



Venous thromboembolism and occult cancer: impact on clinical practice

Afshan Gheshmy, Marc Carrier*

Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, ON, Canada

KEYWORDS

Venous thrombosis
Venous thromboembolism
Malignancy

ABSTRACT

Unprovoked venous thromboembolism (VTE) can be the first manifestation of cancer. Given this relationship between unprovoked VTE and cancer, it is appealing for clinicians to screen their patients with a first episode of acute unprovoked VTE for a potential occult malignancy. Five different studies have compared a limited (thorough history and physical exam, basic bloodwork) to a more extensive occult cancer screening strategy (e.g. computed tomography, fludeoxyglucose positron emission tomography, etc.). Most of these studies have failed to show that an extensive occult cancer screening strategy diagnoses more occult cancer (including early cancers), misses fewer cancers during follow-up or improves overall and/or cancer-related mortality suggesting that extensive occult cancer screening should not be performed routinely. Therefore, patients with a first unprovoked VTE should undergo a limited cancer screening only and clinicians should ensure that their patients are up to date regarding age- and gender- specific cancer screening (colon, breast, cervix and prostate) as per their national recommendations. Current evidence does not support a net clinical benefit to perform an extensive occult cancer screening on all patients, and a decision to do additional testing should be made on a case by case basis.

© 2016 Elsevier Ltd. All rights reserved.

Short and long-term risk of occult cancer in patients with venous thromboembolism

There is an abundance of literature to support the relationship between underlying cancer and the development of deep vein thrombosis and pulmonary embolism, collectively termed venous thromboembolism (VTE). Not uncommonly, VTE can be the first manifestation of cancer [1–3]. A systematic review of 34 studies reporting the prevalence of occult cancer detection following diagnosis of VTE reported that up to 10% (95% confidence intervals (CI): 8.6% to 11.3%) of patients with unprovoked VTE will have a new diagnosis of cancer within the first year following their diagnosis as compared to only 2.6% (95% CI: 1.6 to 3.6) in patients with provoked events [4]. Therefore, patients with unprovoked VTE are at highest risk of underlying malignancy and therefore represent a clinical challenge in long-term management.

More recently conducted clinical studies have reported lower rates of occult cancer detection in patients with unprovoked VTE [5,6]. A prospective cohort study showed rates of occult cancer diagnosis of 3.7 to 5.0% over a median of 2.5 years of follow-up after the completion of cancer screening in patients with unprovoked VTE [5]. Similarly, a recently published trial has reported an overall rate of occult cancer detection of only 3.9% (95% CI: 2.8 to 5.4%)

after 12 months of follow up in patients with first unprovoked VTE [6]. In contrast, in 2015, 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). Therefore, despite contemporary data suggesting a lower short-term risk of occult cancer detection compared to what was previously described, patients with unprovoked VTE remain at a clinically-relevant higher risk (6-fold increase) of underlying cancer diagnosis and current clinical practice guidelines from the National Institute for Health Care Excellence (NICE - United Kingdom) and the Anticoagulation Forum (United States) recommend that clinicians have a low index of suspicion of occult cancer detection in this patient population [7,8].

The data assessing the longer term risk of cancer detection among patients with VTE is scarce and controversial. Whereas some studies have reported a rate of cancer detection similar to the general population 12 months following a diagnosis of VTE [9,10], others have not [11]. Two registry studies suggest that the standardized incidence ratio of occult cancer detection dropped to baseline levels 12 months after presentation with VTE [9]. Similarly, a study comparing the risk of cancer diagnosis among patients with unprovoked VTE (n=1485) with that among matched controls (n=1495) over a 30-month follow-up period reported a cumulative incidence of 3.2% (95% CI: 2.3 to 4.4) among patients with VTE and 2.9% (95% CI: 2.0 to 4.0) among patients without VTE [10]. However, a large recently published case-control study including 1.2 million cancer cases and 200,000 controls using Linked Surveillance, Epidemiology, and End Results (SEER) and Medicare data suggested that although the risk of occult cancer was strongest within the first

* Corresponding author at: Senior Scientist, Ottawa Hospital Research Institute, Director, Thrombosis Fellowship Program, Associate Professor, University of Ottawa, 501 Smyth Road, Box 201A, Ottawa, ON, Canada. Tel.: (613) 737-8899 ext. 73034; fax: (613) 739-6266.

E-mail address: mcarrier@toh.on.ca (M. Carrier).

12 months following the diagnosis, the risk remained elevated for up to 6 years for certain types of tumors including colon cancer (Odds ratio (OR): 1.2; 95% CI: 1.1 to 1.4), pancreatic cancer (OR: 1.3; CI: 1.2 to 1.5) and myeloma (OR: 1.4; 95% CI: 1.1 to 1.7) [11]. The heightened short-term risk might be driven by enhanced screening as currently recommended by the clinical practice guidelines. However, the long-term risk (up to 6 years), especially with hematological malignancies and cancers of the digestive tract, cannot be readily explained by cancer screening given the lack of long-term screening recommendations but rather may be explained by the detection of small, slow-growing cancer precursors that exist for extended periods of time. Long-term prospective data are desperately needed in order to address this important knowledge gap.

Occult cancer screening in patients with unprovoked venous thromboembolism

Given the relationship between unprovoked VTE and cancer, the significance and potential benefit of identifying occult cancer upon diagnosis of unprovoked VTE has become an area of intense debate [12,13]. It is appealing for clinicians to screen their patients with unprovoked VTE for a potential occult malignancy. Identifying occult cancers may potentially allow both detection of finding the disease at a curable stage and prevention of malignancy-associated comorbidities, all in the hopes of ultimately increased survival benefit with earlier detection. Similarly, confirming the existence of an underlying cancer would potentially change VTE management: low molecular weight heparin is the preferred treatment in this population, significantly lowering the risk of symptomatic, recurrent VTE among patients with active cancer compared with vitamin K antagonists [14]. However, in a resource-limited healthcare system, the economical investment required for extensive screening must also be taken into consideration when weighing the costs and benefits of this investigation strategy. Likewise, the psychological impact and therefore quality of life surrounding a diagnosis of cancer needs to be carefully weighed against the potential survival benefit of an earlier diagnosis.

The available data focuses around two clinical approaches to this dilemma: “limited” versus “extensive” occult cancer screening. The limited workup strategy generally includes thorough history and physical exam, basic bloodwork (complete blood count and differential, electrolytes, creatinine, liver function tests, LDH) and chest radiograph, while an extensive investigation adds one or more of computed tomography (CT) of the abdomen, pelvis and thorax, ultrasound of the abdomen and pelvis, endoscopy, mammography and/or serum tumor markers. Several studies suggest that a limited approach is sufficient [1,15–18] whereas others are proponents of a more extensive screening approach [19–22]. While a more extensive occult cancer screening strategy seems to increase the number of cancers detected, current evidence does not support a net clinical benefit [6,23].

Limited occult cancer screening

Retrospective studies have suggested that a limited occult cancer screening is adequate to detect up to 90% of occult cancers in patients with VTE [15,17,24]. In a retrospective cohort study of 1389 patients with confirmed provoked and unprovoked VTE, 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 [17]. 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 [15]. 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, especially when one factors in the cost to the healthcare system and the potential added distress that would come with more extensive testing for seemingly minimal clinical gain.

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 [4]. 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 [21,23]. The largest prospective cohort study followed 864 VTE patients (40% unprovoked and 60% provoked) undergoing a two-step screening strategy [21]. 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 radiograph. 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 of the abdomen/pelvis and serum tumour markers (carcinoembryonic antigen (CEA), prostate-specific antigen (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 might be 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 address whether cancer screening would offer a beneficial effect on the prognosis, namely mortality and morbidity in VTE patients.

Limited vs. extensive occult cancer screening

Five studies have previously directly compared limited and extensive occult cancer screening strategies [5,6,23,25,26]. The SOMIT trial randomized patients with first unprovoked VTE and negative limited occult cancer screening to either no further testing or additional investigations including ultrasound and CT of the abdomen and pelvis, gastroscopy or double barium swallowing, colonoscopy or sigmoidoscopy, barium enema, hemoccult, sputum cytology and tumor markers including CEA, alpha-fetoprotein and CA-125 [23]. Women also received mammography and Pap smear while men received trans-abdominal ultrasound of the prostate and total PSA. The trial was stopped early (N=200) due to difficult recruitment. Overall, approximately 10% of patients in the control group were diagnosed with cancer by the end of the follow-up period. Cancers were generally less advanced in patients belonging to the extensive screening group ($p=0.047$) and they were diagnosed with a mean delay of 1 month compared to 11.6 months in the control group ($p<0.001$). A non-statistically significant absolute risk reduction of cancer-related mortality of 1.9% in favor of the extensive occult cancer screening group over the 2-year follow-up period was also reported. Although the lack of statistical significance of the cancer-related mortality difference might be due to lack of power

Download English Version:

<https://daneshyari.com/en/article/3026926>

Download Persian Version:

<https://daneshyari.com/article/3026926>

[Daneshyari.com](https://daneshyari.com)