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ORIGINAL ARTICLE

Safety and oncological efficacy of bilateral recurrent laryngeal nerve lymph-node dissection after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma: a propensity-matched analysis

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Abstract

Background We sought to evaluate the safety and oncological efficacy of bilateral recurrent laryngeal nerve (RLN) lymph-node dissection (LND) in patients with esophageal squamous cell carcinoma (ESCC) who had undergone neoadjuvant chemoradiotherapy (nCRT).

Methods We retrospectively examined the records of ESCC patients who were judged to be ycN-RLN(-) following nCRT. Patients were divided into two groups according to the extent of LND [standard two-field LND (STL group) versus total two-field LND (TTL group)]. Only lower mediastinal and upper abdominal lymph nodes were removed in the STL group. In addition to the standard procedure, patients in the TTL group underwent resection of upper mediastinal lymph nodes located along the bilateral RLN. Using propensity score matching, 29 pairs were identified and compared with regard to perioperative complications, lymph-node metastases rates, overall survival (OS), and disease-specific survival (DSS).

Results No significant intergroup differences were identified in terms of in-hospital mortality and morbidity. Metastases to the RLN lymph nodes were identified in 20.7% (6/29) of TTL patients, being the only site of lymph-node metastases in three of them. TTL was associated with lower upper mediastinal lymph-node recurrence rate (6.5%) compared with STL (21.5%, $p=0.134$), although the overall recurrence rate was similar (STL, 44.8% versus TTL, 46.4%). No significant intergroup differences were also evident with regard to 3-year DSS and OS rates.

Conclusions RLN LND can be safely performed in ESCC patients who had undergone nCRT, ultimately resulting in an improved local control, and should be practiced as part of the surgical routine.

Keywords Esophageal cancer · Squamous cell carcinoma · Neoadjuvant chemoradiotherapy · Lymph-node dissection

Introduction

Esophageal cancer—one of deadliest malignancies—is characterized by a high likelihood of nodal spread. Nodes located in the upper mediastinum—especially along the bilateral recurrent laryngeal nerve (RLN)—are common site of metastases in patients with esophageal squamous cell carcinoma (SCC). [1–3]. In this regard, the rate of metastases to RLN nodes has been shown to be as high as 20–40% after primary surgery in ESCC [1, 2, 4]. In general, dissection of nodes along the RLN is deemed to exert positive effects on clinical outcomes [2, 5]. However, RLN lymph-node dissection (LND) is not yet part of the routine surgical practice—mainly because of the potential morbidity risks [6, 7]. Specifically, it has been reported that the rates of RLN palsy after such extensive nodal dissections could be as high as 60%—potentially impairing quality of life, predisposing to serious postoperative complications (e.g., aspiration pneumonia), and even resulting in postoperative deaths [8–10].

The need to dissect RLN lymph nodes in patients who had undergone neoadjuvant chemoradiotherapy (nCRT) is even

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more controversial for at least two reasons. First, chemoradiation may clear occult lymph-node metastases, ultimately reducing the clinical usefulness of an extensive nodal dissection. Second, radiation therapy may induce mediastinal fibrosis, a complication which renders RLN LND even more hazardous. Unfortunately, no data are currently available on the clinical utility and implications of RLN nodal dissection in nCRT-treated patients with esophageal cancer.

In light of these knowledge gaps, we designed the current study to assess the safety and oncological efficacy of RLN LND in ESCC patients who had undergone nCRT. To minimize the effect of potential confounders, only patients without clinical evidence of lymph-node metastases to the RLN area following nCRT were examined. Patients were divided into two groups based on the use of RLN LND and compared in terms of perioperative complications, rates of RLN palsy, lymph-node yields, and rates of lymph-node metastases in the RLN area. Propensity score matching was used to identify well-matched pairs for comparison purposes.

Materials and methods

Patients

We retrospectively reviewed the clinical charts of ESCC patients who had undergone esophagectomy in the Chang Gung Memorial Hospital between 2010 and 2015. Of them, patients who received nCRT as first-line treatment and had no clinical evidence of lymph–node metastases to the RLN area before surgery were selected for this study. The study patients were divided into two groups according to the extent of LND [standard two-field LND (STL group) versus total two-field LND (TTL group)]. The classification of LND was based on the 1994 consensus conference of the International Society of Disease of Esophagus criteria [11]. Only lower mediastinal and upper abdominal lymph nodes were removed in the STL group. In addition to the standard procedure, patients in the TTL group underwent a bilateral resection of lymph nodes located along the RLN. Pretreatment staging was based on the results of chest and abdomen CT scans, PET imaging, and endoscopic ultrasound. Patient staging was performed according to the American Joint Committee on Cancer (AJCC) staging criteria, seventh edition (2010). The last follow-up date was December 31, 2018. The study protocol was reviewed and approved by the local Institutional Review Board (CGMH-IRB-201800087B0). Owing to the retrospective nature of the study, the need for informed consent was waived.

Neoadjuvant chemoradiotherapy and restaging workup

Two nCRT regimens were utilized throughout the study period. The first regimen (PF regimen) consisted of 5-fluorouracil (5-FU; 1000 mg/m^2 per day, continuously infused over 96 h between days 1 and 4 and between days 29 and 33) and cisplatin (75 mg/m^2; administered as an intravenous infusion over 3 h on day 1 and day 29). Radiotherapy was delivered between days 8 and 29. The total dose was 30 Gy, administered in daily fractions of 200 cGy, 5 days per week. The second scheme (TC regimen, available as of 2012) was based on the weekly administration of carboplatin (with doses titrated to achieve an area under curve of 2 mg per mL per min) and paclitaxel (50 mg/m^2 of body-surface area) for 5 weeks and concurrent radiotherapy (41.4–45 Gy in 23–25 fractions, 5 days per week).

Surgical resection after nCRT and definition of postoperative complications

Upon nCRT completion, tumor response was assessed via a thorough restaging workup (consisting of upper endoscopy as well as CT and PET imaging). Complete nodal response was considered to be present when (1) the originally involved nodes were no longer evident on CT scans (as described in the RECIST guidelines) and (2) fluorodeoxyglucose (FDG) uptake in the affected nodes decreased to a level that was indistinguishable from that of the surrounding normal tissues on PET images.

All surgical operations were carried out in the same institution within 12 weeks of nCRT by a team consisting of four surgeons. The thoracic phase was performed using thoracotomy or video-assisted (alternatively, robot-assisted) thoracoscopic surgery. The abdominal phase consisted of either laparotomy or laparoscopy. As far as LND is concerned, the use of STL or TTL was not randomized. Before 2013, STL accompanied by neck or chest anastomosis was the standard procedure utilized by all of the four surgeons operating in our hospital. As of 2013, two surgeons started the implementation of routine TTL with neck anastomosis. However, the operating policy of the remaining two surgeons remained unchanged.

Definition of outcomes

The presence of RLN palsy—defined as any dysmotility affecting the vocal cords—was assessed by laryngoscopy. The occurrence of anastomotic leaks was confirmed by imaging findings (contrast-enhanced CT scans or water-soluble contrast studies), endoscopy, or during surgical exploration. Pneumonia was considered to be present when a lung infiltration was evident and/or the patient received antibiotics for pneumonia. Chyle leaks were diagnosed when milky white effusions from the thoracic cavity or the neck were evident. Perioperative mortality was defined as any death (regardless of its cause) occurring either (1) within 30 days after surgery (independent of the place of death), or (2) after 30 days during the same hospitalization subsequent to the operation.

Patterns of treatment failure were defined according to the first site of recurrence. Local recurrence (LR) was defined as either an anastomotic recurrence or a recurrence in the original tumor bed. Regional recurrence (RR) was defined as any recurrence occurring in the locoregional lymph nodes and further divided according to the involvement (yes versus no) of the upper mediastinal nodes (i.e., RLN lymph-node chain). A distant recurrence (DR) was considered to be present when recurrence was evident beyond the primary tumor and regional lymph nodes. Overall survival (OS) was calculated from the date of surgery to the date of death (or censored on the date of the last follow-up). Disease-specific survival (DSS) was measured from the date of surgery to the date of cancer-related death.

Data analysis

Normally distributed continuous variables were given as means [standard deviations (SDs)] and compared with a two-sample (unpaired) Student's *t* test. Skewed variables are summarized as medians [interquartile range (IRQ)] and compared using the Mann–Whitney *U* test. Categorical variables are given as absolute counts and compared with the Chi-square test or the Fisher's exact test (as appropriate). To control for potential confounding factors, patients were matched according to four variables (age, sex, pre-nCRT cN-RLN status, and thoracic surgical approach). Propensity scores for all patients were estimated with multiple logistic regression. Two comparable treatment groups were identified using a 1:1 match ratio based on eight digits of the estimated propensity score. The main study endpoints were OS and DSS. Survival curves were plotted with the Kaplan–Meier method (log-rank test). All calculations were performed with the SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

General characteristics of the study patients

A flowchart of patient recruitment is reported in Fig. 1. Of the 330 ESCC patients who received esophagectomy during the study period, 190 were treated with nCRT before surgery. Patients with positive ycN-RLN ($n = 16$) or R2 resections ($n = 17$) were not included in the study. We also excluded patients who received only unilateral RLN nodal dissection only ($n = 39$). Therefore, a total 118 patients (113 males and

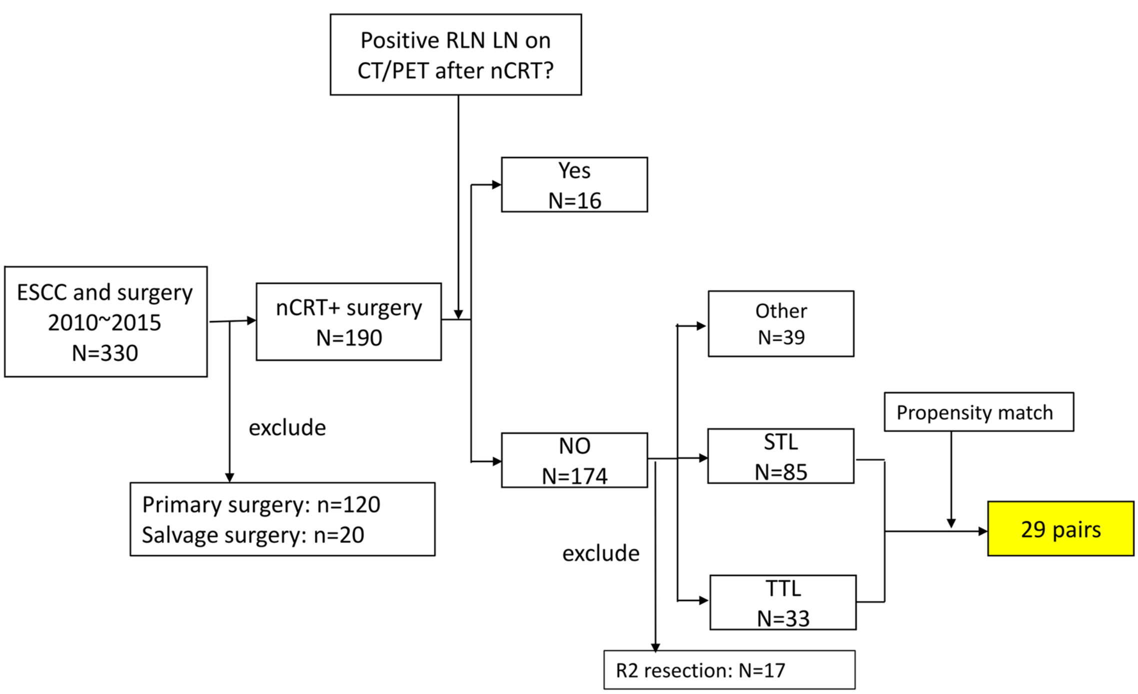

Fig. 1 Flow diagram of the progress through the study

5 females; mean age: 54.1 years) were examined. The majority of tumors were located in the middle third of the esophagus (42.4%). Pretreatment clinical stages were II and III and 8 and 110 patients, respectively. The STL and TTL groups consisted of 85 and 33 patients, respectively. Table 1 shows the demographic/clinical characteristics and the surgical procedures implemented in the study patients before and after propensity matching. A higher number of patients in the TTL group had radiological evidence of pretreatment RLN LN involvement (i.e., cN-RLN[+]). The RLN area was included in the RT field in 98.3% (116/118) of the study patients—without significant intergroup differences. After

Table 1 Demographic/clinical/surgical data of the study patients before and after propensity matching

	Entire study cohort			Propensity-matched cohort		
	STL group (*n* = 85)	TTL group (*n* = 33)	*p* value	STL group (*n* = 29)	TTL group (*n* = 29)	*p* value
Age (years); mean ± SD	54.24 ± 8.6	54.34 ± 8.6	0.952	54.97 ± 9.01	53.55 ± 7.99	0.531**
Sex			0.618			1.0**
Male	82 (96.5%)	31 (93.9%)		28 (96.6%)	28 (96.6%)	
Female	3 (3.5%)	2 (6.1%)		1 (3.4%)	1 (3.4%)	
Charlson score			0.097			0.103
0/1	66 (77.7%)	30 (90.9%)		20 (69%)	26 (89.7%)	
> 1	19 (22.3%)	3 (9.1%)		9 (31%)	3 (10.3%)	
Clinical stage			0.365			0.553
II	4 (4.7%)	4 (12.1%)		1 (3.4%)	2 (6.9%)	
III	81 (95.3%)	29 (87.9%)		28 (96.6%)	27 (93.1%)	
Pre-nCRT cN-RLN			0.001			0.426**
Negative	60 (70.6%)	12 (36.4%)		14 (48.3%)	11 (37.9%)	
Positive	25 (29.4%)	21 (63.6%)		15 (51.7%)	18 (62.1%)	
Tumor location			0.754			0.850
Upper third	18 (21.2%)	8 (24.2%)		10 (34.5%)	8 (27.6%)	
Middle third	35 (41.2%)	15 (45.5%)		11 (37.9%)	12 (41.4%)	
Lower third	32 (37.6%)	10 (30.3%)		18 (27.6%)	9 (31.0%)	
RT to RLN area			1.0			N/A
No	2 (2.4%)	0 (0%)		0 (0%)	0 (%)	
Yes	83 (97.6%)	31 (100%)		29 (100%)	29 (100%)	
RT dose to RLN area			< 0.001			0.001
0 Gy	2 (2.4%)	0 (0%)		0 (0%)	0 (0%)	
< 40 Gy	70 (82.4%)	12 (38.7%)		23 (79.3%)	11 (37.9%)	
≥ 40 Gy	13 (15.3%)	19 (61.3%)		6 (20.7%)	18 (62.1%)	
CT regimen			< 0.001			0.004
PF	65 (76.5%)	12 (36.4%)		22 (75.9%)	11 (37.9%)	
TC	20 (23.5%)	21 (63.6%)		7 (24.1%)	18 (62.1%)	
Surgery type			< 0.001			0.023
McKeown	44 (51.7%)	33 (100%)		23 (79.3%)	29 (100%)	
Ivor-Lewis	41 (48.3%)	0 (0%)		6 (20.7%)	0 (0%)	
Thoracic approach			< 0.001			N/A**
VATS/RATS	55 (64.7%)	33 (100%)		29	29	
Thoracotomy	30 (35.3%)	0 (0%)		0	0	
Abdominal approach			0.369			0.788
Laparoscopy	49 (57.6%)	22 (66.7%)		17	18	
Laparotomy	36 (42.4%)	11 (33.3%)		12	11	

The PF regimen consisted of cisplatin plus 5-fluorouracil, whereas the TC regimen was based on paclitaxel plus carboplatin

STL standard two-field lymph-node dissection, *TTL* total two-field lymph-node dissection, *nCRT* neoadjuvant chemoradiotherapy, *cCR* clinical complete response, *RT* radiotherapy, *CT* chemotherapy, *VATS* video-assisted thoracoscopic surgery, *RATS* robot-assisted thoracoscopic surgery, *SD* standard deviations

**Propensity-matched variable

propensity matching for age, sex, pre-nCRT clinical stage, pre-nCRT cN-RLN status, and thoracic approach, the two groups became homogenous and a total of 29 patient pairs were selected.

Surgery and perioperative outcomes

Table 2 provides the details of postoperative course before and after propensity matching. The median operation time showed a trend toward a longer duration in the TTL than in the STL group, albeit not significantly so ($p = 0.460$). As far as the postoperative course is concerned, the duration of mechanical ventilator use, intensive-care unit stay, and length of hospital stay did not show significant differences. Moreover, the rates of RLN palsy and postoperative pneumonia were similar.

Surgical quality and pathological variables

Table 3 summarizes the surgical quality and the pathological variables in the study patients. Despite a similar R0 resection rate, TTL increased the median number of resected lymph nodes compared to STL (28 versus 23, respectively, $p = 0.006$). The median number of nodes removed from the RLN area was 7. The two groups did not differ significantly in terms of rates of lymph-node metastases.

Table 2 Perioperative outcomes of the study patients before and after propensity matching

	Entire study cohort			Propensity-matched cohort		
	STL group ($n = 85$)	TTL group ($n = 33$)	p value	STL group ($n = 29$)	TTL group ($n = 29$)	p value
Operation time (min); median(IQR)	410 (367–469)	446 (393–480)	0.134	426 (370–463)	446 (390–480)	0.460
MV time (min); median (IQR)	324 (234–873)	287 (237–847)	0.838	650 (272–979)	288 (237–894)	0.216
RLN palsy	11 (12.9%)	3 (9.1%)	0.562	3 (10.3%)	3 (10.3%)	1.0
Pneumonia	11 (12.9%)	3 (9.1%)	0.562	3 (10.3%)	3 (10.3%)	1.0
MV > 72 h	2 (2.4%)	1 (3%)	1.0	1 (3.4%)	1 (3.4%)	1.0
Anastomotic leaks	3 (3.5%)	0 (0%)	0.559	3 (10.3%)	0 (0%)	0.237
Chyle leaks	6 (7.1%)	2 (6.1%)	0.846	1 (3.4%)	2 (6.9%)	1.0
LOS (days); median(IQR)	19 (15–22.5)	16 (13–18)	0.035	18 (15–27.5)	16 (13–19.5)	0.093
Perioperative mortality	2 (2.4%)	0 (0%)	1.0	1 (3.4%)	0 (0%)	1.0

IQR interquartile range, *STL* standard two-field lymph-node dissection, *TTL* total two-field lymph-node dissection, *NA* not applicable, *MV* mechanical ventilator, *RLN* recurrent laryngeal nerve, *LOS* length of hospital stay

Table 3 Surgical quality and pathological variables of the study patients before and after propensity matching

	Entire study cohort			Propensity-matched cohort		
	STL group ($n = 85$)	TTL group ($n = 33$)	p value	STL group ($n = 29$)	TTL group ($n = 29$)	p value
Margin status			0.348			1.0
R0	74 (87.1%)	31 (93.9%)		27 (%)	28 (%)	
R1	11 (12.9%)	2 (6.1%)		2 (%)	1 (%)	
Number of dissected Nodes; median (IQR)	20 (15–25)	28 (23–37)	< 0.001	23 (13.5–27)	28 (23–37)	0.006
ypT stage			0.216			0.110
0	19 (22.4%)	11 (33.3%)		3 (10.3%)	10 (34.5%)	
1	9 (10.6%)	6 (18.2%)		4 (13.8%)	5 (17.2%)	
2	8 (9.4%)	4 (12.1%)		5 (17.2%)	2 (6.9%)	
3	49 (57.6%)	12 (36.4%)		17 (58.6%)	12 (41.4%)	
ypN stage			0.388			0.497
0	58 (68.2%)	21 (63.6%)		22 (75.9%)	18 (62.1%)	
1	20 (23.5%)	11 (33.3%)		6 (20.7%)	10 (34.5%)	
2	7 (8.3%)	1 (3.1%)		1 (3.4%)	1 (3.4%)	

IQR interquartile range, *STL* standard two-field lymph-node dissection, *TTL* total two-field lymph-node dissection

Recurrence and survival

The mean follow-up time for patients who survived was 36 months [median 32.9 months, interquartile range (IRQ) 21.5–48.6 months]. A total of 33 (56.9%) patients had died at the time of analysis. Specifically, 24 died of cancer recurrences and 9 from other causes (one case died in-hospital, two of second primary cancer, one of delayed gastro-tracheobronchial fistula, and five of sepsis). The 3-year DSS and OS rates in the entire cohort were 57.1 and 53.2%, respectively. There were no significant differences in 3-year DSS and OS between STL group and TTL group (DSS: 53.8% versus 60.7%, respectively, $p=0.439$; Fig. 2a; OS: 48.3% versus 58.6%, respectively, $p=0.233$; Fig. 2b).

Among patients who survived the perioperative period ($n=57$), cancer recurrence was observed in 26 (45.6%) cases (13 in each group). RR occurred in 18 patients (8 in the STL and 10 in the TTL groups, respectively). Of them, ten were nodal recurrences alone and the remaining 8 were nodal recurrences associated with hematogenous spread. The anatomical location of the first neck recurrence was as follows: neck only ($n=4$), mediastinum only ($n=7$), abdomen only ($n=3$), both neck and mediastinum ($n=2$), and both mediastinum and abdomen ($n=2$). Among the 11 patients with mediastinal nodal recurrence, 8 showed involvement of the upper mediastinum area. The upper mediastinal nodal recurrences rates in the STL and TTL groups were 21.4% (6/28) and 6.5% (2/29), respectively ($p=0.134$).

Incidence and predictors for positive ypN-RLN in the TTL group

In the TTL group, 6 (20.7%) patients showed nodal involvement in the RLN area [ypN-RLN(+)]. Four and two patients had positive RLN nodes on the right side and left side, respectively. Notably, RLN nodes were the only positive station in 27.3% (3/11) of the ypN(+) patients. The clinical characteristics of patients with positive and negative ypN-RLN are summarized in Supplemental Table 1. No significant risk factors for RLN nodal involvement were identified. Specifically, no impact of nCRT regimen, nCRT response, and tumor location on RLN nodal involvement was identified.

Discussion

Previous studies have consistently shown that an extensive LND in patients with primarily resected esophageal cancer exerts beneficial effects by providing more accurate staging information and superior local control rates [5, 12–14]. However, the question as to whether the same concept can be applied to nCRT-treated cases remains open [15–17]. Because nCRT and extensive LND are both aimed at increasing local control rates, here, we specifically investigated whether the addition of the latter approach to the former could result in better oncological outcomes. Importantly, the thoroughness of LND does not only depend on

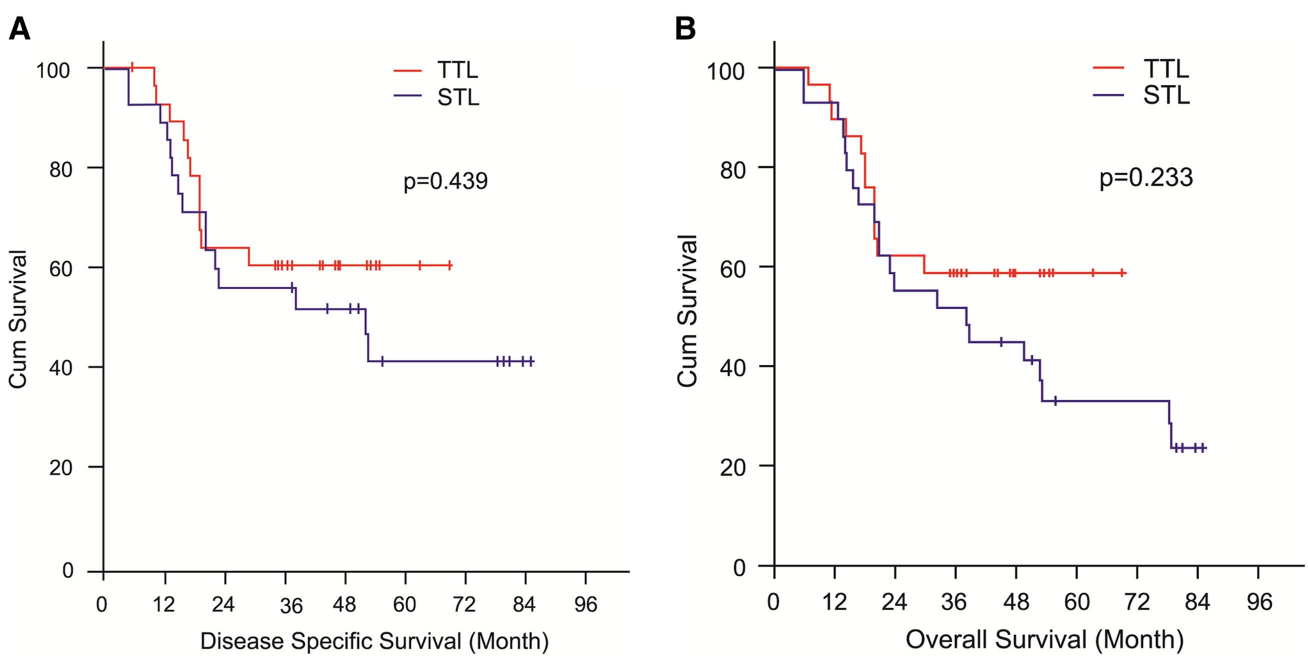

Fig. 2 **a** Disease-specific survival of patients who received total two-field and standard two-field lymph-node dissection. **b** Overall survival of patients who received total two-field and standard two-field lymph-node dissection

the number of sampled nodes but also on their exact anatomical location [2]. For example, sampling of a few nodes from areas at high risk for metastases may result in a better oncological efficacy than an extensive LND in a location at low risk of nodal involvement. Upper mediastinal nodes—especially located around RLN bilaterally—represent the anatomical area with the highest risk of metastases after primary surgery in ESCC [1, 3]. In our sample of ESCC patients who had been treated with nCRT and did not show evidence of clinical RLN lymph-node involvement on the preoperative workup, the rate of RLN nodal metastases remained high (20.7%). Moreover, we were able to observe a 15% increase in the superior mediastinum recurrence rate among patients who did not receive bilateral RLN LND (i.e., the STL group). Albeit subject to future confirmation, our findings seem to suggest that RLN LND should be practiced as part of the surgical routine for ESCC patients after nCRT (even in the absence of positive nodes identified during the preoperative workup).

Dissection of nodes located around the RLN area is technically demanding. Although we were able to demonstrate a low post-RLN LND morbidity in experienced hands, this approach remains time-consuming. Theoretically, selective removal of RLN lymph nodes would be desirable if specific risk factors could be identified preoperatively. Unfortunately, we were unable to find any significant predictor of RLN nodal involvement after nCRT. Previously reported risk factors for RLN LNM in primarily resected patients (e.g., tumor location or clinical stage) do not seem to have a significant predictive value in nCRT-treated cases. Of note, metastatic spread to the RLN nodes was also observed in patients who showed a pathological complete response at the primary tumor site (ypT0; Supplemental Table 1). The omission of such cases would have led to an erroneous classification of some ypT0N+ patients as ypT0N0, ultimately resulting in an incorrect prognostic stratification [18].

Despite being promising, our results should be interpreted in light of some limitations. First, because data collection was conducted retrospectively and the decision to perform RLN LND was not randomized, we cannot exclude a selection bias. Second, during the early study period when TTL has not yet been implemented as part of surgical routine, we used low-dose radiotherapy (30 Gy) combined with the PF regimen with the main goal of decreasing chemoradiotherapy toxicity. This has resulted in different radiation doses being delivered to the RLN LN area in two groups. Third, although we were able to observe a lower upper mediastinum nodal recurrence rate following TTL (compared with STL), the addition of RLN area into routine LND did not translate into a significantly better survival (possibly because of the small sample size). Future studies in larger cohorts are needed to confirm and expand our findings.

Conclusion

The addition of the RLN area into routine LND in ESCC patients who had undergone nCRT may improve local control without increasing the operative risk and should be practiced as part of the surgical routine.

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Compliance with ethical standards

Ethical statement All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 (and subsequent versions). The study protocol was reviewed and approved by the local Institutional Review Board (CGMH-IRB-201800087B0). Owing to the retrospective nature of the study, the need for informed consent was waived.

Conflict of interest All authors declare that there are no conflicts of interest.

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