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Incidental venous thromboembolic events in cancer patients: what we know in 2016

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Abstract

Cancer patients are at high risk of venous thromboembolism (VTE). Previous reports on the epidemiology and incident of thrombotic complications in cancer patients are based upon documented symptomatic events. However, the frequent use of contrast enhanced computerized tomography for cancer staging has documented a high incidence of unsuspected venous thrombosis (DVT), pulmonary embolism (PE) and abdominal visceral thrombosis in cancer patients. Recent studies focusing on the findings of incidental PE when compared to symptomatic PE find no significant difference in pulmonary distribution of clots, incidence of VTE recurrence or survival in these patients. Based upon these studies, current guidelines recommend treatment for incidental PE as recommended for symptomatic PE.

Keywords

Cancer; Venous thromboembolism; Pulmonary embolism; Computerized tomography

Introduction

Venous thromboembolism (VTE), inclusive of deep vein thrombosis (DVT), pulmonary embolism (PE and intra-abdominal thrombosis, is a common complication of cancer and its treatment. Cancer patients have a 4 to 7 fold increased risk of symptomatic VTE and a 5–7 fold increased risk of bleeding on anticoagulation as compared to patients without cancer [1–6]. The development of VTE in cancer patients is strongly influenced by tumor type, stage and treatment modality [4]. Thrombotic events contribute significantly to morbidity and mortality among cancer patients, and VTE has been reported in one study to be the second leading cause of death among ambulatory cancer patients [7].

Our current knowledge of the incidence, demographics and outcome of cancer-related VTE is based upon reported symptomatic events. However, the unsuspected finding of PE, DVT, or intra-abdominal thrombosis of the splanchnic or visceral veins in cancer patients is not

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uncommon on routine staging CT scans of chest, abdomen and pelvis utilized for tumor staging [8–10]. A number of recent reports have clearly shown that these events are of clinical significance. Because clinical trials among patients undergoing cancer treatments have not consistently distinguished between incidental and symptomatic VTE, we have limited prospective data on these patients and thus, no high-grade recommendations can be made in regard to their treatment. This problem was addressed in a set of guidance recommendations by the Scientific Subcommittee of the International Society of Thrombosis and Hemostasis in 2012 and 2015 which address the use of proper nomenclature, reporting of radiographic techniques, notation of clot location, distinction between symptomatic and incidental VTE in cancer clinical trials and recommendations regarding anticoagulation management [8,9].

Epidemiology, diagnosis and clinical outcome of incidental VTE

The prevalence of incidental PE (IPE) is reported between 2 to 4% [10], with incidental DVT (IDVT) involving the lower extremities or abdominal vessels occurring in 1–3% of unselected cancer patients [11,12]. However, an analysis restricted to patients with gastrointestinal malignancies revealed a much higher prevalence of IDVT (7.3%), including lower extremity and visceral vein clots [13], highlighting the impact of cancer type on the epidemiology and sites of VTE. Retrospective studies suggest that as many as half of all cancer-related VTE are incidentally detected [14], and in select patient populations exceed symptomatic events [15]. The pulmonary distribution of incidental emboli is no different than that of symptomatic emboli, with nearly half being in major pulmonary vessels [16,17]. Moreover, a majority of patients with incidental PE actually have PE-related symptoms such as shortness of breath or fatigue [17,18].

The variation in the reported incidence of incidental VTE most likely reflects differences in CT technology, with newer scanners having greater speed and resolution. . This may be of particular importance in the identification of subsegmental IPE. The experience of the radiologist in recognition of IPE in imaging studies, not dedicated to identification of suspected PE, may also explain differences in the reported incidence of IPE. However, two studies have clearly demonstrated, using blinded adjudication of reported IPE, that experienced pulmonary radiologists can accurately identify IPE even in segmental and subsegmental vessels [17,19].

While there are no prospective data regarding the outcome of IPE among cancer patients, retrospective studies suggest that these clots cause significant morbidity, and that their impact on mortality is comparable to that of symptomatic PE [18,20–25]. While some of these data may be flawed by inclusion of various cancer types, stages and treatment modalities known to impact survival, the general conclusion of nearly all published studies is that there is no significant difference in clinical outcome between patients with incidental and symptomatic DVT and PE. Abdel-Razeq performed a retrospective review of 34 cancer patients with IPE among whom 60% were symptomatic, 26.5% experienced sudden death within 30 days, 5.9% suffered pulmonary hypertension and 5.9% developed recurrent PE [18]. In the single study that utilized a control group of cancer patients without PE matched for age, cancer histology and stage, patients with IPE complained of fatigue and shortness of

breath significantly more frequently than did matched controls unaffected by VTE [17,20]. Median overall survival was 8 months for the IPE cohort compared to 12 months for the matched controls [20]; moreover, among the patients with IPE, those with symptoms had poorer survival than those who were truly asymptomatic [23]. In 2 additional retrospective analyses of heterogeneous groups of cancer patients, IPE conferred a similar adverse impact on survival as compared to cancer patients with symptomatic PE, with death rates just under 50% at 6 months [21] and just over 50% at 12 months [21]. In addition, the report by den Exter and colleagues [22] found s similar incidence of VTE recurrence between the patients with symptomatic VTE and patients IPE (16.9% vs., 13.3%; P=.77).

Two studies included more homogenous cohorts of cancer patients to evaluate the clinical impact of IPE. In a small series of patients with non-Hodgkin's lymphoma (NHL) diagnosed with IPE, median survival was only 2 months, whereas median survival among the NHL patients without clots was not reached [24]. Sun et al compared a relatively large cohort of lung cancer patients with IPE (n=113) to similar patients with suspected PE (n=67) and although there was no difference in the distribution of clots between the groups, the median overall survival was significantly better among the IPE group (median overall survival 9.3 vs. 4.2 months, p=0.001) [25]. These findings are contrary to the findings of all of the other studies, and could be due to assignment of only truly asymptomatic patients to the IPE group as a previous report found survival of symptomatic IPE patients worse than true asymptomatic patients [23].

The largest cohort of cancer patients with unsuspected SSPE (uSSPE) published to date for whom survival data is available was included in the retrospective, matched cohort study by O'Connell et al. [17,20,23]. The authors found no significant difference in survival between the 17 patients with uSSPE and their age-, histology-, and stage- matched controls [20]. Despite data suggesting that SSPE may not impact survival in the general population or in cancer patients, the majority of patients are treated when the diagnosis is known [26]. A survey of 47 physician members of the Thrombosis Interest Group of Canada indicated the physicians were more likely treat a SSPE if metastatic cancer was present [27].

There are very little data regarding the presence of coincident DVT among cancer patients diagnosed with IPE, suggesting that it is not routine practice to test. However, ultrasonography to detect DVT may help determine whether or not to treat a patient with IPE confined to the subsegmental pulmonary arteries. In one study, half of patients with SSPE in whom ultrasound was performed demonstrated unsuspected DVT [17]. Therefore the detection of a SSPE in cancer patients can in some circumstances reflect significant clot burden in other sites such as the lower extremities

Management of incidental VTE

Unfortunately, there are no specific published guidelines regarding the management of cancer patients diagnosed with IPE and this group of patients was not addressed within the recently published international guidelines [28]. In the study by Sun and colleagues, anticoagulation therapy was used to treat only 45% of the IPE patients, and these patients had a higher burden of disease than those who were not treated [25]. Nonetheless, median survival was significantly better in the treated group (30.9 vs. 6.1 months, p

<0.001) [25]. The majority of surveyed physicians self-report use of anticoagulation to treat cancer patients with incidental VTE [29]. ASCO guidelines suggest that appropriate treatment of IPE identified proximal to the subsegmental pulmonary is not different from the standard treatment recommendation for cancer-associated VTE [30]. Unfortunately, cancer patients have a higher risk of major bleeding than non-cancer patients when treated with anticoagulation. A recent report of a combined analysis of 11 cohorts comprising 926 cancer patients with IPE found the weighted pooled 6-month risks of recurrent VTE, major haemorrhage and mortality were 5.8% (95% CI 3.7–8.3), 4.7% (95% CI 3.0–6.8) and 37% (95% CI 28–47) respectively [31]. VTE recurrence risk in patients treated with low molecular weight heparins (LMWH) or LMWH followed by vitamin-K antagonists (VKA) was comparable (6.2% vs. 6.4%; adjusted hazard ratio (HR) 0.9; 95% CI 0.3–3.1), while higher in patients left untreated (12%; adjusted HR compared to treatment 2.6; 95% CI 0.91–7.3). Risk of major haemorrhage was higher in patients under VKA than LMWH treatment (13% vs 3.9%, adjusted HR 3.9; 95% CI 1.6–10) [31]. Major bleeding for patients treated with LMW heparin was not dissimilar to that reported in the dalteparin treated patients from the CLOT study (6%) which also included one fatal bleed [32].

The decision to treat incidental isolated subsegmental PE (SSPE) in cancer patients on staging CT scans can be a particularly vexing problem for oncologists, especially in light of the suggestion that these may not be clinically significant in a non-cancer population [33,34]. In a recent meta-analysis by Carrier et al, the rate of SSPE was 9.4% in patients that underwent multi-row detector CT pulmonary angiography (MD-CTPA) compared to 4.7% in patients that underwent a single-detector CTPA [28]. The VTE risk at 3 months in patients with suspected PE who were left untreated based a negative CTPA was 0.9% (95% CI: 0.4–1.4) and 1.1% (95% CI: 0.7–1.4) for single- and multi-detector CTPA, respectively. Because MD-CTPA leads to increased diagnosis of SSPE without lowering the 3-month risk of recurrent VTE, Carrier and colleagues suggest SSPE in an unselected group of patients presenting with PE-related symptoms may not be clinically relevant. However, in cancer patients receiving ongoing cancer therapy, the continued high risk of recurrent VTE may strongly support a decision to initiate anticoagulation. However, in the recent report on VTE recurrence from a combined analysis of multiple cohorts of cancer patients with IPE, isolated subsegmental IPE was not associated with a more favourable VTE recurrence risk [31].

Despite the present limitations of the clinical data available regarding the management of incidental DVT and PE in cancer patients, the weight of evidence strongly suggests that these patients have a clinical outcome similar to symptomatic patients. In this regard the recommendations of several expert advisory groups have recommended that patients with incidental DVT and PE be managed similar to symptomatic patients with extended treatment with LMW heparin [28,30].

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