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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Lymph Node Station-Based Nodal Staging System for Esophageal Squamous Cell Carcinoma: A Large-Scale Multicenter Study

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ABSTRACT

Background. The American Joint Committee on Cancer (AJCC) nodal staging for esophageal squamous cell carcinoma (ESCC) has been defined by the number of metastatic lymph nodes (N system). However, the precise counting of individual positive lymph nodes is difficult and unreliable in some clinical settings, which calls for a more available and reliable system. This study examined the performance of a newly proposed nodal staging category, termed the S system, based on the number of metastatic lymph node stations.

Methods. Using the Kaplan–Meier method and Cox-regression analysis, this study retrospectively analyzed the overall survival (OS) of 2285 ESCC patients who underwent esophagectomy in three major China hospitals. Predictive models were constructed, and C-indices were computed to evaluate the discriminatory power of the S system, and to compare it with the N system.

Results. The categories defined by the S system were more homogeneous in terms of OS than those defined by the N system. Overall, the S system had a slightly better C-index ($p = 0.659$) than the N system (($p = 0.658$). Subgroup analyses also showed that the C-index of the S system was slightly better than that of the N system for each subgroup of sex and age, but the two were comparable for each subgroup defined by the tumor location.

Conclusion. The S system demonstrated a competing prognostic performance compared with the current AJCC N system. Due to the relatively easy accessibility of the number of metastatic lymph node stations, the S system may offer an easier option for cancer staging without a loss of discriminative power.

Esophageal cancer, the sixth most common cause of death for males and the ninth most common cause of death for females worldwide, constitutes a major disease burden globally because of its poor prognosis.[1] The main histologic type of esophageal cancer is esophageal squamous cell carcinoma (ESCC), for which the choice of the initial treatment method is based on the stage of cancer at diagnosis.[2]

The most widely used system for cancer staging is the tumor-node-metastasis (TNM) system, maintained by the American Joint Committee on Cancer (AJCC) and the

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International Union for Cancer Control (UICC), which is based on the depth of tumor invasion (T), the lymph node (LN) status (N), and the presence of metastasis (M). In particular, LN status is considered one of the most important prognostic factors for patients with esophageal cancer.[3,4] The N category in the latest edition of AJCC TNM staging for esophageal cancer is defined based on the number of metastatic LNs as follows: N0 (no positive LNs), N1 (1–2 positive LNs), N2 (3–6 positive LNs), and N3 (> 6 positive LNs). These mirror the definitions of the N categories in the 7th edition of AJCC TNM staging for esophageal cancer and are considered superior to those from the 6th edition (N0: 0 LNs; N1: ≥ 1 LNs) for better stratification performance.[5,6]

Although the optimal extent of lymphadenectomy for esophageal cancer still remains controversial, the number of harvested LNs during the operation is critical for an accurate nodal staging.[7] As a result, the 7th edition of the AJCC/UICC staging system required at least 12 harvested nodes for accurate staging. Furthermore, the 8th edition requires an en bloc resection of LNs with connective tissues and an accurate counting of LNs.[8] However, in some clinical settings, the exact number of metastatic LNs is extremely challenging to obtain, especially when several positive nodes are fused together into the same macroscopic mass, or a single enlarged node is broken into several pieces during surgical resection.[9,10] It also is well known that the esophagus has a complex pattern of lymphatic metastases, and metastatic LNs located in one station have different characteristics than positive LNs scattered in different stations, even when the number of positive LNs is the same.[9,11,12] In fact, some previous studies have reported that the N staging strategy in the 7th or 8th edition of AJCC has failed to discriminate survival for N2- and N3-staged patients.[11–14]

Meanwhile, several studies have suggested that the number of metastatic LN stations may be a simpler and more reliable prognostic factor than the total number of metastatic LNs.[11,13,15] As a result, several authors have proposed a convenient nodal categorization system, termed the S system, based on the number of metastatic LN stations.[11,15] Specifically, the S system classifies cancer into S0 (0 LN stations), S1 (1 LN station), S2 (2–3 LN stations), and S3 (> 3 LN stations). Based on a small-scale study from a single center, the S system seems to show better prognostic performance than the latest AJCC/UICC N system.[11,15] Our study aimed to examine the performance of the S system using a large-scale study with 2285 patients who underwent surgical therapy for ESCC from three high-volume hospitals in China and to compare its efficacy and validity with those of the 8th edition AJCC/UICC N system.

METHODS

Subjects

We extracted data from all the ESCC patents who underwent esophagectomy between 2008 and 2012 in three tertiary esophagus centers: the West China Hospital, Shantou University Medical College, and Sun Yat-sen University Cancer Centre.

The inclusion criteria specified a pathologic diagnosis of ESCC, no reception of neoadjuvant therapy, no evidence of distant metastasis found before surgery, and achievement of radical (R0) resection. The exclusion criteria ruled out harvested LNs fewer than 12 (according to recommendation of the 7th edition of AJCC/UICC staging system for esophageal cancer), the presence of cervical esophageal cancer and observation of the esophagogastric junction, and death from early postoperative complications within 1 month after the operation.

This multicenter retrospective study was approved by the institutional review boards of all of the involved institutions. Informed consent was waived because of the study's retrospective nature.

Surgery and LN Identification

Esophagectomy was performed via the McKeown, Ivor Lewis, or left transthoracic approach depending on the location and extent of the tumor. Standard two-field (abdominal and thoracic) LN resection was performed for all the patients. Three-field LN dissection was not a common practice in the study centers, and cervical LN dissection was highly selected for patients with suspected cervical LN metastasis, assessed by preoperative computed tomography (CT) and ultrasound.

The LN stations were identified by surgeons during the operation according to the 7th edition of the AJCC TNM staging system for esophageal cancer. Lymph nodes were detached from the operative specimen by the surgeon or an associate at the backtable and subgrouped into stations 1 (cervical LN) to 20 (celiac LN).

All resected specimens, including the primary tumor and LNs, were examined and recorded by expert pathologists in a standard manner.[16] The S system classifies the cancer into S0 (0 LN stations), S1 (1 LN station), S2 (2–3 LN stations), and S3 (> 3 LN stations).

Follow-Up Evaluation

Postoperative follow-up visits were scheduled at 3-month intervals for the first 2 years, and then at 6-month intervals for the following 3 years. After that, follow-up visits were conducted annually until death or June 2016.

The OS was measured from the date of the operation to the date of the last follow-up visit or death from any cause, whichever occurred first.

Statistical Analysis

For the analyses, the Kaplan–Meier estimator, the log-rank test, and Cox regression models were used. Based on the Cox models, the hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated after adjustment for confounders such as age, gender, tumor differentiability, and tumor location. The C-index and the concordance between the observed survival and the model-based prediction also were used as a criterion for predictive performance: the higher, the better.

All analyses were performed using R version 3.0.2 (The R Project for Statistical Computing, www.r-project.org). The criterion for statistical significance was a two-sided p value lower than 0.05.

RESULTS

Patient Characteristics

This study analyzed 2285 ESCC patients (1805 [79.9%] males and 480 [20.1%] females) from three centers in China. The mean age of the patients was 59.0 ± 8.47 years. The patients' clinicopathologic characteristics are presented in Table 1. All the patients received radical esophagectomies with mediastinal and abdominal lymphadenectomies. Most of the tumors were located in the middle of the esophagus (58%), followed by the lower part (28%).

LN Status

Overall, 1137 (49.8%) patients had LN metastases. The median number of resected LNs was 19 (range, 12–78), whereas the median number of positive LNs was 0 (range, 0–39). The median number of harvested LN stations was 5 (range, 2–12), whereas the median number of metastatic LN stations was 0 (range, 0–10).

Figure 1a, b show the distributions of the number of resected LNs and LN stations for all 2285 patients. The rates of positive nodes within each of the stations are displayed in Fig. 1c. The upper thoracic tumors had a higher metastatic frequency of upper mediastinal nodes, and the lower thoracic tumors tended to involve abdominal LNs. Correlations between each nodal station involvement and tumor locations were assessed, and the findings showed that metastases of stations 3p, 16, and 17 were significantly correlated with tumor locations ($p < 0.05$) (Fig. 1d).

Survival

The median follow-up period was 44.1 months. During the follow-up period, a total of 1082 deaths (47.4%) were observed. The 5-year OS rate estimated by Kaplan–Meier estimator was 44.3%.

Univariable Cox regression analyses showed that the effects of age, gender, tumor differentiation, T stage, N system, and S system all were significant (Table 1). We fitted two multiple Cox regression models, using N system and S system respectively as a major predictor, after adjustment for potential confounders such as age, sex, tumor differentiation, T stage, and location of tumors. The results indicated that the N system ($p < 0.001$) and the S system ($p < 0.001$) were significant predictors in their respective models.

Figure 1e, f show the Kaplan–Meier curves across different categories defined by the N system or the S system. Overall, the survival differed significantly across both the N categories ($p < 0.0001$) and the S categories ($p < 0.001$). Pairwise comparisons using the log-rank test all were significant at the 0.001 level even after adjustment for multiple comparisons.

Comparisons of Discriminative Performance Between the S System and the N System

Table 2 presents the number of patients in each group defined by the N and S systems. Figure 2 compares the discriminative power between the S and N systems. It appears that OS was more heterogeneous in the N categories than in the S categories. For example, in the S1 or S3 categories, survival did not differ significantly across the categories defined by the N system (S1 [$p = 0.461$], S3 [$p = 0.128$]). Only in the S2 subgroup were the survival differences significant across the categories defined by the N system ($p = 0.01$). In contrast, significant survival differences were observed across the categories defined by the S system for N1 ($p = 0.022$), N2 ($p = 0.047$), and N3 ($p = 0.028$). This result may indicate that the S system is more homogeneous for OS within each category than the N system.

We also examined the prediction accuracy of the N and S systems using the C-index, which gauges the concordance between the observed values and the model-based predictions. The C-index for the S system was slightly better than for the N system ($p = 0.659$ vs 0.658), indicating that the S system has competing predictive power compared with the N system.

Finally, we computed the C-indices across various subgroups of interest. Again, the S system had C-indices comparable with those of the N system for all ages, sexes, and tumor subgroups (Table 3).

TABLE 1 Patient characteristics and Cox regression analysis (n = 2285)

Variables	%	Univariable Cox model		Multivariable Cox model 1		Multivariable Cox model 2	
		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex							
Male	79.2	–		–		–	
Female	20.8	0.785 (0.672–0.917)	0.002	0.928 (0.793–1.086)	0.333	0.908 (0.776–1.062)	0.239
Differentiation							
Well	10.5	–		–		–	
Moderate	50.0	1.192 (0.960–1.478)	0.111	1.007 (0.810–1.251)	0.131	1.011 (0.814–1.256)	0.205
Poor	39.5	1.458 (1.171–1.814)	0.001	1.130 (0.904–1.413)	0.062	1.115 (0.891–1.394)	0.112
Adjuvant therapy							
No	63.1	–					
Yes	36.9	1.044 (0.923–1.182)	0.494				
T stage							
1	10.3	–		–		–	
2	17.7	1.580 (1.612–2.147)	< 0.001	1.278 (0.939–1.741)	0.119	1.277 (0.938–1.739)	0.121
3	63.8	2.721 (2.078–3.562)	< 0.001	1.966 (1.494–2.586)	< 0.001	1.933 (1.496–2.544)	< 0.001
4	8.2	4.065 (2.970–5.562)	< 0.001	2.607 (1.893–3.592)	< 0.001	2.549 (1.849–3.514)	< 0.001
N							
N0	54.9	–		–			
N1	26.3	2.001 (1.727–2.318)	< 0.001	1.849 (1.593–2.146)	< 0.001		
N2	15.0	3.264 (2.790–3.818)	< 0.001	2.934 (2.500–3.445)	< 0.001		
N3	3.9	5.071 (4.031–6.380)	< 0.001	4.516 (3.578–5.700)	< 0.001		
S							
S0	54.9	–				–	
S1	23.4	1.917 (1.645–2.234)	< 0.001			1.794 (1.537–2.094)	< 0.001
S2	18.9	3.218 (2.776–3.731)	< 0.001			2.872 (2.468–3.343)	< 0.001
S3	2.9	5.595 (4.337–7.218)	< 0.001			4.844 (3.743–6.269)	< 0.001
Tumor location (thoracic)							
Upper	14.0	–					
Middle	58.0	0.900 (0.761–1.063)	0.215				
Lower	28.0	0.881 (0.730–1.062)	0.184				
Age							
< 65	74.2	–		–		–	
≥ 65	25.8	1.210 (1.056–1.386)	0.006	1.280 (1.120–1.463)	0.011	1.265 (1.107–1.446)	< 0.001
Comorbidity							
Yes	42.6	–					
No	57.4	1.172 (0.930–1.517)	0.131				

HR hazard ratio, *CI* confidence interval

Validation of the S System for Patients With or Without Nodal Skip Metastasis Based on Tumor Location (Japan Esophageal Society Criteria)

In the Japanese nodal staging system, regional nodes are subgrouped into five patterns according to tumor location.[17] For the S system, the same as for the UICC system, the main tumor locations have not been considered. We further explored the effects of nodal skip metastasis on survival based on the S system. Within the S1, S2, and S3 categories, the OS was compared between patients with and without nodal skip metastasis according to the criteria of the Japanese Esophageal Society (JES).[17] The patients with and without nodal skip metastasis showed no significant survival differences within the S1, S2, and S3 stratifications (Table 4), indicating that the predictive power of the S system could not be compromised by the

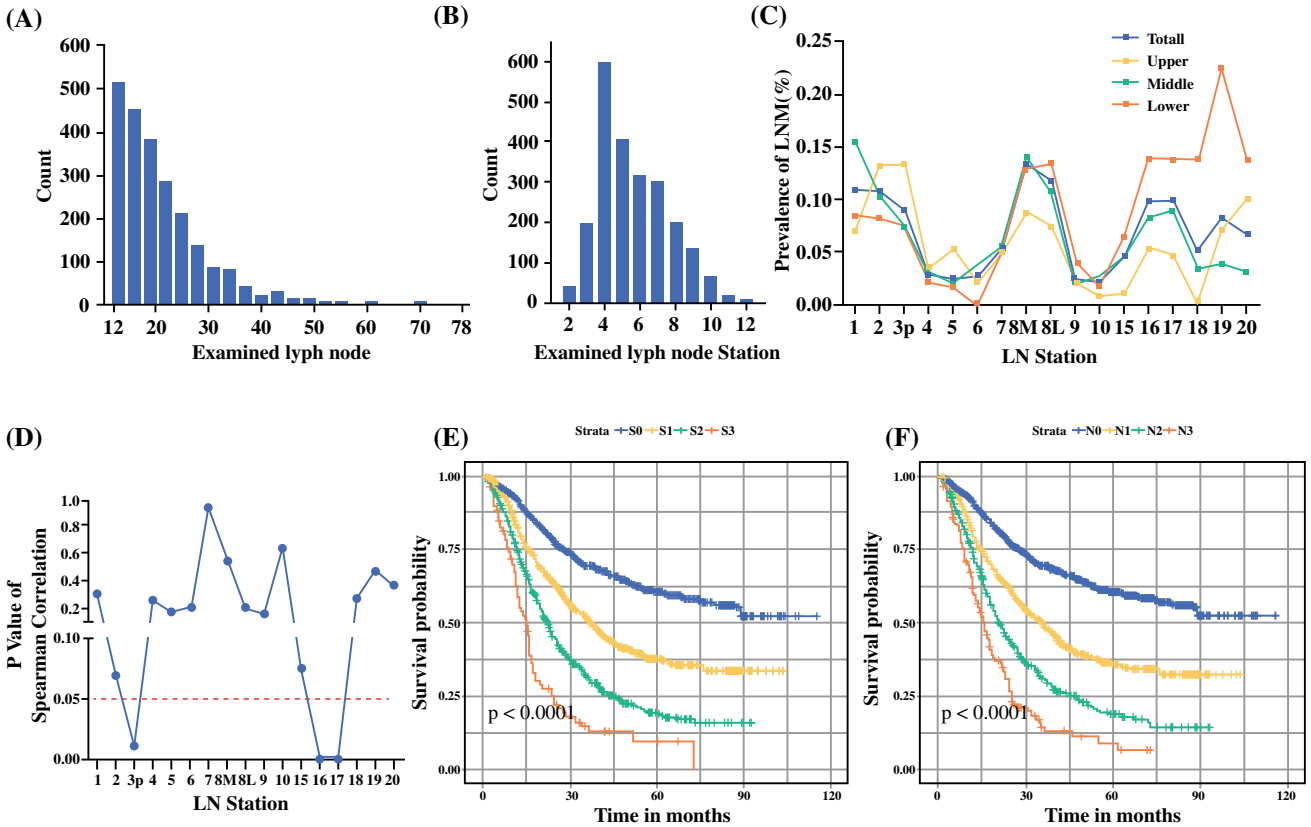

FIG. 1 **a** Distributions of the number of resected lymph nodes (LNs). **b** Distributions of the number of resected LN stations. **c** LN metastasis rate for each LN station. **d** Correlation between each LN station involvement and tumor location. **e** Kaplan–Meier curves for the N system. **f** Kaplan–Meier curves for the S system

TABLE 2 The number of patients presented in each category of the S and N systems

	S0	S1	S2	S3
N0	1148	0	0	0
N1	0	490	133	0
N2	0	58	310	29
N3	0	2	55	60

presence of nodal skip metastasis based on main tumor location.

DISCUSSION

An accurate, universally acceptable staging system is urgently needed for precision medicine and cancer treatment. An esophageal cancer staging system, the TNM system, has been periodically updated by the AJCC and UICC.

The latest TNM staging system for esophageal cancer, presented in the 8th edition of the *AJCC Cancer Staging Manual,* has been in effect worldwide since 1 January 2018.[8] It improves the 7th AJCC staging system in terms of OS prediction.[18] Although the T categorization has been revised, the definition for the N categories in the 8th AJCC system has remained the same as in the 7th edition AJCC system, which was based on the number of metastatic LNs.[19–21] However, there are several challenges with the LN-based staging system. First, regional LNs are defined as LNs from the neck to the abdomen.[8] Due to that broad coverage, survival may differ between patients whose metastatic LNs all are within one anatomic station and those whose LNs are found in several stations. Second, the LN-based staging system has been challenged in several studies for its predictive performance.[11,13,14,22] Third, counting the exact number of metastatic LNs during an operation is cumbersome and sometimes impossible.

To overcome these challenges, many studies have attempted to improve the N system by considering the LN ratio (LNR), the station ratio (SR), and the number of negative LNs.[13,22–24] With a focus on the extent of LN metastasis, LNR was defined as the ratio of the number of metastatic LNs to the number of total harvested LNs. However, although LNR has proved to be strongly associated with the long-term survival of esophageal cancer patients, its wide acceptance is hampered by a lack of consensus on defined cutoff points among various studies.[24–26] Moreover, the ratio-based nodal staging systems,

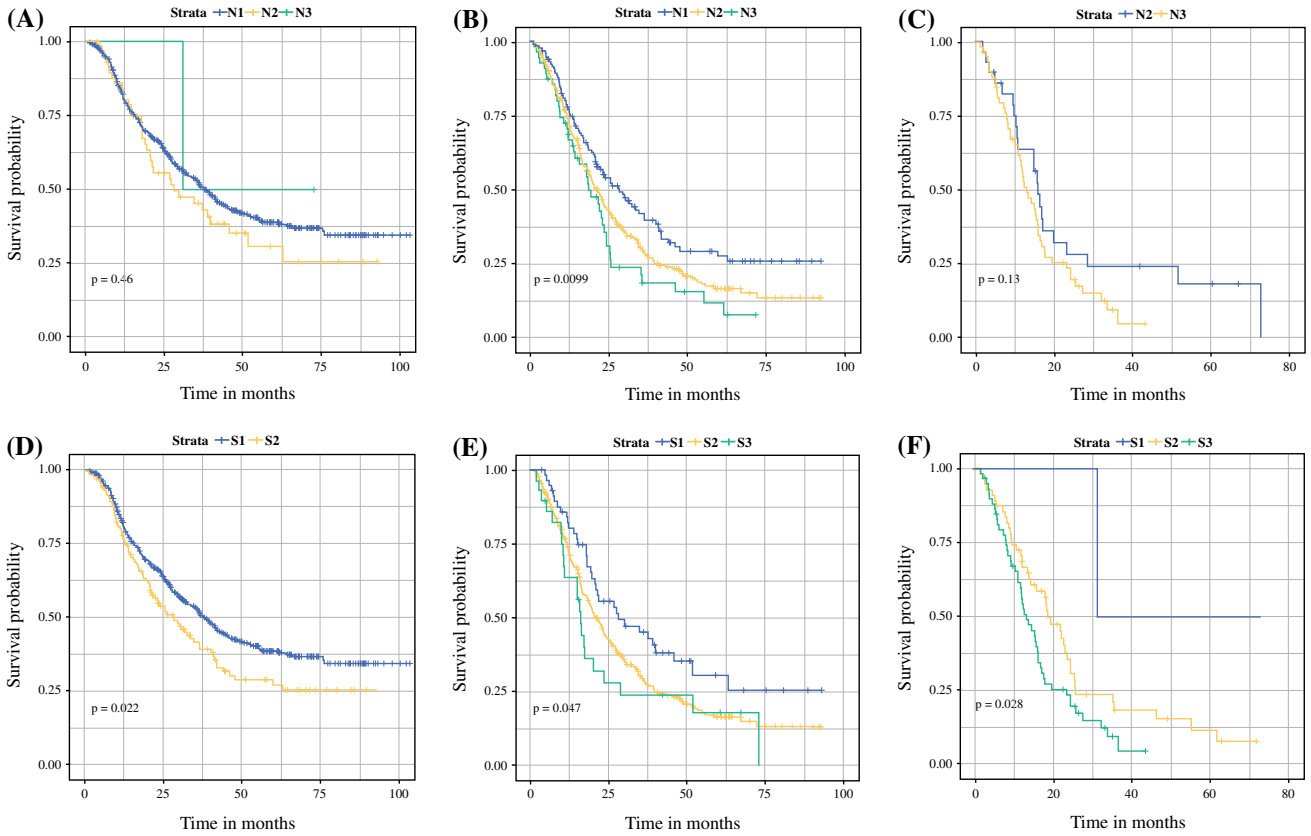

FIG. 2 Survival comparisons across S categories stratified by each N category, and across N categories stratified by each S category. **a** Kaplan–Meier curves for N1, N2, and N3 within the S1 category. **b** Kaplan–Meier curves for N1, N2, and N3 within the S2 category. **c** Kaplan–Meier curves for N1, N2, and N3 within the S3 category. Note that no N1 is available within S3. **d** Kaplan–Meier curves for S1, S2, and S3 within the N1 category. Note that no S3 is available within N1. **e** Kaplan–Meier curves for S1, S2, and S3 within the N2 category. **f** Kaplan–Meier curves for S1, S2, and S3 within the N3 category

TABLE 3 C-indexes for each subgroup

Variable	Subgroups	N system	S system
Sex	Male (n = 1825)	0.663 (0.010)	0.663 (0.010)
	Female (n = 460)	0.632 (0.022)	0.632 (0.022)
Age	< 65 (n = 1695)	0.651 (0.011)	0.652 (0.011)
	≥ 65 (n = 590)	0.657 (0.018)	0.658 (0.018)
Location of tumors (thoracic)	Upper esophagus (n = 320)	0.649 (0.023)	0.655 (0.023)
	Middle esophagus (n = 1326)	0.655 (0.012)	0.656 (0.012)
	Lower esophagus (n = 639)	0.673 (0.018)	0.669 (0.018)

Standard error (SE) shown in parentheses

such as LNR and SR (metastatic LN stations/examined LN stations), present a large possibility for stage migration. Patients with different numbers of metastatic LNs or LN stations might possess the same LNR or SR due to varying scopes of lymphadenectomy (standard vs extended; two-field vs three-field). Similarly, for patients with a fixed number of metastatic LNs or LN stations, a more extensive lymphadenectomy could lower the LNR or SR and result in overestimated survival. Meanwhile, using the number of negative LNs has, to some extent, similar caveats as using LNR.[23]

Recently, several authors have proposed the S system, a nodal staging system based on the number of metastatic LN stations for ESCC.[11,15] To the best of our knowledge, our study is the first to validate the S system using a large-scale multicenter study. We observed a significant difference in survival for each category defined by the S system within each category of the N system, but not vice versa. More

TABLE 4 Comparisons of *p* values for survival between patients with and without nodal skip metastasis

Tumor location	S1	S2	S3
Overall	0.647	0.231	0.413
Upper thoracic	0.926	0.223	0.210
Middle thoracic	0.577	0.211	–
Lower thoracic	0.736	0.993	–

Japan Esophageal Society criteria stratified by each S category. Note that there is no nodal skip metastasis for middle or lower thoracic cancer within the S3 category

specifically, within each of the N1, N2, and N3 subgroups, significant survival differences were observed across the categories defined by the S system. This suggested that the S categories might be more homogeneous in OS than the N categories, justifying the use of the S system.

Our results also indicated that the predictive performance of the S system category was comparable with that of the 8th AJCC/UICC N classification, and that the C-indices of the S system were comparable with those of the N system for various subgroups. This warrants more studies to investigate further the effects of tumor location in cancer staging.

Accurate clinical assessment of LNs is important in the selection of adequate treatment strategies for individual patients with esophageal cancer. However, the power of preoperative clinical diagnosis of LN metastasis still is far from ideal.[27,28] Evaluation of the current AJCC/UICC clinical N category relies heavily on imaging examinations, which often are impractical and unreliable, making the preoperative nodal staging system difficult to implement. Even for postoperative pathologic N staging, it might be difficult to count the actual number of metastatic LNs after surgery, especially in situations involving several metastatic LNs fused into one mass or one metastatic LN mechanically broken into pieces during lymphadenectomy.

On the other hand, the S system data can be obtained by positron emission tomography (PET) scans or by either endobronchial ultrasound-guided transbronchial needle aspiration (EBUSTBNA) or endoscopic ultrasound-guided fine-needle aspiration (EUSFNA). This system could be more straightforward, more measurable, and less invasive than counting metastatic LNs, which is required for the N system.

The Japanese Classification of Esophageal Cancer by the Japan Esophageal Society is another classification widely used for staging of esophageal cancer. Regional LNs are subgrouped according to tumor location, and the highest number of the LN group with metastasis is defined as the N category for the patient.[17] Given the complicated lymphatic spreading biology of esophageal cancer depending on tumor locations, the Japanese system seems more reasonable. However, the requirements of radical surgery with extensive LN dissection and a strict, detailed definition of LN stations were considered to be a large obstacle for surgeons from other countries. Because of its accessibility, the station-based nodal category may offer an easier option for cancer staging.

However, some limitations in the interpretation of our results must be mentioned. First, only a small number of patients were subjected to cervical LN dissection in this study, making it difficult to assess the validation of the S system for esophageal cancer patients undergoing radical three-field LN dissection. Second, we included squamous cell carcinoma exclusively. More patients with esophageal adenocarcinoma are needed to validate our findings. Third, this study focused on pathologic nodal staging for patients without neoadjuvant therapy. Further studies are required to determine whether this S system can be used for patients receiving neoadjuvant therapy.

CONCLUSION

In conclusion, based on a large cohort of ESCC patients, our analyses showed that the S system's prognostic performance competes with that of the current AJCC/UICC N system, justifying its readiness for implementation in clinical practice.

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DISCLOSURE There are no conflicts of interest.

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