Original Article

Short-term outcomes of three- and two-field lymphadenectomy with minimally invasive esophagectomy for esophageal cancer: a propensity score-matching analysis

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Background: Whether patients can benefit from three-field lymphadenectomy (3-FL) in minimally invasive esophagectomy (MIE) remains unclear. This study retrospectively compared short-term outcomes between 3-FL and two-field lymphadenectomy (2-FL) in MIE for patients with esophageal cancer (EC) and aimed to evaluate the clinical significance of 3-FL.

Methods: There were 284 patients enrolled in the study (124 patients with 3-FL and 160 patients with 2-FL). The cases were matched based on their propensity scores using a matching ratio of 1:1, the nearest neighbor matching protocol, and a caliper of 0.02. Patients were propensity-score matched for sex, cancer location, Age-adjusted Charlson Comorbidity Index (ACCI), and neoadjuvant treatment. The short-term outcomes were postoperative complications, operation characteristics, pathology results and postoperative hospital stay.

Results: There were no significant differences in intraoperative hemorrhage, postoperative hospital stay, or postoperative complications between the 2-FL and 3-FL groups. The operation time of the two groups was significantly different (227.1±46.2 *vs.* 248.5±45.9 min, P=0.001); the operation time of the 3-FL group was about 20 minutes longer than that of the 2-FL group. The number of lymphatic nodes (LNs) obtained in the 3-FL group was significantly higher than that in the 2-FL group (31.3±12.9 *vs.* 54.6±18.0, P<0.001). Pathological N stage was also significantly different (P=0.002); the 3-FL group was more advanced than the 2-FL group.

Conclusions: Compared to 2-FL MIE, 3-FL MIE does not increase postoperative complications, can obtain more LNs, and improves the accuracy of tumor LN staging.

Keywords: Esophageal cancer (EC); minimally invasive esophagectomy (MIE); two-field lymphadenectomy (2-FL); three-field lymphadenectomy (3-FL)

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Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide and one of the deadliest malignancies (1). Although great progress has been made in the treatment of this tumor, the 5-year overall survival rate is only around 30% in most countries (2). It is widely accepted that lymph node (LN) metastasis is independent predictor of poor prognosis (3). For resectable EC, multidisciplinary comprehensive treatment based on surgery is still the main strategy. Cervical lymph node metastasis (CLNM) is very common in EC, and the metastasis rate is about 20% (4,5). CLNM of EC is an important basis for lymphadenectomy of EC. Radical surgery of EC can be divided into two-field lymphadenectomy (2-FL) and three-field lymphadenectomy (3-FL). Patients with definite CLNM need 3-FL for radical treatment. For patients with unclear CLNM status, whether to perform 2-FL or 3-FL is still controversial (6-12). Although some studies suggested that 3-FL improved overall survival compared to 2-FL, the evidence remains insufficient. Moreover, many surgeons believe that 3-FL causes more trauma and postoperative complications (13). These concerns have hindered the widespread clinical use of 3-FL. In recent years, with improvements of surgical instruments and skill, minimally invasive esophagectomy (MIE) is gradually being performed in high-volume centers worldwide. Compared to open esophagectomy, MIE has a better perioperative complication rate and is more beneficial in terms of quality of life (14,15). As for survival benefits, MIE is superior to, or at least not inferior to, open esophagectomy (16,17). However, previous studies on MIE focused on surgical technique and the advantages over open esophagectomy. Whether patients benefit more from 3-FL with MIE compared to 2-FL remains to be studied (16-18).

Since 2015, our department has performed 3-FL and 2-FL MIE in patients with EC. In this study, we retrospectively compared the short-term outcomes of 3-FL and 2-FL in MIE, with the goal of providing a clinical basis for determining the extent of LN dissection in MIE. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2356/rc).

Highlight box

Key findings

- Compared with two-field lymphadenectomy (2-FL), three-field lymphadenectomy (3-FL) with minimally invasive esophagectomy (MIE) improved the accuracy of tumor LN staging and did not increase postoperative complications for esophageal cancer (EC).

What is known and what is new?

- For patients with unclear cervical lymph node metastasis (CLNM) status, whether to perform 2-FL or 3-FL is still controversial. Although some studies suggested that 3-FL improved overall survival compared to 2-FL, the evidence remains insufficient. In recent years, MIE is gradually being performed in high-volume centers worldwide. Previous studies on MIE focused on surgical technique and the advantages over open esophagectomy. Whether patients benefit more from 3-FL with MIE compared to 2-FL remains to be studied.
- This study reports short-term outcomes of 3-FL and 2-FL with MIE for EC, which provides strong evidence for the selection of 3-FL with MIE and also lays the foundation for the follow-up long-term survival study.

What is the implication, and what should change now?

- For patients with unclear CLNM status, Three-field lymphadenectomy with MIE compared with two- field lymphadenectomy is more appropriate. Because it can improve the accuracy of tumor LN staging which guides the next step of treatment and do not increase postoperative complications.

Methods

Population

Between July 2015 and November 2022, a total of 430 patients diagnosed with esophageal squamous cell carcinoma in our department underwent esophagectomy. Of those patients, 146 were ruled out according to the study exclusion criteria, which were as follows: (I) patients who received salvage esophagectomy (n=6); (II) patients who had another primary malignancy (n=24); (III) patients who had R1 or R2 resection (n=40); (IV) patients with a history of previous thoracic surgery (n=6); and (V) non-McKeown MIE procedure (n=70). Finally, we included 124 patients in the 3-FL group and 160 patients in the 2-FL group.

Surgical procedure and extent of lymphadenectomy

Surgical procedures including cervical lymphadenectomy were performed by T.Q.G., the director of thoracic surgery department at the Sixth Medical Center of PLA General Hospital. In this study, McKeown esophagectomy, consisting of three regular portions, was the basic procedure for all patients. The mainly surgical procedures were as follows: (I) thoracoscopic procedure: patients were at a left lateral prone position, through thoracoscope in

the right thorax, undergoing ligation of azygos vein, free esophagus, lower ligation of thoracic duct, tumor exploration and resection, esophagus suspension for the recurrent laryngeal nerve (RLN) dissection and total mediastinal lymphadenectomy; (II) cervical procedure: patients were at a supine position with cephalic retroversion, undergoing cervical esophagus mobilization and stapler-assisted esophagogastric anastomosis at the left side of neck; (III) laparoscopic procedure: patients were at a supine position, undergoing abdominal exploration, stomach mobilization and lymphadenectomy (10,18). The gastric tube construction and needle catheter jejunostomy were carried out in an open way. Pyloroplasty was not performed routinely.

Dissected LNs were grouped according to the Japanese classification of esophageal cancer, 11th edition (19). Cervical LNs dissected included Nos. 101, 102 and 104. The dissected mediastinal LNs included Nos. 105, 106, 107, 108, 109, 110, 111, 112 and TG. Dissected abdominal LNs included the Nos. 1, 2, 3, 7, 8a, 9 and 11p groups. The extent of dissected LNs in 2-FL consisted of mediastinal LNs and abdominal LNs, and 3-FL included the cervical LNs besides the extent of 2-FL. Postoperative pathological tumor node metastasis (pTNM) staging was performed by pathologists according to the 8th edition staging system of the American joint committee on cancer (20).

Patient characteristics

Clinical characteristics and surgical and postoperative outcomes were extracted from the medical records database of the Sixth Medical Center of PLA General Hospital. The parameters involved in propensity score matching (PSM) were sex, cancer location, Age-adjusted Charlson Comorbidity Index (ACCI) and neoadjuvant treatment. The Charlson Comorbidity Index (CCI) was calculated using the method previously reported by Charlson (21). ACCI was calculated using the CCI and additional scores based on age. The outcome parameters were operation characteristics, pathology results, postoperative hospital stay, and postoperative complications defined by the Esophagectomy Complications Consensus Group, including anastomotic leakage, chyle leak, RLN palsy, pulmonary complications, pneumonia, and cardiac and cardiac complications.

Statistical analysis

A propensity score-matched analysis was performed to minimize selection bias. Propensity scores were calculated using logistic regression. All cases were entered into the regression model as dependent variables according to surgical method (3-FL group or 2-FL group). The cases were matched based on their propensity scores using a matching ratio of 1:1, the nearest neighbor matching protocol, and a caliper of 0.02. Cases were not reusable after matching. Data were analyzed using SPSS 26 software (SPSS Inc., Chicago, IL, USA). Measured data were expressed as mean ± standard deviation (SD) or median, and the groups were compared using Student's *t*-test or the Mann-Whitney *U* test. Count data were expressed as number or percent, and comparisons were conducted using the Chi-square test or Fisher's exact test. A two-sided P value <0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Sixth Medical Center of PLA General Hospital (No. HZKY2023-19) and individual consent for this retrospective analysis was waived.

Results

Demographic and clinical characteristics

The flow diagram is shown in *Figure 1*. Of 430 screened patients, 146 were excluded for not fulfilling the inclusion criteria, leaving 284 eligible patients in this study (124 cases with 3-FL and 160 cases with 2-FL). The demographic and clinical characteristics of the 284 patients are described in *Table 1*. Before PSM, there were significant differences in the ACCI (P=0.001) and neoadjuvant treatment (P=0.005) between the 2-FL and 3-FL groups. After PSM, there was no statistically significant difference in sex, cancer location, ACCI, or neoadjuvant treatment between the two groups (P>0.99). In total, 202 patients participated in the analysis (101 per group). Detailed patient characteristics before and after matching are shown in *Table 1*, and detailed matching information is shown in *Figure 2*.

Primary and secondary results

The results before and after PSM are shown in *Table 2*. After matching, the incidence of postoperative complications in the 2-FL and 3-FL groups was 53.5% and 60.4%, respectively (P=0.32). In the 2-FL group, the

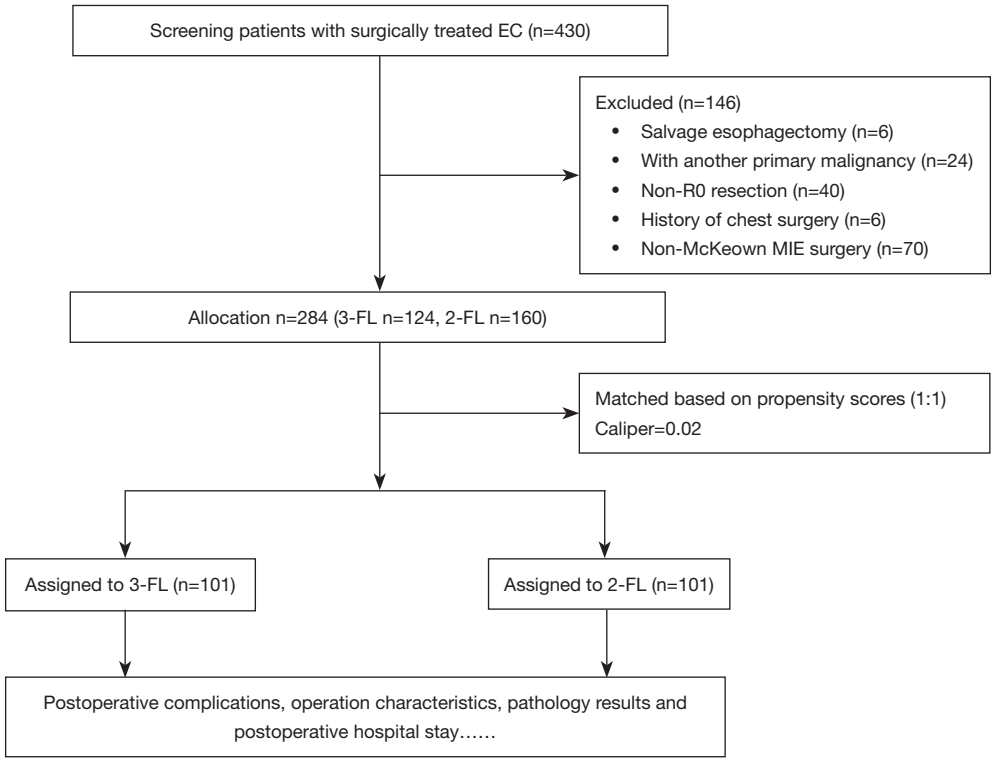

Figure 1 The flow diagram. EC, esophageal cancer; MIE, minimally invasive esophagectomy; FL, field lymphadenectomy.

Table 1 Comparison of case mix characteristics in the overall population, and undergoing (3-FL MIE versus 2-FL MIE, before and after propensity score matching)

Variables	All patients (n=284)	Before matching			After matching		
		2-FL (n=160)	3-FL (n=124)	P	2-FL (n=101)	3-FL (n=101)	P
Sex				0.90			>0.99
Male	235 (82.7)	132 (82.5)	103 (83.1)		84 (83.2)	84 (83.2)	
Female	49 (17.3)	28 (17.5)	21 (16.9)		17 (16.8)	17 (16.8)	
Cancer location				0.67			>0.99
Upper	44 (15.5)	23 (14.4)	21 (16.9)		16 (15.8)	16 (15.8)	
Middle	148 (52.1)	87 (54.4)	61 (49.2)		56 (55.4)	56 (55.4)	
Lower	92 (32.4)	50 (31.2)	42 (33.9)		29 (28.7)	29 (28.7)	
ACCI				0.001			>0.99
ACCI ≤2	89 (31.3)	38 (23.8)	51 (41.1)		33 (32.7)	33 (32.7)	
2< ACCI ≤5	191 (67.3)	118 (73.7)	73 (58.9)		68 (67.3)	68 (67.3)	
5< ACCI	4 (1.4)	4 (2.5)	0 (0.0)		0 (0.0)	0 (0.0)	
Neoadjuvant treatment				0.005			>0.99
No	186 (65.5)	116 (72.5)	70 (56.5)		64 (63.4)	64 (63.4)	
Yes	98 (34.5)	44 (27.5)	54 (43.5)		37 (36.6)	37 (36.6)	

Data are presented as n (%). 3-FL, three-field lymphadenectomy; 2-FL, two-field lymphadenectomy; MIE, minimally invasive esophagectomy; ACCI, Age-adjusted Charlson Comorbidity Index.

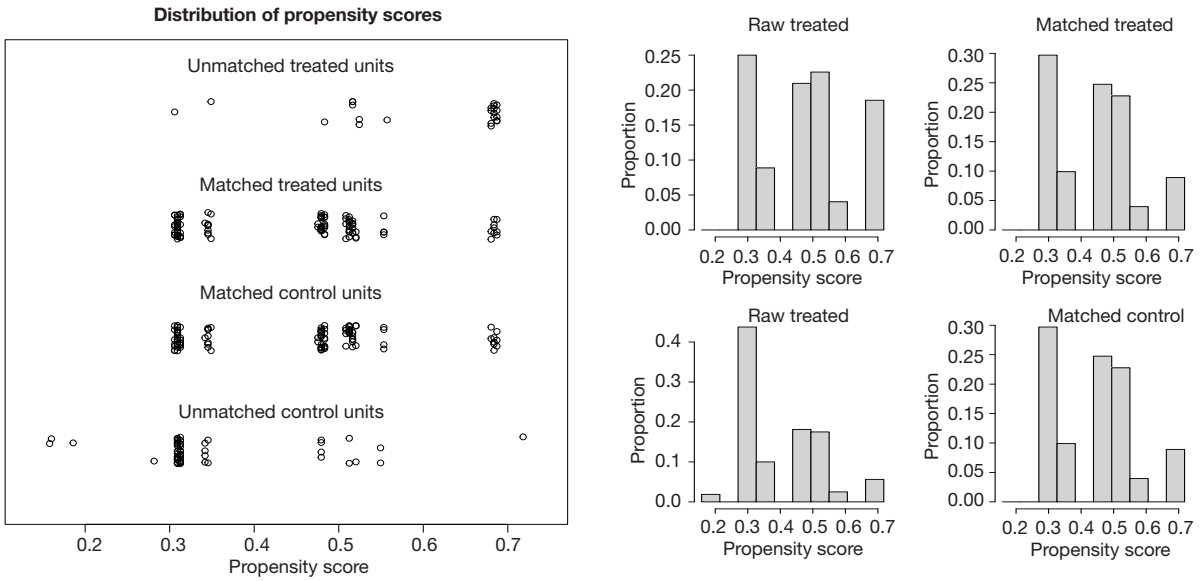

Figure 2 The detailed information of propensity score matching analysis.

incidence of anastomotic leak was 11.9%, that of chyle leak was 2.0%, that of RLN palsy was 19.8%, that of pulmonary complications was 33.7%, that of pneumonia was 10.9%, and that of cardiac complications was 5.9%. In 3-FL group, the incidence of anastomotic leak was 8.9%, that of chyle leak was 5.9%, that of RLN palsy was 27.7%, that of pulmonary complications was 36.6%, that of pneumonia was 16.8%, and that of cardiac complications was 1.0%. The severity of postoperative complications was not significantly different between the two groups (P=0.29). The incidence of ≥ grade III complications was 31.7% (32/101) in the 2-FL group and 27.8% (28/101) in the 3-FL.

Operation time in the 2-FL group was approximately 20 minutes shorter than that in the 3-FL group {220 [52.5] *vs.* 240 [65] minutes, P=0.001}. There was no significant difference in intraoperative hemorrhage {150 [100] *vs.* 170 [95] mL, P=0.57} or postoperative hospital stay {13 [5.5] *vs.* 13 [6] days, P=0.12} between the 2-FL and 3-FL groups. According to the postoperative pathological examination, fewer LNs were dissected in the 2-FL group compared to the 3-FL {29 [15] *vs.* 50 [24.5], P<0.001}. There was 1 [4] positive LN in the 3-FL group and 0 [3] in the 2-FL group (P=0.005). Notably, pathological N stage was also significantly different between the two groups, as follows: N3 stage, 5.0%; N2 stage, 21.8%; N1 stage, 16.8%; and N0 stage, 56.4% in the 2-FL group versus N3 stage, 17.8%; N2 stage, 16.8%; N1 stage, 28.7%; and N0 stage, 36.6% in the 3-FL group (P=0.002).

Discussion

In previous studies, the debate about postoperative complications of 3-FL and 2-FL has focused on RLN palsy, pulmonary complications and anastomotic leak (14,15). A randomized controlled trial (RCT) study by Professor Li and colleagues of Fudan University reported that there was no significant difference in the overall postoperative complication rate between 2-FL and 3-FL groups of patients with squamous carcinoma of the middle and lower esophagus who underwent the Ivor Lewis procedure (22). A recent meta-analysis of postoperative complications noted no significant differences in postoperative mortality and overall complication rates, including postoperative pneumonia, or anastomotic leak between 2-FL and 3-FL groups. However, 3-FL is associated with a longer operative time, longer hospital stay, greater blood loss, more severe postoperative hoarseness, and a greater number of lymph nodes (LNs) (23). RLN injury is mainly caused by thermal injury from strain and energy instruments used during thoracoscopic lymphadenectomy; tissue adjacent to the RNL can also be affected. In terms of the incidence of RLN palsy, there are many studies showing a higher incidence in the 3-FL group compared to the 2-FL group (6,8,9,14). However, in our study, the incidence of RLN palsy was similar in both groups (3-FL: 27.7%; 2-FL: 19.8%, P=0.19). Because patients in both groups underwent complete mediastinal lymphadenectomy, the dissection of No.106

Table 2 Comparison of outcome parameters between 3-FL MIE and 2-FL MIE

Variables	Before matching			After matching		
	2-FL (n=160)	3-FL (n=124)	P	2-FL (n=101)	3-FL (n=101)	P
Anastomotic leak			0.51			0.49
Yes	18 (11.3)	11 (8.9)		12 (11.9)	9 (8.9)	
No	142 (88.8)	113 (91.1)		89 (88.1)	92 (91.1)	
Chyle leak			0.16			0.28
Yes	3 (1.9)	6 (4.8)		2 (2.0)	6 (5.9)	
No	157 (98.1)	118 (95.2)		99 (98.0)	95 (94.1)	
RLN palsy			0.09			0.19
Yes	29 (18.1)	33 (26.6)		20 (19.8)	28 (27.7)	
No	131 (81.9)	91 (73.4)		81 (80.2)	73 (72.3)	
Pulmonary complications			0.81			0.66
Yes	52 (32.5)	42 (33.9)		34 (33.7)	37 (36.6)	
No	108 (67.5)	82 (66.1)		67 (66.3)	64 (63.4)	
Pneumonia			0.24			0.22
Yes	17 (10.6)	19 (15.3)		11 (10.9)	17 (16.8)	
No	143 (89.4)	105 (84.7)		90 (89.1)	84 (83.2)	
Cardiac complications			0.04			0.054
Yes	10 (6.3)	1 (0.8)		6 (5.9)	1 (1.0)	
No	150 (93.8)	123 (99.2)		95 (94.1)	100 (99.0)	
Overall complications			0.22			0.32
Yes	80 (50.0)	71 (57.3)		54 (53.5)	61 (60.4)	
No	80 (50.0)	53 (42.7)		47 (46.5)	40 (39.6)	
Clavien-Dindo classification			0.25			0.29
0	64 (40.0)	47 (37.9)		38 (37.6)	35 (34.7)	
I	18 (11.3)	25 (20.2)		12 (11.9)	20 (19.8)	
II	29 (18.1)	19 (15.3)		19 (18.8)	18 (17.8)	
III	45 (28.1)	28 (22.6)		31 (30.7)	24 (23.8)	
IV	4 (2.5)	5 (4.0)		1 (1.0)	4 (4.0)	
No. of lymph nodes, median	30	49	<0.001	29	50	<0.001
No. of positive lymph nodes, median	0	1	0.002	0	1	0.005
Pathological N stage			<0.001			0.002
N0	89 (55.6)	43 (34.7)		57 (56.4)	37 (36.6)	
N1	27 (16.9)	38 (30.6)		17 (16.8)	29 (28.7)	
N2	35 (21.9)	22 (17.7)		22 (21.8)	17 (16.8)	
N3	9 (5.6)	21 (16.9)		5 (5.0)	18 (17.8)	
Operation time (min), median	220	235	0.001	220	240	0.001
Postoperative hospital stay (days), median	13	14	0.17	13	13	0.12
Intraoperative hemorrhage (mL), median	150	150	0.20	150	170	0.57

Data are presented as n (%). 3-FL, three-field lymphadenectomy; 2-FL, two-field lymphadenectomy; MIE, minimally invasive esophagectomy; RLN, recurrent laryngeal nerve.

LNs resulted in similar rates of RLN injury.

In this study, the 2-FL was not the traditional 2-FL procedure, and this should now be called extended 2-FL or 2.5-FL, in which we dissected fewer cervical LNs (Nos. 101, 102, and 104) than in the 3-FL group. In addition, the basic procedure in both groups was the McKeown procedure, in which the gastroesophageal anastomosis was performed in the neck. The surgical method for handling the anastomosis and the influence of the surrounding tissues on the anastomotic environment were similar, so the incidence of anastomotic leak was also similar (3-FL: 8.9%; 2-FL: 11.9%, P=0.49). The overall incidence of complications in our study was not entirely consistent with those reported in the literature (24-28). These inconsistencies were mainly attributed to different surgical techniques, anastomotic locations, numbers of cases, or patient backgrounds.

In previous studies, the incidence of anastomotic leak after esophagectomy for EC was 6–20% (24,29). In this study, the incidence was 11.9% and 8.9% in the 2-FL and 3-FL groups, respectively, which was in accordance with previous studies, and there was no significant difference between the two groups. Postoperative anastomotic leak is common after EC surgery and is associated with increased hospital costs, higher incidence of anastomotic strictures, and decreased long-term survival. According to the definition of anastomotic leak of the Esophagectomy Complications Consensus Group, postoperative anastomotic leak in EC can be classified into three types. In this study, the incidence of type II in the 2-FL group was 11.9% (12/101), the incidence of types I and II in the 3-FL group were 1.0% (1/101) and 7.9% (8/101), respectively, and no type III occurred in either group. Through dietary modification, interventional radiology drain, and bedside opening or packing of the incision, healing can be achieved within 2 months without secondary surgical treatment.

In Japan, a retrospective study of 4,590 patients reported rates of 42.3%, 27.5%, and 19% for cervical LN metastasis for upper, middle, and lower EC, respectively (30). In this study, the rate of cervical LN metastasis in the 3-FL group was 26.7%. The above data suggest that 20–30% of these patients would have developed residual metastatic LNs in the neck if they had not received 3-FL treatment. Here, we did not analyze the relationship between CLNM and tumor location because almost 40% of the cervical LN dissections were elective. This inevitably introduces bias.

This study had several limitations. First, it was a single-center retrospective study. To reduce the bias caused by potential confounders, PSM analysis was used. The sample size was somewhat reduced although not by much. Furthermore, with the increasing use of neoadjuvant therapy, the need for 3-FL after neoadjuvant therapy is unclear. We did not analyze this topic, but rather included it as one of the factors for PSM. Finally, the pathology in this study was squamous cell carcinoma, and the results have limited capacity to serve as a guide to adenocarcinoma.

Conclusions

In conclusion, our study indicated the safety and efficacy of 3-FL in MIE for EC. Compared with 2-FL, 3-FL MIE improved the accuracy of tumor LN staging and did not increase postoperative complications. Future study is needed to compare the differences in survival between the two procedures.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2356/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2356/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2356/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2356/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised

in 2013). The study was approved by the Sixth Medical Center of PLA General Hospital (No. HZKY2023-19) and individual consent for this retrospective analysis was waived.

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