SPECIAL ARTICLE

Risks, diagnosis, and management of recurrent cancer-associated thrombosis (CAT): a narrative review

Kodwo Dickson[1] · Kwame Koom-Dadzie[1] · Norman Brito-Dellan[1] · Carmen Escalante[2]

Abstract

This paper aims to provide a narrative review of the risks, diagnosis, and management of recurrent venous thromboembolism (VTE) in cancer patients. There is an established association between cancer and VTE, with cancer being a major risk factor for VTE. A history of VTE, short duration of oral anticoagulation, and a proximal DVT are all associated with increased risk for recurrent VTE. Studies have shown that certain cancers (e.g., metastatic genitourinary, lung, and colorectal cancers) are associated with recurrent VTE. Published literature shows that cancer is prothrombotic, and various mechanisms have been postulated as pathways for increased thrombogenesis and hence recurrent VTE in cancer. The symptoms, signs, laboratory information, and imaging results for the diagnosis of recurrent VTE are similar to those of an initial VTE. Management of recurrent VTE involves using low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC). Vitamin K antagonists (VKA) or inferior vena cava (IVC) filters are less commonly used.

Keywords Recurrent venous thromboembolism · Cancer · Cancer-associated thrombosis · Low molecular weight heparin · Direct oral anticoagulants · Vitamin K antagonist

Introduction

Case report

A 68-year-old man was diagnosed with sigmoid colon adenocarcinoma 2 months before presentation and for which he was on chemotherapy. Five weeks prior to his initial visit to the emergency room, he noticed the sudden onset of left calf pain without any preceding trauma. His initial physical exam revealed a tender and swollen left calf. Left leg venous ultrasonography demonstrated deep vein thrombosis (DVT) of the left popliteal vein. He was prescribed enoxaparin 1 mg/kg subcutaneously every 12 h; he adhered to this regimen. A month later, he presented back to the emergency room with progressive swelling in his left leg and left thigh, accompanied by pain. Physical examination revealed a sinus tachycardia of 122 beats per minute and a swollen, tender left lower extremity. Distal pulses were adequate and equal in both lower extremities. A 12-lead electrocardiogram (EKG) confirmed sinus tachycardia. Venous ultrasonography revealed an extension of the left popliteal DVT with a new DVT in his left thigh. Computed tomography of the chest with contrast did not show pulmonary embolism (PE). After an expert recommendation, the enoxaparin dose was increased by 20% to manage recurrent venous thromboembolism. This case is unique as it demonstrates the challenges faced when managing recurrent venous thromboembolism despite adherence to therapeutic anticoagulation.

Purpose of review

We conducted a literature search on diagnosing and managing recurrent cancer-associated thrombosis (CAT) in major electronic literature databases (PubMed, EMBASE, and Google scholar). Queries included recurrent venous thromboembolism (VTE) and cancer, VTE treatment and cancer, and recurrent VTE treatment and cancer. Only studies in English were considered, and no other limits were applied. Articles were chosen based on their relevance after

✉ Kodwo Dickson
kbdickson@mdanderson.org

1 Department of Hospital Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

2 Department of General Internal Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

discussion among the authors. We excluded case reports. The objectives of this manuscript were to give an up-to-date review of current literature on aspects of recurrent CAT, including risk factors, diagnosis, management, and controversies in management. Additional objectives included comparing low molecular weight heparins and direct oral anticoagulants, including their risks and benefits, the role of an inferior vena cava filter (IVC), and future perspectives.

Risk factors for VTE recurrence in cancer

Cancer is a major risk factor for DVT and PE, and the association between VTE and cancer is well established [1]. It is estimated that 20–30% of all first-time VTE events are cancer-associated. For example, White et al. identified CAT in approximately 20% of patients among a cohort of 21,002 patients hospitalized with incident VTE in 1996, who were identified from the California Discharge Data Set [2]. In the Tromsø study, a population-based prospective follow-up study of more than 26,000 participants followed from 1994 to 2007 to assess the incidence of VTE, 462 patients had a first-ever VTE, and 106 (23%) of them had active cancer [3].

VTE is known to have a recurrence rate of 5–10% per year [4]. To define risk factors for recurrent VTE in cancer patients, a risk assessment model known as the Ottawa score was developed [5]. It combines four clinical patient characteristics (sex, cancer type and stage, and history of VTE) and allows stratification of cancer patients according to their VTE recurrence risk. The Ottawa score has been successfully validated in more than 800 patients from 2 prospective VTE treatment studies. However, management studies and impact analyses are required before introducing this risk assessment model into routine clinical practice [6].

The site of DVT, history of VTE, duration of oral anticoagulation therapy, and sex all affect the risk of recurrent VTE. In addition, poor adherence to anticoagulation, temporary cessation, inadequate dosage, and heparin-induced thrombocytopenia can all lead to recurrent VTE in cancer patients [7]. Proximal DVT, short duration of oral anticoagulation therapy, and history of VTE independently predicted an increased risk of recurrent events in a multivariate survival analysis, and patients with postoperative DVT had a lower recurrence rate. In a population-based cohort study, the overall incidence rate for recurrence was 9.6 (95% CI 8.8–10.4) per 100 person-years, with a peak at 22.1 in the first 6 months. Recurrence rates were similar after initial pulmonary embolism and after initial DVT [8]. The risk of recurrent VTE also varies by sex and with a prior history of recurrent VTE. In a study of 826 patients following an average of 36 months after a first episode of spontaneous VTE and the withdrawal of oral anticoagulants, the risk of recurrent VTE was higher among men than that of women [9]. There is also a risk of further recurrence after an initial recurrence of VTE, shown in a retrospective cohort study of 70 cancer patients who had VTE recurrence while receiving anticoagulant treatment. At the time of the recurrence, 67% of patients were receiving low-molecular-weight heparin (LMWH), and 33% were receiving a vitamin K antagonist (VKA). The recurrence was treated with either the initiation of LMWH treatment at a therapeutic dose in patients on VKA or with dose escalation of LMWH in patients already receiving LMWH, from subtherapeutic to therapeutic dose or from therapeutic dose to 120% of the initial dose. During a minimum follow-up of 3 months, the incidence of further recurrence was 9.9% per 100 patient-years, with a median survival rate of 11.4 months [10].

Certain cancers and metastatic disease are more associated with initial and subsequent VTE recurrences. In an observational study of 212 patients who were followed for a maximum of 3 months, the most common sites of cancer were genitourinary (24%), lung (21%), and colorectal (17%). In 59% of patients, the cancer type was adenocarcinoma, and in 73% of patients, the cancer was metastatic. At the time of the breakthrough event, 70% of patients were being treated with LMWH and 27% with VKA. The most common LWMH was dalteparin (57%), followed by enoxaparin (24%). Anticoagulant intensity at the time of recurrence was therapeutic or supratherapeutic in 70% of the patients. Management strategies to treat the recurrent event were extremely heterogeneous. In the acute phase (defined as the first week of treatment), about 25% of patients were switched to a different drug (in most cases from VKA to LMWH), and 31% of patients were continued on the same drug at increased doses. After the first week, about 25% of patients continued to receive anticoagulant treatment at higher doses. During the 3 months of follow-up, 24 patients (11%) had a new recurrence of VTE. The risk of recurrence was not different between patients who had their anticoagulant intensity unchanged versus those with intensity increased. However, the risk of a new recurrence was higher in patients on VKA (29%) than in patients on LMWH (9%) (hazard ratio 0.28; 95% CI 0.11 to 0.70). Recurrences were more common in patients with lung and pancreatic cancer. These findings confirm the high risk of recurrence during anticoagulant treatment in cancer patients with VTE and support the use of LMWH over VKA but do not clarify the need for dose escalation [11]. Prandoni et al. also showed an association between the extent of cancer and the risk of recurrent VTE. This was demonstrated by an almost fivefold risk of CAT in extensive cancer compared with a 2- to threefold increase in risk in patients with less extensive cancer. The frequency of recurrent VTE per 100 patient-years was 54.1 in patients with extensive neoplastic disease, 44.1 in patients with moderately extensive disease, and 14.5 in patients with less extensive disease.

Several other factors should be considered in evaluating VTE risk in cancer patients. IVC filters placed to prevent pulmonary embolism have been associated with recurrent CAT [12]. There is limited published information on the efficacy of IVC filter insertion and recurrent VTE, despite adequate anticoagulant treatment remaining one of the few indications for placing the filter [7] [13]. Other studies have shown that surgical intervention to treat cancer presents a higher risk of a complication of thrombosis, which is further enhanced by prolonged immobilization. Also, central vein catheters, especially those with peripheral access, can increase the risk of thrombosis.

Pathophysiology

Studies show that cancer is widely prothrombotic [14]. The main mechanisms that have been postulated for VTE etiology in cancer include tumor production of pro-coagulants, tumor production of inflammatory cytokines, and the interaction between tumor cells, blood cells, and endothelial damage, which is enhanced by anticancer therapy [15]. The increased risk of recurrent CAT can also be explained by an increase in the release of pro-coagulants by the tumor cells, rendering patients with cancer resistant to the usual intensities of anticoagulants [11]. Prandoni et al. also showed an association between the extent of cancer and the risk of recurrent VTE. This was demonstrated by an almost five-fold risk of CAT in extensive cancer compared with a 2- to threefold increase in risk in patients with less extensive cancer. The frequency of recurrent VTE per 100 patient-years was 54.1 in patients with extensive neoplastic disease, 44.1 in patients with moderately extensive disease, and 14.5 in patients with less extensive disease. Immobilization due to general deconditioning compounds is the risk of VTE.

Cancer patients also have increased expression of intrinsic factor and activation of factors VII and XII and reduction of natural anticoagulants (protein C, protein S, and antithrombin), impairment of fibrinolysis, and platelet aggregation [12]. Other pro-coagulant activation pathways include monocytic tissue factor expression responsive to cytokines [16]. Congenital risk factors such as factor V and prothrombin gene mutation have also shown to be significant risk factors for thrombosis in cancer patients [17].

Vessel wall changes can occur due to bulky tumors directly compressing or infiltrating external to the vessel wall [16]. These changes can also occur through blood and lymphatic dissemination of cancer that leads to metastatic deposition of tumor cells. The disruption of the endothelium allows for tumor neoangiogenesis, owing to an environment of decreased endothelial anticoagulant [16]. The incidence of VTE is also increased with anticancer therapy, including chemotherapy [15]. VTE can also be an adverse effect of hormonal agents and drugs with antiangiogenic activity [12].

Clinical manifestations

The symptoms of recurrent VTE are similar to the initial presentation of a VTE. The typical symptoms of DVT are pain, swelling, redness, and increased warmth in the affected extremity. Physical examination may reveal a painful limb with or without cyanosis if acute, a palpable and tender cord or area, engorged superficial vein(s), and swelling of that extremity in the region distal to the DVT. For portal vein thrombosis, the primary manifestation may be abdominal pain.

A patient with acute PE may present with sudden-onset dyspnea, pleuritic chest pain, cough with or without hemoptysis, wheezing, fast palpitations, and syncope in severe cases. Common signs of acute PE include tachypnea, tachycardia, crackles on lung auscultation, an accentuated pulmonic component of the second heart sound (P2), and jugular venous distension, with hypotension in severe cases. In general, the diagnosis is proven in less than 25% of cancer patients who present with a high clinical suspicion for VTE. In addition, more than 50% of cancer patients with proven acute or subacute VTE do not have typical symptoms or signs. Many do not have symptoms at all.

Diagnosis

Symptoms and signs of recurrent VTE are variable and can be nonspecific, and this remains the case in the presence of cancer. Accurate confirmation or exclusion of VTE is based on laboratory results and objective imaging studies. Assessing the clinical probability of VTE and the severity of the patient's illness and the possibility of alternative diagnoses are also facilitated by an accurate and comprehensive history, a detailed and thorough physical examination, EKG, appropriate laboratory testing, chest x-rays, and a chest CT. To be diagnosed with recurrent CAT, the patient must have a history of VTE in CAT. In a PE, the serum troponin T or I as well as BNP (or N-terminal BNP) may be elevated. Venous doppler ultrasonography of an extremity is commonly used to diagnose recurrent DVT. A chest CT with contrast is commonly used to diagnose PE. Some clinical prediction rules, for example, the Wells score [18] and the Geneva score [19], have been used in the general population to assess the clinical probability of DVT and PE quantitatively. However, because of the lack of validation in the cancer population, these tools should not be used in patients with cancer. A Pulmonary Embolism Severity Index score is used to help determine the severity of PE, which in turn informs the triaging decision of whether to manage the case in the intensive care unit or on the medical floor.

Laboratory findings of VTE include leukocytosis, elevated lactate dehydrogenase, and increased erythrocyte

sedimentation rate. Troponin I and T levels and brain natriuretic peptide levels (BNP) or N-terminal BNP levels are usually elevated in individuals who have significant PE. These increased levels are associated with adverse outcomes [20, 21]. In patients with acute PE, arterial blood gas analysis usually shows respiratory alkalosis, hypoxemia, hypocapnia, and an elevated gradient between the alveolar oxygen and the arterial oxygen. Levels of D-dimer (degradation product of cross-linked fibrin) are often elevated in cancer patients whether they have an acute DVT or not; this limits the utility of a D-dimer level in evaluating VTE in patients with cancer [22].

Changes on an EKG are common but nonspecific in patients with acute PE. The most common EKG manifestation is sinus tachycardia and nonspecific ST-T wave abnormalities. Less commonly, the EKG may show atrial fibrillation or flutter, precordial T wave inversions, a right bundle branch block, or Q waves in the inferior leads.

Management

Management of recurrent CAT in a cancer patient already on therapeutic anticoagulation

LMWH has long been the standard treatment for VTE. It has been shown to reduce the risk of recurrent VTE at 6 months compared to VKA (relative risk 0.58, 95% CI 0.43–0.77; risk difference, 53 fewer per 1000) in a recent meta-analysis in cancer patients with acute VTE [23]. A Cochrane meta-analysis in cancer patients, which included the CLOT trial, showed that LMWH reduced the risk of recurrent VTE compared with VKA (hazard ratio 0.49, 95% CI 0.31–0.78). VKA and fondaparinux treatment are associated with a higher risk of recurrent thrombosis than LMWH in patients with CAT and, therefore, are not generally recommended [24, 25]. A retrospective cohort study by Ihaddadene et al. showed that recurrent CAT could be effectively and safely managed by switching to LMWH while taking VKA or by increasing the dose of the LMWH by 25%. In this study, 11% of patients were on VKA at the time of the first recurrence, and all patients had symptomatic improvement with a small risk of additional recurrent thrombosis (7.5%) or major bleeding [26].

It is recommended that patients receiving VKAs who have symptomatic recurrent VTE in the context of CAT switch to therapeutic weight-adjusted doses of LMWH as per the 2013 guidance statement from the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Hemostasis (ISTH) [24]. The ISTH guidance for patients with CAT also recommended continuing with LMWH at a higher dose, starting at 25% of the current dose for symptomatic recurrent VTE despite anticoagulation, or increasing to the therapeutic weight-adjusted dose

if the patient is receiving non-therapeutic dosing. It also recommended that all CAT with recurrent VTE be assessed 5–7 days after a dose escalation of anticoagulant therapy and that the peak anti-factor 10a (anti-FXa) level be used to estimate subsequent escalated dose [24]. Furthermore, additional dose increases should be considered for patients without symptomatic improvement or with additional recurrent CAT, despite initial LMWH dose escalation.

In a publication looking at the controversies and caveats in the treatment of CAT with LMWH and a direct oral anticoagulant (DOAC), the authors mentioned that no published data answer the question of what should be done for patients with cancer who have clot progression or recurrence while on treatment for VTE. However, the authors agreed that in patients who experience clot progression while taking a DOAC, it is reasonable to switch to a treatment regimen of LMWH such as dalteparin at 200 IU subcutaneously once daily for 1 month, followed by 150 IU subcutaneously daily thereafter, or enoxaparin at 1 mg/kg subcutaneously every 12 h. For patients who have thrombosis progression while receiving LMWH, one option would be to increase the dose by 20%, as suggested by Carrier et al. [24]. The authors also felt that it was reasonable to switch to a DOAC in this setting, given the possibility of noncompliance [27].

The 2021 American Society of Hematology guidelines for the management of recurrent VTE mention that in patients with recurrent VTE, despite treatment with therapeutic enoxaparin, either increasing LMWH to supratherapeutic levels or continuing the same dose is suggested. [28]. However, it is unknown whether outcomes are improved by increasing the anticoagulant dose, continuing the same dose, or transitioning to a different agent [28].

Comparison of DOACs and LMWH

A study by Raskob and colleagues showed that DOACs likely reduced the recurrence of VTE associated with cancer compared with LMWH with up to 12 months of follow-up [29]. Another meta-analysis that pooled results from the Hokusai VTE cancer and Select-D trials revealed a lower recurrence rate of VTE in CAT patients treated with DOACs compared with dalteparin. The rates of major bleeding and clinically relevant nonmajor bleeding were significantly higher in patients treated with a DOAC than those treated with dalteparin. However, this difference did not reach statistical significance (relative risk 0.65, 95% CI 0.42–1.01) [30–32]. Available evidence shows that the decision to start anticoagulation for recurrent VTE in CAT should balance the benefits and harm and consider the patient's preferences and values. Data comparing LMWH and DOACs for treatment are limited concerning recurrent VTE incidence in CAT patients. In another meta-analysis comparing the Hokusai VTE Cancer trial (an open-label, non-inferiority

trial) and the Select-D trial (a prospective randomized trial), the Hokusai VTE Cancer trial showed that patients receiving DOACs had a lower 6-month rate of recurrent VTE (42/725) than patients receiving the LMWH (64/727) [33]. This meta-analysis also showed that DOACs carry a higher risk for major bleeding (40/725) and clinically relevant nonmajor bleeding compared to LMWH (23/727).

Comparison of different DOACs

A limitation of guidance on using DOACs to treat recurrent VTE is the increased risk of bleeding and the lack of formal bleeding scores to help predict this risk in cancer patients. For treatment of CAT, the guidance from ISTH [34] describes the use of only specific DOACs, edoxaban, and rivaroxaban, as they were the only DOACs that had been compared in randomized controlled trials in CAT. This caution also stems from the differences in anticoagulant mechanisms of action (e.g., dabigatran is a direct thrombin inhibitor, while other classes are not). A systematic review and meta-analysis by Song et al. similarly reported that DOACs decreased the risk of VTE recurrence and DVT recurrence but did not decrease PE recurrence or fatal PE in cancer patients [35]. This study showed that rivaroxaban played an important role in decreasing recurrent VTE. However, the risks of major bleeding in this meta-analysis were not increased in the DOACs, while the risks of clinically relevant nonmajor bleeding were significantly elevated [34]. Emphasis should be placed on reinforcing shared decision-making with patients, assessing the risks and benefits of the different anticoagulation regimens, and tailoring the treatment regimens for each patient [33]. In our cancer institution, the common DOACs used are apixaban and rivaroxaban.

Full versus low-dose apixaban

Larsen et al. [36] followed 196 patients for efficacy and safety of low dose apixaban for 30 months after 6 months of full-dose apixaban treatment. They observed a small, short-lived increase in VTE and a substantial reduction in major bleeds with the reduced dose of apixaban. After 12 months, the incidence of recurrent VTE and major bleeding remained low. This showed that low-dose apixaban was effective and acceptably safe.

Prevention of recurrent CAT in patients with thrombocytopenia

It is essential to weigh the relative risks of recurrent thrombosis and serious bleeding. The risk of recurrent thrombosis is highest within the first 4 weeks (acute period) following the diagnosis of VTE [37]. For this reason, it is important to administer therapeutic (maximal) anticoagulant therapy in patients with acute CAT and a platelet count of $\geq 50 \times 109$/L. In patients with a platelet count of $25-50 \times 109$/L, providers can consider reducing the dose of LMWH by 50% or can administer a prophylactic dose of LMWH depending on individual patient characteristics (e.g., tumor burden, clot burden, and risk factors for bleeding) [38].

Prevention of recurrent CAT in patients who are bleeding

Major or severe bleeding episodes occur in approximately 7% of patients with CAT on anticoagulation. In those at high risk for recurrent VTE (e.g., acute CAT), insertion of a temporary IVC filter could be considered. Once the bleeding has resolved, anticoagulation can be initiated or resumed, and the IVC filter, if inserted, should be removed. The decision on initiating or resuming anticoagulation following an episode of intracranial bleeding should be made in collaboration with the neurologist or neurosurgeon [24]. The authors commonly involve the Benign Hematology team as part of this decision-making process in our large academic cancer center.

Abdominal organ vein thrombosis

In the case of recurrent thromboses in the portal vein, splanchnic vein, mesenteric vein, gonadal vein, or hepatic vein, the practice of the authors has been to collaborate with the primary oncologist as well as our Benign Hematology team to decide on anticoagulation with or without the use of an IVC filter [39].

Thromboprophylaxis in hospice/palliative care patients

There has been controversy surrounding thromboprophylaxis at the end of life or Hospice patients because of little data and because the emphasis on their quality of life surpasses the survival consideration [40, 41]. LMWH is an acceptable agent by palliative care providers as demonstrated by Noble et al. [42]. LMWH had little to no effect on the quality of life, and bruising was the main adverse effect. Barbara et al. [43] revealed that DOACs were effective after a meta-analysis of randomized controlled trials which looked at 13,338 cancer patients. Poor performance is an independent risk factor for increased bleeding, and this raises concern about the use of DOACs in advanced cancer [40].

Future perspectives

Presently, it appears unlikely that randomized controlled trials will be designed to compare different anticoagulant strategies for cancer patients with recurrent VTE during active treatment. Therefore, management studies aimed at validating therapeutic

protocols seem to be the only feasible approach to improve our knowledge in this clinical challenge. Therapeutic protocols should try to identify patients who may benefit from dose escalation and to define the optimal duration of those doses.

Conclusion

Our review of the current literature on recurrent CAT revealed limited literature on its management. From the published data, recurrent VTE is more likely to occur in genitourinary, lung, pancreatic, and colorectal cancers, more so if they are metastatic. The risk is higher among men than women. IVC filters are used as part of PE management, but VTE recurrence in these patients remains common. The efficacy of these filters is unclear. The diagnostic labs and imaging modalities are similar to those for an initial VTE. LMWH and DOACs are used for treatment, with dose reductions in LMWH varying with the platelet count. Inserting a temporary IVC filter can be considered for patients who are bleeding yet at high risk for recurrent VTE.

Further studies are needed to determine which subsets of patients may benefit from anticoagulant dose escalation and determine the optimal duration of such dose increases because of the increased bleeding risk. The overall prognosis is poor in patients with recurrent VTE in CAT, and more effective management needs to be defined. We hope this review will generate interest in further research through local and international collaborations to evaluate diagnostic and management strategies, including prevention, and reveal insights into this topic for providers.

Declarations

Code availability Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable

Conflict of interest The authors declare no competing interest.

References

1. Romualdi E, Ageno W (2016) Management of recurrent venous thromboembolism in cancer patients. Thromb Res 140(Suppl 1):S128-131

2. White RH, Zhou H, Murin S (1996) Harvey D (2005) Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in. Thromb Haemost 93:298–305

3. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB (2010) Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol 171:1109–1115

4. Hansson PO, Sorbo J, Eriksson H (2000) Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 160:769–774

5. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, Rodger MA, Zhang J, Lee AY, Meyer G, Wells PS (2012) Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation 126:448–454

6. Kyrle PA (2014) Predicting recurrent venous thromboembolism in cancer: is it possible? Thromb Res 133(Suppl 2):S17-22

7. Schulman S, Zondag M, Linkins L, Pasca S, Cheung YW, de Sancho M, Gallus A, Lecumberri R, Molnar S, Ageno W, Le Gal G, Falanga A, Hulegardh E, Ranta S, Kamphuisen P, Debourdeau P, Rigamonti V, Ortel TL, Lee A (2015) Recurrent venous thromboembolism in anticoagulated patients with cancer: management and short-term prognosis. J Thromb Haemost 13:1010–1018

8. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C (2017) Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. Pop-Based Cohort Study Thromb Haemost 117:57–65

9. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S (2004) The risk of recurrent venous thromboembolism in men and women. N Engl J Med 350:2558–2563

10. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY (2009) Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 7:760–765

11. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100:3484–3488

12. Hindi N, Cordero N, Espinosa E (2013) Thromboembolic disease in cancer patients. Support Care Cancer 21:1481–1486

13. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR (2012) Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines Chest 141: e419S-e496S

14. Jean GW, Kelly K, Mathew J, Larumbe E, Hughes R (2017) Venous thromboembolism treatment outcomes in cancer patients and effect of third-party payers on anticoagulant choice. Support Care Cancer 25:59–66

15. Haltout J, Awada A, Paesmans M, Moreau M, Klastersky J, Machiels G, Ignatiadis M, Kotecki N (2019) Predictive factors for cancer-associated thrombosis in a large retrospective single-center study. Support Care Cancer 27:1163–1170

16. Korte W (2008) Cancer and thrombosis: an increasingly important association. Support Care Cancer 16:223–228

17. Pihusch R, Danzl G, Scholz M, Harich D, Pihusch M, Lohse P, Hiller E (2002) Impact of thrombophilic gene mutations on thrombosis risk in patients with gastrointestinal carcinoma. Cancer 94:3120–3126

18. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs MJ (2001) Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism

presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 135:98–107

19. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, Perrier A (2006) Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 144:165–171

20. Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB (2000) Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 36:1632–1636

21. Sohne M, Ten Wolde M, Boomsma F, Reitsma JB, Douketis JD, Buller HR (2006) Brain natriuretic peptide in hemodynamically stable acute pulmonary embolism. J Thromb Haemost 4:552–556

22. Carrier M, Lee AY, Bates SM, Anderson DR, Wells PS (2008) Accuracy and usefulness of a clinical prediction rule and D-dimer testing in excluding deep vein thrombosis in cancer patients. Thromb Res 123:177–183

23. Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Terrenato I, Sperati F, Barba M, Yosuico VE, Schunemann H, Akl EA (2018) Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 6:CD006650

24. Carrier M, Khorana AA, Zwicker J, Noble S, Lee AY, Subcommittee on H, Malignancy for the SSCotI (2013) Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH J ThrombHaemost 11: 1760-1765

25. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR (2000) Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 18:3078–3083

26. Ihaddadene R, Le Gal G, Delluc A, Carrier M (2014) Dose escalation of low molecular weight heparin in patients with recurrent cancer-associated thrombosis. Thromb Res 134:93–95

27. O'Connell C, Escalante CP, Goldhaber SZ, McBane R, Connors JM, Raskob GE (2021) Treatment of cancer-associated venous thromboembolism with low-molecular-weight heparin or direct oral anticoagulants: patient selection, controversies, and caveats oncologist 26: e8-e16

28. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, Leavitt AD, Lee AYY, Macbeth F, Morgan RL, Noble S, Sexton EA, Stenehjem D, Wiercioch W, Kahale LA, Alonso-Coello P (2021) American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 5:927–974

29. Raskob GE, Van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia DA, Mercuri MF (2017) A randomized, open-label, blinded outcome assessment trial evaluating the efficacy and safety of LMWH/edoxaban versus dalteparinfor venous thromboembolism associated with cancer: Hokusai VTE-Cancer Study Blood 130: LBA-6-LBA-6

30. Frere C, Benzidia I, Marjanovic Z, Farge D (2019) Recent advances in the management of cancer-associated thrombosis: new hopes but new challenges cancers (Basel) 11

31. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Buller HR (2018) Hokusai VTECI Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378:615–624

32. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M (2018) Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 36:2017–2023

33. Li A, Garcia DA, Lyman GH, Carrier M (2019) Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res 173:158–163

34. Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M (2018) Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 16:1891–1894

35. Song X, Liu Z, Zeng R, Shao J, Liu B, Zheng Y, Liu C, Ye W (2021) Treatment of venous thromboembolism in cancer patients: a systematic review and meta-analysis on the efficacy and safety of different direct oral anticoagulants (DOACs). Ann Transl Med 9:162

36. Larsen TL, Garresori H, Brekke J, Enden T, Froen H, Jacobsen EM, Quist-Paulsen P, Porojnicu AC, Ree AH, Torfoss D, Osvik Velle E, Skuterud Wik H, Ghanima W, Sandset PM, Dahm AEA (2022) Low dose apixaban as secondary prophylaxis of venous thromboembolism in cancer patients - 30 months follow-up J Thromb Haemost

37. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M (2003) Randomized comparison of low-molecular-weight heparin versus oral anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer I Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349:146–153

38. Herishanu Y, Misgav M, Kirgner I, Ben-Tal O, Eldor A, Naparstek E (2004) Enoxaparin can be used safely in patients with severe thrombocytopenia due to intensive chemotherapy regimens. Leuk Lymphoma 45:1407–1411

39. (2021) Algorithm for VTE 2021. In: Editor (ed)^(eds) Book algorithm for VTE 2021. UT MD Anderson Cancer Center, City.

40. Zabrocka E, Sierko E (2020) Thromboprophylaxis in the end-of-life cancer care: the update cancers (Basel) 12

41. White C, Noble SIR, Watson M, Swan F, Allgar VL, Napier E, Nelson A, McAuley J, Doherty J, Lee B, Johnson MJ (2019) Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. Lancet Haematol 6:e79–e88

42. Noble SI, Nelson A, Turner C, Finlay IG (2006) Acceptability of low molecular weight heparin thromboprophylaxis for inpatients receiving palliative care: qualitative study. BMJ 332:577–580

43. Barbarawi M, Zayed Y, Kheiri B, Gakhal I, Barbarawi O, Bala A, Alabdouh A, Abdalla A, Rizk F, Bachuwa G, Katato K (2019) The role of anticoagulation in venous thromboembolism primary prophylaxis in patients with malignancy: a systematic review and meta-analysis of randomized controlled trials. Thromb Res 181:36–45