Thrombosis in cancer patients: etiology, incidence, and management

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Abstract: Venous thromboembolism (VTE) is the second most common cause of mortality in cancer patients. The mechanisms of cancer-associated thrombosis (CAT), much like cancer itself, are multi-factorial and incompletely understood. Cancer type, stage, tumor-derived factors and genetics all affect CAT risk. Furthermore, cancer therapies as well as the indwelling vascular devices through which these therapies are delivered can increase the risk for CAT. In this review, we summarize mechanisms of hypercoagulability in cancer patients, patterns of thrombosis associated with cancer, current guidelines for the diagnosis and management of CAT, and important considerations regarding the placement of implantable vascular devices in the care of cancer patients with VTE.

Keywords: Cancer; venous thrombosis; venous access catheters; anticoagulation

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Introduction

Cancer is the second leading cause of death in the United States, and among cancer patients, venous thromboembolism (VTE) is the second highest cause of mortality (1). Though the association between cancer and thrombosis has been appreciated for over 150 years, the mechanisms of cancer-associated thrombosis (CAT), much like cancer itself, are multi-factorial and incompletely understood. Cancer type, stage, tumor-derived factors and genetics all affect CAT risk. The presence of metastasis increases the risk of CAT multi-fold (2). Patients with the highest 1-year incidence rate of VTE are those with cancers of the brain, lung, uterus, bladder, pancreas, stomach and kidney. For these tumor types, CAT risk increases 4–13-fold in patients with metastases as compared with those with localized disease (3). Furthermore, cancer therapies themselves can increase the risk for CAT. The administration of chemotherapy or hormone therapy, the immobilization associated with surgical interventions, and the placement of indwelling central venous catheters (CVCs) elevate VTE risk (3). In this review, we summarize mechanisms of hypercoagulability in cancer patients, patterns of thrombosis associated with cancer, current guidelines for the diagnosis and management of CAT, and important considerations regarding the placement of implantable vascular devices in the care of cancer patients with VTE.

Mechanisms of hypercoagulability in cancer

The interplay between cancer and thrombosis can be
examined from multiple perspectives. The association between these two processes was first described by Bouillard in 1823; Trousseau further expounded upon the relationship, providing the most detailed early description in 1865 (4). In a classical sense, the increased risk of thrombosis seen in cancer patients can be traced to cancer's ability to affect all components of Virchow's triad. That is, tumor compression and bed rest can lead to venous stasis. Cancer also alters the expression and activity of blood components such as procoagulant factors including coagulation cascade proteins, tissue factor (TF), thrombocytes and leukocytes, all of which contribute to a hypercoagulable state. And, abnormal tumor vascularity leads to endothelial dysfunction. Additionally, the pathogenesis of thrombosis in cancer can also be described by a second triad composed of changes in tumor biology, coagulation activation, and inflammation (5). The presence of antiphospholipid antibodies, the activation of platelets and direct factor X, and the subsequent decrease in hepatic clearance of coagulation factors (6) all contribute to CAT. Elevated D-dimer levels are also present which indicate a chronic systemic coagulation activation (7).

From a modern, molecular perspective, cancer genetics play a key role in CAT risk. Oncogenes such as k-ras as well as mutations to the tumor-suppressor gene p-53 lead to increased expression of tissue factor (TF) by tumor cells. Angiogenesis is subsequently promoted further by the elevated TF levels, promoting tumor growth and metastasis. This is achieved by TF increasing platelet activation, increasing thrombin levels, and cleaving fibrinogen. In addition, coagulation-independent mechanisms, such as signaling of protease-activated receptors, enhance tumor cell proliferation. In a retrospective cohort study of 122 patients with pancreatic cancer, CAT risk was 6-fold higher in patients with increased tumor cell TF expression versus those patients with low TF expression (8).

From a cancer immunology standpoint, cancer fosters a state of inflammation leading to the elaboration of proinflammatory cytokines such as interleukin-6, interleukin-8 and interleukin-10. These and various other inflammatory factors promote thrombosis by increasing adhesion molecule levels on the surface of endothelial cells and monocytes. Circulating microparticles bearing TF are shed from platelets, erythrocytes, tumor cells, endothelial cells, lymphocytes and monocytes. These phosphatidylserine-rich membrane vesicles are highly associated with aggregation and activation of coagulation factors (9,10). In a case-control study, these microparticles have been directly linked to a higher risk of VTE in cancer patients (10,11). Furthermore, patients with higher levels of these microparticles treated with prophylactic anticoagulation had a non-significant trend towards lower rates of VTE compared to patients who underwent observation alone (5.6% vs. 27.3%, P=0.06), though this study was not powered to directly address the impact of anticoagulation in this patient population (12).

From an epidemiologic perspective, the risk for CAT is most strongly correlated with the cancer stage and type. Malignancies at very high risk for CAT (3-fold or greater risk for VTE relative to the general population) include gastric and pancreatic cancer. High risk malignancies with overall higher rates of VTE relative to the general population include lung cancer, gynecologic malignancies, lymphoma, and renal cell carcinoma. Some cancers such as prostate cancer and breast cancer have VTE rates at or below the general population. Rates for breast cancers are as low as 2.3% (13,14). However, in absolute numbers more VTE events are seen in breast and prostate cancer patients given the prevalence of these malignancies. Independent of origin, biologically aggressive and metastatic cancers, is highly correlated with CAT. Interestingly, the degree of increased VTE risk seen in cancer patients fluctuates during the progression of the disease. The highest risk for CAT is in the first three months after diagnosis.

Beyond the tumor itself, iatrogenic causes of CAT abound. Chemotherapy contributes to VTE risk through multiple mechanisms: chemotherapy causes endothelial damage, activates coagulation pathways by decreasing coagulation inhibitors (proteins C and S as well as anti-thrombin III), impairs synthesis of natural anticoagulants, causes the release of cell-free DNA, induces aberrant cytokine release and stimulates platelet aggregation. Notable high-risk chemotherapies include L-asparagine, thalidomide and lenalidomide. Other procoagulant chemotherapies include gemcitabine, platinum-based therapies, monoclonal antibodies and anti-hormonal therapies. Some non-chemotherapy intravenous treatments used in cancer may also be prothrombotic including glucocorticoids, antibiotics, red cell growth factors and blood transfusions. Several novel cancer therapies, in particular the antiangiogenic agents such as bevacizumab, are associated with an increased risk of arterial and venous thrombosis. The use of the erythropoiesis-stimulating agents, epoetin alfa and darbepoetin alfa, as well as blood transfusions has also been associated with an increased risk of VTE.

Vessel damage as well as stasis following surgical
interventions also contributes to VTE in cancer patients. Deep venous thrombosis (DVT) is twice as likely and pulmonary embolism three times more likely postoperatively in cancer patients. The increased risk of VTE is also affected by the type of surgery. For example, VTE risk is 13.7% with esophageal resection vs. the relatively lower 1.7% seen in prostatectomy. Cancer patients requiring surgery generally have a 2-fold risk of VTE vs. non-cancer patients undergoing comparable surgery (15,16).

**Patterns of thrombosis in cancer**

In the context of cancer, VTE can have unique clinical presentations that affect both the detection and treatment of thrombi. Cancer patients are far more likely to have bilateral thrombi, iliofemoral thrombi, or upper-limb DVT than non-cancer patients. Additionally, frequent infusion treatments require cancer patients to have temporary or semi-permanent central venous catheters (CVCs); these include tunneled/non-tunneled catheters, implanted ports, and peripherally inserted central catheters (PICCs). These devices put cancer patients at risk for catheter-related thrombosis (CRT). Other forms of aberrant thrombosis are also seen more frequently in cancer including Budd-Chiari syndrome, extrahepatic portal vein obstruction and mesenteric vein thrombosis. These atypical thromboses should always be considered when treating oncology patients. Even with full resolution, recurrence rates are also higher among cancer patients. Recurrence risk is two to threefold higher in cancer patients than in non-cancer patients.

**Cancer and fatal thromboembolic events**

Malignancy not only increases the risk for VTE, it also increases the risk for fatal VTE events. In a review of the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry, a large international prospective registry of patients with acute VTE, a history of malignancy resulted in a 2-fold increase in the risk for a fatal pulmonary embolism (17). Cancer was found to be the strongest independent risk factor for mortality due to all causes and from pulmonary embolism specifically in the three months following the diagnosis of acute VTE (18,19).

**VTE in cancer guidelines**

Since 1986, over 20 guidelines have been published on prevention of VTE in hospitalized patients with cancer. The most prominent guidelines in recent years have been published by the following four bodies: the 2015 National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology: Venous Thromboembolic Disease (20), the European Society for Medical Oncology (2011) (3), the American College of Chest Physicians: Antithrombotic and Thrombolytic therapy guidelines [2012] (21), and the American Society of Clinical Oncology (ASCO) Guidelines on VTE published in 2015 (22). All recommend VTE prophylaxis for hospitalized patients with active cancer, using one of three classes of drugs [unfractionated heparin (UFH), low-molecular weight heparin (LMWH), or a factor Xa inhibitor] and intermittent pneumatic compression or graduated compression stockings when there is a contraindication to pharmacologic prophylaxis.

In the outpatient setting, routine thromboprophylaxis is not recommended for patients with cancer. Multiple myeloma patients on antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either LMWH or low-dose aspirin. Patients undergoing major surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Prophylaxis is suggested up to 4 weeks in abdominal or pelvic surgery. LMWH is recommended for the initial 5 to 10 days of treatment for DVT and PE as well as for long-term secondary prophylaxis (at least 6 months). Use of novel oral anticoagulants is not recommended for patients with malignancy and VTE because of limited data in cancer patients.

However, various contraindications to VTE prophylaxis exist. According to the 2009 NHMRC Australia guideline pharmacological prophylaxis is contraindicated in patients with recent central nervous system bleeding, intracranial or spinal lesion at high risk for bleeding, current active major bleeding (defined as requiring at least two units of blood or blood products to be transfused in 24 hours), current chronic or clinically significant measurable bleeding over 48 hours, thrombocytopenia (platelets <50,000/μL), severe platelet dysfunction (secondary to uremia, medications, or myelodysplasia, etc.), recent major surgical procedure at high risk for bleeding, underlying coagulopathy, coagulation factor abnormalities, concomitant use of medications that may affect the clotting process (e.g., anticoagulants, antiplatelet agents, selective and non-selective non-steroidal anti-inflammatory drugs or thrombolytic agents), regional axial anaesthesia, recent lumbar puncture for any reason, renal impairment and high risk of falls.
For patients with CAT, initial treatment usually consists of UFH or LMWH. Some studies have shown that there is no difference in efficacy between UFH and LMWH (23), including in the prophylactic setting (24). However, since the landmark CLOT trial (25), LMWH has supplanted Coumadin as the anticoagulant of choice in cancer patients. This trial found a statistically significant reduction in mortality risk with LMWH at 3 months follow-up (25). The recent CATCH trial did not find a reduction in mortality or overall bleeding with LMWH compared to Coumadin, though there was a lower rate of non-major bleeding (26). Patients are also less likely to develop heparin-induced thrombocytopenia (HIT) when on LMWH vs. UFH (27,28). LMWH also allows for an easier transition to outpatient management. Hence, LMWH is currently the anticoagulant of choice in initial VTE therapy in cancer patients (22). UFH mainly has a role to play in patients with severe renal impairment due to its hepatic clearance, shorter half-life, and reversibility with protamine sulfate.

Some data exist regarding the use of non-vitamin K oral anticoagulants (NOACs) in patients with cancer. Dabigatran, rivaroxaban, and apixaban have been studied for acute VTE in the general population and were found to be non-inferior to vitamin K antagonists in phase III clinical trials (29-32). However, there have been no phase III trials evaluating NOACs in cancer patients. Most of the large trials for these drugs essentially excluded cancer patients, or cancer patients comprised a small minority of the study population (33). A phase II study for apixaban specifically in cancer patients found that the drug was well tolerated, but the sample size was limited (34). Given the greater risk of thrombosis in cancer patients relative to the general population, the appropriate dose for these drugs in the cancer population remains an unanswered question.

Risk assessment

Several risk assessment tools have been developed for calculating the risk of thrombosis in cancer patients. It is important to note that each risk assessment tool is designed for a specific subset of cancer patients and should thus be utilized only in those patients who meet the criteria.

The Khorana score is the most validated risk assessment model for cancer patients. The Khorana score is used for predicting thrombosis in ambulatory care patients (35). Routine prophylaxis should not be implemented in all ambulatory patients, and the Khorana tool can be used to identify those patients who may benefit. Important factors in this tool include initial site of cancer, erythropoiesis stimulating agents, platelet count, leukocyte count and BMI. This measure factors in the variable hypercoagulability of different cancers. Pancreas, stomach and brain cancers are considered very high risk for VT; lung, gynecologic and genitourinary cancers and lymphoma are high risk; and breast and colorectal cancer are low risk. Patients determined to be low risk (0 points) have a 0.3–0.8% risk of VTE, intermediate (1–2 points) 1.8–2.0% risk of VTE and high and very high (>3 points) are 6.7% to 7.1% risk. The presence of a platelet count >350x10^9/L, hemoglobin concentration <100 g/L, leucocyte count pre-chemotherapy >11x10^9/L and a body max index of >35 kg/m^2 are all hallmarks of high risk for VTE (35).

Alternatively, in an international practice guideline discuss commencing prophylaxis in locally advanced cancer or pancreatic and lung cancer that has metastasized in patients who otherwise are not at risk for excessive bleeding (36). The key about these validated bedside risk stratification scores is the ability to tailor treatment to patient subsets. The Khorana score has been shown to be a useful tool as retrospectively, evaluation in large prospective randomized trials found that the risk of VTE in high-risk patients randomized to prophylactic thromboprophylaxis. However, the score was designed with data from patients with a range of malignancies and may not perform well within cohorts of patients with specific cancers (37). It was also found to underperform in an analysis of the RIETE database (38).

Various other scores have also been developed. The Vienna score is also used to predict VTE in ambulatory patients. It is similar to the Khorana score but also includes measures of D-Dimer and soluble P-selectin (sP-selectin). The Ottawa score is used to assess the risk of VTE recurrence in cancer patients. This score takes into consideration cancer type and stage, sex and history of thrombosis. The Caprini score is another risk assessment model based upon numerous risk factors (39) and has been validated in cancer patients (40). The newly proposed COMPASS score based on patients with breast, colorectal, lung, or ovarian cancer receiving outpatient chemotherapy additional risk factors such as specific anthracycline or anti-hormonal therapy and CVCs.

Each of these scores provides valuable insight into the risk and management of patients with cancer. It is important to consider these scores when planning vascular interventions for cancer patients. As research continues, our ability to risk stratify CAT will continue to become more accurate and precise. However, what is lacking is a blood test
to predict the risk thrombosis in cancer. Biomarkers specific to CAT would allow physicians to quickly and accurately stratify thrombosis risk for individual patients. Biomarkers that have been suggested include thrombocytosis, leukocytosis, elevated D-dimer, elevated prothrombin split products, elevated soluble P-selectin, thrombin-anti-thrombin complexes (TATc), prothrombin fragment 1+2 (F1+2), peak thrombin generation, elevated TF, CD40 ligand, platelet factor-4 (PF4), thrombospondin-1, beta-thromboglobulin, as well as coagulation factors FX, FVII, and FVIII. Few studies have evaluated these biomarkers and they cannot currently provide accurate risk stratification in a clinical setting. The strongest evidence exists for elevated levels of P-selectin but the low clinical availability of this test limits its usefulness.

**Considerations for implantable vascular devices in patients with cancer**

Implantable vascular devices are a cornerstone in the care of patients with cancer. Such devices have spurred new and innovative cancer care strategies, but carry their own thrombotic risk. When treating cancer patients, VTE risk should be considered in two dimensions, disease-based risk and intervention-based risk. Optimal therapy requires the selection of the most effective, lowest risk therapy for a given cancer.

Interventions that require vessel wall puncture and retention of a foreign body within a blood vessel carry the risk for thrombosis. Examples include CVC, IVC filters, and vascular stents. The most common of these procedures among cancer patients is placement of a CVC to provide long-term venous access for administration of medication, chemotherapy and/or parenteral nutrition. There are three general types of CVCs: PICC, tunneled/non-tunneled catheters and implanted ports. Each carries different risk for thrombosis. PICCs have a higher rate of DVT than other central catheters in post-critical care patients (41) and cancer patients (42). Factors contributing to increased PICC thrombosis risk include the use of larger lumen catheters, multilumen catheters, catheter tip location and the use of left-sided veins due to the compressive effect of the arch of the aorta on the left brachiocephalic vein. In addition to these factors, when considering tunneled/non-tunneled catheters, physicians should also consider catheter make and model. Stiff polyethylene catheters are more thrombogenic when compared to newer, more flexible silicone or polyurethane models. Subcutaneous ports pose the lowest risk for VT, however they are invasive and generally reserved for long-term infusion (months to years). Thrombosis risk increases with all CVCs with increasing number of placement attempts. The more times a vein is punctured for access, the more likely it is to thrombose.

Management of catheter induced thrombosis remains unclear. Bern *et al.* in 1990 showed that low dose warfarin was effective in reducing risk of CRT (43). However, larger studies since indicate that both warfarin and LMWH prophylaxis are ineffective, finding no difference between treated and untreated groups (44-46). Therefore ASCO guidelines do not recommend thromboprophylaxis for (47).

When anticoagulation is contraindicated, IVC filters may be used in cancer patients with DVT as prophylaxis for PE. The thrombogenic potential of IVC filters is directly proportional to the duration of time the filter is in place. Interestingly, cancer itself is a contraindication for the retrieval of temporary IVC filters thus increasing the risk for thrombosis in a hypercoagulable population. Careful consideration should be given before placing an IVC filter in high-risk cancer patients including level of risk for thrombosis and possibility of retrieval.

**Prevention and treatment**

CAT treatment protocols are essentially deduced from DVT treatment management, as dedicated clinical randomized controlled trials have yet to be performed. Small patient series have shown that short courses of low-dose LMWH are effective in CAT (48). Hence anticoagulation currently remains the primary prevention and treatment for CAT in the context of endovascular therapies. This is accomplished mainly through the use of LMWH. This class of drug potentiates anti-thrombin III to interfere with the coagulation cascade and has proposed anti-tumoral activity. Multiple studies have shown that prophylactic anticoagulation with LMWH decreases incidence of CAT. However, there is not a corresponding decrease in mortality. Prophylactic anticoagulation also appears to have no effect on CRT. Questions regarding whether line removal is essential to remove the thrombotic source or whether this maneuver is conversely harmful (due to the risk of PE) are unclear (49). Typically, the line is removed if access is no longer required, if there is a suspicion or evidence of sepsis or if the catheter is no longer functioning or defective.

The recent identification of the role of platelets in CAT has led to investigation of antiplatelet drugs such as aspirin being utilized as prophylaxis in cancer patients. While data suggest that antiplatelet drugs may decrease CAT risk, one
Recent review asserts that there is no indication for platelet inhibition as CAT therapy. Statins have also been proposed as a prophylactic measure, but meta-analysis of 22 trials found no significant correlation between statins and CAT. Prophylactic measures are important when considering percutaneous interventions and special consideration should be given to prophylaxis in cancer patients. The role of the novel oral anticoagulants in patients who have cancer with VTE has yet to have been clarified. Randomized, controlled trials evaluating new oral anticoagulants for treatment of VTE have only enrolled a small proportion of patients with cancer (2–9%). The Food and Drug Administration (FDA) has approved rivaroxaban for treatment of VTE, but drug labeling does not include guidance for cancer patients. The detection of extracellular DNA scaffolds in the form of neutrophil extracellular traps in thrombus tissue has raised the potential role of deoxyribonuclease enzymes for the treatment of thrombolysis (50); however, this approach has yet to be studied sufficiently for clinical application.

**Conclusions**

Risk assessment tools are important in determining an individual’s potential for CAT. As understanding of thrombosis continues to expand and endovascular interventions become more prevalent in cancer care, further research is needed to update and improve CAT risk assessment and treatment guidelines. While the use of recently validated clinical risk-stratification models for VTE among ambulatory cancer patients is promising, identification and validation of new clinical and molecular biomarkers for VTE are keenly anticipated to further improve selection of high-risk patients for more personalized prophylactic strategies. Improving and amending existing guidelines such as the ACSO and others which have undergone rigorous systematic review is critical. Novel guidelines will allow physicians to account for both disease-based risk and intervention-based risk when considering endovascular cancer therapy, thereby maximizing efficacy of endovascular procedures while minimizing risk for VT.

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**Footnote**

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**References**


