Incidence and Risk Factors Related to Symptomatic Venous Thromboembolic Events After Esophagectomy for Cancer

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Background. **Major oncologic surgery is associated with a high incidence of venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE). However, the incidence and risk factors for symptomatic VTE during curative treatment for patients with esophageal cancer are poorly documented.**

Methods. **Data were collected from 30 European centers from 2000 to 2010. The incidence of in-hospital VTE was assessed in 2,944 patients with esophageal cancer having surgery with curative intent, and 50 clinically relevant parameters were assessed as potential risk factors for VTE. Patients received low molecular weight heparin prophylaxis during hospital stay and for 4 weeks after surgery.**

Results. **Eighty-four patients (2.9%) developed a symptomatic VTE; all of them had a DVT and 44 were also diagnosed with a PE. In the VTE group there were 19 postoperative deaths recorded, 5 of which (26.3%) were directly caused by PE at postoperative days 7, 10, 21, 45, and 48 despite VTE prophylaxis. In-hospital postoperative mortality was significantly higher in VTE patients (23% versus 7%, $p < 0.001$) and mean hospital stay was also longer in this group (33 ± 24 versus 25 ± 21 days, $p < 0.001$). Multivariable analysis showed that high American Society of Anesthesiologists (ASA) class ($p = 0.008$), pneumopathy ($p = 0.002$), or an acute respiratory distress syndrome (ARDS) ($p = 0.015$) were significantly associated with VTE.**

Conclusions. **Patients with ASA class III or IV and those who present a postoperative pneumopathy or ARDS seem to be at higher risk for VTE. Thus, current VTE screening and thromboprophylaxis for these patients might be inadequate and needs further investigation.**

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Esophageal cancer surgery is associated with high postoperative morbidity reaching 60%, whereby pulmonary complications are the most common followed by infections and anastomotic leakage [1, 2]. Esophageal cancer has also been associated with a high risk of venous thromboembolic events (VTE) [3]. According to recent studies, oncological esophagectomy carries an overall risk of 5.1% to 11.3% for postoperative VTE and an estimated prevalence of pulmonary embolism (PE) of 2.5% [4–7]. Although these are among the highest rates compared to other major cancer operations [8, 9], few data exist on specific risk factors for VTE after esophagectomy. Martin and colleagues [7] recently identified male gender, white race, age, prolonged ventilation, and postoperative complications as risk factors for VTE, however these criteria might lack specificity in the clinical setting.

The aim of the present study was to assess the incidence of in-hospital VTE after esophagectomy for cancer in a large European patient group, and to evaluate several parameters as potential risk factors associated to postoperative VTE.

Patients and Methods

Patient Eligibility Criteria

Data from 2,944 consecutive adult patients undergoing surgical resection for esophageal cancer (including

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Siewert type I and II junctional tumors) with curative intent in 30 European centers between 2000 and 2010 were retrospectively collected through a dedicated website [10]. Data included demographic parameters, details regarding perioperative and surgical treatments, postoperative outcomes, and histological analyses. The database was registered on the clinicaltrials.gov website (NCT01927016), and was accepted by the French North-West Ethics Committee on July 15, 2013.

Definition, Diagnosis, and Treatment of VTE

VTE was defined as any thrombosis of the deep veins of the trunk or the extremities, in particular PE, deep venous thrombosis (DVT) of the lower extremities or splanchnic venous system and central venous line–related events. Given the potential heterogeneity of postdischarge patient follow-up, we focused on in-hospital VTE. All events were diagnosed on the basis of symptom-directed imaging, and thus only symptomatic VTE were identified in this study. PE was diagnosed by means of intravenous (IV) contrast thoracic computed tomography (CT) or ventilation or perfusion scintigraphy and DVT by duplex compression ultrasound of the extremities. If a DVT or PE was detected, immediate anticoagulant treatment was initiated with therapeutic doses of unfractionated heparin according to institutional standards.

Pharmacological thromboprophylaxis started the day before surgery by subcutaneous administration of low molecular weight heparin and all patients received prophylaxis during their hospital stay, to be continued after discharge from 7 to 28 days according to the best practice guidelines [9, 11]. When patients needed anticoagulation for atrial fibrillation or other reasons anterior to the intervention, unfractionated heparin was administered by IV continuous infusion until discharge. No oral anticoagulants were used during the perioperative period. The use of elastic compression stockings or was left at the surgeon's discretion.

Assessment of VTE Risk Factors

The main variables assessed for correlation with postoperative VTE are shown in Table 1. Overall, 50 pre-, intra-, and postoperative parameters were tested (Supplemental Table 1). Preoperative malnutrition was assessed by means of a preoperative weight loss ≥10% of body weight [12]. Tumor stage was defined according to the seventh edition of the TNM/Union Internationale Contre le Cancer classification [13].

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL). Data are presented as prevalence (percentage) and median (range). Continuous variables are expressed as median (range) and categorical variables as a percentage. A Mann-Whitney *U* test was used for intergroup comparisons of continuous variables, whereas a chi-square test or Fisher exact test was used to compare categorical data.

A stepwise binary logistic regression model was built to identify predictive factors of VTE. A p value ≤0.10 on univariable analysis was required for entry into the multivariable model. Only parameters available before the VTE and offering nonredundancy with each other were entered into the multivariable analysis. Additionally, variables statistically nonsignificant but having strong clinical relevance were also introduced in the model. All statistical tests were 1-sided, with the threshold for significance set at $p < 0.05$.

Table 1. Demographic and Tumor-Related Parameters in VTE- and VTE+ Patients

Variables	VTE- (n = 2,860)	VTE+ (n = 84)	*p* Value
Age ≥60 years (%)	1,469 (51.4)	49 (58.3)	0.208
Median age, years (range)	61 (20–93)	62.5 (41–93)	0.132
ASA class III/IV (%)	728 (25.5)	26 (31.0)	0.255
Malnutrition[a] (%)	587 (20.5)	14 (16.7)	0.160
Simultaneous cancer (%)	28 (1.0)	2 (2.4)	0.210
Previous history of cancer (%)	381 (13.3)	13 (15.5)	0.518
Tumor histology (%)			
Adenocarcinoma	1448 (51)	46 (55)	0.744
Squamous cell	1327 (46)	36 (43)	
Other	85 (3)	2 (2)	
Preoperative UICC stage (%)			
0	286 (10)	6 (7)	0.872
I/II	1,478 (52)	42 (50)	
III/IV	1,096 (38)	36 (43)	
Neoadjuvant chemotherapy (%)	1,324 (46.3)	34 (40.5)	0.292
Neoadjuvant radiotherapy (%)	822 (28.7)	25 (29.8)	0.808
Total radiotherapy dose, Gy (range)	45 (12–75)	45 (36–50)	0.121

[a] Malnutrition was defined as significant (>10% of baseline weight) preoperative weight loss [12].

ARDS = adult respiratory distress syndrome; ASA = American Society of Anesthesiologists; UICC = Union Internationale Contre le Cancer; VTE = venous thromboembolic event.

Results

Incidence of VTE, PE, and DVT After Oncological Esophagectomy

In this series VTE was diagnosed in 84 patients (2.9%). PE was diagnosed in 1.5% (44 patients), whereas a DVT was found in all 84 patients presenting with VTE. Given the low incidence of isolated PE, univariable analysis was only conducted for overall VTE and not for PE separately.

Patient and Tumor Characteristics

Our study population consisted of 2944 patients, with a median age of 61 (20 to 93) years and a high proportion of male gender (82.4%) [10]. In univariable analysis, age, gender, and American Society of Anesthesiologists (ASA) class were comparable between VTE+ and VTE- patients as is seen in Table 1. Both groups had a similar number of synchronous cancer (2.4% for VTE+ and 1% for VTE- patients) or personal history of cancer (15.5% for VTE+ and 13.3% for VTE- patients), and tumor histology and

preoperative TNM stage were also comparable between the groups. Malnutrition was identified as a major issue in this series, concerning 20.5% and 16.7% of the VTE+ and VTE-, respectively. In the present series, 182 patients with atrial fibrillation were included, needing the previously mentioned IV full-dose anticoagulation strategy, 3 of whom belong to the VTE+ group. Neoadjuvant treatment was administered in 46% and 41% in the VTE+ and VTE- patients, respectively ($p = 0.292$). All patients had preoperative chemotherapy and the majority of them (84% in the VTE+ and 82% in the VTE- group) had a cisplatin-based regimen, whereas 28.9% of the VTE- and 29.7% of the VTE+ group had also radiotherapy.

Operative Characteristics and Postoperative Parameters

Operative characteristics and technical surgical aspects were comparable between VTE+ and VTE- patients (Table 2). In the majority of cases, the 1-field Lewis technique was used, with upper abdominal and mid- or lower mediastinal lymph node dissection. When the tumor was located in the middle third of the esophagus, 3-field resection with an abdominal, thoracic, and left cervical approach was preferred. Of note, cervical lymph node dissection is not routinely performed in our centers in this case. The transhiatal approach was reserved to some few patients with fairly small tumors who were evaluated by the anesthesiological team as too frail to tolerate thoracotomy. Although the VTE + patients in the 3-field and transhiatal groups were too few to allow subgroup analyses, our data did not suggest any statistical difference of VTE rate with respect to the operative technique used. Laparoscopy was used in 14.6% and 16.7% of VTE- and VTE+ patients, respectively, and in 1.2% of patients thoracoscopy was also performed. Operative time, blood loss and intraoperative bleeding complications were similar in both groups.

Overall complication rate in this series reached 58% [10]. VTE+ patients had significantly more pulmonary complications such as pneumonia, atelectasis, and adult respiratory distress syndrome (ARDS) ($p < 0.001$ for all of these variables). In contrast, cardiovascular complications (excluding PE and DVT) were not significantly different ($p = 0.210$). In terms of surgical morbidity, VTE+ patients had a slightly higher complication rate (34.5% versus 27.1% for VTE-), but this did not reach statistical significance ($p = 0.130$). Patients who underwent a reoperation during the index hospital stay also revealed an increased risk for VTE ($p = 0.034$). Specific complication types such as anastomotic leakage, delayed gastric emptying, and postoperative hemorrhage were analyzed, without revealing any statistical difference (Supplemental Table 1). The oncological quality of surgery was comparable in terms of R0 resection (88.4% for VTE- versus 86.9% for VTE+ patients) and lymph node harvesting. Tumor TNM/Union Internationale Contre le Cancer stage did not correlate with increased VTE risk.

In-Hospital Mortality and Length of Stay

Overall mortality rate reached 7.3% with a significantly higher mortality rate difference between the VTE+ and VTE- groups (23% and 7%, respectively, $p < 0.001$). Of note, in the VTE group 5 of the 19 recorded deaths (26.3%)

Table 2. Operative Characteristics and Postoperative Outcomes for VTE- and VTE+ Patients

Characteristics	VTE- (n = 2860)	VTE+ (n = 84)	*p* Value
Median operative time (min)	320 (105–780)	300 (132–750)	0.562
Operative technique (%)			
Transthoracic (Lewis)	2,122 (72)	61 (2.1)	0.885
Three-field	332 (11.3)	12 (0.4)	
Transhiatal	404 (13.7)	11 (0.4)	
Laparoscopic approach (%)	417 (14.6)	14 (16.7)	0.594
Thoracoscopic approach (%)	35 (1.2)	1 (1.2)	0.920
Intraoperative hemorrhage (%)	168 (5.9)	8 (9.5)	0.164
Overall surgical complications (%)	774 (27.1)	29 (34.5)	0.130
Anastomotic leakage (%)	381 (13.3)	17 (20.2)	0.068
Postoperative hemorrhage (%)	10 (0)	0 (0)	1.000
Reintervention (%)	410 (14.3)	19 (22.6)	0.034
R0 resection (%)	2,527 (88.4)	73 (86.9)	0.609
Median number of harvested lymph nodes (range)	16 (1–78)	14 (1–37)	0.181
Cardiovascular morbidity excluding VTE (%)	247 (8.6)	4 (4.8)	0.210
Overall pulmonary complications, excluding VTE (%)	1,068 (37.3)	54 (64.3)	<0.001
Atelectasis	210 (7.3)	8 (9.5)	
Pneumonia	419 (14.7)	21 (25.0)	
Respiratory failure	226 (7.9)	10 (11.9)	<0.001
ARDS	213 (7.4)	15 (17.9)	
Median length of stay (range)	18 (1–261)	28 (2–158)	<0.001
Mortality (%)	192 (6.8)	19 (22.6)	<0.001

ARDS = adult respiratory distress syndrome; VTE = venous thromboembolic event.

were directly caused by PE at postoperative days 7, 10, 21, 45, and 48 despite VTE prophylaxis. Patients with VTE had a prolonged median hospital stay of 28 (2 to 158) days, compared to 18 (1 to 261) days if no VTE occurred.

Multivariable Analysis

Table 3 shows the results of our multivariable analysis. Among the 8 variables included, the only ones significantly related to the advent of postoperative VTE were ASA class III or IV ($p = 0.008$; odds ratio [OR]: 12.19, 95% confidence interval [CI]: 1.899 to 78.251), postoperative pneumonia ($p = 0.002$; OR: 38.76, 95% CI: 3.912 to 384.04), and ARDS ($p = 0.015$; OR: 31.247, 95% CI: 1.953 to 500.025).

Comment

In this multicenter study including 2944 patients who underwent oncological esophagectomy, the incidence of VTE was 2.9% with a specific rate of 1.5% for PE (44 patients). Factors significantly associated with VTE were ASA class III or IV and postoperative pulmonary complications, specifically pneumonia and ARDS.

Even though thromboprophylaxis is systematically used in patients undergoing major cancer surgery postoperative VTE and deaths linked to PE are still not negligible [9], with a reported incidence of VTE after gastric and esophageal resections between 5.1% and 13.6% [7, 14–16]. In the present study we recorded a lower incidence of VTE (2.9%), which may be at least partly explained by the fact that only clinically symptomatic events were recorded.

We thoroughly analyzed neoadjuvant treatment as a potential risk factor, as it has often been associated with an increased thromboembolic risk in several studies [14, 17]. However, in our series this did not seem to increase postoperative VTE. Only the total dose of preoperative radiotherapy had a significant impact in univariable analysis, but this was not confirmed in the multiple regression model. To our knowledge, no published data exist so far to support a correlation between VTE and preoperative radiotherapy.

Table 3. Multivariable Analysis of Potential VTE Risk Factors in Patients Undergoing Esophageal Cancer Surgery

Variables	Odds Ratio	95% CI	*p* Value
Pneumonia	38.761	3.912–384.046	0.002
ARDS	31.761	1.953–500.025	0.015
ASA III/IV	12.190	1.899–78.251	0.008
Malnutrition	2.465	0.870–6.983	0.090
Surgical morbidity	1.557	0.150–16.103	0.711
Total radiotherapy dose (Gy)	0.968	0.812–1.154	0.719
Age >60 years	0.944	0.861–1.035	0.222

ARDS = adult respiratory distress syndrome; ASA = American Society of Anesthesiologists; CI = confidence interval; VTE = venous thromboembolic event.

Patients with an ASA class III or IV presented a significantly higher risk of postoperative VTE. Older age, however, was not related to a more significant VTE risk, which come in contrast to recently published data have identified age as an independent risk factor for VTE after oncological surgery [5, 7, 18–20]. This attests to the weakness of age, in itself, to define patients at risk. Evaluation of comorbidities should be highlighted as the only important selection criteria [21].

In terms of nutritional status we assessed the impact of malnutrition expressed as a preoperative weight loss $\geq$10% of baseline weight [12], given the metabolic stress it adds to already catabolic patients after esophagectomy. Although it did not reach statistical significance in the multivariable analysis, we did record a slightly higher malnutrition rate in the control group (21% versus 17%). In fact, recent studies have correlated obesity (body mass index $\geq$35 kg/m^2) with thromboembolic complications [5, 18, 20, 22], but we were not able to take this parameter into account due to missing data.

Overall postoperative complications in this series reached 58%. Even after excluding PE, we found a significantly higher pulmonary complication rate for VTE+ patients compared to VTE- (64% versus 37%, $p < 0.0001$). In the multivariate model, pneumonia and ARDS were the most significant parameters correlated to postoperative VTE. These findings are indeed in consistency with recent data, where postoperative complications seem to be a major risk factor for venous thromboembolism [7, 20, 23]. This could be explained partially from the ongoing systemic insult after the initial operation, which takes place in case of a complicated postoperative course. On the other hand, postoperative complications can be responsible for a prolonged recovery time, intensive care surveillance and longer hospital stays, all tightly related to an increased thromboembolic risk [16, 19]. Martin and colleagues identified a correlation of major complications with predischarge and mostly with postdischarge thromboembolic events after esophagectomy (OR: 3.142) [7, 20, 23]. However, definition of major morbidity was somewhat arbitrary based on National Surgical Quality Improvement Program outcomes, including different types of postoperative complications among which we find also postoperative pneumonia and failure to wean. Despite the very interesting hypothesis this study raises upon correlation of complications and VTE, it remains difficult to find its clinical implications as no specific complication group is identified and, as a result, we could not safely identify a high-risk patient group warranting a modified thromboprophylaxis strategy. In our study we assessed postoperative complications by type, and thus could postulate that patients with postoperative pulmonary complications that have an ASA class III or IV could be good candidates for a modified in-hospital or extended anticoagulation regimen.

VTE has been associated with 30-day mortality up to 25% and long-term sequelae for $\geq$30% of patients [24]. In our study, VTE+ patients had a prolonged median length of hospital stay of 28 (2 to 258) days, compared to 18 (1 to 261) days if no VTE occurred.

Similarly, mortality rates were significantly increased for these patients at 23% versus 7% for VTE- cases; PE-specific mortality was estimated at 11%, being directly associated with 5 of 19 deaths in the VTE group. Indeed, we observe 3 cases of late mortality (>3 weeks) due to VTE. As our results suggest, a complicated postoperative course (by ARDS or pneumonia for example) may protract recovery time and confine patients to immobility, thus exposing them to an increased risk of VTE. The cause-effect relationship remains difficult to prove, but this finding stresses out the importance of noticing the association between postoperative complications and VTE, which, in turn, could help identifying patients at risk for this potentially preventable late mortality. Recent data also suggest that long-term survival might be compromised by VTE; shorter survival rates, from approximately 3 months to 1 year, have been reported for esogastric cancer patients who developed venous thrombosis during their chemotherapy or in the postoperative period [15, 17, 25]. Given the serious consequences of thromboembolic events in cancer patients, reduction of postoperative VTE is increasingly considered as a quality index of perioperative care, with many guidelines and standardization protocols being developed in this direction [8, 24, 26].

Identifying risk factors and developing diagnostic tools is a necessary first step in this procedure and individualized thromboprophylaxis strategies should be discussed for high-risk patients [8, 16]. Moreover, cancer surgery seems to increase thromboembolic risk for at least 1 month postoperatively [4, 7, 9, 27], even if thromboprophylaxis is extended beyond 4 postoperative weeks according to the current best practice recommendations [11, 28]. Thus, rigorous and targeted follow-up should be planned for these high-risk patients, not only in the immediate postoperative period but also in the long term.

One of our study's limitations is its retrospective character. Although VTE and PE were specifically searched for in patients' files during the creation of the database, their incidence risks to be underestimated as only symptomatic events were recorded. Even so, this seems to reveal some clinically relevant data that would help optimize patients' management. Potential risk factors for VTE were chosen through the parameters already recorded in the database, thus some other relevant variables were missing and could not be taken into account, such as personal history of VTE or the presence of varicose veins. Moreover, some of the variables are postoperative outcomes so it remains difficult to prove any causality between these parameters and the occurrence of VTE. The goal of this analysis is not to establish cause-effect relationship in this case, but to suggest a potential association between these perioperative parameters and the occurrence of VTE. Indeed there seems to be a strong argument correlating VTE with several forms of pulmonary postoperative complications, which generates an appealing hypothesis for future research. Specific anticoagulation strategies were not recorded in the database, and with more than 30 participating centers there might be some differences on this subject; we do not expect these differences to be significant as the participating centers follow the same perioperative anticoagulation prophylaxis guidelines [9].

This multicentric European study of 2,944 patients revealed a VTE rate of 2.9% after surgery for esophageal cancer, which was also linked with increased mortality. Patients with a preoperative ASA class III or IV who developed pulmonary complications and in particular ARDS and pneumonia were found more likely to develop postoperative VTE; thus, individualized anticoagulation strategies should be discussed for these patients.

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References

1. Lagarde SM, Reitsma JB, Maris AK, et al. Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. Ann Thorac Surg 2008;85:1938–45.
2. Raymond D. Complications of esophagectomy. Surg Clin North Am 2012;92:1299–313.
3. Shah MA, Capanu M, Soff G, Asmis T, Kelsen DP. Risk factors for developing a new venous thromboembolism in ambulatory patients with non-hematologic malignancies and impact on survival for gastroesophageal malignancies. J Thromb Haemost 2010;8:1702–9.
4. Byrne M, Reynolds JV, O'Donnell JS, et al. Long-term activation of the pro-coagulant response after neoadjuvant chemoradiation and major cancer surgery. Br J Cancer 2010;102:73–9.
5. De Martino RR, Goodney PP, Spangler EL, et al. Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. J Vasc Surg 2012;55:1035–1040 e4.
6. Tsutsumi K, Udagawa H, Kajiyama Y, et al. Pulmonary thromboembolism after surgery for esophageal cancer: its features and prophylaxis. Surg Today 2000;30:416–20.
7. Martin JT, Mahan AL, Ferraris VA, et al. Identifying esophagectomy patients at risk for predischarge versus postdischarge venous thromboembolism. Ann Thorac Surg 2015;100:932–8; discussion 938.
8. Cassidy MR, Rosenkranz P, McAneny D. Reducing postoperative venous thromboembolism complications with a standardized risk-stratified prophylaxis protocol and mobilization program. J Am Coll Surg 2014;218:1095–104.
9. Samama CM, Boubli L, Coloby P, et al. Venous thromboembolism prophylaxis in patients undergoing abdominal or pelvic surgery for cancer–a real-world, prospective, observational French study: PReOBS. Thromb Res 2014;133:985–92.
10. Collet D, Mariette C, Meunier, B. Cancer de l'esophage. Monographies de l'association française de chirurgie (AFC). Paris France: Wolters Kluwer France; 2013.
11. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S–77S.
12. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415–21.
13. Sobin LH, Gospodarowicz M, Wittekid C. TNM classification of malignant tumors, 7th edition. Oxford, England: Wiley-Blackwell; 2010.
14. Rollins KE, Peters CJ, Safranek PM, Ford H, Baglin TP, Hardwick RH. Venous thromboembolism in oesophago-gastric

carcinoma: incidence of symptomatic and asymptomatic events following chemotherapy and surgery. Eur J Surg Oncol 2011;37:1072–7.
15. Tetzlaff ED, Correa AM, Baker J, Ensor J, Ajani JA. The impact on survival of thromboembolic phenomena occurring before and during protocol chemotherapy in patients with advanced gastroesophageal adenocarcinoma. Cancer 2007;109:1989–95.
16. Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score. Thromb Res 2010;125 Suppl 2: S1–7.
17. Starling N, Rao S, Cunningham D, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 2009;27:3786–93.
18. Lyman GH, Khorana AA, Kuderer N, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2189–204.
19. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 2006;243: 89–95.
20. Pannucci CJ, Laird S, Dimick JB, Campbell DA, Henke PK. A validated risk model to predict 90-day VTE events in postsurgical patients. Chest 2014;145:567–73.
21. Mariette C, Piessen G. Is advanced age still a contra-indication to surgery for esophageal cancer? J Visc Surg 2012;149:e163–4.
22. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902–7.
23. Celik F, Bounif F, Fliers JM, et al. The impact of surgical complications as a main risk factor for venous thromboembolism: a multicenter study. Obes Surg 2014;24:1603–9.
24. Pollak AW, McBane RD 2nd. Succinct review of the new VTE prevention and management guidelines. Mayo Clin Proc 2014;89:394–408.
25. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thromb Res 2006;118:555–68.
26. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:7S–47S.
27. Van Haren RM, Valle EJ, Thorson CM, et al. Long-term coagulation changes after resection of thoracoabdominal malignancies. J Am Coll Surg 2014;218:846–54.
28. Rasmussen MS, Jørgensen LN, Wille-Jørgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2009;(1):CD004318.