Occult cancers are frequent in patients with unprovoked venous thromboembolism (VTE) and approximately 10% of patients with unprovoked VTE will be diagnosed with cancer within one year of their thrombotic event. A “limited” occult cancer screening (medical history taking, physical examination, routine laboratory blood tests and a chest-X ray) detects a large proportion of these occult malignancies. A more extensive occult cancer screening strategy (computed tomography, ultrasound, tumor markers, etc) seems to increase the number of cancers detected. However, current evidence does not support improvements in malignancy-related mortality, morbidity or quality of life with an extensive cancer screening strategy. Further clinical trials are required to assess the risks and benefits of a comprehensive screening program in patients with unprovoked VTE.
The association between occult cancers and VTE was first described by Dr Armand Trousseau in 1865\(^1\). Over time it has become clear that the strongest association exists between occult malignancies and VTE that are unprovoked. Patients who develop an unprovoked VTE have a four-fold higher risk of receiving a diagnosis of cancer within the next few months compared to patients with VTE triggered by known risk factors\(^2\)-\(^4\). Approximately 10\% of patients with unprovoked VTE will be diagnosed with cancer within one year of their thrombotic event\(^2\)\(^,\)\(^5\), with the highest standardized incidence ratio of cancer observed within the first 6 months of VTE diagnosis \(^6\)\(^,\)\(^7\). The occult tumor types most commonly presenting with unprovoked VTE are cancers of the ovary, pancreas and liver\(^6\)\(^,\)\(^8\).

Given that occult cancers are common in patients with unprovoked VTE, it has been suggested that these patients should undergo cancer screening. However, the utility of a search strategy is controversial. There is presently no consensus and, in fact, there is great diversity in experts opinions and clinical practices regarding whether to screen and what type of tests should be included\(^9\)-\(^12\). Proponents of screening argue that identifying these occult cancers are important for several reasons: 1) occult cancers detected at the time of the VTE diagnosis may be at a curable stage, while if detection is delayed this may no longer be the case; 2) earlier detection and treatment of cancer might help to prevent cancer-related complications (e.g. compression syndromes) or reduce the need for aggressive or highly toxic cancer therapies; and 3) treatment of cancer-associated VTE is different from that for VTE not associated with cancer as with low molecular weight heparin is recommended over vitamin K antagonists\(^13\) to reduce the risk of recurrent VTE \(^14\) and potentially increase survival in cancer patients\(^15\)\(^,\)\(^16\).

**Limited occult cancer screening**

Retrospective studies have suggested that “limited” occult cancer screening (medical history taking, physical examination, routine laboratory blood tests and a chest-X ray) is adequate to detect up to 90\% of occult cancers in patients with
In a retrospective cohort study of 1389 patients with confirmed VTE (provoked and unprovoked), investigators identified 150 cases with occult cancers, of which 83% were easily detected by a combination of medical history, physical examination and routine blood tests. Sixty-six (44%) patients had their cancer detected within the next 6 months. In another retrospective cohort study, 16 of 142 patients (12%) with unprovoked VTE were diagnosed with cancer during their hospitalization. All 16 patients had at least one or more abnormalities on “limited” occult cancer screening. Three patients were diagnosed with cancer during follow-up, two of whom did not have any clinical abnormalities at initial evaluation. Only 3.6% of patients who did not have any abnormal findings on the “limited” occult cancer screening subsequently developed cancer. Based on these two retrospective studies, a “limited” occult cancer screening strategy appears to be a sensible approach to detect a large majority of occult cancers.

**Extensive occult cancer screening**

Several retrospective and prospective cohort studies have assessed the use of more extensive occult cancer screening programs in patients with unprovoked VTE. One randomized controlled trial and one prospective cohort study suggest that a more extensive occult cancer screening can increase the rate of detection of cancer. The largest prospective cohort study followed 864 VTE patients (40% unprovoked and 60% provoked) undergoing a two-step screening strategy. The initial screening step consisted of “limited” occult cancer screening, which included a thorough history and physical examination, blood work (complete blood count, liver and renal function test, sedimentation rate and serum electrophoresis), a urinalysis and a chest X-ray. A total of 167 patients had abnormalities and 34 (20%) of these patients had a confirmed diagnosis of cancer. The remaining 830 patients underwent further investigations including: ultrasonography (U/S) of the abdomen/pelvis and serum tumour markers (carcinoembryonic antigen (CEA), prostate specific antigens (PSA) for men and cancer antigen-125 (CA-125) for women). Fifty four patients (6.5%) had
abnormal findings in the second step of the screening and 13 of these (24%) patients subsequently had a confirmed diagnosis of cancer. During the 1-year follow-up, 14 (1.7%) additional cancers were diagnosed. Therefore the first step or “limited” occult cancer screening had a sensitivity of 56% and adding a second step or “more extensive” screening increased the sensitivity to 77%. This study suggests that “limited” occult cancer screening alone is insufficient to detect all occult cancers, and that almost a quarter of cancers remain undetected despite extensive testing. However, the design of this study does not answer the question of whether cancer screening would offer a beneficial effect on the prognosis (mortality, morbidity) of VTE patients. A recently completed prospective centre-controlled cohort study, the Trousseau study, assessed the added value of performing mammography in women and thoracic and abdominal computed tomography (CT) in all patients presenting with idiopathic VTE20. A total of 630 patients were enrolled, of whom 288 underwent basic investigations and 342 had CT +/- mammography performed in addition to basic investigations. The main patient characteristics were similar for both groups. Malignancy was diagnosed at enrolment in 2.4% of those in the basic investigations group and 3.5% in those who also underwent CT +/- mammography. However, there was no difference in the number of cancers subsequently diagnosed (5.3% vs. 3.7%, respectively) or in overall mortality (8.3% vs 7.6%, respectively) during 31 months of follow up.

Only one randomized controlled trial has evaluated the effect of extensive screening on patient survival. The SOMIT investigators group randomized patients with negative “limited” occult cancer screening to either a strategy of more extensive testing or to no further testing19. The “limited” occult cancer screening consisted of: clinical history, physical examination, complete blood count, liver function tests, calcium, urinalysis and chest X-ray. The more extensive testing battery included U/S and CT of the abdomen/pelvis, gastroscopy or double-contrast barium swallowing, colonoscopy or sigmoidoscopy followed by barium enema, fecal occult blood, sputum cytology, CEA, CA-125, alpha-fetoprotein (α-FP), PSA and trans-abdominal U/S of
prostate for men, Papanicolaou smear and mammography for women. Two hundred and one eligible patients with unprovoked VTE and negative “limited” occult cancer screening were included into the study and randomized. A total of 56 patients were diagnosed with cancer. Thirty two (57%) were diagnosed by the “limited” occult cancer screening. Out of the 99 patients undergoing extensive testing, 13 (13%) were diagnosed with cancer. Only one cancer was missed and became symptomatic in the two-year follow-up period. The sensitivity of the extensive occult cancer screening was 93%. Furthermore, more cases with earlier-stage cancers (T1-2,N0) were detected by extensive screening compared to the control group (64% versus 20%, p=0.047). Although there was an absolute risk reduction of malignancy-related mortality of 1.9% in favor of the extensive testing group during the 2-year follow-up period, this difference was not statistically significant. This result may be secondary to the inadequate statistical power from the small sample size (Type II error) or to no true difference in survival between the groups. The SOMIT investigators were only able to recruit 20% of the expected number of patients and the study was conducted in only 5 of the 40 centers approached. The limited recruitment of participants and centers raises concerns about selection bias and the generalizability of these findings. Furthermore, it is uncertain whether extensive screening simply introduces lead-time and length-time biases, as opposed to prolonging survival.

The components of an ideal extensive malignancy screening program are still unknown. A decision analysis using the data from the SOMIT trial reported that “limited” occult cancer screening in combination with a CT abdomen/pelvis had a number needed to screen (NNS) of 1021. In other words, ten patients with unprovoked VTE need to be screened with a “limited” panel and CT abdomen/pelvis to find one case of occult cancer. A “limited” occult cancer screening in combination with U/S of the abdomen alone, U/S of the abdomen and colonoscopy or U/S abdomen and tumour markers have a NNS of 20, 17 and 17, respectively. Similarly a meta-analysis including 4378 patients from 15 studies demonstrated that extensive occult cancer screening using CT of the abdomen/pelvis statistically significantly increased the proportion of occult cancer
detected from 49% to 70%\textsuperscript{2}. However, investigators could not determine complication rates, cost-effectiveness and difference in morbidity and mortality associated with more extensive screening\textsuperscript{2}.

Before performing extensive screening in patients with unprovoked VTE, a number of factors must be considered. These include: 1) morbidity and risks of invasive diagnostic procedures to confirm the presence of malignancy; 2) cost of extensive testing; 3) incidental findings and their associated morbidity; and 4) psychological burden associated with new diagnosis of malignancy or false-positives. Finally, it is important to bear in mind that improvements in cancer outcome not only depend on accurate and timely screening but also on effective cancer treatments. Currently, one clinical trial is assessing the potential benefits of a comprehensive CT of the abdomen/pelvis\textsuperscript{22}.

In conclusion, occult cancers are found in 10% of patients with unprovoked VTE. A “limited” occult cancer screening detects a large proportion of occult cancers in these patients. A more extensive occult cancer screening strategy seems to increase the number of cancers detected. However, current evidence shows that extensive cancer screening strategy does not improve malignancy-related mortality, morbidity or quality of life. Further clinical trials are required to assess the risks and benefits of a comprehensive screening program in patients with unprovoked VTE. In the meantime, patients should be carefully evaluated by history, physical examination, routine blood work and undergo age- and gender-specific cancer screening (e.g. colon cancer screening in patients over 50 years of age). Further follow-up is only required in patients with abnormal findings.
References


