Thrombosis Research 155 (2017) 6–9

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Additional testing following screening strategies for occult malignancy diagnosis in patients with unprovoked venous thromboembolism

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ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 7 April 2017
Accepted 22 April 2017
Available online 25 April 2017

Keywords:
Positron Emission Tomography
Occult cancer
Screening strategy
Venous thromboembolism

ABSTRACT

^{18}F-Fluorodesoxyglucose Positron-Emission-Tomography combined with Computed-Tomography (FDG PET/CT) might be an attractive tool for cancer screening in patients with venous thromboembolism (VTE), allowing non-invasive whole-body imaging. One of the frequent criticisms to the use of FDG PET/CT for screening is the potential for false positive results leading to unnecessary/invasive investigations.

Our aim was to compare the frequency and invasiveness of additional testing following extensive and limited screening strategies for occult malignancy in patients with unprovoked VTE.

We analysed patients included in the MVTEP study, a randomized trial that compared a screening strategy based on FDG-PET/CT with a limited screening strategy for occult malignancy diagnosis in patients with unprovoked VTE. All additional diagnostic procedures following screening were recorded and classified as invasive or non-invasive.

A total of 394 patients were analysed. Additional diagnostic procedures realized in patients of each group consisted of 59 tests in patients of the FDG PET/CT group versus 53 tests among the patients from the limited screening group ($p = 0.65$). Overall, 45 (22.8%) patients in the FDG PET/CT group underwent additional diagnostic tests, versus 32 (16.2%) in the limited screening group (absolute risk difference + 6.6%, 95% CI −1.3 to + 14.4%, $p = 0.13$). Sixteen (8.1%) patients in the FDG PET/CT group underwent invasive procedures, versus 6 (3%) in the limited screening group (absolute risk difference + 5.1%, 95% CI +0.5 to +10.0%, $p = 0.03$).

We found no statistical difference in the number of additional procedures following each screening strategy. However, a higher number of invasive tests were performed in the FDG PET/CT group.

1. Introduction

Venous thromboembolism (VTE) can occur as the first manifestation of an underlying occult malignancy [1]. Previous studies reported a 6% to 15% incidence of cancer in the year following the diagnosis of an unprovoked venous thromboembolism episode (i.e., venous thromboembolism not provoked by a major risk factor) [2–8]. Screening for occult malignancy at the time of a venous thromboembolism is appealing, with the hope to be able to detect and treat these malignancies as early as possible in order to improve prognosis. Different screening strategies have been proposed [9–12]. Because all types and locations of cancer may be found in patients with venous thromboembolism, many investigations would have to be performed, resulting in expensive,

Abbreviations: FDG PET/CT, ^{18}F-Fluorodesoxyglucose Positron-Emission-Tomography combined with Computed-Tomography; MRI, magnetic resonance imaging; US, ultrasonography; VTE, venous thromboembolism.

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http://dx.doi.org/10.1016/j.thromres.2017.04.022
0049-3848/

invasive and time-consuming screening strategies [10]. Clear guidelines for the investigation of occult malignancy after unprovoked venous thromboembolism are not yet available.

^{18}F-Fluorodesoxyglucose Positron-Emission Tomography combined with low-dose Computed Tomography (FDG PET/CT) is routinely used for the diagnosis, staging and restaging of various malignancies [13,14]. It might offer an attractive alternative allowing non-invasive whole body imaging. We recently reported the result of a multicenter open-label randomized trial comparing limited screening to limited screening plus FDG PET/CT in patients with unprovoked VTE. The study failed to demonstrate a significant increase in the rate of occult cancer detection in the FDG PET/CT arm at inclusion, which was the primary outcome. However, the rate of cancer diagnosis was 5.6% in the limited screening plus FDG PET/CT, vs. 2.0% in the limited screening arm. We also found a significantly lower incidence of cancer diagnosis during the two-year follow-up period among patients randomized to the limited screening plus FDG PET/CT strategy [15]. Another finding was a lower overall prevalence of cancer than previously described (6%, vs. 10% in a previous systematic review) [2], which could account for our negative result. This lower prevalence was in line with other recent studies on cancer screening in VTE [9,11]. A better selection of patients for screening might lead to more efficient screening strategies, and FDG PET/CT appears promising in this regards.

However, one of the frequent criticisms to the use of extensive screening strategies, particularly to the use of FDG PET/CT for screening, is the potential for false positive results ('incidentalomas'), leading to unnecessary investigations. Previous non-randomized studies reported positive predictive values for FDG PET/CT ranging from 4 to 54% [16–18], but data on additional testing following a positive or suspicious FDG PET/CT finding remain limited, and no comparison with the rate of additional testing following limited screening is available.

To fill this knowledge gap, we assessed whether or not the frequency and invasiveness of additional testing following two screening strategies for occult malignancy were different in a population of patients enrolled in a prospective, multicenter, randomized, controlled study comparing a limited screening strategy with a strategy combining limited screening and FDG PET/CT in patients with unprovoked venous thromboembolism.

2. Methods

2.1. Study population

This is a post-hoc analysis of an open label, multicenter, randomized study that compared a screening strategy based on FDG PET/CT with a limited screening strategy for detection of occult malignant disease in patients with unprovoked VTE. Methods have been previously described in detail [15].

Patients aged 18 years or older, diagnosed with unprovoked venous thromboembolism were invited to participate in the study if they did not present any exclusion criteria: ongoing pregnancy, active malignancy (defined as known malignancy, active and/or treated during the previous five years), unable or unwilling to give consent.

2.2. Study design

Patients were randomized into two arms. In the limited screening arm, patients underwent medical history, complete physical examination, routine laboratory tests including complete blood count, erythrocyte sedimentation rate or C-reactive protein, transaminases, alkaline phosphatase, calcium, chest X-ray, and recommended age- and gender-specific cancer screening tests (i.e. prostate-specific antigen in men over 50 years of age, mammography in women over 50 years of age and Pap-smear in all women). In the limited plus FDG PET/CT arm, patients underwent the same limited screening and a FDG PET/CT, which was performed in all patients in this arm, regardless of the results of the limited screening tests. FDG PET-CT were performed using Gemini GXLi, Philips in Brest University Hospital; Discovery ST, General Electric in Angers University Hospital; Biograph 6 LSO Pico 3D HI-REZ, Siemens Medical in Saint Etienne University Hospital; Gemini GXL, Philips and Discovery 690, General Electric in Paris (HEGP). Patients fasted for at least 6 h before PET acquisitions, and blood glucose had to be less than 7 mmol/L before injection of 3 to 5 MBq/kg of ^{18}F-FDG. Intravenous injection was followed by a period of approximately 60 min when the patients remained in a quiet room. Computed tomography was performed from mid-forehead to the feet in normal shallow respiration using a low-dose setting. Intravenous iodinated contrast was not administered. Data obtained from the CT-scan were used for attenuation correction of PET data and for fusion with attenuation-corrected PET images. In case of positive finding on initial screening, patients were referred for appropriate diagnostic procedures at the discretion of the treating physician.

All patients underwent clinical follow-up every 6 months for 24 months. Medical history and physical examination were performed, and in case of new symptoms or clinical signs, further testing was ordered. Information on any investigation for suspected malignancy requested at any time during follow-up was collected.

All patients provided written informed consent. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol was approved for all study sites by our institutional Ethics committee (Comité de Protection des Personnes Ouest VI, 2008-541). The study was registered on clinicaltrials.gov (NCT00964275).

2.3. Additional diagnostic procedures

All additional diagnostic procedures performed following positive findings at screening were recorded and classified as invasive or non-invasive. Diagnostic procedures performed during the remainder of follow-up were not considered in this study.

An additional diagnostic procedure was considered as invasive when the body was entered by a device, tube or instrument, with potential procedure-related complications, e.g. any biopsy, surgery, image-guided biopsy, upper and lower gastrointestinal endoscopy, endoscopic ultrasonography, needle cytology. *A contrario*, an additional diagnostic procedure that did not meet the definition above was considered as non-invasive, e.g., thoracic, abdominal or pelvic imaging: ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), nuclear imaging, tumor markers, and additional laboratory tests.

2.4. Statistical analysis

General characteristics of the population were described using median (IQR) or numbers and proportions, as appropriate. The number of additional diagnostic procedures was determined in each group, and compared using a *t*-test. Moreover, the proportion of patients who underwent additional diagnostic test and invasive test was determined in each group, and compared using a χ^2 test. We also estimated the absolute risk difference between the groups along with its 95% confidence interval. Positive predictive value (PPV, define as the number of true positives divided by the number of investigated patients) and false positive rate (FPR, define as the number of false positives divided by the number of investigated patients) of additional tests performed in each group were calculated. Statistical analysis was done with IBM SPSS Statistics (version 23).

3. Results

Between March 3, 2009, and August 18, 2012, 748 patients were assessed for eligibility, and 399 were included and randomized to one of the two study groups. 200 patients were allocated to the FDG PET/