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EUS–derived maximum tumor thickness and tumor shrinkage rate as independent prognostic factors in locally advanced esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy

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ABSTRACT

Background and Objectives: EUS–derived maximum tumor thickness (MTT) pre- and post-neoadjuvant chemoradiotherapy (NCRT) for locally advanced esophageal squamous cell carcinoma (LA-ESCC) indicates treatment response. However, the accuracy of predicting long-term survival remains uncertain. This study aimed to investigate the association between EUS-derived MTT pre- and post-NCRT and tumor shrinkage rate as well as long-term survival in patients with LA-ESCC receiving NCRT.

Methods: We retrospectively enrolled patients with LA-ESCC who underwent EUS examination from 2017 to 2021. Tumor shrinkage rate was the ratio of the difference between pre- and post-MTT to pre-MTT. The most fitted cutoff values were determined by the receiver operating characteristic curve. Univariate and multivariate Cox regression analyses and Kaplan-Meier curves were used to calculate overall survival (OS) and progression-free survival. Data from another center were also used for external validation testing.

Results: Two hundred thirty patients were enrolled. Of the patients, 178 completed the first EUS pre-NCRT and obtained pre-MTT, 200 completed the reexamined EUS post-NCRT and obtained post-MTT, and 148 completed both EUS and achieved tumor shrinkage. For all the patients, the 1- and 3-year OS rates were 93.9% and 67.9%, and progression-free survival rates were 77.7% and 54.1%, respectively. The median follow-up period was 30.6 months. Thinner post-MTT (≤8.8 mm) and EUS responder (tumor shrinkage rate ≥52%) were independently associated with better OS.

Conclusions: EUS–derived MTT and tumor shrinkage post-NCRT are independent prognostic factors for long-term survival and may be an alternative method for evaluating tumor response in patients with LA-ESCC after NCRT.

Key words: EUS; Esophageal neoplasms; Maximum tumor thickness; Neoadjuvant therapy

INTRODUCTION

Esophageal cancer is a major global health issue, ranking eighth in terms of incidence and sixth in terms of mortality.[1] It is more common in developing countries.[2] In locally advanced esophageal squamous cell carcinoma (LA-ESCC), neoadjuvant chemoradiotherapy (NCRT) is increasingly used. Neoadjuvant chemoradiotherapy has been demonstrated to improve the 10-year survival rate from 23% to 46% and increase the median survival time by 33.6 months compared with surgery alone.[3,4] Currently, NCRT followed by surgery is the standard treatment for LA-ESCC.[5] However, an appropriate strategy to determine the therapeutic effects of NCRT on the primary lesions of LA-ESCC has not yet been established. Computed tomography (CT) is used for preoperative assessment of esophageal carcinoma after NCRT. However, CT cannot be used in some cancers in luminal organs, such as the esophagus, unless its size is >20 mm.[6] In clinical studies, CT scan results for assessing the response to NCRT in esophageal cancer are inaccurate.[7] Meanwhile, EUS is a highly accurate method for the initial staging of local and regional tumors in locally advanced esophageal cancer.[8] After NCRT, EUS does not accurately assess the T stage because NCRT disintegrates and blurs anatomic structures

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because of inflammation, necrosis, and fibrosis.[9] Despite the destruction of the esophageal wall structure by NCRT, a high-frequency ultrasound transducer inside the esophageal lumen produces detailed images of the esophageal wall and the tumor close to the esophagus.[10,11] Moreover, the cross-sectional shrinkage and tumor length of esophageal cancer examined by EUS were reportedly related to the degree of postoperative pathological tumor retraction.[12,13] Therefore, this study used EUS to examine the maximum tumor thickness (MTT) and assess its potential usefulness as a method to clinically predict the long-term prognosis of patients with LA-ESCC receiving NCRT. Meanwhile, we explored the relationship between whether tumor infiltration breaks through the adventitia layer and prognosis.

SUBJECTS AND METHODS

Patient selection

The data of 321 patients with LA-ESCC who had received NCRT followed by surgery in Sichuan Cancer Hospital between May 2017 and June 2021 were retrospectively analyzed.

The inclusion criteria were as follows: patients with histologically confirmed resectable LA-ESCC (cT1b-T2,N+ or cT3-cT4a, any N; according to the eighth edition of the American Joint Committee on Cancer edition[14,15]), patients who had not received previous treatment, and a Karnofsky Performance Scale score of ≥80. The exclusion criteria were as follows: radiotherapy dose of <40 or >45 Gy (n = 19), incomplete clinical data (n = 5), presence of distant metastases (n = 11), postoperative pathological diagnosis confirmed as nonsquamous cell carcinoma (n = 2), died of postoperative complications (n = 4), lack of pre– and post–neoadjuvant EUS (n = 41), and other exclusion criteria (n = 9). In total, 230 patients with LA-ESCC who had received NCRT followed by surgery in Sichuan Cancer Hospital were included in the final analysis. Altogether, 73 patients with LA-ESCC who had complete data from the Cancer Hospital Chinese Academy of Medical Sciences from May 2001 to June 2012 were included for external validation [Figure 1]. In the later section, we used pre-MTT to represent the MTT before NCRT and post-MTT to represent the MTT after NCRT, and tumor shrinkage rate was the ratio of the difference between pre- and post-MTT to pre-MTT. Tumor shrinkage rate ≥52% was defined as responder according to the optimal cutoff value of the receiver operating characteristic (ROC) curve.

Written informed consents were obtained from all patients before treatment. This study was approved by the institutional review board of Sichuan Cancer Hospital & Institute (SCCHEC-02-2020-015) and performed in accordance with the principles of Declaration of Helsinki.

Treatment

Therapeutic regimen

Patients were treated with 2 cycles of chemotherapy regimen based on carboplatin in combination with paclitaxel, and the concurrent radiotherapy dose was 40 to 45 Gy with 1.8 to 2 Gy per fraction. All patients underwent McKeown or Ivor Lewis esophagectomy.

EUS measurements

Maximum tumor thickness was measured using EUS [Figure 2]. All patients were uniformly examined using a 7.5-MHz ultrasound lens. Our equipment is from OLYMPUS, the main unit models are EU-ME1 and EU-ME2, and the conductor models are GF-UE260-AL5. During the examination, we have a general idea of the extent of the tumor through endoscopic white light and ultrasound

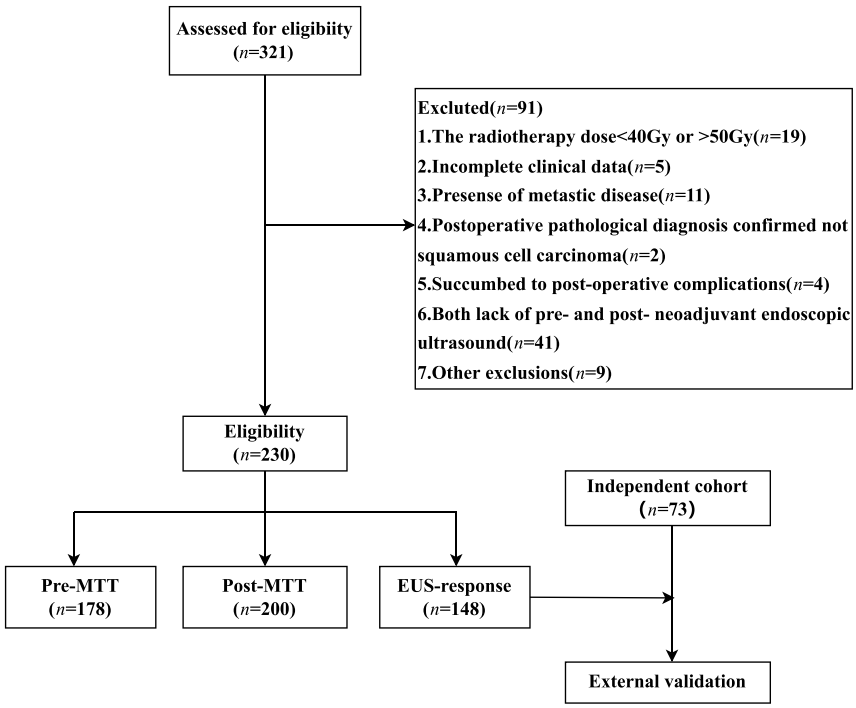

Figure 1. The study flow diagram. MTT, maximum tumor thickness; pre-MTT, pretreatment maximal tumor thickness; post-MTT, posttreatment maximal tumor thickness; tumor shrinkage rate, the ratio of the difference between pre- and post-MTT to pre-MTT.

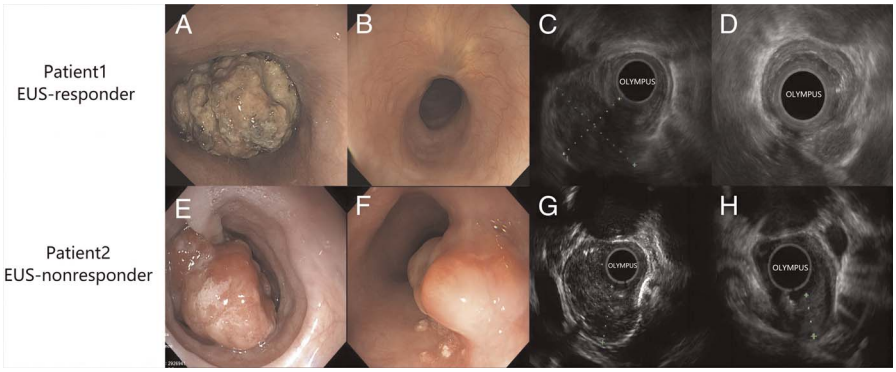

Figure 2. EUS measurement. A, B, C, and D were gastroscopy before treatment, gastroscopy after treatment, ultrasound before treatment, and ultrasound after treatment for patient 1, respectively; E, F, G, and H were gastroscopy before treatment, gastroscopy after treatment, ultrasound before treatment, and ultrasound after treatment for patient 2, respectively. EUS responder, tumor shrinkage rate ≥52%; EUS nonresponder, tumor shrinkage <52%.

probing, and then we start from the deepest part of the serration and perform a continuous circular scan from the bottom to the top, finally determining the largest cross-section. Patients received concurrent chemoradiotherapy after the first examination and were reexamined 1 to 4 weeks preoperatively. Under 2 unified and standardized operations by the physicians in the endoscopy center, the standardized measurement values (the distance between the retraction position and the incisors) and the tumor thickness imaged in the largest transverse tumor area were recorded for both inspections. To ensure that the tumor thickness measurement was performed at the same position, we reviewed the records, pictures, and videos of EUS examinations; screened and excluded cases with inconsistent planes between the 2 examinations; and ensured that the positions with the largest transverse tumor area in the posttreatment examination and initial examination were the same for thickness measurement and comparative evaluation. The experienced endoscopists independently analyzed the records and pictures. This facilitates quality assurance of the final enrollment data.

Statistical analysis

We calculated the values of the data of patients who possessed the pre-MTT and post-MTT and the regression rate separately and analyzed them separately. Data are expressed as mean ± SD. Multivariate Cox and logistic regression analyses were performed for variables with $P < 0.05$ in univariate analysis. Survival curves were constructed using the Kaplan-Meier (KM) method. Kaplan-Meier curves were calculated for overall survival (OS) or progression-free survival (months). Results of the Cox regression analysis and KM curve were summarized as hazard ratio (HR), 95% confidence intervals (CIs), and P value. Logistic regression data were summarized by odds ratio with 95% CIs. Statistical analysis was performed in SPSS (version 22.0; IBM Corp, Armonk, New York); data visualization was performed using the ggplot2 package in R software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). The P value reported was 2-sided, and $P < 0.05$ was considered significant.

RESULTS

Patient characteristics

According to the inclusion criteria, 230 patients were enrolled in the study. Seventy percent (161/230) were smokers, and 69.1% (159/230) were alcohol drinkers. The distribution of tumor locations was as follows: 13.5% (31/230) in the upper thoracic esophagus, 35.2% (81/230) in the middle thoracic esophagus, and 51.3% (118/230) in the lower thoracic esophagus. Clinical staging revealed that 7%, 20.9%, and 49.1% of patients were at stages II, III, and IVa. Following the initial EUS examination, patients were diagnosed with LA-ESCC and subsequently underwent NCRT. A second EUS examination was conducted after the completion of NCRT, with an average time interval of 40.7 days. Tumor pathologic complete response was obtained in 90 (39.1%) based on the surgical pathology results [Table 1]. The median follow-up time was 30.6 months. For all the patients, the 1- and 3-year OS rates were 93.9% and 67.9%, and progression-free survival rates were 77.7% and 54.1%, respectively [Figure 3]. An ROC curve was plotted to determine the optimal cutoff value. The best cutoff values of pre-MTT, post-MTT, and tumor shrinkage rates were established at 24 mm, 8.8 mm, and 52%, respectively. We predefined thinner post-MTT and thicker post-MTT as MTT <8.8 mm and ≥8.8 mm, and predefined responder and nonresponder as tumor shrinkage rates ≥52% and <52% (Supplementary Figures 1–3, http://links.lww.com/ENUS/A326; http://links.lww.com/ENUS/A327; http://links.lww.com/ENUS/A328).

Absolute MTT before NCRT

In total, 178 patients completed the first EUS before NCRT and obtained pre-MTT. An ROC curve was plotted to determine the optimal cutoff of the pre-MTT as 24 mm.

We used a cutoff value to transform the continuous variable of pre-MTT into a binary variable, including thinner pre-MTT and thicker pre-MTT. A univariate analysis was performed for all continuous and categorical variables (Supplementary Table 1, http://links.lww.com/ENUS/A330). Pre-MTT indicated no significant correlation with long-term survival ($P > 0.05$). However, we demonstrated that the pre-MTT was not a prognostic factor in patients with LA-ESCC.

Absolute MTT after NCRT

Pretreatment MTT was not associated with long-term survival. However, of the 200 patients who achieved the post-MTT, we used an optimal cutoff to transform the post-MTT into a binary

Table 1

Clinicopathological characteristics

Variables	All patients (*n* = 230)	Pre-MTT group (*n* = 178)	Post-MTT group (*n* = 200)	EUS response group (*n* = 148)
Age, y				
<65	158 (68.7)	122 (68.5)	138 (69.0)	102 (68.9)
≥65	72 (31.3)	56 (31.5)	62 (31.0)	46 (31.1)
Sex				
Male	199 (86.5)	151 (84.8)	173 (86.5)	125 (84.5)
Female	31 (13.5)	27 (15.2)	27 (13.5)	23 (15.5)
BMI, kg/m^2				
<18.5	18 (7.8)	14 (7.9)	15 (7.5)	11 (7.4)
18.5–24	136 (59.1)	104 (58.4)	119 (59.5)	87 (58.8)
>24	76 (33.0)	60 (33.7)	66 (33.0)	50 (33.8)
KPS				
≤80	202 (87.8)	156 (87.6)	176 (88.0)	130 (87.8)
80–90	28 (12.2)	22 (12.4)	24 (12.0)	18 (12.2)
Smoking				
No	69 (30.0)	56 (31.5)	57 (28.5)	44 (29.7)
Yes	161 (70.0)	122 (68.5)	143 (71.5)	104 (70.3)
Drinking				
No	71 (30.9)	58 (32.6)	60 (30.0)	47 (31.8)
Yes	159 (69.1)	120 (67.4)	140 (70.0)	101 (68.2)
Tumor location				
Upper	31 (13.5)	25 (14.0)	25 (12.5)	19 (12.8)
Middle	81 (35.2)	67 (37.6)	73 (36.5)	59 (39.9)
Lower	118 (51.3)	86 (48.3)	102 (51.0)	70 (47.3)
Time interval	40.8 ± 12.5	40.7 ± 11.6	40.8 ± 12.5	40.7 ± 11.6
Clinical T stage				
2	16 (7.0)	17 (9.6)	15 (7.5)	15 (10.1)
3	48 (20.9)	48 (27.0)	31 (15.5)	31 (20.9)
4	113 (49.1)	113 (63.5)	102 (51.0)	102 (68.9)
Unknown	53 (23.0)	0	52 (26.0)	0
t-PCR				
PCR	90 (39.1)	66 (37.1)	80 (40.0)	92 (62.2)
Non-PCR	140 (60.9)	112 (62.9)	120 (60.0)	56 (37.8)
Pre-MTT, mean ± SD, mm	16 ± 7	16 ± 7	15 ± 6	15 ± 6
Post-MTT, mean ± SD, mm	6 ± 6	6 ± 6	6 ± 6	6 ± 6
Tumor shrinkage rate, mean ± SD	0.6 ± 0.4	0.6 ± 0.4	0.6 ± 0.4	0.6 ± 0.4

BMI, body mass index; EUS response, tumor shrinkage ≥52%; KPS, Karnofsky Performance Status; MTT, maximum tumor thickness; PCR, pathologic complete response; post-MTT, posttreatment maximal tumor thickness; pre-MTT, pretreatment maximal tumor thickness; time interval, the time between the end of NCRT and reexamined; t-PCR, tumor pathologic complete response; tumor shrinkage rate, the ratio of the difference between pre- and post-MTT to pre-MTT.

variable, including thinner pre-MTT (≤8.8 mm) and thicker pre-MTT (>8.8 mm). The univariate analysis for all the continuous and categorical variables revealed a significant correlation between thinner pre-MTT and better long-term survival, and no other variables with $P < 0.05$ were recorded [Table 2]. The effect of post-MTT on long-term survival was significant ($P < 0.001$) in the univariate Cox regression analysis, with an HR of 0.35 (95% CI, 0.2–0.64). On average, every millimeter decrease in thinner post-MTT reduces the risk of death by 65%. The KM survival curves of thinner and thicker cells post-MTT are presented in Figure 4A. Overall survival had a significant difference between the 2 groups. For patients in the thinner group, the median OS was not achieved, whereas it was only 34.9 months for those in the thicker group. The univariate Cox regression analyses and KM curves indicated that a thinner post-MTT was independently associated with better OS. The prognostic power of the post-MTT was independent of confounding factors based on known major clinical prognostic factors [Table 2].

Tumor shrinkage rate as an independent prognosis factor

The univariate Cox regression analyses revealed a significant correlation between better long-term survival and responders (tumor shrinkage rate ≥52%) in 148 patients [Table 3]. A multivariate analysis was not performed because only the EUS responder had a $P < 0.05$ in the univariate analyses. The effects of responders in the univariate analysis demonstrated that a tumor shrinkage rate ≥52% was an independent prognostic factor as a dichotomous variable ($P < 0.05$). Moreover, the univariate Cox regression analyses indicated that EUS response was independently associated with better OS (HR 0.44; 95% CI, 0.239–0.86; $P = 0.016$). The KM survival curve analysis demonstrated significant survival discrepancies between the responder and nonresponder groups in Figure 4B. The median OS was not identified for the 2 groups. The survival curve demonstrated a lower likelihood of survival in the responder group than in the nonresponder group. The prognostic power of the EUS responders was independent of confounding factors based on known major clinical prognostic factors [Table 3].

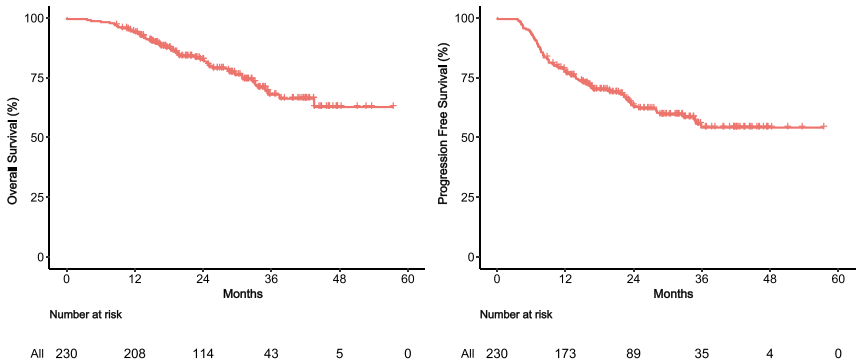

Figure 3. Overall survival and disease-free survival of all patients. A, The OS for all patients. B, The DFS for all patients.

External validation

We assessed the robustness of the conclusion that tumor shrinkage is an independent prognostic factor using external validation data sets from the Cancer Hospital Chinese Academy of Medical Sciences (n = 73). We defined the ratio of the difference between pre- and post-MTT to pre-MTT of greater than 52% as EUS responders. In the univariate and multivariate Cox regression analyses, the EUS responder status was confirmed as an independent prognostic factor and was associated with better OS ($P < 0.05$) (HR, 0.3; 95% CI, 0.1–0.88; $P = 0.029$) (Supplementary Table 3, http://links.lww.com/ENUS/A330). The KM survival curve analysis showed a significant difference in OS between responders and nonresponders (Supplementary Figure 4, http://links.lww.com/ENUS/A329).

Depth of the tumor

We performed a subgroup analysis to explore whether the depth of tumor infiltration beyond the esophageal adventitial layer on ultrasound before initial treatment correlated with regression rates and long-term prognosis after NCRT. Subgroup analysis was carried out by dividing the enrolled patients by ultrasonic T2–T3 and T4 staging; 68.9% (102/148) of patients in the responder and nonresponder groups were ultrasonic T4 staging. Among LA-ESCC patients with initial ultrasonic T2–T3 staging and T4 staging, no statistically significant differences were observed between the responder and nonresponder groups ($P = 0.082$; $P = 0.190$). The T staging-by-subgroup interaction was not statistically significant, indicating that tumor infiltration beyond the esophageal adventitial layer on ultrasound effect did not differ across the responder and nonresponder groups [Table 4].

DISCUSSION

Our study revealed 4 principal findings concerning LA-ESCC after NCRT with EUS. First, the pre-MTT was not an independent prognostic factor. Second, post-MTT ≤8.8 mm indicated a significant correlation with better long-term survival, and post-MTT can be used as a clinically independent prognostic factor in LA-ESCC. Third, tumor shrinkage rate was proven as an independent prognostic factor and as a dichotomous variable, and this conclusion was confirmed by external validation. Fifth, initial tumor infiltration beyond the esophageal adventitial layer on ultrasound effect did not differ across the responder and nonresponder groups.

Table 2

Univariate analysis of maximum tumor thickness for overall survival after neoadjuvant therapy using Cox proportional hazards model

Variables	HR (95% CI)	P
Age, y		0.597
<65	1	
≥65	0.84 (0.43–1.62)	0.602
Sex		0.226
Male	1	
Female	0.52 (0.16–1.67)	0.271
BMI, kg/m^2		0.174
<18.5	1	
18.5–24	4.15 (0.56–30.55)	0.163
>24	4.53 (0.6–34.06)	0.142
KPS		0.671
80–90	1	
≤80	1.21 (0.51–2.86)	0.664
Smoking		0.524
No	1	
Yes	1.25 (0.62–2.53)	0.532
Drinking		0.338
No	1	
Yes	1.4 (0.69–2.82)	0.352
Tumor location		0.312
Upper	1	
Middle	1.26 (0.51–3.13)	0.615
Lower	0.77 (0.31–1.95)	0.585
Time interval	0.99 (0.96–1.02)	0.339
Clinical T stage		0.466
2	1	
3	2.13 (0.54–8.44)	0.282
4	2.39 (0.71–8.03)	0.159
Unknown	1.9 (0.5–7.2)	0.345
t-PCR		0.413
PCR	1	
No PCR	1.29 (0.69–2.4)	0.419
Post-MTT, mm		<0.001
≥8.8	1	
<8.8	0.35 (0.2–0.64)	<0.001

BMI, body mass index; 95% CI, 95% confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Status; MTT, maximum tumor thickness; PCR, pathologic complete response; post-MTT, posttreatment maximal tumor thickness; time interval, the time between the end of NCRT and reexamined; t-PCR, tumor pathologic complete response.

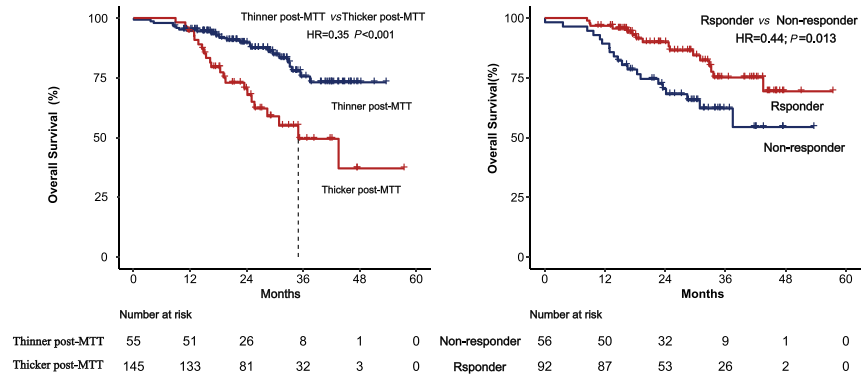

Figure 4. Comparison of overall survival. A, The OS between the thinner MTT group and thicker MTT group in post-MTT population. B, The OS between the EUS responder group and EUS nonresponder group in EUS response population. DFS, disease-free survival; EUS nonresponder, tumor shrinkage <52%; EUS responder, tumor shrinkage ≥52%; HR, hazard ratio; MTT, maximum tumor thickness; OS, overall survival; post-MTT, posttreatment maximal tumor thickness.

Previous studies have reported that endoluminal ultrasound–defined tumor volume emerged as a new prognostic indicator for assessing pathologic tumor regression preoperatively in patients with esophageal cancer.[12,13] These studies used the EUS index to predict the degree of tumor regression after treatment and did not use EUS as an early method to evaluate long-term prognosis. After NCRT, data on early assessment to identify patients with LA-ESCC with different sensitivities and to predict long-term prognosis are lacking. This study mainly aimed to further investigate the association between EUS-derived MTT and long-term survival in patients with LA-ESCC receiving NCRT. Previous studies have demonstrated that tumor area and length could be useful prognostic factors.[9,16,17] These studies used tumor area and tumor length as assessment indices; however, because of the technical difficulty of measuring tumor area by ultrasonography, difficulties in clinical application may exist, especially in developing countries with a high prevalence of esophageal cancer, where the measurement results often vary widely, depending on the technical level of the operator. By contrast, we used a single radial measurement of the MTT, which is directly proportional to the area and is technically easy and more efficient. We demonstrated that the post-MTT and reduction of MTT could offer the same assessment benefits as the maximum cross-sectional area. Similarly, in 2020, Wongwaiyut et al[18] reported that CT-derived pretreatment esophageal wall thickness of T3 locally advanced ESCC is a useful indicator for predicting survival and pathologic complete response after treatment. In clinical studies, CT for assessing the response to neoadjuvant therapy in esophageal cancer can be inaccurate.[7] Therefore, the prognostic value of CT indicators must be verified further. However, EUS is a very accurate method for the initial staging of local and regional tumors and can distinguish between tumor and wall thickening caused by NCRT. Therefore, the EUS index may be more reliable to use as a reference index to predict the prognosis. To further explore the relationship between MTT and prognosis, we performed univariate and multivariate logistic regression analyses to prove the correlation between MTT and tumor pathologic complete response (Supplementary Table 2, http://links.lww.com/ENUS/A330). Moreover, a pathological tumor response has been confirmed to be closely related to a better prognosis. Consequently, the simple access to EUS-MTT facilitated its clinical application, with its strength of health economics and higher credibility. In 2010, Jost et al[19] reported that an EUS-derived post-MTT ≤6 mm and post-MTT/pre-MTT ratio ≤50% might be useful for predicting survival in patients with esophageal carcinoma. However, these differences did not reach statistical significance because of the low number of cases per group (17 cases of squamous carcinomas in this study). All the aforementioned studies included only adenocarcinoma or a very small number of cases on squamous cell carcinomas. Therefore, the applicability of these conclusions in patients with esophageal squamous carcinoma remains to be verified. Meanwhile, our study was of sufficient size to determine the relationship between the reduction in tumor regression and prognosis in LA-ESCC. All included studies were single-center studies. In addition, we used data from another center to confirm our findings and obtained similar results, thus ensuring the reliability of our findings. In addition to this, we have demonstrated for the first time that whether or not the tumor infiltrates through the adventitia at initial treatment is not associated with prognosis, in either the responder or the nonresponder group. The esophageal adventitia is composed of loose connective tissue. Before the tumor breaks through the adventitia under ultrasound, a small number of tumor cells have infiltrated into the adventitia or metastasize through lymph and blood vessels in the adventitia. Therefore, whether the tumor breaks through the adventitia under ultrasound is not strongly related to the prognosis Because of the small sample size of T3 subgroups, this conclusion needs to be verified by prospective studies with larger samples.

This study has several limitations that warrant further discussion. First, as a retrospective study, there is a risk of information bias and incomplete data. To mitigate this issue, we established an external validation data set to verify our research results. Nevertheless, multicenter prospective studies are still necessary to further validate our conclusions. Second, because of missing thickness measurement data, we resorted to retrospective measurements performed by 2 experienced endoscopists, and the average value was calculated to eliminate the impact of missing data. In addition, for some patients with pathological stenosis, the esophagus could not be entered during endoscopic examination, and a reentry method was used while excluding cases where reentry attempts were unsuccessful. Third, this study has a relatively short follow-up period, and longer follow-up is needed to validate our

conclusions. Therefore, studies with longer follow-up will be conducted in the future to further validate our conclusions and explore additional predictive factors.

In conclusion, our assessment of a sufficiently large-scale retrospective cohort of patients with LA-ESCC who underwent esophagectomy provided a high-level evidence that EUS-measured MTT and MTT regression rate after NCRT were independent prognostic factors for long-term survival, and initial tumor infiltration beyond the esophageal adventitial layer on ultrasound could not predict the long-term prognosis.

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Table 3

Univariate analysis of tumor shrinkage rate for overall survival after neoadjuvant therapy using Cox proportional hazards model

Variables	HR (95% CI)	P
Age, y		0.551
<65	1	
≥65	0.8 (0.37–1.7)	0.558
Sex		0.246
Male	1	
Female	0.53 (0.16–1.72)	0.288
BMI, kg/m^2		0.325
<18.5	1	
18.5–24	3.46 (0.46–25.72)	0.226
>24	3.43 (0.45–26.32)	0.235
KPS		0.4
80–90	1	
≤80	1.48 (0.62–3.57)	0.379
Smoking		0.435
No	1	
Yes	1.36 (0.62–2.98)	0.447
Drinking		0.26
No	1	
Yes	1.55 (0.7–3.39)	0.278
Tumor location		0.193
Upper	1	
Middle	1.35 (0.5–3.62)	0.55
Lower	0.7 (0.25–1.99)	0.502
Time interval	0.99 (0.96–1.02)	0.661
Clinical T stage		0.348
2	1	
3	1.98 (0.5–7.86)	0.332
4	2.25 (0.67–7.59)	0.189
Unknown		
t-PCR		0.781
PCR	1	
No PCR	0.91 (0.46–1.79)	0.782
EUS response		0.016
Nonresponder	1	
Responder	0.44 (0.23–0.86)	0.016

BMI, body mass index; EUS response, tumor shrinkage ≥52%; KPS, Karnofsky Performance Status; MTT, maximum tumor thickness; PCR, pathologic complete response; time interval, the time between the end of NCRT and reexamined; t-PCR, tumor pathologic complete response; tumor shrinkage rate, the ratio of the difference between pre- and post-MTT to pre-MTT.

Table 4

Subgroup analyses of ultrasonic T staging

	Variable	n	No. events (%)	HR (95% CI)	P
Ultrasonic T staging					0.351
T2–3	Nonresponder	18	7 (38.9)	1 (Ref)	
	Responder	28	4 (14.3)	0.34 (0.1–1.15)	0.082
T4	Nonresponder	38	12 (31.6)	1 (Ref)	
	Responder	64	14 (21.9)	0.58 (0.26–1.31)	0.190

95% CI, 95% confidence interval; nonresponder, tumor shrinkage <52%; responder, tumor shrinkage ≥52%.

Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xue Chen, Xi Chen, Yu Bao, Qifeng Wang, and Rui Zhao. The first draft of the manuscript was written by Xue Chen, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Xue Chen, Xi Chen and Yu Bao contributed equally to the work and should be regarded as co-first authors. Qifeng Wang and Rui Zhao contributed equally to the work and should be regarded as co-corresponding authors.

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