



Influence of Neoadjuvant Therapy on Poor Long-Term Outcomes of Postoperative Complications in Patients with Esophageal Squamous Cell Carcinoma: A Retrospective Cohort Study

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ABSTRACT

Background. Postoperative complications have a negative impact on overall survival after esophagectomy because systemic inflammation may induce residual cancer cell growth. A solution that could suppress micrometastasis is neoadjuvant therapy; however, to date, no study has shown that neoadjuvant therapy suppresses proliferation of cancer cells due to postoperative complications after esophagectomy. The aim of this study is to investigate the influence of neoadjuvant therapy on poor long-term outcomes of postoperative complications in patients with esophageal carcinoma.

Patients and Methods. In total, 431 patients who underwent esophagectomy for esophageal squamous cell carcinoma were included in this study. We investigated the relationship between complications, such as pneumonia, and long-term oncologic outcomes with and without neoadjuvant therapy.

Results. Among the patients, the 3-year overall survival (OS) rate was 69.5% and the disease-free survival (DFS) rate was 59.0%. The patients were categorized into two groups: the neoadjuvant therapy (+) group ($n = 217$) and neoadjuvant therapy (−) group ($n = 214$). Among patients

not undergoing neoadjuvant therapy, patients with pneumonia or pyothorax had significantly poorer OS and DFS than patients without these complications. However, among patients undergoing neoadjuvant therapy, there were no significant differences in long-term outcomes, regardless of presence of complications. On multivariate analysis, pneumonia ($p = 0.003$), pyothorax ($p < 0.001$), and chylothorax ($p = 0.002$) were identified as predictors of death in the neoadjuvant therapy (−) group.

Conclusion. The negative impact of postoperative complications on long-term prognoses can be reduced by performing neoadjuvant therapy in patients with esophageal carcinoma.

Theoretically, in patients with esophageal squamous cell carcinoma, esophagectomy with two- or three-field lymph node dissection is considered the most promising treatment to achieve long-term survival. However, despite improvements in surgical techniques and perioperative management, postoperative morbidity and mortality after esophagectomy remain poor due to its high malignancy. Our previous study using data from a Japanese nationwide web-based database showed that 3.4% of patients experienced operative mortality, 15.4% developed pneumonia, and 13.3% had postoperative anastomotic leakage.¹

Although some predictive factors for long-term prognosis after esophagectomy have been reported,^{2,3} many studies, including ours, have indicated a relationship between postoperative complications and long-term prognosis in patients with esophageal cancer.^{4–8} In a previous study, we reported that postoperative pneumonia has a negative effect on overall survival (OS) after

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esophagectomy.^{4,5} Our results suggested that systemic inflammation compromises cell-mediated immunity and induces residual cancer cell growth.⁹

A solution that could suppress micrometastasis is neoadjuvant therapy, which is the standard treatment in patients with stage II/III squamous cell carcinoma, based on the results of a Japanese randomized trial.¹⁰ By eliminating micrometastasis by neoadjuvant therapy, even if postoperative complications occur, residual cell carcinoma progression can be suppressed. However, to date, no study has shown that neoadjuvant therapy suppresses proliferation of cancer cells due to postoperative complications after esophagectomy. We hypothesized that the negative effect of postoperative complications on long-term outcomes can be reduced by performing neoadjuvant therapy in patients with esophageal squamous cell carcinoma. Moreover, we assessed whether the intensity of neoadjuvant therapy affects long-term survival.

PATIENTS AND METHODS

Patients

We conducted a single-institution, retrospective cohort study between 2000 and 2017, wherein 431 patients who underwent esophagectomy for primary esophageal squamous cell carcinoma without distant metastasis (cM1) were referred to our department. Patients who were diagnosed with cM1 due to supraclavicular lymph node metastasis, which is considered a regional lymph node in the Japanese Classification of Esophageal Cancer, were included.¹¹

Neoadjuvant therapy comprised 5-fluorouracil (5-FU) and cisplatin (FP), or 5-FU and cisplatin combined with docetaxel (DCF), or comprised 5-FU and CDDP combined with a radiation dose of 40–50 Gy (FP-RT). We primarily performed neoadjuvant therapy in patients with clinical node-positive cancer or tumors greater than T1 without distant metastases since 2000. Patients with clinical T1N0 tumor (clinically negative nodes), those who could not receive chemotherapy, and those who refused to undergo chemotherapy did not undergo neoadjuvant therapy. Moreover, patients with evident unresectable local advanced tumor underwent definitive chemoradiotherapy. Until 2009, neoadjuvant FP-RT as primary treatment was selectively administered to patients with locally advanced carcinoma or multiple lymph node metastases. Commencing in 2010, DCF was administered with the same indication. Patients who underwent definitive CRT followed by salvage esophagectomy were excluded from our study. Moreover, patients with macroscopic residual tumors (R2) in the pathological findings and those who underwent two-term operations were excluded.

From hospital records, we retrospectively evaluated the patients' clinical characteristics, including age, sex, clinical findings, and surgical procedure. The patients' postoperative complications were collected from our database records retrospectively. The clinical and pathological stages of the cancer were determined according to the International Union Against Cancer, 7th edition.¹² The evaluation of residual tumors was classified as pR0 for no residual tumor or pR1 for microscopic residual tumor.¹³

This study was conducted with the approval of the ethics committee of Keio University School of Medicine.

Surgical Procedures

At our institution, we perform thoracic procedures through a right thoracic incision or video-assisted thoracic surgery in hybrid position, combining the left decubitus and prone positions.^{14,15} With regard to alimentary tract reconstruction, the gastric conduit through the posterior mediastinal route is mainly used. An ileocolic conduit via an antesternal or retrosternal route is also used in patients with synchronous double cancer of the stomach or previous history of gastrectomy. Clavien–Dindo classifications are used to assess postoperative complications:¹⁶ Pneumonia is defined as fever > 38 °C with an abnormal shadow on the chest radiograph and positive sputum and/or white blood cell count $> 12,000/\text{mm}^3$.^{5,17} Anastomotic leakage is diagnosed on the basis of computed tomography (CT) scan findings or esophagography and/or the characteristics of the anastomotic drains. Wound infections indicate superficial and deep incisional surgical-site infections. In this study, we considered pneumonia and anastomotic leakage of Clavien–Dindo classification grade II or greater as well as other complications of Clavien–Dindo classification grade I or greater as postoperative complications.

Statistical Analysis

Statistical analyses were performed using Stata/SE 12.1 for Mac (StataCorp, College Station, TX, USA). Categorical variables were analyzed using the Chi squared test for univariate analysis, and continuous variables were analyzed using the Mann–Whitney *U* test. We also investigated prognosis using the Kaplan–Meier method and log-rank tests, and entered significant variables into a Cox hazard regression model for multivariate analysis. OS was calculated from primary treatment date. Cancer-specific survival (CSS) also indicated the term from treatment date to date of death due to the cancer.

RESULTS

Patient Characteristics

The 431 included patients were categorized into two groups: the neoadjuvant therapy (+) group ($n = 217$) and neoadjuvant therapy (−) group ($n = 214$). In the neoadjuvant therapy (+) group, 163 (75.1%), 31 (14.3%), and 23 patients (10.6%) underwent FP, DCF, and FP-RT therapy, respectively, before esophagectomy. We introduced neoadjuvant therapy in 2000, and this treatment has been offered in earnest since 2008. Therefore, 70 stage II–IV patients (32.7%), particularly those treated prior to 2007, were included in the neoadjuvant therapy (−) group. In the same period, 31 patients who had progressive disease, or who refused to undergo esophageal resection, or who had poor general condition after NAC could not undergo surgery. The clinicopathological characteristics of the study patients are presented in Table 1. Significant between-group differences were observed in clinical cancer stage ($p < 0.001$), adjuvant therapy ($p < 0.001$), operation year ($p < 0.001$), tumor classification [pT ($p < 0.001$)], lymph node classification [pN ($p < 0.001$)], and pathological classification [pStage ($p < 0.001$)] (Table 1).

Recurrent laryngeal nerve paralysis [97/431 patients (26.4%)] was the most commonly observed complication after esophagectomy, followed by pneumonia [85/431 patients (19.7%)], anastomotic leakage [68/431 patients (15.8%)], wound infection [39/431 patients (9.1%)], and atrial fibrillation [37/431 patients (8.6%)]. Hospital death occurred in five patients (1.2%) (Table 2). No significant complications were observed in the neoadjuvant therapy (+) group compared with the neoadjuvant therapy (−) group.

Long-Term Outcomes

Among all patients, the 3-year OS rate was 69.5% and the DFS rate was 59.0%. During the follow-up period, 156 patients (36.2%) developed recurrence and 136 patients (31.6%) died.

Among the patients not undergoing neoadjuvant therapy, patients with pneumonia had poor OS [median survival: pneumonia (+) 70 months versus pneumonia (−) not reached, $p = 0.005$]; however, among the patients undergoing neoadjuvant therapy, no significant differences were observed between patients with or without pneumonia ($p = 0.216$) (Fig. 1). In addition to pneumonia, the other two complications (pyothorax and chylothorax) were also associated with poor OS in the neoadjuvant therapy (−) group (Fig. 2). Moreover, pneumonia was also a significant predictive factor for DFS ($p = 0.008$), and patients with pneumonia tended to have lower CSS compared with

patients without pneumonia in the neoadjuvant therapy (−) group ($p = 0.100$) (Supplemental Figure 1).

According to univariate analyses, pStage was the only risk factor for death in the patients undergoing neoadjuvant therapy; however, several factors, including pneumonia, pyothorax, and chylothorax, were identified as significant risk factors in the neoadjuvant therapy (−) group (Supplemental Tables 1, 2). On multivariate analysis using a Cox regression model that included these factors, pStage III and IV, American Society of Anesthesiologists (ASA) class 3, chronic obstructive pulmonary disease (COPD), operation year, pneumonia, pyothorax, and chylothorax were identified as predictors of death in the neoadjuvant therapy (−) group (Table 3). However, no complications were significant predictive factors of OS in the neoadjuvant therapy (+) group. Two types of complications, viz. pneumonia and pyothorax, were also significant predictive factors for DFS in the neoadjuvant therapy (−) group (Supplemental Table 3).

Recurrence Pattern

The most common pattern of first recurrence was locoregional in 84 patients, followed by distant recurrence (36 patients), and both locoregional and distant recurrences (35 patients). We investigated the association between recurrence pattern and pneumonia in the neoadjuvant therapy (+) and neoadjuvant therapy (−) groups. In the neoadjuvant therapy (−) group, patients with postoperative pneumonia tended to exhibit a higher distant recurrent rate [pneumonia (+), 4/36 (11.1%) versus pneumonia (−), 8/178 (4.5%), $p = 0.116$] (Supplemental Table 4).

Subgroup Analysis for OS

We examined the relationship between pneumonia and OS with or without neoadjuvant therapy at each pStage. Of 267 patients who had pStage I and II, 116 patients underwent neoadjuvant therapy before surgery and 151 patients did not undergo neoadjuvant therapy. Although pneumonia was not a predictive factor for OS in the 116 patients who underwent neoadjuvant therapy ($p = 0.693$), pneumonia tended to be a predictive factor for OS in the 151 patients who did not undergo neoadjuvant therapy ($p = 0.083$) (Fig. 3a). Of 164 patients who had pStage III and IV, 101 patients underwent neoadjuvant therapy and 63 patients did not undergo neoadjuvant therapy. In addition to early-stage tumor, although pneumonia was not a predictive factor for OS in patients who underwent neoadjuvant therapy ($p = 0.772$), it was a significant predictive factor for OS in patients who did not undergo neoadjuvant therapy ($p = 0.029$) (Fig. 3b).

TABLE 1 Patient characteristics

	All (n = 431)	Neoadjuvant therapy (+) group (n = 217)	Neoadjuvant therapy (-) group (n = 214)	p-Value
Sex				0.527
Male	370 (85.9%)	184 (84.8%)	186 (86.9%)	
Female	61 (14.1%)	33 (15.2%)	28 (13.1%)	
Age, median (min–max)	64 (34–85)	64 (34–79)	63 (44–85)	0.922
ASA class				0.086
1	119 (27.6%)	54 (24.9%)	65 (30.4%)	
2	298 (69.1%)	159 (73.3%)	139 (65.0%)	
3	14 (3.3%)	4 (1.8%)	10 (4.7%)	
Location				0.542
Cervical	3 (0.7%)	2 (0.9%)	1 (0.5%)	
Upper	60 (13.9%)	26 (12.0%)	34 (15.9%)	
Middle	238 (55.2%)	119 (54.8%)	119 (55.6%)	
Lower	130 (30.2%)	70 (32.3%)	60 (28.0%)	
cStage				< 0.001
I	178 (41.3%)	34 (15.7%)	144 (67.3%)	
II	101 (23.4%)	62 (28.6%)	39 (18.2%)	
III	130 (30.2%)	102 (47.0%)	28 (13.1%)	
IV	22 (5.1%)	19 (8.8%)	3 (1.4%)	
Neoadjuvant regimen				N.A.
FP	163 (75.1%)	163 (75.1%)	–	
FP-RT	23 (10.6%)	23 (10.6%)	–	
DCF	31 (14.3%)	31 (14.3%)	–	
COPD	13 (3.0%)	7 (3.2%)	6 (2.8%)	0.798
Smoking	208 (48.3%)	108 (49.8%)	100 (46.7%)	0.528
Adjuvant	67 (15.5%)	21 (9.7%)	46 (21.5%)	< 0.001
Year				< 0.001
2000–2007	141 (32.7%)	43 (19.8%)	98 (45.8%)	
2008–2017	290 (67.3%)	174 (80.2%)	116 (54.2%)	
VATS	300 (69.6%)	143 (65.9%)	157 (73.4%)	0.092
FD				0.103
2FLND	106 (25.4%)	46 (21.9%)	60 (28.9%)	
3FLND	312 (74.6%)	164 (78.1%)	148 (71.2%)	
Operating time (min), median (range)	511 (230–1170)	517 (268–926)	506 (230–1170)	0.320
Amount of bleeding (ml), median (range)	208 (0–4858)	208 (0–4500)	212 (0–4858)	0.491
pT 0/1/2/3/4	11/216/45/152/7	11/69/30/101/6	0/147/15/51/1	< 0.001
pN 0/1/2/3	205/128/68/30	82/78/43/14	123/50/25/16	< 0.001
pM 0/1	398/33	196/21	202/12	0.112
pStage				< 0.001
I	148 (34.3%)	42 (19.4%)	106 (49.5%)	
II	119 (27.6%)	74 (34.1%)	45 (21.0%)	
III	131 (30.4%)	80 (36.9%)	51 (23.8%)	
IV	33 (7.7%)	21 (9.7%)	12 (5.6%)	
Residual cancer				0.971
R0	405 (94.0%)	204 (94.0%)	201 (93.9%)	
R1	26 (6.0%)	13 (6.0%)	13 (6.1%)	

ASA American Society of Anesthesiologists, FP cisplatin and 5-fluorouracil, FP-RT cisplatin and 5-fluorouracil plus radiotherapy, DCF docetaxel plus cisplatin and 5-fluorouracil, COPD chronic obstructive pulmonary disease, VATS video-assisted thoracic surgery, FLND field lymph node dissection, p pathological

TABLE 2 Postoperative complications

	All (<i>n</i> = 431)	Neoadjuvant therapy (+) group (<i>n</i> = 217)	Neoadjuvant therapy (–) group (<i>n</i> = 214)	<i>p</i> -Value
Medical complications	133 (30.9%)	66 (30.4%)	67 (31.3%)	0.841
Pneumonia	85 (19.7%)	49 (22.6%)	36 (16.8%)	0.133
Af	37 (8.6%)	7 (3.2%)	30 (14.0%)	< 0.001
PE	8 (1.9%)	5 (2.3%)	3 (1.4%)	0.488
DVT	7 (1.6%)	2 (0.9%)	5 (2.3%)	0.245
Surgical complications	174 (40.4%)	77 (35.5%)	97 (45.3%)	0.037
Anastomotic leakage	68 (15.8%)	27 (12.4%)	41 (19.2%)	0.056
RLNP	97 (26.4%)	48 (26.8%)	49 (25.9%)	0.846
Wound infection	39 (9.1%)	14 (6.5%)	25 (11.7%)	0.058
Chylothorax	12 (2.8%)	9 (4.2%)	3 (1.4%)	0.083
Pyothorax	9 (2.1%)	5 (2.3%)	4 (1.9%)	0.752
Hospitalized death	5 (1.2%)	2 (0.9%)	3 (1.4%)	0.642

Af atrial fibrillation, PE pulmonary embolism, DVT deep vein thrombosis, RLNP recurrent laryngeal nerve paralysis

Furthermore, we evaluated whether the intensity of neoadjuvant therapy affected long-term survival by comparing the FP group (*n* = 163) and the DCF and FP-RT groups (*n* = 64). Although there were no significant differences between the groups, pneumonia tended to be a predictive factor for OS in the FP group (*p* = 0.085) but not in the DCF and FP-RT groups (*p* = 0.776) (Fig. 4).

DISCUSSION

The present study demonstrates that, in patients with esophageal squamous cell carcinoma, the negative impact of postoperative complications on long-term outcomes, including OS DFS, and CSS, can be reduced by performing neoadjuvant therapy. Furthermore, these outcomes were influenced by the intensity of neoadjuvant therapy, and strong neoadjuvant therapy, such as DCF or FP-RT therapy, had greater efficacy than FP therapy. Although some studies have shown an association between long-term outcomes and postoperative complications, to the best of the authors' knowledge, this is the first report demonstrating the influence of neoadjuvant therapy on poor long-term outcomes of postoperative complications in patients with esophageal squamous cell carcinoma. While reporting on a different type of carcinoma, a study by Eto et al.¹⁸ indicated the potential of neoadjuvant chemotherapy to abolish poor prognosis induced by postoperative complications after curative resection for gastric cancer.

Some institutions, including ours, have reported that postoperative complications (particularly infectious complications such as pneumonia) have a negative impact on long-term outcomes. Baba et al.⁷ showed that postoperative pulmonary complications are an independent predictor of poor long-term survival, as in our study. Rizk et al.¹⁹ also

reported that technical complications, including anastomotic leakage, a paralyzed vocal cord, and chylothorax, have a negative impact on long-term outcomes. Complications adversely affect long-term survival for several reasons. First, as our previous studies have reported, changes in the levels of cytokines, such as interleukin (IL)-6 or IL-8, caused by postoperative complications might correlate with residual cancer cell progression.^{20,21} Moreover, proinflammatory cytokines could promote programmed cell death 1 ligand 1 (PD-L1) expression in the tumor microenvironment. Chen et al.²² suggested that immunosuppression by increased PD-L1 expression is associated with poor prognosis. Neoadjuvant therapy could reduce floating residual cancer cell progression by reducing tumor volume, thereby suppressing tumor progression induced by postoperative complications. As described in the present study, these effects were greater in patients who underwent DCF or FP-RT therapy than in those who underwent FP therapy, and the optimal regimen of neoadjuvant therapy can be determined according to the patients' systemic status and surgical risk. The upcoming outcomes of the Japan Clinical Oncology Group 1109 study, which is a prospective study comparing DCF, FP-RT, and FP therapy for neoadjuvant therapy, will provide clearer evidence in this respect.²³

However, unlike in this study, our previous study showed that the negative impact of postoperative pneumonia could not be reduced by performing definitive chemoradiotherapy in salvage surgery.⁵ Compared with preoperative chemotherapy of less than 50 Gy, the general condition of patients who underwent definitive chemoradiotherapy followed by salvage esophagectomy could be more exacerbated by pneumonia, causing cancer-unrelated

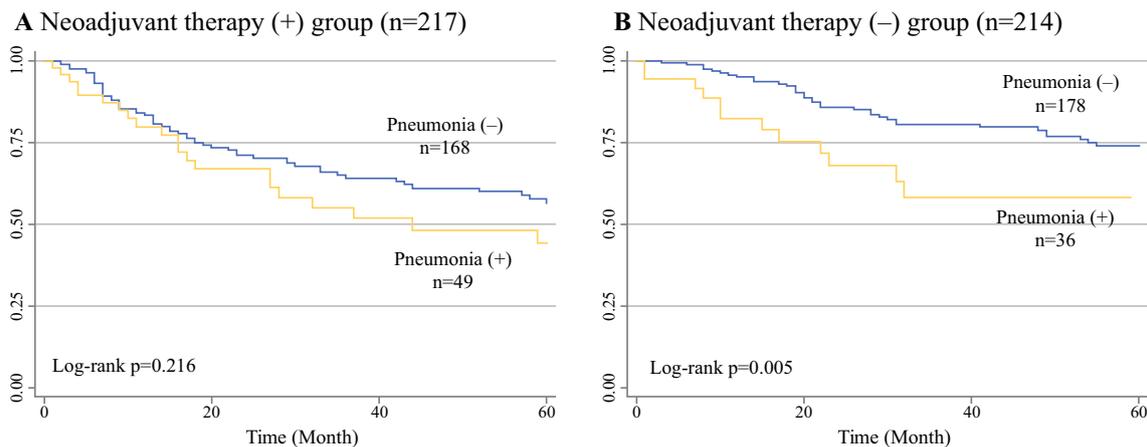


FIG. 1 Kaplan–Meier curves for overall survival (OS) associated with pneumonia in the (A) neoadjuvant therapy (+) group and (B) neoadjuvant therapy (-) group. Yellow and blue lines indicate groups with and without pneumonia, respectively

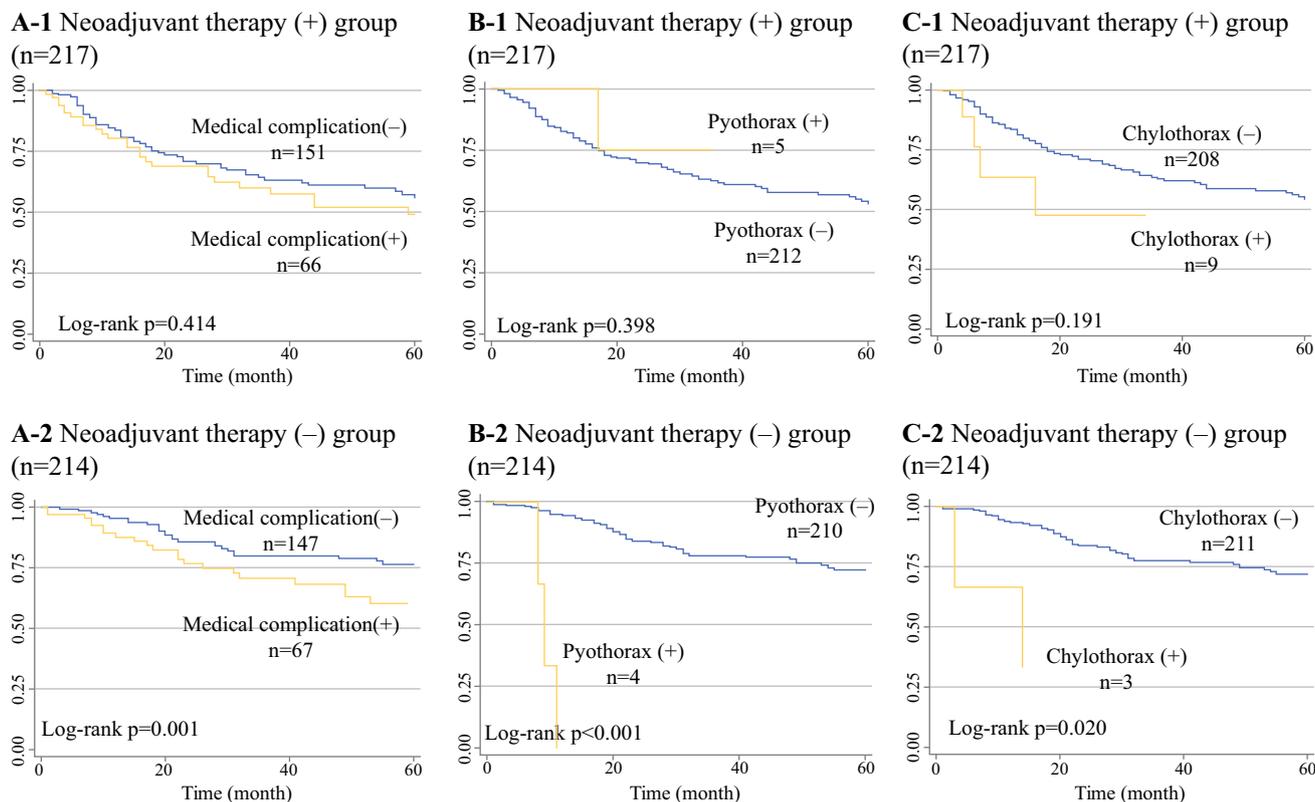


FIG. 2 Kaplan–Meier curves for overall survival (OS) associated with medical complications in the (A-1) neoadjuvant therapy (+) group and (A-2) neoadjuvant therapy (-) group; Kaplan–Meier curves for OS associated with pyothorax in the (B-1) neoadjuvant therapy (+) group and (B-2) neoadjuvant therapy (-) group; Kaplan–

Meier curves for OS associated with chylothorax in the (C-1) neoadjuvant therapy (+) group and (C-2) neoadjuvant therapy (-) group. Yellow and blue lines indicate groups with each complication and those without each complication, respectively

death. In our previous study, 56% of patients who were diagnosed with postoperative pneumonia in the salvage group died from causes unrelated to cancer.⁵

Contrary to our study, Kataoka et al.⁶ reported the exploratory analysis of a prospective study showing that patients in the neoadjuvant group showed association

TABLE 3 Risk factors for death on multivariate analysis

	Neoadjuvant therapy (+) group		Neoadjuvant therapy (−) group	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
pStage III, IV	3.58 (2.23–5.73)	<0.001	2.19 (1.22–3.93)	0.009
ASA class 3			3.66 (1.36–9.83)	0.010
COPD			3.96 (1.18–13.24)	0.025
Year (2008–2017)			0.33 (0.16–0.68)	0.003
RI	1.85 (0.85–4.06)	0.122		
Pneumonia			2.59 (1.38–4.87)	0.003
Pyothorax			21.29 (5.44–83.38)	< 0.001
Chylothorax			10.85 (2.48–47.45)	0.002

p pathological, *ASA* American Society of Anesthesiologists, *COPD* chronic obstructive pulmonary disease, *RI* microscopic residual tumor, *HR* hazard ratio, *CI* confidence interval

between any infectious complications and survival, whereas patients in the adjuvant group showed no association. Although that report indicated that one of the interpretations of this contraindication is that infectious complications after neoadjuvant therapy have a strong negative influence on survival, complications were not defined in accordance with objective criteria, as it was described. Furthermore, Hirao et al.²⁴ suggested that neoadjuvant therapy does not lead to critical systemic status due to postoperative complication compared with adjuvant. However, this prospective study has the advantage of using the data of a randomized controlled trial compared with ours, therefore this discrepancy requires careful consideration.

In addition to infectious complications such as pneumonia and pyothorax, chylothorax and atrial fibrillation have also been associated with long-term outcomes. A few studies have shown an association between chylothorax and prognoses.^{7,19} Kranzfelder et al.²⁵ reported that rapid chyle loss can result in immunosuppression, which is associated with loss of immunoglobulins, T lymphocytes, and proteins. The state of immunosuppression could result in tumor progression; therefore, chylothorax could be related to long-term outcomes. Furthermore, Cormack et al. reported that, although there was no impact on oncologic outcomes, atrial fibrillation was associated with systemic inflammation.²⁶ In our study, postoperative inflammation might have caused atrial fibrillation, resulting in poor prognosis.

In the subanalysis, negative impact of postoperative complications on long-term outcomes was observed in early and advanced tumor stage. Although only a few studies considering tumor stage have been reported, Saeki et al.⁸ suggested that patients at early stage are more likely to be affected by postoperative complications in terms of cancer progression than those with advanced-stage tumors. This may suggest that prognosis is more affected by

oncologic malignancy than postoperative complications in patients with advanced stage. However, unlike in our study, they did not consider the influence of neoadjuvant therapy on long-term outcomes. In our study, the adverse effects of postoperative complications on prognosis could be reduced by performing neoadjuvant therapy, even for advanced stage. Further studies are needed regarding the impact of complication on prognosis in each tumor stage.

This study has several limitations. First, this is a retrospective, single-center study limited to a Japanese population, which could have introduced an element of selection bias. Moreover, the time span (20 years) was long. Therefore, during this time, there were changes in the indication for neoadjuvant therapy, regimens of such therapy, management of postoperative complications, and different therapeutic approaches. However, we recruited a large group, including approximately 500 patients, with esophageal squamous cell carcinoma. To the best of the authors' knowledge, there have only been five studies focusing on prognosis and postoperative complications that included more than 500 patients with esophageal cancer.^{7,8,19,27,28} Second, results of surgical treatment can be affected by hospital volume and training status, particularly for high-risk operations such as esophagectomy. Third, we did not account for the relationship between the severity of complication and survival in this study.

In conclusion, the present study demonstrates that the negative impact of postoperative complications on oncological prognosis can be reduced if patients with esophageal squamous cell carcinoma undergo neoadjuvant therapy. Furthermore, outcomes were also influenced by the intensity of the neoadjuvant therapy. Postoperative complications have been directly associated with hospitalized mortality, length of hospital stay, readmission rate, costs and resource utilization, and patients' quality of life.²⁹ To decrease complication rates, both surgical techniques and perioperative management have been improved.

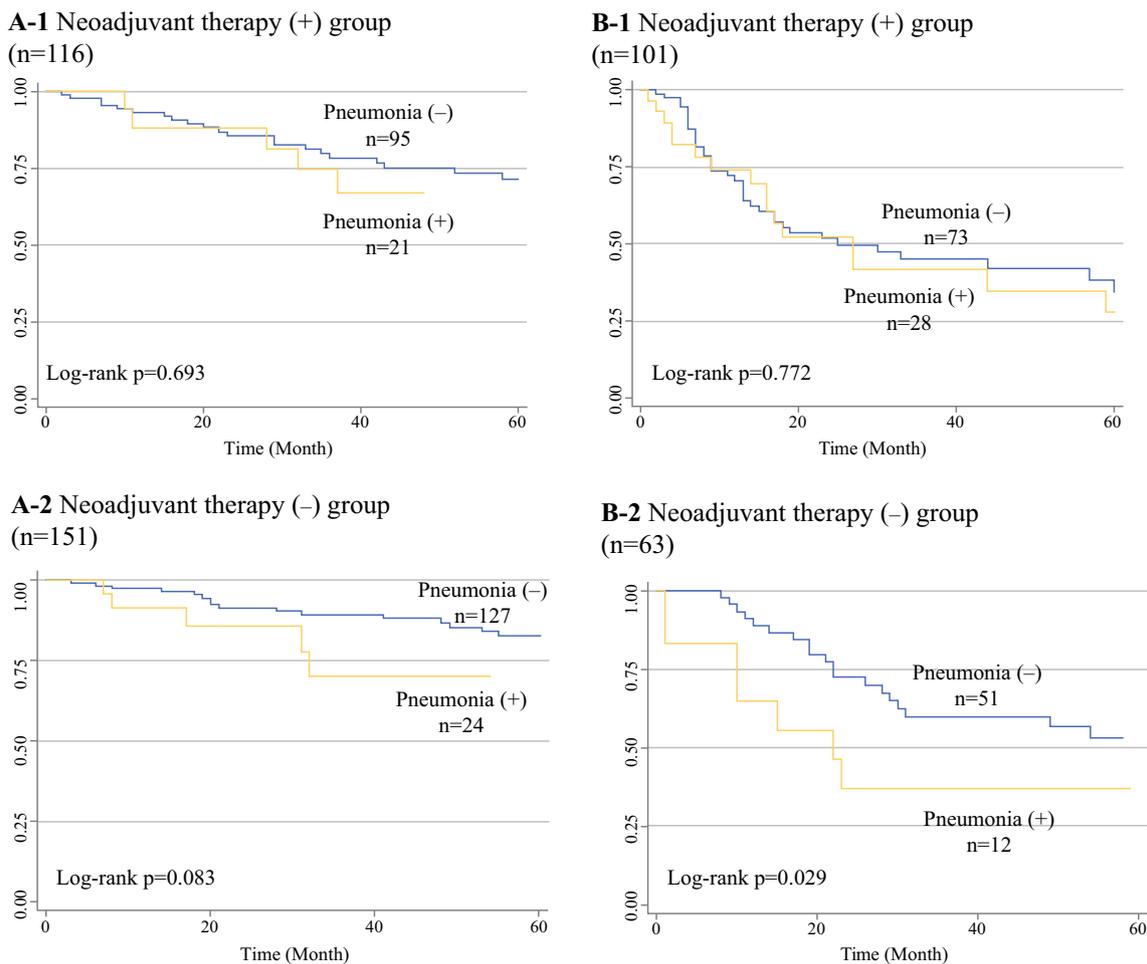


FIG. 3 Patients with pStage I/II: Kaplan–Meier curves for overall survival (OS) associated with pneumonia in the (A-1) neoadjuvant therapy (+) group and (A-2) neoadjuvant therapy (-) group. Patients with pStage III/IV: Kaplan–Meier curves for OS associated with

pneumonia in the (B-1) neoadjuvant therapy (+) group and (B-2) neoadjuvant therapy (-) group. Yellow and blue lines indicate the groups with and without pneumonia, respectively

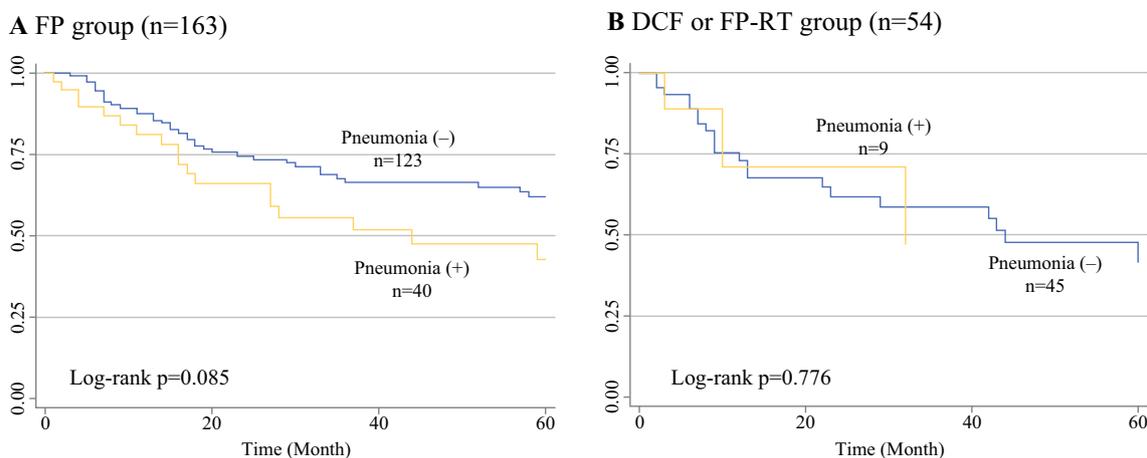


FIG. 4 Kaplan–Meier curves for overall survival (OS) associated with pneumonia in the (A) FP group and (B) DCF and FP-RT groups. Yellow and blue lines indicate groups with and without pneumonia, respectively

It is clear that careful surgery is necessary regardless of presence or absence of NAC to eliminate postoperative complications. However, this study reveals that, even if postoperative complications unfortunately occur, sufficient neoadjuvant therapy may reduce the adverse effects on long-term prognosis.

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