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Revisiting occult cancer screening in patients with unprovoked venous thromboembolism

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ABSTRACT

Unprovoked venous thromboembolism (VTE) can be the first manifestation of an unknown cancer. A recently published individual patient data meta-analysis (IPDMA) reported a prevalence of occult cancer detection of 5.2% (95% CI, 4.1% to 6.5%) over a one-year follow-up period, approximately 50% lower than the previously reported 12-month period prevalence. Although an extensive screening strategy was associated with a 2-fold higher probability of cancer detection at initial screening in the IPDMA, not enough evidence exists yet to support the routine use of these tests in patients with unprovoked VTE. It is likely that a subgroup of patients with unprovoked VTE is at higher risk of occult cancer detection and might benefit from closer clinical surveillance. A newly derived and validated clinical predictive rule seems to be able to stratify patients with unprovoked VTE accordingly to their underlying risk of occult cancer detection. The low incidence of occult cancer detection (< 3%) in the low-risk group is reassuring for clinicians. Future studies are required to better define the risks and benefits of an extensive occult cancer screening strategy in high risk patients sub-group with unprovoked VTE. To date, the Scientific and Standardized Committee from the International Society of Thrombosis and Haemostasis suggests that patients with unprovoked VTE should only undergo a limited cancer screening including thorough medical history and physical examination, basic laboratory investigations, chest X-ray as well as age- and gender-specific cancer screening according to national guidelines.

1. Short-term prevalence of occult cancer detection in patients with unprovoked VTE (≤ 12 months)

Venous thromboembolism (VTE) can occur as the first manifestation of an underlying occult cancer [1]. In order to properly counsel patients and guide clinical decisions about occult cancer screening for these patients, precise estimates of the prevalence of occult cancer at the time of VTE diagnosis and during follow-up are needed. Previous studies have suggested that up to 10% of patients with unprovoked VTE are diagnosed with cancer in the following year [2–8]. Two recently published randomized trials reported a much lower rate of occult cancer detection in this patient population. In 2015, the SOME trial, a Canadian multicenter study including 854 patients randomized to either a limited cancer screening alone or in combination with a comprehensive computed tomography reported an overall rate of occult cancer detection of 3.9% (95% CI:1.6 to 3.6) over a 12-month follow-up period [9]. In 2016, the MVTEP study, a French multicenter randomized controlled trial which compared a limited screening strategy alone or in combination with a 18F-Fluorodesoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT), reported an overall cancer incidence of 6.3% (95% CI: 4.3 to 9.2) over a 2-year follow-up period (25 occult cancer diagnosed in 394 included patients) or ((5.3% (95% CI, 3.5 to 8.0) over a one-year follow-up period (21 occult cancer diagnosed in 394 included patients) [10]. More recently, a systematic review and individual patients-level data meta-analysis (IPDMA) confirmed this lower cancer prevalence by combining patient-level data from recent prospective published studies on occult cancer screening (total of 2316 patients with unprovoked VTE) [9–18]. Of the 10 included studies, seven enrolled patients before screening [9–11,15–18], and yield a 12-month prevalence of occult cancer detection of 5.2% (95% CI, 4.1% to 6.5%) [19,20]. This estimate is approximately 50% lower than the previously reported 12-month period prevalence from a previous systematic review including older studies published in 2008 [2]. The reasons for a lower prevalence of occult cancer detection over time (10% in 2008 vs. 5.2 in 2017) are unclear. The included studies' inclusions and exclusions criteria might partly explain this finding. For

Abbreviations: CDN, Canadian dollars; CI, confidence intervals; FDG PET/CT, 18F-Fluorodesoxyglucose Positron Emission Tomography/Computed Tomography; HR, Hazard ratio; IPDMA, individual patient data meta-analysis; VTE, venous thromboembolism

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example, in the MVTEP study, about 25% of the population was under 50 years old [10]. Similarly, in the SOME trial, the mean age of included patients was 53 years old [9]. Including younger patients in some studies might partially account for the low rate of cancer. Moreover, the definitions of unprovoked VTE across the studies included in the IPDMA were heterogeneous. Some studies included patients with a previous history of VTE, or with an estrogen-related VTE. These patients might also potentially have a lower risk of occult cancer [10]. Next to these differences in patient characteristics, there are other potential explanations for this substantial difference. Previous retrospective studies might have included patients in whom diagnosis of cancer was highly suspected at the time of VTE diagnosis. Nonetheless, the most recent estimate of 5.2% is less likely to be prone to overestimation due to single-center bias and more likely to be representative of the current clinical practice.

2. Long-term prevalence of occult cancer detection (> 12 months)

Previously published population-based and cohort studies showed that occult cancer detection prevalence in patients with VTE after 6 to 12 months of follow-up seem to be similar to the prevalence of the general population [21,22]. In the MVTEP study, only 4 cancers (1%) were diagnosed the second year of the follow-up period [10]. Similarly, the previously described IPDMA reported a prevalence of cancer between 12 and 24 months of 1.1% (95% CI, 0.62% to 1.8%) [20].

3. Limited or extensive occult cancer screening strategy?

Screening for occult cancer at the time of VTE is appealing for clinicians. The obvious aim is to potentially diagnose earlier stage cancer and, therefore, improve cancer-related mortality. However, many studies have failed to demonstrate that different extensive occult cancer screening strategies diagnosed more cancers, early stage tumors, or improve cancer-related mortality in comparison with limited screening strategies [9–10].

The recently published IPDMA adds new data on cancer screening for these patients and showed an increase in cancer detection with an extensive screening strategy. The prevalence of cancer was higher in patients who initially received extensive screening (mostly including either CT scan or FDG PET/CT) than in those who received a more limited screening strategy. Occult cancer was diagnosed at screening in 21 of 885 patients (2.4%, 95% CI, 1.6% to 3.6%) who had a limited screening strategy, compared with 50 of 1116 patients (4.5%, 95% CI, 3.4% to 5.9%) who underwent an extensive screening strategy. Thus, an extensive screening was associated with a 2-fold higher probability of occult cancer detection at screening ($p = 0.012$) ((9–11, 20). However, no statistically significant difference was found in the proportion of early-stage cancer between the 2 strategies ($p = 0.30$), nor on overall or cancer-related mortality but data on long-term mortality was not available for most of the included studies.

The most promising diagnostic modality for extensive occult cancer screening might be the FDG PET/CT. FDG-PET/CT is routinely used for the diagnosis, staging and restaging of various cancers. It has the advantage of providing non-invasive whole body imaging and showed promising performances in occult cancer diagnosis [14,18]. Although the MVTEP trial, did not show that FDG PET/CT detected higher rate of occult cancers at initial screening, the incidence of subsequent cancer diagnosis (i.e. occult cancers missed by screening) over a two-year follow-up period was significantly lower in patients randomized in the limited plus FDG PET/CT strategy. Of the 186 patients who had a negative initial screening in the FDG PET/CT, only one (0.5%) patient was diagnosed with cancer as compared to 9 (4.7%) of the 193 patients who underwent the limited screening alone (absolute risk difference 4.1%, 95% CI 0.8 to 8.4, $p = 0.01$) [10]. A post-hoc analysis of the MVTEP trial assessing diagnostic accuracy indices of FDG PET/CT for occult cancer diagnosis in patients with unprovoked VTE reported sensitivity ranging from 70 to 90%, and specificity from 85 to 98% based to how equivocal test results were considered [23]. However, standardized interpretation criteria dedicated to this specific clinical indication are still missing [23] and it remains unclear if these findings will translate into lower morbidity or improved survival for these patients.

An important potential limitation of extensive occult cancer screening strategies, especially for FDG PET/CT, is the detection of incidental findings and false positive results leading to unnecessary investigations. Additional diagnostic procedures had to be performed in approximately 15% and 23% of patients who underwent the extensive occult cancer strategy in the SOME trial and the MVTEP study respectively [9,10]. A post-hoc analysis of the MVTEP trial showed no statistically significant differences in the number of additional procedures following the limited or extensive screening strategy including a FDG PET/CT. A total of 45 (22.8%) patients required additional testing following a FDG PET/CT group as compared to 32 (16.2%) following the limited occult cancer screening strategy (absolute risk difference + 6.6%, 95% CI − 1.3 to + 14.4%, $p = 0.13$. However, a higher number of invasive tests were performed following FDG PET/CT group. Sixteen (8.1%) and 6 (3%) patients that underwent the FDG PET/CT or limited occult cancer screening alone required invasive procedures (absolute risk difference + 5.1%, 95% CI + 0.5 to + 10.0%, $p = 0.03$), respectively. Most invasive procedure following the FDG PET/CT led to occult cancer diagnosis. Among the 16 patients of the FDG PET/CT group who underwent an invasive test, 9 explorations led to an occult cancer diagnosis [24]. Another potential consideration of extensive occult cancer screening strategies is the potential additional costs A cost-effectiveness analysis using data collected during the SOME trial showed that the addition of a comprehensive CT scan of the abdomen/pelvis was associated with an increased cost ($551 CDN) without providing a clinically significant benefit in comparison with limited screening alone [25]. The same conclusion has been established in a cost analysis of the Trousseau prospective cohort study including 630 patients with unprovoked VTE, with an increase in costs of 365.75€ [26]. A summary of post-hoc analyses of MVTEP, SOME and Trousseau studies is reported Table 1.

4. Risk factors of occult cancer in patients with unprovoked VTE

Although the prevalence of occult cancer detection is lower than previously thought, it is likely that a subgroup of patients with unprovoked VTE are at higher risk of occult cancer detection and might benefit from closer clinical surveillance. A post-hoc analysis of the SOME trial showed that age ≥ 60 years (HR = 3.11, 95% C·I. 1.41–6.89, $p = 0.005$), previous provoked VTE (HR = 3.20, 95% C.I. 1.19–8.62, $p = 0.022$) and current smoker status (HR = 2.80, 95% C.I. 1.24–6.33, $p = 0.014$) might be predictors of occult cancer in patients presenting with a first episode of unprovoked VTE [27]. An ancillary analysis of the MVTEP trial demonstrated that baseline characteristics (male gender, age) and some laboratory tests (high leukocytes or platelets count) might be associated with the risk of occult cancer in patients with unprovoked VTE [28]. Age seems to be the most important risk factors. The IPDMA on occult cancer detection in patients with unprovoked VTE reported that the 12-month prevalence of cancer ranged from 0.5% (95% CI, 0.03% to 8.2%) in patients younger than 40 years to 9.1% (95% CI, 5.6% to 15%) in patients older than 80 years. The prevalence of occult cancer detection seems to increase linearly with age and was sevenfold higher in patients aged 50 years and older. By contrast, gender, smoking status, and history of VTE were less predictive of occult cancer in the IPDMA. The 12-month prevalence of occult cancer detection was 5.7% (95% CI, 3.8 to 8.5), 5.7% (95% CI, 4.3 to 7.4), 6.4% (95% CI, 3.7 to 11) for male, for current or former smoker, and for previous VTE respectively, in comparison with 5.0% (95% CI, 3.4 to 7.5), 3.9% (95% CI, 2.5 to 6.0) and 5.2% (95% CI, 3.8 to 7.1) for female, never-smoked patients and no history of VTE respectively. Finally, the probability of occult cancer detection seems to be