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CHAPTER 9

Outcome of incidentally diagnosed pulmonary embolism in patients with malignancy

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ABSTRACT

Purpose of review
With improvements in the quality of computed tomography (CT) examinations, pulmonary embolism (PE) is increasingly being detected incidentally in oncology patients undergoing routine cancer staging CT scans. The purpose of this review is to update current evidence on the prognosis of cancer patients diagnosed with incidental PE.

Recent findings
Several recent observational studies have shed some light on the prognostic implications of diagnosing incidental PE in cancer patients. In general, anticoagulant treatment is initiated in these patients. Even during treatment, recurrent venous thromboembolic events may occur with a frequency that is comparable to cancer patients who have symptomatic PE. It has been demonstrated that the diagnosis of incidental PE is associated with adverse survival in cancer patients, and long-term mortality rates in incidental PE patients seem to approach that of symptomatic PE patients.

Summary
Overall, the body of literature on patients with incidental PE is sparse and does not allow firm recommendations on the therapeutic approach to these patients. Yet, in the absence of data on the natural clinical course of these patients, and the presence of cohort studies suggesting that incidental PE may impact recurrent venous thromboembolism and mortality, current consensus is to treat these patients in the same manner as symptomatic patients.
INTRODUCTION

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is a frequent complication of cancer and its treatment. Patients with active malignancy carry a 7-fold increased risk of developing VTE. The occurrence of VTE causes significant morbidity and mortality in these patients. In fact, VTE is the second leading cause of death in oncology patients. Furthermore, patients with cancer and established VTE are shown to have more advanced stages of malignancy and, consequently, poorer survival rates compared to cancer patients without VTE. Treatment of VTE in this specific patient group is challenging as the underlying malignancy exposes these patients to a high risk of recurrent VTE, while at the same time cancer patients more frequently experience anticoagulant-related bleeding complications than VTE patients without cancer.

Clinically manifest VTE is diagnosed in approximately 15% of all patients with malignant disease. The actual prevalence of VTE among cancer patients is likely even higher when subclinical or asymptomatic VTE patients are taken into account. It is well-known that patients with PE may commonly present with non-specific symptoms or even remain completely asymptomatic. For instance, silent PE is present in up to 32% of the patients diagnosed with DVT. Also, PE is frequently diagnosed at autopsy while unsuspected ante mortem. The overall prevalence of PE identified at autopsies of cancer patients has been reported to be as high as 23%.

Now that computed tomography (CT) imaging techniques have evolved significantly over the past few decades, PE is increasingly being detected incidentally in cancer patients in whom PE was not clinically suspected at the time of the CT examination. To determine the clinical relevance of these incidental findings, data on the prognosis of cancer patients with incidental PE is of great importance. The current review describes the scope of this problem and summarizes recent studies addressing the clinical course and outcome of cancer patients with incidental PE.

PREVALENCE OF INCIDENTAL PULMONARY EMBOLISM IN ONCOLOGY PATIENTS

The introduction of thin-section multidetector row CT scanners with fast acquisition times has resulted in major improvement of visualization of the pulmonary vasculature, while intravenous contrast administration has been optimized. As a result, many routinely performed thoracic contrast-enhanced CT examinations are now of adequate diagnostic value for the identification of PE. This has led to an increasing number of PE diagnoses, incidentally found in patients who had undergone CT-scanning for reasons
other than suspected acute PE (Figure 1 and 2). In the general population, incidental PE has been reported to be diagnosed in 1.5% of all patients undergoing routine helical CT scans.\textsuperscript{11} However, this prevalence is significantly higher among high-risk patients, including inpatients and patients with cancer; the vast majority of incidental PE diagnosis are made in the latter group.\textsuperscript{12} This is not surprising, since patients with malignant disease are at high risk of developing PE.\textsuperscript{13} Furthermore, oncology patients far more frequently undergo CT scanning compared to patients without cancer, for reasons including diagnosing, staging and treatment evaluation of the malignancy. In oncology patients, the reported prevalence of incidental PE ranges from 1.9 to 4.4%.\textsuperscript{14-18} The detection of incidental pulmonary emboli may vary upon detector collimation and image reconstruction thickness used. In symptomatic patients, it has been clearly established that the introduction of multidetector computed tomographic pulmonary angiography (CTPA) has significantly improved the detection of PE, in particular those emboli

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1}
\caption{59-year-old male patient with metastasized melanoma. CT indication was follow-up after partial remission following chemotherapy. CT maximum intensity projections (A, B) and average reconstructions (C, D), in coronal (A) and axial (B-D) view. Progression of disease was found with metastases to liver, peritoneum, mesenterium and mediastinum (not shown). Pulmonary embolism was found as incidental finding (arrows in A-C), with central (C) and segmental (A, B) emboli in the right pulmonary artery. The patient had no symptoms suggestive of pulmonary embolism. Slight enlargement of the right ventricle (RV) as compared to the left ventricle (LV) with RV/LV ratio >1 (normal ratio is <1).}
\end{figure}
located in the subsegmental branches of the pulmonary arteries.\textsuperscript{19} For the detection of incidental PE, a recent systematic review reported a pooled prevalence of 2.0\% for studies using CT scans with slice thickness $\geq 5$mm and 3.0\% for studies in which CT scans with slice thickness $< 5$mm were used.\textsuperscript{20} Brown et al.\textsuperscript{16} hypothesized that systematically adapting a CTPA imaging protocol, by using 1 – 1.5 mm slices and optimizing the timing of the contrast delivery to the pulmonary vessels, in oncology patients undergoing routine CT examinations, would improve the detection of incidental PE. In the 407 out of 408 enrolled patients in whom CTPA was considered adequate to detect intravascular contrast filling defects, PE was diagnosed in 18 (4.4\%) patients. Of note, PE would not have been diagnosed in 39\% of these patients if the CT scans were performed without a CTPA protocol.

Figure 2. 43-year-old male patient with follicular lymphoma. CT indication was progression of pain in back and lower abdomen. Progression of disease was diagnosed. Incidental segmental pulmonary emboli in right pulmonary artery (arrows in A, B). Cause of pulmonary emboli is shown in C and D. C: large, partly necrotic lymph node tumor (N) with encasement of the aorta (Ao) and inferior vena cava (IVC, between arrows), causing flow obstruction from the lower extremity to the heart. Note deep venous thrombus in the left and right extern iliac veins (arrows in D).
Chapter 9

RISK FACTORS

The increased risk of thrombosis in cancer patients is primarily attributed to the hyper-coagulable state associated with malignancies, with the risk being greatest in patients with newly diagnosed malignancy. Several risk factors have been identified that further predispose cancer patients to VTE, these include: older age, obesity, immobility, surgery, comorbid conditions, cancer-associated factors such as primary cancer site and cancer stage, and treatment-associated factors including the use of chemotherapy, hormone therapy and radiation therapy.

Di Nisio et al. performed a retrospective cohort study in cancer patients receiving chemotherapy, to characterize these patients’ risk factors for incidental VTE. Out of 1921 patients, they identified 62 patients with incidental VTE, of whom 24 had PE. As for symptomatic VTE patients, metastatic disease, high leukocyte count and chemotherapy with platin agents were found to correlate with the occurrence of incidental VTE. Also, the majority of the incidental VTE cases were diagnosed within the first few months following initiation of chemotherapy, which has previously been recognized in patients with symptomatic VTE. Although this study is limited by its small sample of patients and retrospective design, it does assume that cancer patients with incidental and symptomatic VTE share similar risk factors.

PROGNOSIS OF PATIENTS WITH INCIDENTAL PULMONARY EMBOLISM

Knowledge on the short and long-term prognosis of patients with incidental PE, in terms of the risk of recurrent VTE and mortality, is of major importance to guide clinical-decision making for physicians who are now increasingly being confronted with incidentally detected PE.

Incidence of recurrent VTE

As for the development of VTE, the presence of an active malignancy is an important risk factor for VTE recurrences. In cancer patients with established symptomatic VTE, the one-year cumulative incidence of recurrent VTE was reported to be 20.7%, compared to 6.8% for VTE patients without cancer. In the past decade, several trials indicated low-molecular-weight heparin (LMWH) monotherapy to be of superior efficacy compared to conventional treatment with Vitamin K antagonists, for the long-term management of cancer-associated VTE. Still, even during LMWH-treatment, recurrent VTE occurs in up to 9% of the patients in the initial six months. It would be important to know whether this strong association between cancer and recurrent VTE disease is also seen in patients with incidental PE. In contrast to symptomatic PE however, the body of literature
addressing cancer patients with incidental PE is scarce. Only few, small observational studies give some insight of the clinical course and outcome of these patients (table 1).

Browne et al.\textsuperscript{16} retrospectively followed 18 cancer patients with incidental PE for a period of 6 months. Anticoagulant treatment was initiated in 17 patients and none of these treated patients developed recurrent VTE during follow-up. However, the one patient in whom anticoagulation therapy was withheld, because of a perceived high bleeding risk, was diagnosed with recurrent symptomatic PE 5 weeks later. In another case series of 34 cancer patients with incidental PE, of whom 29 patients received anticoagulant treatment, acute symptomatic recurrent PE was diagnosed in two patients (5.9%).\textsuperscript{28} It was not stated at what time these recurrences were diagnosed and whether or not they occurred whilst on treatment. In a smaller study including 3 cancer patients with incidentally detected PE, no recurrent events occurred during 3 months of follow-up.\textsuperscript{29}

Gladish et al.\textsuperscript{18} identified 16 patients with incidental PE by re-assessing contrast-enhanced thoracic CT-scans of oncology patients. In 12 of those patients, PE was not detected at the initial clinical CT image interpretation and those patients thus did not receive anticoagulation. During a variable follow-up period (range: 2 days to 24 months; average: 13 months), symptomatic DVT was diagnosed in one patient, whilst two patients developed asymptomatic recurrent embolic disease (DVT in one patient, PE and DVT in the other patient). Of the four patients in whom PE was initially reported, treatment was initiated in 3 patients. None of these patients developed recurrent events during a short follow-up period (ranging from 1 day to 3 months).

Font et al.\textsuperscript{30} prospectively followed a cohort of 340 cancer patients with VTE. In 94 patients, VTE was detected incidentally, and the majority (60%) of them had PE. All patients were treated with LMWH; in most of the patients indefinitely. Recurrent VTE was observed in 10 (11%) of the patients with incidental VTE and 44 (18%) of the symptomatic VTE patients (mean follow-up time: 477 days). Recurrent rates were not specified for PE patients separately. The one year cumulative risk of recurrent VTE was significantly lower

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of patients</th>
<th>Number of patients</th>
<th>Patients treated</th>
<th>Follow-up time</th>
<th>Recurrent VTE</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Browne et al.\textsuperscript{16}</td>
<td>2010</td>
<td>18</td>
<td>17 (94%)</td>
<td>6 months</td>
<td>1 (5.6%)</td>
<td>NR</td>
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<td>2 (5.9%)</td>
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<tr>
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<td>3</td>
<td>2 (67%)</td>
<td>3 months</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Font et al.\textsuperscript{30}</td>
<td>2011</td>
<td>94*</td>
<td>94 (100%)</td>
<td>Mean: 477 days</td>
<td>10 (10.6%)</td>
<td>67 (71.3%)</td>
</tr>
<tr>
<td>den Exter et al.\textsuperscript{31}</td>
<td>2011</td>
<td>51</td>
<td>51 (100%)</td>
<td>12 months</td>
<td>5 (9.8%)</td>
<td>27 (52.9%)</td>
</tr>
<tr>
<td>Dentali et al.\textsuperscript{37}</td>
<td>2011</td>
<td>60*</td>
<td>60 (100%)</td>
<td>6 months</td>
<td>NR</td>
<td>27 (45%)</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; NR, not reported

*These studies also included patients with incidental thrombosis at other locations and did not specify the outcome for PE patients separately.
for incidental (7%) than for symptomatic (18%) patients \( (P = 0.043) \). In a retrospective cohort study including 51 cancer patients with incidental and 144 with symptomatic PE, den Exter et al.\(^{31}\) did not find a difference in the one year cumulative risk of symptomatic recurrent VTE in the incidental PE group compared to the symptomatic PE patients (13.3% and 16.9% respectively, \( P = 0.77 \)). All patients included in this study received anticoagulant therapy with LMWH or vitamin K antagonists. The recurrent events in the incidental PE group comprised two cases of PE and three cases of DVT.

To summarize, these observational studies suggest that the risk of recurrent VTE for cancer patients with incidental PE is at least non-negligible, or may even be as high as for those with symptomatic PE; even while receiving anticoagulant treatment. The natural clinical course of incidental PE, without anticoagulant treatment being prescribed, has too rarely been investigated to draw any meaningful conclusions.

**Impact on survival**

Symptomatic VTE has clearly been established as a poor prognostic marker in cancer patients, as it is associated with both short- and long-term overall mortality.\(^2\),\(^{21}\) With an aim to assess the impact of incidental PE on the survival of cancer patients, O’Connell et al.\(^{32}\) performed a matched cohort study. Seventy patients with incidental PE were matched to 137 patients without VTE, in terms of age, cancer type and cancer stage. Compared to the matched control patients, patients with incidental PE had a hazard ratio for death of 1.51 (95% CI: 1.01-1.27). Notably, the increased risk of death appeared to be driven by proximally located PE, as cancer patients with isolated subsegmental PE did not have poorer outcomes than control patients. The fact that the negative impact on survival was not significant at two months but became and was sustained significant at 6 months, suggests that most mortality was not directly related to the initial PE event. This is not surprising as PE-related death is predominately caused by impaired right ventricular function\(^{33}\), which is unlikely to be present in patients without symptoms. The adverse impact on long-term survival in these patients is most likely caused by progression of the underlying malignancy. Given that the PE patients were matched to the control patients for cancer type and stage, mortality could not directly be attributed to more aggressive types of cancer or more advanced disease stages at baseline in the PE group. However, for patients with symptomatic VTE, it has previously been demonstrated that the occurrence of VTE was a predictor of mortality in specific types of cancer (namely, breast and lung cancer) even after adjusting for cancer stage and other variables associated with death.\(^{34,35}\) A possible explanation for this finding might be that the occurrence of VTE, reflecting the cancer-associated hypercoagulable state, is a surrogate for adverse tumor biology, which in turn increases the risk of tumor progression and adversely impacts survival.\(^{36}\)
In line with the findings of the matched cohort study mentioned above, Dentali et al. found the 6-month mortality rate in cancer patients with asymptomatic VTE to be significantly higher compared to cancer patients in whom VTE was clinically suspected but ruled out (45% versus 27%, \( P = 0.036 \)). Furthermore, the mortality rate among incidental VTE patients did not differ from the rate found in cancer patients with symptomatic VTE (45% and 47.5% respectively, \( P = 0.75 \)). This is in agreement with the cohort study of den Exter et al., who did not find a difference in the one-year mortality risk of incidental PE patients (52.9%) compared to symptomatic PE patients (53.3%; \( P = 0.7 \)). The majority of the deaths (77.8%) in the incidental PE group were a related to progressive cancer and none of the patients died of fatal (recurrent) PE. Consistently, Font et al. reported similar long-term mortality rates for incidental (71%) and symptomatic VTE patients (71%). Three patients (3.2%) in the incidental group and 13 (5.3%) in the symptomatic group died of fatal VTE. Finally, in a cohort of pancreatic cancer patients, both the occurrence of incidental and symptomatic VTE appeared to adversely affect three-month survival (survival rates not specified). Of note, the majority of the incidental patients had asymptomatic visceral vein thrombosis (82%) and only a small proportion (7%) had PE.

**ANTICOAGULANT TREATMENT**

The central question for clinicians confronted with incidental PE, is whether the initiation of anticoagulant therapy improves the prognosis of these patients. Until now, no randomized trials have evaluated anticoagulant therapy in patients with incidental PE. Furthermore, patients with incidental PE are routinely excluded from trials evaluating treatment strategies for patients with acute PE. Therefore, management of incidental PE is mainly extrapolated from clinical trials of symptomatic PE patients. Observational studies reveal that anticoagulant therapy is generally instituted once incidental PE is diagnosed.

Given that the occurrence of incidental PE by definition does not give symptoms, the primary objective of initiating anticoagulant therapy would be the prevention of recurrent, potentially fatal, VTE events. In this respect, the risk reduction in recurrent VTE must be carefully balanced to the risk of anticoagulant-related bleeding complications, in order to determine their clinical benefit. The risk of bleeding complications among cancer patients receiving anticoagulant therapy has well been recognized. It has however been hypothesized, and some of the previously discussed studies may support this hypothesis, that incidental PE could be a harbinger of symptomatic VTE, and this may justify initiating anticoagulant treatment. There is a clear need for further research addressing the risk benefit ratio of anticoagulant therapy in patients with incidentally diagnosed PE. Until then, and in the absence of any data suggesting that the occurrence of
incidental PE is harmless, the general consensus is that these patients should be treated. This has also been recommended in the latest edition of the American College of Chest Physicians guidelines, which suggests the same initial and long-term anticoagulation for incidental PE patients as for those with symptomatic PE, in particular if these patients are not at high risk of bleeding (Grade 2B).41

CONCLUSION

The increased prevalence of incidental PE diagnoses has made this a significant issue among cancer patients. With little knowledge on the prognosis of these patients, the greatest challenge for clinicians is to determine the best therapeutic approach. The lack of clinical trials and the limited number of observational studies do not allow firm treatment recommendations. However, some recent cohort studies suggest that the occurrence of incidental PE in cancer patients mirrors the pro-thrombotic state of these patients, which may be associated with both recurrent VTE and mortality. Further studies are needed to clarify the risk-benefit ratio of anticoagulant therapy in these patients. Currently, it is recommended to treat cancer patients with incidental PE in the same manner as those with symptomatic PE.
REFERENCES


