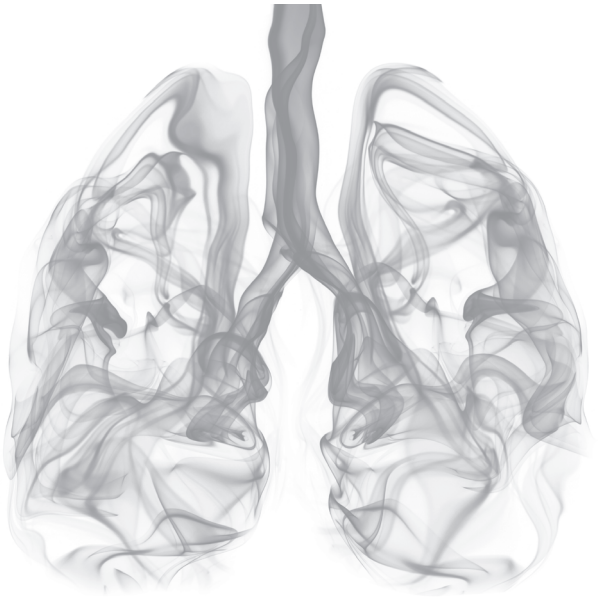
CHAPTER 12

Risk of recurrent venous thromboembolism and mortality in cancer patients incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients



P.L. den Exter, J. Hooijer, O.M. Dekkers and M.V. Huisman

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ABSTRACT

Purpose

The routine use of modern CT-scanners has led to an increased detection of incidental pulmonary embolism (PE), in particular in patients with cancer. The clinical relevance of these incidental findings is unknown.

Patients and methods

In this retrospective cohort study, oncology patients in whom PE was objectively proven between 2004 and 2010 and anticoagulant treatment was started, were included. Fifty-one patients with incidental PE and 144 with symptomatic PE were followed for one year to compare the risks of recurrent venous thromboembolism (VTE), bleeding complications and mortality. Kaplan-Meier and Cox survival analyses were performed.

Results

Incidental and symptomatic patients did not differ with respect to mean age, gender, cancer type and stage, and risk factors for VTE. As a result from evolving treatment guidelines, approximately half of the patients in both groups received long-term treatment with vitamin K antagonists in stead of currently recommended low-molecular-weight heparin. The 12-month cumulative incidence of recurrent VTE was 13.3% in the incidental group versus 16.9% in the symptomatic group ($p = 0.77$). Notably, 20% VTE events recurred after premature termination of anticoagulant therapy. The risk of major bleeding complications was also comparable in the two groups (12.5% for incidental patients and 8.6% for symptomatic patients; $p = 0.5$). The respective 12-month mortality risks were 52.9% and 53.3% ($p = 0.7$).

Conclusion

Our findings suggest that oncology patients diagnosed with and treated for incidental PE, have similar high rates of recurrent VTE, bleeding complications and mortality, as compared with oncology patients who develop symptomatic PE.

INTRODUCTION

With recent advances in the quality of computed tomography (CT) examinations, in particular with the introduction of multidetector CT scanners, the detection of incidental, asymptomatic pulmonary embolism (PE) has become relatively common, particularly in patients with malignancy.[1] A recent meta-analysis reported a weighted pooled prevalence of 2.6% of incidental PE in oncology patients.[2] To guide medical decision making for clinicians confronted with these incidental findings, knowledge on the prognosis of oncology patients with incidental PE is relevant. However, whereas it has been clearly established that symptomatic PE in cancer patients causes significant morbidity and mortality[3], there is a lack of knowledge on the outcome of incidental PE in cancer patients.

Therefore, this study was performed in aim to investigate the follow-up of cancer patients incidentally diagnosed with PE. In a cohort of oncology patients diagnosed with and treated for PE, we compared incidental with symptomatic PE cases regarding the rate of recurrent venous thromboembolism (VTE), the frequency of major hemorrhage and survival.

METHODS

Patients

A single-center, retrospective cohort study was conducted in a university hospital (Leiden University Medical Center). Patients with a diagnosis of PE between January 2004 and January 2010 were identified using ICD-9 codes. These included hospital discharge diagnoses as well as outpatient and emergency department encounters. Adult patients (age ≥ 18 years) with objectively proven PE and a concomitant active malignancy were eligible. Active malignancy was defined as cancer diagnosed within six months before the index PE, recently recurrent or progressive cancer or any malignancy that deserved curative or palliative treatment within the previous six months. Both solid and hematologic malignancies were eligible. PE had to be confirmed by pulmonary angiography, contrast-enhanced computed tomography or V/Q scanning showing a high probability of PE. PE was classified as 'incidental' if PE was detected on CT scans ordered for reasons other than suspected PE (e.g. CT scans performed for cancer staging, treatment evaluation or cancer recurrence detection).

Patients were treated with anticoagulation therapy according to local clinical practice. Before 2007, patients initially received low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) followed by vitamin K antagonists (VKA). From 2007, patients received long-term therapy with LMWH. To minimize potential bias because of diverse

treatment regimes, patients in whom anticoagulation treatment was withheld and patients treated with thrombolytic therapy, were excluded.

Institutional review board approval was not required for this observational and retrospective study.

Clinical data

The medical charts of all eligible patients were comprehensively reviewed for the following data: patient demographics; diagnosis, localization and management of the index PE; type and duration of anti-coagulation therapy; cancer type, stage and treatment; date of diagnosis, localization and management of recurrent VTE events; the occurrence of major bleeding incidents; and date and cause of death. In addition, the following risk factors for VTE were recorded at baseline: immobilization (complete bed rest for 3 or more days in the 4 weeks before PE); major surgery in the 4 weeks before PE; prior history of VTE; obesity (BMI > 30 kg/m^2); and active chemotherapy, hormonal therapy or anti-angiogenic therapy (these therapies were defined as active if they were ongoing or if PE occurred < 30 days after cessation).

Outcome

All patients were retrospectively followed during one year after initial PE. Endpoints of this study were the occurrence of recurrent symptomatic VTE, major bleeding events and all-cause mortality.

Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or spiral CT pulmonary angiography, a new high probability perfusion defect on VQ-scan or any new defects after earlier normalizing of the scan, or confirmation of a new PE at autopsy. Recurrent deep vein thrombosis (DVT) was confirmed by compression duplex ultrasonography or contrast venography.

Major bleeding was defined as fatal bleeding; symptomatic bleeding in a critical area or organ; clinically overt bleeding causing a fall in hemoglobin level of at least 20 g L^{-1} (1,24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.[4]

Cause of death was verified by reviewing the pathology report. If autopsy was not performed, the likely cause of death was verified with the treating physician by reviewing the medical records and death certificates. For patients who were lost to follow-up, general practitioners (GP) were contacted to determine whether endpoints had occurred. In case of death, the likely cause of death was verified with the GP.

Statistical analysis

Differences in baseline characteristics between patients with incidental and symptomatic PE were tested for statistical significance using the Chi-square-test or the Fishers

exact test for categorical data and the student-t test for continuous variables. According to the method of Kaplan and Meier[5], the cumulative incidence of recurrent VTE, major bleeding and all cause mortality were estimated and the groups were compared for statistical differences with the log-rank test. Patients were censored at time of event, at time of death, at date of last medical chart documentation, or after one year of follow-up, whichever came first. A Cox proportional hazard model was used to estimate hazard ratios (HR) for recurrent VTE and mortality. The HRs were adjusted for age and sex. In a second analysis the model was additionally adjusted for treatment type, mean duration of treatment and variables that were previously described as risk factors for VTE. The proportional hazards assumption was tested with inspection of log-log survival curves. SPSS, version 17.0.1 (SPSS Inc, Chicago, IL), was used for all analysis.

The reporting of this study conforms to the STROBE guidelines for reporting of observational studies.[6]

RESULTS

Patient selection

Between January 2004 and January 2010, 201 patients with established PE and active malignancy were identified. Two patients incidentally diagnosed with PE were excluded from analysis because the PE was interpreted by the radiologist to be long-standing and anticoagulation therapy was not initiated. All other incidental PE cases discovered in the study period received anticoagulation therapy. Four symptomatic patients with massive PE requiring thrombolytic therapy or surgical intervention were excluded. Follow-up was limited to four weeks in one patient, because of geographical inaccessibility.

The accuracy of case ascertainment was cross-checked with a database from the Radiology department in which consecutive patients with a diagnosis of PE were registered. From November 2008, the reports of thoracic CT scans, performed for any indication, were daily reviewed for the presence of PE. In the 15 months that this database overlapped with our study period, one patient with incidental PE and three patients with symptomatic were found that were undetected by using ICD-coding.

Patient characteristics

Of the 195 included patients, 51 (26%) were classified as incidental PE and 144 (74%) as symptomatic PE. The majority (n = 39, 77%) of the incidentally diagnosed PE was detected on CT-scans performed for the diagnoses, staging, or treatment evaluation of the malignancy. The other 12 were diagnosed during CT examinations performed for the evaluation of other (acute) medical illnesses, including abscess detection in postoperative patients.

The demographic and clinical characteristics of the study population at baseline are presented in table 1. Mean age was 64 years in the incidental group versus 60 years in the symptomatic group. In the incidental and symptomatic group respectively, 59% versus 49% were male patients, 63% versus 66% were outpatients, 8% versus 13% had isolated subsegmental PE, 12% versus 17% had hematologic malignancies, and of the patients with solid tumors, 69% versus 67% had metastatic disease. None of these differences reached statistical significance.

Lung tumors most frequently accounted for the concomitant malignancy in both groups, followed by breast cancer and colorectal cancer. No clear differences were seen in the proportion of patients with obesity or previous VTE, and similar proportions of patients were recently exposed to immobilization, major surgery, hormonal therapy, anti-angiogenic therapy, or chemotherapy.

Table 1. Baseline characteristics of the patients

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Mean age ± SD (years)	64 ± 15	60 ± 14	0.079
Male sex, No. (%)	30 (58.8)	71 (49.3)	0.242
VTE site, No. (%)			0.987
Isolated PE	46 (90.2)	130 (90.3)	
Combined PE and DVT	5 (9.8)	14 (9.7)	
Largest artery involved, No. (%)			0.421
Main or lobar	11 (21.6)	34 (23.6)	
Segmental	30 (58.8)	84 (58.3)	
Subsegmental	4 (7.8)	18 (12.5)	
Unknown	6 (11.8)	8 (5.6)	
Hospitalization status, No. (%)			0.678
Inpatient	19 (37.3)	49 (34.0)	
Outpatient	32 (62.7)	95 (66.0)	
Hematologic cancer, No. (%)	6 (11.8)	25 (17.4)	0.348
Cancer type			
NHL	4 (7.8)	5 (3.5)	
Multiple myeloma	0 (0)	8 (5.6)	
Other hematologic	2 (3.9)	12 (8.3)	
Solid cancer, No. (%)	45 (88.2)	119 (82.6)	0.348
Cancer type			
Lung	8 (15.7)	20 (13.9)	
Colorectal	5 (9.8)	8 (5.6)	
Other GI	10 (19.6)	16 (11.1)	
Breast	4 (7.8)	12 (8.3)	

Table 1 (continued)

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Brain	2 (3.9)	9 (6.3)	
Gynaecological	5 (9.8)	10 (6.9)	
Testicular	2 (3.9)	8 (5.6)	
Other solid	9 (17.6)	36 (25.0)	
Solid cancer stage			0.839
Localized disease	14 (31.1)	39 (32.7)	
Metastatic disease	31 (68.9)	80 (67.2)	
Risk factors for VTE, No. (%)			
Immobilization	23 (45.1)	68 (47.2)	0.794
Recent major surgery	9 (17.6)	31 (21.5)	0.555
Prior history of VTE	2 (3.9)	8 (5.6)	0.649
BMI* > 30 kg/m^2	6 (11.8)	17 (11.8)	0.994
Active chemotherapy	11 (21.6)	29 (20.1)	0.828
Active anti-angiogenic therapy	2 (3.9)	6 (4.2)	1.000
Active hormonal therapy	1 (2.0)	6 (4.2)	0.679

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep venous thrombosis; NHL, Non-Hodgkin lymphoma; GI, gastrointestinal tract; BMI, body mass index.

* Data on BMI was missing in 5 patients with incidental and 15 patients with symptomatic PE.

Anticoagulation therapy

Details on the type and duration of anticoagulation therapy are provided in table 2. VKA was prescribed as long-term therapy to 45% of patients in the incidental group and 51% of the patients of symptomatic group (p= 0.23).

Considering those patients who survived the first six months after the index PE, in 30% of the incidental patients and 35% of the symptomatic patients, treatment was terminated after six months or earlier. The main reasons for discontinuing therapy were bleeding complications and definitive treatment of the malignancy. In 10% of the incidental patients and 13% of the symptomatic patients, treatment was discontinued after 6 months whilst there was still active malignancy. This was primary a result of evolving institutional treatment guidelines during the inclusion period.

Recurrent VTE

During one year of follow-up, symptomatic recurrent VTE was diagnosed in 5 (9.8%) patients with incidental PE and in 15 (10.4%) patients with symptomatic PE. None of these events were fatal.

The 12-month cumulative recurrent VTE incidence was 13.3% for patients with incidental and 16.9% for patients with symptomatic PE (Figure 1; $p = 0.77$ from the log-rank test).

Table 2. Treatment Pulmonary Embolism

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Initial treatment, No. (%)			0.06
LMWH	42 (82.4)	87 (60.4)	
UFH	9 (17.6)	55 (38.2)	
VCF	0 (0)	2 (1.4)	
Long-term treatment*, No. (%)			0.225
LMWH	27 (52.9)	58 (40.3)	
VKA	23 (45.1)	74 (51.4)	
Duration of treatment, No. (%)			0.547
3 months or shorter	16 (31.4)	53 † (36.8)	
Death	14 (27.5)	46 (31.9)	
Bleeding complications	2 (3.9)	4 (7.5)	
Physician's judgment to stop treatment	0 (0)	2 (1.4)	
3 – 6 months	17 (33.3)	58 (40.3)	
Death	4 (7.8)	13 (9.0)	
Bleeding complications	1 (2.0)	2 (1.4)	
Malignancy cured	7 (13.8)	20 (13.9)	
Physician's judgment to stop treatment	0 (0)	5 (4.4)	
Reasons for discontinuing treatment not specified	5 (9.8)	18 (12.5)	
6 – 9 months	4 (7.8)	6 (4.2)	
Death	3 (5.9)	5 (3.5)	
Malignancy cured	1 (2.0)	1 (0.7)	
9 – 12 months	1 (2.0)	3 (2.1)	
Death	0 (0)	3 (2.1)	
Physician's judgment to stop treatment	1 (2.0)	0 (0)	
At least 12 months	13 (25.5)	24 (16.7)	

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VCF, vena cava filter; VKA, vitamin K antagonist.

* 13 patients died before long-term therapy was initiated.

† Information on total treatment duration was missing in 1 patient because of geographical inaccessibility after 4 weeks of follow-up.

After adjustment for age, sex and treatment duration, the HR for recurrent VTE was not statistically significant for symptomatic versus incidental patients (HR: 1.0; 95% CI: 0.4–2.9). Adjustment for the additional risk factors did not materially influence the study results.

Two patients in the group of incidental PE patients had recurrent PE, two patients developed lower-extremity DVT and one patient experienced upper-extremity DVT. In the symptomatic group, eight patients had recurrent PE and seven patients developed lower-extremity DVT.

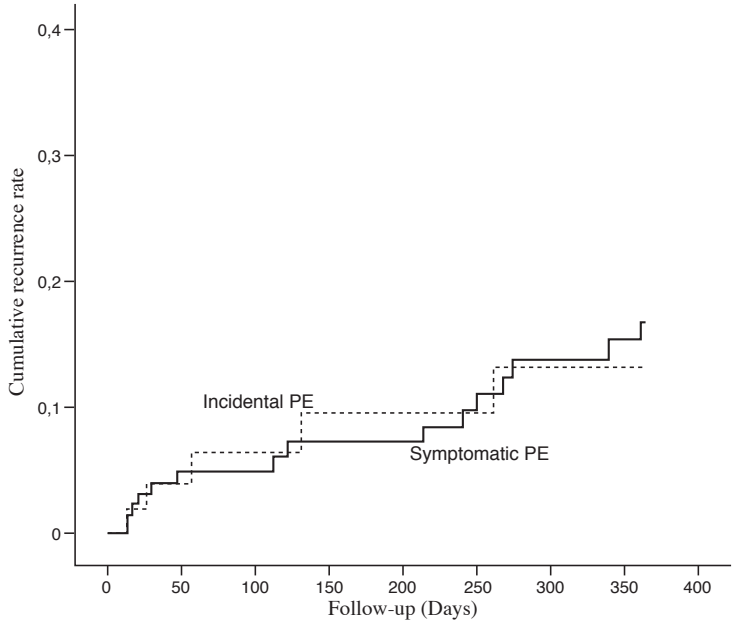

Figure 1. Cumulative risk of recurrent venous thromboembolism for cancer patients with incidental versus symptomatic pulmonary embolism ($p = 0.77$).

In one patient with incidentally detected subsegmental pulmonary embolism, a follow-up CT-scan 8 months later revealed recurrent asymptomatic PE localized in a lobar pulmonary artery. No other recurrent asymptomatic emboli were detected during follow-up of both asymptomatic and symptomatic patients.

In the incidental group, one recurrent VTE event occurred after temporary cessation of anticoagulation therapy and insertion of an inferior vena cava filter because of a surgical intervention. Of the 15 recurrent VTE events in the symptomatic group, two recurred whilst receiving prophylactic LMWH doses. One event (20%) in the incidental group and three (20%) in the symptomatic group occurred while anticoagulation was discontinued after six months whilst there was still active malignancy. All other recurrent events in both groups occurred under adequate anticoagulation therapy.

Bleeding complications

Nine patients with symptomatic and five patients with incidental PE had major bleeding; the respective 12-month cumulative incidences were 12.5% and 8.6% ($p = 0.50$ from the log-rank test; adjusted HR 0.75, 95% CI: 0.2-2.3).

In the incidental group, three patients had intracranial bleeding of whom two patients died, and two patients had gastrointestinal tract bleeding leading to blood transfusion. At time of bleeding, three patients were treated with VKA, one with LMWH and one with UFH. In the symptomatic group, two patients had bleeding at a critical site: one

patient died of fatal intracranial bleeding and one patient had retroperitoneal bleeding. The other bleeding complications caused a significant fall in hemoglobin level or led to blood transfusion; including one hematothorax, one case of severe epistaxis, two intra-abdominal and two gastro-intestinal bleeding, and one post-operative bleeding nine days after a neck surgery. At time of bleeding, three patients received UFH, four patients were treated with VKA and two with LMWH.

Mortality

During follow-up, 27 (52.9%) patients with incidental PE and 76 (52.8%) patients diagnosed with symptomatic PE died. In both groups, the majority of the deaths were a result of progressive cancer (77.8% and 78.5% for patients with incidental and symptomatic PE respectively). In the symptomatic group, the index PE was fatal in six patients.

The respective 12-month mortality risks for patients with incidental and symptomatic PE were 52.9% and 53.3% (Figure 2; $p = 0.70$). The adjusted HR for mortality was not statistically significant for patients with symptomatic versus patients with incidental PE (HR: 1.1; 95% CI: 0.7-1.8).

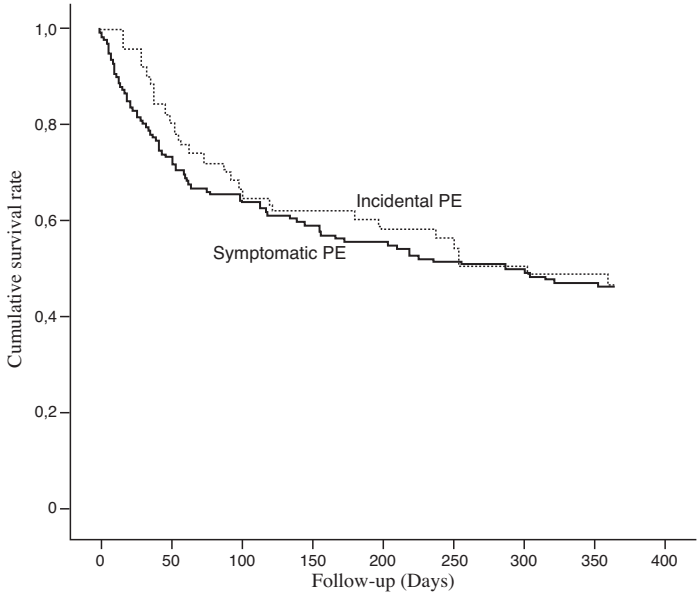

Figure 2. Kaplan-Meier survival curve until overall death for cancer patients with incidental versus symptomatic pulmonary embolism ($p = 0.70$).

DISCUSSION

This study aimed to evaluate the clinical outcome of oncology patients who were incidentally diagnosed with and treated for PE. We found that the one-year recurrence risk for VTE, the risk of major bleeding complications and overall survival in incidental patients were similar to those diagnosed with symptomatic PE.

So far, only few studies addressed the outcome of cancer patients with incidental PE, and those were small, uncontrolled series with limited follow-up. In a retrospective case series, incidental PE was detected in 16 out of 403 oncology patients by reassessing CT scans. Of the 12 patients who did not receive anticoagulant treatment, four developed further thromboembolic disease during an average follow-up of 13 months.[7] In a prospective study, unsuspected PE was detected in 18 out of 407 oncology patients on routine CT-scanning. During six months of follow-up, one patient developed recurrent symptomatic PE.[8] Remarkably, this was the only patient in whom treatment was withheld. Douma and colleagues reported no further thromboembolic events during three months of follow up of three patients with incidental PE; one of these patients was not treated.[9] Compared with these studies, our cohort was larger and our follow-up was longer. Furthermore, our study is the first to directly compare the VTE recurrence rate in cancer patients with incidental PE to those with symptomatic PE.

In the absence of convincing evidence that anticoagulation therapy can be safely withheld, current ACCP guidelines recommended treating patients who are unexpectedly diagnosed with asymptomatic PE exactly as comparable patients with symptomatic PE (Grade 1C).[10] We found that cancer patients with incidental PE, despite receiving anticoagulant treatment, display a high recurrence rate, which was even comparable to those with symptomatic PE. In our view, these results provide indirect evidence for a comparable treatment effect in both groups. However, our study was not designed to definitively determine whether anticoagulation therapy is indicated for these patients. Of note, as international guidelines now recommend treating these patients, performing a randomized controlled trial would probably be very difficult to perform or even regarded unethical.

To date, LMWH has become the agent of choice for the long-term treatment of patients with cancer-associated thrombosis.[11] Resulting from evolving treatment guidelines, a substantial number of patients in both groups received VKA in stead of LMWH. It might therefore be that the found incidence in our study is an overestimation of the incidence if all patients would have been treated according to current guidelines. Still, the patients with symptomatic PE were selected within the same study period and type and duration of anticoagulation treatment did not differ significantly between the groups.

We found that the one-year mortality rates of incidental and symptomatic PE patients were well comparable. These findings are consistent with Dentali et al[12], who found

similar 6-month mortality rates for cancer patients with asymptomatic and symptomatic VTE (51% and 48.6% respectively), which were both significantly higher compared to the mortality rate of cancer patients without VTE (27.1%). Another recent study indicated that the detection of unsuspected PE had a negative impact on survival of cancer patients, compared with matched cancer patients without VTE (HR: 1.5; 95% CI: 1.01-2.27).[13]

Our study has several limitations. First, its retrospective design may enhance information bias. In an attempt to minimize this bias, we used a pre-specified and standardized protocol to thoroughly review all medical charts of included patients and GPs were contacted in case data was incomplete. As our primary outcomes are clearly defined and serious medical events, we assumed that these would be accurately recorded in the medical charts. Second, although we used broad inclusion criteria, the exclusion of untreated incidental patients may restrict the generalisibility of our findings.[14] However, treatment was initiated in the vast majority (96%) of the incidental patients identified in the study period, which is in line with earlier reports.[8] Although we cannot claim complete case ascertainment by relying on ICD-9 codes for the identification of patients diagnosed with PE, a cross-check with the Radiology department for a period of 15 months revealed only one additional patient with incidental PE, and treatment was initiated in this patient. Third, the incidental PE cohort included a relatively limited number of patients in a single-center. Although we did not detect a difference in outcome between the symptomatic and asymptomatic group, our study might be underpowered to detect small differences.

In conclusion, we found similar rates of recurrent VTE, bleeding complications and mortality in cancer patients diagnosed with and treated for incidental PE compared with cancer patients with symptomatic PE. Given the limitations of this retrospective analysis, these findings should be considered hypothesis generating and need to be confirmed prospectively in larger studies.

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