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ORIGINAL ARTICLE

Incidence of and risk factors for venous thromboembolism during surgical treatment for esophageal cancer: a single-institution study

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Abstract
Purpose During the treatment of esophageal cancer with curative intent, patients sometimes experience deep vein thrombosis, pulmonary embolism or a central venous catheter-associated thrombus. In this study, we retrospectively reviewed our new-onset esophageal cancer patients and determined the incidence of venous thromboembolism (VTE), the location of the thrombus and the risk factors for VTE.
Methods One hundred and fifty-three patients undergoing treatment with curative intent were reviewed as candidates. The existence of VTE was assessed from the neck to the pelvis with computed tomography at the initial visit, after neo-adjuvant chemotherapy and postoperatively.
Results Twenty-one VTE events (13.7 %) were observed, 16 of which (76.2 %) were suggested to be associated with central venous catheterization. When both the pre-therapeutic plasma fibrinogen and C-reactive protein levels were high (≥350 mg/dL and ≥0.2 μg/mL, respectively), the risk of preoperative VTE and overall VTE were significantly higher than normal ($p = 0.040$, and $p = 0.030$, respectively). Adenocarcinoma histology and neck lymph node dissection were the independent risk factors that significantly increased the overall risk of VTE ($p = 0.015$, and $p = 0.017$, respectively).
Conclusions This study revealed that the pre-therapeutic plasma fibrinogen level, C-reactive protein level, adenocarcinoma histology and neck lymph node dissection are the risk factors for venous thromboembolism in patients with esophageal cancer undergoing treatment with curative intent.

Keywords Esophageal cancer · Esophagectomy · Venous thromboembolism

Introduction

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide because of its poor prognosis [1]. Although the efficacy of chemoradiotherapy for esophageal cancer has been reported [2–4], radical surgery with extended lymphadenectomy has been the main treatment method used for resectable esophageal cancer [5–7]. Although the surgical techniques used for esophageal cancer have been improving, the postoperative mortality and complication rates are still higher than those associated with other gastroenterological surgeries. We previously reported that the mortality rate after thoracoscopic esophagectomy in 78 patients was 2.6 %, and that the major postoperative complications were pneumonia and anastomotic leakage [8].

On the other hand, during the treatment for esophageal cancer with curative intent, our patients sometimes experience deep vein thrombosis (DVT), pulmonary embolism (PE) or central venous catheter-associated thrombus either perioperatively or during neo-adjuvant chemotherapy. Venous thromboembolism (VTE) comprises both DVT and PE. Virchow [9] stated that the three major inciting factors of thrombosis are stagnating blood, intravenous endothelial damage and increased blood clotting. Prolonged immobility, the use of anesthesia, a central intravenous catheter, the presence of a malignant tumor, highly invasive surgery, dehydration and infection are all associated with

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esophagectomy for esophageal cancer; therefore, patients undergoing this surgery appear to be at high risk for VTE. However, the perioperative incidence of VTE has not been clearly shown. We hypothesized that the incidence of VTE is relatively high because of the invasiveness of esophagectomy.

In our institution, all patients undergoing esophagectomy are examined by computed tomography (CT) at the initial visit, after neo-adjuvant chemotherapy and again postoperatively. This allowed us to accurately investigate the incidence of VTE.

In this study, we defined VTE as thrombotic disease including DVT, PE and catheter-associated thrombus. We retrospectively reviewed all new-onset esophageal cancer patients and determined the incidence of VTE, including the location of the thrombus and risk factors.

Methods

One hundred and fifty-three patients with esophageal cancer undergoing treatment with curative intent between March 2008 and December 2012 at Keio University Hospital were reviewed as candidates. Patients were included if they had undergone surgical treatment with or without neo-adjuvant chemotherapy. Patients who underwent salvage surgery after definitive chemoradiotherapy were excluded. Patients who underwent neo-adjuvant chemoradiotherapy were also excluded because there were very few such patients. None of the patients had undergone neo-adjuvant radiotherapy.

All patients underwent a contrast-enhanced CT scan from their neck to their pelvis during staging; patients receiving neo-adjuvant chemotherapy were scanned again after systemic therapy. Furthermore, all patients had CT scans to detect postoperative complications such as pneumonia or anastomotic leakage on postoperative day (POD) 5 or 6. When PE was found in a patient, the patient's legs were checked by ultrasound scanning to detect DVT.

During neo-adjuvant chemotherapy, agents were generally given through an internal jugular vein catheter. No thromboprophylaxis was given during chemotherapy. A peripherally inserted central catheter was inserted just before the operation and was used as the main route of perioperative administration. Intermittent pneumatic compression (IPC) was applied to both lower legs at the start of anesthesia for all patients and was left in place until patients became ambulatory. After surgery, the patients were kept in the intensive care unit on a ventilator and extubated on POD1. They were moved to a general ward and started walking on POD2 at the earliest. There was not routine use of an anticoagulant as a precaution in the perioperative period.

Heparin was used as a basic therapy in patients diagnosed with VTE. When they were able to take oral medications, they took warfarin instead of heparin. The patients stopped taking warfarin when the attending doctor thought it was no longer necessary, usually after about 6 months.

Preoperative and postoperative VTEs were counted, and the locations of all thrombi were reviewed. We compared the patients who developed VTE to those who did not and analyzed perioperative factors that might be associated with the occurrence of VTE. The patient characteristics (age, sex and body mass index), tumor characteristics, blood test results, neo-adjuvant chemotherapy, surgical procedure, length of the operation, blood loss and day of first ambulation were compared. The values of fibrinogen, fibrin degradation products, C-reactive protein (CRP) and perioperative D-dimer were reviewed. The information about the surgical procedure consisted of the surgical approach, neck dissection and reconstruction route. Endpoint risks were calculated for preoperative VTE, postoperative VTE and overall VTE.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. Proportions were compared using the χ^2 test and continuous variables were compared using the Mann–Whitney *U* test. Analyses were performed using the SPSS Statistics, version 19 software program. Values of $p < 0.05$ were considered to be statistically significant. A multiple regression model was used for the multivariate analysis of variables predicting the development of VTE. Endpoints with values of $p < 0.15$ in the univariate analysis were also calculated through the multivariable analysis. Laboratory data were excluded from the multivariable analysis because some values were missing.

Results

Central venous catheter-associated thrombus

Figure 1 is a CT scan image of a representative VTE taken on POD6 of a 70-year-old male who underwent total esophagectomy with a three-field lymph node dissection. A thrombus in the right internal jugular vein (arrow) is shown. This thrombus was formed from the bifurcation of the internal jugular vein and the subclavian vein and extended distally. The central venous catheter inserted from the peripheral vein to the right subclavian vein seemed to have caused the stagnation of his blood.

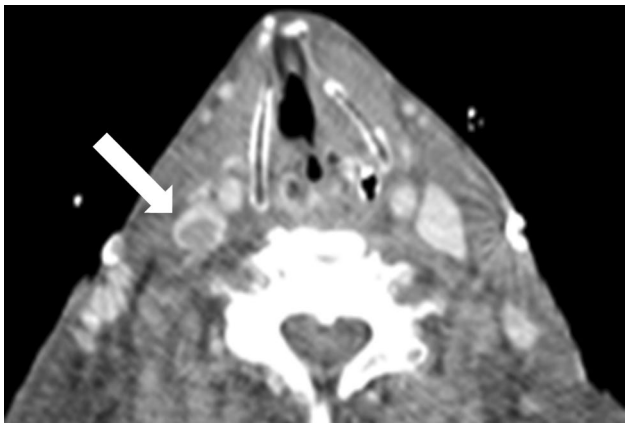

Fig. 1 Central venous catheter-associated thrombus. A computed tomography scan taken on postoperative day 6 of a 70-year-old male who underwent total esophagectomy with a three-field lymph node dissection. The arrow points to a central venous catheter-associated thrombus in the right internal jugular vein

Table 1 Patient characteristics ($N = 153$)

	Number (%)
Age (mean, range)	63.8 (36–81)
Sex	
Male	138 (90.2)
Female	15 (9.8)
Body mass index (mean ± standard deviation)	22.2 ± 2.9
Tumor site	
Cervical	1 (0.7)
Thoracic (upper third)	16 (10.5)
Thoracic (middle third)	73 (47.7)
Thoracic (lower third)	47 (30.7)
Abdominal	16 (10.5)
Histology	
Squamous cell carcinoma	136 (88.9)
Adenocarcinoma	15 (9.8)
Basaloid carcinoma	2 (1.3)
cT category	
1	62 (40.5)
2	45 (29.4)
3	45 (29.4)
4	1 (0.7)
cN category	
0	103 (67.3)
1	37 (24.2)
2	12 (7.8)
3	1 (0.7)
cStage	
I	86 (56.2)
II	33 (21.6)
III	34 (22.2)
IV	0 (0)
Neo-adjuvant chemotherapy	
No	58 (37.9)
Cisplatin + 5-FU	91 (59.5)
Docetaxel + Cisplatin + 5-FU	4 (2.6)
Surgical approach	
Right thoracotomy	61 (39.9)
VATS (right thoracoscopic)	90 (58.8)
Transhiatal	2 (1.3)
Neck dissection	
Yes	81 (52.9)
No	72 (47.1)
Reconstruction route	
Posterior mediastinum	134 (87.6)
Anterior chest wall	19 (12.4)

Patient characteristics

The patient characteristics are shown in Table 1. The majority of patients were male (90.2 %) with an average age of 63.8 years old, and the most common diagnosis was squamous cell carcinoma of the midthoracic esophagus. The clinical staging was based on the Union for International Cancer Control TMN Classification of Malignant Tumours (7th edition) [10].

Of 153 patients, 95 (62.1 %) received neo-adjuvant chemotherapy and 58 (37.9 %) did not. Ninety-one patients received 5-fluorouracil and cisplatin (FP), and four received docetaxel, cisplatin and 5-fluorouracil (DCF).

Right thoracotomy was the surgical approach used for 61 patients (39.9 %), and video-assisted thoracoscopic surgery (right thoracoscopic) was used for 90 patients (58.8 %). Eighty-one patients (52.9 %) underwent neck dissection. The posterior mediastinum (87.6 %) was more often selected as the reconstruction route than was the anterior chest wall route (12.4 %).

Incidence of VTE

The incidence and locations of the VTE are summarized in Table 2. Twenty-one VTEs (13.7 %) were observed in 153 patients, six of which occurred preoperatively and were considered to be associated with neo-adjuvant chemotherapy, 14 were detected postoperatively and one occurred just after inserting a peripherally inserted central catheter preoperatively. No patient experienced metachronous VTE events. Nineteen VTEs were asymptomatic events and two were detected after arm swelling which was caused by a catheter-associated thrombus. Seven patients (33.3 %) had asymptomatic PE and 14 had a thrombus that occurred in a brachiocephalic vein, internal jugular vein, subclavian vein or cephalic vein (33.3, 23.8, 4.8 and 4.8 %, respectively). Of

Table 2 Incidence and locations of VTE

Location of thrombosis	Non-VTE	Preoperative	Postoperative	Overall
Asymptomatic PE		1	6	7
Brachiocephalic vein		3	4	7
Internal jugular vein		2	3	5
Subclavian vein		0	1	1
Cephalic vein		1	0	1
CV catheter associated (yes/no)		4/3	12/2	16/5
Total (%)	132 (86.3)	7 (4.6)	14 (9.2)	21 (13.7)

all 21 VTEs, 16 (76.2 %) were suggested to be associated with a central venous catheter. Venous ultrasound scanning was performed on the seven patients with PE, and two of them had DVT. Our patients did not experience any symptomatic PE; therefore, we did not provide immediate thrombolysis therapy. Heparin was given to the 14 VTE patients, and we did not provide any therapy to the other seven patients because the thrombi were small and were not in the patients' lung arteries. Regardless of whether patients were given heparin, the VTEs decreased soon after detection in almost all cases. Four (57.1 %) of the preoperative VTEs disappeared before esophagectomy, and the other three (42.9 %) disappeared within 9 months. Eleven (78.6 %) of the postoperative VTEs disappeared within 5 months. No death from a VTE was observed during the treatment phase.

Association of VTE with patient characteristics

We assessed the correlation between VTE and the clinicopathological characteristics (Table 3). Adenocarcinoma tended to be associated with more overall VTE events than other histological types ($p = 0.129$). On the other hand, there was a tendency for overall VTE to occur when the clinical tumor depth was greater than T2 ($p = 0.074$). With regard to the preoperative VTEs, this association showed a significant difference ($p = 0.024$). The patient age, sex, tumor location and lymph node grade did not affect the incidence of VTE. The administration of neo-adjuvant chemotherapy and the body mass index also did not significantly affect the incidence of VTE.

Association of VTE with laboratory data

In the pre-therapeutic laboratory data examined at the initial visit, high plasma fibrinogen and CRP levels were associated with an increased risk of preoperative VTE ($p = 0.078$ and $p = 0.040$, respectively; Table 3). A preoperative high fibrinogen level just before surgery had an even stronger correlation with preoperative VTE ($p = 0.004$). When both the pre-therapeutic plasma fibrinogen and CRP levels were high (≥350 mg/dL, and ≥0.2 μg/mL, respectively), the calculated risk of preoperative VTE and overall VTE were significantly higher than in other cases ($p = 0.040$, and $p = 0.030$, respectively; Table 4). The perioperative D-dimer level, which is often used to predict the occurrence of VTE, was relatively higher in the VTE group than in the non-VTE group, but this difference did not reach statistical significance.

Association of VTE with surgical factors

Patients who underwent neck dissection had more postoperative VTEs than those who did not ($p = 0.16$; Table 3). The surgical approach was not related to the incidence of postoperative VTE. Similarly, the length of the operation, blood loss and day of first ambulation were not associated with the incidence of VTE.

Multivariable analysis

A logistic regression analysis was performed to determine which factors were predictive of overall VTE (Table 5). When the tumor histology, tumor depth, neck dissection and reconstruction route were included in this model, adenocarcinoma and neck dissection were revealed to be the independent factors that predicted the risk of overall VTE ($p = 0.015$ and $p = 0.017$, respectively).

Discussion

VTEs are found relatively frequent in patients with esophageal cancer, although there is wide variation in the quoted incidence. A study of more than one million Medicare patients reported that the rate of VTE was 0.43 % in patient with esophageal cancer [11]. Tetzlaff et al. [12] reported that the incidence of VTE in 198 patients with localized gastroesophageal cancer was 4.0 % at baseline and 6.1 % during chemoradiotherapy. Rollins et al. [13] found a 13 % incidence of VTE in patients undergoing therapy with curative intent for gastroesophageal cancer, and they noted that there was a statistically significant association between neo-adjuvant chemotherapy and VTE.

The frequency of postoperative PE has been reported to be lower in Japan than in the West. However, Tsutsumi et al. [14] reported that the incidence of PE was 2.5 % in patients with esophageal cancer, which is higher than with other types of general surgery in the West. This indicates that postoperative PE is not a rare complication in Japan.

This study revealed an incidence of 13.7 % for VTE in patients undergoing multimodal treatment with curative

Table 3 The relationship between clinical parameters and the incidence of VTE

	Non-VTE ($N = 132$)	Preoperative VTE ($N = 7$)	p value	Postoperative VTE ($N = 14$)	p value	Overall VTE ($N = 21$)	p value
Age (years)	63.8 ± 8.0	61.1 ± 10.2	0.57	65.1 ± 7.9	0.38	63.8 ± 8.7	0.70
Sex (male/female)	119/13	6/1	1.00	13/1	1.00	19/2	1.00
Body mass index (kg/m^2)	22.6 ± 3.4	23.8 ± 3.9	0.31	21.9 ± 3.0	0.94	22.2 ± 2.9	0.60
Location (Ce Ut Mt/Lt Ae)	77/55	2/5	0.24	11/3	0.16	13/8	0.82
Adeno/SCC/others	11/119/2	1/6/0	1.00	3/11/0	0.135	4/17/0	0.129
Tumor depth (cT1–2/cT3–4)	96/36	2/5	**0.024**	9/5	0.54	11/10	0.074
Lymph node grade (cN0/cN1–2)	90/42	3/4	0.22	10/4	1.00	13/8	0.62
Neo-adjuvant chemotherapy (yes/no)	82/50	6/1	0.26	7/7	0.40	13/8	1.00
Pre-therapeutic data							
Fibrinogen (mg/dL)	323 ± 86	372 ± 64	0.078	346 ± 125	0.98	354 ± 107	0.32
FDP (μg/mL)	3.35 ± 1.11	3.63 ± 0.99	0.41	3.61 ± 0.67	0.149	3.62 ± 0.79	0.114
CRP (μg/mL)	0.22 ± 0.43	0.74 ± 1.08	**0.040**	0.19 ± 0.29	0.46	0.41 ± 0.75	0.48
Preoperative data							
Fibrinogen (mg/dL)	313 ± 78	398 ± 61	**0.004**	343 ± 95	0.30	362 ± 87	**0.015**
FDP (μg/mL)	3.89 ± 1.73	3.64 ± 1.08	0.91	3.76 ± 1.22	0.94	3.72 ± 1.14	0.99
CRP (μg/mL)	0.14 ± 0.23	0.27 ± 0.23	**0.032**	0.13 ± 0.20	0.64	0.18 ± 0.21	0.42
Perioperative data							
D-dimer (μg/mL)	7.5 ± 4.7	6.0 ± 3.5	–	19.5 ± 26.0	0.24	16.1 ± 23.1	0.45
Surgical approach							
Right thoracotomy	53	2	–	6	1.00	8	1.00
Video assisted	77	5		8		13	
Transhiatal	2	0		0		0	
Neck dissection (yes/no)	66/66	5/2	–	10/4	0.16	15/6	0.098
Reconstruction route							
Posterior mediastinum	118	5	–	11	0.37	16	0.144
Anterior chest wall	14	2		3		5	
Length of operation (min)	529 ± 99	572 ± 106	–	504 ± 102	0.73	534 ± 106	0.54
Blood loss (mL)	296 ± 541	267 ± 163	–	274 ± 271	0.88	271 ± 223	0.55
Day of first ambulation (POD)	3.03 ± 3.20	2.29 ± 0.49	–	3.10 ± 2.51	0.48	2.76 ± 1.95	0.21

Bold values indicate p values less than 0.05

Table 4 The relationship between pre-therapeutic data and the incidence of VTE ($N = 96$)

	Non-VTE ($N = 81$)	Preoperative VTE ($N = 6$)	p value	Postoperative VTE ($N = 9$)	p value	Overall VTE ($N = 15$)	p value
Fibrinogen ≥ 350 mg/dL ∧ CRP ≥ 0.2 μg/mL	9	4 (30.7 %)	**0.040**	3 (25.0 %)	0.097	7 (43.8 %)	**0.030**
Others	72	2 (2.7 %)		6 (7.7 %)		8 (10.0 %)	

Bold values indicate p value less than 0.05

intent for esophageal cancer. Because we checked the CT scans of all the patients routinely before neo-adjuvant chemotherapy, preoperatively and again postoperatively, this is likely to represent a very good estimate of the incidence of VTE in Japan. This is a major advantage of the present study.

In our study, a high pre-therapeutic plasma fibrinogen level was a predictor of preoperative VTE ($p = 0.078$). In

Table 5 The results of the multivariable analysis

	Non-VTE ($N = 132$)	Overall VTE ($N = 21$)	Univariate p value	Multivariate p value	HR (95 % CI)
Adeno/SCC or others	11/121	4/17	0.129	**0.015**	7.87 (1.50–41.26)
Tumor depth (cT1–2/cT3–4)	96/36	11/10	0.074	0.087	2.45 (0.88–6.80)
Neck dissection (yes/no)	66/66	15/6	0.098	**0.017**	4.93 (1.33–18.21)
Reconstruction route					
Posterior mediastinum	118	16	0.144	0.210	2.24 (0.63–7.94)
Anterior chest wall	14	5			

Bold values indicate p values less than 0.05

addition, a larger tumor depth increased the risk of preoperative VTE ($p = 0.024$). The association between malignancy and VTE was first recognized by Trousseau in 1867 [15], and the link between thrombosis and various carcinomas has been well established. VTE is a common cause of death in patients with malignancy (3.5 %) [16]. Patients with cancer who present with VTE are significantly more likely to have distant metastases than those without [17]. VTE has been reported as an independent prognostic factor for survival in patients with localized gastroesophageal cancer [12]. In a previous study, we reported that higher levels of fibrinogen correlated with tumor progression, metastasis and poor responsiveness to chemoradiotherapy in esophageal squamous cell carcinoma patients [18]. We also previously reported that patients with increased plasma fibrinogen levels during neo-adjuvant treatment for esophageal cancer showed significantly shorter postoperative disease-free survival [19]. The results of the present study suggest that tumor malignancy causes a hypercoagulable state in esophageal cancer patients, which may result in the occurrence of VTE.

Cancer patients frequently present with an elevated CRP level, which is directly associated with the tumor burden. Patients with inoperable tumors had significantly higher CRP levels than patients who had undergone curative surgery (1.21 ± 2.2 vs. 0.40 ± 0.4 mg/dL; $p < 0.0001$) [20]. Some studies have revealed that an elevated CRP level is associated with an increased risk of VTE. A prospective population-based study suggested that the hazard ratio of VTE was 1.76 for a CRP level above versus below the 90th percentile [21]. In the present study, a high pre-therapeutic plasma CRP level was another predictor of preoperative VTE ($p = 0.040$). Tumor malignancy and an elevated CRP level seem to increase the risk of VTE in esophageal cancer patients in the neo-adjuvant chemotherapy phase.

When both the pre-therapeutic plasma fibrinogen and CRP levels were high, the risk of preoperative and overall VTE was significantly higher than that of other patients (Table 4). The combination of a high fibrinogen level and a high CRP level can be used to predict the risk of VTE during the treatment phase in patients with esophageal cancer. Such high-risk patients should be assessed with CT scans again preoperatively to detect any thrombi, and should be carefully observed so that symptoms are not overlooked.

Starling et al. [22] showed a significant association between the use of central venous access devices and VTEs. Mino et al. noted that in 1857 patients who underwent general surgery, 39 (2.1 %) had VTE and 51.3 % of these were catheter-associated thrombi [23]. In our study, most VTE events (76.2 %) were associated with a central venous catheter. Because we placed a catheter for most patients who underwent neo-adjuvant chemotherapy or esophagectomy, the incidence of catheter-associated VTE seemed to be relatively high. The risk of VTE can be reduced by minimalizing the duration of catheterization or using a peripheral intravenous route for neo-adjuvant chemotherapy.

We found that adenocarcinoma histology was an independent risk factor for overall VTE ($p = 0.015$). Autopsy and retrospective studies have indicated that various adenocarcinomas are more strongly associated with VTE than are other histological types [24, 25]. Blom et al. [26] reported that patients with adenocarcinoma of the lung had a threefold higher risk of VTE than did patients with squamous cell carcinoma of the lung. Mucin-producing adenocarcinomas are believed to increase the risk of VTE [26]. Our findings support the concept that adenocarcinomas are a risk factor for VTE.

In our study, the patients who underwent neck dissection had more VTE events postoperatively than those who did not ($p = 0.16$). A multivariate analysis showed that neck dissection was another independent risk factor for overall VTE occurrence ($p = 0.017$). Tsutsumi's data [14] showed that the incidence of postoperative PE was higher after an esophagectomy with a three-field lymphadenectomy than with a two-field lymphadenectomy (3.2 vs. 2.2 %). This previous study corresponded with our results. The dissection area of the neck is very close to major blood vessels (e.g., internal jugular vein, subclavian vein) when three-field lymphadenectomy is performed. Invasive interventions around these vessels and pressure from drains might cause VTE events after surgery.

A limitation of this study is that we could not detect asymptomatic DVT in the patients' legs, because the

routine CT scan was from the neck to the pelvis only. Moreover, many laboratory data were defective because we did not routinely measure all of the pre-therapeutic and preoperative data evaluated in this study. As a result, we could not evaluate the importance of the fibrinogen and CRP levels in the multivariate analysis.

The 2009 American College of Chest Physicians guidelines state that low-molecular-weight heparin, low-dose unfractionated heparin or fondaparinux is recommended as VTE prophylaxis for "high-risk" surgery patients, including those undergoing esophageal cancer resections. Hata et al. [27] showed that fondaparinux was safe and effective for venous thromboembolism prophylaxis in Japanese patients undergoing colorectal cancer surgery. In our institution, the main prophylaxis for DVT was IPC, and prophylactic anticoagulation therapy was not given routinely at the time of this study. However, the IPC was likely effective for thromboprophylaxis, because there were no cases of symptomatic PE in this study.

In conclusion, the present study indicates that the incidence of VTE was 13.7 % in Japanese esophageal cancer patients treated with surgery with curative intent. Most VTE events were associated with a central venous catheter. High pre-therapeutic plasma fibrinogen and CRP levels were risk factors for preoperative and overall VTE. Adenocarcinoma and neck dissection were the independent factors that significantly increased the risk of overall VTE. Every effort should be made to minimize the risk of VTE, and further research into the role of thromboprophylaxis is warranted.

Conflict of interest Fumihiko Kato and co-authors have no conflicts of interest to declare.

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