original report

Treatment and Long-Term Clinical Outcomes of Incidental Pulmonary Embolism in Patients With Cancer: An International Prospective Cohort Study

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abstract

PURPOSE Pulmonary embolism is incidentally diagnosed in up to 5% of patients with cancer on routine imaging scans. The clinical relevance and optimal therapy for incidental pulmonary embolism, particularly distal clots, is unclear. The aim of the current study was to assess current treatment strategies and the long-term clinical outcomes of incidentally detected pulmonary embolism in patients with cancer.

PATIENTS AND METHODS We conducted an international, prospective, observational cohort study between October 22, 2012, and December 31, 2017. Unselected adults with active cancer and a recent diagnosis of incidental pulmonary embolism were eligible. Outcomes were recurrent venous thromboembolism, major bleeding, and all-cause mortality during 12 months of follow-up. Outcome events were centrally adjudicated.

RESULTS A total of 695 patients were included. Mean age was 66 years and 58% of patients were male. Most frequent cancer types were colorectal (21%) and lung cancer (15%). Anticoagulant therapy was initiated in 675 patients (97%), of whom 600 (89%) were treated with low-molecular-weight heparin. Recurrent venous thromboembolism occurred in 41 patients (12-month cumulative incidence, 6.0%; 95% CI, 4.4% to 8.1%), major bleeding in 39 patients (12-month cumulative incidence, 5.7%; 95% CI, 4.1% to 7.7%), and 283 patients died (12-month cumulative incidence, 43%; 95% CI, 39% to 46%). The 12-month incidence of recurrent venous thromboembolism was 6.4% in those with subsegmental pulmonary embolism compared with 6.0% in those with more proximal pulmonary embolism (subdistribution hazard ratio, 1.1; 95% CI, 0.37 to 2.9; $P = .93$).

CONCLUSION In patients with cancer with incidental pulmonary embolism, risk of recurrent venous thromboembolism is significant despite anticoagulant treatment. Patients with subsegmental pulmonary embolism seemed to have a risk of recurrent venous thromboembolism comparable to that of patients with more proximal clots.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer and is associated with significant morbidity and mortality.[1] Widespread use of multidetector computed tomography (CT) scanners and improved resolution have led to enhanced visualization of the pulmonary arteries, which has resulted in higher sensitivity for PE and increased detection of distal clots in subsegmental arteries.[2-5] Approximately one half of all PEs in patients with cancer is now incidentally detected on imaging undertaken for cancer staging, evaluation of treatment response, or routine follow-up.[6] The prevalence of incidental PE in the population of patients with cancer is reported to be as high as 5%.[7]

International guidelines suggest the same anticoagulant treatment for patients with cancer with incidentally detected PE as for those with symptomatic PE.[8-10] In the absence of prospective data, these suggestions are mostly based on risk estimates from retrospective studies combined with treatment effects extrapolated from trials that evaluated symptomatic PE. Optimal management of subsegmental PE, in particular, remains debated. A systematic review has suggested that subsegmental PE may not be clinically relevant in the general population, as the higher detection rate of subsegmental PE by multidetector CT compared

with single-detector CT did not lower the risk of VTE in patients who were left untreated on the basis of a negative scan.[4] In contrast, retrospective data in the population of patients with cancer demonstrated a comparable risk of recurrent VTE in those treated for subsegmental and more proximal incidental PE.[11]

The objective of the current cohort study was to assess the current treatment strategies for incidental PE in patients with cancer and associated risks of recurrent VTE, major bleeding, and mortality. In addition, we sought to compare the risk of recurrent VTE in those with subsegmental versus segmental, lobar, or central PE, as well as to compare the risk of major bleeding in those receiving prophylactic or intermediate-dose anticoagulation with therapeutic-dose anticoagulation.

PATIENTS AND METHODS

Design

This was an international, prospective, observational cohort study conducted in 32 centers in nine countries in Europe and North America between October 22, 2012, and December 31, 2017. Participating centers and investigators are listed in Appendix Table A1 (online only). The protocol was approved by the research ethics boards of all participating centers. Written informed consent was not required by some boards because of the observational nature of the study. The current report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12]

Patients

Unselected adults with active solid or hematologic cancer and a first diagnosis of incidental PE were included. Active cancer was defined as objectively confirmed recurrent, regionally advanced, or metastatic cancer, or cancer that was diagnosed or treated within the 12 months before to enrollment. Incidental PE had to be diagnosed in the 2 months before inclusion and was defined as an intraluminal filling defect in one or more pulmonary arteries on CT in the absence of a clinical suspicion of PE. Patients were included regardless of any outcome event that may have occurred in the 2-month inclusion window. Patients were excluded if they had already received anticoagulant therapy at the time of incidental PE diagnosis or if they had a life expectancy of less than 3 months. A patient screening list was not routinely collected at all centers.

Outcomes

Main study outcomes were recurrent VTE, major bleeding, and all-cause mortality (definitions are listed in Appendix Table A2, online only). Recurrent VTE was defined as objectively confirmed symptomatic or incidental DVT of the lower extremity or PE, or PE-related death.

Major bleeding was defined as clinically overt bleeding that was associated with a 2-g/dL or more decrease in hemoglobin that required transfusion of two or more units of RBCs, or that occurred in a critical site or as fatal bleeding.[13] All outcomes were centrally adjudicated by a committee whose members were unaware of patients' treatment.

Data Collection and Follow-Up

Baseline variables were collected during clinic or telephone visits in a standardized electronic case report form (Oracle Clinical Remote Data Capture 4.6.6; Oracle, Redwood City, CA) and included demographic characteristics; medical history; medication use, including cancer therapy, laboratory test results, incidental PE characteristics, and treatment; and signs and symptoms before incidental PE diagnosis. Treatment decisions were left to the discretion of the treating physician. Patients were observed for 12 months with scheduled clinic or telephone visits at 3, 6, and 12 months or until the last study visit in December 2017. During these visits, we performed patient interviews using a standardized electronic case report form and data were collected on recurrent VTE, bleeding, death, changes in anticoagulant treatment, cancer therapy, hospitalization, and recent imaging. In the case of suggestive outcome events, standardized forms were completed for central adjudication. Frequent quality checks of the electronic case report form and adjudication forms were performed by the study coordinators to ensure the completeness of data.

Statistical Analysis

Sample size calculation was estimated at an α of .05, a power of 80%, and two-sided target CI width of 0.5 to assess overall risk of recurrent VTE. Overall assumed recurrent VTE rate was 13%,[14] with an additional assumption that 95% CI was between 12.5% and 13.5%, requiring 193 patients. An additional 361 patients were needed for comparison of the risk of recurrent VTE in those with (sub) segmental PE and more proximal PE at the assumption of a 3-to-1 ratio of (sub)segmental PE versus more proximal PE, and a VTE recurrence rate of 10% in (sub)segmental PE and 20% in more proximal PE. In total, 610 patients were required at an expected dropout rate of 10%.

We used standard descriptive statistics to summarize baseline characteristics. Cumulative incidence of recurrent VTE and major bleeding was estimated using a competing risk model in which death not related to PE or bleeding was treated as a competing event. Patients were censored at the time of the last visit, end of follow-up, or when lost to follow-up. Recurrent VTE was assessed during the overall study period and during the on-treatment period, which was defined as the time during anticoagulant therapy and up to 7 days after discontinuation. Major bleeding was assessed during the on-treatment period. We assessed all-cause mortality using the Kaplan-Meier method and log-rank test to evaluate subgroup differences.

Subgroup analyses were performed in patients with subsegmental PE compared with those with more proximal—segmental, lobar, or central—PE, patients with isolated

TABLE 1. Baseline Characteristics of the 695 Patients With Incidental PE

Characteristic	Value
Mean age, years (SD)	66 (12)
Male sex, No. (%)	404 (58)
Median Karnofsky performance status, % (IQR)	80 (70-90)
Risk factors for venous thromboembolism, No. (%)	
Previous venous thromboembolism	69 (10)
Recent surgery*	52 (7.5)
Recent immobilization of at least 3 days*	91 (13)
Central venous catheter	181 (26)
Ongoing chemotherapy*	374 (54)
Ongoing hormonal therapy*	37 (5.3)
Median creatinine clearance, mL/min (IQR)	79 (63-93)
< 50 mL/min, No. (%)	51 (7.3)
Median platelet count, No. × 100,000/mL (IQR)	229 (167-295)
< 150,000/mL, No. (%)	125 (18)
Cancer type, No. (%)†	
Colorectal	145 (21)
Lung	107 (15)
Gynecologic	77 (11)
Breast	56 (8.1)
Pancreas	38 (5.5)
Kidney	38 (5.5)
Prostate	37 (5.3)
Esophageal	33 (4.7)
Gastric	29 (4.2)
Hematologic	27 (3.9)
Other	150 (22)
Distant metastases, No. (%)	448 (64)
Signs and symptoms (within 14 days before incidental PE diagnosis), No. (%)	309 (44)
Fatigue	194 (28)
Dyspnea on exertion	120 (17)
Chronic dyspnea	75 (11)
Tachycardia (pulse rate > 100/min)	50 (7.2)
New onset atrial fibrillation	3 (0.4)
Other complaints	49 (7.1)
Most proximal extent incidental PE, No. (%)	
Central	100 (15)
Lobar	285 (41)
Segmental	238 (34)
Subsegmental	63 (9.1)
Unknown	9 (1.3)

Abbreviations: IQR, interquartile range; PE, pulmonary embolism; SD, standard deviation.

*Occurring or administered in the 4 weeks before incidental PE diagnosis.

†Forty-two patients (6%) had multiple tumors.

subsegmental PE in a single branch compared with subsegmental PE in multiple branches or more proximal PE, and patients who received prophylactic or intermediate-dose anticoagulation versus therapeutic-dose long-term anticoagulation (defined in Appendix Table A3, online only). Subgroup differences were estimated by calculating subdistribution hazards ratios (SHR) using the Fine and Gray competing risk model.[15] Subgroup analysis of different anticoagulation dose intensities was adjusted for possible confounders associated with a higher bleeding risk, including age, creatinine clearance, platelet count, and primary brain tumor or brain metastasis. For this analysis, multiple imputation was used to replace missing variables 20 times using both baseline and outcome data, assuming a missing-at-random pattern. Results across imputed data sets were combined using Rubin's rule.[16]

A *P* value less than .05 was statistically significant. All statistical analyses were performed using R (version 3.5.1; http://www.r-project.org) using the cmprsk v2.2-7 package for competing risk analyses and the mice v3.3.0 package for multiple imputation.

RESULTS

A total of 695 patients were included. Table 1 lists baseline characteristics. Mean age was 66 years, 58% of patients were male, and median Karnofsky performance status was 80%. Most common cancer types were colorectal (21%), lung (15%), and gynecologic cancer (11%). Sixty-four percent of patients had metastatic disease. Signs and symptoms possibly related to PE in the 2 weeks before incidental PE diagnosis were reported by 44% of patients. PE was confined to the subsegmental arteries in 63 patients (9.1%).

Median duration between index incidental PE and the consent date was 6 days (interquartile range [IQR], 1 to 26 days). Median follow-up duration was 305 days (IQR, 170 to 377 days). Eighty-nine patients (13%) were included after January 1, 2017, and therefore had a follow-up duration that ranged between 6 and 12 months. Thirty-six patients (5.2%) were lost to follow-up, of whom 26 (72%) completed 3-month follow-up and 20 (55%) a 6-month follow-up.

Treatment of Incidental PE

Long-term treatment regimens are listed in Table 2. Anticoagulant treatment was initiated in 675 patients (97%). Most frequently reported reasons for withholding anticoagulant therapy were bleeding risk (n = 7) and thrombocytopenia (n = 2; Table 2 legend). Median overall treatment duration was 216 days (IQR, 136 to 360 days). A majority of patients were treated with low-molecular-weight heparins (n = 600; 89%), administered at a therapeutic dose in 437 patients (73%). Anticoagulant treatment was permanently discontinued in 189 patients (28%) during follow-up, mainly as a result of the end of the intended treatment

TABLE 2. Long-Term Treatment Regimens of Patients With Incidental PE

Treatment Regimen	Value
Total No. of patients	695
No anticoagulant treatment, No. (%)*	20 (2.9)
Inferior vena cava filter, No. (%)	8 (1.2)
Anticoagulant treatment	n = 675
Median treatment duration, days (IQR)†	216 (136-360)
Anticoagulant treatment type, No. (%)	
Low-molecular-weight heparin	600 (89)
Therapeutic dose	437 (73)
Intermediate dose	84 (14)
Prophylactic dose	14 (2.3)
Unknown	65 (11)
Direct oral anticoagulant	36 (5.3)
Vitamin K antagonist	16 (2.4)
Fondaparinux	11 (1.6)
Unfractionated heparin	9 (1.3)
Aspirin	3 (0.4)
Treatment of patients with subsegmental PE	n = 63
No anticoagulant treatment, No. (%)	7 (11)
Anticoagulant treatment, No. (%)	56 (89)
Therapeutic dose‡	47 (84)
Prophylactic/intermediate dose‡	7 (13)
Unknown	2 (3.6)

Abbreviations: IQR, interquartile range; PE, pulmonary embolism.

*Reported reasons for withholding anticoagulant therapy were: high bleeding risk (n = 7; 35%), thrombocytopenia (n = 2; 10%), recent bleeding (n = 2; 10%), patient in palliative care or deceased (n = 2; 10%), planned surgery (n = 1; 5%), burden of treatment (n = 1; 5%), patient preference (n = 1; 5%), drug allergy (n = 1; 5%), asymptomatic subsegmental PE without deep vein thrombosis (n = 1; 5%), or unknown (n = 7; 35%).

†Median treatment duration was 214 days (IQR, 138 to 360 days) with low-molecular-weight heparins, 227 days (IQR, 110 to 331 days) with direct oral anticoagulants, and 269 days (IQR, 200 to 367 days) with vitamin K antagonists.

‡Definitions of therapeutic- and prophylactic/intermediate-dose anticoagulation are provided in Appendix Table A2.

period (n = 69; 37%), resolution of the index incidental PE on imaging (n = 40; 21%), or bleeding (n = 26; 14%).

Recurrent VTE

Recurrent VTE was diagnosed in 41 patients (5.9%), including eight fatal events, which corresponds to a 12-month cumulative incidence of 6.0% (95% CI, 4.4% to 8.1%). Thirty-two recurrent VTE events (78%) occurred during the on-treatment period. The 12-month cumulative incidence of on-treatment recurrent VTE was 4.9% (95% CI, 3.4% to 6.8%). The types and time course of recurrent VTE events are listed in Table 3 and Appendix Figure A1 (online only). Recurrent VTE was symptomatic in 53% of patients and incidentally detected in 47% of patients.

TABLE 3. Clinical Outcomes During 12 Months of Follow-Up

Outcome	No. (%)
Total No. of patients	695
Recurrent venous thromboembolism	41 (5.9)
Nonfatal PE with or without DVT	23 (56)
DVT alone	10 (24)
PE-related death	8 (20)
Objectively confirmed fatal PE	1 (13)
Death for which PE could not be ruled out	7 (87)
Major bleeding events during on-treatment period	39 (5.6)
All-cause mortality	283 (41)
Progression of cancer	265 (94)
PE-related death	8 (2.8)
Fatal bleeding	3 (1.1)
Other	7 (2.5)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Recurrent VTE occurred in four of 63 patients with subsegmental PE (12-month cumulative incidence, 6.4%; 95% CI, 2.0% to 14%) and in 37 of 623 of those with more proximal PE (12-month cumulative incidence, 6.0%; 95% CI, 4.3% to 8.2%; crude SHR, 1.1; 95% CI, 0.37 to 2.9; P = .93; Fig 1). Recurrent VTE events in patients with subsegmental PE were symptomatic PE (n = 1), incidental PE (n = 1), symptomatic DVT (n = 1), and death for which PE could not be ruled out (n = 1). All events occurred during the on-treatment period; three patients received therapeutic-dose low-molecular-weight heparin and one

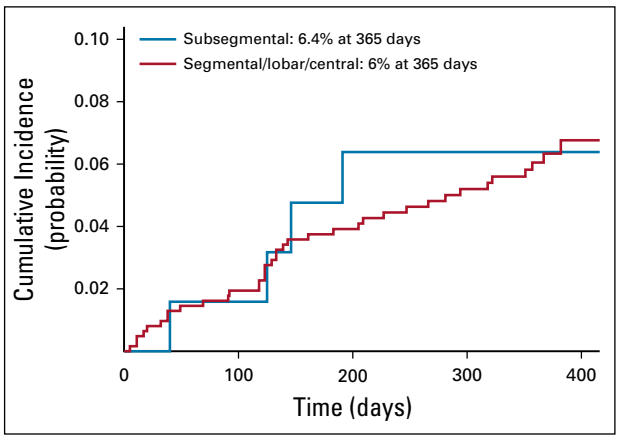

FIG 1. Cumulative incidence of recurrent venous thromboembolism (VTE) in patients with subsegmental pulmonary embolism (PE) versus those with segmental, lobar, or central pulmonary embolism. Recurrent VTE occurred in four of 63 patients with subsegmental PE and in 37 of 623 of those with more proximal PE.

patient received intermediate-dose low-molecular-weight heparin.

In the group of patients with PE isolated to a single subsegmental artery, three of 36 patients (12-month cumulative incidence, 8.4%; 95% CI, 2.1% to 21%) had recurrent VTE compared with 38 of 643 patients with multiple subsegmental or more proximal PE (12-month cumulative incidence, 6.0%; 95% CI, 4.3% to 8.1%; crude SHR, 1.4; 95% CI, 0.4 to 4.6; $P = .56$; Fig 2).

Six of 103 patients who received prophylactic or intermediate-dose anticoagulation had recurrent VTE (12-month cumulative incidence, 5.9%; 95% CI, 2.4% to 12%) and 24 of 539 patients receiving therapeutic-dose anticoagulation had recurrent VTE (12-month cumulative incidence, 4.8%; 95% CI, 3.2% to 6.9%; adjusted SHR, 1.25; 95% CI, 0.50 to 3.11; $P = .63$; Appendix Fig A2, online only).

Major Bleeding

Major bleeding occurred in 39 patients (12-month cumulative incidence, 5.7%; 95% CI, 4.1% to 7.7%; Table 3 and Appendix Fig A3, online only). Most frequent major bleeding locations were gastrointestinal (n = 21), intracranial (n = 4), and urogenital (n = 3); three (7.7%) were fatal.

Major bleeding occurred in seven of 103 patients who received prophylactic or intermediate-dose anticoagulation (12-month cumulative incidence, 6.9%; 95% CI, 3.0% to 13%) and in 32 of 539 patients who received therapeutic- dose anticoagulation (12-month cumulative incidence, 6.0%; 95% CI, 4.1% to 8.3%; adjusted SHR, 1.31; 95% CI, 0.57 to 3.0; $P = .53$; Fig 3). We used multiple imputation to replace the missing values of the variables for which SHR was adjusted, including age (2.6% missing), creatinine clearance (25% missing), platelet count (8.5% missing), and primary brain tumor or brain metastasis (no missing values).

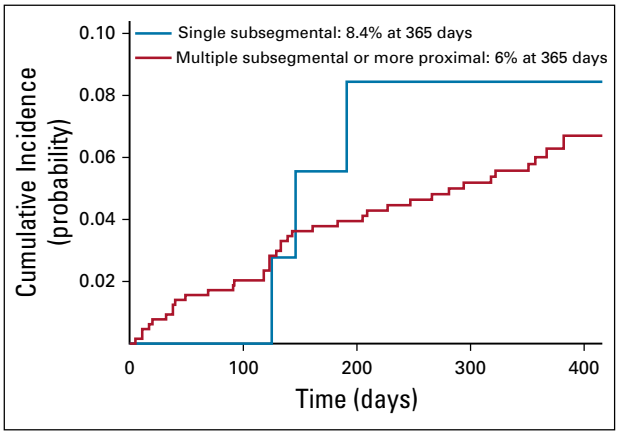

FIG 2. Cumulative incidence of recurrent venous thromboembolism (VTE) in patients with single subsegmental pulmonary embolism (PE) versus those with multiple subsegmental or more proximal PE. Recurrent VTE occurred in three of 36 patients with single subsegmental PE and in 38 of 643 patients with multiple subsegmental or more proximal PE.

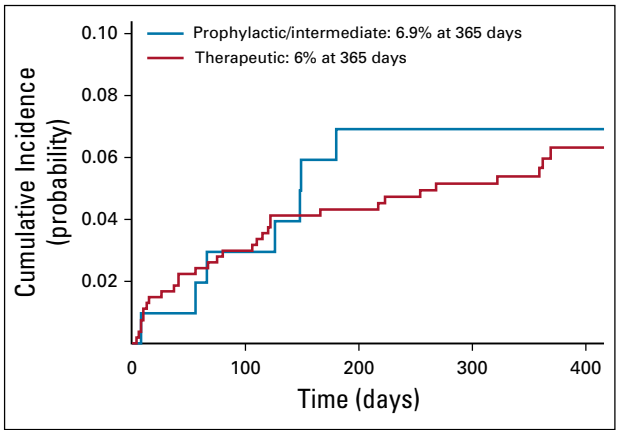

FIG 3. Cumulative incidence of on-treatment major bleeding in patients who received prophylactic or intermediate-dose anticoagulation versus therapeutic-dose anticoagulation. Major bleeding occurred in seven of 103 patients receiving prophylactic or intermediate-dose anticoagulation and in 32 of 539 those receiving therapeutic-dose anticoagulation.

Mortality

Overall, 283 patients died (41%), which corresponds to a cumulative incidence at 12 months of 43% (95% CI, 39% to 46%; Appendix Fig A4, online only). Cancer was the most frequent cause of death (Table 3). Bleeding and PE accounted for 3.8% of all deaths. Mortality was comparable in patients with subsegmental PE and in those with more proximal PE (Appendix Fig A5, online only).

DISCUSSION

The current report describes the results of a large prospective cohort study on current treatment strategies and associated clinical outcomes in patients with cancer with incidental PE. Although almost all patients received anticoagulant therapy, the risk of recurrent VTE during treatment was significant (12-month incidence, 6%). Patients with subsegmental incidental PE seemed to have a comparable risk of VTE recurrence compared with those with more proximal PE.

As a result of the widespread use of CT scanning for cancer diagnosis, staging, and follow-up, oncologists today face a diagnosis of incidental PE in approximately one in every 20 patients.[7] Current clinical guidelines suggest a similar anticoagulant treatment of at least 3 to 6 months for incidental PE as for symptomatic PE in patients with cancer,[8-10] mainly on the basis of retrospective studies that have reported comparable rates of recurrent VTE, major bleeding, and mortality in patients with incidental and symptomatic PE.[14,17-19] For example, a cohort study by den Exter[14] and colleagues that retrospectively included patients with cancer with incidental PE (n = 51) and symptomatic PE (n = 144) reported a 12-month cumulative

incidence of recurrent VTE of 13.3% and 16.9%, respectively (adjusted hazard ratio, 1.0; 95% CI, 0.4 to 2.9). In the current study, we observed a lower 12-month cumulative incidence of recurrent VTE of 6.0%, possibly because of differences in treatment regimens and patient characteristics. A majority of patients in the current study were treated with low-molecular-weight heparin, whereas almost one half of patients in the study by den Exter et al received vitamin K antagonist therapy, which is associated with a higher risk of recurrent VTE in patients with cancer.[20] In addition, patients with a short life expectancy were excluded from the current study, whereas patients with advanced stage cancer may have a higher risk of recurrent VTE.[21] Nonetheless, the risk of recurrence in the current study was still significant despite anticoagulant treatment, which supports current clinical guidelines that suggest standard-of-care anticoagulant therapy for all incidental PE.

The clinical relevance of subsegmental PE remains a matter of debate, as the increased detection of these peripheral clots over time has not been paralleled by a decrease in PE-related mortality,[22] interobserver agreement on the location of the most peripheral pulmonary emboli is reported to be poor,[23,24] and the risks of anticoagulation may be greater than the benefits.[4,25] In patients with cancer, limited data are available to guide decisions on the management of subsegmental PE. Similar to the findings of the current study, a meta-analysis of mostly retrospective cohorts that totaled 926 patients with cancer with incidental PE reported a comparable 6-month risk of recurrent VTE in those with subsegmental and more proximal PE (7.8% *v* 5.5%; adjusted hazard ratio 1.3; 95% CI, 0.57 to 3.0).[11] In addition, in the current analysis, patients with single subsegmental PE also seemed to have a significant risk of recurrence that was comparable with multiple subsegmental or more proximal PE, regardless of treatment strategy. An alternative management approach to these patients has previously been proposed by the International Society on Thrombosis and Haemostasis, which included bilateral compression ultrasonography of the lower extremities to exclude incidental DVT.[10] It is suggested that in patients without concomitant DVT, the decision to prescribe anticoagulant treatment can be individualized by balancing the risks of recurrent VTE and bleeding, the patient's preference, and performance status. If anticoagulation is withheld, frequent monitoring is suggested, including serial bilateral compression ultrasonography after 1 week in those with distal DVT to evaluate thrombus extension. Although we were unable to validate this approach as patients were not routinely screened for proximal DVT, the high risk of recurrent VTE despite anticoagulation in patients with isolated single subsegmental PE does not seem to support this wait-and-see management.

Anticoagulant treatment regimens were found to be heterogeneous. Although the reasons for subtherapeutic dosing were not collected, it could be speculated that lower dose anticoagulation may have been administered to patients with a higher risk of bleeding or small PE.

Of interest, the risk of major bleeding was found to be similar in those who received subtherapeutic-dose anticoagulation and therapeutic-dose anticoagulation. This finding suggests that the risk of major bleeding is high, regardless of dose intensity. Although we adjusted for several risk factors for bleeding, residual confounding by indication could be a contributing factor.

The strengths of the current study include the prospective design, large study group, and low rate of loss to follow-up. Information that was entered in the electronic case report form and adjudication forms was regularly assessed for inconsistencies, which ensured high-quality data. The risk of outcome bias was low as all clinical outcomes were centrally adjudicated by a committee whose members were blinded to treatment.

Several limitations also deserve acknowledgment. The observational nature of the study limited our ability to adjust for potentially important unmeasured confounders, which may have led to biased risk estimates. Treatment regimens were not mandated by protocol. As a consequence, different dose intensities, agents, and durations may have led to an underestimation of bleeding rates and an overestimation of recurrent VTE rates. The rate of recurrent VTE and the proportion of patients with (sub)segmental PE were lower than anticipated, which potentially limited the statistical power of subgroup analyses. However, the point estimates of recurrence VTE rates in subsegmental PE and more proximal PE were similar and the CIs greatly overlap, which strengthens the conclusion that the recurrent rates are indeed not different.

As patients were included in the current study up to 2 months after incidental PE diagnosis, recall bias may have occurred with regard to preceding signs and symptoms. Nevertheless, almost one half of patients reported symptoms or signs possibly related to PE in the 2 weeks before incidental PE diagnosis, which is in line with previous reports.[17,18]

Results of the current study indicate that patients with cancer with incidental PE have a high risk of recurrent VTE despite anticoagulant treatment, which strengthens current guideline advice to treat incidental PE as symptomatic PE for at least 3 to 6 months. Patients with subsegmental PE seemed to have a risk of VTE recurrence that was comparable with that of patients who had more proximal PE, regardless of the type and dose of anticoagulation, although this subgroup analysis should be considered hypothesis generating. Future intervention studies should validate our findings in patients receiving a standardized treatment regimen and assess whether anticoagulation may be withheld in selected cancer patients with isolated single subsegmental PE who are deemed to have a low risk of recurrent VTE.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.01977.

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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment and Long-Term Clinical Outcomes of Incidental Pulmonary Embolism in Patients With Cancer: An International Prospective Cohort Study

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No other potential conflicts of interest were reported.

APPENDIX

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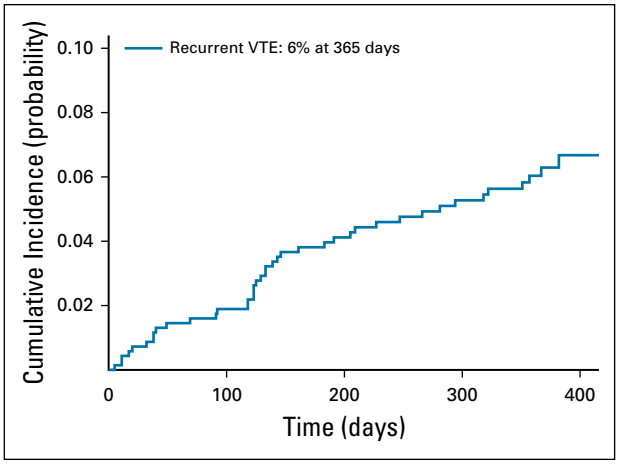

FIG A1. Cumulative incidence of recurrent venous thromboembolism (VTE). Recurrent VTE occurred in 41 patients.

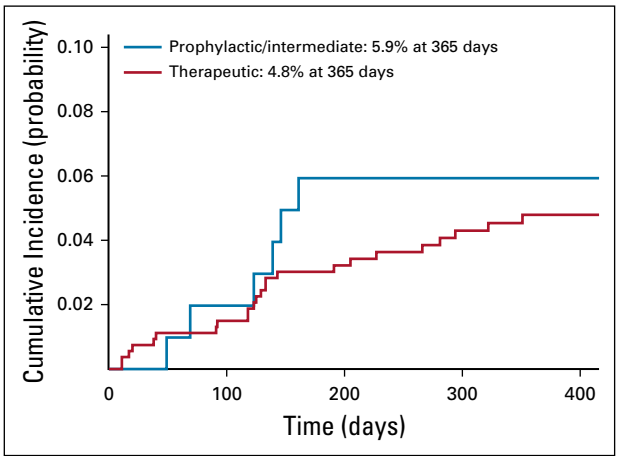

FIG A2. Cumulative incidence of on-treatment recurrent venous thromboembolism (VTE) in patients who received prophylactic or intermediate-dose anticoagulation versus therapeutic-dose anticoagulation. Recurrent VTE occurred in six of 103 patients receiving prophylactic or intermediate-dose anticoagulation and in 24 of 539 those receiving therapeutic-dose anticoagulation.

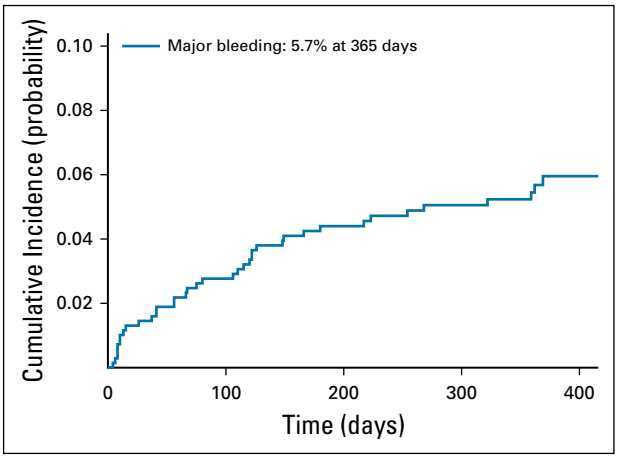

FIG A3. Cumulative incidence of major bleeding during the on-treatment period. Major bleeding occurred in 39 patients.

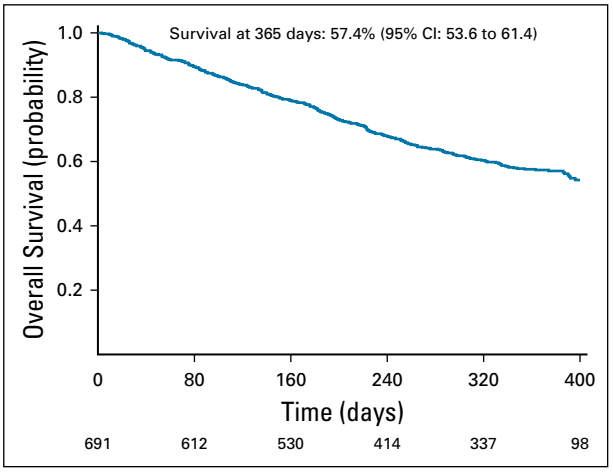

FIG A4. Kaplan-Meier curve for survival. Overall, 283 patients died.

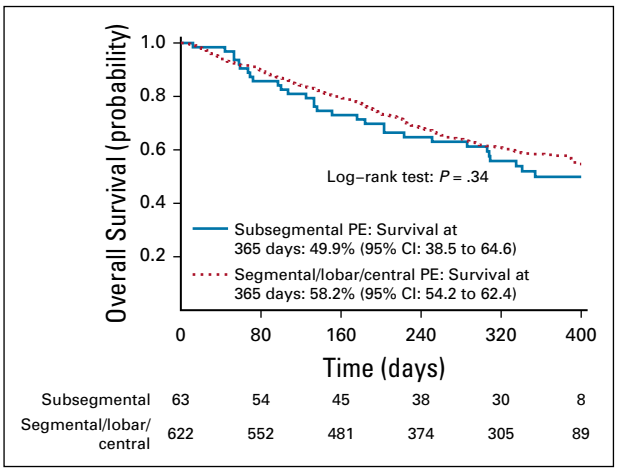

FIG A5. Kaplan-Meier curve for survival in patients with subsegmental pulmonary embolism (PE) versus segmental, lobar, or central PE. Thirty of 63 patients with subsegmental PE and 251 of 623 patients with more proximal PE died during the course of the study.

TABLE A1. Participating Centers and Investigators of the Unsuspected Pulmonary Embolism Study

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Hospital Santa María Nai, Ourense	Mercedes Salgado Fernández
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United States	
Washington DC Veterans Affairs Medical Center, Washington, DC	Anita Aggarwal, Frederick Rickles
Canada	
The Ottawa Hospital, Ottawa, Ontario	Marc Carrier

Abbreviations: CHRU, Centre Hospitalier Régionaux et Universitaire; CHU, Centre Hospitalier Universitaire; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico.

TABLE A2. Definitions of Study Outcomes

Definition
Recurrent venous thromboembolism
Defined as objectively confirmed symptomatic or incidental DVT of the lower extremity or PE, or PE-related death
Criteria for objectively confirmed recurrent PE were as follows: a new intraluminal filling defect on computed tomography or magnetic resonance imaging, or extension of an existing defect, a new sudden cutoff of vessels of > 2.5 mm in diameter on pulmonary angiogram, or as a new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation perfusion lung scan
DVT, either proximal or distal, was confirmed by noncompressibility on compression ultrasonography, an intraluminal filling defect on venography, or extension of a previous noncompressible venous segment or intraluminal filling defect
Death was considered to be related to PE if the PE was objectively confirmed by imaging tests shortly before death or by autopsy, or in the case of an unexplained death for which PE could not be ruled out
Major bleeding
Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 2 g/dL that required transfusion of two or more units of RBCs, occurring in a critical site (intracranial, intraocular, intraspinal, retroperitoneal, pericardial, intra-articular, or intramuscular with compartment syndrome), or as fatal bleeding, per International Society on Thrombosis and Haemostasis criteria[13]
Mortality
Defined as being related to cancer, PE, bleeding, or other causes

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

TABLE A3. Definitions for Different Anticoagulant Dose Intensities

Dose Intensity	Definition
Prophylactic dose	Low-molecular-weight heparin at a prophylactic dose as indicated by the study physician
	Fondaparinux 2.5 mg once per day
	Direct oral anticoagulants at a prophylactic dose
	Rivaroxaban 10 mg once per day
	Apixaban 2.5 mg twice per day
	Aspirin 80 or 100 mg once per day
Intermediate dose	Low-molecular-weight heparin at an intermediate dose as indicated by the study physician
Therapeutic dose	Low-molecular-weight heparin at a therapeutic dose as indicated by the study physician
	Unfractionated heparin
	Fondaparinux 7.5 mg once per day
	Vitamin K antagonists
	Direct oral anticoagulants at a therapeutic dose
	Rivaroxaban 15 mg twice per day or 20 mg once per day
	Apixaban 5 or 10 mg twice per day
	Dabigatran 150 mg twice per day
	Edoxaban 60 mg once per day