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Impact of esophageal cancer staging on overall survival and disease-free survival based on the 2010 AJCC classification by lymph nodes

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This retrospective study investigated the effect of modifications presented in the seventh edition of the American Joint Committee on Cancer (AJCC) Manual for staging esophageal cancer on the characterization of the effectiveness of post-operative chemotherapy and/or radiotherapy, as measured by overall and disease-free survival. The seventh edition of the AJCC Manual classifies the number of lymph nodes (N) positive for regional metastasis into three subclasses. We used the AJCC classification system to characterize the cancers of 413 Chinese patients with esophageal cancer who underwent radical resection plus regional lymph node dissection over a 10-year period. The 10-year survival rate was 14.3% for stage N1 patients and 6.1% for stage N2 patients. Only one stage N3 patient was followed >4 years (53.4 months). The 10-year disease-free rate was 13.6% for stage N1 patients. Patients with stage N2 or N3 cancer were more likely to have tumor recurrences, metastases or death than patients with stage N1 cancer. Post-operative radiotherapy provided no survival benefit, and may have had a negative effect on survival. In this study, the N stage of esophageal cancer was an independent factor affecting overall and disease-free survival. Our results did not clarify whether or not radiotherapy after radical esophagectomy offers any survival benefit to patients with esophageal cancer.

Keywords: Esophageal cancer; prognosis; lymphatic metastasis; esophagogastric junction; survival analysis; chemotherapy; radiotherapy

INTRODUCTION

Esophageal cancer is one of the most common malignancies in China, with 11 mortalities per 100 000 in 2005 [1]. The current treatments for esophageal cancer have poor efficacy, and consequently the 5-year survival rates in the United States are 37% and 19% for localized and regional esophageal cancer, respectively [2]. The current treatment recommendations for esophageal squamous cell carcinoma are radical resection followed by radiotherapy and/or chemotherapy for patients with residual microscopic or macroscopic tumors. Chemoradiotherapy, chemotherapy and chemoradiotherapy followed by surgery are also standard treatment options for esophageal cancer. For patients undergoing complete resection (R0), the prognosis is influenced by the presence of regional lymph node metastases. The use of post-operative radiotherapy and/or chemotherapy is still controversial, with conflicting conclusions regarding effectiveness.

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The seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [2], which was published in 2010, modified the classification of esophageal cancer largely by changing the lymph node (N) categories. The seventh edition of the AJCC Manual is data-driven, and the esophageal cancer classifications were harmonized with those of gastric cancer. Accordingly, the groupings are for patients with esophageal and esophagogastric junction cancers. Previous editions of the AJCC defined positive regional lymph nodes as N1, which could include all positive lymph nodes. The seventh edition defines the N categories into three subclasses according to the number of positive lymph nodes, as follows: N1, one or two positive lymph nodes; N2, three to six positive lymph nodes; and N3, seven or more positive lymph nodes. These staging categories are used by physicians to determine whether post-operative therapy is required. Notably, a recent study showed that the new descriptors in the AJCC staging system were not significant prognostic factors, though the new descriptors did exhibit better performance [3].

Although the AJCC staging system does not define the minimum number of lymph nodes that should be examined for accurate staging, an analysis of the relationship between the total number of examined lymph nodes and death from esophageal cancer showed that at least 18 lymph nodes should be resected to accurately stage operable esophageal carcinoma [4]. This finding was in agreement with another study that showed at least 18 lymph nodes should be resected due to prognostic and treatment implications [5]. Similarly, the number of metastatic lymph nodes was shown to be an important factor affecting patient survival [6, 7].

We reviewed the clinical records of patients with esophageal cancer who underwent radical resection to retrospectively determine if the new staging system would have changed decisions regarding the use of post-operative chemotherapy and/or radiotherapy. We sought to clarify how N staging according to the new AJCC classification impacts overall survival (OS) and disease-free survival (DFS).

PATIENTS AND METHODS

Patients

In this study we retrospectively analyzed the medical records of 413 patients with esophageal cancer who were treated between June 1990 and December 2002 at the Cancer Center of Sun Yat-Sen University (Guangzhou, Guangdong, P. R. China). The study was approved by the Institutional Review Board of the Cancer Center of Sun Yat-Sen University, and informed consent was waived due to the retrospective nature of the study. Inclusion criteria for the study were: (1) patients with resectable thoracic esophageal cancer who underwent radical resection and regional lymph node dissection; (2) post-operative pathology demonstrating negative surgical margins; (3) pathologically confirmed mediastinal lymph node metastasis and cancer classified as T2-4N1-3M0 according to the seventh edition of the AJCC Cancer Staging Manual; (4) neoadjuvant therapy not performed before surgery; and (5) no severe concomitant diseases. The endpoints of the study were OS and DFS, with DFS defined as no recurrence, metastasis or death.

Therapy protocol

All patients with esophageal cancer underwent radical resection plus regional lymph node dissection. The esophageal cancers were characterized as follows: (1) location in the upper, middle or lower thoracic regions; (2) tumor size ≤5 cm or >5 cm; (3) tumor stage T2, T3 or T4; and (4) lymph node stage N1, N2 or N3 [9]. Textbooks of Chinese clinical medicine recommend post-operative therapy for patients with stage III esophageal cancer with metastases to the mediastinal lymph nodes, while no post-operative therapy is provided to patients with left gastric lymph node metastasis. Because no standard of care for radiation treatment following surgery exists in China, the physician makes an independent decision regarding post-operative treatment based on experience; thus, not all of the patients receive post-operative radiotherapy.

The median post-operative radiation dose was 50 Gy (range 46–50 Gy). The majority of patients received radiotherapy 2 months after surgery, which was delivered with a ^{60}Co or a linear accelerator (6–8 MV) to the supraclavicular lymph nodes, whole mediastinal lymph nodes and anastomotic regions. Radiotherapy was initially delivered in a single anterior field (total dosage to the irradiated area (DT), 36–40 Gy/18–20 f), then the field was changed to avoid the spinal cord. The radiation field included the mediastinal areas with metastases. In the middle supraclavicular area, a Cerrobend block was used, followed by boosted irradiation. In the mediastinal and anastomotic regions, bilateral horizontal fields or two slanted anterior fields were used for irradiation. The total radiation dose reached 46–50 Gy.

Statistical analysis

Continuous variables, which had non-normal distributions, were presented as the median with inter-quartile range (IQR; the range between the 25th and 75th percentiles). Category variables were presented as counts with percentages. The OS and DFS were calculated using the Kaplan–Meier method, and compared between groups using log-rank tests. The factors impacting OS and DFS were summarized as hazard ratios with 95% confidence intervals (CIs) in univariate and multivariate Cox proportional hazard models. The possible independent impact factors

with P values < 0.1 in the corresponding univariate Cox proportional hazard model were entered into the multivariate analysis. The significance level for the hypothesis test was set at 0.05. All statistical analysis was performed using the SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient demographic and clinicopathologic characteristics

There were 328 men and 85 women, with a median age of 57 years (range 25–79 years) included in the study (Table 1). Twenty-seven esophageal cancers were located in the upper thoracic area, 231 in the mid-thoracic area and 155 in the lower thoracic area. A total of 147 tumors were ≤5 cm and 266 were >5 cm in size. There were 121 stage T2 lesions, 289 stage T3 lesions and 3 stage T4 lesions. A total of 261 lesions were stage N1, 121 were stage N2 and 31 were stage N3. The median number of lymph nodes dissected was 9 (range 2–57). The median number of positive lymph nodes was 2 (range, 1–20). The proportion of positive lymph nodes among the total number of dissected lymph nodes was ≤20% in 199 patients, and >20% in 214 patients. All esophageal malignancies were squamous cell carcinoma, of which 8 were undifferentiated, 123 were poorly differentiated, 177 were moderately differentiated, 92 were well-differentiated and 13 were of unknown types.

Fifty-three patients received radiotherapy alone, 16 were treated with chemotherapy alone (primarily cisplatin (CDDP) regimens or regimens that included 5-fluorouracil) and 7 received chemotherapy followed by radiotherapy. The remaining 337 patients received no further treatment following surgery.

OS and DFS after surgery

The median post-operative follow-up was 35.4 months (range 0.3–171.6 months; IRQ 23.8–54.1 months). A total of 317 patients died during the follow-up period; 311 due

Table 1. Patient characteristics ($n = 413$)

Age[a] (years)		57.0 (50.0, 64.0)
Gender[b]	Male	328 (79.4%)
	Female	85 (20.6%)
Tumor location[b]	Upper thoracic	27 (6.5%)
	Middle thoracic	231 (55.9%)
	Lower thoracic	155 (37.5%)
Tumor size[b]	≤5 cm	147 (35.6%)
	>5 cm	266 (64.4%)
T stage[b]	2	121 (29.3%)
	3	289 (70.0%)
	4	3 (0.7%)
N stage[b]	1	261 (63.2%)
	2	121 (29.3%)
	3	31 (7.5%)
Number of positive lymph nodes[a]		2.0 (1.0, 3.0)
Number of lymph nodes dissected[a]		9.0 (6.0, 14.0)
Positive lymph nodes:lymph node dissected[b]	≤20%	199 (48.2%)
	>20%	214 (51.8%)
Pathologic grade[b]	Unknown	13 (3.1%)
	Highly differentiated	92 (22.3%)
	Moderately differentiated	177 (42.9%)
	Poorly differentiated	123 (29.8%)
	No differentiation	8 (1.9%)
Post-operative therapy[b]	No further therapy	337 (81.6%)
	Only radiotherapy	53 (12.8%)
	Only chemotherapy	16 (3.9%)
	Both radio- and chemotherapy	7 (1.7%)
Follow-up period[a] (months)		35.4 (23.8, 54.1)

[a]Data are expressed as median and inter-quartile range.
[b]Data are expressed by count and percentage.

to tumor recurrences or metastases, 1 due to radiation toxicity and 5 due to other causes. Of the 96 surviving patients, 22 had tumor recurrences or metastases. The median survival time was 20.0 months, and the 10-year survival rate was 11.0%. The median DFS was 13.0 months, and the 10-year DFS rate was 9.3%. Patients who did not receive post-operative therapy had a significantly better DFS rate than patients treated with radiation or chemotherapy ($P = 0.045$; Supplemental Fig. 1).

Based on the classification of the esophageal cancer according to the seventh edition of the AJCC tumor staging system, significant differences in OS were noted between patients with various N stages ($P < 0.001$) and DFS rates ($P < 0.001$) (Fig. 1). The median OS was 24.1, 15.0 and 12.5 months for stage N1, N2 and N3 disease, respectively. The 10-year survival rate was 14.3% for N1 stage and 6.1% for N2 stage disease. The median DFS was 16.0, 9.7 and 6.2 months for stage N1, N2 and N3 disease, respectively. The 10-year DFS rate was 13.6% for stage N1 disease. Patients with stage N3 disease had a 2-year OS rate of 28.1% and a DFS rate of 20.8%. Only 1 patient with stage N3 disease was followed >4 years (53.4 months).

Factors impacting prognosis

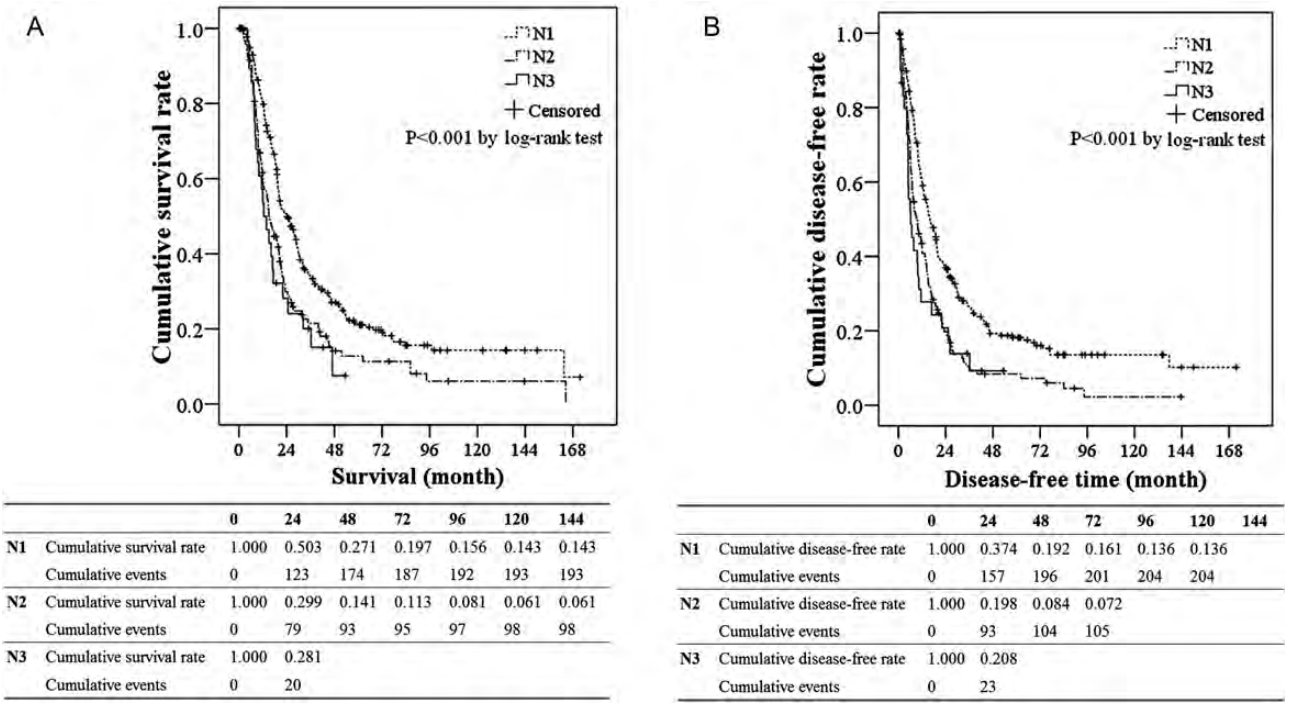
Univariate analyses showed that OS and DFS were significantly impacted by the number of positive lymph nodes, the ratio of positive lymph nodes to the number of lymph nodes dissected and the N stage (Table 2). Additionally, DFS was significantly impacted by post-operative therapy. The multivariate analysis did not include the number of positive lymph nodes and the ratio of positive lymph nodes to the number of lymph nodes dissected because these factors are co-linear with N stage.

The multivariate analysis that included T stage, N stage and pathologic grade showed that N stage alone was an independent factor affecting OS, while a multivariate analysis that included T stage, N stage and the use of radio- or chemotherapy versus no further therapy showed that N stage was the only independent factor affecting DFS (Table 3). Patients with stage N2 or N3 disease were more likely to have recurrences, metastases or death than patients with stage N1 disease.

Patients were also stratified by T and N stage to identify possible associations between post-operative therapy and the OS and DFS in the various stages (Supplemental Table). No stratification of T stage, N stage, or T and N stages revealed any significant difference in OS or DFS between patients with and without post-operative radio- or chemotherapy.

DISCUSSION

Our retrospective analysis of patients with esophageal cancer showed that N stage, based on the N stage classification introduced in the seventh edition of the AJCC Staging Manual [8], which subdivides positive lymph



		0	24	48	72	96	120	144
N1	Cumulative survival rate	1.000	0.503	0.271	0.197	0.156	0.143	0.143
	Cumulative events	0	123	174	187	192	193	193
N2	Cumulative survival rate	1.000	0.299	0.141	0.113	0.081	0.061	0.061
	Cumulative events	0	79	93	95	97	98	98
N3	Cumulative survival rate	1.000	0.281					
	Cumulative events	0	20					

		0	24	48	72	96	120	144
N1	Cumulative disease-free rate	1.000	0.374	0.192	0.161	0.136	0.136	
	Cumulative events	0	157	196	201	204	204	
N2	Cumulative disease-free rate	1.000	0.198	0.084	0.072			
	Cumulative events	0	93	104	105			
N3	Cumulative disease-free rate	1.000	0.208					
	Cumulative events	0	23					

Figure 1. Summary of overall survival (**A**) and disease-free survival (**B**) by N stage. One stage N3 patient was followed >4 years (53.4 months).

Table 2. Factors impacting OS and DFS by univariate Cox proportional hazard model

		OS		DFS	
		HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age (years)		1.008 (0.996, 1.021)	0.167	0.999 (0.988, 1.010)	0.827
Gender	Female	0.862 (0.655, 1.134)	0.287	0.979 (0.754, 1.270)	0.872
	Male	–		–	
Tumor location	Upper thoracic	–		–	
	Middle thoracic	1.045 (0.627, 1.743)	0.866	1.055 (0.659, 1.692)	0.822
	Lower thoracic	1.153 (0.684, 1.945)	0.593	1.146 (0.707, 1.857)	0.581
Tumor size	>5 cm	0.971 (0.772, 1.222)	0.802	1.119 (0.895, 1.399)	0.325
	≤5 cm	–			
T stage	2	–		–	
	3	1.033 (0.808, 1.319)	0.798	1.077 (0.850, 1.364)	0.541
	4	3.168 (0.998, 10.056)	0.050	2.646 (0.834, 8.398)	0.099
N stage	1	–		–	
	2	1.569 (1.230, 2.002)	<0.001*	1.659 (1.312, 2.098)	<0.001*
	3	1.877 (1.226, 2.876)	0.004*	1.913 (1.269, 2.881)	0.002*
Pathologic grade	Highly differentiated	–		–	
	Moderately differentiated	0.969 (0.722, 1.300)	0.833	0.909 (0.686, 1.205)	0.506
	Poorly differentiated	1.034 (0.757, 1.412)	0.836	0.990 (0.735, 1.333)	0.947
	No differentiation	2.078 (0.995, 4.336)	0.051	1.770 (0.851, 3.682)	0.126
Number of positive lymph nodes		1.076 (1.036, 1.117)	<0.001*	1.067 (1.030, 1.105)	<0.001*
Number of lymph nodes dissected		1.004 (0.986, 1.022)	0.661	1.012 (0.995, 1.028)	0.161
Positive lymph nodes:lymph nodes dissected	>20%	1.706 (1.364, 2.134)	<0.001*	1.580 (1.272, 1.961)	<0.001*
	≤20%	–		–	
Radio- or chemotherapy vs. no further therapy		1.233 (0.936, 1.623)	0.137	1.313 (1.005, 1.715)	0.046*

– indicates the reference group.
*Corresponding variable had a significant impact on OS or DFS.

nodes into three subclasses based on the number of positive lymph nodes, is an independent factor impacting OS and DFS. Patients with stage N2 or N3 disease were more likely than those with stage N1 disease to have recurrences and metastases. The number of positive lymph nodes, the ratio of positive lymph nodes to the number of lymph nodes dissected and N stage impacted OS and DFS, and DFS was affected by administration of post-operative therapy.

Previously, esophageal cancers with positive regional lymph nodes were classified as stage N1 cancers. However, in-depth studies have demonstrated that the number of positive lymph nodes plays a crucial role in the prognosis of cancer patients [4, 5, 7, 9]. Classifying esophageal cancers based on the number of positive lymph nodes has been a source of controversy [6, 10, 11]. In 2010, the AJCC modified the existing TNM and N staging systems to be based on the number of positive lymph nodes. This is the first study to show how the new AJCC N staging system may affect post-operative chemotherapy and/or radiotherapy for esophageal cancer, which in turn may impact treatment decisions. Other studies have also reported an overlap in the survival curves for patients with stage N2 and N3 cancers [3, 12]. Additionally, the lymph node ratio (the ratio of the number of positive lymph nodes to the number of dissected lymph nodes) has been shown to be the strongest predictor of death in patients with gastric cancer and esophageal carcinoma [13, 14]. Furthermore, the pathologic assessment of a minimum of 12 lymph nodes has been reported to provide sufficient prognostic information [15].

The high rate of tumor recurrence in the current study suggests that surgery alone may not be sufficient for treating patients with esophageal cancer who have positive regional lymph nodes. Theoretically, post-operative radio-

Table 3. Factors impacting OS and DFS by multivariate Cox proportional hazard model

		OS		DFS	
		HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
T stage	2	–		–	
	3	0.994 (0.770, 1.282)	0.960	1.009 (0.793, 1.283)	0.942
	4	2.737 (0.660, 11.349)	0.165	1.983 (0.615, 6.394)	0.252
N stage	1	–		–	
	2	1.530 (1.190, 1.968)	<0.001*	1.624 (1.282, 2.058)	<0.001*
	3	2.014 (1.292, 3.140)	0.002*	1.849 (1.222, 2.798)	0.004*
Pathologic grade	Highly differentiated	–			
	Moderately differentiated	0.995 (0.740, 1.337)	0.972		
	Poorly differentiated	1.064 (0.774, 1.463)	0.703		
	No differentiation	1.843 (0.876, 3.876)	0.107		
Post-operative therapy vs. no further therapy				1.189 (0.904, 1.564)	0.216

– indicates the reference group.

*Corresponding variable had a significant impact on OS or DFS.

The possible independent impact factors with a P-value < 0.1 in the univariate Cox proportional hazard models were entered into the multivariate analysis, except for number of positive lymph nodes and the ratio of positive lymph nodes to lymph nodes dissected. These were not included into the multivariate analysis because they are co-linear with N stage.

therapy may increase the local–regional control rate, which may be beneficial for survival; however, the clinical importance of radiotherapy following radical resection of esophageal cancer is controversial as most studies have shown that post-operative radiotherapy improves the local–regional control rate, but does not affect OS [16, 17], and may even shorten survival [17]. We suggest several possible reasons for the high recurrence rate in patients with stage N2 esophageal cancer. Specifically, the survival rate of patients with R0 radical resection may be reduced by post-operative radio- and chemotherapy, a post-operative radiation dose of approximately 50 Gy may result in toxicity to patients with advanced esophageal cancer and post-operative radiotherapy may reduce immune activity.

A meta-analysis [18] and a prior retrospective study [19] reported that pre-operative chemoradiotherapy improves the surgical resection rate, improves the local-regional control rate and leads to increased survival in patients with esophageal cancer. A study by Xiao *et al.* [20] showed that post-operative radiotherapy increased the 5-year survival rate, though the results did not reach statistical significance. In that study, among patients who received surgery alone, the 5-year survival rates were 14.7% for patients with positive lymph nodes and 13.1% for patients with stage III disease, while patients with positive lymph nodes and patients with stage III disease who received surgery plus radiotherapy had 5-year survival rates of 29.2% and 35.5%, respectively [20].

Esophageal cancer is associated with a high rate of regional recurrence following radical resection, with 32–45% of patients affected [21–25]. Mariette *et al.* [25] reported that >50% of patients who underwent a complete resection had recurrences; 12.1% regional recurrences, 20.5% lymph node recurrences and 19.8% distant recurrences. In Japan, a randomized trial (JCOG9907) [26] showed that patients with stage II or III esophageal cancer treated with pre-operative chemotherapy (cisplatin plus 5-fluorouracil) had a 5-year survival rate of 55%, which was higher than the 5-year survival rate of 43% for patients treated with post-operative chemotherapy (cisplatin plus 5-fluorouracil). Japanese patients with esophageal cancer have been reported to have 5-year survival rates of 80.0% after endoscopic mucosal resection, 21.9% with concurrent chemoradiotherapy, 30.3% with radiotherapy alone, 3.0% with chemotherapy alone and 46.6% with esophagectomy [27]. In the current study, the majority (approximately 81%) of patients did not receive post-operative treatment and the 10-year survival rates were 14.3% for patients with stage N1 disease and 6.1% for patients with stage N2 disease. Additionally, the 2-year survival rate for patients with stage N3 disease in the current study was 28.1%. Our findings do not clarify the value of post-operative radiotherapy for patients with stage N2 disease, as post-operative therapy had no effect on the OS rate when we considered all of the patients in the study ($P = 0.137$). Not all patients in the current study received post-operative therapy because no standard exists regarding post-operative therapy for patients with esophageal cancer in China. When we analyzed the 76 patients in our study who did receive post-operative therapy, we found no relationship between N stage and post-operative therapy ($P = 0.197$).

Pre-operative chemotherapy followed by radical surgical resection is considered standard care for patients with stage II or III esophageal cancer in Japan [28]. We did not investigate pre-operative chemotherapy and/or radiotherapy in this study. A larger study investigating the importance of pre-operative chemotherapy and/or radiotherapy therapy for esophageal cancer staged by the new AJCC N staging system is needed in China to help establish a standard treatment for esophageal cancer.

Our study was limited by its retrospective nature, the small sample size and by the small number of lymph nodes dissected (median of nine). Additionally, irradiation using a single anterior field with a ^{60}Co gamma-ray, bilateral horizontal fields, and two slanted anterior fields is now considered primitive. Furthermore, we did not evaluate local, regional and distant recurrence rates, which would better demonstrate the relationship between stage, recurrence and treatment.

In summary, N stage of the new AJCC classification was an independent factor affecting OS and DFS in esophageal cancer patients. The efficacy of radiotherapy in patients with esophageal cancer following radical esophagectomy is still uncertain, thus additional studies are needed.

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