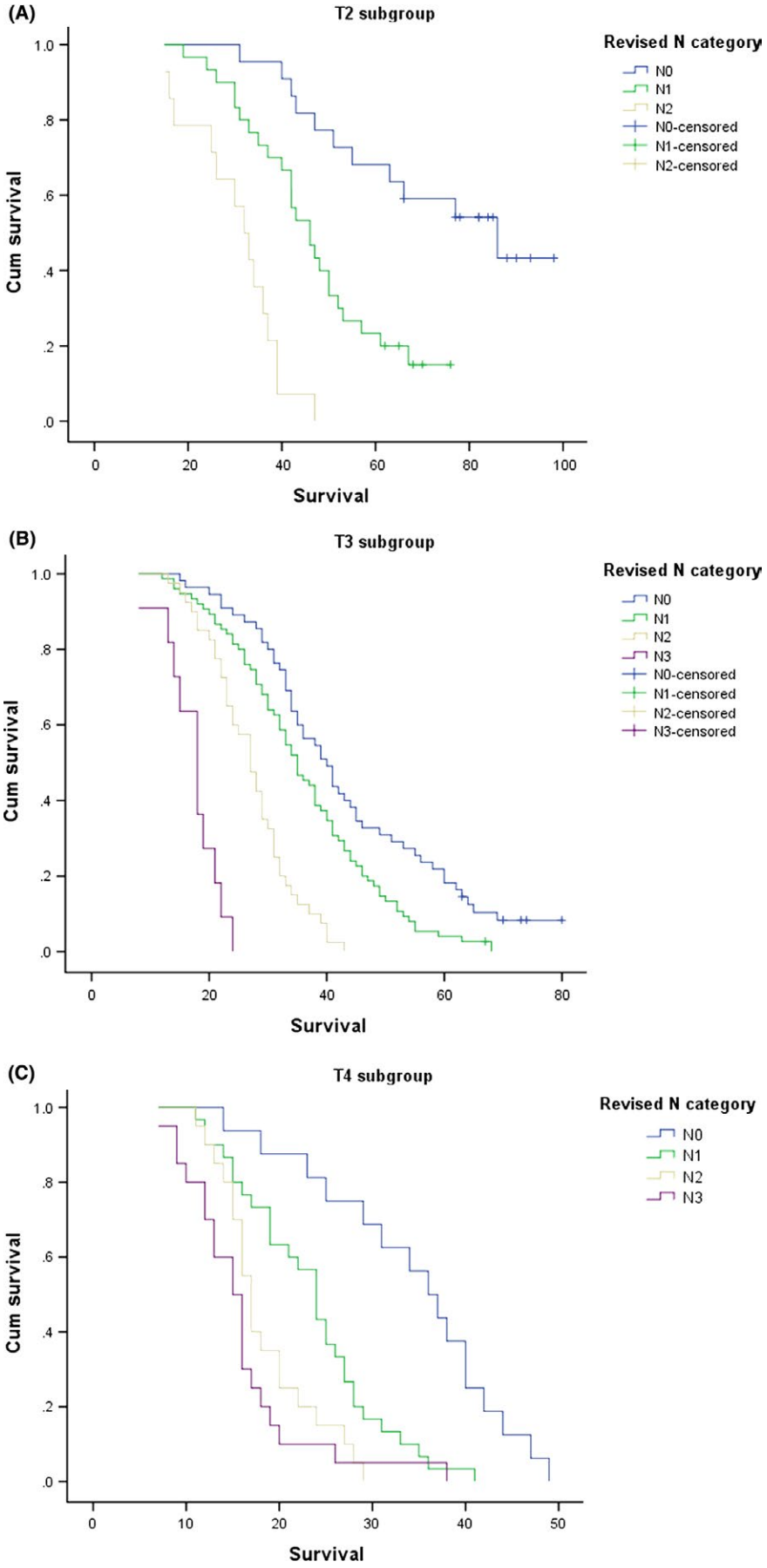

FIGURE 2 Survival curves for T2 (A), T3 (B) and T4 (C) patients stratified according to the revised N categories

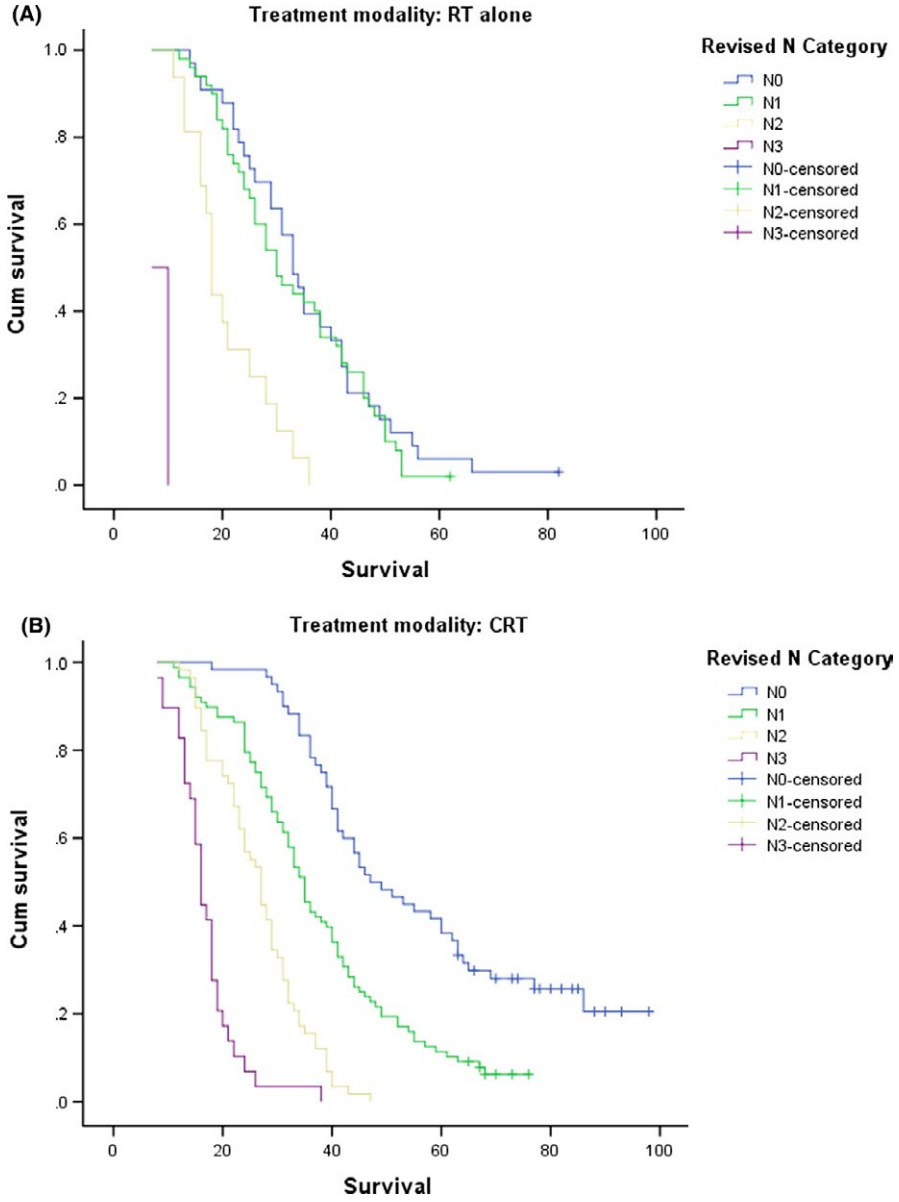

FIGURE 3 Survival curves for patients who underwent radiotherapy alone (A) and chemoradiotherapy (B) stratified according to the revised N categories

patients still alive at the end of follow-up. A total of 235 patients in this study received chemoradiotherapy, while the remaining 101 patients received radiotherapy alone due to old age, cardiopulmonary insufficiency, or refusal of chemotherapy for personal reasons. The clinicopathological characteristics of the patients are presented in Table 2.

3.2 | Univariate and multivariate analyses of prognostic factors

Table 2 also presents the results of the univariate analyses for 3-year OS. The T stage, revised N category, modified TNM staging system, age, sex and treatment modality were significantly associated with prognosis. Furthermore, multivariate analysis showed that T stage, revised N category, age, sex and treatment modality were independent risk factors, with the revised N category being the most significant variable affecting prognosis (Table 3).

Kaplan-Meier survival curve analysis based on the revised N category and modified TNM staging system indicated that they had good discriminatory ability in each subgroup ($P < .001$ for all; Figure 1A,B). Both showed a relatively ordered monotonic distribution of survival.

To evaluate the utility of the revised N category for predicting survival in different T stages, we performed a stratified analysis in the T2, T3 and T4 subgroups based on the 8th edition of the AJCC staging system. We excluded cases with T1 stage for subgroup analysis because the group size was too small (n = 3). In the T2 subgroup, survival could be distinguished between patients

with the revised N categories ($P < .001$; Figure 2A). Similar results were also observed in the T3 and T4 subgroup ($P < .001$ for all; Figure 2B,C).

Subsequently, we also explored the utility of the revised N category in patients who were stratified according to whether they received chemotherapy. These results showed that, in both the radiotherapy alone and chemoradiotherapy subgroup, survival could be well discriminated between patients with the revised N categories ($P < .001$ for all; Figure 3A,B).

Furthermore, considering that the condition of LN involved varied both in the revised N1 and N2 categories, we evaluated the survival differences between different anatomic regions of LN metastasis in the N1 and N2 subgroups. There were no differences in survival between patients with different anatomic regions of LN metastasis in either the N1 or N2 subgroup, which shows that the revised N categories are reasonable ($P = .747$ for N1 subgroup and $P = .769$ for N2 subgroup; Figure 4A,B).

4 | DISCUSSION

An accurate cancer clinical staging system is important for patient stratification, treatment protocol decisions, prognosis assessment and comparison of treatment efficacy from different institutions worldwide. Considering the status of LN metastasis is a critical prognostic factor for patients with EC.[14-16] In the 7th edition of the AJCC-TNM staging system, released in 2009, the node classification system was changed from being determined by the presence or absence of LN involvement to the number of metastatic LN; this appears to have more clinical significance than the criteria in the previous edition.[17-19] However, the 7th edition TNM staging for esophageal cancer is also pathological and not applicable for non-surgical EC. Clinically, surgery is not an option for many patients with EC who have a locoregional disease extension or are ineligible for surgery due to reasons such as older age or cardiopulmonary insufficiency. Some patients may also refuse surgery for personal reasons.

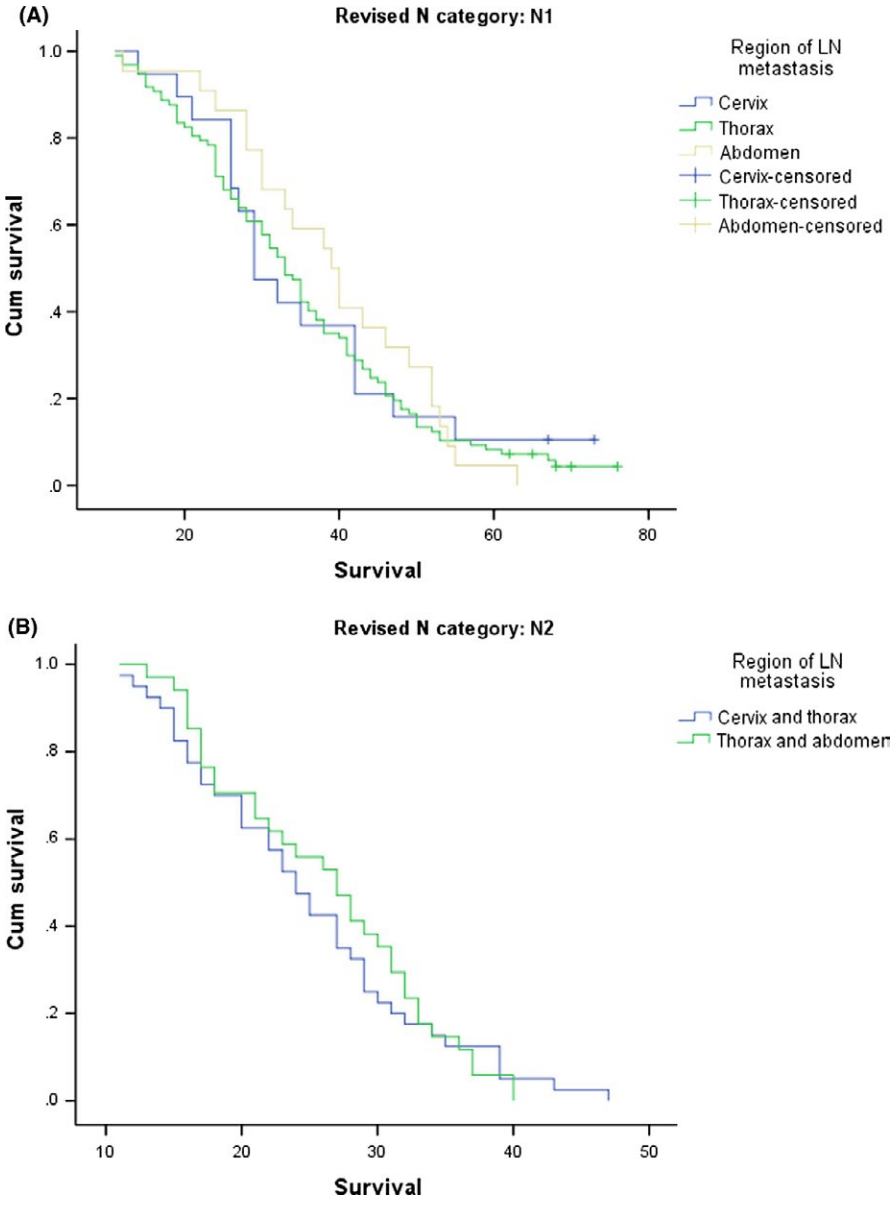

FIGURE 4 Survival curves for the revised N1 (A) and N2 (B) patients stratified by different anatomic regions of involved lymph node

Therefore, it is important to obtain an appropriate cancer clinical stage system for non-surgical EC.

To address this issue, the 8th edition of the AJCC-TNM staging system classified the clinical (c), pathologic (p) and postneoadjuvant pathologic (yp) stages separately, while the clinical stage is considered to be used for patients with non-surgical EC.[20-22] However, the N stage still uses the number of LN involved for classification despite the difficulty in accurately determining the number of involved LN without surgery. Another challenging factor is the high incidence of lymph node tuberculosis in China, which can often be confused with metastatic LN.[23]

In addition, several studies have reported that the 7th edition of the AJCC-TNM staging system, particularly the N stage, cannot clearly distinguish among different patient risk groups. A study by Chen et al[24] found no significant differences in survival between patients with pN2 and pN3 among 2011 patients with ESCC who underwent surgical resection. Another study by Yamasaki et al[25] also reported no significant differences in survival between pN2 and pN3 subgroups. Moreover, Ning et al[26] showed insignificant survival differences between not only N2 and N3 categories, but also between stages IIIB and IIIC based on the 7th edition of the AJCC-TNM staging system. Given that the 8th and 7th editions use the same standard for N stage, the 8th edition has similar issues. Therefore, we believe that the 8th edition of the AJCC-TNM staging system also needs further improvement and modification. Our study is useful in that it shows that both the revised N category and modified 8th edition of the AJCC-TNM staging systems have a distinctive and monotone relationship of stage group to overall survival for patients with ESCC who have undergone radiotherapy or chemoradiotherapy without surgery. Survival curves stratified according to the revised N category and the modified TNM staging system did not overlap. Further stratified analysis in the T2, T3 and T4 subgroups based on the 8th edition of the AJCC-TNM staging system also showed that the revised N category is useful. We found similar prognoses in patients with the revised N1 or N2 category that had different anatomic regions of involved LN.

Previous studies have also shown that the anatomic regions of LN metastasis (cervix, thorax and abdomen) can be a prognostic factor in patients with EC. Zhu et al[27] reported that nodal skip metastasis (NSM) was a common pattern of metastatic LN involvement in thoracic ESCC, but that the presence of NSM did not predict prognosis. Similarly, Cavallin et al[28] found that neither OS nor disease-free survival was associated with NSM occurrence in thoracic ESCC. Obviously, their studies were only focused on thoracic ESCC. Another study by Li et al[29] retrospectively reviewed 1361 patients with ESCC who underwent R0 esophagectomy to determine the pattern of LN metastasis and found that 31.2% of patients presented with 1 field involvement, 18.7% with 2 fields and 2.6% with 3 fields. Furthermore, An et al[11] reported that the fields of LN involved could predict the survival of patients with EC who underwent 3-field lymphadenectomy. Shimada et al[12] also investigated the significance of the extent of positive LN on long-term survival in patients with EC who underwent surgery and reported the following 5-year survival rates of patients with different extent of LN metastasis: 69% for none, 50% for 1 field, 29% for 2 fields and 11% for 3 fields of LN metastasis. The survival curves in our study also support that the revised N category and modified TNM staging system can better stratify patients, particularly patients with non-surgical ESCC. The revised N category divides the esophageal lymphatic drainage into 3 groups according to anatomic region, which is simple and practical, and the anatomical position is easy to determine; thus, it is suitable for clinical application.

To the best of our knowledge, this is the first study to propose a revised N category based on the anatomic regions of LN metastasis and a modified version of the 8th edition of the AJCC-TNM staging system in patients with non-surgical ESCC. Our study was conducted in 2 institutions, thus avoiding the possible limitations of a single-center setting and suggesting that our conclusions may be more generalizable. However, the present study has several limitations. First, this is a retrospective study with a relatively small patient size. Second, the small number of patients in some subgroups, especially in the T1 subgroup, may limit statistical power. Third, our study has relatively low 3-year and 5-year OS rates. Some patients cannot undergo surgery due to advanced stage or old age. Fourth, we did not compare the prognostic performance between the original N stage of the 8th edition of the AJCC-TNM staging system and the revised N category, due to the difficulty of accurately determining the number of metastatic LN without surgery. Fifth, we did not analyze the effect of histologic differentiation on prognosis in our study, as histologic grade could not be confirmed in some patients via biopsy only.

In summary, our findings strongly indicate that the anatomic regions of LN metastasis (cervix, thorax and abdomen) are appropriate as prognostic factors for non-surgical ESCC. Thus, we suggest that the N categories for non-surgical ESCC can be based on these anatomic regions and classified into the following 4 groups: N0 (no region involved), N1 (1 region involved), N2 (2 regions involved) and N3 (3 regions involved). The revised N categories and modified TNM staging system determined in this study can be used to fill gaps in the staging system for patients with non-surgical ESCC, which can help clinicians to make better treatment decisions and more effectively predict patient prognoses. Future large-scale studies are required to validate these results.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

ORCID

Jinming Yu https://orcid.org/0000-0001-5933-9912

REFERENCES

1. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health*. 2018;6:e555-e567.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115-132.
4. Chen W, Zheng R, Zuo T, Zeng H, Zhang S, He J. National cancer incidence and mortality in China, 2012. *Chin J Cancer Res*. 2016;28:1-11.
5. Rustgi AK, El-Serag HB. Esophageal carcinoma. *N Engl J Med*. 2014;371:2499-2509.
6. Law S, Wong J. Changing disease burden and management issues for esophageal cancer in the Asia-Pacific region. *J Gastroenterol Hepatol*. 2002;17:374-381.
7. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. *J Thorac Oncol*. 2017;12:36-42.
8. Rice TW, Apperson-Hansen C, DiPaola LM, et al. Worldwide Esophageal Cancer Collaboration: clinical staging data. *Dis Esophagus*. 2016;29:707-714.
9. Rice TW, Lerut TE, Orringer MB, et al. Worldwide Esophageal Cancer Collaboration: neoadjuvant pathologic staging data. *Dis Esophagus*. 2016;29:715-723.
10. Rice TW, Chen LQ, Hofstetter WL, et al. Worldwide Esophageal Cancer Collaboration: pathologic staging data. *Dis Esophagus*. 2016;29:724-733.
11. An FS, Huang JQ, Chen SH. Analysis of lymph node metastases of 217 cases of thoracic esophageal carcinoma and its impact on prognosis. *Ai Zheng*. 2003;22:974-977. (Article in Chinese).
12. Shimada H, Okazumi S, Matsubara H, et al. Impact of the number and extent of positive lymph nodes in 200 patients with thoracic esophageal squamous cell carcinoma after three-field lymph node dissection. *World J Surg*. 2006;30:1441-1449.
13. Expert Panel of Clinical Staging for Non-surgical Esophageal Cancer. Clinical staging criteria for esophageal cancer treated with non-surgical methods (draft). *Chin J Radiat Oncol*. 2010;19:179-180. (Article in Chinese).
14. Rice TW, Ishwaran H, Hofstetter WL, et al. Esophageal cancer: associations with (pN+) lymph node metastases. *Ann Surg*. 2017;265:122-129.
15. Purwar P, Bambarkar S, Jiwnani S, Pramesh CS. Prognostic significance of lymph node counts in operable esophageal cancer. *Ann Thorac Surg*. 2014;97:2229.
16. Chen J, Pan J, Zheng X, et al. Number and location of positive nodes, postoperative radiotherapy, and survival after esophagectomy with three field lymph node dissection for thoracic esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2012;82:475-482.
17. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17:1721-1724.
18. Hsu PK, Wu YC, Chou TY, Huang CS, Hsu WH. Comparison of the 6th and 7th editions of the American Joint Committee on Cancer tumor-node-metastasis staging system in patients with resected esophageal carcinoma. *Ann Thorac Surg*. 2010;89:1024-1031.
19. Talsma K, van Hagen P, Grotenhuis BA, et al. Comparison of the 6th and 7th editions of the UICC-AJCC TNM classification for esophageal cancer. *Ann Surg Oncol*. 2012;19:2142-2148.
20. Rice TW, Ishwaran H, Blackstone EH, et al. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016;29:913-919.
21. Rice TW, Ishwaran H, Hofstetter WL, et al. Recommendations for pathologic staging (pTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016;29:897-905.
22. Rice TW, Ishwaran H, Kelsen DP, et al. Recommendations for neoadjuvant pathologic staging (ypTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016;29:906-912.
23. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. *Lancet*. 2014;383:2057-2064.
24. Chen SB, Weng HR, Wang G, et al. Prognostic factors and outcome for patients with esophageal squamous cell carcinoma underwent surgical resection alone: evaluation of the seventh edition of the American Joint Committee on Cancer staging system for esophageal squamous cell carcinoma. *J Thorac Oncol*. 2013;8:495-501.
25. Yamasaki M, Miyata H, Miyazaki Y, et al. Evaluation of the nodal status in the 7th edition of the UICC-TNM classification for esophageal squamous cell carcinoma: proposed modifications for improved survival stratification: impact of lymph node metastases on overall survival after esophagectomy. *Ann Surg Oncol*. 2014;21:2850-2856.
26. Ning ZH, Wang ZG, Chen J, et al. Proposed modification of nodal staging as an alternative to the seventh edition of the American Joint Committee on Cancer Tumor-Node-Metastasis Staging System Improves the Prognostic Prediction in the Resected Esophageal Squamous-Cell Carcinoma. *J Thorac Oncol*. 2015;10:1091-1098.
27. Zhu Z, Yu W, Li H, et al. Nodal skip metastasis is not a predictor of survival in thoracic esophageal squamous cell carcinoma. *Ann Surg Oncol*. 2013;20:3052-3058.
28. Cavallin F, Alfieri R, Scarpa M, et al. Nodal skip metastasis in thoracic esophageal squamous cell carcinoma: a cohort study. *BMC Surg*. 2017;17:49.
29. Li B, Chen H, Xiang J, et al. Pattern of lymphatic spread in thoracic esophageal squamous cell carcinoma: a single-institution experience. *J Thorac Cardiovasc Surg*. 2012;144:778-785.

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