In patients with cancer-associated thrombosis, landmark studies have demonstrated that effective prophylaxis and treatment of thrombosis reduces morbidity and increases survival. However, the decision to initiate anticoagulant treatment in patients with venous thromboembolism (VTE) may expose the cancer patient to significant risks, including bleeding and adverse drug-drug interactions. Therefore, accurate identification of patients with VTE is vital to reduce the risk for thrombosis while also avoiding exposing patients to unnecessary risks associated with anticoagulant therapy.

Cancer-associated thrombosis (CAT) may present as a vast range of clinically significant thrombotic complications including deep vein thrombosis, pulmonary embolism, arterial thrombosis, nonbacterial thrombotic endocarditis, superficial thrombophlebitis, catheter-related thrombosis and hepatic venoclusive disease. As diagnosis of the condition based on clinical grounds alone is unreliable, physicians should select an appropriate objective diagnostic test to confirm or refute their clinical impressions.

DVT

Deep venous thrombosis (DVT) is clotting of blood in a deep vein of an extremity (usually calf or thigh) or in the pelvis. DVT is the primary cause of pulmonary embolism. When present, the symptoms and signs of DVT are nonspecific, vary in frequency and severity and are similar in arms and legs. They include, but are not limited to, leg pain, tenderness, ankle oedema, calf tenderness, swelling, and dilated veins.

WELLS’ CRITERIA

The diagnostic accuracy for DVT improves when the clinical probability is estimated before the use of diagnostic tests. The Canadian Wells’ Prediction Score, which stratifies proximal, but not distal, DVT into high, intermediate and low-risk categories, can be used to calculate pre-test probability of DVT, as follows (each factor scores 1 point):

- Recent treatment for cancer (last six months) or current palliation
• Paralysis, paresis, or cast of lower extremity
• Bedridden at least 3 days in last 4 weeks or major surgery in last 12 weeks
• Tenderness along deep venous system
• Unilateral calf swelling > 3 cm compared to other side
• Unilateral pitting oedema
• Superficial collateral veins
• Prior DVT

If an alternative diagnosis is considered more likely than DVT, 2 points are subtracted. Total scores are characterised as follows: low pre-test probability (PTP): 0; moderate PTP: 1 to 2; high PTP: 3 or greater.

### Wells Criteria for Assessment of Pretest Probability of DVT

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within 6 months, or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or recent plaster immobilisation of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for more than 3 days or major surgery within 12 weeks requiring general or regional anaestesia</td>
<td>1</td>
</tr>
<tr>
<td>Localised tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm larger than asymptomatic side</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

### Clinical probability simplified score

- DVT "likely" 2 points or more
- DVT "unlikely" 1 point or less
It is important to note that, when using the scoring system by itself, DVT cannot be ruled out completely in patients with a low probability score or confirmed in patients with a high probability score. However, use of such a score can help inform interpretation of subsequent diagnostic tests and reduce the need for invasive testing.\textsuperscript{12}

**D-DIMER LEVELS**

Levels of D-dimer, the degradation product of a cross-linked fibrin blood clot, are frequently elevated in patients with DVT. However, the validity of available DVT diagnostic algorithms in patients with cancer is compromised for a number of reasons, including the fact that D-dimer levels may be elevated in patients with cancer in the absence of thrombosis.\textsuperscript{13} A large study reported that 7.8\% of patients with cancer with a negative D-dimer test had acute DVT compared with 3.5\% in patients without cancer.\textsuperscript{14} Researchers also found that 88\% to 94\% of patients with cancer required further investigations beyond D-dimer testing, potentially negating the value of D-dimer testing as a screening tool for DVT in this population.\textsuperscript{14} A UK study found that a combination of Wells score, D-dimer and ultrasound (with repeat if negative) are feasible at most UK hospitals and are among the most clinical and cost-effective non-invasive diagnostic testing strategies for DVT.\textsuperscript{12}

**DVT SCREENING**

Gomes et al recommended that compressive duplex ultrasonography was the best initial imaging test for both suspected upper and lower-extremity deep venous thrombosis in cancer patients.\textsuperscript{10} The authors also suggested that magnetic resonance venography (MRV) is a valid alternative when ultrasound is inconclusive, but contrast venography remains the "gold standard."

**Pulmonary embolism**

The risk of pulmonary embolism (PE) is increased several-fold in the cancer population when compared with the general population,\textsuperscript{15} and is associated with significant morbidity and mortality in these patients.\textsuperscript{16} Patients with PE generally present with chest pain – either sudden in onset or evolving over a period of days or weeks - that worsens on taking a deep breath; shortness of breath; cough with blood-streaked sputum, and fatigue.

However, as with DVT, the diagnosis of PE may be difficult to make from clinical presentation alone because the symptoms tend to be nonspecific and are highly dependent on the size of the emboli and the patient's pre-existing cardiopulmonary status. As a result, objective testing is required to confirm or rule out a diagnosis of PE. A recent study highlighted the potential of cancer symptoms in obscuring the signs and symptoms of PE.\textsuperscript{17} O’Connell et al found that almost half (44\%) of cancer patients found to have unsuspected PE on cancer staging CT scans had previously exhibited signs or symptoms commonly associated with PE. In fact, that percentage increased to 75\% when fatigue was included as a symptom.
When compared to control patients, cancer patients with unsuspected PE were significantly more likely to have had a prior history of VTE (20% versus 3%), complain of fatigue (54% versus 20%) and shortness of breath (22% versus 8%). This research indicates that cancer patients with PE often have signs and symptoms that are overlooked by their health care professionals.17

There are several scoring systems and models of clinical likelihood of PE, which are included in guidelines for the diagnosis and management of PE18 (eg, one developed by Wells, or the revised Geneva score). Clinical characteristics and associated score, as set out in the modified Wells’ Criteria for Pulmonary Embolism for diagnosing pulmonary embolism, are as follows:19

Previous pulmonary embolism or deep vein thrombosis (+1.5)
Heart rate >100 beats per minute (+1.5)
Recent surgery or immobilisation (within the last 30 days) (+1.5)
Clinical signs of deep vein thrombosis (+3)
Alternative diagnosis less likely than pulmonary embolism (+3)
Haemoptysis (+1)
Cancer (treated within the last 6 months) (+1)

<table>
<thead>
<tr>
<th>Wells Criteria for Assessment of Pretest Probability of Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
</tr>
<tr>
<td>Suspected DVT</td>
</tr>
<tr>
<td>An alternate diagnosis is less likely than PE</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
</tr>
<tr>
<td>Immobilisation or surgery in the previous four weeks</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
</tr>
<tr>
<td>Haemoptysis</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in past six months)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score range</th>
<th>Mean probability of PE</th>
<th>% with this score</th>
<th>Interpretation of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 points</td>
<td>3.6%</td>
<td>40%</td>
<td>Low</td>
</tr>
<tr>
<td>3-6 points</td>
<td>20.5%</td>
<td>53%</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 6 points</td>
<td>66.7%</td>
<td>7%</td>
<td>High</td>
</tr>
</tbody>
</table>
ADDITIONAL TESTS

If PE is suspected, a careful assessment based on the history, physical examination, and known risk factors is necessary; additional studies, including electrocardiography (ECG), chest radiography, arterial blood gas analysis and D-dimer measurement may be considered. Electrocardiographic abnormalities, including unexplained tachycardia, are common in patients with acute PE but nonspecific. Chest radiographs are usually nondiagnostic, although it may exclude PE by uncovering an alternative diagnosis.

D-DIMER

Levels of D-dimer are generally elevated in patients with PE. When used alone, this test is nonspecific, because it can be positive in patients with cancer, infection, and other inflammatory states. This test is primarily valuable when used in conjunction with clinical-prediction scores, and may obviate the need for more costly evaluation.

In the case of PE diagnosis, data analysis from 1,721 patients showed that an ELISA D-dimer assay could be used to exclude PE in patients with cancer, although it was recommended that a higher cut-off value be used.

A recent prospective study of oncology patients found D-dimer levels to have a high negative predictive value and a high sensitivity in the diagnosis of PE.

IMAGING

Gomes et al suggested that suspected pulmonary embolism should be initially evaluated by helical (spiral) computed tomography (CT) or ventilation/perfusion lung scintigraphy, the former being preferred in cases of obvious pulmonary or pleural disease.

The authors added that indeterminate studies should prompt performance of contrast pulmonary angiography. Inferior vena cava thrombosis is also best assessed by contrast venography, with MRV and CT reserved as alternative imaging modalities.

Idiopathic DVT/PE

Commonly, however, DVT and PE can present without any symptoms. While identification of a patient’s risk factors is no doubt crucial in the initial diagnostic process, up to 30% of cases of PE develop idiopathically (ie. without an identifiable risk factor). Sometimes, a DVT or PE may only be discovered incidentally on a CT scan performed to assess the cancer patient’s response to cancer therapy or to screen for metastases. With the widespread use of CT examinations, in particular with the introduction of multidetector CT scanners, the detection of unsuspected DVT/PE has become increasingly common.

OCCULT CANCERS
There is general agreement that patients with idiopathic thrombosis present a higher risk of occult cancer (a cancer of unknown primary site or origin). Approximately 10% of patients who present with an idiopathic or unprovoked VTE are diagnosed with cancer within the next 1 to 2 years.26 The prospective SOMIT trial (Screening for Occult Malignancy in Patients with Symptomatic Idiopathic Venous Thromboembolism) showed that an extensive screening programme was able to identify most of the hidden malignancies with a high degree of sensitivity.27 The extensive screening led not only to an early detection of malignancies, but also to the identification of malignancies at an early stage. However, there was no improvement in overall survival, which was the primary endpoint of the study.

NICE guidelines (CG144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing) recommend that all patients diagnosed with unprovoked DVT or PE, who are not already known to have cancer, should be offered the following investigations for cancer:

- A physical examination (guided by the patient's full history) and
- A chest X-ray and
- Blood tests (full blood count, serum calcium and liver function tests) and
- Urinalysis.

In addition, physicians should consider further investigations for cancer with an abdominopelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation.28

References