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Patients with cancer are at increased risk of venous thromboembolism, which can be life-threatening. Health professionals and patients need to understand the risk factors

Minimising VTE in patients with cancer

In this article...

- The pathophysiology of venous thromboembolism
- The link between cancer and VTE
- Treatment of VTE in patients with cancer

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Abstract Watson J. (2016) Minimising VTE in patients with cancer. *Nursing Times*; 112: 8, 18-21.

Patients with cancer are at increased risk of venous thromboembolism, and health professionals and patients need to understand risk factors, the link with cancer and the management process. This article outlines the pathophysiology and epidemiology of VTE, its diagnosis, treatment and management, particularly in patients who have cancer.

Incidence of venous thromboembolism (VTE) is estimated at 1-2 per 1,000 of the population in England. Although often preventable, it is a significant cause of mortality and morbidity, and accounts for one-in-10 deaths in hospital (Health Select Committee, 2005). Patients with cancer have a one-in-five risk of developing a VTE, and thrombotic events are the second highest cause of death in patients with cancer (Khorana, 2010).

Pathophysiology

Blood clotting is necessary for the body to manage any internal or external injury. The damaged tissue causes platelets in the blood to become sticky and clump around the injury, where they become "activated" by the injured tissue releasing chemicals and mediators, which react with clotting factors to initiate a complex cascade. The end product is a fibrin mesh that traps blood cells and platelets, creating a clot.

Although a necessary part of the repair process, blood clotting can also result in VTE – the formation of thrombi in the blood vessels. The development of VTEs is associated with three main factors that predispose patients to the condition, known as Virchow's triad. These are:

- Haemodynamic changes (alterations in normal blood flow, stasis, turbulence);
- Endothelial injury (dysfunction or injury to the vascular endothelium);
- Hypercoagulability (alterations in the constitution of the blood).

Cancer, particularly solid tumours, negatively influence the three elements that Virchow associates with clot formation (Fig 1), which explains why people with cancer are at increased risk of VTE.

Risk factors

Risk factors associated with VTE include:

- Obesity;
- Immobilisation;
- Smoking;
- Oral contraception;
- Prothrombotic mutations.

The presence of malignancy can increase the impact of these risk factors.

The association between cancer and VTE is significant – it occurs in up to 20% of people with a cancer diagnosis (Gounaris et al, 2010), and the more advanced the cancer, the higher the risk. As a result, rates are higher in patients with metastatic disease (Mandelà et al, 2007). Many patients with cancer present late, so some present simultaneously with cancer and VTE; these patients appear to have a poorer prognosis than those with cancer alone (Sørenson et al, 2000).

Mortality is increased in patients with both VTE and cancer; for example, a large pulmonary embolism secondary to major surgery is three times more likely to be fatal in patients with cancer than in those having

5 key points

1. Venous thromboembolism can lead to serious complications and can be fatal
2. Patients with cancer are at increased risk of developing VTE, which is more likely to occur in some types of cancer than others
3. VTE can negatively affect outcomes for patients with cancer
4. The condition can recur more often in patients with cancer
5. Some cases of VTE may be avoidable

Risk factors such as obesity are associated with venous thromboembolism incidence

Alamy

TABLE 1. **VTE RATES BY MALIGNANCY**

Malignancy	VTEs per 1,000 patients
Ovary	120
Brain	117
Pancreas	110
Lymphoma	96
Stomach	85
Renal	84
Leukaemia	81
Colon	76
Liver	69
Rectal	62
Lung	61

Source: Levitan et al (1999)

similar surgery for non-malignant causes (Horsted et al, 2012). Patients with cancer who undergo major complex surgery are also at twice the risk of developing a VTE than those without cancer undergoing the same operation (Lee and Levine, 2003).

The risk of patients with cancer developing VTE is primarily influenced by tumour types (Table 1). However, treatment variables, such as disease stability and treatment, influence this risk. Central venous access devices and inpatient episodes can also increase risk, as can familial predispositions and clotting disturbances.

Consequences of VTE

Evidence suggests that clinical occurrence of symptomatic VTE negatively affects disease response rate, progression-free survival and overall survival (Chew et al, 2006). This suggests symptomatic VTE in patients with cancer may reflect the presence of a biologically more aggressive malignancy, or it may be the effect of thrombosis that in turn leads to a poorer prognosis.

VTE can have long-term consequences: patients may develop thromboembolic pulmonary hypertension or chronic venous obstruction, resulting in a permanently painful, swollen leg that is prone to ulceration (Palareti, 2012); Lukas et al (2009) also suggested that many experience significant fatigue and psychological morbidities following a venous thromboembolic event, greatly affecting morbidity and quality of life.

Presentation and diagnosis

The vast majority of VTEs present as a deep vein thrombosis (DVT) in the legs. Patients usually present with calf pain/tenderness, erythema and swelling, but signs can be subtle. However, cancer is more prevalent in patients with bilateral DVT, early recurrence or very high D-dimers (Watson et al, 2015). A tenth of DVTs occur in the arm, often secondary to the presence of a CVAD (Boersma et al, 2008).

In patients who present with a first DVT and no predisposing risk factors, the possibility of an occult malignancy should be considered, as it may be the first clue in the presentation of cancer. Investigations should include:

- Physical examination based on presenting complaint and patient history;
- Chest X-ray;
- Blood tests, including full blood count, serum calcium, liver function tests;
- Urinalysis.

Further investigations may be considered in patients aged over 40 years, such as an abdominopelvic computerised tomography (CT) scan, and a mammogram in women. However, Carrier et al (2015) proposed that routine screening with a CT scan of the abdomen and pelvis does not provide clinically significant benefit. Piccioli et al (2004) concurred that, while early detection of cancer may be associated with improved treatment possibilities, it remains uncertain whether this is translated into improved prognosis.

While VTE may be diagnosed in isolation and screening may not identify a malignancy, approximately 8% of patients with VTE will be diagnosed with cancer; this prevalence increases over time, especially in the over-60s (Carrier, 2015). Patients are also at increased risk of developing VTE in the period immediately following a new diagnosis of cancer (Prandoni et al, 1992).

Numbers of VTEs are underestimated, particularly in patients with cancer (Kahil, 2015). Many can be asymptomatic, and in patients with cancer, about 3% are diagnosed as an incidental finding on routine disease-staging CT scans (Moore et al, 2011).

Moderate and large pulmonary embolisms (PEs) can cause symptoms, which can depend on underlying lung health. The following are most common:

- Dyspnoea;
- Pleuritic chest pain;
- Cough and/or haemoptysis.

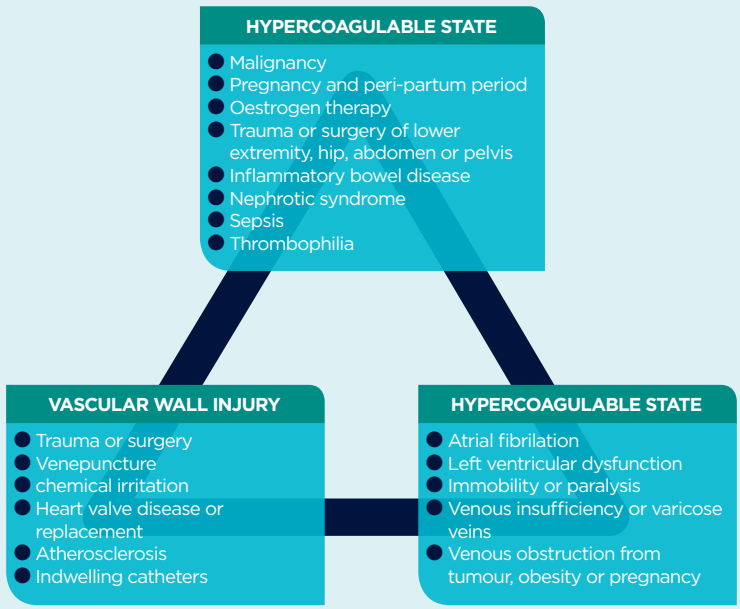
Fatal PEs are usually large, with more immediate clinical signs, including:

- Tachypnea;
- Tachycardia;
- Hypoxia;
- Hypotension;
- Signs of right-sided heart failure.

Incidental PEs may have some symptomology, such as breathlessness and cough, but can also be overlooked as the symptoms may be attributed to the malignancy.

Diagnosis of VTE is similar regardless of whether patients have cancer – ultrasound or CT for suspicion of DVT or PE respectively – but the signs and symptoms of cancer and its treatment may be misleading. The Wells test (Bit.ly/WellsTest) is recommended by the National Institute for Health and Care

FIG 1. **CANCER TREATMENT AND VIRCHOW'S TRIAD**



Source: Bayer Pharma AG, (2012). www.thrombosisadviser.com

Excellence (2012) but is not specifically validated in patients with cancer.

The use of the D-dimer as a screening tool before imaging is also not necessarily recommended in patients with cancer because of its false positive results, but a negative result may be useful in excluding a PE (King et al, 2008). Given the high incidence of VTE and cancer, clinicians must be vigilant and have a low threshold to exclude or include VTE as part of differential diagnoses.

Treatment and management

Incidental VTEs must be treated in the same way as symptomatic VTEs (Lyman et al, 2013). The American Society of Clinical Oncology published clinical guidelines on VTE prophylaxis and treatment in 2007, and a subsequent review explored best practice in patients with cancer (Lyman et al, 2015) (Box 1).

NICE (2010) also highlights the importance of patient information and working in partnership with patients. In oncology in particular, it is essential that patients understand the potential changes in risk in the context of treatment: risk peaks during episodes of hospitalisation, surgery and chemotherapy, but dips during episodes of recovery and good levels of mobility.

Low-molecular-weight heparin

Low-molecular-weight heparin (LMWH) is the anticoagulant of choice in patients with cancer (Barbosa, 2014). This is heparin broken into smaller parts, which makes it more predictable and requires less monitoring from the laboratory. However, platelets need to be >50 x 10^9 to achieve full anticoagulation without excessive risk (Carrier et al, 2015), although the dose may be halved if platelets of 25-50 x 10^9 fail to rise despite transfusion (Watson et al, 2015). LMWH is also less likely to cause thrombocytopenia, and is used in prophylaxis and treatment of VTE.

There is also evidence that LMWH is associated with much lower rates of VTE recurrence and similar rates of bleeding complications compared with other anticoagulants (Barbosa, 2014). Its shorter half-life facilitates temporary interruption, which is beneficial when negotiating procedures. There are also fewer drug interactions or food/diet restrictions. LMWH should be used for 3-6 months, or indefinitely in patients with active cancer.

Inferior vena cava filter

The role of inferior vena cava (IVC) filters remains controversial. They can be used in oncology patients before major surgery and those who have had:

- Active major bleed;
- Intracranial bleed;
- Thrombocytopenia or platelet/coagulation abnormalities.

However, their use has had mixed success, with some studies suggesting they lead to an increase in recurrent DVTs in non-cancer patients and no survival advantage (Lyman et al, 2013). Retrievable filters are preferable in the oncology setting and should be removed as soon as anti-coagulation can be commenced (Watson et al, 2015).

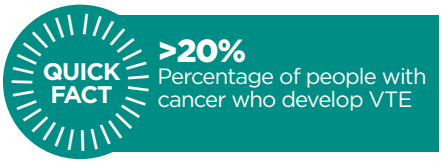
Direct oral anticoagulants

There is no evidence base on the use of direct oral anticoagulants, formerly known as novel oral anticoagulants, in oncology.

Recurrent VTE

A recurrent VTE is a clot at a site that was previously uninvolved or where resolution of the clot was documented (Heit et al, 2000). Recurrent clots are usually diagnosed with a set of new signs and symptoms, but may be picked up incidentally on re-staging CT scans/positron emission tomography scans.

Management of VTE recurrence in patients receiving anti-coagulant treatment is a challenge in the oncology setting because treatment may force an increase in anticoagulation, which increases the risk of bleeding. However, doses of LMWH may be divided into two to minimise the increased risk of bleeding (Merli et al, 2001). Adherence to treatment must be assessed as patients may find the daily/twice-daily injections challenging, while patients should also be monitored for the development of heparin-induced thrombocytopenia. The duration of treatment must also be considered, as well as the potential need for dose escalation in those already on anticoagulation therapy. If LMWH is used, it would be prudent to also check anti-factor Xa levels.



Recurrent PEs are the strongest risk factor in developing pulmonary hypertension, and patients with recurrent DVTs in the same leg have a strong risk of developing postphlebitic syndrome (Palareti, 2012). There is also a particularly high risk of recurrent VTE if patients stop anticoagulation therapy, especially if they have metastatic disease (Palareti, 2012).

Raising awareness

The close associations between VTE and cancer mean a VTE in a patient with cancer is not necessarily avoidable but, instead, may be part of the disease process. However, scrupulous attention must be paid to oncology patients' risk assessment, prophylaxis (where appropriate) and level of patient information to minimise those VTEs that may be avoidable.

Local initiatives

Much work has been completed at the Royal Marsden to raise awareness of VTE; the trust has consistently attained its Commission for Quality and Innovation (CQUIN) targets, through which a proportion of health providers' income is linked to the achievement of clinical targets.

Although much work has been completed in the organisation to ensure inpatients are informed about, and aware of, the risks associated with VTE, a gap was identified in day care. This is where ambulatory patients receive cycles of chemotherapy, often over several months, and it was identified as important to raise awareness in patients about:

- What VTE is;
- The signs and symptoms of a clot;
- What patients should do and where they should go if a VTE is suspected;
- How patients can help to minimise their risk of VTE.

The nursing team in day care developed an educational programme offered to all patients before chemotherapy. This explores VTE risks and how to minimise them. It is augmented by a poster and leaflet campaign, while an animated educational film is planned.

National initiatives

Organisations such as NICE, Lifeblood and the All-Party Parliamentary Thrombosis Group have been pivotal in raising national awareness about VTE, including:

- Challenges associated with assessment;
- VTE avoidance strategies;
- Timely diagnosis;
- Prompt and appropriate treatment and management.

Assessing the VTE risk of all inpatients within 24 hours of admission is mandatory in England (NICE, 2010), and its inclusion in the CQUIN framework appears to have provided sufficient political and clinical pressure for organisations to focus on the issue. Further CQUINs associated with appropriate VTE prophylaxis have compelled organisations to invest in and focus on VTE prevention. This focus has reduced the incidence of VTE-related secondary

BOX 1. **MANAGING VTE IN PATIENTS WITH CANCER**

Hospitalised patients

Patients with active malignancy and acute illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications. Those without additional risk factors may be considered for thromboprophylaxis in the absence of bleeding or other contraindications.

Ambulatory patients receiving systemic chemotherapy

Routine prophylaxis with an antithrombotic agent is not recommended for these patients. Clinicians may consider LMWH in selected outpatients with solid tumours who are receiving chemotherapy. The uncertainty of benefits and harms, as well as dose and duration of prophylaxis, must be discussed with the patient. Those with multiple myeloma, who are receiving thalidomide or lenalidomide-based regimens with chemotherapy, should receive pharmacologic thromboprophylaxis.

Patients undergoing surgery

All patients with malignant disease who are undergoing major surgery should be considered for pharmacologic thromboprophylaxis unless it is contraindicated. Prophylaxis should be commenced pre-operatively.

Mechanical methods may be added but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated. A combination of pharmacologic and mechanical prophylaxis may improve efficacy, especially in high-risk patients.

Pharmacological thromboprophylaxis should be continued for at least 7-10 days post-operatively. Extended prophylaxis with LMWH for up to four weeks should be considered in patients undergoing major abdominal or pelvic surgery for cancer, who have high-risk features, such as restricted mobility, obesity or a history of VTE.

Preventing recurrence in patients with established VTE

LMWH is preferred over unfractionated heparin for the initial 5-10 days of anti-coagulant treatment of patients with cancer and a newly diagnosed VTE, who do not have severe renal impairment. For long-term anti-coagulation therapy, LMWH for at least six months is preferred.

Anticoagulation therapy with LMWH beyond the initial six months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.

Risk prediction and patient awareness of VTE

Patients with cancer should be educated about VTE, particularly when they are at increased risk, such as when undergoing surgery, having chemotherapy or in hospital.

Source: Lyman et al (2015)

diagnoses and mortality (Catterick and Hunt, 2014). The initiative may influence other health economies in developed countries as they look to emulate the success achieved in the UK. **NT**

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