

## ORIGINAL ARTICLE

# Should the clinical significance of supraclavicular and celiac lymph node metastasis in thoracic esophageal cancer be reevaluated?

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## Abstract

**Background:** Lower thoracic esophageal cancer (LTEC) with celiac node metastasis and upper thoracic esophageal cancer (UTEc) with supraclavicular node metastasis were previously categorized as M1a diseases. Our study aimed to investigate whether the clinical significance of supraclavicular and celiac lymph node metastasis should be reevaluated in thoracic esophageal cancer.

**Methods:** A total of 6178 patients with thoracic esophageal cancer were identified from the Surveillance, Epidemiology, and End Results (SEER) database during 2004–2015. Treatment strategies and outcomes (OS, overall survival; CSS, cancer-specific survival) of patients with different nodal status were reviewed. The Cox proportional hazards regression model was applied to evaluate the prognostic factors. Statistical analyses were performed in all subgroups.

**Results:** Multivariate analysis identified supraclavicular node metastasis but not celiac node metastasis as an independent predictor of both OS and CSS in LTEC. However, metastasis to supraclavicular or celiac nodes was not an independent predictor of OS and CSS in UTEc. Surgery was not associated with increased OS and CSS for UTEc with celiac or supraclavicular node metastasis but was favored as a predictor of better OS and CSS for LTEC with celiac or supraclavicular node metastasis. Radiotherapy benefited OS and CSS in LTEC involving celiac or supraclavicular nodes and in UTEc involving celiac nodes, while only OS benefited from radiotherapy in UTEc involving supraclavicular nodes.

**Conclusions:** These results provide preliminary evidence that the clinical significance of supraclavicular and celiac lymph node metastasis should be reevaluated in thoracic esophageal cancer with different prognostic information according to the primary sites.

## Introduction

Esophageal cancer is ranked as one of the most common digestive system cancers worldwide<sup>1,2</sup> and as the seventh most frequent cause of cancer-related death for males in the United States.<sup>3</sup> Surgical resection has been the mainstay of therapy for localized operable esophageal cancer.<sup>4</sup> However, the therapeutic strategies for patients with advanced-stage esophageal cancer remain controversial,

especially for those involving nonregional lymph nodes.<sup>5–8</sup>

The latest eighth edition of the Union for International Cancer Control–American Joint Committee on Cancer (UICC–AJCC) TNM staging system for esophageal cancer and the Eleventh edition of the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society (JES) are the two major classifications widely accepted for staging of

esophageal cancer.<sup>9–12</sup> However, these two major staging systems have not reached a consensus on the prognostic significance of regional and nonregional lymph node involvement in thoracic esophageal cancer, or more specifically on the implication of supraclavicular node metastasis. Recently, many Japanese surgeons have proposed that the supraclavicular nodes should be classified as regional ones for upper thoracic esophageal cancer (UTEC)<sup>5,8,13</sup> which was supported by some Asian and Western surgeons.<sup>14,15</sup> In fact, involvement of celiac lymph nodes (nodal station 20) was previously classified as metastatic (M1a) disease for lower thoracic esophageal cancer (LTEC) in the sixth edition of the AJCC staging system;<sup>5</sup> similarly, involvement of the supraclavicular lymph nodes (nodal station 1) was designated as M1a disease for UTEC.<sup>7,16</sup> However, in later editions of the AJCC staging system, celiac lymph nodes were redefined as regional ones for LTEC, whereas supraclavicular lymph nodes remained as nonregional ones for UTEC.<sup>16–19</sup> Subsequently, celiac node involvement was reclassified as nodal (N) disease, while supraclavicular node involvement remained as metastatic (M1) disease. Therefore, it is important to ask if supraclavicular and celiac node metastasis can be classified into the M and N staging parameters respectively, which definitely affects the treatment for esophageal cancer.

In the present study, we reevaluated the prognostic significance of supraclavicular and celiac lymph node metastasis and assessed the treatment strategies for patients with either metastasis using the Surveillance, Epidemiology, and End Results (SEER) database.

## Methods

### Patients and population cohort

The National Cancer Institute's SEER database was utilized for the present study with information of cancer patients.<sup>20</sup> Data for patients with esophageal cancer diagnosed between 2004 and 2015 were extracted from the SEER database with eligibility criteria as follows: (i) age older than 18 years and histologically confirmed cancer arising from the esophagus (ICD-O-3 codes: 8000–8576, 8940–8950, 8980–8981); (ii) primary tumor located in the upper or lower thoracic esophagus;<sup>21</sup> (iii) survival time  $\geq 3$  months. The Collaborative Stage Data Collection System codes at DX (Distant) and Lymph Nodes were used to query cases with celiac, supraclavicular or regional lymph node metastasis. All eligible patients were staged according to the sixth edition of the AJCC staging manual.<sup>22</sup>

### Statistical analysis

The primary outcomes were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the

interval between the diagnosis of cancer and death or last follow-up. CSS was measured from the date of initial treatment to death from esophageal cancer. Prognostic factors were compared by the log-rank test and Kaplan-Meier methods. The chi-squared test was used to compare categorical variables and Student's *t*-test was employed for continuous data. Multivariate analyses were performed by Cox regression. Hazard ratios (HR) with 95% confidence intervals (CI) were used to quantify the strength of the association between predictors and survival. All statistical analyses were performed using R software version 3.4.4 (Institute for Statistics and Mathematics, Vienna, Austria). A two-tailed *P*-value  $< 0.05$  was considered statistically significant.

## Results

### General information

The entire cohort consisted of 6178 patients with thoracic esophageal cancer, including 5803 patients with LTEC and 375 patients with UTEC. Table 1 lists the demographic parameters of all patients. Among patients with LTEC, there were 492 patients (8.5%) with supraclavicular lymph node involvement and 588 patients (10.1%) with celiac lymph node involvement. Among patients with UTEC, there were 25 patients (6.7%) with supraclavicular lymph node involvement and 27 patients with celiac lymph node involvement (7.2%).

### Status of lymph node metastases and survival rates

As shown in Figure 1a,b, the prognostic impact of different nodal status on UTEC was compared. In this subgroup, there was no significant difference in OS ( $P = 0.56$ ; Fig 1a) and CSS ( $P = 0.36$ ; Fig 1b) between UTEC with regional node metastasis and those with supraclavicular or celiac node metastasis. In contrast, Figure 1c,d presents the prognoses of LTEC stratified by nodal status. In this subgroup, significantly worse OS ( $P < 0.0001$ ; Fig 1c) and CSS ( $P < 0.0001$ ; Fig 1d) were observed in LTEC with supraclavicular node metastasis compared to those with regional or celiac node metastasis.

### Univariate and multivariate analysis of prognostic factors

As for the OS and CSS of LTEC, univariate analysis identified 13 significant risk factors, including nodal status (supraclavicular and celiac), surgery, chemotherapy and radiotherapy (Table S1).

**Table 1** Characteristics of patients in the entire cohort

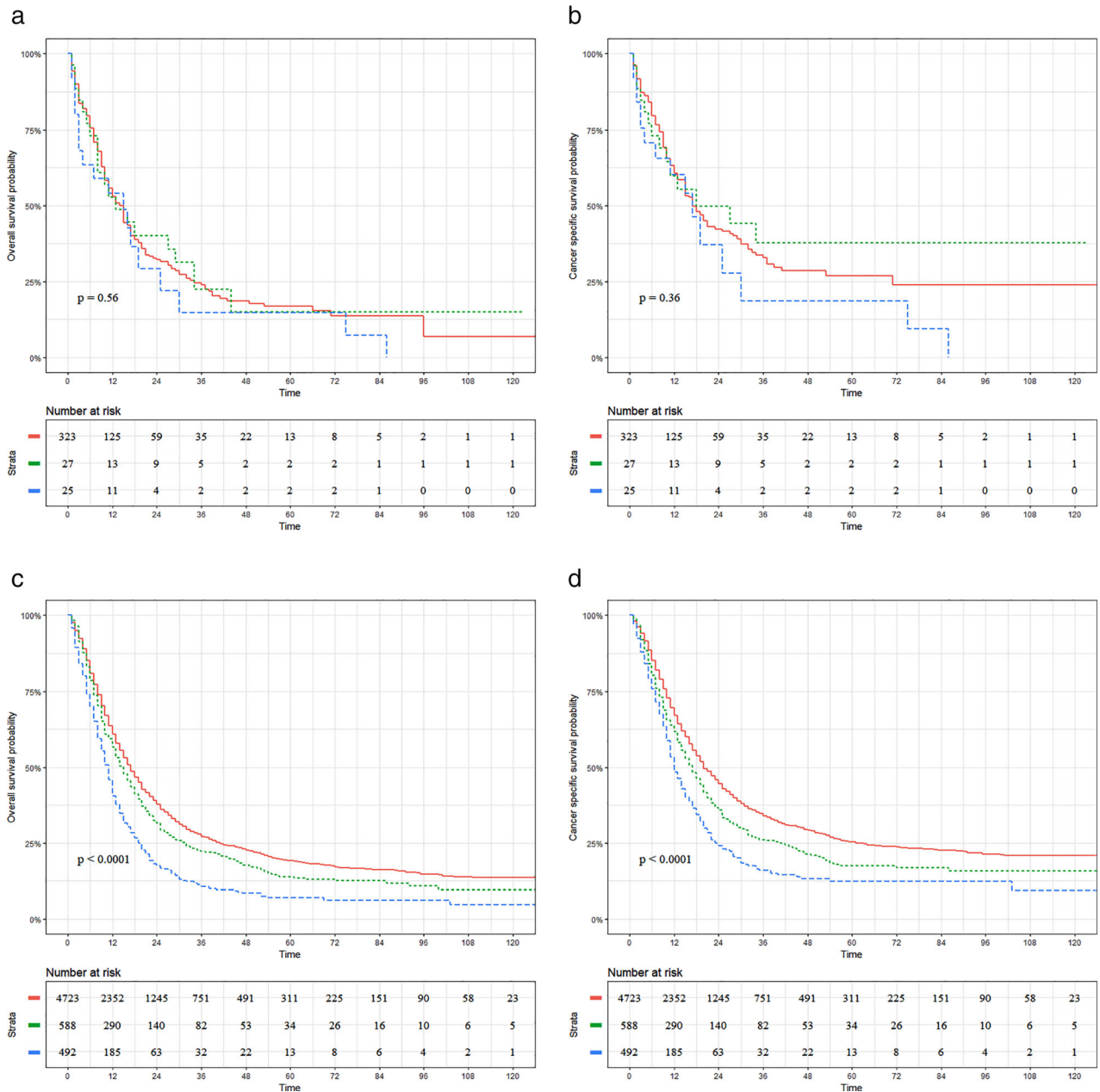
Clinicopathological characteristics Stratified by Site		Lower	Upper	<i>P</i>
Number of patients		5803	375	
Nodal status (%)	Regional node metastasis	4723 (81.4)	323 (86.1)	0.067
	Supraclavicular node (station 1) metastasis	492 (8.5)	25 (6.7)	
	Celiac node (station 20) metastasis	588 (10.1)	27 (7.2)	
Age at diagnosis (mean [SD])		64.83 (11.10)	65.35 (10.73)	0.377
Sex (%)	Female	816 (14.1)	119 (31.7)	<0.001
	Male	4987 (85.9)	256 (68.3)	
CHSDA region (%)	East	2224 (38.3)	163 (43.5)	0.167
	NP	743 (12.8)	39 (10.4)	
	PC	2594 (44.7)	161 (42.9)	
	SW	242 (4.2)	12 (3.2)	
Marital status (%)	Married (including common law)	3850 (66.3)	183 (48.8)	<0.001
	Separated/widowed/divorced	1159 (20.0)	117 (31.2)	
	Single (never married)	794 (13.7)	75 (20.0)	
Histology type (%)	Adenocarcinoma	4372 (75.3)	32 (8.5)	<0.001
	Squamous cell carcinoma	816 (14.1)	328 (87.5)	
	Others	615 (10.6)	15 (4.0)	
T stage (%)	T1	819 (14.1)	58 (15.5)	<0.001
	T2	805 (13.9)	50 (13.3)	
	T3	3544 (61.1)	169 (45.1)	
	T4	635 (10.9)	98 (26.1)	
N stage (%)	N0	2263 (39.0)	116 (30.9)	0.002
	N1	3540 (61.0)	259 (69.1)	
Tumor size (%)	≤5 cm	2562 (44.1)	169 (45.1)	0.809
	>5 cm	1603 (27.6)	106 (28.3)	
	Unknown	1638 (28.2)	100 (26.7)	
Surgery (%)	No	2949 (50.8)	325 (86.7)	<0.001
	Yes	2854 (49.2)	50 (13.3)	
Surgery type (%)	Esophagectomy	2827 (48.7)	44 (11.7)	<0.001
	Endoscopic treatment	27 (0.5)	6 (1.6)	
Radiotherapy (%)	No	1311 (22.6)	69 (18.4)	0.068
	Yes	4492 (77.4)	306 (81.6)	
Chemotherapy (%)	No/unknown	944 (16.3)	75 (20.0)	0.069
	Yes	4859 (83.7)	300 (80.0)	
Race (%)	White	5293 (91.2)	257 (68.5)	<0.001
	Black	277 (4.8)	72 (19.2)	
	Others	233 (4.0)	46 (12.3)	
Grade (%)	G1	240 (4.1)	22 (5.9)	0.002
	G2	2230 (38.4)	175 (46.7)	
	G3	3227 (55.6)	173 (46.1)	
	G4	106 (1.8)	5 (1.3)	
Diagnosed year (%)	2004–2009	2446 (42.2)	133 (35.5)	0.013
	2010–2015	3357 (57.8)	242 (64.5)	

CHSDA, Contract Health Service Delivery Areas; NP, Northern Plains; PC, Pacific Coast; SW, South West; SD, standard deviation.

In the multivariate analysis, supraclavicular node metastasis was shown to be a significant independent predictor of both OS (HR, 1.19; 95% CI: 1.06–1.34;  $P = 0.004$ ) and CSS (HR, 1.17; 95% CI: 1.02–1.33;  $P = 0.02$ ) for LTEC (Table S2). In addition, surgery (OS, HR: 0.47; 95% CI: 0.43–0.5;  $P < 0.001$ ; CSS, HR: 0.45; 95% CI: 0.42–0.49;  $P < 0.001$ ), chemotherapy (OS, HR: 0.58; 95% CI: 0.52–0.63;  $P < 0.001$ ; CSS, HR: 0.58; 95% CI: 0.52–0.65;

$P < 0.001$ ) and radiotherapy (OS, HR: 0.81; 95% CI: 0.74–0.88;  $P < 0.001$ ; CSS, HR: 0.81; 95% CI: 0.74–0.9;  $P < 0.001$ ) were independent predictors of prognoses.

For patients with UTEC, eight significant risk factors were identified in univariate analysis for OS and CSS (Table S3). Notably, neither supraclavicular nor celiac nodal location was an independent predictor of OS and CSS for UTEC.



**Figure 1** Prognostic impact of different nodal status on patients with thoracic esophageal cancer. (a) Overall Survival (OS) for upper thoracic esophageal cancer (UTEC) involving regional nodes (UR), supraclavicular nodes (U1) or celiac nodes (U20). (b) Cancer-specific survival (CSS) for UTEC involving UR, U1 or U20 nodes. (c) OS for lower thoracic esophageal cancer (LTEC) involving regional nodes (LR), supraclavicular nodes (L1) or celiac nodes (L20). (d) CSS for LTEC involving LR, L1 or L20 nodes.

In the multivariate analysis, surgery (OS, HR: 0.63; 95% CI: 0.42–0.95;  $P = 0.026$ ; CSS, HR: 0.6; 95% CI: 0.37–0.96;  $P = 0.034$ ) and chemotherapy (OS, HR: 0.37; 95% CI: 0.26–0.52;  $P < 0.001$ ; CSS, HR: 0.33; 95% CI: 0.21–0.51;  $P < 0.001$ ) were significant independent predictors of both OS and CSS for UTEC (Table S4).

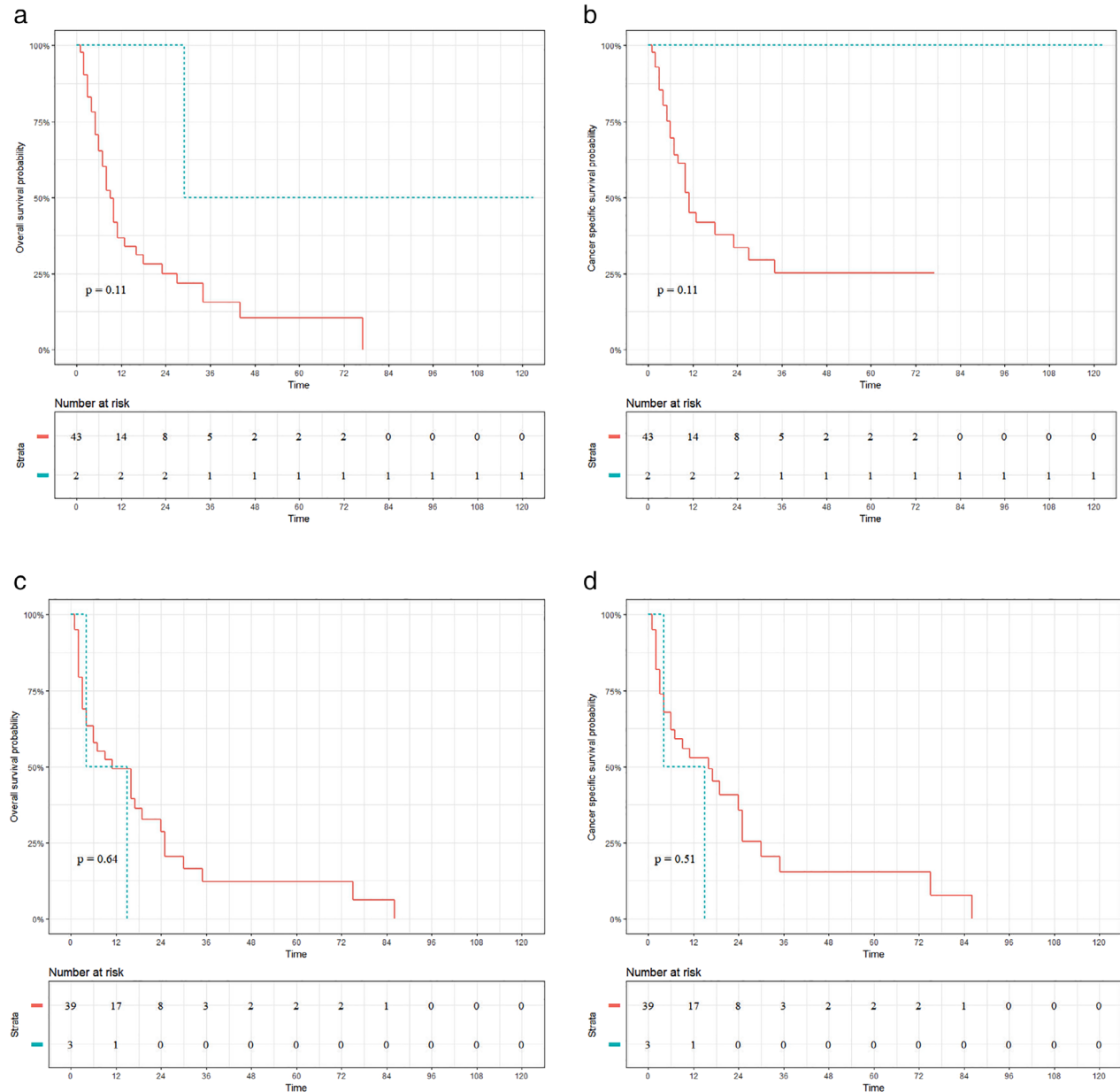
### Nodal status and therapeutic role of treatment

Figures 2 and 3 exhibit the therapeutic role of surgery in patients with UTEC (Fig 2a,d) and LTEC (Fig 3a,d). Surgery was not associated with increased OS (surgery vs. nonsurgery:

50.00% vs. 10.38%;  $P = 0.11$ ; Fig 2a) or CSS (surgery vs. nonsurgery: 100.00% vs. 25.11%;  $P = 0.11$ ; Fig 2b) for UTEC with celiac node metastasis. Similar results are displayed in Figure 2c,d which demonstrate that surgery did not improve the OS (surgery vs. nonsurgery: 0.00% vs. 12.20%;  $P = 0.635$ ) or CSS (surgery vs. nonsurgery: 0.00% vs. 15.30%;  $P = 0.513$ ) for UTEC with supraclavicular node metastasis. In contrast, significantly better OS (surgery vs. nonsurgery: 25.40% vs. 5.80%;  $P < 0.001$ ) and CSS (surgery vs. nonsurgery: 31.40% vs. 7.90%;  $P < 0.001$ ) were observed in

LTEC with celiac node metastasis, as shown in Figure 3a,b. In addition, surgery was also associated with increased OS (surgery vs. nonsurgery: 27.00% vs. 6.10%;  $P < 0.001$ ; Fig 3c) and CSS (surgery vs. nonsurgery: 42.70% vs. 9.10%;  $P < 0.11$ ; Fig 3d) for LTEC with supraclavicular node metastasis.

Figures 4 and 5 present the prognostic impact of radiotherapy on patients with UTEC (Fig 4a,d) and LTEC (Fig 5a,d), respectively. Significantly better OS (radiotherapy vs. nonradiotherapy: 17.20% vs. 0.00%;  $P < 0.001$ ; Fig 4a) and CSS (radiotherapy vs. nonradiotherapy: 15.60% vs. 0.00%;



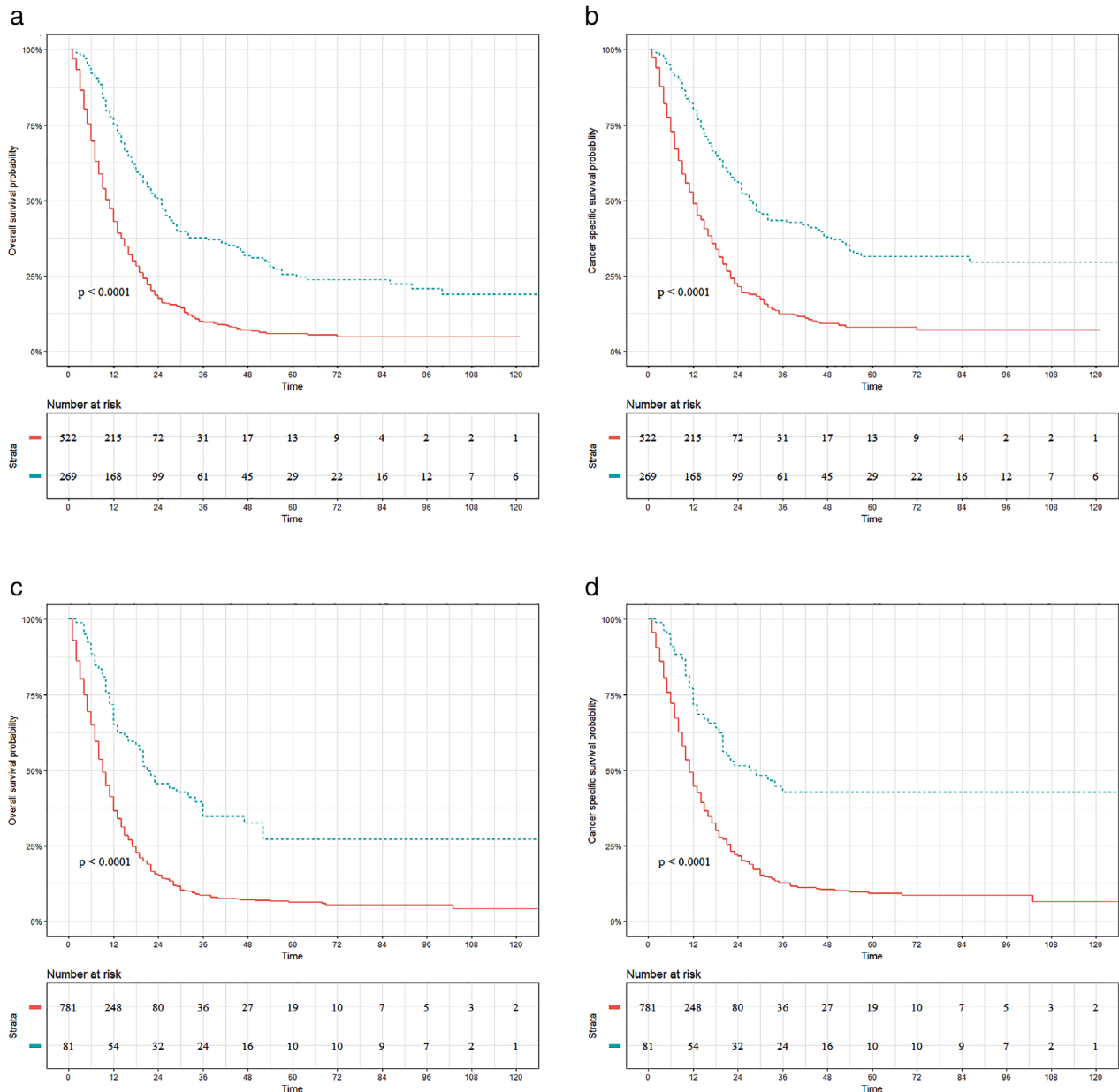
**Figure 2** Prognostic impact of surgery on patients with upper thoracic esophageal cancer (UTEC). (a, b) Overall survival (OS) and cancer-specific survival (CSS) for UTEC with celiac node metastasis. (c, d) OS and CSS for UTEC with supraclavicular node metastasis. (—) surgery=No, and (---) surgery=Yes.

$P < 0.001$ ; Fig 4b) were observed in patients with celiac node metastasis who underwent radiotherapy. Interestingly, there was a significant difference in OS (radiotherapy vs. nonradiotherapy: 15.90% vs. 0.00%;  $P = 0.012$ ; Fig 4c) but not in CSS (radiotherapy vs. nonradiotherapy: 17.70% vs. 0.00%;  $P = 0.075$ ; Fig 4d) between radiotherapy and nonradiotherapy in UTEC with supraclavicular node metastasis. Meanwhile, radiotherapy was associated with improved OS (radiotherapy vs. nonradiotherapy: 14.50% vs. 4.20%;  $P < 0.001$ ; Fig 5a) and CSS (radiotherapy vs. nonradiotherapy: 18.90% vs. 5.50%;  $P < 0.001$ ; Fig 5b) for LTEC with celiac

node metastasis. Similar results were also observed in LTEC with supraclavicular node metastasis (OS: radiotherapy vs. nonradiotherapy: 11.40% vs. 5.00%;  $P < 0.001$ ; Fig 5c; CSS: radiotherapy vs. nonradiotherapy: 14.90% vs. 11.90%;  $P = 0.004$ ; Fig 5d).

### Discussion

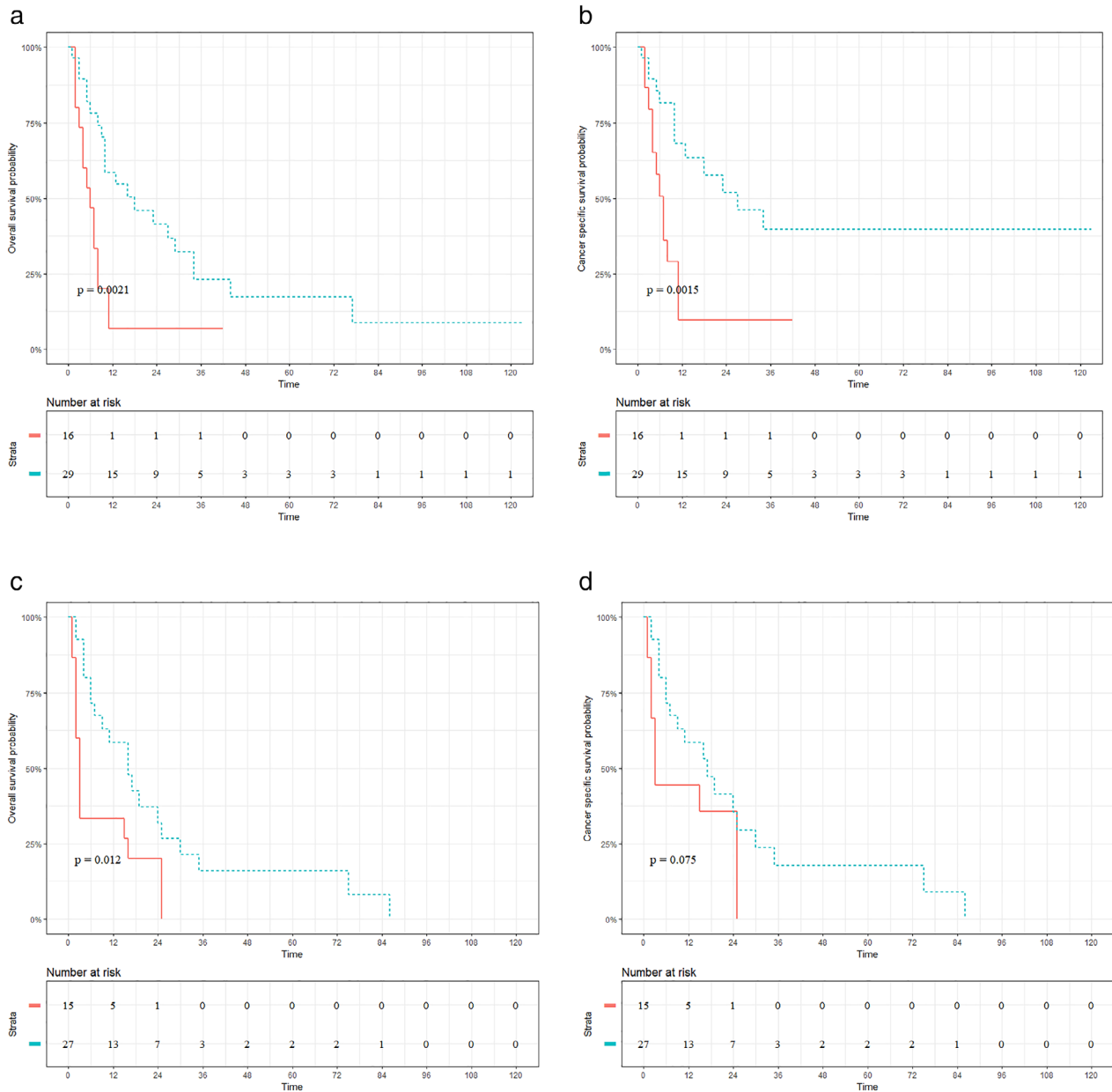
Despite progress in esophageal cancer staging systems, the sixth edition of the AJCC staging system has continued to be the most widely used in China. However, the



**Figure 3** Prognostic impact of surgery on patients with lower thoracic esophageal cancer (LTEC). (a, b) Overall survival (OS) and cancer-specific survival (CSS) for LTEC with celiac node metastasis. (c, d) OS and CSS for LTEC with supraclavicular node metastasis. (—) surgery=No, and (---) surgery=Yes.

prognostic impact and therapeutic strategies for esophageal cancer with supraclavicular node metastasis remain controversial. As mentioned above, the implication of supraclavicular node metastasis in the AJCC and JES systems is very different. The AJCC TNM classification defines lymph nodes located in the defined area as “regional lymph nodes” regardless of the tumor location. Metastasis to lymph nodes other than regional lymph nodes, especially supraclavicular nodes, is categorized as

M1.<sup>23</sup> In the latest JES classification, regional nodes are subgrouped into groups 1 to 4 in five different patterns according to the main tumor location.<sup>24</sup> In particular, supraclavicular nodes are classified as group 3 nodes for LTEC.<sup>24</sup> Because group 3 nodes are the most distant regional nodes, proposals for their selective dissection have been reported.<sup>25–27</sup> On the other hand, supraclavicular nodes are classified as group 2 for UTEC,<sup>24</sup> the dissection of which has been widely accepted in

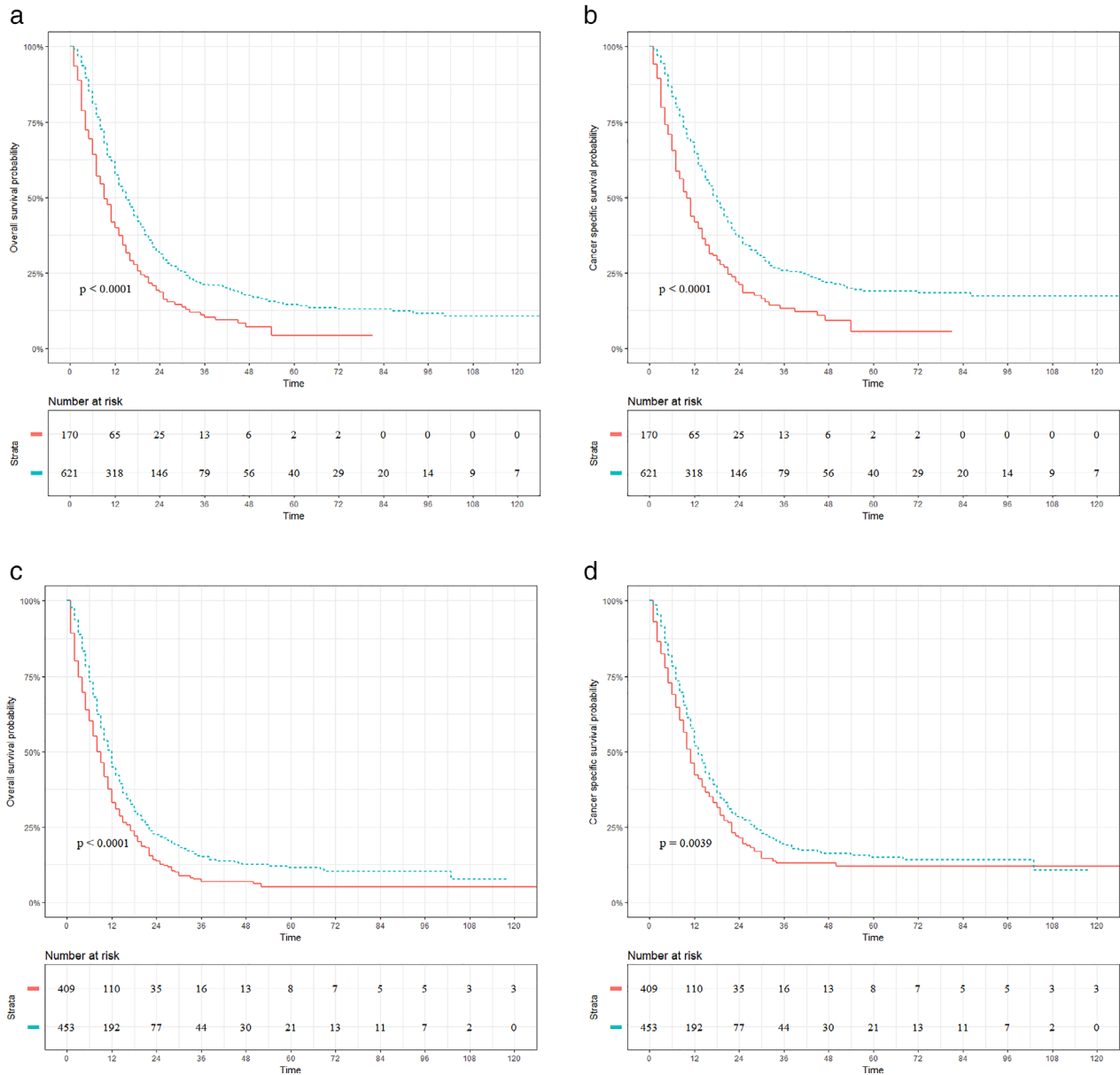


**Figure 4** Prognostic impact of radiotherapy on patients with upper thoracic esophageal cancer. (a, b) Overall survival (OS) and cancer-specific survival (CSS) for UTEC with celiac node metastasis. (c, d) OS and CSS for UTEC with supraclavicular node metastasis. (—) radiotherapy=No, and (- - -) radiotherapy=Yes.

Japan.<sup>9</sup> Our study revealed that the prognostic impact of supraclavicular node metastasis in UTEC was similar to that of regional or celiac node metastasis, which validates the subgrouping of regional nodes in the Japanese classification. Our study also coincides with a multi-institutional study in which the prognostic impact of supraclavicular nodes was similar to that of regional nodes for thoracic esophageal cancer.<sup>8</sup> Meanwhile, we showed that LTEC involving supraclavicular nodes resulted in significantly worse prognoses compared with those involving previously designated regional or celiac

nodes, which supports the reclassification of regional nodes.

Although the outcomes of LTEC with celiac node metastasis were relatively worse than those with regional node metastasis, our data revealed no statistically significance between them. Moreover, celiac node metastasis was not an independent predictor of worse OS and CSS in either UTEC or LTEC. Our findings justify the reclassification of celiac node metastasis into the N parameter in seventh and eighth editions of the AJCC staging system which is consistent with other studies.<sup>16,18,28</sup>



**Figure 5** Prognostic impact of radiotherapy on patients with lower thoracic esophageal cancer (LTEC). (a, b) OS and CSS for LTEC with celiac node metastasis. (c, d) OS and CSS for LTEC with supraclavicular node metastasis. (—) radiotherapy=No, and (---) radiotherapy=Yes.



Several studies<sup>7,19,29</sup> have reported that treatment on esophageal cancer with supraclavicular node metastasis has been mainly palliative but not curative. However, other studies have demonstrated that surgery can benefit the prognosis of thoracic esophageal cancer with supraclavicular node metastasis.<sup>5,6,18,28</sup> In addition, up to 20% of patients with supraclavicular node metastasis showed reasonable survival after chemoradiation and surgical resection.<sup>14</sup> From our data, surgery, chemotherapy and radiation were predictors of prolonged OS and CSS in both UTEC and LTEC, consistent with previous studies.<sup>8,14</sup> Meanwhile, our subgroup analysis indicated both surgery and radiotherapy were associated with better outcomes in LTEC with supraclavicular or celiac node metastasis. Our findings were also supported to some extent by studies which demonstrated that postoperative radiotherapy could not only improve the survival of stage II–III esophageal cancer irrespective of the tumor location, but also control local-regional LTEC with supraclavicular node involvement.<sup>2,30</sup> Given that surgery could not improve prognoses of UTEC with either supraclavicular or celiac node metastasis, radiotherapy nonetheless exhibited its value in improving prognoses of UTEC. Our data thus indicate different therapeutic strategies should be considered according to the primary location of esophageal cancer.

We must acknowledge several limitations of this study. First, potential biases were inevitable because of the retrospective nature of our study. Although some advanced statistical methods were applied to balance the covariates among the arms, there were still some latent biases. Another potential criticism of the present study is that most patients included with UTEC had squamous cell carcinoma, whereas the majority of patients with LTEC had adenocarcinoma. The different main histology types might affect the therapeutic roles of surgery and radiotherapy. Also, compared with those without surgical resection, fewer UTEC patients with celiac node or supraclavicular node metastasis received surgery, which might affect the statistical power of our results. Furthermore, in the present study, patients diagnosed with upper esophageal cancer were more likely to have T4 stage and were less likely to receive surgery, which means this entity might be treated with less curative intent. However, according to the NCCN guideline, even for those with inoperable disease, surgical resection can also be considered for select patients.<sup>31</sup> Moreover, the primary aim of this study was to evaluate the prognostic significance of supraclavicular and celiac lymph node metastasis. The large sample size of our study (especially those diagnosed with esophageal cancer located in the lower third) made our conclusion convincing. As a final comment, the SEER database could only provide a small number of thoracic esophageal cancer patients with

supraclavicular node metastasis who underwent surgery. Large-scale prospective randomized trials are needed to further validate our findings and better define the regional lymph nodes linked to tumor location.

In summary, our results provide preliminary evidence that the clinical significance of supraclavicular and celiac lymph node metastases should be reevaluated in thoracic esophageal cancer utilizing different prognostic information according to the primary sites.

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Jiayan Chen, Yuhuan Zhao and Di Liu carried out a formal analysis and validation. Wenjia Wang was responsible for the Methodology. Xinyan Xu and Chang Chen reviewed and edited the manuscript. Min Fan and Yongbing Chen were responsible for supervision, funding acquisition and also assisted in reviewing and editing the manuscript. The authors also wish to thank International Science Editing (<http://www.internationalscienceediting.com>) for editing the manuscript.

## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1.** Univariate analysis of overall survival and cancer-specific survival in patients with lower thoracic esophageal cancer.

**Table S2.** Cox proportional hazards regression model for overall

survival and cancer-specific survival in patients with lower thoracic esophageal cancer.

**Table S3.** Univariate analysis of overall survival and cancer-specific survival in patients with upper thoracic esophageal cancer.

**Table S4.** Cox proportional hazards regression model for overall survival and cancer-specific survival in patients with upper thoracic esophageal cancer.