REVIEW

How to treat incidental pulmonary embolism in cancer patients? Recent advances

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Kardiol Pol. 2021; 79 (12): 1305–1310;
DOI: 10.33963/KP.a2021.0164

Received:
November 17, 2021

Revision accepted:
November 29, 2021

Published online:
November 29, 2021

ABSTRACT

Patients with cancer have an increased risk of venous thromboembolism (VTE). In addition, due to the growing use of computed tomography scans in these patients and the improved scanners and imaging qualities, many cases of VTE are diagnosed incidentally on images obtained for reasons other than suspicion of VTE. Studies have shown that as many as half of all cancer-related pulmonary embolism (PE) cases could be incidental. Despite the common occurrence, the optimal management of incidental PE in patients with cancer remains unclear. This review will summarize pertinent literature related to incidental PE in the cancer population and discuss their outcomes and recommended treatments.

Key words: pulmonary embolism, venous thromboembolism, malignancy, cancer

Kardiol Pol 2021; 79, 12: 1305–1310

INTRODUCTION

Incidental pulmonary embolism (PE) refers to PE diagnosed in an asymptomatic or symptomatic patient undergoing imaging for reasons other than suspicion of PE. The incidence of incidental PE has been estimated to be in the range of 0.5% to 5.7% of chest computed tomography (CT) scans, depending on the population screened. Malignancy is the most frequent risk factor associated with incidental PE (39% of patients with unsuspected vs. 23% of patients with suspected PE had malignancy) [1]. Still, the clinical significance of incidental PE does not seem to differ according to the underlying risk factors [2]. Most recent data suggest approximately 50% of all cancer-related PE are detected on diagnostic imaging obtained for reasons other than suspicion of venous thromboembolism (VTE) [3, 4].

The increased use of CT scans in cancer patients and the introduction of multiple-detector CT scanners with their imaging quality that evolved over recent years have increased the incidence of incidental cancer-associated PE. In a recent systematic review and meta-analysis including 28 626 patients, the prevalence of incidental PE in cancer patients was 3.4% (95% confidence interval [CI], 3.2%–3.6%), with the lowest frequency observed in tumors of male reproductive organs (0.8%, 95% CI, 0.2%–1.4%) and the highest observed in patients with prostate cancer (8.6%, 95% CI 3.7%–13.4%) [5]. Several studies have evaluated the prognosis and the clinical course of incidental VTE in the cancer population, but the optimal management of these patients is still debated. Recent large randomized controlled trials (RCTs) evaluating direct oral anticoagulants (DOACs) as treatments for cancer-associated VTE included patients with incidental VTE and provided more insights into the outcomes of this population. Herein we will review pertinent literature related to incidental PE in the cancer population, summarize patient outcomes by different characteristics, discuss the screening process and recommended management.

OUTCOMES OF INCIDENTAL PE

Incidental vs. suspected

Historical trials in cancer-associated thrombosis, such as the CLOT trial, only included patients with symptomatic VTE [6]. More recent

RCTs comparing DOAC to low-molecular-weight heparin (LMWH) in the treatment of cancer-associated thrombosis started to include patients with incidental VTE and provided important information regarding their outcomes. The Hokusai VTE Cancer trial (edoxaban vs. dalteparin, total 1046 patients) included 32.8% of patients with incidental VTE. In contrast, the SELECT-D trial had 27.8% (rivaroxaban vs. dalteparin, total 406 patients), and the Caravaggio trial had 19.9% (apixaban vs. dalteparin, total 1155 patients) of patients with incidental VTE [7–9].

In the Hokusai VTE Cancer trial, 331 patients (32.8%) had incidental VTE, and 679 (67.2%) had symptomatic VTE [10]. During the study period of 12 months, recurrent VTE was found in 7.9% in the incidental VTE group compared with 10.9% in the symptomatic VTE group (adjusted hazard ratio [HR], 0.68; 95% CI, 0.42–1.11). Major bleeding events were seen in 6.6% of those with incidental VTE and 4.9% with symptomatic VTE (HR, 1.22; 95% CI, 0.66–2.20). Similarly, in the Caravaggio trial, 230 (19.9%) patients had incidental VTE, and 925 (80.1%) had symptomatic VTE [11]. During the follow-up of 6 months, 4.3% and 7.4% of patients developed recurrent VTE in incidental and symptomatic VTE groups, retrospectively (HR, 0.57; 95% CI, 0.29–1.10). Major bleeding events occurred in 5.2% vs. 3.6% (incidental vs. symptomatic) (HR, 1.43, 95% CI, 0.74–2.77). Both trials showed that cases of incidental VTE were more likely to be PE (as compared to deep vein thrombosis [DVT]). They had less extensive extent and were more likely to be in patients with gastrointestinal cancer (less likely hematological cancer) and better Eastern Cooperative Oncology Group (ECOG) performance status (≤1). All these findings could have contributed to the differences in outcomes. Important differences in inclusion/exclusion criteria between both trials must also be highlighted when interpreting their results and before making clinical decisions. Unlike the Hokusai VTE Cancer and SELECT-D trials, the Caravaggio trial excluded patients with a primary brain tumor, known intracerebral metastases, or acute leukemia [7–9]. The decision to start anticoagulation for the treatment of acute VTE in patients with such conditions is extremely difficult, and strong evidence from trials is lacking. Although the Hokusai VTE Cancer and SELECT-D trials did not exclude these patients, the numbers enrolled were small, and it is likely those enrolled were deemed at lower bleeding risk.

To summarize the currently available literature, our group recently conducted a systematic review and meta-analysis to evaluate outcomes in cancer patients with incidentally detected VTE compared to those with suspected events [4]. Our eligibility criteria included studies that enrolled adult patients with cancer-associated VTE and reported the efficacy and safety of anticoagulation in patients with incidental and symptomatic index events. For the systematic review, we included 3 recent RCTs comparing DOAC to LMWH (SELECT-D, Hokusai VTE Cancer, and Caravaggio) and 20 observational studies. The meta-analysis of the 3 RCTs showed a significantly lower rate of recurrent VTE at 6 months in patients with incidental VTE than in those with symptomatic VTE (relative risk [RR], 0.62; 95% CI, 0.44–0.87). The 6-month risk of major bleeding events was numerically higher in those with incidental VTE compared to symptomatic VTE (RR, 1.47; 95% CI, 0.99–2.20). There was no difference in overall mortality. The reasons for differences in outcomes are unclear, but factors including different baseline characteristics (for example, patients with incidental VTE are more likely to have gastrointestinal malignancies and less likely to hematological ones) and acuity or type of PE (incidental PE could be tumor thrombus and/or subacute or chronic at the time of diagnosis). Among the 20 observational studies, there was one case-control study, four prospective, and 15 retrospective cohort studies. The proportion of patients with incidental cancer-associated VTE varied from 3.8% to 80.8%. In 16 of the 20 observational studies, the overall mortality was lower in patients with incidental events [4].

Symptomatic vs. asymptomatic

Numerous studies have suggested that many incidental PEs were, in fact, symptomatic. Thus the International Society on Thrombosis and Haemostasis (ISTH) strongly recommended using the term "incidental" instead of "asymptomatic" [12]. The entire pulmonary vasculature can be involved in incidentally diagnosed PE, ranging from isolated sub-segmental PE (SSPE) to lobar or main pulmonary branches, which explains why not all affected patients are symptomatic. Nevertheless, patients diagnosed with incidental PE are often symptomatic, although symptoms could be missed or misattributed. A recent prospective cohort study of 695 patients with cancer-associated incidental PE revealed that typical signs and symptoms consistent with PE had been present within 14 days before incidental PE diagnosis in 44% of the cases [13]. Many PE symptoms (chest pain, shortness of breath) are non-specific and can often be attributed to malignancy itself and/or cancer therapies and may be missed or not perceived as related to VTE by patients and/or clinicians.

Furthermore, the presence of symptoms in cancer patients with incidental PE should not be overlooked as they could be associated with important outcomes such as mortality. The EPIPHANY study evaluated outcomes stratified by the presence of symptoms in patients with incidental cancer-associated PE [14]. In total, 497 patients were prospectively assessed for symptoms. One hundred and fifty-four had truly asymptomatic incidental PE, 129 had symptomatic incidental PE, and 214 had suspected PE. Thirty- and 90-day VTE recurrence and major bleeding rates were similar in all the groups. However, the overall 30-day mortality rate was significantly lower in patients with truly asymptomatic incidental PE events (3%) than in those with symptomatic incidental PE (20%) or suspected PE (21%) (P <0.0001). Another study by O'Connell et al. [15, 16] revealed that in patients with cancer and unsuspected VTE, survival was significantly reduced in those with

Table 1. Summary of major guideline recommendations on treatment of incidental PE and SSPE

	Incidental PE	SSPE
ACCP 2012, 2016, and 2021	Same initial and long-term anticoagulation as for comparable patients with symptomatic PE (grade 2B)	The presence of cancer may favor choosing anticoagulation or more aggressive surveillance (such as serial venous ultrasound)
ASCO 2020	Should be treated in the same manner as symptomatic VTE	Treatment determined individually
ASH 2021	Conditional recommendation of short-term treatment (3–6 months)	Conditional recommendation of short-term treatment (3–6 months)

Abbreviations: ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; PE, pulmonary embolism; SSPE, subsegmental pulmonary embolism

symptomatic events compared to those who were truly asymptomatic ($P = 0.002$). In the above-mentioned prospective cohort study of 695 ambulatory cancer patients with unsuspected PE, respiratory symptoms within 14 days prior to the diagnosis of PE and ECOG performance status were the two most important predictors for overall survival in this population [17]. These data suggest the importance of carefully assessing symptoms in cancer patients, including those that might not typically be thought of as related to PE (such as fatigue).

Treated vs. untreated VTE

Current guidelines recommend therapeutic anticoagulation for incidental VTE as one would have done for symptomatic VTE (Table 1), so most incidental PEs are treated with anticoagulation. The literature reports that more than 90% of patients with incidental VTE receive therapeutic anticoagulation. Hence, data on outcomes in patients not treated with anticoagulation remained very limited and often biased towards those with poorer prognoses [4]. An individual patient data meta-analysis from 11 registries shed some light on the outcomes of cancer-associated incidental PE when patients were left untreated [18]. Of the 926 patients in the study, 53 (5.7%) never received anticoagulation. Their 6-month VTE recurrence risk was 12%, twice as high as for patients treated with anticoagulants. Although it is possible that these patients were left untreated for specific reasons, the patient characteristics did not differ from those of treated patients. In patients who did not receive any treatment, the weighted pooled 6-month mortality was 47% (95% CI, 28%–66%), as compared with 37% (95% CI, 29%–44%) in patients treated with LMWH and 28% (95% CI, 18%–40%) in those treated with vitamin K antagonists.

Subsegmental pulmonary embolism

The thinner slices of CT scans allow a better description of smaller arteries. In a prospective longitudinal cohort study of oncological patients who had a chest CT for reasons other than suspicion of PE, the prevalence of incidental PE was noted to be 4.4% [19]. A 64-multi detector CT scan with a 5 mm slice was compared to a 1–1.5 mm slice reconstruction for pulmonary arteries assessment, and it turned out that almost 40% of all PE were only detected using the 1 mm thickness [19]. Interestingly, such as symptomatic PEs, this increased number of PE diagnosis seen in different studies seemed to principally involve peripheral, segmental, and subsegmental pulmonary arteries [19–22]. However, the true prevalence and thrombosis load are uncertain in the context of potentially suboptimal pulmonary arteries opacification of a CT scan not dedicated to PE detection [3, 18, 23, 24].

The clinical significance of SSPE in the absence of DVT is a matter of debate, and management strategies differ among physicians. Studies assessing the safety of withholding anticoagulation in non-cancer patients are ongoing (NCT01455818, NCT04263038). "A preliminary" report of one of these studies suggested elderly patients (age ≥65 years) and those with multiple SSPE had a higher risk of VTE recurrence during the 3-month follow-up when anticoagulation was withheld [25]. It is worth noting that patients with cancer were excluded from this study.

Subgroup analyses of other studies involving cancer patients with unsuspected PE suggested that patients with SSPE had a similar prognosis compared to the ones with more proximal PEs, with 12-month VTE recurrence rates of 6.4% and 6.0%, respectively ($P = 0.93$) and 12-month mortality rates of 49.9% and 58.2% ($P = 0.34$), respectively [13]. In another single-center retrospective study of 206 patients with SSPE and active cancer, the majority (67%) of SSPE cases were incidental, and most (88.3%) were treated with anticoagulation [26]. During the 12-month follow-up, 8.7% had recurrent PE, 5.3% had major bleeding by ISTH criteria, and 7.3% had non-major bleeding events. All bleeding events occurred in patients on anticoagulants. Patients treated with anticoagulation had a numerically lower PE recurrence rate than those who were not (8% vs. 13%; $P = 0.58$). Multivariable analysis showed that only poor ECOG performance status and stage IV disease (not anticoagulation use) were associated with worsened survival in this population. Therefore, the optimal treatment in incidental SSPE in the cancer population remains unclear. Currently, in clinical practice, many providers are likely to provide anticoagulation in the absence of bleeding concerns.

Screening for asymptomatic VTE

As the presence of VTE may impact cancer prognosis, one can hypothesize that early detection of VTE may be beneficial for patients. However, the practice of routine screening to detect asymptomatic VTE remains controver-

sial and is not standard of care. In a study of 62 unselected ambulatory lung cancer and lymphoma patients, none were found to have DVT on screening ultrasound before starting chemotherapy [27]. Another study of 32 patients deemed at high risk of VTE (Khorana score ≥3) found 3 cases (9.3%) of asymptomatic DVT at baseline [28]. A more recent retrospective analysis of PHACS (Prophylaxis of High-Risk Ambulatory Cancer Patients Study) similarly showed a 9% prevalence of incidental VTE in 117 asymptomatic patients with Khorana score ≥3 [29]. In a prospective cohort study, incidental VTE was systematically screened with chest-abdomen-pelvic CT scans and whole-leg compression ultrasonography in 97 cancer patients before starting chemotherapy and again after 3 months [30]. VTE was detected in 29 patients (31%), of whom 14 (14%) had isolated distal DVT and 2 (2%) had PE. More recently, the CASSINI trial performed screening lower limb ultrasound prior to randomization [31]. The CASSINI trial is an RCT comparing low-dose rivaroxaban or placebo for primary prevention of VTE in ambulatory patients starting a systemic cancer therapy and at intermediate-to-high risk of VTE (Khorana score ≥2) [31]. Of the 1080 patients initially enrolled in the trial, 49 (4.5%) were found to have a proximal DVT of the lower limbs on a screening compression ultrasonography and were not randomized. Despite these reports of screen-detected DVT, the clinical significance of these incidental DVTs detected on screening ultrasonography has never been assessed. Furthermore, the cost-effectiveness of these screening approaches requires further evaluation. Therefore, there is no evidence to suggest CT screening as routine in clinical practice at this time.

MANAGEMENT OF INCIDENTAL PE

Management of incidental PE follows a 3-step approach: confirm, assess for bleeding risk, and determine treatment strategies. The first step in managing incidental PE is to confirm the diagnosis. This is especially important in the case of SSPE due to the potential high disagreement among radiologists on the true presence of a thrombus [32]. In addition, incidental PE is typically diagnosed on a routine CT scan used for cancer staging and not a dedicated CT pulmonary angiogram. When in doubt, repeating imaging with a dedicated CT pulmonary angiogram and/or requesting a second opinion to review the imaging are recommended. Evaluation of signs and symptoms of a concurrent lower limb DVT may also assist in achieving diagnostic and treatment clarity. Once the presence of PE is confirmed, assessment for bleeding risks is important before initiation of anticoagulation. This is especially crucial for patients with cancer, as they have a heightened risk of bleeding due to anti-cancer therapies, potential thrombocytopenia, and/or vessel invasion by the malignancy.

Regarding treatment, several international guidelines have emphasized the absence of good quality evidence for the management of incidental PE. Still, currently, all major guidelines suggest the same initial and long-term anticoagulation management strategies as for comparable patients with symptomatic PE (Table 1). The American College of Chest Physicians (ACCP) guidelines graded this recommendation 2B in 2012 (i.e. weak recommendation, moderate-quality evidence), did not mention incidental PE in the first update in 2016 and did not modify the recommendation in the second update in 2021 [33–35]. Based on expert consensus, the American Society of Clinical Oncology (ASCO) guidelines recommended that incidental PE and DVT be treated similarly to symptomatic VTE [36]. Treatment for incidental SSPE should be determined individually, weighing risks and benefits of anticoagulation, as there is insufficient evidence. The American Society of Hematology (ASH) provided a conditional recommendation for short-term treatment (3–6 months) under observation for patients with incidental PE as well as SSPE, acknowledging very low certainty from available evidence [37]. Practically, we manage patients with incidental cancer-associated PE in the same manner as suspected ones. We prefer using DOACs for patients at low risk of bleeding and with no potential drug-drug interactions with current systemic therapy [38]. In patients at high risk of bleeding (e.g. patients with luminal gastrointestinal cancerwith an intact primary tumor, patients with uterus, renal, or bladder cancers), we usually initiate anticoagulation with LMWH. We follow the approved regimens for each drug (Table 2) and decide on treatment duration and dose reduction on a case-by-case basis. The currently ongoing API-CAT study (NCT03692065) is an RCT aiming to assess the use of low-dose apixaban for extended anticoagulation after an initial 6 months of treatment in patients with cancer-associated VTE [39]. Patients with an incidental index event are eligible for this trial, which soon will provide more insight on the optimal management of these patients in the long term.

Table 2. Approved anticoagulation regimens in patients with a creatinine clearance greater than 30 ml/min

Direct oral anticoagulants	
Apixaban	10 mg twice daily for 7 days, then 5 mg twice daily
Edoxaban	5-day lead-in with parenteral anticoagulant followed by 60 mg once daily[a]
Rivaroxaban	15 mg twice daily for 21 days, then 20 mg once daily
Low-molecular-weight heparins	
Dalteparin	200 IU/kg of body weight once daily for 28 days, then 150 IU/kg once daily
Enoxaparin	1 mg/kg of body weight twice daily or 1.5 mg/kg once daily
Tinzaparin	175 IU/kg of body weight once daily

[a]Dose reduction to 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml/min, or body weight of 60 kg or less, or in those receiving concomitant treatment with potent P-glycoprotein inhibitors

CONCLUSIONS

To conclude, incidental PE is frequently encountered in patients with cancer. Given the risk of recurrent VTE in this population, guidelines recommend the same anticoagulation management as for symptomatic VTE, which is

routinely done in clinical practice. However, recent RCTs indicate a lower risk of recurrent VTE and a higher risk of bleeding events in cancer patients with incidental VTE compared to symptomatic ones. This discrepancy is likely to be due to different patient populations involved and other differences in baseline characteristics. It is important to keep these in mind in the design of future clinical trials as they may be an important stratifying factor that can affect outcomes.

Article information

Conflict of interest: AD reports grants from Leo Pharma and Pfizer, personal fees from BMS, Leo Pharma, Pfizer, Servier. T-FW reports research funding from Leo Pharma and advisory honoraria from Servier. AD and T-FW are both recipients of a University of Ottawa Department of Medicine research award.

How to cite: Delluc A, Wang T-F. How to treat incidental pulmonary embolism in cancer patients? Recent advances. Kardiol Pol. 2021; 79(12): 1305–1310, doi: 10.33963/KP.a2021.0164.

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