Screening for occult cancer in patients with unprovoked venous thromboembolism: Belgian expert guidance

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SUMMARY

Unprovoked venous thromboembolism (VTE) may be the earliest sign of malignancy, and as a result, screening for occult cancer in these patients has become routine practice. However, the elaborateness of this screening is subject to debate and varies between medical centres. This study's expert panel, consisting of oncologists and thrombosis specialists, aimed to develop a practical Belgian guidance for adequate cancer screening in patients with unprovoked VTE. In summary, comprehensive non-invasive cancer screening consisting of a medical history assessment, physical examinations, basic blood tests and a chest X-ray is sufficient to pick up the vast majority of occult cancers. When specific abnormalities are picked up by the battery of tests in the comprehensive non-invasive cancer screening, more extensive screening using CT scans are recommended. Routine CT screening in all patients presenting with an unprovoked VTE does not provide a significant clinical benefit and should not be routinely performed. In the presence of specific risk factors (e.g., older age, smoking history, previous VTE), physicians are advised to be more vigilant. Finally, given the significant anxiety that cancer screening may cause to patients, accurate and clear patient communication is key. A complete list of guidance statements is provided at the end of the article.

(BELG J MED ONCOL 2018;12(7):326-329)

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Conflict of interest: This publication is based on the Belgian expert consensus meeting logistically organised by Leo Pharma.

Keywords: occult cancer, screening, unprovoked, venous thromboembolism.

INTRODUCTION

It is well established that an unprovoked venous thromboembolism (VTE) may be the earliest sign of malignancy.[1,2] As a result, screening for occult cancer in these patients (i.e., a VTE that cannot be explained by surgery, trauma or any other obvious trigger) has become routine practice. However, the elaborateness of this screening is subject to debate and varies between medical centres. The rationale for this screening is that early identification of malignancy may allow earlier management, potentially prevent cancer-associated morbidity and improve overall survival and quality of life. In recent years, several studies have been published that question the clinical benefit of extensive cancer screening in this setting. Moreover, extensive screening, including CT scans, also come at a substantial healthcare cost and may cause, often avoidable, anxiety to patients and their families. This study's expert panel, consisting of oncologists and thrombosis specialists, aimed to develop a practical Belgian guidance for adequate cancer screening in patients with unprovoked VTE.

INCIDENCE OF OCCULT CANCER DETECTION IN PATIENTS WITH UNPROVOKED VENOUS THROMBOEMBOLISM

One of the first studies demonstrating the link between unprovoked VTE and cancer was published by Nordstrom *et al.* back in 1994, demonstrating that the presence of a deep venous thrombosis (DVT) was associated with a significantly higher frequency of malignancy during the first six months after diagnosis.[3] In 2008, a pooled analysis including 3,286 patients with unprovoked VTE demonstrated a prevalence of previously undiagnosed cancer at twelve months of 10%.[5] Since then, three more studies have been published demonstrating a prevalence decreasing to about 4%.[5-7] Importantly, more than 60% of occult cancers are detected shortly after the diagnosis of unprovoked VTE. Thereafter, the incidence rate of cancer diagnosis gradually declines and returns to the rate of the general population after one year.[7-9]

SCREENING FOR OCCULT CANCER IN PATIENTS WITH UNPROVOKED VENOUS THROMBOEMBOLISM

The most important reason to screen patients with unprovoked VTE is the detection of cancers in an early (and perhaps curable) stage. However, as said before, screening for occult cancer can also cause anxiety, increases healthcare costs and may lead to unnecessary invasive procedures not devoid of complications. Cancer screening is only justified when having impact on the outcome of the screened population concerning morbidity and mortality.

In this paper, two screening types will be discussed. With comprehensive non-invasive cancer screening we refer to the assessment of the patient history, physical examination, basic blood analyses (complete blood count [CBC], electrolytes, urea, liver function tests), a chest X-ray and a urine analysis. Extensive cancer screening on the other hand consists of all examinations above in combination with computed tomography (CT) of the abdomen and the pelvis, ultrasound of the abdomen/pelvis, colonoscopy or test for occult blood in stool, assessment of tumour markers (e.g., PSA, CEA, CA-125), Pap smear and mammogram, and/or positron emission tomography (PET) CT.

Back in the '90s, limited screening was the gold standard. This was based on the results of four studies demonstrating that this screening type allows the detection of approximately 90% of occult cancers.[10-13] This practice changed in 2004 with the publication of the SOMIT (extensive Screening for Occult Malignancy in Idiopathic venous Thromboembolism) data.[14] In this study, 201 eligible patients with a negative limited screening were randomised to observation or an extensive screening (ultrasound and CT of abdomen/pelvis, gastroscopy, colonoscopy, hemoccult, sputum cytology, tumour markers, Pap smear and mammogram).[14] In the extensive screening group, a single (1.0%) malignancy became apparent during follow-up, whereas in the control group a total of 10 (9.8%) malignancies became symptomatic (relative risk: 9.7; $p<0.01$). Moreover, compared to observation, extensive screening detected more early-stage cancers (20% *vs* 64%, $p=0.047$).[14] As such, the SOMIT investigators concluded that the limited screening strategy alone was insufficient to detect occult cancers. It was, however, still unclear if extensive screening offers a beneficial effect on prognosis.[14]

The battery of tests that was used in the SOMIT trial was very elaborate and not feasible for clinical practice. In a study by Carrier *et al.*, assessing the incremental benefit of the different tests, it became clear that a CT of abdomen/pelvis was the only examination that led to a meaningful increase in the detection of occult cancers.[4] Based on these findings, a CT of abdomen/pelvis became a frequently used test in the cancer screening of patients with unprovoked VTE. The National Institute for Health and Care Excellence (NICE) guidelines were also changed in response to SOMIT and suggested that a CT of abdomen/pelvis (and a mammography in women) could be added to a limited cancer screening in patients with an unprovoked VTE aged 40 or above.[15]

Since then, however, three studies have been published challenging the clinical benefit of extensive cancer screening.[5-7] In the Trousseau study (n=630), no difference in overall mortality was seen between comprehensive non-invasive cancer screening and extensive screening (i.e., limited screening

KEY MESSAGES FOR CLINICAL PRACTICE

1. The prevalence of occult cancer in patients with unprovoked venous thromboembolism (VTE) is lower than previously reported and is believed to be approximately 4%.
2. Comprehensive non-invasive cancer screening consisting of a medical history assessment (personal and assessment of familial cancer history), physical examinations, basic blood tests and a chest X-ray is sufficient to pick up the vast majority of occult cancers.
3. Age- and gender-specific cancer screening that applies for the general population is recommended.
4. Routine CT screening in all patients presenting with an unprovoked VTE does not provide a significant clinical benefit (no increased detection of early cancers, no impact on mortality) and should not be routinely performed.
5. When specific abnormalities are picked up by the battery of tests in the comprehensive non-invasive cancer screening, more extensive screening using CT scans are recommended. The type of CT scan should be based on the clinical presentation and the observed risk factors.
6. In the presence of specific risk factors (e.g., older age, smoking history, previous VTE), physicians are advised to be more vigilant.
7. In case of recurrent VTE, the chance of underlying malignancy is much higher in case of early recurrence or recurrence while under anticoagulation.
8. Given the significant anxiety that cancer screening may cause to patients, accurate and clear patient communication is key (i.e., avoid unneeded anxiety, explain the risk, explain what is being tested, explain why more extensive screening is not warranted in the absence of risk factors or abnormal signs in the comprehensive non-invasive cancer screening battery).

plus CT of chest/abdomen plus mammogram). During a median follow-up of 2.5 years, cancer was diagnosed in 3.7% and 5.0% in the extensive and comprehensive non-invasive screening groups, respectively.[5] In the MVTEP trial (n=494), the addition of an (18)F-fluorodeoxyglucose PET/CT scan to comprehensive non-invasive cancer screening was assessed. This study revealed a non-significant absolute difference of 3.6% in the detection of occult cancers (2.0% *vs* 5.6%). No difference was seen in the detection of early cancers, overall survival, or cancer-related survival.[6] Finally, the SOME (Screening for Occult Malignancy in patients with idiopathic VTE) trial included 854 patients with unprovoked VTE and compared comprehensive non-invasive cancer screening (basic blood work, chest X-ray and breast/cervical/prostate screening) with the same test battery complemented with comprehensive CT of abdomen/pelvis.[7] Between randomisation and the one-year follow-up, 3.2% of patients in the comprehensive non-invasive screening group and 4.5% of patients in the CT group were diagnosed with occult cancer (p=0.28). No difference was found in the rate of missed cancers, the detection of early cancers, overall mortality, cancer-related mortality, the time to cancer diagnosis and the rate of recurrent VTE between both screening strategies.[7] The findings of these studies indicate that routine screening with comprehensive CT of abdomen/pelvis does not provide a clinically significant benefit. In line with this, the anticoagulation forum recently recommended that patients with unprovoked VTE should only take a medical history assessment and undergo physical examination, basic laboratory investigations, a chest X-ray and age- and gender-specific cancer screening (i.e., cervical, breast, prostate and colon).[16]

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