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Full Length Article

In patients with unprovoked VTE, does the addition of FDG PET/CT to a limited occult cancer screening strategy offer good value for money? A cost-effectiveness analysis from the publicly funded health care systems

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ABSTRACT

Introduction: Unprovoked venous thromboembolism (VTE) may be the first manifestation of an undiagnosed cancer. We assessed the cost-effectiveness of ^{18}F-Fluorodesoxyglucose Positron Emission/Computed Tomography (FDG PET/CT) plus limited screening and limited screening strategies in patients with unprovoked VTE from the perspectives of the Ontario (Canada) and French health care systems.

Methods: We conducted a cost-effectiveness analysis based on a published randomized controlled trial of 394 patients aged 18 years or older who were diagnosed with unprovoked VTE. We obtained data with respect to efficacy and health care utilization from the published trial. The primary measure of effectiveness was the number of avoided cases of delayed cancer diagnosis and the secondary measure of effectiveness was the quality adjusted life year (QALY) at the end of the study in each group. We used generalized linear models to estimate incremental cost-effectiveness ratios (ICER) while controlling for patient demographic and clinical characteristics. Results were presented as the incremental cost to avoid one case of delayed cancer diagnosis and the incremental cost per QALY gained. The 95% confidence intervals (CIs) were estimated using bootstrap resampling procedures with 5000 iterations.

Results: Compared to a limited screening strategy, the ICER of limited strategy plus FDG PET/CT scan was C$ 26,840.19 (95% CI: C$ 24,046.51; C$ 34,581.53) per one avoided case of delayed cancer diagnosis from the Ontario health system perspective and €16,370.45 (95% CI: € 9904.48; € 39,578.91) per one avoided case of delayed cancer diagnosis from the French health system perspective. The probabilities that addition of FDG PET/CT to limited screening is cost-effective rose with increasing willingness to pay values. Compared with the limited screening, the extensive screening was associated with C$ 3412.85 per QALY gained (95% CI: 1463.89; −13,935.88) from the Ontario health system perspective and €2162.83 per QALY gained (95% CI 958.78; −10,544.42) from the French health system perspective.

Conclusion: Addition of a FDG PET/CT for occult cancer diagnosis was associated with better health outcomes

Abbreviations: CI, Confidence interval; CT, Computed Tomography; DVT, Deep Vein Thrombosis; FDG PET/CT, ^{18}F-Fluorodesoxyglucose Positron-Emission-Tomography combined with Computed-Tomography.; ICER, Incremental-cost effectiveness ratios; INB, Incremental net benefit; ITT, Intention-to-treat; PE, Pulmonary embolism; VTE, Venous thromboembolism; WTP, Willingness to pay

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(fewer cases of delayed cancer diagnosis and greater QALYs) and a higher cost from the perspective of publicly funded health care systems; the cost-effectiveness results are however highly uncertain.

1. Introduction

Venous thromboembolism (VTE), which encompasses deep-vein thrombosis (DVT) and pulmonary embolism (PE), can be the earliest sign of cancer [1–5]. It was previously demonstrated that between 6% to 15% of patients presenting with unprovoked VTE will be diagnosed with cancer in the year following the diagnosis of an unprovoked VTE episode (i.e. VTE not provoked by a major risk factor) [6]. Recent studies reported that approximately 5% of patients are diagnosed with cancer within the first year following VTE diagnosis [7,8].

Identifying occult cancers at the time of VTE diagnosis may lead to significant improvement of patient care since the cancer may be at a curable stage and early cancer treatment might prevent cancer-associated morbidity. However, the extent to which patients with unprovoked VTE should be screened for occult cancer is still controversial. Two recent randomized controlled trials failed to demonstrate that an extensive screening strategy for occult cancer provides a clinically-significant benefit in patients with unprovoked VTE [7,8]. The SOME trial failed to demonstrate the superiority of a limited cancer screening strategy plus a comprehensive Computed Tomography (CT) of the abdomen and pelvis over a limited cancer screening strategy alone on the proportion of avoided cases of delayed cancer diagnosis in patients with a first unprovoked VTE [7]. Moreover, the MVTEP trial also failed to demonstrate the superiority of a limited cancer screening strategy plus ^{18}F-Fluorodesoxyglucose Positron Emission/Computed Tomography (FDG PET/CT) over a limited cancer screening strategy alone on the proportion of cancers diagnosed during the screening period [8]. Nevertheless, a secondary outcome analysis of the MVTEP trial showed that FDG PET/CT significantly reduced the number of delayed cancer diagnosis cases in comparison to limited screening alone (absolute risk difference 4.1%, 95% CI: 0.8 to 8.4%, p = 0.01).

Despite potential health benefits, little is known about whether the addition of FDG PET/CT would increase or decrease the health system cost. Few studies have been conducted that reported the financial implications of extensive screening for occult cancer diagnosis among patients with unprovoked VTE [9,10]; however, none of these studies focused on FDG PET/CT. The Trousseau study suggested that extensive screening using abdominal and chest Computed Tomography (CT) scans and mammography was associated with higher mean costs (€530.92 for extensive screening vs. €165.17 for limited screening) [10]. Another cost-effectiveness study using data collected alongside the SOME trial found that the addition of a comprehensive CT scan to limited screening was associated with higher costs (C$551) with no significant improvement in utility values or number of avoided cases of delayed cancer diagnosis [9].

The aim of this study was to assess the cost effectiveness of an extensive screening strategy including a FDG PET/CT in addition to a limited screening in comparison with a limited screening alone from the publicly funded health care system perspective in patients with unprovoked VTE.

2. Methods

2.1. Study design

We conducted a cost-effectiveness analysis based on a published open label, multicenter, randomized study (MVTEP) 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 [8].

Briefly, the study included patients aged 18 years or older, diagnosed with unprovoked VTE who did not present any exclusion criteria: ongoing pregnancy, active malignancy (defined as known malignancy, active and/or treated during the previous five years).

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 plus a FDG PET/CT.

All patients underwent clinical follow up every 6 months for 24 months. In case of positive finding on initial screening or during follow up, patients were referred for appropriate diagnostic procedures at the discretion of the treating physician. 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).

2.2. Resource utilization and cost

We chose the perspective of the publicly funded health care systems: Ontario, Canada and France. For each trial participant, we estimated the total health system cost over the entire study period (i.e. 24 months). Patient health resource use associated with screening strategies was obtained from the trial data.

The unit costs for the Ontario health care system perspective were extracted from the Ontario Ministry of Health and Long-Term Care Schedule of Benefits [11]. The schedule of laboratory fees was used to estimate the costs of lab tests [12]. The unit cost of a FDG PET/CT for the Ontario health system perspective was taken from CADTH Optimal Use Report - 2012 and was inflated to 2017 prices using a consumer price index, Statistics Canada [13] (see Appendices, Table A1). The unit costs for the French health system perspective were taken from the Classification Commune des Actes Médicaux version 49 [14]. Information regarding the laboratory fees and the unit cost of a FDG PET/CT for the French health system perspective was elicited from clinicians (see Appendices, Table A2). Costs were presented in Canadian dollars (C$) for the Ontario health system perspective and in Euros (€) for the French Health system perspective.

The following health resource components were included in total health system costs: costs of screening and diagnostic tests, costs of additional procedures conducted at the physician's discretion and costs of specialist physician consultations at initial screening and during follow-up visits.

2.3. Analysis

We adopted a time horizon of two years to capture costs of additional tests carried out at the physician's discretion during follow up.

As the base case analysis, a secondary outcome measure of the primary trial was used as the primary outcome for this cost effectiveness analysis. We measured the effectiveness of the screening strategies as the number of avoided cases of delayed cancer diagnosis. A delayed