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Full Length Article

Three-field vs two-field lymphadenectomy in thoracic ESCC patients: a multicenter randomized study (NST 1503) ☆

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ABSTRACT

Background: 3-field lymph node dissection (3FL) frequently lead to much more perioperative complications than 2-field lymph node dissection (2FL). This study was designed as a non-inferiority trial to evaluate whether 3FL could be omitted without compromising overall survival (OS) and disease-free survival (DFS) in the patients with resectable thoracic esophageal squamous cell cancer (ESCC) and negative right recurrent laryngeal nerve lymph nodes (RRLN-LNs).

Methods: cT1b-3N0–1M0 thoracic ESCC patients were managed in 3 arms during open or minimally invasive McKeown esophagectomy according to the results of frozen section examination for RRLN-LNs: if positive, direct 3FL (RRLN[+]-3FL); if negative, 2FL (RRLN[-]-2FL) or 3FL (RRLN[-]-3FL) by randomization.

Results: Based on frozen section, of the 829 finally recruited patients, 121 (13.6 %) had positive RRLN-LNs and direct 3FL (RRLN[+]-3FL); 766 had negative RRLN-LNs and were randomized into the RRLN [-]-2FL (386 cases) or RRLN[-]-3FL (380 cases) group. The cervical LN metastasis rate in the RRLN[+]-3FL group (28.9 %) was significantly higher than that in the RRLN[-]-3FL group (8.3 %) ($P<0.001$). The 5-year OS and DFS were 72.2 % and 65.1 % in the RRLN[-]-3FL group and 68.8 % and 62.8 % in the RRLN[-]-2FL group (OS, $P = 0.163$; DFS, $P = 0.378$), versus 50.3 % and 41.2 % in the RRLN[+]-3FL group (both $P<0.001$), respectively.

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Conclusions: Additional cervical lymphadenectomy can be avoided in the patients with middle or lower thoracic ESCC and negative RRLN-LNs by frozen section treated by upfront surgery.

Trial Registration: ClinicalTrials.gov Identifier NCT02448953.

1. Introduction

Surgery currently remains the most effective treatment in the patients with resectable esophageal cancer. Pathologic lymph node (LN) metastasis status is the most important prognostic determinant of outcome after curative surgery or multimodality therapies.[1,2] Once esophageal cancer involves the submucosal layer of the esophagus, via the longitudinal lymphatic network in the submucosa, cancer cells can spread to the LN stations around the esophagus from the neck to the upper abdomen, especially from the upper mediastinum to the lower neck along the recurrent nerves.[3,4] Accordingly, the extent and number of lymphadenectomies significantly affect overall and disease free survival in esophageal cancer patients.[2,5,6]

Although controversial, literature does suggest improved 5-year survival rates in patients with thoracic esophageal cancer who undergo a 3-field lymph node dissection (3FL) encompassing a cervical, thoracic, and abdominal lymphadenectomy, compared with a 2-field lymph node dissection (2FL) excluding a cervical LN (CLN) dissection.[7–10] The pathologic rate of cervical lymph node metastasis is between 20 % and 41.6 % in patients with thoracic esophageal squamous cell cancer (ESCC),[7,11] hence over 50 % of patients may be exposed to the risk of recurrent laryngeal nerve (RLN) injury, respiratory complications, and anastomotic leakage, for probably no oncologic benefit after 3FL.[9,12,13] There is therefore a clear rationale for precise preoperative staging for assessment of involvement of CLNs, including markers of risk; and in this context, the application of intraoperative sentinel lymph node status by frozen section to gauge the necessity of CLN dissection has logical appeal.

The right RLN LNs (RRLN-LNs) are located at the cervicothoracic junction and connected to CLNs through lymphatic vessels. Previous studies have reported that RRLN-LNs have the highest frequency of metastasis in thoracic ESCC patients.[2,16] Therefore, it is meaningful to ascertain whether RRLN-LNs could be used as sentinel LNs to predict the status of CLNs and to determine the necessity of cervical lymphadenectomy. To the best of our knowledge, there are no prospective clinical studies that address this question. This prospective multicenter non-inferiority randomized study was therefore designed to verify whether the patients who have negative RRLN-LNs need a 3FL, and the predictive value of RRLN-LNs as sentinel LNs for the necessity of cervical lymphadenectomy in the patients with resectable thoracic ESCCs (TESCCs) treated by upfront surgery.

2. Materials and methods

2.1. Trial design and patient enrollment

Trial design: During esophagectomy via the right thoracic approach, all the RRLN-LNs were dissected first and sent for frozen section examination. The maximum surface sections of each node were stained with hematoxylin and eosin (H&E) and examined intraoperatively by experienced pathologists. The patients were then managed in 3 arms according to the results of frozen section examination: if any of RRLN-LNs was positive, the patient would undergo 3-FL directly (RRLN[+]−3FL)[7], and if negative, patients were randomized into either the 2-FL arm (RRN[-]−2FL) or the 3-FL arm (RRLN[-]−3FL).

Participants enrollment: All hospitalized thoracic esophageal cancer patients within stage of cT1b-3N0–1M0 who met the following inclusion criteria in 14 centers were recruited into this study. The staging system of the American Joint Committee on Cancer (AJCC) 7th edition for esophageal cancer was used for clinical TNM (cTNM) and pathological TNM (pTNM) staging. Inclusion criteria: (1) pathologically proven ESCC; (2) no previous antitumor therapy, such as neoadjuvant chemotherapy, radiotherapy, or chemoradiation; (3) no other previous or simultaneous malignant tumors; (4) preoperative cTNM stage within cT1b-3N0–1M0; (5) age of 18–75 years, with Eastern Cooperative Oncology Group (ECOG)–World Health Organization (WHO) performance status (0–1) to tolerate esophagectomy; (6) no suspicious cervical lymph node metastasis by the cervical ultrasound/computed tomography (CT; short diameter of lymph node < 0.8 cm or shortest diameter/longest diameter < 0.65);[15] (7) willingness to participate in the clinical trial with a signed informed consent. Exclusion criteria: (1) pathologically proven esophageal non-squamous cell carcinoma by preoperative fiberoesophagoscopic biopsy or postoperative pathological examination; (2) receiving preoperative or postoperative adjuvant antitumor therapies, such as chemotherapy, radiotherapy, or chemoradiation; (3) incomplete preoperative clinical TNM stage assessment or beyond the stage of cT1b-3N0–1M0; (4) refusal of surgery or unwillingness to sign the informed consent or to follow the treatment protocol; (5) having a palliative resection or exploration alone.

Randomization: Through an authorized computer in each selected center, all hospitalized eligible patients from the 14 authorized centers with resectable TESCCs consisting of upper, middle, and lower thoracic esophageal cancers who met the above inclusion criteria were primarily recruited into this study. The RRLN(-) patients were randomized into an RRLN[-]−2FL or RRLN[-]−3FL group by an online central automatic randomizing program (stratified block randomization) from the platform run by a third party. Each random sequence was designed to contain 20 patients, who had equal chance to be randomized into an RRLN [-]−2FL or RRLN [-]−3FL group. The actual enrollment and randomization are presented in Fig. 1.

2.2. Interventions

Chest procedures: All recruited patients underwent a McKeown esophagectomy by open or video-assisted thoracoscopic/laparoscopic surgery (minimally invasive esophagectomy [MIE]), the procedures were via 3 conventional incisions (right posterolateral thoracic incision + midline abdominal incision + neck incision) or small MIE port incisions on the right chest and abdominal wall. During the thoracic phase, the patients undergoing open surgery were usually placed in a left lateral position and intubated with a double-lumen tube, whereas for MIE, a left semiprone position and intubation using a single-lumen tube with or without an occluder in the right main bronchus were applied. After exploration for possible pleural metastasis and resectability of the tumors, all RRLN-LNs were dissected and sent for frozen section examination. All LNs around the thoracic esophagus including the LNs in the subcarinal area and along the left RLN from the left main bronchus to the apex of the chest were dissected.

Abdominal procedures: The stomach was completely mobilized with preservation of the right gastroepiploic artery, and all LNs around the gastric cardia, left gastric artery, splenic artery, and common hepatic artery were dissected. The esophagus was then divided beyond the gastric cardia or in the neck. The tumor was resected with at least 5-cm proximal and distal clearance. Finally, the stomach was pulled out of the abdomen, and a gastric conduit of approximately 4 cm in width was made with the edge being enhanced and embedded by continuous suturing using Porlene for prevention of leakage.

Neck procedures: Based on the results of intraoperative frozen sections, those patients either with positive RRLN-LNs or with negative

RRLN-LNs but randomized into the 3FL cohort received a CLN dissection. The inner CLNs consisting of paraesophageal and deep CLNs and the extra CLNs (supraclavicular LNs) were all dissected through a "U-shaped" lower neck incision. Finally, an end-to-side esophagogastric anastomosis was made with a circular stapler or by hand sewing. On the contrary, for the RRLN[-]−2FL patients, only a small left neck incision was made for the anastomosis, with no cervical lymphadenectomy.

2.3. Outcomes

The primary end point was 3- and 5-year overall survival (OS) and disease-free survival (DFS); secondary end points included perioperative complications, rate of cervical lymph node metastasis after 3FL, recurrence rate after 2FL and 3FL.

2.4. Sample size calculation

Reported CLN metastasis rate for thoracic ESCC is between 20 % and 41.6 %,[7–11] and a documented recurrence rate of CLN is 8.6–28.6 % after a 3FL.[2,16] Therefore, for those patients who have resectable thoracic esophageal cancer and no preoperative suspected CLN metastasis, it was assumed that the average local cervical recurrence rate after 3FL would be about 10 % lower than that after 2FL.[2,7–11,16] The overall 5-year survival was reported to be 33–38 % after 2FL and 49–53 % after 3FL with an average difference of OS was about 10 % between 2FL and 3FL.[8,9,16] A non-inferiority design was applied for sample size estimation. The non-inferiority margin was set at 10 % based on the above results, with a significance level of 0.05 and a power of 90 %, ensuring sufficient statistical power to detect non-inferiority in OS and DFS between the 2FL and 3FL groups. The sample size estimated for the whole RRLN [-] group was 532 cases. If a rate of loss to follow-up was set at 10 %, the number of cases required in the RRLN [-]−2FL and RRLN [-]−3FL groups were about 586 cases in total, with about 293 in each group plus about 200 cases in the RRLN [+]−3FL group. Thus, approximately 800 cases in total were planned for enrollment in this study.

2.5. Statistical analysis

All statistical analysis were carried out using SPSS (IBM Corporation, Armonk, NY, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Baseline clinicopathological characteristics were compared using Student's *t*-tests and Chi-square tests (two-sided). Univariate and multivariate logistic regression analysis were used to identify risk factors associated with cervical lymph node metastases. The variables that were statistically significant in univariate analysis were put into multivariate logistic regression analysis. Five-year cumulative OS and DFS of different groups were calculated by the Kaplan-Meier method and compared by log-rank test. A *P*-value of < 0.05 was deemed statistically significant.

2.6. Data verification

All data points regarding clinical parameters and events on recruited patients was recorded into the database in real time and was verified by coordinators and database managers with medical reports. Intra- and postoperative complications were documented and classified according to the Clavien-Dindo scoring system.[18] All major surgery-related complications beyond Clavien-Dindo grade II, such as bleeding, chylothorax, anastomotic leakage, empyema, RLN paralysis, and infection of the incision, were recorded and compared among the three groups. Other complications, such as arrhythmia and pneumonia, were also included.

2.7. Surgery quality control

All selected centers were required to be high volume centers with a long history of performing esophagectomies (≥ 200 esophagectomies/year), and an agreement on quality control was signed before participation in the study. The esophagectomies were required to be performed by experienced senior surgeons in their preferred approach as outlined in the trial protocol (see in Supplementary materials). All selected centers and investigators were reviewed by live demonstration of esophagectomy before enrolling patients and reassessed on site by the principal investigator every 6 months after enrollment of patients. If the quality of surgery at any center was compromised or did not meet standards, it was removed from the trial. Standard demonstration videos of key procedures and surgical techniques in dissecting LNs and anastomosis performed by authoritative surgeons from the high-volume centers were displayed on the trial platform as a standard for the continuous check and balance of the surgery quality control.

2.8. Follow-up

The recruiting period was from April 15, 2015, to December 31, 2018. All enrolled patients were followed up once every 3 months by a fixed team through telephone calls after surgery. They were asked to see their surgeons for follow-ups and undergo routine examinations at their local hospitals where esophagectomies were performed. Follow-up data were obtained by telephone interview with patients and/or their family members. Oncologic follow-up examinations consisted of high-resolution CT scans of the chest and abdomen, ultrasonography for the CLN, and upper gastrointestinal barium swallowing esophagogram or esophagogastroscopy every 3 months in the first 2 years and every 6 months in the remaining 3 years after the surgery. Other examinations including brain magnetic resonance imaging (MRI) and bone scans were performed to detect recurrence and/or metastasis, when clinically necessary.

Postoperative adjuvant chemotherapy/radiotherapy was not recommended routinely unless patients were confirmed to have recurrence. Locoregional recurrence was defined as recurrence in the operation field, such as in the anastomotic or tumor bed area, or the LNs in neck, chest, and abdomen. Distant metastases were defined as metastasis in the distant organs or the LNs beyond the surgical fields. All recurrences were confirmed based on radiological evidence and/or biopsy, when possible.

3. Results

3.1. Patient enrollment and exclusion

A total of 887 patients with thoracic esophageal cancers were primarily recruited into this study from 14 centers across China. Of these, 121 had positive RRLN-LNs by frozen section and therefore underwent RRLN[+]−3FL; 766 had negative RRLN-LNs by frozen section and were randomized into the RRLN[-]−2FL (386 cases) and RRLN[-]−3FL (380 cases) groups. A total of 58 cases were ruled out for various reasons, including 7 cases in the RRLN[+]−3FL group, 19 cases in the RRLN[-]−2FL group, and 32 cases in the RRLN[-]−3FL group. The reasons for exclusion were as follows: incomplete cTNM staging assessment (5 cases), unwilling to stick to protocol (30 cases), unexpected termination of surgery (2 cases), non-squamous cell carcinoma (10 cases), carcinoma in situ (7 cases), and frozen negative RRLN-LN but pathologic positive RRLN-LN (4 cases). Ultimately, 829 cases were enrolled into the study, including 616 males and 213 females, with a mean age of 60 years (range 41–74 years). There were 114 cases in the RRLN[+]−3FL group, 367 in the RRLN[-]−2FL group, and 348 in the RRLN[-]−3FL group (Fig. 1). The baseline demographic and clinicopathological features are listed in Table 1 and Supplementary Table 1. There was no significant difference in the basic demographic characteristics, including age, sex, tumor location, tumor differentiation, and N classification between the RRLN[-]−2FL and RRLN[-]−3FL groups (all $P > 0.05$). Tumor differentiation showed a slight predominance of moderately differentiated lesions in both groups. No significant difference was found

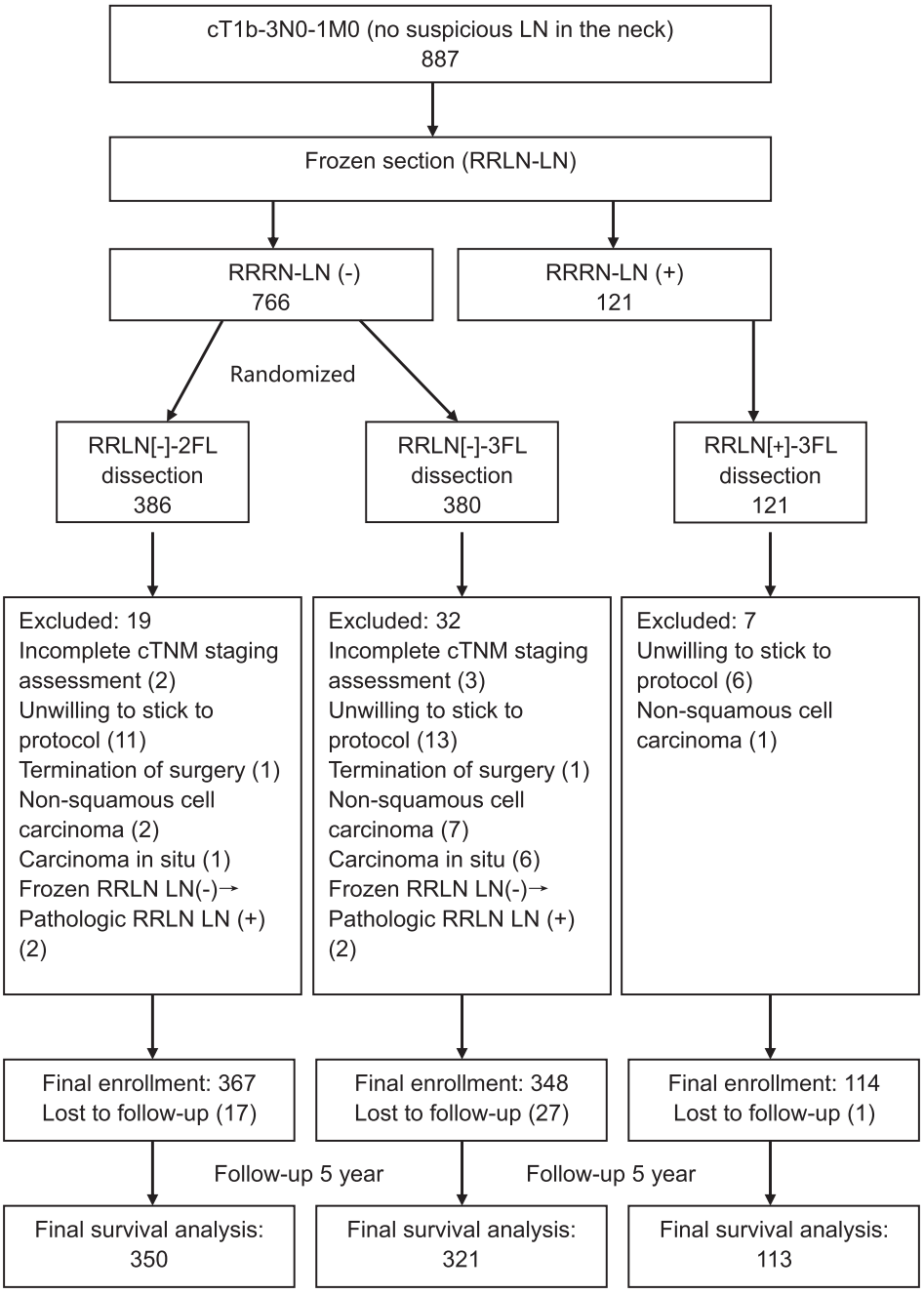

Fig. 1. CONSORT diagram of patient enrollment and randomization. cTNM, clinical tumor–node–metastasis; LN, lymph node; RRLN-LN, right recurrent laryngeal nerve lymph nodes; RRLN-LN(-): negative RRLN-LN; RRLN-LN(+): positive RRLN-LN; RRLN[-]−2FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 2-field lymph node dissection; RRLN[-]−3FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection; RRLN[+]−3FL, patients with positive right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection.

in T classification or TNM stage. Similarly, the proportion of hand-sewn and stapled anastomoses was balanced between the two groups ($P = 0.62$).

3.2. Surgical resection

Minimally invasive McKeown esophagectomies were performed in 795 (95.9 %) cases, open McKeown esophagectomies in 25 (3.0 %) cases, and conversion of MIE to open esophagectomy in 9 cases (1.1 %) due to difficulty in resection of the lesions (7 cases) and severe pleural adhesion (2 cases).

3.3. CLN metastasis and recurrence

Of the 114 cases with positive RRLN-LNs according to intraoperative frozen section examination, 33 cases (28.9 %) had CLN metastasis after 3FL, including inner CLN metastasis in 19 cases (16.7 %) and extra CLN metastasis in 21 cases (18.4 %). However, among the 348 cases with negative RRLN-LNs by intraoperative frozen section examination, only 29 cases (8.3 %) were found to have CLN metastasis after 3FL, including inner CLN metastasis in 21 cases (6.0 %) and extra CLN metastasis in 11 cases (3.2 %). The RRLN[+]−3FL group had a significantly higher CLN metastasis rate than did the RRLN[-]−3FL group (28.9% vs. 8.3 %; $P<0.001$), not only in the inner CLNs (16.7% vs. 6.0 %; $P<0.001$) but also in the extra CLNs (18.4% vs. 3.2 %; $P<0.001$). The comparison of the CLN metastasis rates among the upper, middle, and lower thoracic esophageal cancers between the positive and negative RRLN-LNs by frozen sections is listed in Table 2. The specificity, negative predictive value and accuracy of RRLN-LN frozen section was 77.3 %, 91.7 % and 74.3 %, respectively. Compared with the middle and lower thoracic esophageal cancers, the upper thoracic esophageal cancers had a relatively higher CLN metastasis rate whether the RRLN-LNs were positive (27.6 %) or negative (13.0 %) according to frozen sections (Table 2). The results of univariate and multivariate analysis on the association

Table 1
The baseline clinicopathological characteristics of patients in the RRLN[-]−2FL and RRLN[-]−3FL groups.

Characteristics	RRLN[-]−2FL	RRLN[-]−3FL	*P*	χ^2
Total cases, No.	367	348		
Age, mean±SD, years	59.9 ± 7.0	59.7 ± 6.8	0.63	
Sex, No. (%)				
Male	270 (73.6)	258 (74.1)	0.86	0.030
Female	97 (26.4)	90 (25.9)		
Tumor location, No. (%)				
Upper	51 (13.9)	46 (13.2)	0.96	0.076
Middle	222 (60.5)	213 (61.2)		
Lower	94 (25.6)	89 (25.6)		
Tumor differentiation, No. (%)				
Well	80 (21.8)	83 (23.9)	0.47	1.495
Moderate	218 (59.4)	211 (60.6)		
Poor	69 (18.8)	54 (15.5)		
T classification, No. (%)				
T1a	19 (5.2)	13 (3.7)	0.09	8.147
T1b	88 (24.0)	65 (18.7)		
T2	62 (16.9)	83 (23.9)		
T3	187 (51.0)	180 (51.7)		
T4a	11 (3.0)	7 (2.0)		
M classification, No. (%)				
M0	367	348		
N classification, No. (%)				
N0	238 (64.9)	219 (62.9)	0.54	2.147
N1	91 (24.8)	85 (24.4)		
N2	35 (9.5)	37 (10.6)		
N3	3 (0.8)	7 (2.0)		
TNM stage, No. (%)				
IA	24 (6.5)	16 (4.6)	0.49	5.472
IB	77 (21.0)	56 (16.1)		
IIA	43 (11.7)	50 (14.4)		
IIB	117 (31.9)	122 (35.1)		
IIIA	68 (18.5)	65 (18.7)		
IIIB	27 (7.4)	30 (8.6)		
IIIC	11 (3.0)	9 (2.6)		
Anastomosis, No. (%)				
Handsewn	344 (93.7)	323 (92.8)	0.62	0.240
Stapled	23 (6.3)	25 (7.2)		

Abbreviations: LN, lymph node; RRLN[-]−2FL, 2-Field LN dissection group with negative right recurrent laryngeal nerve lymph nodes by frozen section; RRLN[-]−3FL, 3-field LN dissection group with negative right recurrent laryngeal nerve lymph nodes by frozen section.

of CLN metastasis with the clinicopathological factors are listed in the Table 3.

Tumor differentiation, RRLN-LN status, LRLN-LN status, subcarinal/left tracheobronchial LN metastasis, and abdominal LN status were found to be significantly associated with CLN metastasis in the univariate analysis. All significant univariate factors associated with CLN metastasis were included in the multivariate regression analysis. The multivariate analysis revealed that the presence of positive RRLN-LN (OR, 2.67 [95 % CI, 1.45–4.92]; $P = 0.002$) remained an independent significant factor correlating with CLN metastasis, in addition to tumor differentiation (OR, 3.23 [95 % CI, 1.20–8.60]; $P = 0.019$) and subcarinal/left tracheobronchial LN metastasis (OR, 3.02 [95 % CI, 1.36–6.68]; $P = 0.007$). Tumor stage (T1 vs. T2+T3+T4: OR, 1.6 [95 % CI, 0.70–3.65]; $P = 0.26$), LRLN-LN status (OR, 1.8 [95 % CI, 0.88–3.71]; $P = 0.11$), and abdominal LN involvement (OR, 1.26; [95 % CI, 0.65–2.42]; $P = 0.49$) were not statistically significant predictors of CLN metastasis in the multivariate analysis. The recurrence rate of CLN was 3.4 % in the RRLN[-]−2FL group, 2.5 % in the RRLN[-]−3FL group and 3.5 % in the RRLN [+]−3FL group, there was no significant difference among three groups ($P = 0.746$).

3.4. Peri-operative complication and mortality

The complications of the RRLN[-]−3FL group, the RRLN[-]−2FL group and the RRLN[+]−3FL group classified by ECCG definition were listed and compared in Table 4. There was no significant difference between the RRLN[-]−3FL group and the RRLN[-]−2FL group ($P = 0.35$). Compared with 2FL, 3FL had a significantly increased operating time (276.78±85.505 min vs 254.01±80.238 min, $P<0.001$) and extra blood loss volume of (23.85±19.719 ml vs 0 ml). Of the 114 patients in the RRLN[+]−3FL group, 2 (1.8 %) died of postoperative complications (1 acute myocardial infarction and 1 pneumonia). Among the 348 patients in the RRLN[-]−3FL group, 1 (0.3 %) died of postoperative intrathoracic bleeding, and of the 367 patents in the RRLN[-]−2FL group, 1 (0.3 %) died of postoperative respiratory failure.

3.5. Survival

Of the 829 eligible patients, 44 (5.3 %) were lost to follow-up, including 27 in the RRLN[-]−3FL group, 16 in the RRLN[-]−2FL group, and 1 in the RRLN [+]−3FL group. In all, 785 patients (94.7 %) were successfully followed up until the last follow-up on April 30, 2023. All patients were followed-up for >5 years (range 60–82.3 months). The 5-year OS and DFS were 72.2 % and 65.1 % in the RRLN[-]−3FL group, respectively, and 68.8 % and 62.8 % in the RRLN[-]−2FL group, respectively. This non-inferiority trial demonstrated no significant difference between RRLN[-]−2FL and RRLN[-]−3FL in OS (HR, 0.82 [95 % CI, 0.61–1.08]; $P = 0.163$) and DFS (HR, 0.89 [95 % CI, 0.69–1.15]; $P = 0.378$). Compared with the RRLN[-]−3FL and RRLN[-]−2FL groups, the RRLN[+]−3FL had the worst 5-year OS (50.3 %; HR 2.16 [95 % CI, 1.57–3.04]; $P<0.001$) and DFS (41.2 %; HR, 2.03 [95 % CI, 1.48–2.78]; $P<0.001$; Figs 2 and 3).

4. Discussion

It is well established that the extent and number of metastatic LNs negatively correlate with survival, and a high nodal yield is a positive prognostic measure.[6–10] Theoretically, esophageal cancer can spread to the LNs around esophagus and 3FL is recommended; however, additional CLN increase operative time and trauma, which usually lead to more complications. Some series, mainly from Japan, indicate that 3FL

Table 2
Comparison of the cervical LN metastasis rate among the patients with thoracic esophageal cancers at different locations and 3-field LN dissection.

Location	RRLN-LN	CLN(-), No. (%)	CLN(+), No. (%)	*P* value	χ^2	RR	95 % CI
Upper	(+)	21 (72.4)	8 (27.6)	0.120	2.478	0.473	0.183, 1.224
	(-)	40 (87.0)	6 (13.0)				
Middle	(+)	47 (74.6)	16 (25.4)	< 0.001	15.173	0.296	0.157, 0.557
	(-)	197 (92.5)	16 (7.5)				
Lower	(+)	13 (59.1)	9 (40.9)	< 0.001	15.613	0.192	0.081, 0.459
	(-)	82 (92.1)	7 (7.9)				
Total	(+)	81 (71.1)	33 (28.9)	< 0.001	31.405	0.288	0.183, 0.452
	(-)	319 (91.7)	29 (8.3)				

Abbreviations: (-), negative; (+), positive; CLN, cervical lymph node; LN, lymph node; RRLN-LN, right recurrent laryngeal nerve lymph node.

Table 3
Correlation of cervical LN metastasis and clinicopathological factors.

Clinicopathological characteristics	CLN (+)	CLN (-)	Univariate analysis			Multivariate analysis		
			P	OR	95 % CI	*P*	OR	95 % CI
Total cases, No.	62	400						
Age, No. (%), years								
≤ 60	33 (14.9)	189 (85.1)	0.41	1.23	0.77, 1.96			
> 60	29 (12.1)	211 (87.9)						
Gender, No. (%)								
Male	48 (13.9)	298 (86.1)	0.75	1.15	0.66, 2.00			
Female	14 ((12.1)	102 (87.9)						
Tumor length, No. (%)								
≤5 cm	54 (14.4)	322 (85.6)	0.29	1.54	0.76, 3.12			
> 5 cm	8 (9.3)	78 (90.7)						
Tumor location, No. (%)								
Upper	14 (18.7)	61 (81.3)	0.14	1.51	0.88, 2.59			
Middle & Lower	48 (12.4)	339 (87.6)						
Tumor differentiation, No. (%)								
Well	5 (5.1)	94 (94.9)	0.004	3.11	1.28, 7.55	0.019	3.23	1.20, 8.60
Moderate & Poor	57 (15.7)	306 (84.3)						
Tumor stage, No. (%)								
T1	8 (8.2)	90 (91.8)	0.086	1.96	0.90, 4.27	0.260	1.60	0.70, 3.65
T2+T3+T4	54 (14.8)	310 (85.2)						
RRLN-LNs, No. (%)								
Positive	33 (28.9)	81 (71.1)	< 0.001	3.27	2.08, 5.17	0.002	2.67	1.45, 4.92
Negative	29 (8.3)	319 (91.7)						
LRLN-LNs, No. (%)								
Positive	18 (30.0)	42 (70)	< 0.001	3.48	1.84, 6.57	0.110	1.80	0.88, 3.71
Negative	44 (10.9)	358 (89.1)						
Subcarinal & left tracheobronchial LN								
Positive	17 (40.5)	25 (59.5)	< 0.001	3.78	2.39, 5.98	0.007	3.02	1.36, 6.68
Negative	45 (10.7)	375 (89.3)						
Abdominal LN, No. (%)								
Positive	22 (21.0)	83 (79.0)	0.014	1.87	1.17, 3.00	0.490	1.26	0.65, 2.42
Negative	40 (11.2)	317 (88.8)						

Abbreviations: (-), negative; (+), positive; CLN, cervical lymph node; LN, lymph node; LRLN-LN, left recurrent laryngeal nerve lymph nodes; RRLN-LNs, right recurrent laryngeal nerve lymph nodes.

Table 4
Comparison of complications among the RRLN[-]−2FL, RRLN[-]−3FL and RRLN[+]−3FL groups.

ECCG characteristics	RRLN[-]−2FL, %	RRLN[-]−3FL, %	*P*-value	RRLN[-]−3FL, %	RRLN[+]−3FL, %	*P*-value
Anastomotic leakage						
No	88.8 (326/367)	86.8 (302/348)	0.43	86.8 (302/348)	81.6 (93/114)	0.17
II	11.2 (41/367)	13.2 (46/348)		13.2 (46/348)	18.4 (21/114)	
RLN paralysis						
No	94.8 (348/367)	93.4 (325/348)	0.39	93.4 (325/348)	91.2 (104/114)	0.41
IA	4.9 (18/367)	6.6 (23/348)		6.6 (23/348)	8.8 (10/114)	
IIIB	0.3 (1/367)	0.0		0.0	0.0	
Chylothorax						
No	99.4 (365/367)	98.3 (342/348)	0.23	98.3 (342/348)	95.6 (109/114)	0.15
IIA	0.3 (1/367)	1.4 (5/348)		1.4 (5/348)	4.4 (5/114)	
IIIB	0.3 (1/367)	0.3 (1/367)		0.3 (1/367)	0.0	
Respiratory complications						
Yes	31.9 (117/367)	30.2 (105/348)	0.62	30.2 (105/348)	28.9 (33/114)	0.80
No	68.1 (250/367)	69.8 (243/348)		69.8 (243/348)	71.1 (81/114)	
Wound infection						
Yes	3.8 (14/367)	5.7 (20/348)	0.23	5.7 (20/348)	2.6 (3/114)	0.18
No	96.2 (353/367)	94.3 (328/348)		94.3 (328/348)	97.4 (111/114)	
Post-operative bleedig						
Yes	1.1 (4/367)	1.4 (5/348)	0.68	1.4 (5/348)	2.6 (3/114)	0.40
No	98.9 (363/367)	98.6 (343/348)		98.6 (343/348)	97.4 (111/114)	
Arrhythmia						
Yes	3.0 (11/367)	5.5 (19/348)	0.10	5.5 (19/348)	2.6 (3/114)	0.22
No	97.0 (356/367)	94.5 (329/348)		94.5 (329/348)	97.4 (111/114)	
Unplanned second surgery						
Yes	1.6 (6/367)	0.6 (2/348)	0.18	0.6 (2/348)	0.9 (1/114)	0.73
No	98.4 (361/367)	99.4 (346/348)		99.4 (346/348)	99.1 (113/114)	
Total complications						
Yes	42.5 (156/367)	46.0 (160/348)	0.35	46.0 (160/348)	47.4 (54/114)	0.80
No	57.5 (211/367)	54.0 (188/348)		54.0 (188/348)	52.6 (60/114)	

Abbreviations: ECCG, Esophagectomy Complication Consensus Group; LN, lymph node; RLN, recurrent laryngeal nerve; RRLN[-]−2FL, 2FL group with negative right recurrent laryngeal nerve lymph nodes by frozen section; RRLN[-]−3FL, 3FL group with negative right recurrent laryngeal nerve lymph nodes by frozen section; RRLN[+]−3FL, 3FL group with positive right recurrent laryngeal nerve lymph nodes by frozen section.

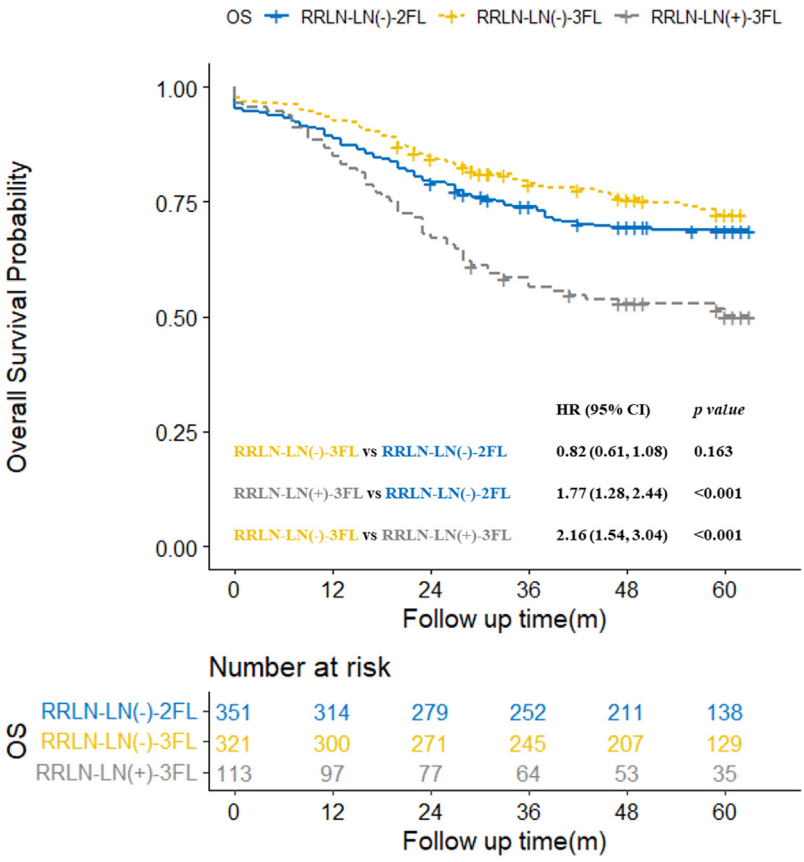

Fig. 2. Comparison of overall survival among the RRLN [-]−3FL, RRLN[-]−2FL, and RRLN[+]−3FL groups. CI, confidence interval; HR, hazard ratio; m, month; OS, overall survival; RRLN[-]−2FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 2-field lymph node dissection; RRLN[-]−3FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection; RRLN[+]−3FL, patients with positive right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection.

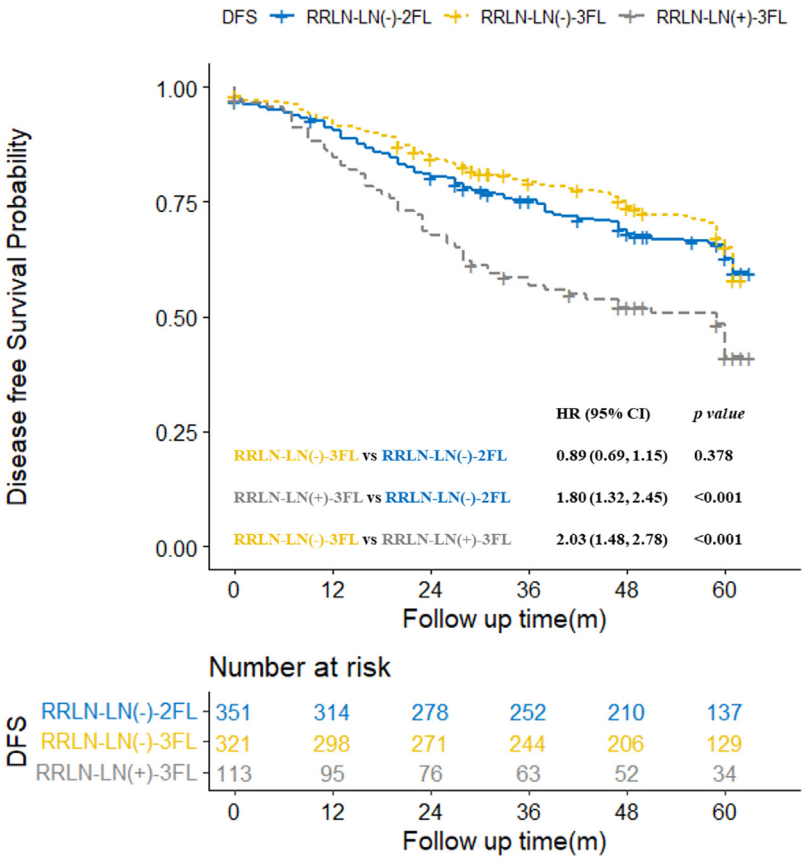

Fig. 3. Comparison of disease-free survival among the RRLN [-]−3FL, RRLN [-]−2FL, and RRLN [+]−3FL groups. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; m, month; RRLN[-]−2FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 2-field lymph node dissection; RRLN[-]−3FL, patients with negative right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection; RRLN[+]−3FL, patients with positive right recurrent laryngeal nerve lymph nodes by frozen sections and 3-field lymph node dissection.

will achieve not only a higher nodal yield but also improved 5-year survival compared with 2FL.[7–10] Liu et al.[6] reported a retrospective comparison study of 1131 thoracic esophageal ESCC patients treated by 3FL and 420 patients treated by 2FL. The overall 5-year survival rate for N0, N1, N2, and N3 metastasis was 77.5 %, 41.2 %, 22.2 %, and 7.0 %, respectively ($P < 0.0001$). A subgroup analysis showed that the 5-year survival in N0 patients with middle and lower thoracic esophageal cancer treated by 3FL and 2FL was 77.5 % and 70.7 % ($P = 0.235$), respectively; in the N1–2 subgroup it was 41.2 % and 32.8 % ($P = 0.006$), respectively; and in the N3 subgroup it was 19.4 % and 19.0 %, respectively. Accordingly, only the group with limited LN metastasis (N1–2), and not the N0 nor N3 patients, could benefit from 3FL. These results were consistent with those reported by several Japanese surgeons.[17, 20, 19] All these results indicated that 3FL may be beneficial only to a subgroup of patients with limited LN metastasis (N1–2), which should be a selective procedure and is not necessary for all esophageal cancer patients who would undergo esophagectomy. The question whether selective use of cervical lymph node dissection can be developed to optimize oncologic outcomes, and meanwhile to reduce operative time, trauma and added operative risk, is important and the main purpose of this study. Our results demonstrated that there was no significant survival advantage in the RRLN[-]−3FL group compared with the RRLN[-]−2FL group for those with cT1b-3N0/N1 disease who underwent upfront surgery, aligning with the non-inferiority trial design. Therefore, our study demonstrated that 2FL procedure is an effective surgical strategy without compromising long-term survival for the negative RRLN-LNs patients, meanwhile, reducing surgical trauma and complications from extra CLN dissection.

Although the RRLN[-]−3FL group had a CLN metastasis rate of 8.3 %, this rate did not exceed the predefined non-inferiority threshold for survival analysis in this study. Additionally, survival outcomes in ESCC are influenced by multiple factors, including TNM stage, tumor differentiation, treatment modalities and associated diseases, etc. On the whole, the potential impact of CLN metastasis and additional CLN dissection on survival of the negative RRLN-LNs patients might be limited and mitigated by the above factors. 3FL increased not only operation time and trauma, but also the risk of complications of recurrent nerves paralysis and anastomotic leakage.[9,16,17] Though the huge differences in trauma and complications between 3FL and 2FL in the era of OE have been remarkably reduced due to application of MIE, the 3FL is more safe than before and does not significantly increase perioperative complications as this study showed; however, with increased risk of perioperative complications caused by added trauma of 3FL and adverse effect of neoadjuvant chemoradiation or chemoimmunotherapy received by more and more patients, it would be logical to limit CLN dissection to a selective group of patients based on precise CLN staging and intraoperative frozen section examination of sentinel LN.

Literature indicates that the most frequent metastasis sites in the chest and lower neck are the lymph nodes near the bilateral RLN, particularly the right RLN in patients with thoracic esophageal cancers.[16,22] Indeed, metastasis in these sites can exist even in stage T1b patients,[3,4,21, 24] and is relatively easy to dissect. In contrast, metastases in the lymph nodes near the left RLN (LRLN-LNs) usually occur in more advanced stages and are more difficult to dissect.[6,22] Given the above rationale, we chose the right rather than left RLN-LNs as sentinel LNs for frozen section examination in this study (Supplementary Fig. 1).

Previously Shiozaki et al.[7] conducted a retrospective study and found that middle and lower thoracic esophageal cancer patients with positive LNs along the recurrent nerve chain had a significantly higher CLN metastasis rate than did those with negative LNs. Furthermore, the RRLN-LN–positive patients treated by 3FL had significantly higher survival than did those treated by 2FL,[8–10, 23] but no significant difference was found in the survival of the negative RRLN-LN patients whether they were treated by 3FL or 2FL. Retrospective studies from Li et al. and Ueda et al.[14,25] also demonstrated similar results to the above-mentioned study. In this study, the data is consistent with this premise, and moreover demonstrated that thoracic ESCC patients with positive RRLN-LNs have a significantly higher CLN metastasis rate and also much worse survival even treated by 3FL than those with negative RRLN-LNs. However, the negative RRLN-LN patients treated by 3FL showed similar survival as the negative RRLN-LN patients treated by 2-FL ($P = 0.25$). Furthermore, the CLN recurrence rate in the RRLN[-]−3FL group and RRLN[-]−2FL group was similar. Therefore, our study results support that RRLN-LNs can be used as sentinel lymph nodes to predict the necessity of CLN dissection, especially for the patients with resectable middle and lower thoracic ESCC who undergo upfront surgery. If they have negative RRLN-LNs by intraoperative frozen section, 3FL can be omitted. If they have positive RRLN-LNs, even treated by additional cervical lymphadenectomy, their survival is still much worse than those with negative RRLN-LNs, which indicates that multimodality treatment might be needed. Further, our data showed that patients with upper thoracic ESCC had a relatively higher rate of CLN metastasis regardless of RRLN-LN status, suggesting this cohort may need 3FL no matter RRLN-LN status is positive or negative.[26,27]

Even though our study was designed as a prospective and randomized non-inferiority trial, there were a few limitations that may confound the results. First, because we intended to identify whether the RRLN-LNs can be used as sentinel LN for ESCC as reported in the literature, our study enrolled some patients with cT3/N1 disease who may need neoadjuvant therapy. Those patients did not receive it due to that neoadjuvant therapy might affect this main purpose. Secondly, this study did not have a control group for the positive RLN-LN patients. This was because retrospective studies have demonstrated that patients with positive RRLN-LNs do benefit from 3FL.[25–27] Thirdly, the RRLN[+]−3FL group did not recruite 200 cases as proposed by protocol because only patients with relatively early-stage diseases (cT1b-3N0–1M0) were included for surgical treatment alone. Fourthly, only high-volume centers were included in this trial due to technical requirement for 3FL, which could not be performed in the low-volume centers. Finally, though the incidence of CLN metastasis was significantly higher in the patients with positive RRLN-LNs than those with negative ones in this study, the sensitivity and positive predictive value of RRLN-LN frozen section were relatively low. However, the negative predictive value and specificity were high and more meaningful for the negative RRLN-LN patients in whom 3FL can be omitted.

5. Conclusions

Our prospective randomized study first time demonstrated for the patients with resectable middle and lower thoracic ESCC and negative RRLN-LNs by intraoperative frozen section, an additional cervical lymphadenectomy can be omitted during upfront surgery.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

This study was conducted in compliance with the principles of the Declaration of Helsinki and formal ethical approval (approval number: 15–032/959) for this study was issued on April 23, 2015 by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences. Informed consents of all enrolled patients were signed and collected before randomization. All deidentified personal health data of these randomized patients including assessment of preoperative surgical risks and cTNM stage, surgery, complications, pathological results, and follow-up information were entered into the National Clinical Trial (NCT) database through authorized computers connected

through a network in each center. Patients' names and personal identification data were replaced by a code number assigned by computer after being input into the NCT database in order to protect the patients' privacy.

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Author contributions

Y.M. and J.H. conceptualized this study. Y.M., S.L., Y.H., S.G., C.C., SG.G., A.H., H.D., W.F., R.Z., Z.Y., X.F., X.L., Q.W., L.T., Z.L. and Y.L. performed the investigation. Y.M. administrated this project and drafted the manuscript. S.L., Y.H., S.G., C.C., SG.G., A.H., H.D., W.F., R.Z., Z.Y., X.F., X.L., Q.W., L.T., Z.L. and Y.L. conducted the principal subcenter investigation and data collection. Y.F., D.F. and X.W. conducted the data curation and verification. L.Y. conducted the data curation and formal analysis. S.M. revised and edited the manuscript. J.H. supervised and final approved the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2025.01.002.

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