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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Postoperative Infectious Complications are Associated with Adverse Oncologic Outcomes in Esophageal Cancer Patients Undergoing Preoperative Chemotherapy

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ABSTRACT

Background. For some types of cancer, postoperative complications can negatively influence survival, but the association between these complications and oncological outcomes is unclear for patients with esophageal cancer who receive preoperative treatments.

Methods. Data were retrospectively analyzed for patients who underwent curative resection following preoperative chemotherapy for esophageal squamous cell carcinoma from 2001 to 2011. Clinicopathological parameters and cancer-specific survival (CSS) were compared between patients with and without severe postoperative complications, grade III or higher, using the Clavien–Dindo classification.

Results. Of 255 patients identified, 104 (40.8 %) postoperatively developed severe complications. The most common complication was atelectasis in 61 (23.9 %), followed by pulmonary infection in 22 (8.6 %). Three-field lymphadenectomy, longer operation time, and more blood loss were significantly associated with a higher incidence of severe complications. Multivariate analysis of CSS revealed severe complications [hazard ratio (HR) = 1.642, 95 % confidence interval (95 % CI) 1.095–2.460, $p = 0.016$] as a significant prognostic factor along with pT stage [HR = 2.081, 95 % CI 1.351–3.266, $p < 0.001$] and pN stage [HR = 3.724, 95 % CI 2.111–7.126, $p < 0.001$], whereas postoperative serum C-reactive protein value was not statistically significant. Among all complications, severe pulmonary infection was the only independent prognostic factor [HR = 2.504, 95 % CI 1.308–4.427, $p = 0.007$].

Conclusions. The incidence of postoperative infectious complications, in particular pulmonary infection, is associated with unfavorable prognosis in patients with esophageal cancer undergoing preoperative chemotherapy.

Surgery is the standard treatment for esophageal squamous cell carcinoma (ESCC), but the postoperative prognosis remains unsatisfactory. The 5-year survival rate is approximately 40 % despite recent advances including three-field lymphadenectomy, suggesting the need for multimodal therapies to improve prognosis.[1] Since a recent randomized phase III trial demonstrated a survival benefit of preoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU) over postoperative chemotherapy with the same regimen, preoperative chemotherapy often has been used for locally advanced ESCC.[2]

Regardless of recent improved assessments of operative risk, refined operative techniques, and better perioperative management, morbidity after curative esophagectomy for ESCC remains high at 52.8–55.3 % even in high-volume centers.[3,4] Furthermore, preoperative treatments could be a risk factor for postoperative complications.[2,5] Previous studies have reported that postoperative complications,

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including anastomotic leakage, are a major independent prognostic factor for long-term survival in some types of cancer, but only a few reports have addressed ESCC in this context.[6–14] Postoperative complications negatively affected disease recurrence and survival after esophagectomy for esophageal cancer patients in some studies but not in others, and little is known about this risk in the setting of curative esophagectomy following preoperative treatments for ESCC.[15–20] The purpose of this study was to determine whether postoperative complications have significant relevance for oncological outcome after curative esophagectomy following preoperative chemotherapy for ESCC.

MATERIALS AND METHODS

Background and Patient Data

Between January 2001 and December 2011, a total of 675 patients underwent esophagectomy for ESCC in our department; among them, 291 patients received preoperative chemotherapy. Excluding 15 patients who had noncurative resection, 11 patients with synchronous or metachronous double cancer, 3 patients with two-stage surgery, and 7 patients with no survival information available, the study analysis included 255 consecutive patients who received preoperative chemotherapy consisting of cisplatin, 5-FU, and either Adriamycin or docetaxel, followed by curative esophagectomy. Our indication for preoperative chemotherapy based on the TNM classification was as follows: cT1-3N1-3 as an absolute indication and either cT2-3N0 with a larger primary tumor or cT4Nany except those with massive infiltration to the bronchus or aorta as a relative indication. Patients who underwent preoperative chemotherapy had an Eastern Cooperative Oncology Group performance status of 0–1 and normal function of bone marrow, kidney, and liver function.[21] This study was conducted with the approval of the ethics committee of Osaka University, Graduate School of Medicine.

Surgical Procedure

Surgical resection was generally performed 3–5 weeks after completion of the chemotherapy. Our standard procedures consisted of subtotal esophagectomy with mediastinal lymphadenectomy via right thoracotomy, upper abdominal lymphadenectomy, reconstruction with a gastric tube via the posterior mediastinum, and anastomosis in the cervical incision.[22] We routinely preserved both sides of the bronchial arteries and resected the thoracic duct. Cervical lymphadenectomy was performed for patients with upper thoracic ESCC and for those with middle or lower thoracic ESCC with supraclavicular lymph node or recurrent laryngeal nerve lymph node metastasis diagnosed by radiological imaging. Methylprednisolone (250 mg/body, only on day of surgery) was intraoperatively administered to all patients right before thoracotomy incision. The placement of a feeding tube was not routinely performed. Information on clinicopathological parameters was collected retrospectively.

Grading of Postoperative Complications

Screening for any complication was performed routinely based on clinical symptoms, blood tests, and x-ray imaging at postoperative days 1, 3, 7, and thereafter. If an aberrant value was detected, complete examinations, such as computed tomography, were added to check more fully for complications. Complications were categorized into six grades according to the Clavien–Dindo (C–D) classification, as follows: no complications (grade 0); deviation from normal hospital course, but no need for medication or intervention (grade I); complications requiring drugs or blood transfusion (grade II); complications requiring interventional treatment (grade III); life-threatening complications requiring ICU admission (grade IV); and postoperative mortality (grade V).[23] Complications were recorded retrospectively during hospitalization, starting from the day of surgery until hospital discharge. If an additional intervention was part of the planned treatment, it was not considered a complication. If multiple complications occurred in a patient, the highest grade was used for analysis.

All complications were categorized as infectious or noninfectious. Infectious complications included pulmonary infection, anastomotic leakage, wound infection, abdominal abscess, pancreatic fistula, fistula of the gastric tube and bronchus, mediastinitis, infection of the pleural cavity, lung abscess, catheter infection, and cholecystitis. Noninfectious complications included atelectasis, disorder of expectoration of sputum, atrial fibrillation, recurrent nerve palsy, pleural effusion, pneumothorax, pneumoderma, seroma, chylothorax, hemorrhage, peritoneal effusion, postoperative anemia, acute respiratory distress syndrome, delirium tremens, ventricular arrhythmia, pericardial effusion, renal failure, anastomotic stenosis, esophageal hiatal hernia, bronchus fistula, intestinal obstruction, cardiovascular failure edema of the extremities, pulmonary embolism, and wound disruption.

Postoperative Follow-up

Patients underwent routine postoperative surveillance using a chest x-ray and computed tomography of the neck,

chest, and abdomen every 3 months for the first 3 years, every 6 months for the following 2 years, and annually thereafter. Biochemical tumor marker [squamous cell carcinoma (SCC)] assays were performed monthly for the first year, every 3 months for the following 2 years, and every 6 months thereafter. Disease recurrence was diagnosed based on radiographic evidence of a new suspicious low-density mass in the region of the mediastinum, lymph nodes, liver, lung, or other distant sites. Equivocal diagnoses were checked by positron-emission tomography.

Statistics

Statistical analyses were performed using SPSS version 12.0 (Statistical Package for the Social Sciences, Chicago, IL). Differences between categories were identified using Student's t test or the χ^2 test. Cumulative cancer-specific survival (CSS) rate, which was cancer (ESCC) survival in the absence of other causes of death, was estimated using the Kaplan–Meier method. Two groups were compared with a two-sided log-rank test. The hazard ratio was calculated, and uni- and multivariate analyses were performed using Cox proportional hazards regression models. P values < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics and Perioperative Parameters

Clinicopathological characteristics of all 255 patients are shown in Table 1. The patient group included 220 men (86.3 %) and 35 women (13.7 %), with a median age of 65 years. Median preoperative serum C-reactive protein (CRP) and preoperative serum albumin values were 0.2 mg/dl (0.04–7.5) and 3.7 mg/dl (2.4–4.5), respectively. All patients underwent preoperative chemotherapy consisting of cisplatin and 5-FU plus either Adriamycin ($n = 206$) or docetaxel ($n = 49$), followed by curative esophagectomy (R0) with either three-field ($n = 93$) or two-field ($n = 156$) lymphadenectomy, and the overall morbidity and mortality rates were 64.7 % (165 patients) and 1.2 % (3 patients), respectively. The median postoperative hospital stay was 27 days (range 3–386). The distribution of postoperative complications according to

TABLE 1 Patient characteristics and perioperative parameters

	$N = 255$
Age: median (range)	65 (35–85)
Gender	
Male/female	220/35
Regimen of preoperative chemotherapy	
FAP/DCF	206/49
Histological differentiation	
well/moderate/poor/unknown	45/137/49/24
ASA-PS 1/2/3	47/199/9
Preoperative serum CRP value (mg/dl): median (range)	0.2 (0.04–7.5)
Preoperative serum albumin value (mg/dl): median (range)	3.7 (2.4–4.5)
Range of lymph node dissection 2/3–fields	156/93
Response to preoperative chemotherapy	
(Clinical grade) PD/NC/PR/CR	2/119/128/6
(Histological grade) 0/1/2/3	23/174/41/17
pT stage 0/1/2/3/4	14/56/52/127/6
pN stage 0/1/2/3	83/89/46/37
pStage 0/I/II/III/IV	10/39/76/120/10
Curability R0/1–2	255/0
Overall morbidity rate (%)	165 (64.7)
Clavien–Dindo classification	
Grade 0/I/II/III/IV/V	90/33/28/92/9/3
Overall mortality rate (%)	3 (1.2 %)
Postoperative hospital stay (days): median (range)	27 (3–386)

CT chemotherapy, *CRT* chemoradiotherapy, *FAP* fluorouracil, adriamycin, cisplatin, *DCF* docetaxel, cisplatin, fluorouracil, *ASA-PS* ASA physical status, *CRP* C-reactive protein

TABLE 2 Clinicopathological parameters between patients with severe and non-severe complications

	All patients ($N = 255$)		
	Non–severe complication (<Grade III) $n = 151$	Severe complication (≥Grade III) $n = 104$	p value
[Preoperative parameters]			
Age: median (range)	65 (35–83)	66 (47–79)	0.113
Gender (male/female)	129/22	91/13	0.713
ASA-PS (1/2/3)	26/120/5	21/79/4	0.803
Preoperative serum CRP value (mg/dl): median (range)	0.1 (0.04–7.52)	0.2 (0.04–4.64)	0.416
Preoperative serum albumin value (mg/dl): median (range)	3.7 (2.4–4.4)	3.7 (2.5–4.5)	0.744
cT-stage (1/2/3/4)	9/27/98/17	5/23/61/15	0.664
cN-stage (0/1/2/3)	21/121/6/3	12/83/9/0	0.130
Regimen of preoperative chemotherapy (FAP/DCF)	117/34	89/15	0.145
Clinical response to preoperative chemotherapy (PD/NC/PR/CR)	1/70/77/3	1/49/51/3	0.954
[Intraoperative parameters]			
Transthoracic procedure (±)	145/6	104/0	0.084
Surgical approach (thoracotomy/VATS)	127/18	98/6	0.086
Range of lymph node dissection (2/3–fields)	63/82	30/74	0.024
Operation time (minutes): median (range)	465 (180–887)	505 (319–1275)	<0.001
Blood loss (ml): median (range)	680 (190–2700)	885 (100–8160)	<0.001
Blood transfusion (±)	67/84	53/51	

ASA-PS ASA physical status, *CRP* C-reactive protein, *FAP* fluorouracil, adriamycin, cisplatin, *DCF* docetaxel, cisplatin, fluorouracil, *PD* progressive disease, *NC* no change, *PR* partial response, *CR* complete response, *VATS* video assisted thoracic surgery

the C–D classification was grade 0 in 90 patients (35.3 %), grade I in 33 (12.9 %), grade II in 28 (11.0 %), grade III in 92 (31.6 %), grade IV in 9 patients (3.5 %), and grade V (in-hospital mortality) in 3 (1.2 %).

All complications were categorized as infectious or noninfectious (Supplemental Table 1). Overall, infectious and non-infectious complications developed in 65 (25.5 %) and 139 cases (54.5 %), respectively. The most common severe complication (C–D classification grade III or higher) was atelectasis and disorder of expectoration of sputum in 61 patients (23.9 %), followed by pulmonary infection in 22 patients (8.6 %).

Risk Factors for Occurrence of Postoperative Complications

Relationships between the occurrence of severe complications and clinicopathological parameters are shown in Table 2. No preoperative factor, including ASA-PS (ASA-physical status), preoperative CRP, or albumin, was associated with development of postoperative complications. Regarding intraoperative factors, three-field lymph node dissection ($p = 0.024$), longer operation time ($p < 0.001$), and more blood loss ($p < 0.001$) were associated with a higher incidence of severe postoperative complications.

Prognostic Significance of Postoperative Complications among Various Clinicopathological Parameters

Disease recurrence after complete resection was diagnosed in 116 patients (45.5 %) in the follow-up period (median 3.3 years). The median time to recurrence was 6.3 months (range 0.6–60.9). Patients with severe complications had significantly poorer CSS than patients with nonsevere complications (5-year CSS, 50.7 % vs. 60.2 %, $p = 0.003$; Fig. 1a). Postoperative serum CRP values, however, did not significantly affect survival regardless of occurrence of severe postoperative complications (Fig. 1b).

Risk Factors Related to CSS

In univariate analysis of CSS confined to preoperative factors, lower serum albumin (<3.5 mg/dl), and poor response to preoperative chemotherapy were significantly associated with unfavorable prognosis (Table 3). Multivariate analysis demonstrated that preoperative serum albumin [hazard ratio (HR) = 1.654, 95 % confidence interval (95 % CI) 1.094–2.462, $p = 0.018$), clinical response to preoperative chemotherapy (HR = 2.050, 95 % CI 1.391–3.047, $p < 0.001$), and cN stage (HR 1.928, 95 % CI 1.025–4.125, $p = 0.041$) were independent

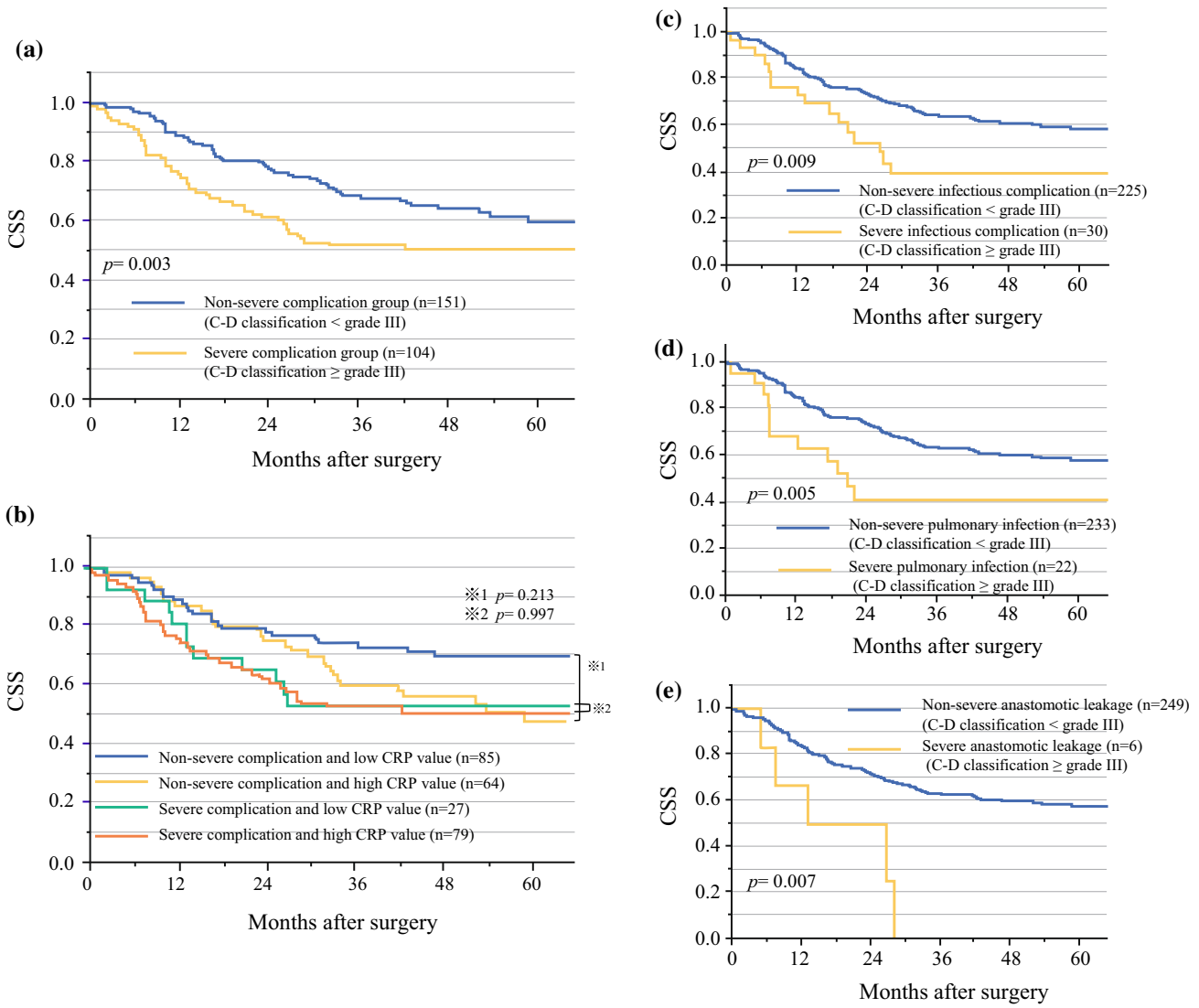

FIG. 1 Cancer-specific survival (CSS) classified by degree of postoperative complications based on Clavien–Dindo (C–D) classification (**a**); postoperative complications relative to postoperative serum C-reactive protein (CRP) value (higher or lower 15 mg/dl) (**b**); occurrence of severe (grade III or higher) infectious complications (**c**); pulmonary infection (**d**); and anastomotic leakage (**e**) based on C–D classification

prognostic factors for CSS. In the same analysis using intra- and postoperative factors, operation time, blood loss, pT stage, pN stage, histological effect of preoperative chemotherapy, and postoperative complications were statistically significant (Table 3). Multivariate analysis identified occurrence of severe complications (HR = 1.642, 95 % CI 1.095–2.460, $p = 0.016$) as an independent prognostic parameter along with pT stage (HR = 2.081, 95 % CI 1.351–3.266, $p < 0.001$) and pN stage (HR = 3.724, 95 % CI 2.111–7.126, $p < 0.001$).

Recurrence Pattern

The most common pattern of first recurrence was lymphatic in 49 patients (42.2 %), followed by multiple in 36 (31.0 %), and hematogenous in 23 (19.8 %). Severe complications did not significantly influence the first pattern of recurrence, but multiple metastases tended to occur in patients with severe postoperative complications (19.2 %) compared with those without (10.6 %; $p = 0.067$; Table 4).

Relation between Specific Complications and Survival

To clarify which type of complication influences oncological outcome, we performed uni- and multivariate analysis of CSS using each complication with five or more events. In univariate analysis, infectious complications were significantly associated with unfavorable prognosis, but noninfectious complications were not (Supplemental

TABLE 3 Univariate and multivariate analysis for cancer specific survival using preoperative and intra/postoperative parameters

	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Preoperative parameters						
Age ≥65/<65	1.152	0.786–1.696	0.467			
Gender female/male	0.904	0.482–1.556	0.731			
cT stage 3–4/1–2	1.484	0.945–2.432	0.088	1.425	0.903–2.346	0.131
cN stage 1–3/0	1.757	0.939–3.746	0.080	1.928	1.025–4.125	0.041
Regimen of preoperative chemotherapy DCF/FAP	0.791	0.454–1.298	0.367			
ASA–PS 3/1–2	1.180	0.360–2.818	0.752			
Preoperative serum CRP value ≥1.0/<1.0 mg/dl	1.322	0.687–2.314	0.380			
Preoperative serum albumin <3.5/≥3.5 mg/dl	1.655	1.097–2.456	0.017	1.654	1.094–2.462	0.018
Clinical response to preoperative chemotherapy PD, NC/PR, CR	1.882	1.281–2.792	0.001	2.05	1.391–3.047	<0.001
Intra and postoperative parameters						
Transthoracic procedure (±)	1.458	0.462–8.845	0.574			
Surgical approach (VATS/Thoracotomy)	1.103	0.587–2.356	0.776			
Range of lymph node dissection 3/2–fields	0.947	0.640–1.416	0.788			
Operation time ≥480/<480 min	1.830	1.243–2.727	0.002	1.415	0.912–2.210	0.121
Blood loss ≥800/<800 ml	1.756	1.192–2.613	0.004	1.130	0.719-1.786	0.595
Blood transfusion (±)	1.441	0.984–2.116	0.060	1.346	0.882–2.060	0.168
pT stage 3,4/0–2	2.306	1.549–3.498	<0.001	2.081	1.351–3.266	<0.001
pN stage 1–3/0	4.542	2.637–8.519	<0.001	3.724	2.111–7.126	<0.001
Histological response to preoperative chemotherapy 0–1/2,3	2.740	1.566–5.268	<0.001	1.235	0.660–2.497	0.522
Postoperative serum CRP ≥15.0/<15.0 mg/dl	1.436	0.973–2.150	0.069	1.023	0.668–1.586	0.917
Postoperative complication (C–D classification) ≥grade III/<grade III	1.596	1.087–2.340	0.017	1.642	1.095–2.460	0.016

HR hazard ratio, *CI* confidence interval, *FAP* fluorouracil, adriamycin, cisplatin, *DCF* docetaxel, cisplatin, fluorouracil, *CRP* C–reactive protein, *PR* partial response; *CR* Complete response, *NC* no change, *PD* progressive disease, *VATS* video assisted thoracic surgery, *C–D classification* Clavien–Dindo classification

Table 2a; Fig. 1c). Among all complications, occurrence of severe pulmonary infection and anastomotic leakage, respectively, had a negative statistically significant effect on CSS (5-year CSS for severe vs. nonsevere complications, 41.6 vs. 58.1 %, $p = 0.005$; 0 vs. 58.6 %, $p = 0.007$; Figs. 1d and e; Supplemental Table 2a). Severe pulmonary infection (HR = 2.504, 95 % CI 1.308–4.427, $p = 0.007$) was identified as an independent prognostic factor along with pT stage (HR = 2.111, 95 % CI 1.367–3.322, $p < 0.001$) and pN stage (HR = 3.892, 95 % CI 2.203–7.453, $p < 0.001$) in multivariate analysis, including each type of complication, respectively, instead of severe postoperative complications (Supplemental Table 2b).

DISCUSSION

We analyzed data for 255 patients who underwent esophagectomy following preoperative chemotherapy. Severe postoperative complications, defined as C–D classification grade III or higher, occurred in 40.8 %. Intraoperative factors, three-field lymphadenectomy, longer operation time, and more blood loss were associated with a higher incidence of severe postoperative complications, and occurrence of severe infectious complications, particularly pulmonary infection, was significantly correlated with shorter CSS. With respect to the pattern of recurrence, patients with severe postoperative complications had a tendency to develop multiple metastases compared to those without complications, although the difference was not statistically significant.

Some reports have described a relationship between postoperative complications and survival in some types of cancer.[6–14] Krarup et al. found that anastomotic leakage increased distant recurrence and long-term mortality after curative resection for colon cancer and anastomotic leakage was strongly associated with cancelled administration of adjuvant chemotherapy.[12] Additionally, severe inflammation from peritonitis and septicemia after anastomotic leakage may have contributed to the metastatic cascade and the association between leakage and distant recurrence in their study. Regarding esophageal cancer, a few prospective reports have shown that postoperative complications

TABLE 4 Relationship between degree of complications (Grade III or higher) and first pattern of cancer recurrence

	$N = 255$	Severe complication (≥Grade III) *n* (%)	Non-severe complication (<Grade III) *n* (%)	*p* value
All	116	51 (49.0)	65 (43.1)	0.372
Local	3	2 (1.9)	1 (0.7)	0.569
Lymphatic	49	17 (16.3)	32 (21.2)	0.419
Hematogenous	23	10 (9.6)	13 (8.6)	0.826
Pleural dissemination	5	2 (1.9)	3 (2.0)	1.000
Multiple	36	20 (19.2)	16 (10.6)	0.067

are independently associated with poor prognosis.[17,18] Among all complications, Lerut et al. found a significant relationship between pulmonary infection and early recurrence of disease, as did Kinugasa et al..[15,18]

Because postoperative therapy was rarely performed in the current study, cancelled or postponed adjuvant chemotherapy would not be a likely explanation for the association between severe complications and poor survival. Two potential mechanisms are possible, however: host immunosuppression or growth stimulation of residual cancer cells by soluble factors induced by severe complication. Inflammatory responses to severe complications correlate with host immunosuppression.[24,25] It also was reported that postoperative intra-abdominal infection increases angiogenesis and recurrence after excision of colon cancer in mice.[26] In addition, neutrophil traps are thought to be released in response to inflammatory cues, sequester circulating tumor cells, and promote metastasis.[27,28] This behavior might partly explain the tendency detected in the present study for multiple metastases to occur more often in patients with severe postoperative complications compared to those without. In esophageal cancer, Matsuda et al. recently reported that postoperatively persistent CRP elevation, defined as >10.0 mg/dl for 6 days or longer, significantly correlated with poor postoperative survival in patients with esophageal cancer but not the occurrence of postoperative complications.[20] In contrast, the highest level of postoperative CRP (≥15.0/<15.0 mg/dl) in this study was not a significant prognostic factor in multivariate analysis; we also evaluated several other cutoff values. Some perioperative factors, including intraoperatively administered methylprednisolone, preoperative chemotherapy, and video-assisted thoracic surgery with a smaller incision, could have affected this result. Other mechanisms not associated with the inflammatory response might underlie cancer progression associated with postoperative complications. It is possible that an immune system suppressed enough to lead to the development of pneumonia also leaves patients susceptible to cancer recurrence. To clarify this possibility, a prospective study is needed to identify the correlation between prognosis and perioperative factors including postoperative complications, inflammatory response, and immune reaction.

A history of heavy smoking, elderly patients, poor pulmonary function, preoperative definitive chemoradiotherapy, and high blood loss during surgery should be regarded as risks for developing pneumonia.[15,29,30] Intriguingly, intraoperative factors significantly correlated with occurrence of severe postoperative complications in this study, although preoperative factors such as serum albumin, CRP, and ASA-PS did not, implying that postoperative complication occurrence depends on the surgical procedure rather than the preoperative general condition in cases undergoing invasive surgery like esophagectomy. Two explanations are possible for this result. The first is patient selection bias; almost all patients who undergo preoperative chemotherapy and subsequent curative esophagectomy need to be in sufficiently good condition to tolerate these invasive therapies. The second is modification of oncological and nutritional status by preoperative treatments. Both response to chemotherapy and adverse effects could profoundly affect these statuses.

Recently, conventional minimally invasive esophagectomy (MIE) was reported to reduce mortality and morbidity.[31–34] In contrast, a report relying on the Japanese national database showed that MIE did not decrease complication rates of pneumonia and anastomotic leakage, but institutional disparities could explain this divergence.[35] In addition, Mori et al. described the utility of nontranthoracic esophagectomy, combining a video-assisted cervical approach for the upper mediastinum and a robot-assisted transhiatal approach for the middle and lower mediastinum and achieving zero incidence of postoperative pneumonia during hospitalization.[36] However, these approaches need to be evaluated with a larger number of patients to verify their usefulness in preventing postoperative pulmonary complications. In addition, we consider that postoperative management also is important for preventing pulmonary infection. In this study, the most common severe complication was atelectasis or disorder of expectoration of sputum. The reason is that the cricothyroidotomy that we often perform prophylactically to prevent severe pulmonary

complications also was defined as a grade III complication in the C–D classification. The occurrence rate of severe pulmonary infection in patients with severe atelectasis or disorder of expectoration of sputum was only 14.8 % (9/61 cases), suggesting the effectiveness of cricothyroidotomy in averting postoperative pulmonary infection, which might lead to improved survival.

CONCLUSIONS

This study showed a significant association of an unfavorable prognosis with the development of postoperative infectious complications, in particular pulmonary infection, in ESCC patients undergoing curative esophagectomy following preoperative chemotherapy. In addition, there was a trend for patients with severe postoperative complications to develop multiple metastases more frequently compared with those without complications. A limitation of this study was that it was retrospective and a single-institutional investigation with a limited number of patients, and a larger-scale prospective study is necessary to validate the clinical significance of our findings. However, the present report offers important information that we believe can ultimately contribute to improvement of patient survival in ESCC.

CONFLICT OF INTEREST There are no conflicts of interest.

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