



Full Length Article

Incidence, risk factors, and outcomes of venous thromboembolism after oncologic surgery: A systematic review and meta-analysis

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ABSTRACT

Background: The risk and prognosis of VTE associated with oncologic surgery need to be quantified to guide patient management. We aimed to examine the availability of data and to report the incidence of venous thromboembolism (VTE) in cancer patients after surgery, as well as the clinical outcomes of VTE following oncologic surgery.

Methods: We searched multiple databases for terms related to VTE after oncologic surgery from inception to November 1, 2017. A random-effects meta-analysis was done to calculate the pooled incidence of VTE.

Results: Of the 8611 citations identified, 136 studies including 1,481,659 patients met the eligibility criteria. The overall incidence of VTE was estimated to be 2.3% (95% CI 2.1–2.5). Bone and soft tissue cancer (10.6%, 95% CI 2.9–18.2) and lung cancer (8.1%, 95% CI 3.7–12.6) were associated with the highest and second highest risk of postoperative VTE, respectively. Age (standardized mean difference [SMD] = 0.46, 95% CI 0.40–0.53; $I^2 = 93.8\%$), radiation (OR 1.29, 95% CI 1.03–1.62; $I^2 = 34.6\%$), transfusion (OR 1.96, 95% CI 1.48–2.59; $I^2 = 57.0\%$), and operative time (SMD = 1.12, 95% CI 1.07–1.16; $I^2 = 100\%$) were possible risk factors for postoperative VTE. Patients with VTE versus those without had increased odds of all-cause fatal events (11.15, 95% CI 4.07–30.56; $I^2 = 92.0\%$).

Conclusions: The risk of VTE after oncologic surgery remains high, and this risk varied according to the cancer type, study region, surgical location, and thromboprophylactic strategy. VTE is associated with increased mortality at the early stage of cancer surgery.

1. Introduction

Malignancy is associated with an elevated risk of venous thromboembolism (VTE), which causes heavy burden to health-care resources [1]. Among all patients with VTE, 15%–20% are accompanied with a diagnosis of cancer [2]. In patients with cancer, VTE is estimated to be the second leading cause of death after the progression of cancer [3]. Cancer patients always tend to undergo consequent surgical procedures, experience immobility, and need prolonged central intravenous access, which are all independent risk factors for VTE [4]. Operations in cancer patients are often more extensive and lead to venous trauma [5]. The odds ratio (OR) for the incidence of VTE in surgical patients with known cancer is about 2.0 when compared with patients with non-cancer disease undergoing the same procedure [5]. Considering the duration of postoperative VTE, the risk of VTE in patients who underwent surgery could substantially increase within 12 postoperative weeks, compared with patients who had not undergone surgery [6].

The existence of postoperative VTE could interfere with consequent cancer therapies such as radiotherapy and chemotherapy [7]. At the same time, the use of anticoagulants for VTE has a risk of causing haemorrhage. Thus, there remain challenges in the treatment of

postoperative VTE in cancer patients. Existing data report wide estimates of the incidence of VTE related to cancer managed surgically or medically, ranging from 1% to 20%, which varied according to cancer type and time since diagnosis [8]. Some studies indicated that aging, advanced cancer, and radiotherapy were risk factors for VTE in patients undergoing surgery for cancer [5]. Despite these findings, substantial knowledge gaps remain. The precise incidence data of postoperative VTE in cancer patients and the risk of mortality in patients with VTE relative to those with no VTE are needed for an accurate estimation of disease burden. Furthermore, cumulative data are lacking about the risk factors for VTE in patients undergoing surgery for cancer, which serve as critical evidence for clinicians on which to base the choice for thromboprophylaxis.

Consequently, we conducted this systematic review and meta-analysis to assess the incidence of postoperative VTE in cancer patients, and to identify the risk factors in these patients. We also sought to compare the relative risk of mortality between cancer patients undergoing surgery with and without VTE.

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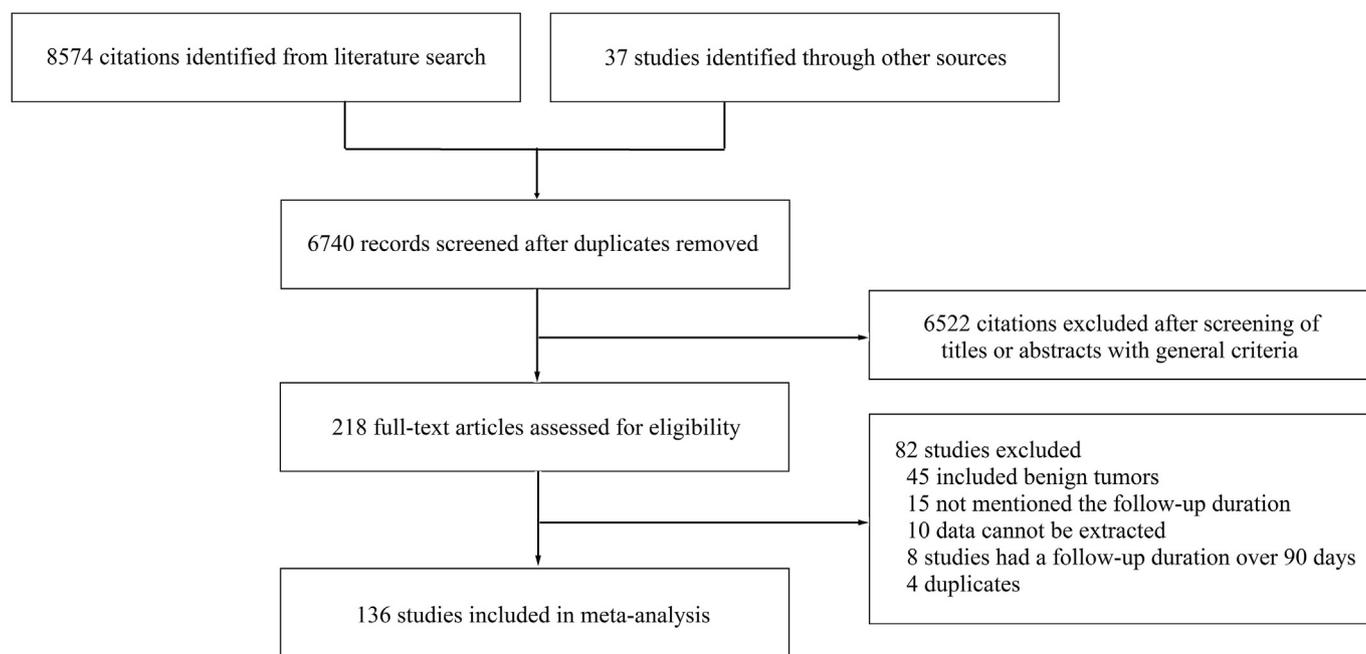


Fig. 1. PRISMA flow diagram.

2. Methods

2.1. Search strategy and selection criteria

We identified relevant studies through a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (Supplementary File 1) [9]. We did serial searches for English and non-English articles. We searched Medline (up to November 1, 2017), Embase (up to November 1, 2017), and the Cochrane Library (up to November 1, 2017). We used three groups of search terms, as follows: (1) ‘venous thromboembolism’, ‘deep vein thrombosis’, and ‘pulmonary embolism’; (2) ‘cancer’, ‘malignancy’, and ‘oncologic’; and (3) ‘surgery’, ‘operation’, and ‘surgical intervention’ (specific search strategies are listed in Supplementary File 2).

We included all full-text studies and abstracts with information on the incidence of VTE in cancer patients after surgery, as well as the clinical outcomes of VTE following oncologic surgery. These studies included hospital-, population-, and registry-based cohorts. The follow-up duration of these studies was restricted to within 3 months. These studies were randomized trials or observational studies, and case reports, case series, in vitro studies, and animal studies were excluded. Three investigators independently assessed all trials for eligibility and extracted data with the assistance of Google’s translation tools for non-English reports. Disagreements about the inclusion of studies or extraction of data were resolved through consensus after a discussion.

2.2. Data extraction

The following details from each eligible study were extracted by two authors: name of the first author, study location, study design, number of patients, type of surgery, use of pharmacological thromboprophylaxis, methods of ascertainment, and duration of follow-up. We extracted data on the incidence of VTE in cancer patients after surgery, and when available, the cumulative risk of VTE-caused death. Possible predictive factors for the development of VTE in cancer patients after surgery were also extracted when available, including age, sex, stage of cancer, smoking status, perioperative transfusion history, perioperative chemotherapy, perioperative radiotherapy, and operation time.

The methodological quality of each study was assessed by two

authors by using the Newcastle-Ottawa scale (NOS), which assigns 4 points for selection, 2 points for comparability, and 3 points for outcome [10]. The higher the score of an assessed study, the higher its quality.

2.3. Definition of outcomes and comparison

The primary outcome was the occurrence of VTE after cancer surgery. VTE consists of deep vein thrombosis (DVT, symptomatic or asymptomatic) and pulmonary embolism (PE).

The secondary outcome was the occurrence of death. If the study results reported mortality events, we contacted the study authors to check whether data for VTE-related death were available. If the data were not available, the study was excluded from the final analysis. The impact of VTE on mortality was expressed by comparing all-cause fatal events in cancer patients who underwent surgery complicated with VTE and those without VTE.

2.4. Statistical analysis

The pooled incidence of VTE after cancer surgery and the rate of mortality adjudicated to be caused by VTE after cancer surgery during the follow-up period were assessed using the DerSimonian and Laird random-effects model when significant study heterogeneity was present ($I^2 > 50\%$), or a fixed-effects model in the absence of significant heterogeneity. We performed separate analysis for each cancer type. Given that differences in study region, DVT detection method, thromboprophylaxis use, and location of the operation would affect the result, we performed subgroup analysis based on these factors. The association of potential risk factors with VTE were summarized as OR (95% confidence interval [CI]). We also assessed the odds of fatal events by comparing cancer patients who underwent surgical intervention complicated with VTE and those without VTE. Publication bias was assessed through graphical visualization of the funnel plot, Begg’s test, and Egger’s test. All statistical analyses were done using Stata 12.0. Statistical tests were two-tailed.

Table 1
Subgroup analysis for incidence of VTE events.

Study subgroup	No. of studies	Total no. of participants	Pooled prevalence	95% CI	I ²
VTE					
Total VTE	136	1,481,659	0.023	0.021–0.025	98.8
Thromboprophylactic strategy					
Thromboprophylaxis studies	40	19,489	0.066	0.054–0.078	96.2
No thromboprophylaxis studies	17	9206	0.083	0.064–0.103	94.9
Location					
Abdominopelvic studies	92	580,821	0.028	0.026–0.031	98.7
Nonabdominopelvic studies	33	280,516	0.019	0.015–0.022	98.5
Region					
North American studies	62	1,054,569	0.020	0.018–0.023	99.3
European studies	30	16,123	0.066	0.053–0.079	95.0
East Asian studies	31	403,199	0.026	0.021–0.031	94.0
Follow-up duration					
< 30 d	97	989,108	0.019	0.017–0.021	98.7
31–60 d	11	390,404	0.023	0.017–0.030	95.3
61–90 d	28	102,087	0.053	0.043–0.062	99.1
DVT					
Total DVT	106	546,611	0.015	0.013–0.017	97.3
Symptomatic DVT	64	224,147	0.009	0.008–0.011	94.7
Routinely scanned DVT	36	8935	0.096	0.078–0.115	93.9
PE					
Total PE	99	544,177	0.008	0.007–0.009	96.1
VTE-related death	64	36,639	0.003	0.002–0.004	56.5

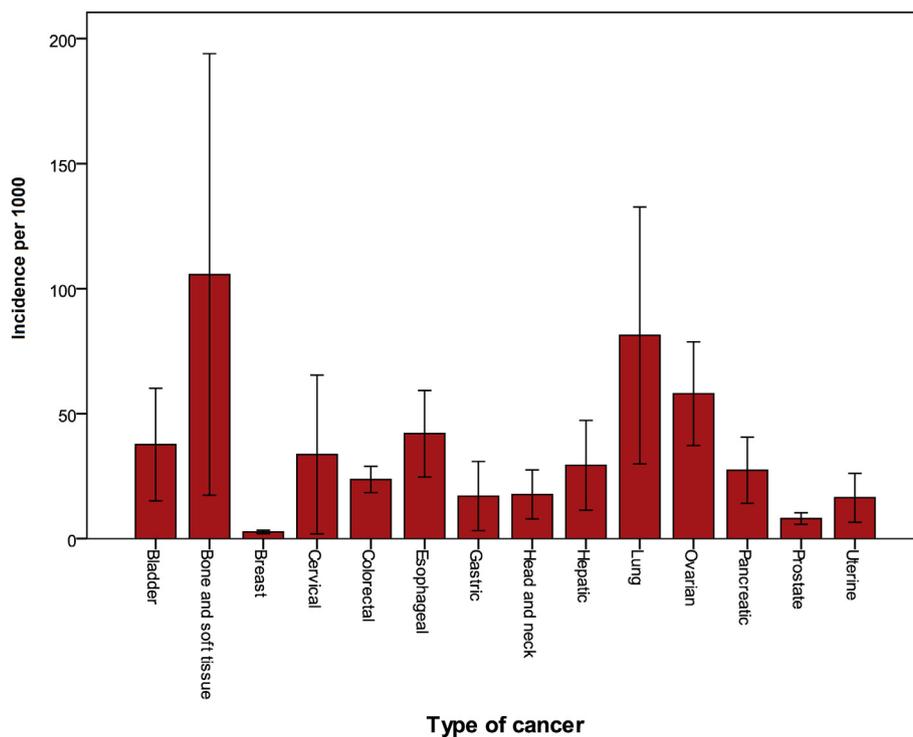


Fig. 2. Pooled estimates for 14 cancer types.

3. Results

We identified 8611 reports, of which 136 studies [11–146] undertaken between 1983 and 2017 were described and included in the analysis. The process of identifying eligible studies for our systematic review and meta-analysis is shown in Fig. 1. Key design features of the included studies are available in the Supplementary Table 1. Of the 136 studies, 59 were prospective and 77 were retrospective. The size of the studies varied between 30 and 93,663 participants. The diagnosis method for DVT and the follow-up duration varied between the studies. All the included studies were of good quality, as assessed using the NOS

quality assessment scale for cohort studies (Supplementary Table 2).

The studies included 1,481,659 patients who were followed-up for 7–90 days, during which 18,957 patients developed VTE. The pooled incidence of VTE was 2.3% (95% CI 2.1–2.5) (Supplementary Fig. 1). The results of subgroup analysis are listed in Table 1. The incidence of VTE in patients who received routine pharmacological thromboprophylaxis for cancer surgery was 6.6% (95% CI 5.4–7.8), as compared with 8.3% (95% CI 6.4–10.3) in patients without any pharmacological thromboprophylaxis. We repeated the analysis by stratifying the patients according to the region of study. We found regional variations of incidence estimates from North America (62 studies, 2.0%, 95% CI

1.8–2.3), East Asia (31 studies, 2.6%, 95% CI 2.1–3.1), and Europe (30 studies, 6.6%, 95% CI 5.3–7.9). Twenty-eight of the included 136 studies had a follow-up period of 61–90 days, whereas 11 studies had a follow-up period of 31–60 days and 97 studies had a follow-up period of within 30 days. The pooled incidence of VTE was 5.3% (95% CI 4.3–6.2), 2.3% (95% CI 1.7–3.0), 1.9% (95% CI 1.7–2.1), respectively. Of the included studies, 106 studies provided data on the incidence of DVT. The pooled estimated incidence of DVT was 1.5% (95% CI 1.3–1.7). About one-third of the 106 studies involved routine scanning for DVT with ultrasonography, venography, or labelled fibrinogen during the follow-up period. Sixty-four of these studies reported symptomatic DVT. The pooled incidence of DVT was 9.6% (95% CI 7.8–11.5) and 0.9% (95% CI 0.8–1.1), respectively. In the 36 studies with routine scanning for DVT, a total of 472 DVT events were detected, of which only 53 cases were symptomatic. The pooled incidence of symptomatic DVT in these studies was 1.0% (95% CI 0.5–1.4). A total of 99 studies reported the risk of PE after cancer surgery, and the pooled incidence of PE was 0.8% (95% CI 0.7–0.9).

The pooled estimates for 14 cancer types are summarized in Fig. 2 and Supplementary Table 3. For abdominopelvic cancer surgery, the pooled incidence was 2.8% (95% CI 2.6–3.1). For the rest of the cancer types, the pooled incidence was 1.9% (95% CI 1.5–2.2). Bone and soft tissue cancer (10.6%, 95% CI 2.9–18.2) and lung cancer (8.1%, 95% CI 3.7–12.6) were associated with the greatest and second greatest risk of postoperative VTE, respectively. Breast cancer was associated with the lowest risk of VTE after surgery (0.3%, 95% CI 0.2–0.3).

We included age, male sex, advanced cancer, current smoker status, transfusion, chemotherapy, radiation, and operation time as potential risk factors. The association of potential risk factors with VTE is summarized in Table 2. Age (standardized mean difference [SMD] = 0.46, 95% CI 0.40–0.53; $I^2 = 93.8\%$), radiation (OR1.29, 95% CI 1.03–1.62; $I^2 = 34.6\%$), transfusion (OR1.96, 95% CI 1.48–2.59; $I^2 = 57.0\%$), and operative time (SMD = 1.12, 95% CI 1.07–1.16; $I^2 = 100\%$) were possible risk factors for postoperative VTE, and a current smoker versus a non-smoker status had lower odds of postoperative VTE (OR0.80, 95% CI 0.70–0.92; $I^2 = 17.2\%$). Sex (OR0.99, 95% CI 0.69–1.42; $I^2 = 85.6\%$), advanced cancer (OR1.11, 95% CI 0.75–1.64; $I^2 = 67.0\%$), and chemotherapy (OR1.12, 95% CI 0.96–1.30; $I^2 = 0\%$) were not risk factors for VTE after cancer surgery.

A total 64 studies including 36,639 patients assessed fatal outcomes caused by VTE; however, 44 of the 64 studies reported no death caused by VTE. The overall incidence of mortality caused by VTE was estimated to be 0.3% (95% CI 0.2–0.4) (Supplementary Fig. 2). Thirteen studies evaluated the impact of VTE on all-cause mortality. Patients with VTE versus those without had significantly increased odds of fatal events (11.15, 95% CI 4.07–30.56; $I^2 = 92.0\%$) (Fig. 3).

4. Discussion

Although recent evidence suggests that both cancer and surgery are associated with VTE, the precise incidence and risk of this outcome

Table 2
Pooled ORs for association of commonly studied risk factors with VTE events.

Potential risk factors	No. of studies	Total no. of participants	Pooled OR/SMD	95% CI	P value	I^2
Male	17	85,997	0.99	0.69–1.42	0.964	85.6
Age	14	104,390	0.46	0.40–0.53	< 0.001	93.8
Advanced cancer	13	28,500	1.11	0.75–1.64	0.612	67.0
Chemotherapy	17	234,278	1.12	0.96–1.30	0.143	0
Radiation	10	172,762	1.29	1.03–1.62	0.030	34.6
Smoker	19	335,163	0.80	0.70–0.92	0.001	17.2
Transfusion	8	111,108	1.96	1.48–2.59	< 0.001	57.0
Operative time	7	148,399	1.12	1.07–1.16	< 0.001	100

remain uncertain. In this systematic review and meta-analysis, we found a 2.3% incidence of VTE worldwide, with further subgroup variations. Compared with patients without VTE, cancer patients with postoperative VTE events were also 10 times more likely to be associated with death in the first 3 months. These findings suggest that the risk of VTE after cancer surgery remains high, and the prognosis of these patients might be worse than clinically perceived.

In view of the heightened risk of VTE, should cancer patients routinely receive preoperative pharmacological thromboprophylaxis? This study indicated that in the non-comparison studies, the incidence of VTE in patients who received routine pharmacological thromboprophylaxis for cancer surgery was 6.6% (95% CI 5.4–7.8), as compared with 8.3% (95% CI 6.4–10.3) in patients without any pharmacological thromboprophylaxis. The guidelines for the prevention of VTE in patients with cancer recommend that patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days [147,148]. Although our previous meta-analysis suggested that routine pharmacological thromboprophylaxis for cancer patients undergoing surgery resulted in a relatively reduced incidence of DVT compared with without thromboprophylaxis, it also involved a significantly increased incidence of bleeding events [149]. Consequently, it is critical to identify the risk factors for VTE events so that thromboprophylaxis could be prescribed for patients with a high risk. Alternatively, as the risk of VTE varied among different cancer types, the recognition of the precise incidence of this complication in different cancers is also necessary. Tissue factor-positive microparticles, thrombelastography and the presence of activated protein C resistance (APC-r) not caused by a factor V gene mutation represents valuable methods which may provide extensive information on haemostasis in cancer patients before surgery [150–152]. The ninth edition of the antithrombotic therapy and prevention of thrombosis guidelines of the American College of Chest Physicians used the Caprini score to stratify the risk of VTE in non-orthopaedic surgical patients [148]. Although the Caprini score involves many predictive factors, some cancer-related possible risk factors are not mentioned in the scoring system. We therefore gathered the available evidence to assess the possible risk factors for VTE after cancer surgery and the precise incidence in different cancer types.

There are many possible factors associated with the development of VTE after cancer surgery. Cancer-related factors include the primary site, stage, and histology [153]. The procoagulant state in cancer arises from an interaction between the tumour cells and the haemostatic system. Tumour cells may invade the vasculature and expose the plasma to tumour procoagulants such as tissue factor, and then directly activate coagulation [153]. The incidence among different groups of cancer varies considerably depending on different levels of plasma tumour procoagulants. Treatment-related factors include chemotherapy, radiotherapy, and transfusion [154–156]. Both chemotherapy and radiotherapy could possibly injure the endothelium of blood vessels, which results in a shift from an anticoagulant status to a procoagulant status [154]. Moreover, transfusion of stored red blood cells could selectively activate human neutrophils to release interleukin-8 and secretory PLA2, which may promote a hypercoagulable state that leads to an increased incidence of VTE [154]. This may be especially true in patients already at an increased risk of developing postoperative VTE, such as cancer patients. Patient-related factors include age, race, and comorbidities [107,116]. The serum levels of procoagulant factors generally increase with age while anticoagulant protein levels remain stable or slightly decrease, which may contribute to the higher incidence of VTE in older patients. Some studies also identified the Asian race as a protective factor in the development of VTE [107,116]. In this study, we identified age (SMD = 0.46, 95% CI 0.40–0.53), radiation (OR1.30, 95% CI 1.03–1.65), transfusion (OR 2.07, 95% CI 1.52–2.82), and operative time (SMD1.12, 95% CI 1.07–1.16) as possible risk factors for postoperative VTE. This information would be readily available to guide decision making on VTE prophylaxis. These patients may

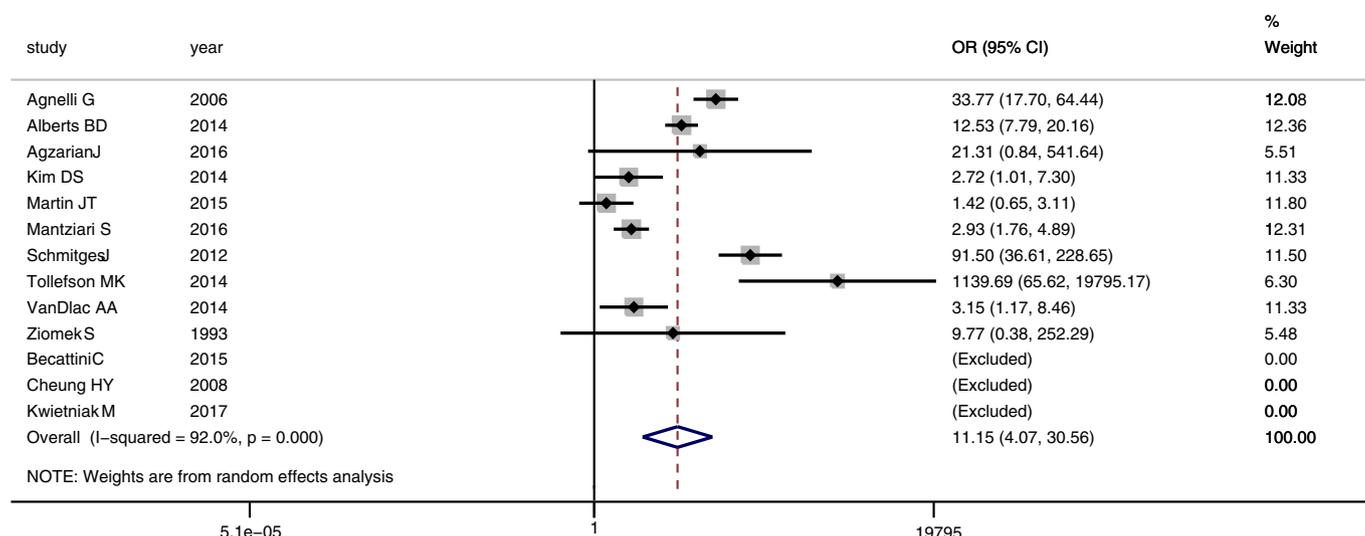


Fig. 3. Summary forest plot for VTE vs no VTE studies.

benefit from longer VTE prophylaxis or more aggressive surveillance postoperatively. However, we noted that a current smoker versus a non-smoker status had lower odds of postoperative VTE (OR0.76, 95% CI 0.64–0.92; $I^2 = 43.8\%$). Smoking has long been considered a risk factor for atherosclerotic disease; however, its role as a protective factor against VTE remains unclear. We could not find an appropriate explanation for this relationship, but this area merits further investigation.

In the subgroup analysis, we found that European studies (30 studies, 6.6%, 95% CI 5.3–7.9) showed a higher incidence of VTE than East Asian studies (31 studies, 2.6%, 95% CI 2.1–3.1) and North American studies (62 studies, 2.0%, 95% CI 1.8–2.3). Various explanations have been suggested. First, many American studies were based on national databases with large populations, and in some of these studies, post-discharge VTE events were identified on the basis of re-admission of patients with a diagnosis of DVT or PE. As a result, some other patients with VTE who were not hospitalized might not have been included. Conversely, many of the studies from East Asia and Europe involved routine scanning for VTE during the study period. In this study, the pooled incidence of DVT in the studies with routine scanning for DVT, by using ultrasonography, venography, or labelled fibrinogen, was 9.6% (95% CI 7.8–11.5), which is 10 times higher than that in studies that only reported symptomatic DVT (0.9%, 95% CI 0.8–1.1). Finally, as mentioned above, the Asian race has been proved to be associated with a decreased risk of VTE. There might exist ethnic differences in VTE occurrence.

In the 36 studies with routine scanning for DVT, only about 11% (53 of 472) of the DVT events detected were symptomatic. The pooled incidence of symptomatic DVT in these studies was 1.0% (95% CI 0.5–1.4). It is important to clarify whether routine scanning for DVT by using ultrasonography is necessary in cancer patients after surgery because asymptomatic VTE also has the possibility of causing a mortality event. Routine scanning could detect more DVT events, leading to anticoagulation use in these patients, which could reduce the mortality rate caused by VTE but might increase the incidence of bleeding events. Furthermore, the results of the ENOXACAN study indicated that although venography was performed routinely during hospitalization, more than half of the deaths caused by VTE occurred within 3 months after discharge [43]. Thus, another question arises: is follow-up imaging surveillance needed for postoperative VTE in cancer patients? There is a lack of a direct comparison of the clinical outcomes of routine scanning for VTE and selective scanning for VTE in this group of patients. Moreover, no previous study concentrated on the cost-effectiveness of routine scanning for VTE after cancer surgery. Further

studies are needed to answer the above questions.

Different from other types of surgery, a previous population-based study suggested that the relative risk after surgery for cancer remained high at the period of postoperative weeks 7–12 [6]. Two other studies confirmed that although most VTE events occurred within 1 month, a proportion of these events occurred during the following 2 months [96,105]. The relative risks for VTE in cancer surgery then significantly decreased after 3 months postoperatively. Thus, in this study, we restricted the follow-up duration of the included studies to 3 months. In this study, the pooled incidence of VTE in the included studies with a follow-up period of 61–90 days was 5.3% (95% CI 4.3–6.2), and that in studies with a follow-up period of within 30 days was 1.9% (95% CI 1.7–2.1). These results might explain the effectiveness of extended antithrombotic prophylaxis for cancer surgery [157].

Our findings suggest that the risk of mortality in the 90 days after cancer surgery in the presence of VTE was 10 times higher than without VTE. On the one hand, both PE and the consequences of VTE events, such as bleeding caused by anti-thrombotic therapy, could directly lead to death. On the other hand, as our results suggest, age is a risk factor for VTE; thus, aged patients have an increased risk of postoperative mortality. Moreover, a complicated postoperative course or an existing preoperative comorbidity might result in immobility, which could increase the risk of VTE [95]. The cause-effect relationship remains difficult to prove; however, in this study, the overall incidence of mortality directly caused by VTE was estimated to be 0.3% (95% CI 0.2–0.4), which is a non-negligible number.

This study has a number of strengths. First, we exploited the power of meta-analysing many studies, including data published worldwide during three decades. This study is the largest and most comprehensive review thus far of the incidence, risk factors, and prognosis of VTE after oncologic surgery. Second, to increase the robustness of our results, we performed many subgroup analyses based on study characteristics, and also separately evaluated almost every type of common cancer. Third, to test the clinical impact of VTE, we also explored the relationship between VTE and survival, and through the meta-analysis, for the first time to our knowledge, we identified VTE as a potentially preventable risk factor for late mortality.

This study also has some limitations. First, the included studies varied in the types of malignant neoplasms, anti-thrombotic prophylaxis methods, diagnostic methods, and follow-up durations. Although we tried our best to perform subgroup analyses to investigate the impact of these characteristics, significant study heterogeneity still existed in most analyses ($I^2 > 50\%$). Second, insufficient studies provided data on some types of malignant neoplasms; thus, the results of these studies

have relatively weaker power. Third, although some studies indicated that a non-O blood type and body mass index were also related to VTE, too few studies provided data on these factors; thus, they were not included in the final meta-analysis as possible risk factors for VTE after cancer surgery.

In conclusion, our systematic review and meta-analysis revealed an overall incidence of 2.3% among patients who underwent oncologic surgery, with further variations according to the cancer type, study region, surgical location, and thromboprophylactic strategy. Age, radiation, transfusion, and operative time were possible risk factors. The heightened risk of mortality suggests that there is a need for preventive strategies against VTE.

Acknowledgments

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Disclosures

All the authors have no conflicts of interest or financial ties to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2018.11.012>.

References

- [1] J.W. Blom, C.J. Doggen, S. Osanto, F.R. Rosendaal, Malignancies, prothrombotic mutations, and the risk of venous thrombosis, *JAMA* 293 (2005) 715–722.
- [2] A.Y. Lee, M.N. Levine, Venous thromboembolism and cancer: risks and outcomes, *Circulation* 107 (2003) 117–121.
- [3] H.T. Sørensen, L. Mellemejkjaer, J.H. Olsen, J.A. Baron, Prognosis of cancers associated with venous thromboembolism, *N. Engl. J. Med.* 343 (2000) 1846–1850.
- [4] J.A. Heit, M.D. Silverstein, D.N. Mohr, T.M. Petterson, W.M. O'Fallon, L.J. Melton 3rd, Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study, *Arch. Intern. Med.* 160 (2000) 809–815.
- [5] K.A. Behranwala, R.C. Williamson, Cancer-associated venous thrombosis in the surgical setting, *Ann. Surg.* 249 (2009) 366–375.
- [6] S. Sweetland, J. Green, B. Liu, A. Berrington de González, M. Canonico, G. Reeves, V. BeralMillion Women Study collaborators, Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study, *BMJ* 339 (2009) b4583.
- [7] R. Camidge, B. Reigner, J. Cassidy, S. Grange, M. Abt, E. Weidekamm, D. Jodrell, Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer, *J. Clin. Oncol.* 23 (2005) 4719–4725.
- [8] F. Horsted, J. West, M.J. Grainge, Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis, *PLoS Med.* 9 (2012) e1001275.
- [9] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, *PLoS Med.* 6 (2009) e1000100.
- [10] G. Wells, Proceedings of the Third Symposium on Systematic Reviews Beyond the Basics. SBOD: Improving Quality and Impact: The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-randomised Studies in Meta analysis, Oxford (July 3–5, 2000).
- [11] M. Ailawadi, G. Del Priore, A comparison of thromboembolic prophylaxis in gynecologic oncology patients, *Int. J. Gynecol. Cancer* 11 (2001) 354–358.
- [12] G. Agnelli, G. Bolis, L. Capussotti, R.M. Scarpa, F. Tonelli, E. Bonizzoni, M. Moia, F. Parazzini, R. Rossi, F. Sonaglia, B. Valarani, C. Bianchini, G. Gussoni, A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project, *Ann. Surg.* 243 (2006) 89–95.
- [13] R.H. Andtbacka, G. Babiera, S.E. Singletary, K.K. Hunt, F. Meric-Bernstam, B.W. Feig, F.C. Ames, M.I. Ross, Y. DeJesus, H.M. Kuerer, Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways, *Ann. Surg.* 243 (2006) 96–101.
- [14] R.A. Auer, A.S. Scheer, J.I. McSparron, J. Gonsalves, Y. Fong, Postoperative venous thromboembolism predicts survival in cancer patients, *Ann. Surg.* 255 (2012) 963–970.
- [15] B.D. Alberts, S.L. Woldu, A.C. Weinberg, M.R. Danzig, R. Korets, K.K. Badani, Venous thromboembolism after major urologic oncology surgery: a focus on the incidence and timing of thromboembolic events after 27,455 operations, *Urology* 84 (2014) 799–806.
- [16] H. Alsubaie, C. Leggett, P. Lambert, A.R. Schulman, S. Tuorto, S. Doucette, A. McKay, Diagnosis of VTE postdischarge for major abdominal and pelvic oncologic surgery: implications for a change in practice, *Can. J. Surg.* 58 (2015) 305–311.
- [17] J. Agzarian, W.C. Hanna, L. Schneider, C. Schieman, C.J. Finley, Y. Peysakhovich, T. Schnurr, D. Nguyen-Do, L.A. Linkins, J. Douketis, M. Crowther, M. De Perrot, T.K. Waddell, Y. Shargall, Postdischarge venous thromboembolic complications following pulmonary oncologic resection: an underdetected problem, *J. Thorac. Cardiovasc. Surg.* 151 (2016) 992–999.
- [18] C. Baykal, A. Al, E. Demirtaş, A. Ayhan, Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind clinical study, *Eur. J. Gynaecol. Oncol.* 22 (2001) 127–130.
- [19] S. Boncinelli, M. Marsili, P. Lorenzi, L.P. Fabbri, S. Pittino, M. Filoni, F. Bressan, E. Sarti, S. Cinotti, M. Morfini, Haemostatic molecular markers in patients undergoing radical retropubic prostatectomy for prostate cancer and submitted to prophylaxis with unfractionated or low molecular weight heparin, *Minerva Anestesiol.* 67 (2001) 693–703.
- [20] D. Bergqvist, G. Agnelli, A.T. Cohen, A. Eldor, P.E. Nilsson, A. Le Moigne-Amrani, F. Dietrich-Neto, ENOXACAN II Investigators, Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer, *N. Engl. J. Med.* 346 (2002) 975–980.
- [21] J. Beyer, S. Wessela, O.W. Hakenberg, E. Kuhlisch, K. Halbritter, M. Froehner, M.P. Wirth, S.M. Schellong, Incidence, risk profile and morphological pattern of venous thromboembolism after prostate cancer surgery, *J. Thromb. Haemost.* 7 (2009) 597–604.
- [22] D.J. Bosch, Q.A. Van Dalen, V.E. Mul, G.A. Hospers, J.T. Plukker, Increased risk of thromboembolism in esophageal cancer patients treated with neoadjuvant chemoradiotherapy, *Am. J. Surg.* 208 (2014) 215–221.
- [23] G. Bouchard-Fortier, W.H. Geerts, A. Covens, D. Vicus, R. Kupets, L.T. Gien, Is venous thromboprophylaxis necessary in patients undergoing minimally invasive surgery for a gynecologic malignancy? *Gynecol. Oncol.* 134 (2014) 228–232.
- [24] C. Becattini, F. Rondelli, M.C. Vedovati, G. Camporese, M. Giustozzi, M. Boncompagni, S. Pucciarelli, R. Balzarotti, E. Mariani, E. Filippucci, A. Donini, G. Agnelli, Incidence and risk factors for venous thromboembolism after laparoscopic surgery for colorectal cancer, *Haematologica* 100 (2015) e35–e38.
- [25] E.L. Barber, P.A. Gehrig, D.L. Clarke-Pearson, Venous thromboembolism in minimally invasive compared with open hysterectomy for endometrial cancer, *Obstet. Gynecol.* 128 (2016) 121–126.
- [26] G. Bellini, A. Teng, N. Kotecha, E. Sutton, C.K. Yang, M. Passeri, D.Y. Lee, K. Rose, The identification of risk factors for venous thromboembolism in gastrointestinal oncologic surgery, *J. Surg. Res.* 205 (2016) 279–285.
- [27] D.L. Clarke-Pearson, F.R. Jelovsek, W.T. Creasman, Thromboembolism complicating surgery for cervical and uterine malignancy: incidence, risk factors, and prophylaxis, *Obstet. Gynecol.* 61 (1983) 87–94.
- [28] A.J. Crandon, J. Koutts, Incidence of post-operative deep vein thrombosis in gynaecological oncology, *Aust. N. Z. J. Obstet. Gynaecol.* 23 (1983) 216–219.
- [29] D.L. Clarke-Pearson, I.S. Synan, R.E. Coleman, W. Hinshaw, W.T. Creasman, The natural history of postoperative venous thromboemboli in gynecologic oncology: a prospective study of 382 patients, *Am. J. Obstet. Gynecol.* 148 (1984) 1051–1054.
- [30] H.Y. Cheung, C.C. Chung, K.K. Yau, W.T. Siu, S.K. Wong, E. Chiu, M.K. Li, Risk of deep vein thrombosis following laparoscopic rectosigmoid cancer resection in Chinese patients, *Asian J. Surg.* 31 (2008) 63–68.
- [31] C.M. Chen, J.J. Disa, P.G. Cordeiro, A.L. Pusic, C.M. McCarthy, B.J. Mehrara, The incidence of venous thromboembolism after oncologic head and neck reconstruction, *Ann. Plast. Surg.* 60 (2008) 476–479.
- [32] C. Clément, P. Rossi, K. Aissi, P. Barthelemy, N. Guibert, P. Auquier, E. Ragni, D. Rossi, Y. Frances, C. Bastide, Incidence, risk profile and morphological pattern of lower extremity venous thromboembolism after urological cancer surgery, *J. Urol.* 186 (2011) 2293–2297.
- [33] R. Chandra, G. Melino, M. Thomas, M.J. Lawrence, R.A. Hunter, J. Moore, Is extended thromboprophylaxis necessary in elective colorectal cancer surgery? *ANZ J. Surg.* 83 (2013) 968–972.
- [34] D.R. Clayburgh, W. Stott, T. Cordiero, R. Park, K. Detwiller, M. Buniel, P. Flint, J. Schindler, P. Andersen, M.K. Wax, N. Gross, Prospective study of venous thromboembolism in patients with head and neck cancer after surgery, *JAMA Otolaryngol. Head Neck Surg.* 139 (2013) 1143–1150.
- [35] S.Y. Chan, V.F. Leung, C.H. Yee, E.S. Chan, S.S. Hou, W. Chu, C.F. Ng, Incidence of postoperative deep vein thrombosis after robotic-assisted laparoscopic prostatectomy: a prospective study in Chinese patients, *Int. Urol. Nephrol.* 46 (2014) 2139–2142.
- [36] E.C. Chen, N. Papa, N. Lawrentschuk, D. Bolton, S. Sengupta, Incidence and risk factors of venous thromboembolism after pelvic uro-oncologic surgery—a single center experience, *BJU Int.* 117 (2016) 50–53.
- [37] M. Dahan, B. Boneu, J. Renella, Prevention of deep venous thromboses in cancer thoracic surgery with a low-molecular-weight heparin, Fraxiparine: a comparative randomized trial [abstract], *Thromb. Haemost.* 62 (1989) 519.
- [38] R.L. DeBernardo Jr., R.B. Perkins, R.D. Littell, C.N. Krasner, L.R. Duska, Low-molecular-weight heparin (dalteparin) in women with gynecologic malignancy, *Obstet. Gynecol.* 105 (2005) 1006–1011.
- [39] T.A. Damron, Z. Wardak, B. Glodny, W. Grant, Risk of venous thromboembolism in bone and soft-tissue sarcoma patients undergoing surgical intervention: a report from prior to the initiation of SCIP measures, *J. Surg. Oncol.* 103 (2011) 643–647.

- [40] D.L. Davenport, H.D. Vargas, M.W. Kasten, E.S. Xenos, Timing and perioperative risk factors for in-hospital and post-discharge venous thromboembolism after colorectal cancer resection, *Clin. Appl. Thromb. Hemost.* 18 (2012) 569–575.
- [41] R.C. Doiron, C.M. Booth, X. Wei, D.R. Siemens, Risk factors and timing of venous thromboembolism after radical cystectomy in routine clinical practice: a population-based study, *BJU Int.* 118 (2016) 714–722.
- [42] European Fraxiparin Study (EFS) Group, Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery, *Br. J. Surg.* 75 (1988) 1058–1063.
- [43] Enoxacan Study Group, Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment, *Br. J. Surg.* 84 (1997) 1099–1103.
- [44] J.B. Eifler, A.W. Levinson, M.E. Hyndman, B.J. Trock, C.P. Pavlovich, Pelvic lymph node dissection is associated with symptomatic venous thromboembolism risk during laparoscopic radical prostatectomy, *J. Urol.* 185 (2011) 1661–1665.
- [45] A. Ejaz, G. Spolverato, Y. Kim, D.L. Lucas, B. Lau, M. Weiss, F.M. Johnston, M. Kheng, K. Hirose, C.L. Wolfgang, E. Haut, T.M. Pawlik, Defining incidence and risk factors of venous thromboembolism after hepatectomy, *J. Gastrointest. Surg.* 18 (2014) 1116–1124.
- [46] J.P. Fricker, Y. Vergnes, R. Schach, A. Heitz, M. Eber, L. Grunebaum, M.L. Wiesel, A. Kher, P. Barbier, J.P. Cazenave, Low dose heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery, *Eur. J. Clin. Investig.* 18 (1988) 561–567.
- [47] E. Friis, J. Horby, L.T. Sørensen, B. Pilsgaard, P. Wille-Jørgensen, L. Johansen, T. Jørgensen, Thromboembolic prophylaxis as a risk factor for postoperative complications after breast cancer surgery, *World J. Surg.* 28 (2004) 540–543.
- [48] M. Samare Fekri, M. Khalily Zade, S. Fatehi, The association of deep vein thrombosis with cancer treatment modality: chemotherapy or surgery? *Iran Red Crescent Med J* 16 (2014) e14722.
- [49] J.P. Fischer, A.M. Wes, C.T. Tuggle, L.C. Wu, Venous thromboembolism risk in mastectomy and immediate breast reconstruction: analysis of the 2005 to 2011 American College of Surgeons National Surgical Quality Improvement Program data sets, *Plast. Reconstr. Surg.* 133 (2014) 263e–273e.
- [50] A.H. Freeman, A. Barrie, L. Lyon, R.D. Littell, C. Garcia, C. Conell, C.B. Powell, Venous thromboembolism following minimally invasive surgery among women with endometrial cancer, *Gynecol. Oncol.* 142 (2016) 267–272.
- [51] D. Fu, Y. Zhao, J. Shen, Z. Cai, Y. Hua, Comparison of venous thromboembolism after total artificial joint replacement between musculoskeletal tumors and osteoarthritis of the knee by a single surgeon, *PLoS One* 11 (2016) e0158215.
- [52] A. Gallus, J. Cade, P. Ockelford, S. Hepburn, M. Maas, H. Magnani, T. Bucknall, J. Stevens, F. Porteous, Orgaran (Org 10172) or heparin for preventing venous thrombosis after elective surgery for malignant disease? A double-blind, randomised, multicentre comparison, *Thromb. Haemost.* 70 (1993) 562–567.
- [53] A. Grail, N. Latif, X. Zhang, L.T. Dean, M. Morgan, R. Giuntoli, R. Burger, S. Kim, E. Ko, Incidence of venous thromboembolism by type of gynecologic malignancy and surgical modality in the National Surgical Quality Improvement Program, *Int. J. Gynecol. Cancer* 27 (2017) 581–587.
- [54] L. Heilmann, G.F.V. Tempelhoff, C. Kirkpatrick, Comparison of unfractionated versus low molecular weight heparin for deep vein thrombosis prophylaxis during breast and pelvic cancer surgery: efficacy, safety, and follow-up, *Clin. Appl. Thromb. Hemost.* 4 (1998) 268–273.
- [55] P. Hennessey, Y.R. Semenov, C.G. Gourin, The effect of deep vein thrombosis on short-term outcomes and cost of care after head and neck cancer surgery, *Laryngoscope* 122 (2012) 2199–2204.
- [56] P.D. Hewes, K.J. Hachey, X.W. Zhang, Y. Tripodis, P. Rosenkranz, M.I. Ebricht, D. McAneny, H.C. Fernando, V.R. Litle, Evaluation of the Caprini model for venothromboembolism in esophagectomy patients, *Ann. Thorac. Surg.* 100 (2015) 2072–2078.
- [57] K.J. Hachey, P.D. Hewes, L.P. Porter, Y. Tripodis, P. Rosenkranz, M.I. Ebricht, H.C. Fernando, V.R. Litle, Caprini venous thromboembolism risk assessment permits selection for postdischarge prophylactic anticoagulation in patients with resectable lung cancer, *J. Thorac. Cardiovasc. Surg.* 151 (2016) 37–44.
- [58] K. Hata, T. Kimura, S. Tsuzuki, G. Ishii, M. Kido, T. Yamamoto, H. Sasaki, J. Miki, H. Yamada, A. Furuta, K. Miki, S. Egawa, Safety of fondaparinux for prevention of postoperative venous thromboembolism in urological malignancy: a prospective randomized clinical trial, *Int. J. Urol.* 23 (2016) 923–928.
- [59] J.C. Iannuzzi, C.T. Aquina, A.S. Rickles, B.J. Hensley, C.P. Probst, K. Noyes, J.R. Monson, F.J. Fleming, Risk factors for postdischarge venothromboembolism after colorectal resection, *Dis. Colon Rectum* 59 (2016) 224–229.
- [60] O. Jeong, S.Y. Ryu, Y.K. Park, Y.J. Kim, The effect of low molecular weight heparin thromboprophylaxis on bleeding complications after gastric cancer surgery, *Ann. Surg. Oncol.* 17 (2010) 2363–2369.
- [61] A. Jakhetiya, N.K. Shukla, S.V. Deo, P.K. Garg, S. Thulker, Deep vein thrombosis in Indian cancer patients undergoing major thoracic and abdomino-pelvic surgery, *Indian J. Surg. Oncol.* 7 (2016) 425–429.
- [62] C.K. Kum, E.K. Sim, S.S. Ngoi, Deep vein thrombosis complicating colorectal surgery in the Chinese in Singapore, *Ann. Acad. Med. Singap.* 22 (1993) 895–897.
- [63] J. Kodama, N. Seki, S. Masahiro, T. Kusumoto, K. Nakamura, A. Hongo, Y. Hiramatsu, D-dimer level as a risk factor for postoperative venous thromboembolism in Japanese women with gynecologic cancer, *Ann. Oncol.* 21 (2010) 1651–1656.
- [64] V.V. Kakkar, J.L. Balibrea, J. Martínez-González, P. Prandoni, CANBESURE Study Group, Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study, *J. Thromb. Haemost.* 8 (2010) 1223–1229.
- [65] J.N. Keith, T.W. Chong, D. Davar, A.G. Moore, A. Morris, M.L. Gimbel, The timing of preoperative prophylactic low-molecular-weight heparin administration in breast reconstruction, *Plast. Reconstr. Surg.* 132 (2013) 279–284.
- [66] J.W. Kim, E.J. Chun, S.I. Choi, D.J. Park, H.H. Kim, S.M. Bang, M.J. Kim, J.H. Lee, M.S. Lee, J.O. Lee, Y.J. Kim, J.H. Kim, J.S. Lee, K.W. Lee, A prospective study on the incidence of postoperative venous thromboembolism in Korean gastric cancer patients: an inquiry into the application of Western guidelines to Asian cancer patients, *PLoS One* 8 (2013) e61968.
- [67] S.M. Kim, J.M. Park, S.H. Shin, S.W. Seo, Risk factors for post-operative venous thromboembolism in patients with a malignancy of the lower limb, *Bone Joint J.* 95 (2013) 558–562.
- [68] S. Kumar, Z. Al-Wahab, S. Sarangi, J. Woelk, R. Morris, A. Munkarah, S.C. Dowdy, A. Mariani, W. Cliby, Risk of postoperative venous thromboembolism after minimally invasive surgery for endometrial and cervical cancer is low: a multi-institutional study, *Gynecol. Oncol.* 130 (2013) 207–212.
- [69] D.S. Kim, K.M. Park, Y.S. Won, J.Y. Kim, J.K. Lee, J.G. Kim, S.T. Oh, S.S. Jung, W.K. Kang, Occurrence and prognosis of symptomatic venous thromboembolism in colorectal cancer surgery patients, *Vasc. Specialist Int.* 30 (2014) 49–55.
- [70] Y. Kimura, E. Oki, K. Ando, H. Saeki, T. Kusumoto, Y. Maehara, Incidence of venous thromboembolism following laparoscopic surgery for gastrointestinal cancer: a single-center, prospective cohort study, *World J. Surg.* 40 (2016) 309–314.
- [71] Y. Kakei, M. Akashi, T. Hasegawa, T. Minamikawa, S. Usami, T. Komori, Incidence of venous thromboembolism after oral oncologic surgery with simultaneous reconstruction, *J. Oral Maxillofac. Surg.* 74 (2016) 212–217.
- [72] F. Kato, H. Takeuchi, S. Matsuda, H. Kawakubo, T. Omori, Y. Kitagawa, Incidence of and risk factors for venous thromboembolism during surgical treatment for esophageal cancer: a single-institution study, *Surg. Today* 46 (2016) 445–452.
- [73] B.J. Kim, R.W. Day, C.H. Davis, N. Narula, M.H. Kroll, C.W.D. Tzeng, T.A. Aloia, Extended pharmacologic thromboprophylaxis in oncologic liver surgery is safe and effective, *J. Thromb. Haemost.* 15 (2017) 2158–2164.
- [74] J.S. Kim, K.A. Mills, J. Fehniger, C. Liao, J.A. Hurteau, C.V. Kirschner, N.K. Lee, G.C. Rodriguez, S.D. Yamada, E.S. Diaz Moore, M.E. Tenney, Venous thromboembolism in patients receiving extended pharmacologic prophylaxis after robotic surgery for endometrial cancer, *Int. J. Gynecol. Cancer* 27 (2017) 1774–1782.
- [75] M. Kwietniak, T. Al-Amawi, T. Błazkowski, V. Sulzyc-Bielicka, J. Kładny, The usefulness of D-dimer in diagnosis and prediction of venous thromboembolism in patients with abdominal malignancy, *Pol. Przegl. Chir.* 89 (2017) 27–30.
- [76] I. Leibovitch, R.S. Foster, J.L. Wass, R.G. Rowland, R. Bihrlé, J.S. Little Jr., K.K. Kopecky, J.P. Donohue, Color Doppler flow imaging for deep venous thrombosis screening in patients undergoing pelvic lymphadenectomy and radical retropubic prostatectomy for prostatic carcinoma, *J. Urol.* 153 (1995) 1866–1869.
- [77] F.Y. Lee, W. Chu, R. Chan, Y.F. Leung, K.H. Liu, S.M. Ng, P.B. Lai, C. Metreweli, W.Y. Lau, Incidence of deep vein thrombosis after colorectal surgery in a Chinese population, *ANZ J. Surg.* 71 (2001) 637–640.
- [78] V. Lemaire, C. McCarthy, K. Kaplan, B. Mehrara, A.L. Pusic, P.G. Cordeiro, J.J. Disa, Venous thromboembolism following microsurgical breast reconstruction: an objective analysis in 225 consecutive patients using low-molecular-weight heparin prophylaxis, *Plast. Reconstr. Surg.* 127 (2011) 1399–1406.
- [79] J.N. Ladders, S. Parmar, N.L. Stienen, T.J. Martin, K.H. Karagozlu, M.W. Heymans, T. Forouzanfar, Incidence of symptomatic venous thromboembolism in oncological oral and maxillofacial operations: retrospective analysis, *Br. J. Oral Maxillofac. Surg.* 53 (2015) 244–250.
- [80] E. Lee, S.B. Kang, S.I. Choi, E.J. Chun, M.J. Kim, D.W. Kim, H.K. Oh, M.H. Ihn, J.W. Kim, S.M. Bang, J.O. Lee, Y.J. Kim, J.H. Kim, J.S. Lee, K.W. Lee, Prospective study on the incidence of postoperative venous thromboembolism in Korean patients with colorectal cancer, *Cancer Res. Treat.* 48 (2016) 978–989.
- [81] J. Liu, N. Wang, Y. Chen, R. Lu, X. Ye, Thrombelastography coagulation index may be a predictor of venous thromboembolism in gynecological oncology patients, *J. Obstet. Gynaecol. Res.* 43 (2017) 202–210.
- [82] A. Marassi, G. Balzano, G. Mari, S.V. D'Angelo, P. Della Valle, V. Di Carlo, A. D'Angelo, Prevention of postoperative deep vein thrombosis in cancer patients. A randomized trial with low molecular weight heparin (CY 216), *Int. Surg.* 78 (1993) 166–170.
- [83] R.S. McLeod, W.H. Geerts, K.W. Sniderman, C. Greenwood, R.C. Gregoire, B.M. Taylor, R.E. Silverman, K.G. Atkinson, M. Burnstein, J.C. Marshall, C.J. Burul, D.R. Anderson, T. Ross, S.R. Wilson, P. Barton, Canadian Colorectal Surgery DVT Prophylaxis Trial investigators, Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial, *Ann. Surg.* 233 (2001) 438–444.
- [84] D.P. Mason, M.A. Quader, E.H. Blackstone, J. Rajeswaran, M.M. Decamp, S.C. Murthy, A.K. Quader, T.W. Rice, Thromboembolism after pneumonectomy for malignancy: an independent marker of poor outcome, *J. Thorac. Cardiovasc. Surg.* 131 (2006) 711–718.
- [85] M.A. Martino, E. Borges, E. Williamson, S. Siegfried, A.B. Cantor, J. Lancaster, W.S. Roberts, M.S. Hoffman, Pulmonary embolism after major abdominal surgery in gynecologic oncology, *Obstet. Gynecol.* 107 (2006) 666–671.
- [86] M. Maksimović, M. Maksimović, M. Gojnić, Z. Maksimović, S. Petković, A. Ljubić, A. Stefanović, K. Jeremić, Surgical treatment of ovarian cancer and early detection of venous thromboembolism, *Eur. J. Gynaecol. Oncol.* 32 (2011) 415–418.
- [87] R.P. Merkow, K.Y. Bilimoria, M.D. McCarter, M.E. Cohen, C.C. Barnett, M.V. Raval, J.A. Caprini, H.S. Gordon, C.Y. Ko, D.J. Bentrem, Post-discharge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis, *Ann. Surg.* 254 (2011) 131–137.
- [88] K. Mita, H. Ito, R. Murabayashi, K. Sueyoshi, H. Asakawa, M. Nabetani,

- A. Kamasako, K. Koizumi, T. Hayashi, Postoperative bleeding complications after gastric cancer surgery in patients receiving anticoagulation and/or antiplatelet agents, *Ann. Surg. Oncol.* 19 (2012) 3745–3752.
- [89] B. Mokri, A. Mariani, J.A. Heit, A.L. Weaver, M.E. McGree, J.R. Martin, M.A. Lemens, W.A. Cliby, J.N. Bakkum-Gomez, Incidence and predictors of venous thromboembolism after debulking surgery for epithelial ovarian cancer, *Int. J. Gynecol. Cancer* 23 (2013) 1684–1691.
- [90] Z. Moghadamyeghaneh, M.H. Hanna, J.C. Carmichael, N.T. Nguyen, M.J. Stamos, A nationwide analysis of postoperative deep vein thrombosis and pulmonary embolism in colon and rectal surgery, *J. Gastrointest. Surg.* 18 (2014) 2169–2177.
- [91] A. Morimoto, Y. Ueda, T. Yokoi, Y. Tokizawa, K. Yoshino, M. Fujita, T. Kimura, E. Kobayashi, S. Matsuzaki, T. Egawa-Takata, K. Sawada, T. Tsutsui, T. Kimura, Perioperative venous thromboembolism in patients with gynecological malignancies: a lesson from four years of recent clinical experience, *Anticancer Res.* 34 (2014) 3589–3595.
- [92] J.T. Martin, A.L. Mahan, V.A. Ferraris, S.P. Saha, T.W. Mullett, J.B. Zwischenberger, C.W. Tzeng, Identifying esophagectomy patients at risk for pre-discharge versus post-discharge venous thromboembolism, *Ann. Thorac. Surg.* 100 (2015) 932–938.
- [93] M. Rajabi Mashhadi, R. Bagheri, M.J. Ghamari, S. Shahidsales, M. Salehi, R. Shahkaram, M.R. Majidi, S. Sheibani, The effect of neoadjuvant therapy on early complications of esophageal cancer surgery, *Iran. J. Otorhinolaryngol.* 27 (2015) 279–284.
- [94] H. Mahdi, Q. Aljebori, D. Lockart, L. Moulton, Risk of venous thromboembolism after laparoscopic surgery for gynecologic malignancy, *J. Minim. Invasive Gynecol.* 23 (2016) 1057–1062.
- [95] S. Mantziari, C. Gronnier, A. Pasquer, J. Gagnière, J. Théreaux, N. Demartines, M. Schäfer, C. Mariette, FREGAT Working Group–FRENCH–AFC, Incidence and risk factors related to symptomatic venous thromboembolic events after esophagectomy for cancer, *Ann. Thorac. Surg.* 102 (2016) 979–984.
- [96] T. Melancon, C. Bivona, S. Klenke, M. Rockey, J. Huh, D. Henry, D. Grauer, M. Al-Kasspoles, G. Johnson, E. Reynolds, J. Chapman, Comparison of postoperative venous thromboembolism incidence in gastrointestinal and gynecologic solid tumors, *Thromb. Res.* 147 (2016) 104–107.
- [97] H. Nathan, M.J. Weiss, G.A. Soff, M. Stempel, R.P. Dematteo, P.J. Allen, T.P. Kingham, Y. Fong, W.R. Jarnagin, M.I. D'Angelica, Pharmacologic prophylaxis, postoperative INR, and risk of venous thromboembolism after hepatectomy, *J. Gastrointest. Surg.* 18 (2014) 295–302.
- [98] C. Nagata, H. Tanabe, S. Takakura, C. Narui, M. Saito, N. Yanaiharu, A. Okamoto, Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy, *J. Obstet. Gynaecol. Res.* 41 (2015) 1440–1448.
- [99] D.W. Nelson, V.V. Simianu, A.L. Bastawrous, R.P. Billingham, A. Fichera, M.G. Florence, E.K. Johnson, M.G. Johnson, R.C. Thirlby, D.R. Flum, S.R. Steele, Thromboembolic complications and prophylaxis patterns in colorectal surgery, *JAMA Surg.* 150 (2015) 712–720.
- [100] I. Nwaogu, Y. Yan, J.A. Margenthaler, T.M. Myckatyn, Venous thromboembolism after breast reconstruction in patients undergoing breast surgery: an American College of Surgeons NSQIP analysis, *J. Am. Coll. Surg.* 220 (2015) 886–893.
- [101] H. Onarheim, T. Lund, A. Heimdal, B. Arnesjö, A low molecular weight heparin (KABI 2165) for prophylaxis of postoperative deep venous thrombosis, *Acta Chir. Scand.* 152 (1986) 593–596.
- [102] M. Ouassif, C. Frascini, D. Mege, L. Panicot-Dubois, L. Boiron, L. Dahan, P. Deboudeau, C. Dubois, D. Farge, I. Sieleznoff, Impact of venous thromboembolism on the natural history of pancreatic adenocarcinoma, *Hepatobiliary Pancreat. Dis. Int.* 14 (2015) 436–442.
- [103] H.S. Ong, S. Gokavarapu, L. Al-Qamachi, M.Y. Yin, L.X. Su, T. Ji, C.P. Zhang, Justification of routine venous thromboembolism prophylaxis in head and neck cancer reconstructive surgery, *Head Neck* 39 (2017) 2450–2458.
- [104] T. Patel, W. Kirby, G. Hruby, M.C. Benson, J.M. McKiernan, K. Badani, Heparin prophylaxis and the risk of venous thromboembolism after robotic-assisted laparoscopic prostatectomy, *BJU Int.* 108 (2011) 729–732.
- [105] A. Peedicayil, A. Weaver, X. Li, E. Carey, W. Cliby, A. Mariani, Incidence and timing of venous thromboembolism after surgery for gynecological cancer, *Gynecol. Oncol.* 121 (2011) 64–69.
- [106] A. Pant, D. Liu, J. Schink, J. Lurain, Venous thromboembolism in advanced ovarian cancer patients undergoing frontline adjuvant chemotherapy, *Int. J. Gynecol. Cancer* 24 (2014) 997–1002.
- [107] K. Parry, A.H. Sadeghi, S. van der Horst, J. Westerink, J.P. Ruurda, R. van Hillegersberg, Intermittent pneumatic compression in combination with low-molecular weight heparin in the prevention of venous thromboembolic events in esophageal cancer surgery, *J. Surg. Oncol.* 115 (2017) 181–185.
- [108] S. Rakić, P. Pesko, M. Jagodić, M.S. Dunjić, Z. Maksimović, Venous thromboprophylaxis in oesophageal cancer surgery, *Br. J. Surg.* 80 (1993) 1145–1146.
- [109] C.E. Reinke, R.A. Hadler, G.C. Karakousis, D.L. Fraker, R.R. Kelz, Does the presence of thyroid cancer increase the risk of venous thromboembolism in patients undergoing thyroidectomy? *Surgery* 150 (2011) 1275–1285.
- [110] K.E. Rollins, C.J. Peters, P.M. Safranek, H. Ford, T.P. Baglin, R.H. Hardwick, Venous thromboembolism in oesophago-gastric carcinoma: incidence of symptomatic and asymptomatic events following chemotherapy and surgery, *Eur. J. Surg. Oncol.* 37 (2011) 1072–1077.
- [111] C.E. Reinke, G.C. Karakousis, R.A. Hadler, J.A. Drebin, D.L. Fraker, R.R. Kelz, Incidence of venous thromboembolism in patients undergoing surgical treatment for malignancy by type of neoplasm: an analysis of ACS-NSQIP data from 2005 to 2010, *Surgery* 152 (2012) 186–192.
- [112] R. Simanek, R. Vormittag, M. Hassler, K. Roessler, M. Schwarz, C. Zielinski, I. Pabinger, C. Marosi, Venous thromboembolism and survival in patients with high-grade glioma, *Neuro-Oncology* 9 (2007) 89–95.
- [113] F.P. Secin, T. Jiborn, A.S. Bjartell, G. Fournier, L. Salomon, C.C. Abbou, G.P. Haber, I.S. Gill, L.E. Crocitto, R.A. Nelson, J.R. Cansino Alcaide, L. Martínez-Pineiro, M.S. Cohen, I. Tuerk, C. Schulman, T. Gianduzzo, C. Eden, R. Baumgartner, J.A. Smith, K. Entezari, R. van Velthoven, G. Janetschek, A.M. Serio, A.J. Vickers, K. Toujzer, B. Guillonnet, Multi-institutional study of symptomatic deep venous thrombosis and pulmonary embolism in prostate cancer patients undergoing laparoscopic or robot-assisted laparoscopic radical prostatectomy, *Indian J. Gastroenterol.* 27 (2008) 71–73.
- [114] P.J. Shukla, R. Siddachari, S. Ahire, S. Arya, S. Ramani, S.G. Barreto, S. Gupta, S.V. Shrikhande, P. Jagannath, L.J. Desouza, Postoperative deep vein thrombosis in patients with colorectal cancer, *Eur. Urol.* 53 (2008) 134–145.
- [115] M. Sakon, T. Kobayashi, T. Shimazui, Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study, *Thromb. Res.* 125 (2010) e65–e70.
- [116] J. Schmitges, Q.D. Trinh, M. Sun, F. Abdollah, M. Bianchi, L. Budäus, G. Salomon, T. Schlomm, P. Perrotte, S.F. Shariat, F. Montorsi, M. Menon, M. Graefen, P.I. Karakiewicz, Venous thromboembolism after radical prostatectomy: the effect of surgical caseload, *BJU Int.* 110 (2012) 828–833.
- [117] K. Sugimachi, H. Tajiri, N. Kinjo, M. Ikebe, H. Wang, K. Tanaka, J. Tanaka, S. Tsukamoto, S. Mii, H. Higashi, Incidence and predictors of enoxaparin thrombosis after abdominal oncologic surgery: prospective Doppler ultrasound screening, *J. Surg. Res.* 178 (2012) 657–661.
- [118] S. Sandadi, S. Lee, A. Walter, G.J. Gardner, N.R. Abu-Rustum, Y. Sonoda, C.L. Brown, E. Jewell, R. Parameswaran, R.R. Barakat, M.M. Leitao Jr., Incidence of venous thromboembolism after minimally invasive surgery in patients with newly diagnosed endometrial cancer, *Obstet. Gynecol.* 120 (2012) 1077–1083.
- [119] K.M. Schmeler, G.L. Wilson, K. Cain, M.F. Munsell, P.T. Ramirez, P.T. Soliman, A.M. Nick, M. Frumovitz, R.L. Coleman, M.H. Kroll, C.F. Levenback, Venous thromboembolism (VTE) rates following the implementation of extended duration prophylaxis for patients undergoing surgery for gynecologic malignancies, *Gynecol. Oncol.* 128 (2013) 204–208.
- [120] F. Saadeh, L. Norris, S. O'Toole, N. Gleeson, Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 170 (2013) 214–218.
- [121] C.H. Sung, J.H. Shim, C.H. Park, K.Y. Song, Low molecular-weight heparin for thromboprophylaxis in patients undergoing gastric cancer surgery: an experience from one Korean institute, *Ann. Surg. Treat. Res.* 86 (2014) 22–27.
- [122] K.Y. Song, H.M. Yoo, E.Y. Kim, J.I. Kim, H.W. Yim, H.M. Jeon, C.H. Park, Optimal prophylactic method of venous thromboembolism for gastrectomy in Korean patients: an interim analysis of prospective randomized trial, *Ann. Surg. Oncol.* 21 (2014) 4232–4238.
- [123] N. Sermathanasawadi, R. Thangrod, K. Hongku, C. Wongwanit, C. Ruangsetakit, K. Chinsakchai, C. Leelaphatanadit, S. Therasakvichya, P. Mutirangura, Prevalence of perioperative asymptomatic proximal deep vein thrombosis in Thai gynecologic cancer patients, *J. Med. Assoc. Thai.* 97 (2014) 153–158.
- [124] A.J. Sun, H. Djaladat, A. Schuckman, G. Miranda, J. Cai, S. Daneshmand, Venous thromboembolism following radical cystectomy: significant predictors, comparison of different anticoagulants and timing of events, *J. Urol.* 193 (2015) 565–569.
- [125] V.A. Singh, L.M. Yong, A. Vijayanathan, Is DVT prophylaxis necessary after oncology lower limb surgery? A pilot study, *Springerplus* 5 (2016) 943.
- [126] S. Tsutsumi, R. Yajima, Y. Tabe, T. Takaaki, F. Fujii, H. Morita, W. Kigure, T. Kato, H. Yamauchi, T. Suto, T. Asao, H. Kuwano, The efficacy of fondaparinux for the prophylaxis of venous thromboembolism after resection for colorectal cancer, *Hepato-Gastroenterology* 59 (2012) 2477–2479.
- [127] L. Thai, K. McCarn, W. Stott, T. Watts, M.K. Wax, P.E. Andersen, N.D. Gross, Venous thromboembolism in patients with head and neck cancer after surgery, *Head Neck* 35 (2013) 4–9.
- [128] B.H. Tran, T.J. Nguyen, B.H. Hwang, E.N. Vidar, G.B. Davis, L.S. Chan, K. Woo, A.K. Wong, Risk factors associated with venous thromboembolism in 49,028 mastectomy patients, *Breast* 22 (2013) 444–448.
- [129] M.K. Tollefson, R.J. Karnes, L. Rangel, R. Carlson, S.A. Boorjian, Blood type, lymphadenectomy and blood transfusion predict venous thromboembolic events following radical prostatectomy with pelvic lymphadenectomy, *J. Urol.* 191 (2014) 646–651.
- [130] S.I. Tyrirtzis, A. Wallerstedt, G. Steineck, T. Nyberg, J. Hugosson, A. Bjartell, U. Wilderäng, T. Thorsteinsdottir, S. Carlsson, J. Stranne, E. Haglund, N.P. Wiklund, LAPPRO Steering Committee, Thromboembolic complications in 3,544 patients undergoing radical prostatectomy with or without lymph node dissection, *J. Urol.* 193 (2015) 117–125.
- [131] K. Tokuhara, H. Matsushima, Y. Ueyama, K. Nakatani, K. Yoshioka, M. Kon, Efficacy and safety of thromboembolism prophylaxis with fondaparinux in Japanese colorectal cancer patients undergoing laparoscopic surgery: a phase II study, *Int. J. Surg.* 42 (2017) 203–208.
- [132] A.A. Vandiac, N.G. Cowan, Y. Chen, R.E. Anderson, M.J. Conlin, J.C. La Rochelle, C.L. Amling, T.M. Koppie, Timing, incidence and risk factors for venous thromboembolism in patients undergoing radical cystectomy for malignancy: a case for extended duration pharmacological prophylaxis, *J. Urol.* 191 (2014) 943–947.
- [133] M.C. Vedovati, C. Becattini, F. Rondelli, R.E. Anderson, M.J. Conlin, J.C. La Rochelle, E. Mariani, O. Flamini, S. Pucciarelli, A. Donini, G. Agnelli, A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer, *Ann. Surg.* 259 (2014) 665–669.
- [134] F.J. Vázquez, M.S. Bilbao, J. Saimovici, C. Vaccaro, Improving adherence rate of extended prophylaxis for venous thromboembolic disease after abdominal and

- pelvic oncologic surgery: a pilot educational study, *Clin. Appl. Thromb. Hemost.* 21 (2015) 750–754.
- [135] D. Weida, L.Y. Patrick, Y.W. Andrew, Is it safe to perform operation for colorectal malignancy in Chinese patients without DVT prophylaxis? An 8-year experience from a regional hospital in Hong Kong, *Chin. Med. J.* 123 (2010) 1973–1975.
- [136] A. Weinberg, J. Wright, C. Deibert, Y.S. Lu, D. Hershman, A. Neugut, B. Spencer, Nationwide practice patterns for the use of venous thromboembolism prophylaxis among men undergoing radical prostatectomy, *World J. Urol.* 32 (2014) 1313–1321.
- [137] J.D. Wright, L. Chen, S. Jorge, W.M. Burke, A.I. Tergas, J.Y. Hou, J.C. Hu, A.I. Neugut, C.V. Ananth, D.L. Hershman, Prescription of extended-duration thromboprophylaxis after high-risk, abdominopelvic cancer surgery, *Gynecol. Oncol.* 141 (2016) 531–537.
- [138] E.S. Xenos, H.D. Vargas, D.L. Davenport, Association of blood transfusion and venous thromboembolism after colorectal cancer resection, *Thromb. Res.* 129 (2012) 568–572.
- [139] T.J. Yates, M. Abouljoud, A. Lambing, P. Kuriakose, Risk of venous thrombosis in patients with hepatic malignancies undergoing surgical resection, *Indian J. Gastroenterol.* 27 (2008) 159–161.
- [140] Y. Yamashita, Y. Bekki, D. Imai, T. Ikegami, T. Yoshizumi, T. Ikeda, H. Kawanaka, A. Nishie, K. Shirabe, Y. Maehara, Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer, *Thromb. Res.* 134 (2014) 826–831.
- [141] H.Y. Yhim, M.J. Jang, S.M. Bang, K.H. Kim, Y.K. Kim, S.H. Nam, S.H. Bae, S.H. Kim, Y.C. Mun, I. Kim, C.W. Jung, D. Oh, Incidence of venous thromboembolism following major surgery in Korea: from the Health Insurance Review and Assessment Service database, *J. Thromb. Haemost.* 12 (2014) 1035–1043.
- [142] Y. Yamaoka, M. Ikeda, M. Ikenaga, N. Haraguchi, M. Miyake, M. Sekimoto, Safety and efficacy of fondaparinux for prophylaxis of venous thromboembolism after colorectal cancer resection: a propensity score matched analysis, *Dig. Surg.* 32 (2015) 190–195.
- [143] S. Ye, W. Zhang, J. Yang, D. Cao, H. Huang, M. Wu, J. Lang, K. Shen, Pattern of venous thromboembolism occurrence in gynecologic malignancy: incidence, timing, and distribution a 10-year retrospective single-institutional study, *Medicine (Baltimore)* 94 (2015) e2316.
- [144] T. Yanagita, H. Kusanagi, Safety and effectiveness of enoxaparin as venous thromboembolism prophylaxis after gastric cancer surgery in Japanese patients, *Am. Surg.* 82 (2016) 1232–1237.
- [145] S. Ziomek, R.C. Read, H.G. Tobler, J.E. Harrell Jr., J.C. Gocio, L.M. Fink, T.J. Ranval, E.J. Ferris, D.L. Harshfield, D.R. McFarland, Thromboembolism in patients undergoing thoracotomy, *Ann. Thorac. Surg.* 56 (1993) 223–226.
- [146] S.G. Zammar, B.A. Pockaj, C.C. Stucky, N. Wasif, R.J. Gray, Is forgoing chemical venous thromboembolism prophylaxis for women undergoing breast-conserving surgery for breast cancer safe? *Am. J. Surg.* 212 (2016) 1162–1166.
- [147] G.H. Lyman, K. Bohlke, A.A. Khorana, N.M. Kuderer, A.Y. Lee, J.I. Arcelus, E.P. Balaban, J.M. Clarke, C.R. Flowers, C.W. Francis, L.E. Gates, A.K. Kakkar, N.S. Key, M.N. Levine, H.A. Liebman, M.A. Tempero, S.L. Wong, M.R. Somerfield, A. Falanga, Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014, *J. Clin. Oncol.* 33 (2015) 654–656.
- [148] M.K. Gould, D.A. Garcia, S.M. Wren, P.J. Karanicolas, J.I. Arcelus, J.A. Heit, C.M. Samama, Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed., 141 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest*, 2012, pp. e227S–e277S.
- [149] Q. Guo, B. Huang, J. Zhao, Y. Ma, D. Yuan, Y. Yang, X. Du, Perioperative pharmacological thromboprophylaxis in patients with cancer: a systematic review and meta-analysis, *Ann. Surg.* 265 (2017) 1087–1093.
- [150] I. Pabinger, J. Thaler, C. Ay, Biomarkers for prediction of venous thromboembolism in cancer, *Blood* 122 (2013) 2011–2018.
- [151] L. Zhao, Y. Bi, J. Kou, J. Shi, D. Piao, Phosphatidylserine exposing-platelets and microparticles promote procoagulant activity in colon cancer patients, *J. Exp. Clin. Cancer Res.* 35 (2016) 54.
- [152] M.L. Papa, F. Capasso, L. Pudore, S. Torre, S. Mango, V. Russo, P. Delrio, R. Palaia, F. Ruffolo, M.D. d'Eufemia, D. De Lucia, M. Napolitano, P. Di Micco, V. Parisi, Thromboelastographic profiles as a tool for thrombotic risk in digestive tract cancer, *Exp. Oncol.* 29 (2007) 111–115.
- [153] D. De Lucia, F. De Francesco, R. Marotta, G. Maisto, D. Meo, M. Sessa, M. Misso, M. Galante, T. Russo, O. Pignalosa, M. Napolitano, M.L. Papa, A. Niglio, P. Di Micco, Phenotypic APC resistance as a marker of hypercoagulability in primitive cerebral lymphoma, *Exp. Oncol.* 27 (2005) 159–161.
- [154] A.A. Khorana, G.C. Connolly, Assessing risk of venous thromboembolism in the patient with cancer, *J. Clin. Oncol.* 27 (2009) 4839–4847.
- [155] G. Zallen, E.E. Moore, D.J. Ciesla, M. Brown, W.L. Biffi, C.C. Silliman, Stored red blood cells selectively activate human neutrophils to release IL-8 and secretory PLA2, *Shock* 13 (2000) 29–33.
- [156] A.W. Nielsen, M.C. Helm, T. Kindel, R. Higgins, K. Lak, Z.M. Helmen, Perioperative bleeding and blood transfusion are major risk factors for venous thromboembolism following bariatric surgery, *Surg. Endosc.* 32 (2018) 2488–2495.
- [157] A. Fagarasanu, G.S. Alotaibi, R. Hrimiuc, A.Y. Lee, C. Wu, Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: a systematic review and meta-analysis, *Ann. Surg. Oncol.* 23 (2016) 1422–1430.