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Postesophagectomy pneumonia has a close association with swallowing dysfunction [6, 7]. Swallowing studies of patients who developed pneumonia after esophagectomy have shown significantly impaired swallowing function, owing in particular to reduced laryngeal elevation in the pharyngeal stage and incomplete airway protection [7–10], and dysphagia is typically more severe after esophagectomy with cervical lymphadenectomy or anastomotic leakage. The prevention of aspiration is the most important factor for reducing the incidence of pneumonia.

In a previous study comparing postoperative swallowing function in patients who underwent esophagectomy with or without cervical lymphadenectomy (3-field and 2-field lymphadenectomy; 3FL and 2FL, respectively), we found that laryngeal elevation was significantly impaired in patients with 3FL as a result of defective relaxation of the sternohyoid and sternothyroid muscles due to postoperative scarring, and that the complete division of these muscles, a procedure we designed, improved laryngeal elevation of these patients, reducing the risks of postoperative aspiration and laryngeal penetration [11]. Multivariate logistic regression analysis identified defective laryngeal elevation and age as significant risk factors for postoperative incomplete airway protection after esophagectomy with 3FL.

Older age is a well-established and prominent risk factor for aspiration, and silent aspiration especially is often observed in the elderly, who have decreased pharyngeal and cough reflexes [12], and in patients with cerebrovascular damage [13]. Recent research into aspiration pneumonia in the elderly has revealed a close relationship between substance P (SP) and silent aspiration [14, 15]. This peptide is synthesized in response to dopamine stimulation in the basal ganglia of the brain and is secreted into the pharynx and trachea, regulating the cough and swallowing reflexes [16–18]. This would suggest that SP is dependent on the rates of dopamine synthesis and cerebral blood flow. Since SP secretion is likely to be decreased in the elderly, the reduced secretion would probably be a major contributor to weakened pharyngeal and cough reflexes and subsequent subclinical silent aspiration [14–20]. Patients with esophageal cancer requiring esophagectomy are mostly elderly. In addition, cerebral blood flow is likely to fluctuate greatly in the perioperative period. Thus, even in patients who have undergone esophagectomy, decreased SP secretion followed by silent aspiration likely has a close association with the development of postoperative pneumonia. However, there have been no reports on the association of SP secretion with surgical stress.

Consequently, we hypothesized that decreased SP secretion might reduce the pharyngeal and cough reflexes, leading to silent aspiration and thus possible development of pneumonia. Following on from our previous study on swallowing dysfunction after esophagectomy, here we sought to verify the our hypothesis by measuring changes in SP concentration and cough reflex sensitivity during the perioperative period and comparing the results with the presence or absence of aspiration.

Methods

Study design and patients

This study was performed as an exploratory, prospective, single-center clinical study. The study included patients with histologically proven primary thoracic esophageal cancer who were scheduled to undergo esophagectomy at Kinki University Hospital after initial staging and met the following criteria: age $\geq$20 years; performance status according to the criteria of Eastern Cooperative Oncology Group [21] of 0 or 1; ability to seat themselves without assistance; no history of cerebrovascular disease or treatment for any throat problem; and no history of treatment with psychotropic drugs or a present mental disorder requiring treatment. All patients who met the eligibility criteria during the study period (January 2009–June 2010) were included in the study.

The measurement of plasma and salivary SP concentrations and the cough reflex test were performed within the week prior to esophagectomy and on postoperative day (POD) 2 and POD 7. We then examined the association between perioperative changes in these parameters, and in individual values at the three measurement points, and the occurrence of postoperative aspiration. The protocol was approved by the Kinki University Ethics Committee. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from each patient.

Surgical treatment

A transthoracic subtotal esophagectomy and reconstruction with retrosternal gastric tube was performed. A 3FL was performed for patients with supraclavicular or recurrent laryngeal nerve lymph node metastasis or with the primary tumor located in the upper third of the thoracic esophagus [22]; the remaining patients underwent 2FL.

Plasma and salivary SP concentrations

Blood [14], sputum [15], and saliva [23] samples are useful for the measurement of SP concentrations [23]. Because SP is secreted into the pharynx and trachea, sputum and saliva

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samples are more sensitive than blood samples to changes in SP concentration; however, they are not always collected accurately. Therefore, we evaluated plasma and salivary SP concentrations in this study. Blood (5 ml) was collected in a tube containing 500 KIU/ml aprotinin and 1.2 mg/ml ethylenediaminetetraacetic acid. Saliva samples were collected in a Salivette (Sarstedt, Nümbrecht, Germany). After centrifugation (1600×g for 15 min in blood samples and 1000×g for 2 min in saliva samples), the supernatants were stored at −80 °C. The samples were purified as follows. Each frozen sample was diluted by adding an equal volume of 1 % trifluoroacetic acid (TFA) and was centrifuged at 4 °C, 17,000×g for 15 min. After adding 1 ml of acetonitrile and 15 ml of 1 % TFA to a 200-mg Strata® C18 Sep column (Phenomenex; CA), the supernatant was added to a Sep-Pak column and washed with 15 ml of 1 % TFA. The sample was then extracted by slowly adding 3 ml of a 6:4 mixture of acetonitrile and 1 % TFA, and was dried in a Savant Speed Vac SC 100 (Thermo Scientific, MA) and stored at −20 °C. The recovery rate of this extraction procedure was 78.4 ± 28.1 % (mean ± SE). SP concentrations were measured by enzyme-linked immunosorbent assay using the Correlate-EIA, Substance P Enzyme Immunoassay Kit (Assay Designs, Ann Arbor, MI). Absorbance was measured immediately at 405 nm and corrected at 570 nm with a microplate reader (BioRad model 680; Bio-Rad, CA).

Cough reflex sensitivity

Cough reflex sensitivity was evaluated by the citric acid inhalation cough challenge, which is described in the European Respiratory Society's guidelines on the assessment of cough [24]. Citric acid, which induces coughing in a dose-dependent, reproducible manner, was dissolved in saline solution, providing twofold incremental concentrations from 0.7 to 360 mg/ml and referred to as levels 1–10. Patients inhaled the nebulized solution delivered by an ultrasonic nebulizer (Ne-U07, Omron Healthcare Co. Ltd., Kyoto, Japan) [25]. The cough reflex threshold was defined as the concentration at which patients coughed at least three times during a 1-min period of breathing the citric acid aerosol. Each nebulizer application had a 3-min interval. When the development of pneumonia was confirmed in a patient, subsequent cough reflex sensitivity tests were canceled for ethical reasons, because there is no evidence that citric acid inhalation is safe for patients with pneumonia.

Evaluation of recurrent laryngeal nerve palsy and aspiration

The presence or absence of recurrent laryngeal nerve palsy and aspiration was evaluated by fiberoptic laryngoscopy or bronchofiberscopy before the operation by an otolaryngologist, and on POD 2 and POD 7 by two surgeons [7]. In addition, when aspiration or pneumonia was clinically suspected, the presence of aspiration was immediately examined by fiberscopy. The procedure was performed with the head of the bed raised to at least 45°. The endoscope was inserted through the nose without local anesthesia or any sedation, and was then held in the oropharynx to maintain an adequate view of the epiglottis, aryepiglottic folds, laryngeal vestibule, and vocal cords. The patient was then asked to swallow for an evaluation of swallowing function with saliva. When saliva penetrated the laryngeal ventricle and invaded below the true vocal cord without cough reflex, we diagnosed aspiration.

Statistics

The following statistical tests were used: repeated measures one-way analysis of variance for comparison of perioperative SP concentration and cough reflex sensitivity for the whole model and between measurement time points, Student's t test for comparison of mean values between the two groups, Fisher's probability test or the likelihood ratio test with simple logistic regression analysis for the association of each variable with the occurrence of postoperative aspiration in univariate analysis, and the likelihood ratio with multiple logistic regression analysis for identifying risk factors by multivariate analysis. Significance was set at $p < 0.05$.

Results

Patient characteristics

The characteristics of included patients ($n = 30$) are shown in Table 1. Advanced tumors of cStage III or higher (UICC/AJCC TNM staging version 6) were found in 11 patients, 8 of whom received preoperative treatment. Esophagectomy through a right thoracotomy was performed in all patients except one, who underwent transhiatal esophagectomy due to interstitial pneumonia during steroid treatment, and reconstruction with gastric tube was performed in all patients except one, who was reconstructed through subcutaneous route with a pedicled jejunum due to a history of gastrectomy. All patients were extubated on the day after surgery and were discharged from the intensive care unit to a general ward after a 2-night stay. Vital signs and general conditions were stable in all cases; nevertheless, aspiration was observed in 6 patients by laryngoscopic inspection on POD 2, 4 of whom showed an increased white blood cell count and C reactive

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Table 1 Patient characteristics

Characteristics	
No. of patients	30
Sex	
Male	22
Female	8
Age	
Mean ± SD	63.2 ± 8.6
Range	38–78
Brinkman index	
Mean ± SD	638 ± 655
Range	0–2720
Location	
Upper	4
Middle	15
Lower	11
Clinical stage	
I	10
IIA	5
IIB	4
III	5
IVA	4
IVB	2
Preoperative therapy	
None	20
Chemotherapy	7
Chemoradiotherapy	3
Surgical procedure	
Esophagectomy	
Transthoracic	29
Transhiatal	1
Reconstruction	
Retrosternal	28
Orthotopic	1
Subcutaneous	1
LN dissection	
2-field	18
3-field	12
Recurrent nerve palsy	3
Aspiration	6
Pneumonia	4

protein concentration and high fever above 38 °C and were diagnosed with pneumonia by chest X-ray. However, none of them required reintubation and all were managed conservatively with antibiotic therapy. Aside from these 6 patients, none of the remaining patients exhibited symptoms of aspiration or pneumonia or had vital signs or laboratory data suggestive of aspiration or pneumonia after POD 2. No anastomotic leaks were observed.

Changes in perioperative plasma and salivary SP concentrations

Preoperative values for plasma SP concentrations were obtained from all 30 patients. POD 2 values were obtained from 26 patients; the remaining 4 had delirium ($n = 3$) or refused ($n = 1$). POD 7 values were obtained from 22 patients; the remaining 8 developed pneumonia ($n = 4$) or refused ($n = 4$). No significant perioperative changes were observed in either the whole model comparison or comparison between measurement points (Fig. 1a). Samples could be collected on POD 2 in 5 of 6 patients who showed aspiration. The mean plasma SP concentration on POD 2 was 19.7 ± 9.7 pg/ml, compared with the mean preoperative value of 30.3 ± 7.9 pg/ml, showing no significant decrease ($p = 0.422$).

Preoperative values for salivary SP concentration were obtained from all patients. However, because saliva samples could not be obtained from some patients due to postoperative dry mouth, sample collection for the measurement of salivary SP concentration was terminated after samples were sought from 23 patients: on POD 2, samples could be collected from 21 patients, 1 patient refused to provide a sample, and another had delirium and was not sampled. Seven of the 21 samples could not be measured due to insufficient volume, leaving only 14 samples for evaluation. POD 7 values were obtained from 19 patients, excluding 4 patients who developed pneumonia ($n = 3$) or refused ($n = 1$), but only 1 patient had an insufficient sample. A marginally significant change in salivary SP concentration was observed over the perioperative measurement time points ($p = 0.074$), with 12 of 14 (85.7 %) patients showing increased concentrations on POD 2 compared with preoperative levels (Fig. 1b). However, only 2 of the patients who exhibited aspiration on POD 2 could be sampled, and they showed almost no change; therefore, perioperative change of salivary SP concentration could not be assessed. Both mean preoperative plasma and salivary SP concentration in patients with aspiration were lower, but not significantly so, than in patients without aspiration, 30.3 pg/ml vs. 97.2 pg/ml ($p = 0.115$) and 29.5 pg/ml vs. 65.8 pg/ml ($p = 0.144$), respectively.

Changes in perioperative cough reflex sensitivity

Preoperative values were obtained from all 30 patients. POD 2 values were obtained from 22 patients; the remaining 8 had delirium ($n = 3$), refused ($n = 4$), or withdrew during testing ($n = 1$). POD 7 values were obtained from 24 patients; the remaining 6 developed

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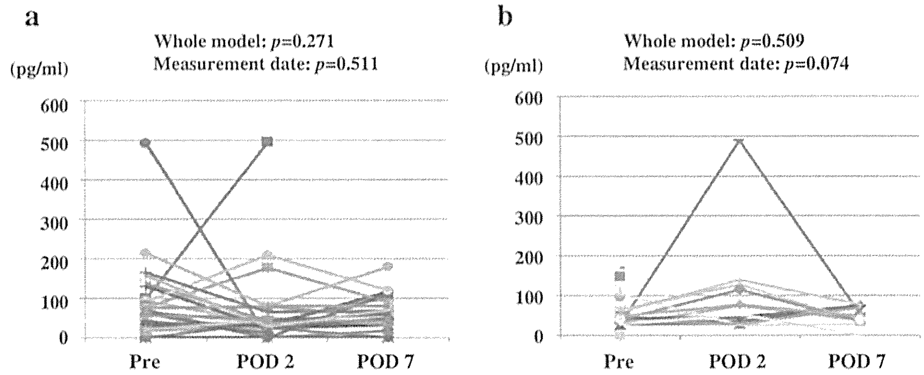

Fig. 1 Changes in perioperative plasma and salivary SP concentrations. The *vertical axis* represents SP concentration (pg/ml) and the *horizontal axis* represents three measurement time points: Pre, preoperative day; POD 2, postoperative day 2; and POD 7, postoperative day 7. **a** Perioperative change in plasma SP concentration in each patient. **b** Perioperative change in salivary SP concentration in each patient. The *p* value indicates the level of significance for the whole model comparison and the comparison between measurement points

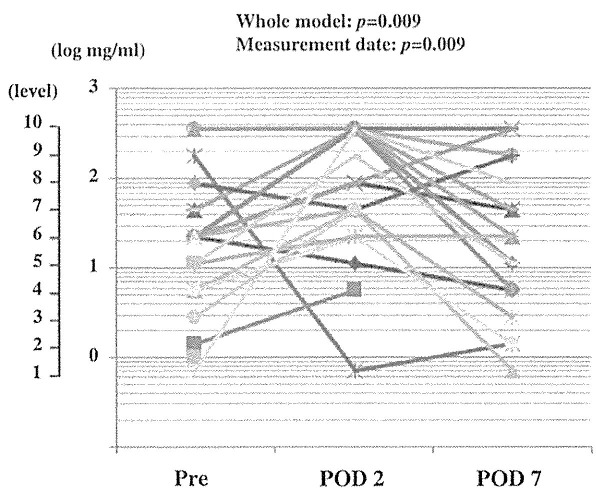

Fig. 2 Changes in perioperative cough reflex sensitivity. The *vertical axis* represents the cough reflex threshold on a logarithmic scale. The 10-level inhaled citric acid concentrations, corresponding to serial dilutions ranging from 0.7 to 360 mg/ml, are presented on the bar to the *left of the vertical axis*. The *horizontal axis* represents three measurement time points: Pre, preoperative day; POD 2, postoperative day 2; and POD 7, postoperative day 7. *P* values are shown for the whole model comparison and the comparison between measurement points

pneumonia ($n = 4$) or refused ($n = 2$). Significant changes were observed in both the whole model comparison and in the comparison between measurement points ($p = 0.009$). An increased cough reflex threshold was observed in 19 of 22 (86.4 %) patients on POD 2 (Fig. 2). Increased cough reflex threshold on POD 2 was observed also in 3 patients who exhibited aspiration and consented to measurement, suggesting no unique change in cough reflex threshold in aspiration patients.

Univariate and multivariate analysis with multiple logistic regression of risk factors for postoperative aspiration

To identify the factors contributing to postesophagectomy aspiration, univariate analysis was performed with preoperative and POD 2 values and the POD 2 to preoperative ratio for plasma SP concentration, preoperative salivary SP concentration, and cough reflex threshold, as well as patients' preoperative clinicopathological and surgery-related factors. The analysis revealed a significant correlation between sex, preoperative plasma SP concentration, and preoperative salivary SP concentration with postoperative aspiration ($p = 0.039$, $p = 0.008$, and $p = 0.004$, respectively, Table 2). Multivariate analysis was then performed to identify preoperative or surgery-related risk factors predictive of postoperative aspiration. First, a stepwise forward selection method was used to select variables from patients' clinicopathological factors, surgery-related factors, preoperative cough reflex threshold, and preoperative plasma and salivary SP concentrations. Age, tumor location, recurrent laryngeal nerve palsy, and preoperative plasma SP concentration were selected as variables for multivariate analysis. Multiple logistic regression analysis of the four variables identified preoperative plasma SP concentration as the only risk factor significantly associated with postoperative aspiration ($p = 0.023$) (Table 2).

Discussion

The peptide SP has been the subject of recent investigations, conducted mainly by Japanese researchers, into the

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Table 2 Univariate analysis and multivariate logistic regression analysis of the risk factors for postoperative aspiration

Risk factor	No. of patients		Univariate analysis	Multivariate analysis with multiple logistic regression analysis		
			p value	Unit odds ratio	95 % CI	*p* value
Sex	30	M vs. F	0.039			
Age	30		0.177	1.037	0.923–1.228	0.544
Brinkman index	30		0.202			
Tumor location	30	Ut vs. Mt/Lt	0.793	1.251	0.031–22.64	0.886
cStage	30	III/IV vs. 0/I/II	0.849			
Preoperative therapy	30	presence vs. absence	1.000			
LN dissection	30	3F vs. 2F	0.579			
Reconstruction route	30	Retrosternal vs. others	0.336			
Recurrent nerve palsy	30	presence vs. absence	0.556	0.738	0.014–13.69	0.849
Plasma SP (pg/ml)	30	Pre-op	0.008	0.964	0.919–0.996	0.023
	26	POD 2	0.080	Not included		
	26	POD 2/pre-op	0.653	Not included		
Salivary SP (pg/ml)	23	Pre-op	0.004			
Cough reflex (level)	30	Pre-op	0.837			

M male, *F* female, *Ut/Mt/Lt* upper/middle/lower thoracic esophagus, *LN* lymph node, *2F/3F* 2-field/3-field, *pre-op* preoperative day, *POD* postoperative day, *Not included* not included in the multivariate analysis

causes of silent aspiration in the elderly. This is the first study examining the association between SP and surgical stress. We performed this study to test our hypothesis that a postoperative decrease in SP secretion would be involved in the development of postoperative pneumonia through silent aspiration. However, postoperative changes could not be examined sufficiently due to a lack of samples collected. Plasma SP concentration on POD 2 was measured in 26 of 30 patients and no significant decrease was observed; therefore, we did not obtain definitive results supporting our hypothesis that SP secretion decreased postoperatively due to surgical stress. In contrast, patients with aspiration tended to show low preoperative plasma SP concentration compared to patients without aspiration, and multivariate analysis suggested that preoperative decreased plasma SP concentration is likely to be a significant risk factor for postoperative silent aspiration.

Our hypothesis could not be examined sufficiently in this study, primarily for reasons of insufficient postoperative sample collection. Initially, we speculated that salivary SP might reflect the role of the swallowing reflex more directly and accurately than plasma SP. However, we were not able to obtain postoperative salivary samples of sufficient volume from one-third of patients due to decreased saliva secretion associated with postoperative fluid restriction; therefore, salivary SP concentration was not deemed to be reliable or useful because of measurement inaccuracy due to sample condensation and a low collection rate. Postoperative cough reflex sensitivity was also difficult to measure accurately in over 30 % of patients for ethical reasons or patient unwillingness to be tested, and postoperative change could not be assessed. Regarding plasma SP concentration, POD 2 values could be measured in most patients; nevertheless, we found no significant postoperative decrease of plasma SP concentration and no relationship with the incidence of silent aspiration.

Another reason our hypothesis could not be sufficiently examined is that none of the patients needed reintubation due to severe pneumonia or needed long-term swallowing rehabilitation due to persistent aspiration, even though all the patients underwent cervical anastomosis and more than one-third underwent cervical lymphadenectomy. Postoperative dysphagia is mainly caused by impaired laryngeal elevation due to the scar change after a cervical surgical procedure [6–10]. In our previous study on postoperative swallowing dysfunction, the addition of our newly designed surgical procedure to improve swallowing function decreased the incidence of postoperative aspiration to 10 % [11]. All the patients enrolled in the present study also received this surgery to assist swallowing, and therefore no patients exhibited clinically distinct aspiration. As the incidence of postoperative aspiration was low, larger sample sizes are needed to fully verify our hypothesis.

Multivariate logistic regression analysis in this study identified only preoperative plasma SP concentration as a risk factor for postesophagectomy aspiration. Generally, a major cause of pneumonia after esophagectomy is aspiration induced by swallowing dysfunction due to impaired laryngeal elevation; fiberoptic or videofluoroscopic study also reveals the involvement of subclinical silent aspiration

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[6, 7]. In a previous study, we performed an additive surgical procedure designed specifically to assist swallowing function to patients who underwent esophagectomy with 3-field lymphadenectomy; however, 10 % of patients still developed postesophagectomy aspiration and multivariate analysis identified age as a risk factor [11]. Many analyses with perioperative variables also recognized age as a risk factor for pulmonary complication or aspiration after esophagectomy [1–3]. Recent research indicates that pneumonia in the elderly is mainly caused by silent aspiration, in which decreased SP secretion due to clinical or subclinical cerebrovascular damage is involved [26, 27]. SP is a peptide consisting of 11 amino acids [23], which is synthesized in the glossopharyngeal nerve and the cervical sympathetic ganglion of the sensory branch of the vagus nerve, transported in a retrograde fashion through the nerve, and secreted into the pharynx and trachea to regulate the cough and swallowing reflexes [17, 18]. Synthesis of SP is stimulated and promoted by dopamine in the basal ganglia [20, 28]. Cerebrovascular damage in the basal ganglia, even in asymptomatic patients, affects dopamine synthesis in the substantia nigra and corpus striatum in deeper layers of the cerebral cortex, leading to decreased synthesis and secretion of SP and subsequent reductions in the cough and swallowing reflexes, and the eventual development of silent aspiration. However, such patients with subclinical cerebral damage do not always have dysphagia, and aspiration is not a severe postoperative problem following surgeries other than esophagectomy.

Recent studies have revealed that the cough and swallowing reflexes do not decrease with age [29, 30]. Human brain imaging has provided an evidence that cortical and subcortical structures play a critical role in controlling cough and swallowing [31]. Moreover, the most recent functional magnetic resonance imaging study has revealed that the sensory processing areas in the cortex involved in swallowing, rather than the motor processing areas, deteriorate with age [32]. However, the cough reflex threshold was actually not to differ between young and elderly subjects and the net performance of the cough reflex was compensated in the elderly [33]. Meanwhile, surgery for esophageal cancer is accompanied by muscle destruction and denervation related to breathing and swallowing. This means that the compensation mechanism in the motor component is disrupted by esophagectomy, and the airway is likely susceptible to invasion by foreign bodies in the early postoperative period.

Although patients without a clear evidence of cerebrovascular damage were eligible for this study, >70 % of Japanese patients with esophageal cancer are aged ≥60 years [34]. In addition, asymptomatic cerebral infarction has been reported in 53 % of those aged ≥60 years, nearly half of whom have infarctions in the basal ganglia [35], meaning that about one-fifth of patients are at high risk of aspiration after esophagectomy even though they show no swallowing abnormality. This finding is similar to that of our previous study in which incomplete airway protection (laryngeal penetration and aspiration) was observed in one-fourth of patients who underwent esophagectomy despite undergoing our newly designed surgical technique to assist swallowing [11]. To date, however, there has been no way to identify patients preoperatively who are at high risk of postoperative aspiration despite normal swallowing preoperatively, and therefore the measurement of preoperative plasma SP concentration would appear to be a promising method with clinical significance.

In addition, decreased preoperative plasma SP concentration may be restored by pharmacological intervention with the following agents: angiotensin converting enzyme (ACE) inhibitors, which inhibit degradation of SP [36, 37]; capsaicin, which promotes SP secretion [38]; amantadine, which promotes dopamine synthesis [39]; and cilostazol, an antiplatelet agent expected to promote dopamine synthesis by improving cerebral blood flow [40]. These agents have been used in clinical studies for patients with cerebrovascular damage; ACE inhibitors demonstrated 11 % efficacy for pneumonia prevention [36], and amantadine and cilostazol reduced the incidence of pneumonia over 3 years by 20 % [39] and 40 % [40], respectively. Patients with decreased preoperative plasma SP concentration who have undergone esophagectomy may, theoretically, respond to pharmacological treatment with the above agents. Given the link this study found between SP and postoperative aspiration, such medication may provide such benefit.

The present study suggested a new finding instead of verifying our hypothesis; however, the study has several limitations. First, the sample population is small. Second, this study was not designed to verify the usefulness of preoperative plasma SP concentration for risk evaluation for postoperative aspiration, which is the result obtained from the subanalyses of this study. Finally, the possible association of plasma SP concentration and silent cerebrovascular damage was not investigated in this study. Further large-scale studies are required to validate the efficacy of preoperative plasma SP concentration as a preoperative predictor of patients with high risk of postoperative aspiration.

In conclusion, in an attempt to elucidate the mechanism of postoperative aspiration in patients undergoing surgery for esophageal cancer, we found that patients with decreased preoperative plasma SP concentration carry an increased risk of developing aspiration during the perioperative period, and the decreased plasma SP concentration may indicate the presence of silent cerebrovascular damage.

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At the present stage, our results are still speculative. However, if pneumonia prevention can be achieved by controlling plasma SP concentration, it will reduce the risk of postoperative pneumonia and substantially improve the safety of surgery and quality of life of patients. There is an urgent need to verify our findings in future studies.

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Ethical Statement This study was approved by the Institutional Review Board of Ethics Committee and was conducted in accordance with Helsinki Declaration of 1975, as revised in 2000 and 2008, and informed consent was obtained from all patients. Those were involved in the prerequisites for publication in the certification form as No. 5 item and all authors certified and put their own signatures on the form.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

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Aortic stent-grafting facilitates a successful resection after neoadjuvant treatment of a cT4 esophageal cancer

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Standard surgical techniques are ineffective in the management of cT4 esophageal cancer (EC) with aortic invasion. Although radical esophagectomy with partial resection of the aortic wall has been reported,[1] fatal hemorrhage may occur during the operation, and the patient's prognosis does not necessarily improve. Meanwhile, chemoradiation therapy (CRT) may induce tumor necrosis, leading to rupture of the aortic wall and fatal hemorrhage.

Endovascular treatment of aortic diseases with stents has emerged as an alternative to conventional surgical intervention. Currently, there are some reports regarding the use of stents for aortomediastinal fistula caused by EC.[2] We hypothesized that the prophylactic use of aortic stent-grafting could facilitate subsequent surgical resection of T4 EC penetrating into the aorta after CRT. Here we report a novel and effective application of intra-aortic stent-grafting.

CLINICAL SUMMARY

A 66-year-old man was admitted to our department with dysphagia. An upper gastrointestinal endoscopy identified squamous cell carcinoma in the middle thoracic esophagus (28-35cm from the incisors; Figure 1, *A*). Computed tomography showed a large tumor invading the descending aorta, with locoregional lymph node metastases (Figure 1, *B*). Although induction CRT (concurrent administration of 50 Gy radiation and 2 courses of a cisplatin regimen with fluorouracil) was performed, penetration of the tumor into the descending aorta unfortunately occurred 4 weeks after the completion of CRT (Figure 1, *C* and *D*). Thoracic aortography revealed a pseudoaneurysm of the descending aorta caused by tumor penetration, and an intra-aortic stent (TAG 34-15; W.L. Gore and Associates, Flagstaff, Ariz) was prophylactically inserted with success (Figure 1, *E* and *F*). On the next day, radical surgical resection (subtotal esophagectomy followed by replacement by gastric conduit through the retrosternal route) was successfully performed through the right chest approach without fatal hemorrhage (Figure 2). The greater omentum of gastric conduit was pulled down through the window of incised mediastinal pleura to fill the space above the descending aorta. Histopathologically, there was only a scattering of viable cells remaining in the adventitial layer of the esophagus indicating grade 2 histologic effect (ypT3N0M0, stage IIB). Broad-spectrum intravenous antibiotic therapy was continued for 17 days after the insertion of the aortic stent. The postoperative course was uneventful, and the patient was discharged on postoperative day 44. At the last follow-up examination, 11 months after the operation, the patient remains free of any sign of disease recurrence.

DISCUSSION

Aortoesophageal fistula is a life-threatening complication of EC treated with irradiation. Fatal hemorrhage develops in 7% of patients with irradiated EC, and more than half of fatal hemorrhages are caused by aortoesophageal fistula.[3] Once aortoesophageal fistula develops, long survival cannot be expected unless immediate and extensive surgical procedures are undertaken.

Endovascular stent-grafting was originally indicated for endovascular repair of aortic aneurysms in patients who could not undergo radical operation. The indications for thoracic intra-aortic stenting have rapidly been expanded, however, to cases with hemorrhage caused by aortic ulceration due to arteriosclerosis, cases with dissecting aneurysm, and cases with aortomediastinal fistula. Stenting has also been used to prevent aortoesophageal fistula after CRT and as an emergency procedure to control massive hemorrhage from aortoesophageal fistula. Here we propose a novel and effective use of prophylactic aortic stent-grafting in the surgical resection of T4 EC penetrating into the aorta after CRT.

The theoretic advantages of endovascular treatment include the following: need for only a simple arteriotomy, without thoracotomy or intraoperative single-lung ventilation and aortic clamping; low risk of medullary ischemia, possibly because of the absence of aortic clamping and the location of the aortic injury; and a relatively low risk of major bleeding complications because the stent-graft can be inserted with only mild anticoagulation, so there is no need for prophylactic anticoagulation therapy afterward. High fever and CRP after stent-grafting are reported as symptoms of "postimplantation syndrome"; this, however, was not observed in our case.[4] Considering the risk for infection of the prosthesis, particularly in the setting of gastrointestinal

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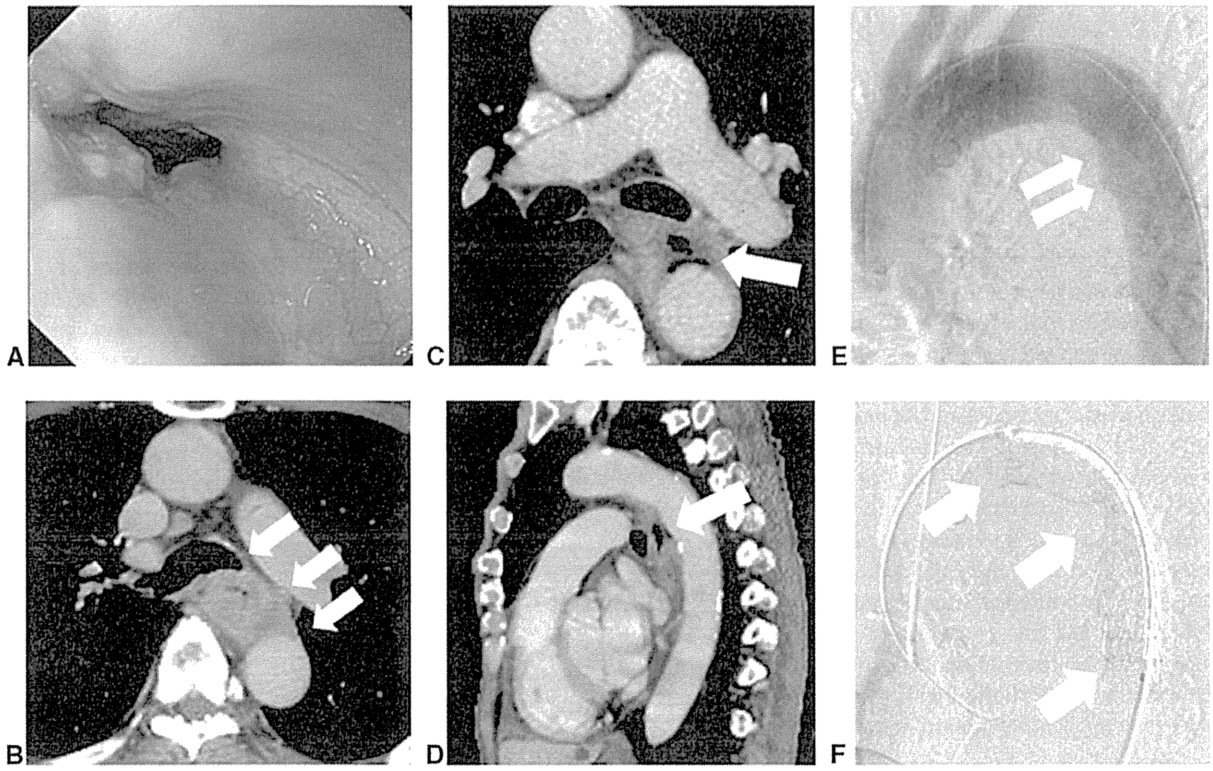

FIGURE 1. A, An upper gastrointestinal endoscopy identified a type3 tumor in the middle thoracic esophagus. B, Computed tomography showed a large tumor (*arrows*) invading the descending aorta. C and D, The axial (C) and sagittal (D) computed tomographic scans demonstrated the penetration of the tumor into the descending aorta (*arrow*) 4 weeks after the completion of chemoradiation therapy. E and F, Findings of thoracic aortography. *Arrows* indicate pseudoaneurysm of the descending aorta caused by tumor penetration (E) and an intra-aortic stent successfully inserted to right distal of the origin of the left subclavian artery (F).

surgery, long-term antibiotic therapy should be considered.[5] In addition, surgical measures, including the use of the greater omentum to cover the exposed graft as in this case, are important to reduce the risk of infection.

Although the clinical indication of intra-aortic stent-grafting should be carefully determined because of the procedure's relative invasiveness and high cost, and because of the large number of cases necessary to evaluate its utility, we conclude that the prophylactic use of stent-grafting for T4 EC penetrating into the aorta after CRT is a novel and effective option that enabled us to perform a potential subsequent radical resection without fatal hemorrhage.

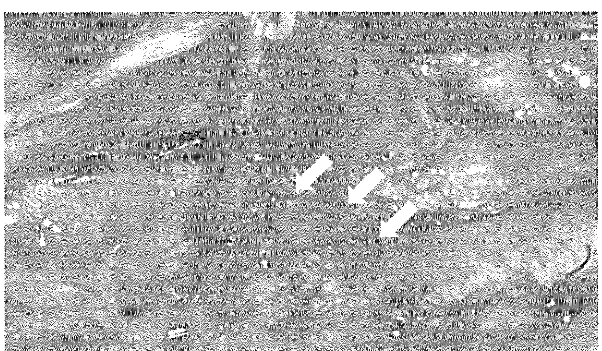

FIGURE 2. Intraoperative finding: *Arrows* point to the descending aortic wall lacking the adventitia, through which the intra-aortic stent could be seen.

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Efficacy and Predictor of Octreotide Treatment for Postoperative Chylothorax After Thoracic Esophagectomy

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Abstract

Background Postoperative chylothorax sometimes follows thoracic esophagectomy for esophageal cancer. The effectiveness of octreotide treatment for it and factors that predict its response are unclear. This study aimed to evaluate the efficacy of octreotide for treating postoperative chylothorax following thoracic esophagectomy for esophageal cancer and factors that might predict successful treatment and allow chest drain removal.

Methods We assessed 521 consecutive patients who underwent thoracic esophagectomy for esophageal cancer to investigate the efficacy of octreotide for postoperative chylothorax. Among those with postoperative chylothorax, one group (group A) underwent conservative management, and the other (group B) was treated conservatively with added octreotide administration. We evaluated the clinical outcomes after octreotide administration and assessed the factors associated with successful treatment.

Results Among the 521 patients, 20 (3.8 %) developed postoperative chylothorax: five in group A and 15 in group B. Two of the five (20 %) group A patients and 13 of the 15 (86.6 %) group B patients were treated successfully ($p = 0.03$). Factors significantly associated with treatment failure were (1) chest drain output of >1,000 ml/day before treatment ($p = 0.04$); (2) no reduction in chest drainage by the second day of treatment ($p = 0.016$); (3) chest drainage of >1,000 ml/day through the second day of treatment ($p = 0.006$).

Conclusions For patients with esophageal cancer who undergo thoracic esophagectomy, octreotide can be an effective treatment for postoperative chylothorax.

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Introduction

Postoperative chylothorax is usually the result of unrecognized injury to the main thoracic duct or its tributaries. Chylothorax is an uncommon complication of esophagectomy, occurring in only 0.6–4.0 % of procedures [1–7]. The complications of chylothorax include hypoproteinemia, lipid loss, and respiratory failure caused by lung compression [8–10].

Most previous studies included only a small number of patients and had variable results with different treatment approaches. Although the optimal management of postoperative chylothorax remains controversial [11, 12], the most common initial approach is conservative management with thoracic drainage and total parenteral nutrition. However, conservative treatment can be prolonged, with significant thoracic effusions lasting several weeks. Moreover, if the accumulation of pleural effusion is excessive and prolonged, conservative management is unlikely to succeed.

Somatostatin [13] and its synthetic analog octreotide [14] have been used successfully to treat postoperative chylothorax, particularly in children [9]. However, the efficacy of octreotide for treating postoperative chylothorax following thoracic esophagectomy performed for esophageal cancer has not been evaluated.

The present study aimed to review patients who received octreotide to treat postoperative chylothorax following thoracic esophagectomy, with particular attention to treatment outcomes and factors that possibly affected treatment success.

Materials and methods

Patients

Patients who underwent thoracic esophagectomy for esophageal cancer from 2001 to 2009 were identified in the database of the Division of Esophageal Surgery, National Cancer Center Hospital East. Patient data were retrospectively evaluated after receiving approval from our institution's investigational review board. Preoperative diagnoses were based on preoperative imaging studies, including upper gastrointestinal studies, endoscopy, and conventional cross-sectional imaging studies (computed tomography). Histologic evaluations of endoscope-guided biopsy specimens were performed in all cases. The patients' medical records were reviewed to determine the following: preclinical stage of their disease, surgical procedures performed, histopathologic findings of the lesions, and clinical outcomes.

For all cases, surgical procedures were performed using either a transthoracic approach (including a thoracoscopic approach) or a transhiatal approach under the direction of the attending surgeons. During a transthoracic approach, subtotal resection of the esophagus was performed with three-field regional lymph node dissection irrespective of the tumor stage. During a transhiatal approach, blunt dissection of the esophagus was performed with the removal of cervical lymph nodes and lymph nodes in the lower third of the mediastinum and abdomen. To allow complete regional lymph node dissection with a transthoracic approach, we primarily removed the thoracic duct ranging from the upper mediastinum to the level of the pulmonary ligament (ligating both cut ends and resecting the tissue together with the esophagus) irrespective of tumor location. In contrast, with a transhiatal approach the thoracic duct was preserved. The esophagus was usually reconstructed with a gastric tube via the posterior mediastinal route. Right hemicolic reconstruction was performed via the posterior sternal route if gastrectomy of the remnant stomach was required.

Postoperative management and octreotide administration for patients with postoperative chylothorax

Perioperative management employed a clinical management pathway for all patients (described elsewhere [15]) irrespective of the approach used for esophagectomy. Briefly, the endotracheal tube was removed either in the operating room or immediately after the patient was shifted to the intensive care unit. On postoperative day (POD) 1, enteral feeding through a nasogastric tube was initiated. On POD 6, a radiographic contrast agent swallow examination was performed to evaluate the anastomosis and any passage problems. If this examination showed no leakage or obstruction, the nasogastric tube was removed, and oral intake was initiated according to the postoperative dietary program.

During the course of enteral feeding, chylothorax was diagnosed if there was a change in the color of chest tube drainage to milky white, irrespective of the amount chest tube output, or if there was excessive chest drain output. The diagnosis was confirmed by physical and biochemical analysis even at 3 days after esophagectomy [16].

Patients were given either conventional conservative treatment (i.e. total parenteral nutrition) or both octreotide and total parenteral nutrition. Octreotide (Sandostatin; Novartis, Basel, Switzerland) was administrated subcutaneously (100 μg every 8 h). Esophageal cancers were evaluated according to the International Union Against Cancer TNM Classification of Malignant Tumors, 6th edition.

Statistical analysis

The two groups were statistically compared using the χ^2 test or Mann–Whitney *U* test, as appropriate. Univariate analysis and multivariate analysis with stepwise regression models were used to evaluate the significance of clinical and histopathologic variables on the success or failure of treatment with octreotide. A value of $p < 0.05$ was considered significant.

Results

Incidence and patient clinical manifestations of chylothorax after esophagectomy

During 2001–2009, a total of 521 patients with esophageal cancer underwent thoracic esophagectomy at the National Cancer Center Hospital East. During this period, 20 patients (3.8 %) developed postoperative chylothorax (Fig. 1). The demographics and characteristics of patients with or without postoperative chylothorax are shown in Table 1. No significant differences in clinical variables were found between those with and without postoperative chylothorax.

During the period 2001–2004, a total of 5 of 153 patients (group A 3.2 %) were found to have postoperative chylothorax. During 2005–2009, a total of 15 of 368

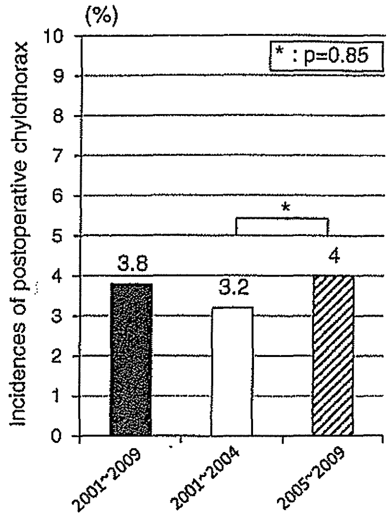

Fig. 1 Incidence of postoperative chylothorax for each time period. Overall incidences of postoperative chylothorax were 3.8 % for 2001–2009, 3.2 % for 2001–2004, and 4.0 % for 2005–2009

Table 1 Demographics and characteristics of 521 patients with or without postoperative chylothorax during 2001–2009

Variable	Without chylothorax ($n = 501$)	With chylothorax ($n = 20$)	p
Age (years)	65.4 ± 10.5	67.5 ± 11.2	0.81
Sex (M:F)	447:54	17:3	0.81
BMI (kg/m^2)	21.3 ± 3.7	20.8 ± 3.5	0.66
Location of tumor (Ut/Mt/Lt)	41/221/239	2/9/9	0.98
cT factor (T1/T2/T3/T4)[a]	207/55/226/13	6/2/12/0	0.79
cN factor (N0/N1)[a]	267/234	8/12	0.34
Preoperative treatment			
Neoadjuvant chemotherapy	201	10	0.37
Chemoradiation	33	2	0.88
Type of esophagectomy			
Transthoracic	443	16	0.43
Transhiatal	58	4	0.43
Surgical removal of thoracic duct	322	11	0.79
Operative blood loss (ml)	372.3 ± 216.9	356.8 ± 213.4	0.32
Total operative time (min)	342.5 ± 58.7	334.4 ± 48.1	0.29

Results are given as the mean ± SD or the number of patients unless otherwise stated

BMI body mass index, *Ut/Mt/Lt* upper/mid/lower thorax

[a] Union Internationale Contra le Cancer (UICC), 6th edition

patients (group B 4.0 %) were found to have postoperative chylothorax ($p = 0.85$) (Fig. 1). For group A, we managed postoperative chylothorax with conventional conservative treatment, whereas for group B we managed it with conventional conservative treatment plus octreotide. The demographics and characteristics of the patients in groups A and B are shown in Table 2. No significant differences in clinical variables were found between the two groups.

Table 2 Demographics and characteristics of patients who developed postoperative chylothorax

Variable	Conservative treatment ($n = 5$)	Octreotide treatment ($n = 15$)	p
Age (years)	64.8 ± 12.2	68.5 ± 10.9	0.82
Sex (M:F)	4:1	13:2	0.71
BMI (kg/m^2)	21.9 ± 2.5	20.5 ± 3.7	0.82
Location of tumor (Ut/Mt/Lt)	0/3/2	2/6/7	0.96
cT factor (T1/T2/T3/T4)[a]	2/1/2/0	4/1/10/0	0.99
cN factor (N0/N1)[a]	3/2	5/10	0.59
Preoperative treatment			
Neoadjuvant chemotherapy	2	8	0.60
Chemoradiation	0	2	0.38
Type of esophagectomy			
Transthoracic	4	12	0.51
Transhiatal	1	3	0.51
Surgical removal of thoracic duct	3	8	0.77
Operative blood loss (ml)	388.6 ± 244.5	346.2 ± 189.6	0.64
Total operative time (min)	364.1 ± 47.7	324.5 ± 51.3	0.75

Results are given as the mean ± SD or the number of patients unless otherwise stated

[a] Union Internationale Contra le Cancer (UICC), 6th edition

To confirm the effectiveness of octreotide, we retrospectively compared the successful removal rates of chest drainage tubes from patients being managed with conventional conservative treatment alone after esophagectomy and those treated with added octreotide under the same conditions. With conventional conservative treatment, two of five patients (40.0 %) were successfully managed, whereas 13 of 15 patients (86.6 %) were successfully managed with added octreotide ($p = 0.03$) (Fig. 2).

Efficacy and adverse events of octreotide for postoperative chylothorax

The mean interval from surgery to beginning treatment with octreotide was 4 days (Table 3). Treatment with octreotide was successful and allowed for chest drain removal in 13 of 15 (86.6 %) patients (Table 3). For the other two patients (13.4 %), octreotide treatment failed to

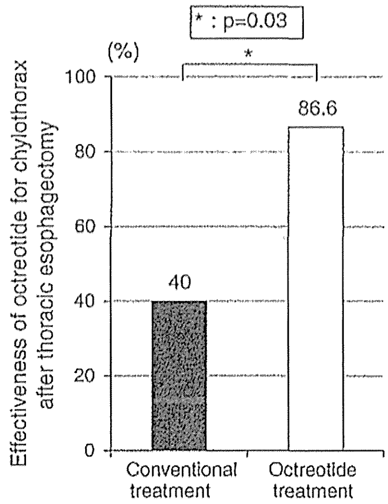

Fig. 2 Effectiveness of octreotide versus conventional conservative treatment for chylothorax after thoracic esophagectomy. Conventional conservative treatment was successful in two of five patients (40.0 %). Octreotide treatment was successful in 13 of 15 patients (86.6 %) ($p = 0.03$)

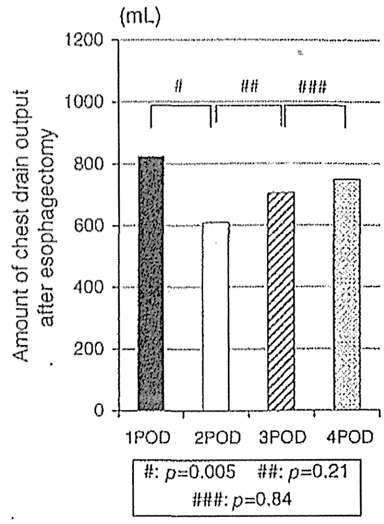

Fig. 3 Mean amounts of chest drainage on postoperative days (PODs) 1, 2, 3, and 4 after esophagectomy in 15 cases. There was a significant reduction in the drainage between PODs 1 and 2. Although there were no other significant reductions, the trend was toward a gradual increase in the amount of drainage during the postoperative course before treatment with octreotide

Table 3 Results of treatment with octreotide for chylothorax after esophagectomy

Variable	Data
Interval from surgery to start of treatment with octreotide[a]	4.0 days
Duration of treatment with octreotide[a]	5.4 days
Reduction in the amount daily drainage (after 2nd day)	34.3 %
Treatment success rate	86.6 %
Adverse events associated with octreotide	0

[a] Mean value

produce a sufficient decrease in the amount of chest drain output, and surgical repair was performed (Table 3). The mean interval between the start of octreotide administration to chest drainage tube removal was 5.4 days (Table 3). After 2 days of octreotide treatment, the amount of chest drainage had decreased by an average of 34.3 % (Table 3). No adverse events were remotely or directly attributed to using octreotide in this study.

Patient clinical courses before and after octreotide treatment

The amounts of chest drain output in 15 patients before treating them with octreotide are shown in Supplemental Fig. 1. For all cases, chest drainage of >400 ml was found on POD 1. In all, 12 of the 15 patients exhibited reescalation of chest drain output during their postoperative course before octreotide treatment. The average amounts of chest drainage on PODs 1, 2, 3, and 4 for these 15 cases are shown in Fig. 3. There were significant reductions in the amounts of drainage on the first and second postoperative days. However, although no significant reductions in amounts were observed, there was a trend for a gradual increase in drainage amounts during the postoperative courses before octreotide treatment.

The amounts of chest drain output before treatment with octreotide and on the first and second days after starting treatment are shown in Supplemental Fig. 2. Most of these patients showed reductions in chest drain output after starting treatment with octreotide. For 4 of the 15 patients (nos. 1, 4, 11, 15), chest drain output had been >1,000 ml/day before starting this treatment. Two of these four patients (nos. 4, 11) showed marked reductions in chest drain output after starting this treatment, such that their chest drains could be removed. The other two patients (nos. 1, 15) showed no response to octreotide even after 2 days of treatment. They eventually required surgical repair. Significant reductions in mean chest drain output were found between the day before treatment (819.6 ml) and the first day after starting treatment (689.3 ml, 15.9 %) ($p = 0.01$) and between the first (689.3 ml, 15.9 %) and second (550.3 ml, 20.6 %) days after starting treatment ($p < 0.01$) (Fig. 4).

Univariate and multivariate analyses for risk factors for octreotide treatment failure

Univariate analysis revealed the following factors to be significantly associated with octreotide treatment failure

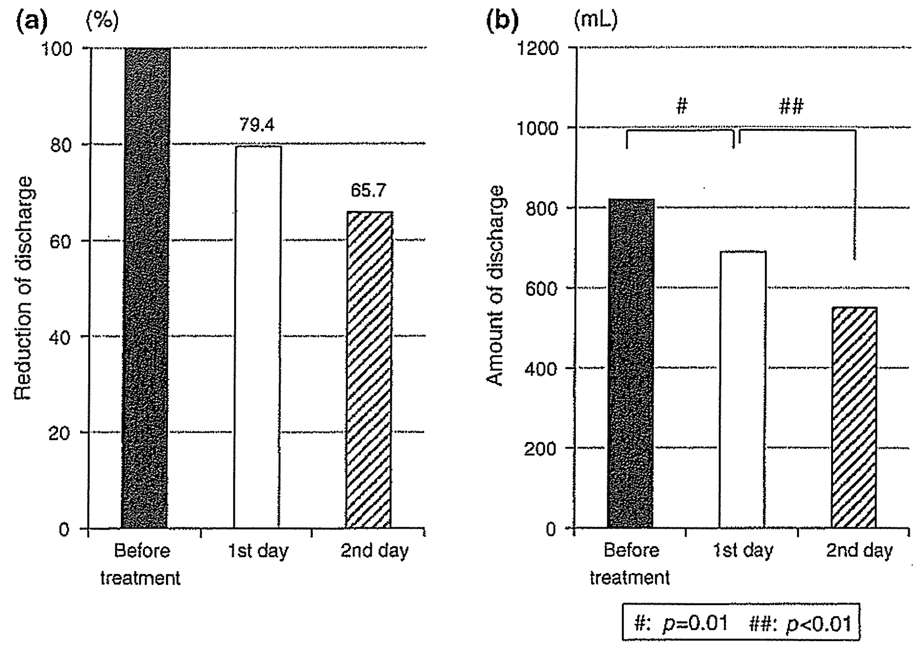

Fig. 4 Amount of chest drainage after administration of octreotide. **a** Drainage was reduced by 20.6 % on day 1 after octreotide administration and by 34.3 % on day 2. **b** There were also significant reductions in the amount of drainage between the day of octreotide administration and the day afterward ($p = 0.01$) as well as between the first and second days after octreotide administration ($p = 0.006$)

Table 4 Analysis of the risk factors for failure of treatment with octreotide in 15 patients

Factor	Treatment successful ($n = 13$)	Treatment failed ($n = 2$)	p
Age (years)[a]	67.1	78.0	0.135
Sex (M:F)	11:2	2:0	0.602
Discharge amount on POD 1 (ml)[a]	844.6	1,085	0.320
Discharge amount on POD 2 (ml)[a]	586.9	915	0.103
Start of treatment (POD)[a]	3.7	4.0	0.888
Discharge amount >1,000 ml/day before treatment with octreotide	15.3 %	100 %	0.04
Reduction in discharge amount on POD 2[a]	59.4 %	−11.5 %	0.016
Discharge amount on POD 2 (ml)[a]	438.4	1275.0	<0.01

POD postoperative day

[a] Results are the means

(Table 4): (1) chest drain output of >1,000 ml/day before treatment with octreotide ($p = 0.04$); (2) a lower percent reduction in chest drain output after the second day of treatment with octreotide ($p = 0.016$); (3) chest drain output of >1,000 ml/day after 2 days of treatment with octreotide ($p < 0.01$). No independent factors associated with octreotide treatment failure were identified by multivariate analysis.

Discussion

Because the thoracic duct transports up to 4 l of chyle daily in a healthy adult, leakage of chyle and lymph fluid results in significant losses of essential water, proteins, fats, and electrolytes, which can result in significant morbidity and mortality [12]. A meta-analysis of 44 studies showed that the incidence of postoperative chylothorax was higher after transthoracic esophagectomy (3.4 %) than after transhiatal esophagectomy (2.1 %) [17]. In our series of 521 esophagectomies, 11.9 % of patients underwent transhiatal esophagectomy and 88.1 % underwent transthoracic esophagectomy. The incidence of postoperative chylothorax was 3.8 % overall and did not differ significantly between transhiatal esophagectomy (6.4 %) and transthoracic esophagectomy (3.4 %; $p = 0.59$). Thus, we believe that the incidence of postoperative chylothorax in our series, which was similar to those previously reported [2, 6], was acceptable.

The optimal management of postoperative chylothorax remains controversial. In animal studies, conservative treatment of disrupted thoracic ducts has been successful [18]. However, treating postoperative chylothorax with a conservative approach using fat-free nutritional management remains challenging. From the 1950s through the 1970s, several authors recommended early surgical intervention for all cases of postesophagectomy chylothorax [19, 20], whereas others suggested discontinuing conservative management if the daily chest drain output exceeded 1.5 l for more than 4 days or persisted for more than 2 weeks [21].

Octreotide has been shown to be a potent, effective treatment for chylous pleural effusion [22]. Octreotide is a synthetic somatostatin analog with antisecretory properties similar to those of somatostatin [23]. Somatostatin is a polypeptide that primarily has inhibitory actions on the release of various hormones, such as growth hormone and insulin, and on lymph fluid excretion [23]. In experimental studies, somatostatin markedly decreased thoracic lymph flow [24]. Rimensberger et al. [13] were the first to treat chylothorax with somatostatin. Subsequent uncontrolled clinical studies suggested that octreotide was effective for treating primary and secondary chylothorax in children [25]. However, few studies have examined the efficacy of octreotide for chylothorax that develops after surgery in adults, particularly after esophagectomy.

The present study provides evidence supporting the efficacy of octreotide for treating postoperative chylothorax following esophagectomy for esophageal carcinoma. Octreotide treatment decreased the amount of chest drainage such that chest drains could be removed in 86.6 % of patients, an unexpectedly high rate of treatment efficacy. Importantly, treatment was successful for two of four patients with chest drain outputs before treatment that exceeded 1,000 ml/day. Therefore, the previous recommendation that surgical repair of the thoracic duct is necessary if the amount of chest drainage is >1,000 ml/day may need to be reconsidered in view of the efficacy of octreotide.

We could not identify any factors that might predict the efficacy of octreotide for patients with chest drain output of >1,000 ml/day. However, further precise evaluations of anatomic variations or hormonal balances may aid in predicting which patients will respond to octreotide.

The present study had several limitations. Because the number of patients who had postoperative chylothorax and were subsequently treated with octreotide was small, rigorous statistical evaluation was not possible. Hence, this treatment strategy was possibly biased. In addition, the mean time until starting treatment was approximately 4 days after surgery, which is relatively delayed. This was partly due to the potential difficulty of diagnosing postoperative chylothorax, particularly in patients with high chest drain output with serous-bloody fluid only. In such cases, we occasionally encountered events caused by postoperative minor oozing into the thoracic cavity. Therefore, we sometimes observed chest drain output and waited using octreotide for an additional 1–2 days. Furthermore, over our 4-year study period, both the preoperative diagnostic accuracy and postoperative follow-up regimens differed slightly. However, perioperative management was consistent, which may be considered a strong point of our study.

Conclusions

We found that treatment with octreotide was successful for 86.6 % of patients with postoperative chylothorax after esophagectomy. However, other treatment options should be considered—such as thoracic duct embolization and surgical repair of the thoracic duct—when chest drain output remains at more than 1,000 ml, even after 2 days of octreotide treatment.

Because the administration of octreotide is safe and noninvasive, it could be considered a first-line treatment for postoperative chylothorax that develops after thoracic esophagectomy for esophageal cancer. However, there are potentially other effective means by which a chyle leak can be addressed nonsurgically, such as thoracic duct embolization. Moreover, we have to consider that even after administering octreotide chylous output remains high (Table 4, bottom data). Therefore, a more aggressive strategy should be considered to reduce chylous output. Additional analyses, including preoperative imaging examinations of the thoracic duct and investigations of a large number of cases in a prospective setting should provide more detailed information for understanding the efficacy of octreotide and predicting the responses after thoracic esophagectomy for esophageal cancer.

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Conflict of interest None declared.

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Recurrence Patterns of Esophagogastric Junction Adenocarcinoma According to Siewert's Classification After Radical Resection

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Abstract. *Background: The treatment strategy for adenocarcinoma of the esophagogastric junction (AEG) remains controversial. In the present study, the recurrence pattern of AEGs according to Siewert's classification after radical resection was reviewed, and predictive factors of recurrence were examined. Patients and Methods: We retrospectively analyzed the clinical data of 127 consecutive patients with Siewert type I, II, and III AEGs who underwent curative resection (R0) without perioperative chemotherapy at the National Cancer Center Hospital East between January 1993 and November 2006. Results: The median follow-up period was 48.9 (range=1.5-179) months. The recurrence rates of type I, II, and III tumors were 57.1%, 44.4%, and 41.0%, respectively. The most frequent relapse site was lymphogenous in type I, hematogenous in type II, and disseminative in type III tumors. The median time-to-recurrence after surgery was 12.6 months in type I, 12.5 months in type II, and 12.7 months in type III disease, with no significant difference. Multivariate analysis revealed that mediastinal lymph node metastasis (p=0.005) (hazard ratio=2.954, 95% Confidence Interval=1.38-6.31) was a significant and independent prognostic indicator for poor recurrence-free survival. The recurrence rate in patients with mediastinal lymph node metastasis at the time of surgery was 100%. Conclusion: The recurrence pattern of AEGs differed according to Siewert's classification. Its tendency should be understood in order to determine the optimal surgical approach. Mediastinal lymph node dissection may be effective for local control, but may not significantly improve prognosis. When mediastinal lymph node metastasis is suspected, perioperative chemotherapy may be recommended.*

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The incidence of adenocarcinoma of esophagogastric junction (AEG) has rapidly increased in Western countries. Although this trend does not necessarily apply to Eastern countries (1-4), it is speculated that it will follow in the near future because of a change to a more Western diet. According to Siewert's classification, proposed in 1996, AEGs are classified into three subtypes based on the distance from the epicenter of the tumor to the anatomical esophagogastric junction line (5). This classification is used worldwide to determine the best surgical strategy. The distribution of the three types of AEG reportedly differs little between Eastern and Western countries (3, 4, 6).

The surrounding structures of AEGs are complicated, and the biological behavior of AEGs is thought to be aggressive. Most cases are diagnosed at an advanced stage. At present, surgical treatment with radical lymphadenectomy is the primary modality in treatment of AEGs. However, despite intensive R0 resection and lymph node dissection, the long-term outcome remains unsatisfactory (6, 7).

The oncological outcomes of AEGs according to Siewert's subtype have been published by many researchers, and we reported our data on overall survival curves in 2012 (4-7). However, only a few reports from Western countries have focused on the recurrence pattern of AEGs (8-10), and as far as we are aware of, there have been no reports from Eastern countries. Therefore, here we highlighted the recurrence pattern of AEGs at a single cancer hospital in Japan to elucidate the best strategy with which to control relapse after radical surgery.

Patients and Methods

Patients. Based on a prospective database for both esophageal and gastric cancer at the National Cancer Center Hospital East in Japan between January 1993 and November 2006, 127 consecutive patients with AEGs (Siewert types I, II, and III) underwent curative (R0) surgical resection. Exclusion criteria included a prior history of surgery for gastric cancer or gastric stump cancer. All patients underwent preoperative chest radiographs, abdominal ultrasonography, or computed tomography (CT) for tumor staging and determination of

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resectability. Upper gastrointestinal endoscopy and barium swallows were performed. From these findings, we determined the preoperative Siewert subtypes and surgical approaches. The operative technique was based on the preoperative diagnosis and estimated length of esophageal invasion. Thus, the operative approach and extent of the procedure performed was tailored to each case with the intention of complete surgical resection. As a result, patients underwent subtotal esophagectomy or total gastrectomy with distal esophagectomy, or proximal gastrectomy with distal esophagectomy. Standard cervical and mediastinal and D2 abdominal lymphadenectomy carried out for subtotal esophagectomy, and lower posterior mediastinal and D2 or D3 abdominal lymphadenectomy applied for distal esophagectomy with gastrectomy. Neither neoadjuvant nor adjuvant chemotherapy was given to any patient because S-1 has been used as a standard adjuvant chemotherapy since 2007 (11).

International Union Against cancer (UICC) seventh TNM classification of esophageal cancer was used to describe tumor progression and histopathological grading (12). Lymph node dissection was categorized according to the Japanese classification of gastric carcinoma (13).

Patients were generally followed up as outpatients every two to three months for the first two years and every six months thereafter. Follow-up studies comprised physical examination, blood chemistry, tumor markers, and chest and abdominal CT. In principle, CT was conducted every four months for the first two years and every six months thereafter. Only the first site of recurrence was considered, and the date of recurrence was defined as the first evidence of recurrence in the follow-up studies. The recurrence patterns were classified as hematogenous (liver, lung, bone, and adrenal gland), lymphogenous, disseminative (pleural and peritoneal), and local. The median follow-up period was 48.9 months (range=1.5-179 months).

Statistical analyses. Statistical analyses were performed using the Chi-square test and *t*-test. Cumulative survival rates were generated by the Kaplan–Meier method. The survival curves were compared with the log-rank test. Significant factors were identified by univariate analysis and further examined by multivariate analysis. Multivariate regression analysis was carried out using the Cox hazards model. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Tokyo, Japan). A *p*-value of less than 0.05 was considered statistically significant.

Results

Patient population and tumor characteristics. A total of 127 patients with AEG who underwent curative resection were enrolled in the present study, including seven (5.5%) with type I tumors, 81 (63.8%) with type II tumors, and 39 (30.7%) with type III tumors. Patients' characteristics, pathological findings, and detailed surgical approaches are shown in Table I. There were no significant differences in age, gender, lymph node metastasis, histopathological grade, or lymphovascular invasion. Larger, deeper tumors were more common in patients' with type III compared to type II tumors. The incidence of mediastinal lymph node metastasis was significantly higher in patients with type I than type III tumors. Surgical approaches varied by tumor type. Sub-total esophagectomy was performed for two patients with type I and four patients with type II tumors. In principle, this surgery was performed with three-field lymphadenectomy in the same manner as radical resection for typical esophageal cancer.

Out of the 127 patients, 56 (44.1%) developed recurrent disease during the follow-up period: four (57.1%) developed type I tumors, 36 (44.4%) developed type II tumors, and 16 (41.0%) developed type III tumors. There was no significant difference in the recurrence rate among the three types. As shown in Figure 1, two out of four patients (50%) with type I tumors developed lymphogenous recurrence. Hematogenous recurrence was the most common type of recurrence in patients with type II tumors. Peritoneal dissemination was the most common in patients with type III tumors, and there was no local recurrence. Twenty-three patients developed hematogenous recurrence of type II and III tumors; liver and bone were the major recurrence sites in these patients. Metastasis to the adrenal gland occurred in one patient with a type III tumor. The cervical and mediastinal lymph regions were the major sites of lymphogenous recurrence of type I tumors; however, the para-aortic region was the most common site in patients with type II and III tumors (Figure 2), and this area was not removed during surgery. In two patients with a type II and one patient with a type III tumor, cervical lymph node recurrence was seen as the first recurrence site; this area was also not dissected during surgery.

The median time-to-recurrence was 11.6 (0.9-67.2) months in hematogenous recurrence, 12.3 (3.2-30.8) months in lymphogenous recurrence, and 21.4 (2.3-141.2) months for dissemination. The duration was longest in the dissemination group, but there was no statistically significant difference. Hematogenous and lymphogenous recurrences occurred relatively early after the operation, and dissemination occurred constantly, as shown in Figure 3; however, no statistically significant difference was seen. The median period to recurrence for each Siewert subtype was 12.6 (7.0-15.2) months in type I, 12.5 (0.9-67.2) months in type II, and 12.7 (2.3-141.3) months in type III (Figure 4). Most recurrence developed within 24 months.

Recurrence-free survival (RFS). The RFS curve for each Siewert type is shown in Figure 5. No significant differences were seen among these survival curves. Five-year RFS rates were 33.3% in type I, 53.8% in type II, and 59.4% in type III. To define the predictive prognostic factors of RFS, we examined 12 items: age (<65 *vs.* >65 years), gender, tumor size (<60 *vs.* >60 mm), Siewert type (type I or II *vs.* III), tumor depth (T1, 2 *vs.* T3, 4), existence of lymph node metastasis, existence of mediastinal lymph node metastasis, existence of para-aortic node metastasis, length of esophageal invasion (<20 *vs.* >20 mm), degree of venous and lymphovascular invasion, and histopathological grade (G1, 2 *vs.* G3, 4) (Table II).

Table I. *Baseline characteristics of patients and surgical approaches (N=127). *According to UICC seventh TNM classification of esophageal cancer.*

Classification	Type I (n=7)	Type II (n=81)	Type III (n=39)	*p*-Value
Age	67.0 (56-83)	67.0 (39-86)	66.0 (52-82)	0346 (I *vs*. II) 0.080 (II *vs*. III) 0322 (I *vs*. III)
Male-female	6:1	63:18	27:12	0.483
Tumor size (mm)	38.1±123	55.1±255	80.4±37.6	0.086 (I *vs*. II) <0.001 (II *vs*. III)
Esophageal invasion (mm)	413±11.3	14.6±11.7	14.0±103	<0.001(I *vs*. II) 0.777 (II *vs*. III)
T Category*				
Tla	0	1(1.2%)	1(2.6%)	(T1 *vs*.T2<)
Tib	3 (42.696)	18(222%)	1 (2.6%)	0.255 (I *vs*. II)
T2	2 (28.6%)	10 (123%)	5(123%)	0.013 (II *vs*. III)
T3	2 (28.6%)	22(27.2%)	10 (25.6%)	0.003 (I *vs*. III)
T4a	0	28(34.6%)	20 (513%)	
T4b	0	2 (2.4%)	2 (5.1%)	
N Category*				
N0	2 (28.6%)	33 (40.7%)	11 (28.2%)	0328 (I *vs*. II)
N+	5 (71.4%)	48 (593%)	28 (713%)	0.182 (II *vs*. III) 0.984 (I *vs*. III)
Mediastinal nodes				
Negative	5 (71A%)	74 (91.4%)	38 (97.4%)	0.095 (I *vs*. II)
Positive	2 (28.6%)	7 (8.6%)	1 (2.6%)	0.211 (II *vs*. III) 0.010 (I *vs*. III)
Histopathotogical grade				
GI/2	4 (57.4%)	56 (69.1%)	23 (59.0%)	0313 (I *vs*. II)
G3/4	3 (42.6%)	25 (30.9%)	16 (41.0%)	0.271 (II *vs*. III) 0.928 (I *vs*. III)
Lymphatic invasion				
No	3 (42.6%)	34(424)%)	16 (41.0%)	0.964 (I *vs*. II)
Yes	4 (57.4%)	47 (58.0%)	23 (59.0%)	0321 (II *vs*. III) 0.928 (I *vs*. III)
Vascular invasion				
No	2 (28.6%)	18(22.2%)	6 (15.4%)	0.148 (I *vs*. II)
Yes	5 (71.4%)	63(773%)	33 (84.6%)	0380 (II *vs*. III) 0397 (I *vs*. III)
Approach				
Transthoracic	5 (71.4%)	26 (32.1%)	8 (203%)	
(righ:left)	(1:4)	(3:23)	(0:8)	
Transhiatal	2 (28.6%)	55 (67.9%)	31 (793%)	
Subtotal esophagectomy	2 (28.6%)	4 (43%)	0	
Total gastrectomy with distal esophagectomy	1 (143%)	57 (70.4%)	35 (89.7%)	
Proximal gastrectomy with distal esophagectomy	4 (57.4%)	20 (24.7%)	4 (103%)	

Univariate analysis showed that the following eight factors were indicated as being associated with RFS: tumor depth ($p<0.001$), lymph node metastasis ($p<0.001$), mediastinal lymph node metastasis ($p<0.001$), para-aortic lymph nodes ($p=0.017$), esophageal invasion of >20 mm ($p=0.001$), venous invasion ($p=0.003$), lymphovascular invasion ($p<0.001$), and histopathological grade of 3/4 ($p=0.065$). In multivariate analysis, only mediastinal lymph node metastasis ($p=0.005$) (95% confidence interval=1.38–6.31) was a significant and independent prognostic indicator of RFS.

Discussion

This study demonstrated the recurrence patterns of 127 AEGs during a period in which neither neoadjuvant nor adjuvant chemotherapy was used in a single cancer center in Japan. We selected the patient population for this study to avoid bias from the effects of chemotherapy and accurately evaluate recurrence features. The recurrence rates of type I, II, and III tumors were 57.1%, 44.4%, and 40.1%, respectively. The median time-to-recurrence after surgery