Received: 29 March 17 | Accepted: 27 April 2017

DOI: 10.1002/rth2.12007

REVIEW ARTICLE

WILEY rpth research and practice in thrombosis and haemostasis | ISTH

Occult cancer detection in venous thromboembolism: the past, the present, and the future

Faizan Khan BSc[1,2] | Alvi Rahman BHSc[1] | Marc Carrier MD, MSc[2,3]

[1]School of Epidemiology, Public Health & Preventive Medicine, University of Ottawa, Ottawa, ON, Canada

[2]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

[3]Department of Medicine, Ottawa Blood Disease Centre, University of Ottawa and The Ottawa Hospital, Ottawa, ON, Canada

Correspondence
Dr. Marc Carrier, The Ottawa Hospital, General Campus, Ottawa, ON, Canada.
Email: mcarrier@toh.ca

@MarcCarrier1

Abstract

Unprovoked venous thromboembolism (VTE) can be the first manifestation of an undiagnosed cancer. Recently published studies have suggested that approximately 4-5% of patients with new unprovoked VTE will be diagnosed with cancer within 12 months of follow-up. Therefore, it is important for clinicians to keep a low threshold of suspicion for occult cancer in this patient population. After an unprovoked VTE diagnosis, patients should undergo a thorough medical history, physical examination, basic laboratory investigations (ie, complete blood count and liver function tests), chest X-ray, as well as age- and gender-specific cancer screening (breast, cervical, colon, and prostate). More intensive cancer screening including additional investigations (eg, computed tomography of the abdomen/pelvis) does not seem to increase the rate of occult cancer detection, decrease cancer-related morbidity, or increase survival or cost-effectiveness.

KEYWORDS

early detection screening, neoplasm, tomography, venous thromboembolism, venous thrombosis

Essentials

- Unprovoked venous thromboembolism (VTE) may be the first manifestation of an undiagnosed cancer.
- The rate of occult cancer detection in patients with unprovoked VTE is approximately 5%.
- Clinicians should keep a low threshold of suspicion for occult cancer in these patients.
- Patients should only undergo a limited as well as age- and gender-specific cancer screening.

1 | INTRODUCTION

Unprovoked venous thromboembolism (VTE) may be the first manifestation of an undiagnosed cancer. To potentially allow earlier cancer detection and treatment and ultimately reduce cancer-related mortality, it is appealing for clinicians to subject their patients to occult cancer screening. However, the degree of aggressiveness to which clinicians should screen for an occult cancer in such patients is an important clinical conundrum. Over the last decade, several studies have been performed to identify which screening strategy may provide the best diagnostic yield for occult cancer detection in this patient population. We sought to review the past, underscore the present, and discuss the future of occult cancer detection in patients with unprovoked VTE.

2 | THE PAST

In order to counsel patients with unprovoked VTE on the risks and benefits of occult cancer screening, clinicians first require a precise estimate of the prevalence of occult cancer detection in this patient population. In 2008, a systematic review of 15 observational studies and RCTs reported that the 12-month period prevalence of occult

cancer detection in patients with unprovoked VTE was 10.0% (95% CI, 8.6-11.3%).[1] Given that approximately 1 in 10 patients with unprovoked VTE will be diagnosed with cancer within 12 months, several studies have assessed the efficacy of limited occult cancer screening strategy (medical history, physical examination, routine laboratory blood tests, and a chest X-ray) alone or in combination with additional testing (eg, computed tomography [CT] abdomen/pelvis). Therefore, clinicians also need to know the diagnostic yield of cancer detection of a limited compared to more extensive occult cancer screening strategy and estimates of the potential additional risks and benefits (cancer-related morbidity, mortality, cost) associated with a more extensive screening strategy.

Initially, it was believed that limited screening was sufficient for detecting undiagnosed cancers in VTE patients. Retrospective cohort studies performed between 1994 and 1996 suggested that a limited cancer screen can detect over 90% of occult cancers.[2,3] However, 2 prospective studies that were conducted in 2004 demonstrated that limited screening strategies may only have a sensitivity of 56% and missed numerous cases.[4,5] The SOMIT trial randomized 201 patients with a first episode of unprovoked VTE and a negative limited occult cancer screening to no further investigations or a more extensive occult cancer screening strategy.[4] The extensive occult cancer screening strategy included an ultrasound and CT abdomen/pelvis, gastroscopy or double contrast barium swallowing, colonoscopy or sigmoidoscopy, barium enema, hemoccult, sputum cytology, and tumor markers. Women also underwent Pap smear and mammography evaluations whereas men had transabdominal ultrasound and total prostate-specific antigen testing. The extensive occult cancer screening strategy had a sensitivity of 93% (95% CI, 66-100%). Furthermore, cancers detected in the patients that underwent extensive cancer screening were less advanced and detected earlier. Finally, investigators also reported absolute risk reduction of cancer-related mortality of 1.9% (95% CI −5.5% to 10.9%) for patients who received extensive occult cancer screening, though this was not statistically significant.[4] Although these results seem to favor performing an extensive occult cancer screening strategy in patients with unprovoked VTE, a number of limitations have limited the generalizability of these results to clinical practice. Unfortunately, the investigators were able to recruit only 20% of the expected number of patients and the study was conducted in only 5 out of 40 proposed centers. Furthermore, it remains unclear if an increase in occult cancer detection led to improvement in patient-important outcomes such as improved survival and decreased cancer-related morbidity. More importantly, the extensive occult cancer screening strategy performed in the SOMIT trial was exhaustive and unpractical for daily clinical practice. Therefore, a decision analysis using the trial's data was performed in order to guide clinicians on which of the diagnostic tests had the best yield for occult cancer detection. An extensive screening strategy including a CT abdomen/pelvis seemed to be the best occult cancer screening strategy.[6] Similarly, a 2008 meta-analysis (n=4378 patients) also suggested that a CT abdomen/pelvis was the optimal diagnostic test for occult cancer screening in patients with unprovoked VTE.[1] A CT abdomen/pelvis significantly increased the proportion of previously occult cancer detection from 49.4% (95% CI, 40.2-58.5%) with limited screening alone to 69.7% (95% CI, 61.1-77.8%) in unprovoked VTE patients. None of the other diagnostic modalities evaluated (U/S abdomen/pelvis or tumor markers) demonstrated a statistically significant increase in occult cancer detection.[1] However, the complication rates, cost-effectiveness, and difference in morbidity and mortality of using an extensive screening strategy including a CT abdomen/pelvis could not be determined. Moreover, over 30% of occult cancers remained undetected despite undergoing extensive occult screening strategy with CT abdomen/pelvis.[1] Nonetheless, based on the evidence available at the time, the 2012 National Institute for Health Care Excellence (NICE, UK) clinical

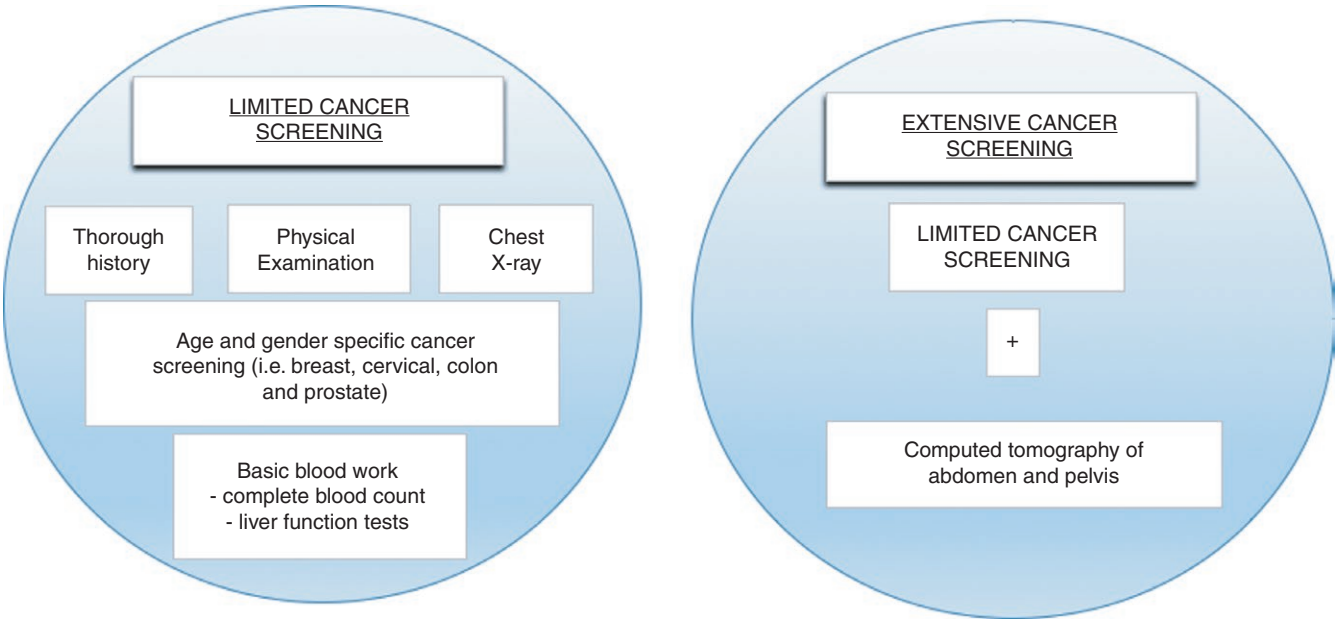

FIGURE 1 Strategies for limited vs extensive occult cancer screening.

TABLE 1 Summary of prospective studies of occult cancer screening in unprovoked VTE

Author (Year) [Reference]	Study design	Sample size	Outcomes			Quality of evidence
			Cancers diagnosed with initial screening	Cancers missed during initial screening	Cancer-related deaths	
Van Doormaal et al. (2011)[10]	OBS	630	2.4% (limited) vs 3.5% (extensive) OR: 1.56 (95% CI; 0.53-4.55)	5.0% (limited) vs 3.7% (extensive) HR: 0.86 (95% CI; 0.38-1.96)	2.8% (limited) vs 5.0% (extensive) HR: 1.79 (95% CI; 0.74-4.35)	Moderate (non-randomized study)
Carrier et al. (2015)[8]	RCT	854	14 (limited) vs 19 (extensive) (P=.28)	Absolute difference 0.25% (95% CI, −1.12 to 1.63)	1.4% (limited) vs 0.9% (extensive) (P=.75)	High
Robin et al. (2016)[9]	RCT	394	absolute risk difference 3.6% (95% CI, −0.4 to 7.9, P=.07)	absolute risk difference 4.1% (95% CI, 0.8 to 8.4, P=.020)	2.5% (limited) vs 1.0% (extensive)	High
Prandoni et al. (2016)[12]	RCT	195	absolute difference 2.0% (95% CI, −7.2 to 11.2, P=.81)	2 (limited) vs 2 (extensive)	4.0% (limited) vs 2.0% (extensive)	Moderate (prematurely terminated; small sample size)

OBS, prospective observational study; RCT, randomized controlled trial; OR, odds ratio; HR, hazard ratio.

TABLE 2 RIETE prediction score for occult cancer detection cancer after venous thromboembolism

Variable	Points
Male sex	1
Age >70 years	2
Chronic lung disease	1
Anemia	2
Platelet count ≥350×10^6/mm^2	1
Post-operative status	−2
Prior venous thromboembolism	−1
High risk	≥3

practice guidelines recommended that all patients diagnosed with unprovoked VTE should undergo a limited screening that includes a physical examination guided by the patient's medical history, a chest X-ray, blood tests (full blood count, serum calcium, and liver function tests), and urinalysis. Furthermore, for all patients over the age of 40, physicians were suggested to consider a CT abdomen/pelvis, as well as mammography for women (see Figure 1).[7]

3 | THE PRESENT

The reported rates of occult cancer detection in patients with unprovoked VTE seem to have been decreasing significantly over time. Recently published trials (see Table 1) assessing different strategies of occult cancer detection in this patient population have reported much lower overall rates of occult cancer detection (approximately 4-5%) within 12 months of follow-up.[8,9] Similarly, a large prospective study reported a rate of occult cancer detection of 5% over a 30-months follow-up period.[10] Therefore, these new event rates should be reassuring for patients and clinicians. Nowadays, the risk of occult cancer detection in patients with unprovoked VTE seems to be approximately 1 in 25 instead of the previously reported 1 in 10. It is unclear why more recent studies have reported a lower rate of occult cancer detection. The systematic review reporting a 12-month period prevalence of 10% included retrospective studies which might have been limited by selection bias and led to an overestimation of the actual rate of occult cancer detection.[1] It is also possible that recent changes in clinical practice, including availability of national recommendations for age- (colon) and gender- (breast, cervix, and prostate) specific cancer screening programs, resulted in these lower rates of occult cancer detection in this specific population. Although the rate of occult cancers is only approximately 4% over a 12-month follow-up period, this still represents a 6- to 7-fold heightened risk compared to the incidence of new cancer diagnosed reported in the general population.[1] The annual incidence of cancer expected in the same age group in Canada is approximately 0.65% (34 720/5 383 000 Canadians) (Canadian Cancer Society, 2015). Therefore, clinicians should maintain a low-threshold of suspicion for cancer in this patient population. Furthermore, the risk of occult cancer detection may remain elevated for a few years

for certain types of tumors. A large case-control study suggested that although the risk of occult cancer was strongest within the first 12 months following VTE diagnosis, the risk remained elevated for up to 6 years for colon cancer, pancreatic cancer, and multiple myeloma.[11] Hence, long-term follow up focused on these cancers among patients with unprovoked VTE might be warranted.

Since the publication of the 2012 NICE recommendation, one prospective observational study and 3 large randomized controlled trials comparing the effectiveness of a limited vs an extensive screening strategy were completed and published.[8–10,12] The Trousseau study compared an extensive occult screening strategy including a CT thorax/abdomen/pelvis for all patients and a mammography in women to a limited occult cancer screening in patients presenting with unprovoked VTE. Occult cancer was detected at enrolment in only 2.4% of patients that underwent a limited screening strategy compared to 3.5% in those that underwent the extensive strategy. There was no difference in the number of occult cancers missed during follow-up or in the overall mortality.[10] In 2015, the Canadian Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) randomized controlled trial (n=854) evaluated the efficacy and safety of adding a CT abdomen/pelvis to a limited screening strategy for occult cancer detection in patients with unprovoked VTE. The study demonstrated that there was no significant difference in the primary outcome of the number of cancers missed by the limited or extensive occult cancer screening strategy (absolute difference of 0.25%; 95% CI, −1.12% to 1.63%). There was also no significant difference in the overall number of occult cancers detected, time to cancer diagnosis or reduction in cancer-associated death between the 2 strategies.[8] The findings of the SOME trial are consistent with another trial published in 2016. An Italian randomized controlled trial reported that a CT-based screening strategy did not provide any significant benefits compared to a more limited screening strategy for the detection of occult cancer (absolute difference, 2.0%; 95% CI −7.2 to 11.1, *P*=.81) among patients with unprovoked VTE.[12] The study also failed to demonstrate any reduction in overall and cancer-associated mortality.[12] Furthermore, a UK cohort study reported that none of the CT abdomen/pelvis done as per the 2012 NICE recommendations for occult cancer screening in patient with unprovoked VTE revealed any occult cancer over a median follow-up period of 22 months.[13] Finally, in 2017, an economic analysis demonstrated that the addition of a CT abdomen/pelvis to a limited screening strategy was not cost effective for the detection of occult cancer in this patient population.[14] Taken together, current evidence suggests that an extensive cancer screening strategy including a CT abdomen/pelvis does not appear to provide a significant benefit over a more limited approach. Additionally, a more intensive cancer screening strategy does not seem to provide value, and is associated with potential harms including stress, fear, anxiety, as well as excessive radiation exposure to patients.[15]

Other diagnostic imaging modalities have been evaluated as potential additional investigations to include within an extensive occult cancer screening strategy. A large French trial randomized 394 patients with unprovoked VTE patients to undergo either limited occult cancer screening alone or in combination with fludeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT scan. In the primary outcome analysis, the study concluded that there is no significant difference in the rate of occult cancer detection between the two study groups (absolute risk difference 3.6%, 95% CI, −0.4 to 7.9, *P*=0.07).[9] Interestingly, the extensive screening strategy was associated with a lower number of missed occult cancers (absolute difference 4.1% [95% CI: 0.8-8.4%]) during the 2-year follow-up period.[9] Nonetheless, it remains unclear if lower rate of missed occult cancer detections would translate into a similar decrease in cancer-related morbidity or an increase survival in this patient population.

The recently published clinical guidance from Anticoagulation Forum seems to be consistent with the most recent medical literature on occult cancer screening in patients with unprovoked VTE. This clinical practice guidance document suggests to physicians to keep a low threshold of suspicion for occult cancer and for patients to undergo a thorough medical history, physical examination, basic laboratory investigations (ie, complete blood count and liver function tests) and chest X-ray.[16] It also suggests ensuring that patients are up to date with age- and gender-specific cancer screening (ie, breast, cervical, colon, and prostate).

4 | THE FUTURE

Within the next few years, clinicians might be able to tailor occult cancer screening management by stratifying patients according to their underlying risk of cancer detection. Extensive occult cancer screening strategies might potentially be more effective in subgroups at high risk of occult cancer detection. Risk factors predictive of occult cancer in patients with unprovoked VTE have already been identified. These include smoking, previous provoked VTE and older age (≥60 years).[17] Similarly, clinical prediction models incorporating multiple risk factors represent a promising approach for such risk stratification. In 2017, the RIETE investigators developed and internally validated a risk-prediction score, the first of its kind, to help identify acute VTE patients at high risk of occult cancer (see Table 2). In their prediction model, 1 point is assigned for male sex, chronic lung disease, or raised platelet count; 2 points are assigned for age >70 years or anemia; and points are deducted for a postoperative or a prior VTE.[18] The rates of occult cancer detection with ≤2 or ≥3 points were 5.8% (241 of 4150 patients) and 12% (203 of 1713 patients), respectively.[18] Although the RIETE clinical prediction model might be a promising tool for patients and clinicians, prospective validation of this score is needed before it can be adopted in clinical practice. Additionally, an individual patient data meta-analysis (CRD42016033371) evaluating the incidence of occult cancer, the effectiveness of the different occult cancer screening strategies, and whether an extensive screening strategy reduces all-cause mortality in patients with unprovoked VTE is currently ongoing.[19] This study may also further help identify unprovoked VTE patients in whom an extensive cancer screening might be associated with clinical benefits.

It is also possible that biomarkers identifying circulating tumor cells (e.g. RNA markers TWIST1, EPCAM, and KRT19) might improve the diagnostic yield of occult cancer detection in this population.[20]

Similarly, an international clinical study assessing the diagnostic accuracy of platelet RNA profiling for occult cancer detection in patients with unprovoked VTE is currently ongoing (NCT02739867).

In summary, while awaiting validated tools to identify subsets of patients with unprovoked VTE who would benefit from extensive screening, patients should only undergo a thorough medical history, physical examination, basic laboratory investigations (ie, complete blood count and liver function tests), chest X-ray as well as age- and gender-specific cancer screening (breast, cervical, colon, and prostate).

RELATIONSHIP DISCLOSURES

None of the authors have any disclosures relevant to this paper.

REFERENCES

1. Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? Ann Intern Med. 2008;149:323–33.
2. Nordstrom M, Lindblad B, Anderson H, Bergqvist D, Kjellstrom T. Deep venous thrombosis and occult malignancy: an epidemiological study. BMJ. 1994;308:891–4.
3. Cornuz J, Pearson SD, Creager MA, Cook EF, Goldman L. Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep venous thrombosis. Ann Intern Med. 1996;125:785–93.
4. Piccioli A, Lensing AWA, Prins MH, et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. J Thromb Haemost. 2004;2:884–9.
5. Monreal M, Lensing AWA, Prins MH, et al. Screening for occult cancer in patients with acute deep vein thrombosis or pulmonary embolism. J Thromb Haemost. 2004;2:876–81.
6. Di Nisio M, Otten HM, Piccioli A, et al. Decision analysis for cancer screening in idiopathic venous thromboembolism. J Thromb Haemost. 2005;3:2391–6.
7. National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. 2012. 1-2-2016.
8. Carrier M, Lazo-Langner A, Shivakumar S, et al. Screening for occult cancer in unprovoked venous thromboembolism. N Engl J Med. 2015;373:697–704.
9. Robin P, Le Roux PY, Planquette B, et al. Limited screening with versus without (18)F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial. Lancet Oncol. 2016;17:193–9.
10. van Doormaal FF, Terpstra W, van der Griend R, et al. Is extensive screening for cancer in idiopathic venous thromboembolism warranted? J Thromb Haemost. 2011;9:79–84.
11. Marks MA, Engels EA. Venous thromboembolism and cancer risk among elderly adults in the United States. Cancer Epidemiol Biomarkers Prev. 2014;23:774–83.
12. Prandoni P, Bernardi E, Valle FD, et al. Extensive computed tomography versus limited screening for detection of occult cancer in unprovoked venous thromboembolism: a multicenter, controlled, randomized clinical trial. Semin Thromb Hemost. 2016;42:884–90.
13. Vaidyanathan S, Walsh J, Cliffe H, et al. Utility of additional abdominopelvic CT in detecting occult cancer in patients with unprovoked venous thromboembolism. Clin Radiol. 2016;71:501–6.
14. Coyle K, Carrier M, Lazo-Langner A, et al. Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism. Thromb Res. 2017;151:67–71.
15. Khan F, Carrier M, Rodger M. Cancer screening after unprovoked venous thromboembolism: a teachable moment. JAMA Intern Med. 2016;176:739–40.
16. Khorana AA, Carrier M, Garcia DA, Lee AY. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41:81–91.
17. Ihaddadene R, Corsi DJ, Lazo-Langner A, et al. Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism. Blood. 2016;127:2035–7.
18. Jara-Palomares L, Otero R, Jimenez D, et al. Development of a risk prediction score for occult cancer in patients with VTE. Chest. 2017;151:564–71.
19. van Es N, Carrier M. Screening for cancer in patients with unprovoked venous thromboembolism: a systematic review and individual patient data meta-analysis. PROSPERO 2016:CRD42016033371. 2016. PROSPERO International prospective register of systematic reviews. University of York Centre for Reviews and Dissemination.
20. Gaciong Z, Pruszczyk P, Religa P. Cancer screening in unprovoked venous thromboembolism. N Engl J Med. 2015;373:2474–5.

How to cite this article: Khan F, Rahman A, Carrier M. Occult cancer detection in venous thromboembolism: the past, the present, and the future. *Res Pract Thromb Haemost*. 2017;1:9–13. https://doi.org/10.1002/rth2.12007