VTE risk assessment in cancer

Who needs prophylaxis and who does not?

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Keywords

Venous thromboembolism, cancer, hypercoagulability, risk factors, thromboprophylaxis

Summary

Venous thromboembolism (VTE) in patients with cancer is associated with an increased morbidity and mortality, and its prevention is of major clinical importance. However, the VTE rates in the cancer population vary between 0.5% - 20%, depending on cancer-, treatment- and patient-related factors. The most important contributors to VTE risk are the tumor entity, stage and certain anticancer treatments. Cancer surgery represents a strong risk factor for VTE, and medical oncology patients are at increased risk of developing VTE, especially when receiving chemotherapy or immunomodulatory drugs. Also biomarkers have been investigated for their usefulness to predict risk of VTE (e.g. elevated leukocyte and platelet counts, soluble P-selectin, D-dimer, etc.). In order to identify cancer patients at high risk of VTE and to improve risk stratification, risk assessment models have been developed, which contain both clinical parameters and biomarkers.

While primary thromboprophylaxis with low-molecular-weight-heparin (LMWH) is recommended postoperatively for a period of up to 4 weeks after major cancer surgery, the evidence is less clear for medical oncology patients. Thromboprophylaxis in hospitalized medical oncology patients is advocated, and is based on results of randomized controlled trials which evaluated the efficacy and safety of LMWH for prevention of VTE in hospitalized medically ill patients. In recent trials the benefit of primary thromboprophylaxis in cancer patients receiving chemotherapy in the ambulatory setting has been investigated. However, at the present stage primary thromboprophylaxis for prevention of VTE in these patients is still a matter of debate and cannot be recommended for all cancer outpatients.

Schlüsselwörter

Venöse Thromboembolie, Krebs, Hyperkoagulabilität, Risikofaktor, Thromboseprophylaxe

Zusammenfassung

Venöse Thromboembolien (VTE) bei Krebserkrankungen führen zu einer erhöhten Morbidität und Mortalität. Daher ist ihre Prävention von großer klinischer Bedeutung. Die VTE-Rate bei Krebspatienten variiert zwischen 0.5% bis 20% – in Abhängigkeit von Tumor-, Behandlungs- und Patienten-spezifischen Risikofaktoren. Auch die Rolle von verschiedenen Laborparametern und Biomarkern (z.B. erhöhte Thrombozyten und Leukozyten, solubles P-Selektin, D-dimer, etc.) für die Vorhersage des Auftretens einer VTE wurde in rezenten Studien untersucht. Um Krebspatienten mit dem höchsten VTE-Risiko zu identifizieren und die Risikostratifizierung zu optimieren, sind Risiko-Scores entwickelt worden, die sowohl klinische Parameter als auch Laborparameter beinhalten.

Während eine primäre Thromboseprophylaxe mit niedermolekularen Heparinen (NMH) postoperativ nach großen tumorchirurgischen Operationen für eine Dauer von etwa 4 Wochen empfohlen ist, gibt es keine eindeutige Evidenz für eine routinemäßige medikamentöse Thromboseprophylaxe für „internistische" Krebspatienten. Bei stationären Krebspatienten mit einer akut internistischen Erkrankung ist jedenfalls eine Thromboseprophylaxe zu befürworten. Im ambulanten Setting wird die Durchführung einer primären Thromboseprophylaxe bei Patienten diskutiert, die eine Chemotherapie erhalten.

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VTE-Risikobeurteilung bei Krebserkrankungen: Wer braucht eine Thromboseprophylaxe und wer nicht?

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Venous thromboembolism (VTE) is accepted as a common and serious complication of cancer and anti-cancer therapy. In clinical practice, approximately 20% of all VTE events occur in patients with a malignant disease and some of them may already present prior to the final diagnosis of an occult malignancy (1–3). Thrombotic events are a significant cause of morbidity and mortality in these people.

In large, population-based studies the risk of VTE was shown to be increased four- to 7-fold in patients with cancer (2). Other studies, which analysed hospital discharge data, have found also significantly higher VTE incidences of 0.6–7.8% in patients with cancer, more than double the incidence in patients without cancer (4–7). In a recent systematic review and meta-analysis, the annual incidence rate of VTE was between 0.5% and 20% (8). VTE was

also more prevalent during the course of chemotherapy (12.6% in the cancer cohort within 12 months after initiation of chemotherapy and 1.4% in the non-cancer control group) in another analysis (9). Similarly, in a retrospective study of patients treated with cisplatin-based chemotherapy, 18.1% developed VTE (10).

Incidence and risk of VTE according to the type and stage of cancer

The rates of VTE vary significantly according to the type of cancer and its extent. In a prospective cohort study, the Vienna Cancer and Thrombosis Study (CATS), the cumulative incidence of symptomatic VTE was 7.6 % in a cohort of patients with various malignancies (11) (▶Fig. 1). The highest incidence was present in patients with malignancies of the stomach, pancreas and brain (i.e. high grade glioma) followed by colorectal and lung cancer. The risk of VTE is also relatively high in haematologic malignancies, while breast and prostate cancer exhibited a lower risk of VTE. Other studies have found high rates of VTE also in tumors of the ovary and patients with acute leukemia (5, 12, 13).

Furthermore, the extent of the tumor and the presence of metastasis increase the likelihood of developing VTE. An increased risk of VTE was demonstrated among patients with advanced and metastatic disease in several studies (6, 13, 14). Data from the California registry and a Dutch study showed that metastatic disease is the strongest risk factor for occurrence of VTE contributing to a two- to three-fold higher probability of VTE compared to patients without metastasis (12, 14).

Interestingly, recent studies demonstrated similarly increased incidence rates of VTE in solid tumors with distant stage and regional stage (with presence of lymph node metastasis) compared to local stage cancers. In an analysis of CATS that comprised a cohort of 832 prospectively followed patients with solid tumors over 527 days in median, tumor stage was collected at study inclusion; 241 patients had local, 138 patients regional, and 453 patients had distant stage cancer (15). VTE events occurred in 2.9% of patients with local disease, 8.7% with regional cancer (with positive lymph nodes), and 8.4% in patients with distant metastasis. Multivariable analyses revealed a 3.7-fold increase in VTE risk for patients with regional stage and 5.4-fold increase in those with distant metastasis compared to patients with local stage disease.

Risk assessment

An optimized management to prevent cancer-associated VTE would include identification of patients with a substantially increased VTE risk and administration of a highly effective, safe and well-tolerated thromboprophylaxis (16). The risk of VTE may also fluctuate during the course of disease in a cancer patient, so knowing about periods with increased risk might also allow better tailoring of thromboprophylaxis.

The body of literature reporting on risk factors for VTE in patients with cancer is growing continuously. The risk of VTE can further vary substantially according to the clinical setting, the primary site and histological type of cancer, anti-cancer treatments and depends also on an individual background risk. These risk factors can be categorized into cancer-, treatment- and patient-related groups (▶Fig. 2). There has been also a great interest in identifying biomarkers predictive of cancer-associated VTE (17). In recent studies, also risk scoring models for identifying high- and low-risk patients have been explored.

Risk factors for VTE

Cancer-related

As outlined in the previous sections of this review, the primary site of the tumor and the extension of the disease in addition to the histological type are important determinants of the VTE risk. The risk of VTE is particularly increased in patients with a highly aggressive tumor biology as expressed by a high histological grading (G3 and G4) of the tumor (18). Also a time-dependent variation in the VTE risk has been observed. During the first 3 and up to 6 months after cancer diagnosis, patients are at highest risk to develop VTE (19).

The contribution of these clinicopathologic parameters to risk assessment of VTE in cancer patients is particularly valuable because they are readily available in cancer patients.

Treatment-related

Many surgical and non-surgical treatment strategies of cancers have been found to increase the risk of VTE. Surgery in general and cancer surgery in particular represents a strong risk factor for VTE (20). Medical oncology patients are at increased risk of

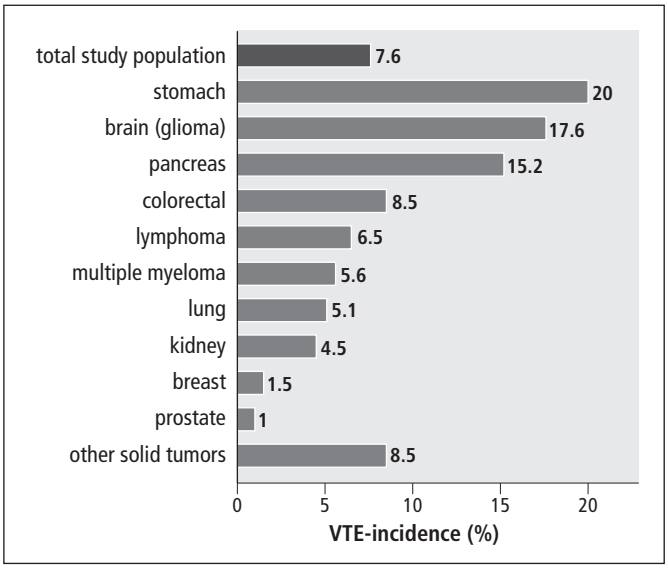

Fig. 1 Rates of venous thromboembolism (VTE) in 825 patients with different types of cancer during a median follow-up of 501 days [IQR 255–731]: data from the Vienna Cancer and Thrombosis Study (CATS), a prospective and observational cohort study (11)

developing VTE especially when receiving chemotherapy. Specifically, platinum-based therapy regimens are associated with an increased risk of VTE (21). Thalidomide (22) and lenalidomide (23) containing regimens as well as bevacizumab (24, 25) have been associated with high incidence rates of VTE. Furthermore, central-venous catheters (26), erythropoiesis-stimulating agents, erythrocyte and platelet transfusions and prolonged hospitalization itself are all additional risk factors for occurrence of VTE in cancer patients (27).

Patient-related

Previous studies investigated the impact of patient characteristics and in the majority of these studies, gender and age could not be shown to be independently associated with VTE in cancer patients (reviewed in 28). While in a study from the United States obesity (BMI >35 km/m²) was found to increase risk of VTE (4), this could not be reproduced in a cohort of European cancer patients (16). Reduced performance status is universally recognized as a predictor of VTE, especially if it leads to immobility in cancer patients (29).

In the general population, the history of VTE is a strong predictor of future VTE events. Also in patients with cancer, the history of VTE was a risk factor for occurrence of new VTE events; reviewed in (28). In a more recent report, however, a significant association of a previous history of VTE and occurrence of new VTE during the course of cancer could not be shown (30). The latter study investigated other venous conditions such as the history of superficial vein thrombosis (also called thrombophlebitis) and the presence of varicose veins as risk factors for cancer-associated VTE, and identified that varicose veins in cancer patients independently increase the propensity to develop VTE (2-fold higher risk).

Biomarkers for cancer-associated VTE

There are emerging data from studies that investigated biomarkers for their capacity of predicting VTE in patients with cancer (17, 31). Parameters of blood count analysis such as elevated leukocyte and platelet counts have turned out to be useful in risk prediction. Soluble P-selectin (sP-selectin), a cell adhesion molecule and biomarker of platelet and endothelial activation, and D-dimer, reflecting global activation of the haemostatic system, were both associated with occurrence of VTE in the general population and have been subsequently demonstrated to be predictors of VTE in cancer patients (11, 32). Furthermore, associations between elevated levels and future VTE have been found for clotting factor VIII and also for prothrombin fragment 1+2 and the in-vitro thrombin generation potential (11, 33, 34). Thrombin plays a central role in coagulation and the measurement of the in-vitro thrombin generation potential is a method that allows, at least to some extent, the global measurement of the haemostatic potential.

Results on the role of tissue factor (TF)-bearing microparticles (MP) for cancer-associated VTE are discordant: an association with occurrence of VTE in pancreatic cancer might be present, whereas in other cancer entities, such as glioblastoma, colorectal, or gastric carcinoma, this could not be confirmed (35, 36). Interestingly, high levels of MP-associated TF (MP-TF) activity significantly correlated with poor overall survival in patients with pancreatic cancer (35). Elevated MP-TF activity levels were shown to correspond to poor differentiation of non-resectable, metastatic, pancreatic tumor and invasiveness of blood vessels (37). This indicates that MP-TF may be involved in cancer invasion, angiogenesis and metastatic spread (38). Similarly, increased C-reactive protein (CRP) levels were suspected of raising VTE risk. In multivariable analysis, this association was not independent (39).

Recently, the association of mean platelet volume (MPV) with cancer-associated VTE was investigated and – unexpectedly – an increase in MPV correlated with a decreased risk of VTE in cancer patients (40). This finding is in contradiction to previous investigations in the general population, which suggested high MPV to be associated with increased risk of venous and arterial thromboembolic events (41).

Risk scoring models

The use of risk scoring models for the stratification of cancer patients according to their probability of developing VTE is a promising approach. In 2008 Khorana et al. developed a risk model for prediction of VTE in ambulatory cancer patients sched-

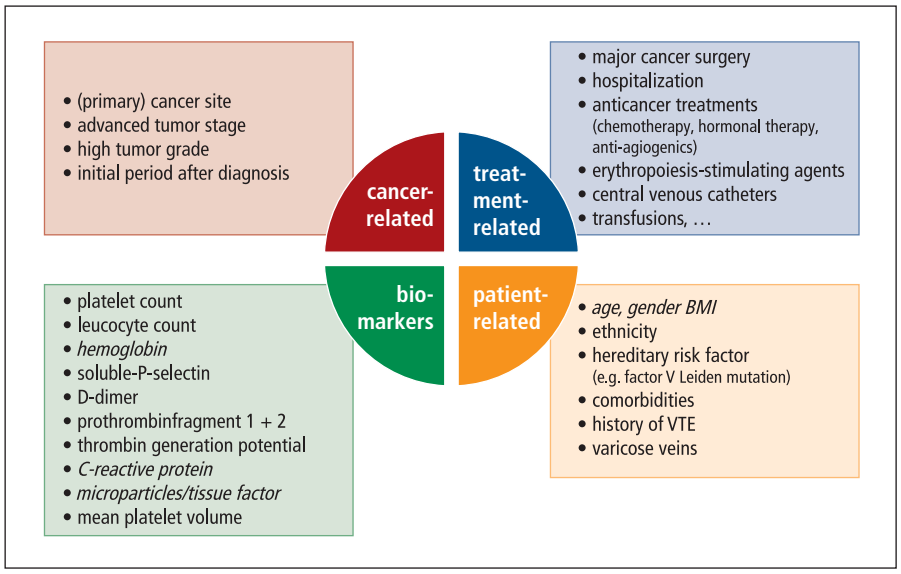

Fig. 2 Risk factors for venous thromboembolism (VTE) in patients with cancer. The risk of cancer-associated VTE is multifactorial. Several cancer-, treatment- and patient-related risk factors may contribute to occurrence of VTE. Also biomarkers and laboratory tests have been associated with risk of VTE. Not all risk factors could be confirmed in independent studies (indicated in *italic*).

Tab. 1 Risk scoring models for stratification of cancer patients into risk categories and identification of those at high or low risk of VTE

risk score	parameter			points
Khorana et al. (42)	site of cancer	very high risk*	stomach, pancreas	2
		high risk	lung, lymphoma, gynecologic, bladder, testicular	1
	platelet count		≥350 × 10^9/l	1
	hemoglobin and/or use of erythropoiesis-stimulating agents		<10 g/dl	1
	leukocyte count		>11 × 10^9/l	1
	body mass index		≥35 kg/m^2	1
Ay et al. (Vienna CATS# score) (43)	D-dimer		≥1.44 µg/ml	1
	sP-selectin		≥53.1 ng/ml	1

* In the Vienna Cancer and Thrombosis Study (CATS) also brain tumors (high-grade glioma) were included. They were allocated to the very high risk sites of cancer.

\# Vienna CATS risk score adds two further biomarkers to the Khorana-score.

uled for chemotherapy (42), which is until today the single validated model (43). The Khorana-score and studies that validated this risk assessment model were discussed in detail in a previous review article (44). Parameters, determined prior to initiation of chemotherapy, that are included in the Khorana-score, are listed (▶Tab. 1). Numerical values (0–2) are assigned to each variable, and patients are stratified into 3 discrete categories according to the total score. Patients assigned to the

- low-risk group (score 0) had a VTE risk of 0.3% during 2.5 months of follow-up,
- those in the intermediate-risk group (score 1–2) had a risk of 2%, and
- those in the high-risk group (score ≥3) had a risk of 6.7%.

This risk scoring model was validated in the cohort of patients included in the Vienna Cancer and Thrombosis Study (CATS) (43). An expanded risk scoring model (Vienna CATS score), incorporating additional biomarkers, namely sP-selectin and D-dimer (▶Tab. 1), was developed by our group (43). With this expanded model, it was possible to considerably improve the risk stratification of VTE. For instance, patients with a high score of 4 had a cumulative probability of developing VTE of 20.4% and those with a score ≥5 had a 35% probability, as opposed to 1% probability of VTE in patients with a score of 0 (lowest risk category). However, future interventional trials have to be performed to investigate whether ambulatory cancer patients assigned to high-risk groups based on risk scoring models might benefit from primary thromboprophylaxis.

Thromboprophylaxis in patients with cancer

After cancer surgery

Since it was observed that the majority of postoperative VTE events occur after discharge from hospital and VTE represented the major postoperative cause of mortality within the first 30 days after surgery (8), randomized controlled trials were conducted to investigate short-term (7–10 days) versus extended (4 weeks) postoperative thromboprophylaxis with low-molecular-weight-heparin (LMWH) after major abdominal and pelvic cancer surgery (45–47). These studies demonstrated that extended postoperative thromboprophylaxis is effective in reducing the rates of VTE after major cancer surgery, and provide the evidence for recommending thromboprophylaxis with LMWH for the postoperative period up to 4 weeks after major cancer surgery, given the bleeding risk is not increased (48, 49).

The risk of postoperative VTE might also be increased in other clinical settings (e.g. after major thoracic surgery or neuro-surgery of brain tumors). However, specific randomized controlled trials evaluating extended postoperative thromboprophylaxis for these types of surgeries are lacking. A special situation includes patients with brain tumors. As thromboprophylaxis reduces the risk of postoperative VTE without an excess of major bleeding, recent guidelines clearly recommend thromboprophylaxis in cancer patients undergoing neurosurgery which should be commenced postoperatively (48).

In hospitalized medical oncology patients

In contrast to surgical cancer patients, the evidence for primary thromboprophylaxis is less clear for medical oncology patients (50, 51). Thromboprophylaxis in hospitalized medical oncology patients is advocated in guidelines for VTE management published by major scientific societies, and is based on results from randomized controlled trials which evaluated the efficacy and safety of LMWH of fondaparinux for prevention of VTE in the general population of hospitalized medical ill patients (48–50,52). These trials, however, included only 5% – 15% patients with cancer. Consequently, pharmacologic thromboprophylaxis is only warranted in patients with active cancer who are admitted with an acute medical illness or reduced mobility.

In clinical practice the population of cancer patients admitted to hospital is heterogeneous and an improved strategy for thromboprophylaxis and validated risk assessment tools for estimating the overall risk of VTE in hospitalized patients with cancer are clearly needed.

In cancer outpatients

A majority of cancer-associated VTE occurs in the outpatient setting. Several randomized controlled trials have focused on thromboprophylaxis with LMWH in cancer patients who received chemotherapy for advanced disease in the ambulatory setting. In two large studies, the PROTECHT and SAVE-ONCO study, patients with selected solid tumors were in-

cluded (53, 54). Although both trials showed and statistically significant relative risk reduction for VTE in patients receiving pharmacological thromboprophylaxis, the absolute event rates in the placebo group were relatively low (3.9% and 3.4%). Other studies focused on single cancer entities, such as malignant glioma in PRODIGE (55), pancreatic cancer in FRAGEM and CONKO-004 (56, 57) or multiple myeloma treated with thalidomide or lenalidomide-based regimens in other studies (58, 59). The latter should receive thromboprophylaxis with either LMWH or low-dose aspirin when thalidomide or lenalidomide is given in combination with chemotherapy and/or dexamethasone (reviewed in 44).

Interestingly, in the CONKO-004 and FRAGEM studies much higher doses than standard thromboprophylaxis dose were used in patients in the LMWH arm (enoxaparin 1 mg/kg per day for 3 months, followed by 40 mg per day for an additional 3 months in CONKO-004, and dalteparin 200 IU/kg per day for the first 4 weeks followed by 150 IU/kg per day for 8 additional weeks). With enoxaparin VTE rates at 12 months were 5% versus 15.3% in the control group ($p < 0.01$), and with dalteparin VTE rates were 12% versus 28% for the control group during the whole follow-up period of 19 months in median (p=0.039). In both studies the VTE risk reduction did not result in significant improvement of survival. It is important to state that higher doses of LMWH than standard thromboprophylaxis dose are not approved for routine use.

However, at the current stage primary thromboprophylaxis for prevention of VTE is still a matter of debate and cannot be recommended for all cancer outpatients (60). Only, high-risk patients might be candidates for thromboprophylaxis with LMWH during chemotherapy. In clinical practice, the definition of a high risk population for primary thromboprophylaxis in the outpatient setting is a challenging issue. A risk stratification scheme such as the Khorana-Score might be useful and needs to be evaluated in interventional trials. Other guideline authors again define patients with pancreatic or lung cancer as potential subjects for primary thromboprophylaxis (48). In the ACCP guidelines cancer patients with additional risk factors are suggested as candidates for thromboprophylaxis (52). According to the authors of the ACCP guidelines, additional risk factors for VTE in cancer outpatients include previous VTE, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

Conclusions

Patients with cancer are at high risk of developing VTE. The risk of VTE depends on the

- tumor type,
- extension of the disease and
- clinical setting.

Individual patient-, cancer- and treatment-related risk factors contribute to the risk of VTE. Over the past years candidate biomarkers predictive of VTE in patients with cancer have been investigated. Consequently, new risk stratification approaches have been adopted to identify patients at high-risk of VTE. The most promising risk assessment models incorporate both clinical parameters and biomarkers. However, theses risk stratification tools need to be validated in interventional and randomized controlled trials selecting ambulatory cancer patients for thromboprophylaxis, until they can be introduced into clinical practice for routine use.

While primary thromboprophylaxis with LMWH is recommended postoperatively for an extended period of up to four weeks after major (abdominal and pelvic) cancer surgery, the evidence is less clear for medical oncology patients, and should be targeted at those with additional risk factors such as acute medical illness or immobilization. In cancer outpatients, the efficacy and safety of primary thromboprophylaxis with LMWH in those with advanced disease receiving chemotherapy in the ambulatory setting has been confirmed. However, at the current stage primary thromboprophylaxis for prevention of VTE cannot be recommended for all cancer outpatients due to some (methodological) limitations of these studies.

Conflict of interest

Dr. Ay received honoraria for lectures from Sanofi, Pfizer, Boehringer-Ingelheim, Bayer and Daiichi-Sankyo.
Dr. Pabinger received honoraria for advisory board meetings and lectures from Bayer, Pfizer and Boehringer-Ingelheim.

References

1. Falanga A, Russo L. Epidemiology, risk and outcomes of venous thromboembolism in cancer. Hämostaseologie 2012; 32: 115–125.
2. Heit JA, O'Fallon WM, Petterson TM et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002; 162: 1245–1248.
3. Spencer FA, Lessard D, Emery C et al. Venous thromboembolism in the outpatient setting. Arch Intern Med 2007; 167: 1471–1475.
4. Khorana AA, Francis CW, Culakova E et al. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007; 110: 2339–2346.
5. Khorana AA, Francis CW, Culakova E et al. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol 2006; 24: 484–490.
6. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. Thromb Haemost 2002; 87: 575–579.
7. Stein PD, Beemath A, Meyers FA et al. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med 2006; 119: 60–68.
8. Horsted F, West J, Grainge MJ.Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med 2012; 9: e1001275.
9. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 2013; 119: 648–655.
10. Moore RA, Adel N, Riedel E et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011; 29: 3466–3473.
11. Ay C, Vormittag R, Dunkler D et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 2009; 27: 4124–4129.
12. Blom JW, Vanderschoot JP, Oostindier MJ et al. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 2006; 4: 529–535.
13. Wun T, White RH. Epidemiology of cancer-related venous thromboembolism. Best Pract Res Clin Haematol 2009; 22: 9–23.
14. Chew HK, Wun T, Harvey D et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006; 166: 458–64.

15. Dickmann B et al. Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study. Haematologica 2013; 98: 1309–14.
16. Pabinger I, Ay C. Risk of venous thromboembolism and primary prophylaxis in cancer. Should all patients receive thromboprophylaxis? Hämostaseologie 2012; 32: 132–137.
17. Pabinger I, Thaler J, Ay C. Biomarkers for prediction of venous thromboembolism in cancer. Blood 2013; 122: 2011–2018.
18. Ahlbrecht J et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 2012; 30: 3870–3875.
19. Blom J, Doggen C. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293: 715–722.
20. Trinh VQ et al. Venous thromboembolism after major cancer surgery: Temporal trends and patterns of care. JAMA Surg 2014; 149: 43–9.
21. Kröger K et al. Risk factors for venous thromboembolic events in cancer patients. Ann Oncol 2006; 17: 297–303.
22. Rajkumar SV et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006; 24: 431–436.
23. Rajkumar SV et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005; 106: 4050–4053.
24. Scappaticci F et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007; 99: 1232–1239.
25. Mandala M et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the "SENDO experience". Ann Oncol 2012; 23: 1416–1421.
26. Tesselaar M et al. Risk factors for catheter-related thrombosis in cancer patients. Eur J Cancer 2004; 40: 2253–2259.
27. Bohlius J et al. Erythropoietin or darbepoetin for patients with cancer – meta-analysis based on individual patient data. Cochrane Database Syst Rev 2009; 8.
28. Königsbrügge O, Pabinger I, Ay C. Risk factors for venous thromboembolism in cancer: novel findings from the Vienna Cancer and Thrombosis Study (CATS). Thromb Res 2014; 133 (Suppl 2): S39–S43.
29. Numico G et al. Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. Cancer 2005; 103: 994–999.
30. Königsbrügge O et al. Presence of varicose veins in cancer patients increases the risk for occurrence of venous thromboembolism. J Thromb Haemost 2013; 11: 1993–2000.
31. Ay C, Pabinger I. Tests predictive of thrombosis in cancer. Thromb Res 2010; 125 (Suppl 2): S12–S15.
32. Ay C et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). Blood 2008; 112: 2703–2708.
33. Vormittag R et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol 2009; 29: 2176–2181.
34. Ay C et al. Prediction of venous thromboembolism in patients with cancer by measuring thrombin generation: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 2011; 29: 2099–2103.
35. Thaler J et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. J Thromb Haemost 2012; 10: 1363–1370.
36. Thaler J, Ay C, Pabinger I. Clinical significance of circulating microparticles for venous thromboembolism in cancer patients. Hämostaseologie 2012; 32: 127–131.
37. Thaler J et al. Microparticle-associated tissue factor activity in patients with pancreatic cancer: correlation with clinicopathological features. Eur J Clin Invest 2013; 43: 277–285.
38. Langer F, Bokemeyer C. Crosstalk between cancer and haemostasis. Implications for cancer biology and cancer-associated thrombosis with focus on tissue factor. Hämostaseologie 2012; 32: 95–104.
39. Kanz R, Vukovich T, Vormittag R et al. Thrombosis risk and survival in cancer patients with elevated C-reactive protein. J Thromb Haemost 2011; 9: 57–63.
40. Riedl J, Kaider A, Reitter E-M et al. Association of mean platelet volume with risk of venous thromboembolism and mortality in patients with cancer: results from the Vienna Cancer and Thrombosis Study (CATS). Thromb Haemost 2014; 111: 670–678.
41. Riedl J, Pabinger I, Ay C. Platelets in cancer and thrombosis. Hämostaseologie 2014; 34: 54–62.
42. Khorana AA, Kuderer NM, Culakova E et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111: 4902–4907.
43. Ay C, Dunkler D, Marosi C et al. Prediction of venous thromboembolism in cancer patients. Blood 2010; 116: 5377–5382.
44. Thaler J, Ay C, Pabinger I. Venous thromboembolism in cancer patients – risk scores and recent randomised controlled trials. Thromb Haemost 2012; 108: 1042–1048.
45. Bergqvist D, Agnelli G, Cohen AT et al. ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346: 975–980.
46. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P et al. FAME Investigators. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006; 4: 2384–2390.
47. Kakkar VV, Balibrea JL, Martínez-González J, Prandoni P, 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 2010; 8: 1223–1229.
48. Farge D, Debourdeau P, Beckers M et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost 2013; 11: 56–70.
49. Lyman GH, Khorana AA, Kuderer NM et al. American Society of Clinical Oncology Clinical Practice. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013; 31: 2189–2204.
50. Di Nisio M, Carrier M, Lyman GH, Khorana AA; Subcommittee on Haemostasis and Malignancy. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 2014; 12: 1746–1749.
51. Carrier M, Khorana AA, Moretto P et al. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. Am J Med 2014; 127: 82–6.e1.
52. Kahn SR, Lim W, Dunn AS et al. American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis. Chest 2012; 141 (2 Suppl): e195S-e226S.
53. Agnelli G, Gussoni G, Bianchini C et al. PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol 2009; 10: 943–949.
54. Agnelli G, George DJ, Kakkar AK et al. SAVE-ONCO Investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 2012; 366: 601–609.
55. Perry JR, Julian JA, Laperriere NJ et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost 2010; 8: 1959–1965.
56. Maraveyas A, Waters J, Roy R et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012; 48: 1283–1292.
57. Riess H, Pelzer U, Optiz B et al. A prospective, randomizedtrial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy. Final Results of the CONKO-004 trial. J Clin Oncol 2010; 28 (Suppl 15): 4033.
58. Larocca A, Cavallo F, Bringhen S et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood 2012; 119: 933–939.
59. Palumbo A, Cavo M, Bringhen S et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011; 29: 986–993.
60. Khorana AA, Otten HM, Zwicker JI et al. Subcommittee on Haemostasis and Malignancy. Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. J Thromb Haemost 2014; 12: 1928–1931.

