Clinical Radiology 71 (2016) 1005–1009

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Investigation of unprovoked venous thromboembolism: a case for a tempered approach?

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ARTICLE INFORMATION

Article history:
Received 28 October 2015
Received in revised form
20 January 2016
Accepted 23 February 2016

AIM: To investigate and review the diagnostic yield for occult malignancy in patients who underwent abdominopelvic computed tomography (CT) after the diagnosis of unprovoked venous thromboembolism (VTE) with reference to the guidelines set by The National Institute for Health and Clinical Excellence (NICE).

MATERIALS AND METHODS: We retrospectively reviewed all unprovoked VTE diagnosed within a large teaching hospital over a period of 21 months for subsequent imaging investigations and cancer diagnoses. The primary outcome was confirmed cancer diagnosis; patients were followed for a minimum of 12 months.

RESULTS: Three hundred and five unprovoked VTEs were diagnosed in the study period, 31% of all VTEs. Of this cohort, 73.1% underwent further imaging for exclusion of occult malignancy. Fifteen (4.9%) cancers were diagnosed; with no subsequent malignancy reported in a 12-month follow-up period of the remaining 290 patients. Of the 15 cancers, seven were post-pulmonary emboli, all of which were identified on the initial CT pulmonary angiogram, thus abdominopelvic CT only was used to locate the primary and to undertake staging. Eight were post-deep-vein thrombosis (DVT). Thus the diagnostic yield for malignancy on abdominopelvic CT post-unprovoked VTE was 2.3%. The majority of diagnosed cancers were advanced with 80% dying in the follow-up period with a mean survival of 3.4 months.

CONCLUSION: The pick-up rate of occult malignancy on abdominopelvic CT post-unprovoked VTE in the present study was 2.3%, far less than the generally quoted rate of 10%; however, similar to other rates in the literature. The benefit abdominopelvic CT brings to the diagnosis of occult malignancy post-unprovoked VTE is irresolute.

Introduction

Venous thromboemboli (VTEs) clinically refers to both deep-vein thrombosis (DVT) and pulmonary emboli (PE).[1,2] There are numerous predisposing factors for VTE,[1,3,4] and a new VTE diagnosis in the absence of these is classed as an

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http://dx.doi.org/10.1016/j.crad.2016.02.017
0009-9260/

unprovoked VTE.[1,5] Recent reviews have shown a 14- to 27-fold increase in the number of computed tomography (CT) pulmonary angiograms (PA) performed from 2001 to 2008 and 2000 to 2010, respectively, with a subsequent increase in VTE diagnosis, which has led to an increased number of investigations searching for the cause of unprovoked VTE.[6,7] Unprovoked VTE may be the initial manifestation of an underlying occult malignancy[1,4,5,8,9]; potentially this may have arisen from any primary site, but particular associations have been seen with pancreas, ovarian, and hepatic malignancies.[1,2,9]

The relationship between unprovoked VTE and occult malignancy was initially identified in the 1800s by Trousseau.[5,10] Numerous clinical studies and trials have shown that patients presenting with VTE are at "high-risk" for occult malignancy or for developing malignancy shortly after the initial diagnosis of VTE[10] with up to 10% of patients diagnosed with malignancy within a year of the initial diagnosis of unprovoked VTE.[2,3,5,8,10–12] Studies have shown that patients presenting with unprovoked DVT and/or PE had risks 3.2–3.3-times higher of having an occult cancer than patients without VTE.[3,9]

As such clinicians do not want to miss the opportunity to diagnose an occult malignancy after unprovoked VTE at the earliest possible stage, thus the identification of potential occult malignancy in patients presenting with unprovoked VTE is at the forefront of the clinical decision-making process. The assumption is that curative intervention is potentially greater at an earlier stage of the disease process, allowing for early initiation of treatment to reduce cancer-related morbidity and mortality[1,5,12]; however, whether the early detection of cancers after unprovoked VTE significantly alters the prognosis has not be made clear.[5] There is currently insufficient evidence concerning the effectiveness of testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) in reducing cancer and VTE-related morbidity and mortality.[1]

This perceived 1 in 10 risk of an occult malignancy, therefore, results in further investigation in patients presenting with unprovoked VTE in order to optimise both the treatment for VTE and for cancer.[1] This not only presents a degree of anxiety and psychological burden for the patient, which should not be underestimated, but also exposure to radiation. The National Institute for Health and Clinical Excellence (NICE) in the UK publishes the best practice guidelines for VTE management.[13] It advises limited first-line investigations, including physical examination and full history, chest X-ray, blood tests including full blood count, bone profile, and liver function tests, as well as urinalysis to investigate for possible causative occult malignancy.[13] It further suggests extending investigations to include an abdominal-pelvis CT examination (and a mammogram in females), in patients over the age of 40 with no signs or symptoms on the initial limited diagnostic investigations.[13] Previous studies have shown that the <40 group of patients show no benefit from extended investigation as the diagnosis of occult malignancy is rare.[13] Recent studies have shown that limited investigations of unprovoked VTEs can miss a significant number (50%) of malignancies.[4,14] It is also worth highlighting that a significant number of malignancies can be incidentally identified on CTPA and should be sought out in examinations, particularly in patients with unprovoked PEs.[3] Dutch studies have demonstrated that extensive screening (particularly with the use of CT) can be up to three-times more expensive than limited screening, the expense of which was felt to be not justified by lives saved or costs spent in the follow-up period.[15]

The lack of consensus opinion and limited varied evidence means that the reference standard for the investigation of occult malignancy remains elusive.[1,4,5,12,15,16] As such, many clinicians have tended to tread cautiously, resulting in a culture of performing abdominopelvic CT examinations for the majority of patients with unprovoked VTE.

The present study was undertaken to further investigate and review the diagnostic yield for occult malignancy in patients who underwent abdominopelvic CT after the diagnosis of unprovoked VTE with reference to the guidelines set by NICE.[13]

Materials and methods

A retrospective review of all available data for 937 consecutive adult patients in a secondary care NHS trust with three hospital sites, with newly diagnosed VTE identified on Doppler ultrasound and CTPA over a 21-month period was performed. VTE diagnoses were identified from the clinical radiology information system (CRIS), as all imaging diagnosed VTE are tagged with a VTE short code to allow for subsequent root cause analysis. VTE diagnosis from nuclear medicine ventilation–perfusion (VQ) scintigraphy examinations were not included in the analysis, as during the study period VQ examinations within the trust were only routinely used for patients under 40-years old.

The identified VTEs were judged to be provoked or unprovoked by reviewing patients' clinical information, electronic discharge summaries, CRIS records including subsequent CT requests, and the electronic results database.

All known provoked VTE were excluded from the analysis. All known provoked VTE were excluded from analysis. A VTE was judged to be provoked based on presence of an antecedent (within 3 months) and transient major clinical risk factor for VTE (Table 1). Unprovoked VTE were embolic events in patients with no antecedent major clinical risk factor for VTE who was not having hormonal therapy or active cancer, thrombophilia or a family history of VTE.[13] All unprovoked VTE were reviewed for subsequent imaging investigations - specifically a portal venous phase CT of the abdomen and pelvis, and cancer diagnosis using patients

Table 1
Transient risk factors for provoked VTE – within 3 months.

Surgery
Trauma
Significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair)
Pregnancy or puerperium
Hormonal therapy (oral contraceptive or hormone replacement therapy).