Facts and figures in occult cancer screening among patients with unprovoked VTE

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ABSTRACT

Venous thromboembolism (VTE) may represent the first clinical manifestation of an underlying malignancy. Approximately 5-10% of patients presenting with an unprovoked VTE are diagnosed with cancer within the following year. This association has prompted interest in systematic cancer screening, although the optimal strategy remains debated due to potential harms, costs, and uncertain clinical benefit. Early studies suggested that extensive screening detects more cancers and may identify them earlier, but subsequent larger trials demonstrated no meaningful reduction in missed cancers, cancer-related mortality, or stage at diagnosis. An individual patient data meta-analysis including over 2,300 patients confirmed that extensive screening increases baseline cancer detection but does not improve 12-month cancer prevalence or survival and is associated with more false positives and downstream testing. Notably, age emerged as the strongest and most consistent predictor of occult cancer, whereas risk prediction scores such as RIETE and SOME showed limited discriminatory performance. Current international guidelines recommend a limited screening approach consisting of careful history and physical examination, basic laboratory tests, chest imaging when appropriate, and routine age- and sex-appropriate cancer screening. Ongoing research focuses on targeted screening in higher-risk patients and the evaluation of novel biomarkers.

Key words: venous thromboembolism; epidemiology; occult cancer.

Introduction

Venous thromboembolism, encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal condition with an annual incidence of approximately 1 to 2 cases per 1,000 persons.[1] While many cases are provoked by transient risk factors such as surgery, trauma, prolonged immobility, or known active cancer, up to 40-50% occur in the absence of an identifiable trigger and are termed unprovoked VTE. These events often raise clinical suspicion for occult cancer, given the well-established relationship between malignancy and thrombosis first described by Armand Trousseau in the 19th century.[2] The link between VTE and cancer reflects complex biological mechanisms involving tumor cell procoagulant activity, cytokine release, immobility, vascular compression, and vascular inflammation. Identifying an underlying malignancy early could potentially improve patient outcomes through earlier initiation of cancer-specific therapy. However, extensive investigations also pose risks of overdiagnosis, anxiety, radiation exposure, complications from invasive procedures, and cost. The optimal balance between thoroughness and prudence has therefore been the subject of intense study and debate.

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Epidemiology and risk factors

The reported incidence of occult cancer detection following an unprovoked VTE varies between 4% and 10% within the first year, depending on the population and screening intensity. The majority of cancers are diagnosed at the same time as VTE diagnosis (e.g., discovered on the CT scan that diagnosed PE) or within the first 6 months, suggesting that most occult malignancies are clinically evident within a relatively short period.[3] Commonly identified cancers include lung, pancreatic, colorectal, ovarian, and renal cell carcinomas, as well as hematologic malignancies, but all locations are possible. Observational studies have consistently shown that patients with unprovoked VTE have a two- to fourfold increased risk of subsequent cancer diagnosis compared with the general population.[3] Several clinical characteristics increase the likelihood of an underlying malignancy: older age, male sex, anemia, thrombocytosis, smoking, or unexplained weight loss. In contrast, patients with transient provoking factors do not have a higher risk for cancer.[4,5] A risk stratification

tool has been proposed by the RIETE investigators to identify higher-risk subgroups. Among 5,863 patients with acute VTE and no known cancer at baseline, 444 individuals (7.6%) were diagnosed with malignancy within 1 to 24 months. Using multivariable modelling, the authors identified several independent predictors of cancer that, when combined, created a weighted score. These variables include male sex (+1), age >70 years (+2), chronic lung disease (+1), anemia (+2), and thrombocytosis (+1). Protective variables were also identified, including recent surgery (-2) and a history of prior VTE (-1). When applied to the cohort, the score stratified patients into low- and high-risk groups. Patients with a score of ≤2 points had a 24-month cancer incidence of 5.8%, whereas those with scores ≥3 had a higher incidence of 12%, doubling the risk.

Ihaddadene *et al*.[6] conducted a post-hoc analysis of the SOME trial and identified three variables independently associated with the detection of occult cancer within one year of an unprovoked VTE: age ≥60 years (OR 3.1; 95% CI 1.4-6.9), a history of provoked VTE (OR 3.2; 95% CI 1.2-8.6), and current smoking (OR 2.8; 95% CI 1.2-6.3). The SOME score allocates one point for each factor. Patients with 0-1 points are categorized as low risk for underlying malignancy, whereas those with scores of 2 or more are considered high risk.

The performance of the RIETE and SOME risk scores was evaluated in an individual patient data meta-analysis among 1,830 patients with unprovoked VTE enrolled in three prospective screening studies[7]. During a median follow-up of around one year, 98 patients (5.4%) were diagnosed with cancer. Both scores showed poor overall discriminatory ability, with pooled AUC values of 0.59 for RIETE and 0.56 for SOME. When dichotomized, the RIETE score identified a subgroup with about a twofold higher cancer risk (5.9% *vs* 2.9%), whereas the SOME score showed no meaningful risk separation. Age was the only consistently significant predictor across analyses.

Rationale for screening

The main goal of occult cancer screening after an unprovoked VTE is to detect cancer at an early, potentially curable stage. In theory, this should translate into improved survival and reduced morbidity. Historically, clinicians have employed a variety of strategies, from targeted history-taking and physical examination to advanced imaging modalities. As many cohort studies suggested that up to 10% of patients with idiopathic VTE had underlying cancer, this prompted enthusiasm for extensive screening.

A systematic review of studies published up to the early 2000s estimated that the period prevalence of occult cancer in patients with unprovoked VTE was 6.1% at baseline and increased to 10% within 12 months (Table 1).[8] About half of cancers were detected at the time of VTE or within the first month, while the remainder emerged during follow-up. When comparing strategies, extensive screening, especially CT imaging of the abdomen and pelvis, detected a greater proportion of cancers at baseline than limited screening (history, examination, basic labs, chest X-ray). However, even extensive testing missed a substantial number of cancers that became clinically apparent later. Data on whether extensive screening improved detection of early-stage disease were limited and inconsistent; although some studies suggested an advantage, the evidence was insufficient to determine whether earlier detection improved patient outcomes such as survival. The review highlighted major gaps: no data on potential harms (false positives, radiation exposure, anxiety), no cost-effectiveness analyses, and wide variability in study designs and screening protocols. Another drawback for extensive cancer screening is that it may lead to unnecessary holding anticoagulation for invasive procedures and complication resulting from additional testing.

In addition, a later individual patient data meta-analysis (IPDMA) of trials comparing limited and extensive cancer screening after unprovoked VTE showed that extensive screening did not reduce overall mortality, and patients in whom an occult cancer was detected had a generally poor prognosis.[9]

Key clinical trials

Four randomized trials have assessed cancer screening in patients with unprovoked VTE (Table 2).

SOMIT trial

In this early randomized trial,[10] 201 patients with idiopathic VTE and no evidence of cancer on routine clinical evaluation were assigned to either extensive systematic cancer screening or no further testing. Extensive screening -which included abdominal/pelvic ultrasound and CT, gastroscopy, colon evaluation, sputum cytology, tumor markers, and sex-specific tests- identified 13 occult cancers (13.1%) at baseline and led to only one additional cancer diagnosis (1%) during two-year follow-up, compared with 10 delayed diagnoses (9.8%) in the control group. Cancers detected in the screening arm were generally at earlier stages and

Table 1. Summary of key systematic reviews evaluating occult cancer screening strategies after unprovoked venous thromboembolism.

Study	Population (n)	Screening strategies	Baseline cancer yield	12-month prevalence	Key findings
Carrier *et al.* Systematic review (2008)[8]	36 studies - 9,516 patients	Limited *vs* extensive (US, CT, tumor markers)	Not uniformly reported	~10% for unprovoked VTE	Extensive screening detects more cancers initially but no evidence of early-stage or survival benefit
van Es IPDMA (2017)[12]	10 studies - 2,316 patients	Limited *vs* extensive (CT, PET/CT, US, markers)	2.4% *vs* 4.5%	4.2% *vs* 5.6% (NS)	Extensive screening increases initial detection, but not 12-month yield; age strongest predictor

IPDMA, individual patient data meta-analysis; US, ultrasonography; CT, computed tomography; VTE, venous thromboembolism; NS, not significant.

Table 2. Summary of key trials evaluating occult cancer screening strategies after unprovoked venous thromboembolism.

Study	Population (n)	Screening strategies	Baseline cancer yield	12-month prevalence	Key findings
SOMIT Trial (2004)[13]	201	Extensive multi-modal screening *vs* no further testing	13.1% *vs* 1%	14.1% *vs* 6.9%	No significant mortality difference; study underpowered
SOME Trial (2015)[10]	854	Limited *vs* limited + CT abdomen and pelvis	2.0% *vs* 3.2%	3.2% *vs* 4.5% (NS)	CT increases baseline detection slightly; no 12-month benefit
MVTEP Trial (2016)[11]	394	Limited *vs* PET/CT	2.0% *vs* 3.6%	4.4% *vs* 3.6% (NS)	PET/CT does not improve detection; more false positives
Prandoni *et al.* (2016)[13]	195	Thoracic/abdominal/pelvic CT + FOBT *vs* limited physician-directed screening	10.2% *vs* 8.2%	NA	No benefit in cancer detection or mortality

CT, computed tomography; FOBT, fecal occult blood test; NS, not significant; NA, not available.

were diagnosed far sooner (mean 1.0 *vs* 11.6 months). Although the trial demonstrated that extensive screening detects more and earlier cancers, it lacked power to show a mortality benefit, and the study was prematurely stopped due to recruitment challenges.

SOME trial

The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial was a multicenter, randomized controlled study that enrolled 854 patients with a first episode of unprovoked VTE.[11] Participants were randomized to limited screening (comprising detailed history, physical examination, basic laboratory testing, chest radiography, and age-appropriate cancer screening) or the same strategy plus CT of the abdomen and pelvis. The proportion of missed cancers after completion of each screening strategy was low and not different between the two groups. At one year, cancer was diagnosed in 3.2% of the limited-screening group and 4.5% of the extensive-screening group - a non-significant difference. Most cancers were identified within six months, and there was no difference in cancer-related mortality or stage at diagnosis. The trial demonstrated that routine addition of CT imaging does not confer a clinically meaningful benefit.

MVTEP trial

The Maladie Veineuse Thromboembolique et PET (MVTEP) trial compared limited screening with whole-body 18F-FDG PET/CT in 394 patients with unprovoked VTE.[12] Cancer was detected in 3.6% of the PET/CT group and 4.4% of the control group, again without a significant difference. However, the secondary outcome of the MVTEP trial showed that FDG PET/CT missed significantly less occult cancer than limited screening alone (absolute risk difference 4.1%, 95% CI: 0.8 to 8.4%, p=0.01).

Prandoni *et al.* - Semin Thromb Hemost

This multicenter randomized trial evaluated whether a CT-based screening strategy (thoracic, abdominal, and pelvic CT plus fecal occult blood test) improves cancer detection compared with a limited, clinician-directed diagnostic approach in 195 patients with unprovoked VTE.[13] At one month, occult cancer was detected in 10.2% of patients in the CT arm and 8.2% in the control arm, a nonsignificant difference (absolute difference 2.0%; p=0.81). Additional cancers detected during follow-up were similarly few in both groups (2 per arm), and cancer-related mortality did not differ. Most cancers in both groups were stage II-IV, and the CT-based approach did not meaningfully improve early-stage detection. Consistent with the SOME trial, this study concluded that extensive CT imaging does not provide a clinically relevant advantage over limited, symptom-guided screening.

In view of these findings, the prior systematic review was updated to reassess the prevalence of occult cancer in patients with unprovoked VTE and to evaluate whether extensive screening offers advantages over limited clinical assessment (Table 1).[14] The authors pooled individual patient data from 10 prospective studies, including 2316 patients, providing the most precise estimates to date.

Across the pooled cohort, the 12-month prevalence of occult cancer was 5.2%, half of the previous estimate that served for the calculation of the sample size of SOME and MVTEP. Two-thirds of cancers were detected at baseline, and the remainder during follow-up. Age was the only predictor of cancer diagnosis, with extremely low cancer prevalence in patients under 50 (1.0%) and nearly 7% prevalence in those aged 50 or older.

Although extensive screening (CT abdomen/pelvis or PET/CT) identified more cancers at the initial evaluation than limited screening (4.5% *vs* 2.4%), there was no significant difference in overall 12-month cancer detection between groups. Moreover, extensive imaging did not meaningfully increase the proportion of early-stage cancers detected. Notably, most cancers discovered in the extensive screening arm were identified by components of the limited screening, such as history, examination, laboratory abnormalities, or chest radiography. Extensive screening also produced more false positives and triggered additional downstream testing. In addition, this individual patient data meta-analysis (IPDMA) showed that extensive screening did not reduce overall mortality, and patients in whom an occult cancer was detected had a generally poor prognosis with a mortality rate of 48.2% in patients from the extensive screening group *vs* 54.8% in patients from the limited screening strategy group.[9]

Current guideline recommendations

Based on the convergence of evidence, multiple professional societies have issued recommendations that favor limited screening approaches.

- The International Society on Thrombosis and Haemostasis (ISTH) recommends a limited screening strategy consisting of comprehensive history and physical examination, complete blood count, serum calcium, liver function tests, urinalysis, and chest radiography, along with age- and sex-appropriate cancer screening such as mammography, colonoscopy, Pap testing, and prostate-specific antigen testing.[15]
- For people with unprovoked DVT or PE who are not known to have cancer, the National Institute for Health and Care Excellence (NICE) guidance recommends reviewing the medical history and performing baseline blood test, including full blood count, renal and hepatic function, PT and APTT, and offering a physical examination.[16]
- Similarly, the European Society of Cardiology (ESC) guidelines developed with the European Respiratory Society (ERS) suggest that the search for occult cancer after an episode of VTE may be restricted to careful history taking, physical examination, basic laboratory tests, and a chest X-ray (if no CTPA was performed to diagnose PE).[17]

Clinical approach in practice

A pragmatic and evidence-based approach to evaluating patients with unprovoked VTE can be summarized as follows:

1. Comprehensive history and physical examination, focusing on constitutional symptoms, recent changes in appetite or bowel habits, and palpable masses.
2. Basic laboratory tests, including complete blood count, renal and liver function tests.
3. Chest radiograph to assess for pulmonary or mediastinal pathology at minimal cost and radiation exposure.
4. Routine age- and sex-appropriate cancer screening, including colonoscopy, mammography, Pap test, and prostate screening per national guidelines.
5. Directed investigations performed when initial evaluation or clinical context raises suspicion.
6. Follow-up surveillance during the first 12 months, when the majority of occult cancers manifest.

Future directions

Future directions for cancer screening in patients with unprovoked VTE include developing targeted strategies for high-risk patients and investigating new, non-invasive biomarkers like liquid biopsies for earlier detection.

Targeted strategies for high-risk patients

Based on the data from van Es IPDMA, our group completed the MVTEP2/SOME2 study, an open label randomized controlled trial of 1276 patients older than 50 years of age with a first unprovoked episode of VTE who were randomized in a 1:1 ratio to have a limited screening alone or in combination with FDG PET/CT. The primary outcome of the trial is the proportion of cancers that were missed by the screening strategy. The last patient was recruited in 2025 and will complete follow-up in July 2026.

PEETAC (NCT03937583) is another trial assessing FDG PET/CT for occult cancer screening that is ongoing in Spain. A total of 650 patients with a new diagnosis of unprovoked VTE at high risk for occult cancer according to the RIETE score will be randomized in a 1:1 ratio to a limited screening strategy (usual management of patients with unprovoked VTE) versus extended screening using FDG PET/CT. The primary outcome of the trial is the number of occult cancers diagnosed by each screening strategy during a 12-month follow-up.

Liquid biopsies

Liquid biopsy is an emerging technology that detects information in bodily fluids. It is considered an appealing alternative to the current screening tools for cancer as it is minimally invasive, affordable, not associated with radiation exposure, and may differentiate between primary tumor locations. Liquid biopsy targets consist of cell-free or structure-free molecules (e.g., proteins, nucleic acids, metabolites) or targets that retain cellular or subcellular structure (e.g., circulating tumor cells, tumor-educated platelets, extracellular vesicles).[18]

PLATO-VTE was a multicenter prospective cohort study of 476 patients with unprovoked VTE evaluating whether platelet RNA sequencing -a promising liquid biopsy approach- could outperform standard limited cancer screening for detecting occult malignancy.[19] Over 12 months, 28 adjudicated cancers were identified (6%), with limited screening detecting 72% of cases at a high specificity of 91%. Platelet RNA sequencing, however, performed poorly: the algorithm generated very high cancer probability scores for most participants, yielding an AUROC of only 0.54 (95% CI, 0.41-0.66). At the predefined "high-sensitivity" threshold (0.54), the test reached 100% sensitivity, but at the cost of an unusable specificity of 8%, and at the "high-specificity" threshold (0.89), both sensitivity (68%) and specificity (36%) were markedly inferior to limited screening. Platelet RNA sequencing failed to meaningfully discriminate cancer from non-cancer cases, likely due to biological and pre-analytical factors such as acute VTE–related inflammation, anticoagulation use, and algorithm mismatch with this population. Nevertheless, a secondary analysis of PLATO using quantitative targeted proteomics identified ten proteins in patients with occult cancer that yielded an adjusted c-statistic of 0.78 (95% CI, 0.70-0.87), suggesting potential of plasma proteomic tests as novel biomarker for occult cancer in patients with unprovoked VTE.[20]

Conclusions

The relationship between unprovoked venous thromboembolism and occult cancer remains an important clinical consideration. Despite the intuitive appeal of extensive screening, high-quality evidence demonstrates that such strategies do not meaningfully increase cancer detection or improve outcomes. The contemporary standard of care emphasizes a limited, symptom-guided approach combined with routine age-appropriate cancer screening.

Clinicians should maintain vigilance during follow-up and respond promptly to evolving clinical signs. Future research focus-

ing on individualized risk prediction, biomarker integration, and innovative diagnostic technologies may further refine the balance between detection and prudence in this complex clinical domain.

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