

Occult cancer and thromboembolism: current epidemiology and its practical implications

Chih-Hao Chao^{1*}, Hsin-Yi Wang^{2,3*}, Chia-Hung Kao^{4,5,6}

1 Division of Chest Medicine, Department of Internal Medicine, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan

2 Department of Nuclear Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

3 Department of Life Sciences, National Chung Hsing University, Taichung, Taiwan

4 Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

5 Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

6 Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

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ABSTRACT

Venous thromboembolism (VTE) may be the first presentation of malignancy. Up to 10% of patients with unprovoked VTE are diagnosed with occult cancer within 1 year. Cancer patients with concomitant VTE have a worse outcome. While limited screening strategy (thorough medical history, physical examination, basic laboratory tests, and chest X-ray) and extensive screening strategy (limited screening plus computed tomography scan of the abdomen/pelvis or ¹⁸F-fluorodeoxyglucose positron emission tomography–computed tomography) have a similar ability to detect early-stage cancer and improve morbidity and mortality of cancer patients with unprovoked VTE, the extensive screening strategy has been shown to diagnose occult cancer earlier. Among the risk factors for occult cancer in patients with unprovoked VTE, age is the most promising one. The risk of occult cancer detection increases with age. The newly developed RIETE score helps identify risk of occult cancer and might decrease unnecessary diagnostic procedures in lower-risk patients. Current guidelines suggest that patients with first unprovoked VTE undergo limited screening, with age- and sex-specific cancer screening, including colon, breast, cervical, and prostate cancers.

Background The most common presentations of venous thromboembolism (VTE) are deep vein thrombosis and pulmonary embolism. Numerous risk factors, most frequently major surgery, trauma, malignancy, or pregnancy, are responsible for development of VTE.¹ VTE is a frequent comorbidity of malignancy, especially common in pancreatic, brain, lung, and ovarian cancers. Around 20% to 30% of VTE cases occur in patients with malignancy.² The incidence of VTE in cancer patients has been rising in recent years.²⁻⁵ VTE without readily identifiable risk factors is called unprovoked VTE; it accounts for around half of VTE patients.⁶⁻⁸ Unprovoked VTE is associated with a significantly higher risk of recurrent VTE.⁹ Up to 10% of patients with unprovoked VTE are diagnosed with occult cancer within 1 year.¹⁰⁻¹²

Epidemiology of occult cancer in patients with unprovoked venous thromboembolism In 1865, Trousseau¹³ was the first to report an association

between unprovoked VTE and occult cancer. Numerous subsequent studies and reviews supported that unprovoked VTE may be the first presentation of occult cancer. The prevalence of occult cancer within 1 year of VTE diagnosis was reported to reach 10%.¹⁰⁻¹² But the reported incidence seems to be lower in more recent studies. A prospective study by Van Doormaal et al¹⁴ reported occult cancer in 3.7% to 5% of patients with unprovoked VTE. The reported prevalence was also lower in multicenter randomized controlled trials. In the Canadian SOME trial (Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism), Carrier et al¹⁵ reported that 3.9% of patients had a new diagnosis of occult cancer within 1 year of VTE diagnosis. The open-label MVTEP study conducted in France (Standard Diagnostic Procedures With or Without Fludeoxyglucose F 18 Positron Emission Tomography in Finding Cancer in Patients With a Blood Clot in a Vein), which enrolled 399 patients with

Correspondence to:

Chia-Hung Kao, MD, Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan, phone: +886 4 22052121, email: d10040@mail.cmuh.org.tw

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* C-HC and H-YW contributed equally to this work.

unprovoked VTE,¹⁶ reported the prevalence of occult cancer of 5.3% within 1 year and 6.3% within 2 years of VTE diagnosis. In a systematic review by van Es et al,¹⁷ who extracted raw data from 10 prospective studies between October 2002 and April 2014 in Europe and North America, the 12-month prevalence of cancer after VTE diagnosis was 5.2%. The incidence of new cancer diagnosis was the highest in the first 6 months following VTE events, and around 40% of patients had metastatic cancer at the time of diagnosis.¹⁸

The prevalence of cancer within 1 year of VTE diagnosis increases with age. The 12-month prevalence of cancer was 0.5% (95% CI, 0.03%–8.2%) in patients younger than 40 years, 1.0% (95% CI, 0.5%–2.3%) in those younger than 50 years, 6.8% (95% CI, 5.6%–8.3%) in those older than 50 years, and 9.1% (95% CI, 5.6%–15%) in those older than 80 years.¹⁷ In a study using data from the multicenter international observational RIETE registry (The Computerized Registry of Patients with Venous Thromboembolism), a total of 5863 patients with acute VTE without cancer diagnosis within 30 days were followed for 24 months.¹⁹ Cancer was diagnosed in 2.94% of patients younger than 50 years and 10.21% of those older than 70 years. Men had a significantly higher risk of occult cancer than women (odds ratio [OR], 1.30, 95% CI, 1.07–1.58, $P = 0.007$).¹⁹ Women without estrogen replacement therapy also had a higher risk of cancer diagnosis: the 12-month prevalence of cancer was 5.8% vs 1.3%.¹⁷ The most common type of cancer associated with VTE varies among studies and includes lung, colorectal, prostate, breast, pancreatic, ovarian, hepatic, brain, and stomach cancers as well as leukemia and lymphoma.¹⁷⁻²⁰

There are several possible explanations for the lower prevalence of occult cancer diagnosis in more recent studies. First, some studies included younger patient populations, which are at lower risk of occult cancer.^{15,21} Second, low-risk patients were included in analyses, such as those with estrogen-related VTE or with history of previous VTE.^{16,21} Finally, recent studies excluded patients with simultaneous VTE and cancer diagnosis or those who were highly suspected of having cancer at the time of VTE diagnosis,²¹ thus reducing the number of patients with newly diagnosed occult cancer.

Occult cancer screening in patients with unprovoked venous thromboembolism

There are 2 different strategies for occult cancer screening: limited and extensive. Limited screening strategy includes medical history, physical examination, standard blood tests, chest X-ray or screening for breast, cervical, colorectal, and prostate cancers. Extensive screening strategy includes all the above tests as well as more expensive and advanced exams such as chest and abdominal computed tomography (CT), abdominal and pelvic ultrasound, and ¹⁸F-fluorodeoxyglucose positron emission tomography–computed tomography (¹⁸F-FDG PET/CT) scan.^{14,15}

In a prospective study including 864 patients with a first episode of unprovoked VTE, 34 patients (3.9%) were diagnosed with cancer by limited screening²²; 13 patients (1.5%) were diagnosed by further workup, including abdominal and pelvic ultrasound and serum tumor markers (prostate specific antigen [PSA], carcinoma embryonic antigen, and cancer antigen 125). Another 14 patients (1.6%) were diagnosed with cancer during 1-year follow-up. In total, 61 patients were diagnosed with cancer within 1 year of VTE episode, of whom 34 patients (56%) were diagnosed by limited screening.

In the SOMIT study,²³ patients with no evidence of cancer by limited screening after an unprovoked VTE episode were randomized into an extensive screening group and a control group. Of the 99 patients in the extensive screening group, cancer was confirmed in 13 patients (13%) and in 1 patient (1%) at baseline and during follow-up, respectively; of the 102 controls, it was diagnosed in 0 patients at baseline and in 10 patients (9.8%) during follow-up. Despite the earlier diagnosis of cancer in the extensive screening group than in controls, the cancer-related mortality reduction was insignificant in both groups (2% vs 4%).

Similar studies have been conducted in more recent years. In a prospective concurrently controlled cohort study,¹⁴ 19 of the 630 patients (3%) were diagnosed with malignancy at baseline after an unprovoked VTE episode. Of those, 12 patients (3.5%) were in the extensive screening group, and 7 patients (2.4%), in the limited screening group. After 2.5 years of follow-up, cancer was potentially curable in 43% of patients in the extensive screening group, compared with 52% in the limited screening group. Cancer-related mortality was 5.0% in the extensive screening group and 2.8% in the limited screening group (adjusted hazard ratio [HR], 1.79; 95% CI, 0.74–4.35). In the SOME trial,¹⁵ 33 (3.9%) of the 854 patients with a first unprovoked VTE episode had a diagnosis of occult cancer within 1-year follow-up: 14 patients (3.2%) were in the limited screening group and 19 patients (4.5%) were in the extensive screening group. There was no significant difference between groups in the mean time to cancer diagnosis or in cancer-related mortality.

¹⁸F-FDG PET/CT is a sensitive and noninvasive screening test for occult cancer. It provides a whole-body scan in a single test with a low radiation dose, and it might help overcome the limitation of a whole-body CT scan in previous extensive screening strategies. Two small studies^{24,25} used ¹⁸F-FDG PET/CT for occult cancer screening in patients with unprovoked VTE and showed a high negative predictive value of the test. The MVTEP study,¹⁶ assessed the ability of the limited screening strategy to diagnose occult cancer in patients with unprovoked VTE and compared it with that of the extensive strategy, which consisted of the limited strategy plus an ¹⁸F-FDG PET/CT scan. There was a higher rate of cancer diagnosis and early-stage cancer diagnosis in

the ^{18}F -FDG PET/CT group than in the limited screening group: 5.6% vs 2.0% and 64% vs 50%, respectively, but the differences were not significant. During 2-year follow-up, cancer was detected in only 0.5% of patients who had negative screening results at baseline in the ^{18}F -FDG PET/CT group, compared with 4.7% in the limited screening group. However, there was no significant difference in cancer-related mortality rates between groups.

One of the most common criticisms of ^{18}F -FDG PET/CT screening is its higher potential for false positive results, which may lead to more diagnostic and invasive procedures that may be harmful to patients. To clarify this issue, Robin et al²⁶ conducted a post hoc analysis of the MVTEP study. Compared with the limited screening group, the ^{18}F -FDG PET/CT group did not receive a higher number of additional diagnostic tests (22.8% vs 16.2%, 95% CI, -1.3 to 14.4%, $P = 0.13$) but underwent more invasive procedures (8.1% vs 3%, 95% CI, 0.5–10.0, $P = 0.03$).

In a systematic review and meta-analysis of individual participant data conducted in 2017, 3 studies that compared limited and extensive screening strategies showed that the 12-month prevalence of cancer was 4.2% in the limited screening group and 5.6% in the extensive screening group (adjusted OR, 1.4; CI, 0.89–2.1, $P = 0.146$).¹⁷ Around twice more cases of occult cancer were detected by extensive screening strategies than by limited screening strategies at initial screening. However, there was no difference in the ratio of early-stage cancer detection between the 2 screening strategies.

So far, no single test, such as an abdominal or pelvic CT scan or ^{18}F -FDG PET/CT scan, showed to be superior in occult cancer detection.^{15,17,27} There is still no evidence that occult cancer screening improves morbidity and mortality of patients after unprovoked VTE diagnosis.^{14,15,17}

Risk factors of occult cancer in patients with unprovoked venous thromboembolism

The risk of occult cancer diagnosis after unprovoked VTE is at least 2- to 6-fold higher than in population without VTE.^{28,29} The survival rate was lower in patient with a simultaneous diagnosis of cancer and VTE than in those with cancer alone (12% vs 36%).³⁰ For metastatic cancer, mortality within 1 year of cancer diagnosis was twice higher in patients with VTE than in those without VTE.³¹ Therefore, screening for occult cancer after an unprovoked VTE could be beneficial. However, considering the limited resources in the health care system, it might be reasonable to focus on patients with higher risk of occult cancer.

Several studies were conducted to identify risk factors for occult cancer in VTE patients. In a retrospective study which extracted a database from a national quality registry in Sweden, Auricula, and crossmatched it with the Swedish National Patient Register, cancer was diagnosed in 9.4% of the 3936 patients within 1 year following a first

unprovoked VTE episode.³² Risk factors for cancer diagnosis were age (HR, 1.03; CI, 1.02–1.03), anemia (HR, 2.13; CI 1.48–3.08), and male sex (HR, 1.38; CI, 1.09–1.76).³² Hypertension (HR, 0.74; CI, 0.57–0.96), dementia (HR, 0.30; CI, 0.10–0.95), and a history of major bleeding (HR, 0.52; CI, 0.28–0.97) reduced the risk of cancer diagnosis.³²

In a post hoc analysis of the MVTEP study, age of 50 years or older, male sex, leukocytosis (≥ 10 g/l), and thrombocytosis (≥ 350 g/l) were associated with increased rates of occult cancer detection.³³ The risk of cancer was 12.9% in patients with leukocytosis and 15.4% in those with thrombocytosis, which was much higher than the risk of 6.4% in the whole study population. The type of VTE (pulmonary embolism or deep vein thrombosis), medical history (oral contraceptive use, family history of cancer, previous cancer history, prior VTE, smoking status, alcohol intoxication, asbestos exposure, asthenia, and anorexia), hemoglobin and hematocrit levels, and liver function tests were not associated with occult cancer detection.

A post hoc analysis of the SOME trial revealed that age of 60 years or older (HR, 3.11; 1.41–6.89), previous provoked VTE episode (HR, 3.20; 1.19–8.62), and current smoking (HR, 2.80; 1.24–6.33) were associated with occult cancer detection within 1 year following unprovoked VTE.³⁴ An increase of 1 year of age was also associated with increased risk of occult cancer detection (HR, 1.06; 1.03–1.08). Hypertension, diabetes mellitus, previous cancer history, and type of VTE were not associated with occult cancer detection.

Risk factors of occult cancer detection were also evaluated in the systematic review and meta-analysis of individual participant data.¹⁷ Age of 50 years or older and no estrogen use were associated with increased risk of occult cancer detection. Male sex, smoking status, type of VTE, and previous VTE were not associated with occult cancer risk.

In the real-world prospective EPIGETBO study,³⁵ which enrolled 526 patients with unprovoked VTE living in the Brest district in France, 13 patients (2.65%) were diagnosed with cancer 1 year following an unprovoked VTE. In a multivariate analysis, only current or former smoking was associated with increased rates of occult cancer diagnosis. When adding 13 patients who had a simultaneous diagnosis of cancer and unprovoked VTE, occult cancer was diagnosed in 26 patients (4.94%). The risk factors of increased occult cancer diagnosis in this combined group were age ≥ 60 years, current or former smoking, and symptomatic pulmonary embolism or deep vein thrombosis.

D-dimer, a marker of hemostasis and fibrinolysis, has been used to exclude VTE or assist in diagnosis.³⁶ Elevated D-dimer levels was associated with worse outcome in patients with malignancy or VTE.³⁷ Schutgens et al³⁸ evaluated the predictive value of D-dimer in the diagnosis of occult cancer in patients with VTE and

demonstrated that higher D-dimer levels at baseline ($>4000 \mu\text{g/l}$) were associated with a higher rate of cancer diagnosis during follow-up than lower D-dimer levels ($<4000 \mu\text{g/l}$) (13% vs 4%, $P = 0.048$). This result became more significant in patients younger than 60 years with higher or lower D-dimer levels (23% vs 3%, $P = 0.001$) but was nonsignificant in those older than 60 years. A similar study conducted by Han et al³⁹ also reported a more than 4-fold higher risk of occult cancer in patients with unprovoked VTE and a D-dimer level exceeding 4000 ng/ml. Moreover, D-dimer levels higher than 4000 ng/ml were associated with a more than 9-fold higher risk of metastatic cancer at diagnosis. However, the study by Schutgen et al³⁸ was a post hoc analysis and that by Han et al³⁹ had a retrospective design with only a small number of patients ($n = 169$). Further prospective studies are needed to confirm the predictive value of D-dimer in occult cancer screening.

In summary, age was the most consistent risk factor associated with diagnosis of occult cancer in patients with unprovoked VTE in all the above studies. The risk of occult cancer development was shown to increase linearly with age.²¹ As for the other factors, there were no conclusive findings to support their association with occult cancer detection, which might be due to a small number of patients with positive cancer diagnosis. Larger studies are needed to confirm the association of other risk factors with the rates of occult cancer detection.

Practical implications of occult cancer screening in patients with unprovoked venous thromboembolism screening The prevalence of cancer diagnosis within the period of 12 to 24 months after an unprovoked VTE was around 1%,¹⁷ which is similar to the annual cancer incidence in the general population in the United States.^{40,41} Patients older than 50 years had a 7-fold higher risk of occult cancer diagnosis than those younger than 50 years following an unprovoked VTE, and there was a very low risk in patients younger than 40 years.¹⁷ Hence, screening for occult cancer in patients with unprovoked VTE beyond 1-year follow-up and in younger patients is less favorable.

A new scoring system has been developed recently in the RIETE registry to identify patients at high risk for occult cancer 30 days to 24 months after VTE.^{19,40,41} It comprises 7 items: male sex, age >70 years, chronic lung disease, anemia, elevated platelet count $\geq 350\,000 \times 1000/\text{mm}^3$, prior VTE, and recent surgery, with the last 2 items scoring negative points. Twelve percent of patients were diagnosed with cancer when the score was higher than or equal to 3 points, compared with 5.8% when it was lower than or equal to 2 points. The cumulative incidence of occult cancer differed significantly between these 2 groups. The RIETE score was externally validated by Bertolotti et al,⁴¹ using the MVTEP study data, in which 11.8% of patients with a high RIETE score

were diagnosed with cancer, compared with only 3.6% of those with a low RIETE score (OR, 3.6; 95% CI, 1.53–8.32). Another retrospective analysis was conducted to evaluate the performance of the RIETE score in an unselective cohort of patients with acute VTE, and 12.0% of patients with a score of 3 points or higher had a cancer diagnosis, compared with 5.9% in those with a score of 2 points or lower (HR, 0.58; CI, 0.47–0.69; $P = 0.04$).⁴² In the data from the RIETE registry, more than half of men with occult cancer had lung, prostate, or colorectal cancer, while two-thirds of women with occult cancer had colorectal, breast, or abdominal cancer.¹⁹ Therefore, the authors suggested rectal examination, serum PSA level measurement, fecal occult blood test, and a chest CT scan in men with acute VTE and a RIETE score of 3 points or higher. In women with acute VTE and a score of 3 points or higher, fecal occult blood test, mammography, and an abdominopelvic CT scan may be helpful.¹⁹

Robin et al⁴³ analyzed patients from the MVTEP study and reclassified the results of ^{18}F -FDG PET/CT into positive, negative, and equivocal by a nuclear medicine physician. The sensitivity of ^{18}F -FDG PET/CT ranged from 70% to 90%, and specificity, from 85% to 98%, depending on whether equivocal results had been classified as positive or negative. Of the 23 patients with equivocal ^{18}F -FDG PET/CT result, 2 patients were diagnosed with cancer but only 1 patient had a positive finding consistent with his actual cancer location on initial ^{18}F -FDG PET/CT scan. Therefore, the authors suggested that considering negative and equivocal results as negative would increase the specificity of the test to 98% and fewer patients would receive unnecessary diagnostic procedures. They also suggested ^{18}F -FDG PET/CT as a potentially useful screening tool in patients with unprovoked VTE. However, there was no clear benefit in terms of patient outcome in occult cancer screening and the psychological impact and stress should also be considered, especially in patients with equivocal results. Moreover, there are no standardized interpretation criteria for the classification of ^{18}F -FDG PET/CT.¹⁶ The benefit of ^{18}F -FDG PET/CT in occult cancer screening should be evaluated in future studies.

The available guidelines have diverse recommendations on occult cancer screening in patients with acute VTE, which partly reflects the lack of solid evidence from current clinical trials. The guidelines of the National Institute for Health Care Excellence in the United Kingdom suggested that all patients diagnosed with unprovoked VTE should undergo limited screening, including physical examination, basic laboratory testing, urinalysis, and chest X-ray. In patients older than 40 years, additional studies included a CT scan of the abdomen or pelvis and, for women, also mammography.²⁸

More recent guidelines, developed by the Anticoagulation Forum and the Scientific and by

the Standardized Committee of the International Society of Thrombosis and Haemostasis, contain different recommendations. They both suggested the limited screening strategy in patients with unprovoked VTE, which included a thorough medical history and physical examination, basic laboratory tests (complete blood count, liver function tests), and chest X-ray. In addition, age- and sex-specific cancer screening, including for colon, breast, cervical, and prostate cancers, is also recommended.^{44,45} The 2 sets of guidelines differed in basic laboratory studies, the one by the Anticoagulation Forum included metabolic profile and the other one included calcium level measurement and urinalysis. However, in busy and overloaded daily clinical practice, it is difficult to take medical history and perform physical examination as thoroughly as in a clinical trial. The very low incidence of occult cancer diagnosis (2.65%) in the EPIGETBO study might partly reflect this clinical dilemma.³⁵

Conclusion Based on the current guidelines, reviews, and clinical trials, it is reasonable to perform limited screening in all patients with unprovoked VTE. More advanced studies such as a CT or ¹⁸F-FDG PET/CT scan should only be considered in high-risk patients, especially elderly individuals. Screening for cancer at a specific location should be done only on a case-by-case basis as per the physician's discretion.

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