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Full Length Article

Effect of occult cancer screening on mortality in patients with unprovoked venous thromboembolism

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ABSTRACT

Introduction: Unprovoked venous thromboembolism (VTE) may be the first manifestation of an underlying cancer. We aimed to determine whether extensive screening for occult cancer in patients with unprovoked VTE was effective in reducing overall mortality among VTE patients included in prospective cancer screening studies.
Methods: This pre-specified analysis of a systematic review and individual patient data meta-analysis included prospective studies comparing extensive screening with limited screening strategies for detection of occult malignant disease in unprovoked VTE patients. Overall mortality was calculated and compared according to the allocated screening strategies.
Results: Among 1830 included patients, occult cancer was detected either at screening or during a 2-year follow-up period in 98 (5.4%, 95% CI 4.4 to 6.5). Twenty-seven out of the 56 patients (48.2%) diagnosed with cancer in the extensive screening group died during follow-up as compared with 23 out of 42 patients (54.8%) in the limited screening group (HR, 0.83; 95% CI, 0.48–1.45). Subgroup analyses according to time of cancer diagnosis (i.e. at screening vs. during follow-up) and according to whether cancer was diagnosed by limited screening or more extensive testing yielded similar results.
Conclusion: In this individual patient data meta-analysis of clinical trials on limited vs. extensive screening, extensive screening for occult malignancy in patients with unprovoked VTE was not effective in reducing overall mortality. Diagnosing an occult cancer in unprovoked VTE patients was associated with a poor outcome.

1. Introduction

Venous thromboembolism (VTE), which encompasses deep-vein thrombosis (DVT) and pulmonary embolism (PE), can occur as the first sign of an underlying occult cancer [1]. Most recent data suggest that the 12-month period prevalence of cancer in patients presenting with an unprovoked VTE (i.e. venous thromboembolism not provoked by a major risk factor) is approximately 5% [2–7]. In patients with an unprovoked VTE, systematic screening for occult cancer has been proposed with the hope of detecting and treating these malignancies as early as possible, and ultimately improving prognosis. The extent to which patients with unprovoked VTE should be screened for occult cancer is still controversial.

A recently published systematic review and individual patient-level data meta-analysis (IPDMA) of prospective cancer screening studies found that in patients with unprovoked VTE, the rate of cancer diagnosis at screening was 2-fold higher in patients who received extensive screening, mostly including either computed tomography (CT) scan or ^{18}F-Fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) (4.5%, 95% CI, 3.4% to 5.9%), than in those who underwent a more limited screening strategy (2.4%, 95% CI, 1.6% to 3.6%) [6].

However, it remains unclear whether an increase in cancer detection diagnosed by extensive screening tests automatically translates into a benefit with regard to mortality, since previously published studies were underpowered to assess the potential impact of cancer

Abbreviations: CT, Computed tomography; DVT, Deep vein thrombosis; FDG PET/CT, ^{18}F-Fluorodeoxyglucose positron-emission tomography/computed tomography; IPDMA, Individual participant data meta-analysis; PE, Pulmonary embolism; VTE, Venous thromboembolism

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screening on mortality, and were limited by a relatively short follow-up duration [3–5]. To fill this knowledge gap, the aim of this study was to determine whether extensive testing for occult cancer in patients with unprovoked VTE was effective in reducing mortality among patients diagnosed with cancer included in prospective screening studies.

2. Material and methods

2.1. Study population

This was a pre-specified analysis of a recently published individual patient data meta-analysis (IPDMA) that included prospective studies assessing cancer screening in patients with unprovoked VTE (PROSPERO: CRD42016033371). Methods, including study selection process, have been previously described in detail [8]. For this analysis, we only included trials that compared extensive screening with limited screening strategies for detection of occult malignant disease in patients with unprovoked VTE. Three trials were identified: the SOME, Trousseau, and MVTEP studies were used to address the question [3–5]. In these studies, adult patients (aged 18 years or older) with unprovoked and objectively confirmed DVT or PE, in the absence of major risk factors such as recent surgery, immobilization, known cancer or ongoing pregnancy, were prospectively included. In this analysis, we focused on patients in whom an unknown malignancy was diagnosed during planned follow-up in each primary study (i.e. 12 months or 24 months). Patients without occult cancer diagnosis during this period were excluded from this analysis.

2.2. Types of interventions

Studies followed a standardized strategy for occult cancer screening consisting of at least medical history taking, physical examination, basic blood tests (including complete blood count, erythrocyte sedimentation rate or C-reactive protein, aminotransferases, alkaline phosphatase, and calcium), a chest X-ray and/or age-specific and gender-specific testing (i.e. limited screening strategy). The extensive screening strategy added to limited screening tests a unique imaging test such as a CT of the chest/abdomen [4], a CT of the abdomen/pelvis [5], or a whole-body FDG PET/CT [3]. All three studies enrolled patients before any screening procedure was performed. All studies were approved by the institutional review boards of participating centers.

2.3. Follow-up

Follow-up data of cancer patients were obtained through medical records and/or by telephone contact to ascertain patients' clinical status. Follow-up duration was defined as time between occult cancer diagnosis and date of death or last encounter in clinic. Information on long-term follow-up was collected for all patients in whom an unknown malignancy was diagnosed during planned follow-up in each primary study.

2.4. Outcomes

The primary objective was to determine whether extensive testing for occult cancer was effective in reducing overall mortality among patients with unprovoked VTE who were diagnosed with cancer. Overall mortality was calculated and compared according to the allocated screening strategies (i.e. extensive screening vs. limited screening).

Several exploratory analyses were planned (Fig. 1). Besides the primary analysis (Fig. 1A), we aimed at comparing mortality rates in patients whose cancer was missed at initial screening between the extensive and limited strategies (Fig. 1B). Secondly, in order to account for the fact that some cancers diagnosed in the extensive strategy were diagnosed by limited testing, we aimed at testing whether mortality would be lower in patients whose cancer was diagnosed by the extensive test of the extensive strategy, than in patients whose cancer was missed by limited screening (Fig. 1C). For each patient, two adjudicators (MC, NvE) reviewed all cancers found by screening and determined which component of the screening strategy led to the diagnosis. They determined if the diagnostic test that led to the cancer detection was part of the limited (e.g. medical history, physical examination and basic blood work) or extensive component (e.g. CT or FDG PET/CT) of the extensive screening strategy. Finally, to test whether additional cancers detected by the extensive test would have a more favorable prognosis, we compared among patients included in the extensive screening group the mortality rates between patients whose cancer was diagnosed by limited screening or by the extensive test (Fig. 1D).

Cause of death was also adjudicated as cancer-related death, defined as death due to the underlying malignant disease itself, or death due to complications of treatments or procedures to diagnose or treat the cancer; and non-cancer related mortality, defined as death from any other cause. Proportion of cancer-related death and non-cancer related mortality was recorded according to time elapsed since cancer diagnosis.

Characteristics of occult cancers (i.e. cancer location, histopathology type, cancer stage) diagnosed at screening and during follow-up were recorded.

2.5. Statistical analysis

General characteristics of the population were described using mean ± standard deviation (SD), median (IQR) or numbers and proportions, as appropriate. Moreover, we estimated the absolute risk difference between the groups along with its 95% confidence interval (CI). Survival curves were plotted by the Kaplan-Meier method, and hazard ratios were estimated using a Cox regression model. Statistical analysis was done with IBM SPSS Statistics (version 23).

3. Results

3.1. Population characteristics

Our analysis comprised 1830 patients included between 2002 and 2008 in the Trousseau [4], and between 2008 and 2014 in the SOME and MVTEP trials [3,5]. An occult cancer was detected either at screening or during a 2-year follow-up period in 98 patients (5.4%, 95% CI 4.4 to 6.5). The median long-term follow-up period after cancer diagnosis was 3.3 years (IQR 0.5–6.3). Baseline characteristics of the 98 patients with cancer are shown in Table 1. Mean age was 67 years, 62% of the patients were men, and 37% had a PE with or without DVT.

3.2. Effect of screening strategies on overall mortality

Twenty-seven out of 56 patients (48.2%) diagnosed with cancer in the extensive screening group died during follow-up as compared with 23 out of 42 patients (54.8%) in the limited screening group (hazard ratio [HR], 0.83; 95% CI, 0.48–1.45; $p = 0.52$) (Fig. 2). Median survival time of patients diagnosed with occult cancer was 11.0 years (IQR 0.5 – unavailable) for patients randomized to the extensive screening group in comparison with 3.3 years (IQR 0.5 – unavailable) for patients randomized to the limited screening group.

We assessed the overall mortality in patients with cancer missed at initial screening (Fig. 1B); in patients whose cancer was diagnosed by extensive test versus patients whose cancer was missed by limited screening (Fig. 1C); and in patients whose cancer was diagnosed by limited screening or by the extensive test of the extensive screening (Fig. 1D). No significant survival difference was detected for any of these subgroup analyses ($p > 0.05$).