Clinical aspects of venous thromboembolism in special patient populations

Bleker, S.M.

Citation for published version (APA):
Cancer-associated unsuspected pulmonary embolism

N. van Es
S.M. Bleker
M. Di Nisio

Abstract

Clinically unsuspected pulmonary embolism (UPE) is frequently diagnosed in cancer patients undergoing routine computed tomography scans for staging purposes or treatment response evaluation. The reported incidence of UPE ranges from 1% to 5% which probably represents an underestimation. A significant proportion of cancer patients with UPE actually do have pulmonary embolism (PE) related symptoms. However, these can erroneously be attributed to the cancer itself or to cancer therapy leading to a delayed or missed diagnosis. The incidence of UPE is likely to increase further with the improvements of imaging techniques. Radiologic features of UPE appear similar to symptomatic PE with nearly half of the UPE located in central pulmonary arteries and one third involving both lungs. UPE in cancer patients is not a benign condition with rates of recurrent venous thromboembolic events, bleeding and a mortality rate comparable to cancer patients with symptomatic PE. Current guidelines suggest that UPE should receive similar initial and long-term anticoagulant treatment as for symptomatic PE. However, direct evidence regarding the treatment of UPE is scarce and treatment indications are largely derived from studies performed in cancer patients with symptomatic venous thromboembolism. Selected subgroups of cancer patients with UPE such as those with sub-segmental UPE may be treated conservatively by withholding anticoagulation and avoiding the associated bleeding risk, although this requires further evaluation.
Introduction

In the last two decades computed tomography pulmonary angiography (CTPA) has progressively replaced ventilation-perfusion scanning as the imaging modality of choice for the diagnosis of clinically suspected pulmonary embolism (PE) (1,2). Advancements in CT scanning technology have led to the introduction of newer generation multi-detector array CT scanners (up to 320 slices) with higher acquisition speed, better spatial resolution, and dramatic improvements of pulmonary artery visualization. Hence, the sensitivity for detecting pulmonary emboli has significantly increased, in particular for more peripherally located clots (3,4). Improved resolution has regarded not only CTPA, but also contrast enhanced CT (CECT) scans which are performed for other reasons than PE evaluation. As a consequence, incidentally diagnosed PE is increasingly detected on CECT scans, especially on those performed in cancer patients.

Compared to healthy individuals, patients with cancer have a four- to sevenfold increased risk of developing venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and PE (5). Several cancer-related factors contribute to the high VTE rate such as the disease-associated state of hypercoagulability and the prothrombotic effects of antineoplastic treatments (5). Moreover, cancer patients frequently undergo CECT scanning for diagnostic or staging purposes and treatment response evaluation, thereby increasing the chances of detecting unsuspected pulmonary emboli. In fact, about half of all PE in cancer patients are incidentally diagnosed (6–8). In this review we will discuss the clinical and radiologic characteristics as well as the prognostic value of unsuspected pulmonary embolism (UPE) in cancer patients.

Definitions

Various terms have been used to describe incidentally diagnosed PE, such as ‘asymptomatic’, ‘incidental’, ‘silent’, ‘unexpected’ and ‘unsuspected’. In order to reduce this heterogeneity, a common definition of this condition has been proposed (9). Since clinically unsuspected PE does not mean that the patient has no symptoms, the term ‘asymptomatic PE’ should be avoided. The terms ‘incidental’ and ‘unsuspected’ are preferred and now recommended for PE with no clinical suspicion at the time of CT examination. We will use ‘unsuspected pulmonary embolism (UPE)’ throughout this review and refer to clinically suspected PE as ‘symptomatic PE’.
### Table 7.1. Incidence of unsuspected pulmonary embolism in cancer patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Cancer patients (N)</th>
<th>Cancer type</th>
<th>CT reassessment</th>
<th>CT scanner</th>
<th>Slice thickness</th>
<th>UPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gosselin et al. (1998)</td>
<td>Prospective cohort</td>
<td>588</td>
<td>Mixed</td>
<td>Yes</td>
<td>4-row MDCT</td>
<td>5–5 mm</td>
<td>10   (1.7%)</td>
</tr>
<tr>
<td>Boswell et al. (2004)</td>
<td>Prospective cohort</td>
<td>2,085</td>
<td>Mixed</td>
<td>NR</td>
<td>NR</td>
<td>2 mm</td>
<td>44   (2.1%)</td>
</tr>
<tr>
<td>Storto et al. (2005)</td>
<td>Retrospective cohort</td>
<td>410</td>
<td>Mixed</td>
<td>Yes</td>
<td>4-row MDCT</td>
<td>5 mm</td>
<td>14   (3.4%)</td>
</tr>
<tr>
<td>Sebastian et al. (2006)</td>
<td>Prospective cohort</td>
<td>385</td>
<td>Mixed</td>
<td>No</td>
<td>4-row MDCT</td>
<td>5–5 mm</td>
<td>10   (2.6%)</td>
</tr>
<tr>
<td>Gladish et al. (2006)</td>
<td>Retrospective cohort</td>
<td>403</td>
<td>Mixed</td>
<td>Yes</td>
<td>4-row MDCT</td>
<td>3.75 mm</td>
<td>16   (4.0%)</td>
</tr>
<tr>
<td>Cronin et al. (2007)</td>
<td>Retrospective cohort</td>
<td>397</td>
<td>Mixed</td>
<td>Yes</td>
<td>NR</td>
<td>8 mm</td>
<td>13   (3.3%)</td>
</tr>
<tr>
<td>Larici et al. (2007)</td>
<td>Retrospective cohort</td>
<td>787</td>
<td>Mixed</td>
<td>Yes</td>
<td>16-row MDCT</td>
<td>2.5 mm</td>
<td>15   (1.9%)</td>
</tr>
<tr>
<td>Ritchie et al. (2007)</td>
<td>Prospective cohort</td>
<td>343</td>
<td>Mixed</td>
<td>Yes</td>
<td>4-row or 16-row MDCT</td>
<td>1–1 mm</td>
<td>18   (5.2%)</td>
</tr>
<tr>
<td>Hui et al. (2008)</td>
<td>Retrospective cohort</td>
<td>765</td>
<td>Mixed</td>
<td>Yes</td>
<td>16-row MDCT</td>
<td>2.5 mm</td>
<td>17   (2.2%)</td>
</tr>
<tr>
<td>Sun et al. (2010)</td>
<td>Retrospective cohort</td>
<td>8,014</td>
<td>Lung cancer patients</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>180  (2.2%)</td>
</tr>
<tr>
<td>Farrell et al. (2010)</td>
<td>Retrospective cohort</td>
<td>342</td>
<td>Mixed</td>
<td>Yes</td>
<td>4-row or 16-row MDCT</td>
<td>1–1 mm</td>
<td>6    (1.8%)</td>
</tr>
<tr>
<td>Di Niso et al. (2010)</td>
<td>Retrospective cohort</td>
<td>1,921</td>
<td>Solid tumors</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>24   (1.2%)</td>
</tr>
<tr>
<td>Browne et al. (2010)</td>
<td>Prospective cohort</td>
<td>407</td>
<td>Mixed</td>
<td>Yes</td>
<td>64-row MDCT</td>
<td>1 mm and 5 mm</td>
<td>18   (4.4%)</td>
</tr>
<tr>
<td>Menapace et al. (2011)</td>
<td>Retrospective cohort</td>
<td>135</td>
<td>Pancreatic cancer</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>4    (3.0%)</td>
</tr>
<tr>
<td>Shingare et al. (2011)</td>
<td>Retrospective cohort</td>
<td>13,783</td>
<td>Mixed</td>
<td>No</td>
<td>4-row or 64-row MDCT</td>
<td>5–5 mm</td>
<td>395  (2.9%)</td>
</tr>
<tr>
<td>Bach et al. (2013)</td>
<td>Retrospective cohort</td>
<td>3,270</td>
<td>Mixed</td>
<td>Yes</td>
<td>64-row MDCT</td>
<td>5 mm</td>
<td>129  (3.9%)</td>
</tr>
</tbody>
</table>

UPE: unsuspected pulmonary embolism; MDCT: multidetector computed tomography; NR: not reported.
Incidence and radiologic characteristics

Incidence

The absolute incidence of UPE in cancer patients ranges from 1% to 5% depending on tumor type and stage, hospitalization status and presence of additional risk factors (Table 7.1). In a meta-analysis by Dentali et al., the weighted incidence of UPE in cancer patients was higher than in non-cancer patients (3.1% vs. 2.5% respectively) (10). The incidence of UPE is influenced by the type of CT scanner (thick-collimation single detector CT versus thin-collimation multidetector CT) and study design (e.g. report by a single radiologist versus double reading by one or two expert radiologists). In a study by Browne et al. the reduction of the slice thickness from 5 mm to 1 mm on CTPA scans increased significantly the sensitivity for clots in smaller arteries. In 7 of 18 (39%) UPE patients, clots were confidentially visualized only on the 1 mm reconstructed slices (11). It is to be expected that, in the near future, the peripheral pulmonary vasculature will be even better depicted with the introduction of 128-slice CT scanners in routine clinical practice.

The incidence and prevalence of UPE may be significantly underestimated. Douma et al. performed a retrospective analysis of the initial radiologic reports of staging CT scans in cancer patients and reported only three UPE in 838 patients corresponding to a prevalence of 0.4% (12). Similarly, Shinagare et al. and Di Nisio et al. reported a UPE prevalence in cancer patients of 1.5% (202 out of 13,783) and 1.2% (24 out of 1921), respectively. By contrast, studies in which CECT scans where systemically reassessed (retrospectively or prospectively) for the presence of UPE showed much higher incidences (Table 7.1). This inconsistency could be, at least in part, explained by the false negative initial readings. In a study by Engelke et al., 2412 CECT images including 1869 images of cancer patients, were reassessed for UPE by a single radiologist (13). The authors found an overall false-negative diagnostic rate of 69.4% (39 out of 56), despite routine double reading during the first evaluation. Other studies reported rates of false-negative diagnosis of UPE up to 75% (14–17). Finally, in autopsy studies the prevalence of PE that was unsuspected ante-mortem was as high as 23% in cancer patients (18–20).

Several factors may explain the high rate of false negative scans. First, as PE evaluation is not the primary goal of CECT scans, clots in the pulmonary arteries may be overlooked. Second, radiologists may use incorrect window displays that are not optimized for pulmonary arteries, resulting in contrast enhanced blood being too dense (21). Third, attention of the radiologist may be drawn to other, more evident, intrapulmonary pathology such as a primary lung tumor or pulmonary metastases, the so-called ‘satisfaction-of-search phenomenon’ (16,22). Lastly, UPE may be underreported when radiologists assume this finding has little or no clinical significance in cancer patients.
Besides the potentially avoidable misdiagnosis of UPE, other technical issues may contribute to the underreporting of UPE on CECT scans. Confident diagnosis of a filling defect can be difficult when images are reconstructed at thick slice due to partial volume effects and movement artefacts (23). Moreover, visualization of the pulmonary artery tree at CECT scans is often suboptimal as the scan is not timed at the point of maximum opacification of the pulmonary trunk, reducing the sensitivity especially for more peripheral clots. Consequently, the diagnosis of UPE can be uncertain in selected cases, as reflected by the considerable inter-observer variability. Inter-observer variability among radiologists may be particularly high for the diagnosis of subsegmental PE (SSPE). Pena et al. reported that an independent expert radiologist agreed with the initial SSPE diagnosis in only 51% of the cases after reassessment of 70 CTPA scans (24). No studies have systematically addressed interobserver variability for PE assessment on CECT scans. In a retrospective study by Gladish et al. (17), PE was identified in 14 out of 403 routine CECT scans by two independent radiologists. Yet another 12 patients had possible emboli that were detected by only one reader, and in just two of them pulmonary emboli were confirmed by consensus.

**Radiologic characteristics**

As for symptomatic PE, about one-half of UPE is located in lobar or more central arteries (Table 7.2) (6–8,11,12,17,23,25–28) and bilateral lung involvement occurs in 23–46% of the cases (Table 7.2). When compared to symptomatic PE, UPE seems to be similar in terms of PE-associated CT-findings such as lung infarction and increased pulmonary artery caliber (29). The embolic burden of UPE in cancer patients was described by Den Exter et al. in a recent retrospective cohort study (30). A series of consecutive CECT scans in 48 cancer patients with UPE were reassessed by a single reviewer and compared to 113 CTPA scans of consecutive patients (cancer and non-cancer) with acute symptomatic PE. The median obstruction index, according to the Qanadli scoring system, was significantly higher in patients with symptomatic PE compared to UPE (30% vs. 18%, \( p = 0.008 \)). However, as acknowledged by the authors, the embolic burden of UPE was probably underestimated. In the group of patients with UPE none was diagnosed with SSPE which may reflect the challenge of correctly detecting peripheral emboli with CECT scans. Similarly, in a study by Bach et al. the embolic burden of 129 cancer patients with UPE was significantly lower compared to 111 cancer patients with symptomatic PE (31). Regarding the relevance of embolic burden, den Exter et al. found no association between the obstruction index in UPE cancer patients and 6-month survival (30). No studies have addressed the presence of right ventricular diameter or dysfunction which was found to be associated with a poor clinical outcome in patients with symptomatic PE (32). Large prospective studies are needed to clarify the prognostic relevance of embolic burden or right ventricular dysfunction in UPE.
Table 7.2. Radiologic characteristics of unsuspected pulmonary embolism in cancer patients

<table>
<thead>
<tr>
<th>Study</th>
<th>UPE (N)</th>
<th>Main artery</th>
<th>Lobar artery</th>
<th>Segmental artery</th>
<th>Subsegmental artery</th>
<th>Central arteries</th>
<th>Peripheral arteries</th>
<th>Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinagare et al. (2011) (8)</td>
<td>202</td>
<td>62 (30.7%)</td>
<td>62 (30.7%)</td>
<td>65 (32.2%)</td>
<td>13 (6.4%)</td>
<td>124 (61.4%)</td>
<td>78 (38.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Sun et al. (2010) (7)</td>
<td>113</td>
<td>NR</td>
<td>NR</td>
<td>56 (49.6%)</td>
<td>0 (0.0%)</td>
<td>57 (50.4%)</td>
<td>56 (49.6%)</td>
<td>32 (28.3%)</td>
</tr>
<tr>
<td>O’Connell et al. (2011) (25)</td>
<td>70</td>
<td>7 (10.0%)</td>
<td>26 (37.1%)</td>
<td>20 (28.6%)</td>
<td>17 (24.3%)</td>
<td>33 (47.1%)</td>
<td>37 (52.9%)</td>
<td>NR</td>
</tr>
<tr>
<td>Sahut d’Izarn et al. (2012)</td>
<td>66</td>
<td>4 (6.1%)</td>
<td>14 (21.2%)</td>
<td>38 (57.6%)</td>
<td>10 (15.2%)</td>
<td>18 (27.3%)</td>
<td>48 (72.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>Font et al. (2011) (6)</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>36 (64.3%)</td>
<td>20 (35.7%)</td>
<td>23 (41.1%)</td>
</tr>
<tr>
<td>Den Exter et al. (2011) (27)</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
<td>30 (66.7%)</td>
<td>4 (8.9%)</td>
<td>11 (24.4%)</td>
<td>34 (75.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Browne et al. (2010) (11)</td>
<td>18</td>
<td>4 (22.2%)</td>
<td>5 (27.8%)</td>
<td>6 (33.3%)</td>
<td>3 (16.7%)</td>
<td>9 (50.0%)</td>
<td>9 (50.0%)</td>
<td>NR</td>
</tr>
<tr>
<td>Gladish et al. (2006) (17)</td>
<td>16</td>
<td>0 (0.0%)</td>
<td>8 (50.0%)</td>
<td>7 (43.8%)</td>
<td>1 (6.3%)</td>
<td>8 (50.0%)</td>
<td>8 (50.0%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Gosselin et al. (1998) (23)</td>
<td>13</td>
<td>4 (30.8%)</td>
<td>4 (30.8%)</td>
<td>5 (38.5%)</td>
<td>0 (0.0%)</td>
<td>8 (61.5%)</td>
<td>5 (38.5%)</td>
<td>6 (46.2%)</td>
</tr>
<tr>
<td>Douma et al. (2010) (12)</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>2 (66.7%)</td>
<td>0 (0.0%)</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>Tiseo et al. (2012) (28)</td>
<td>21</td>
<td>2 (9.5%)</td>
<td>6 (28.6%)</td>
<td>13 (61.9%)</td>
<td>0 (0.0%)</td>
<td>8 (38.1%)</td>
<td>13 (61.9%)</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>609</td>
<td>83 (20.4%)</td>
<td>117 (28.8%)</td>
<td>229 (40.4%)</td>
<td>48 (8.5%)</td>
<td>302 (49.6%)</td>
<td>307 (50.4%)</td>
<td>67 (30.6%)</td>
</tr>
</tbody>
</table>

UPE: unsuspected pulmonary embolism; NR: not reported.
To summarize, the true prevalence and incidence of UPE remain uncertain. Radiologists should carefully evaluate the presence of UPE, especially in high risk groups such as cancer patients. The detection rate of UPE could be further improved by performing CECT scans during the arterial phase (11), provided that the quality of the cancer evaluation does not deteriorate.

**Clinical and demographic characteristics**

Cancer patients with UPE have a mean age of 60 to 70 years (8,27,33) and UPE rates appear similar between males and females. Data on the absolute UPE incidence stratified by tumor type is scarce. In a large retrospective cohort including 13,783 cancer patients, Shinagare et al. found the highest UPE incidence in patients with pancreatic cancer (4.9%), hepatobiliary cancer (4.8%), upper gastrointestinal tract cancer (3.7%), and colorectal cancer (2.6%) (8). Not surprisingly, the risk of UPE is higher in cancer patients who are hospitalized and in those with more advanced stage cancer and worse performance status (10,26). Other factors contributing to the risk of UPE are recent surgery, prior VTE, active chemotherapy, and the presence of a central venous catheter, although the evidence has not been always consistent (25,26). Cancer patients with UPE share a similar risk profile to those with clinically suspected PE, with UPE being more frequently associated with central venous catheters or chemotherapy treatment (26,27,34).

**Symptoms**

The finding of UPE implies that PE was clinically not suspected at the time of CT scanning. This, however, does not mean in itself that there were no symptoms or signs that could, or perhaps should, have raised the suspicion of the physician. Analyses of retrospective data from medical charts of cancer patients with UPE revealed that up to 75% had signs and symptoms possibly linked to the presence of PE at the time of the diagnosis. Compared to cancer patients without PE, shortness of breath, cough, and fatigue were significantly more prevalent among cancer patients with UPE (25). Rates of lung cancer and presence of pulmonary metastases in both groups were comparable. Similarly, in a case-control study by Sahut d’Izarn et al., 27 of the 66 cancer patients (41%) with UPE had one or more symptoms possibly worsened by PE, such as dyspnea (23%), chest pain (9%), hemoptysis (1%) or leg pain (8%) as a sign of potential DVT (26). It is not unlikely that these numbers represent conservative estimates of the frequency of signs and symptoms as they were not systematically recorded in these retrospective studies. Hence, these findings suggest that a proportion of cancer patients with UPE are actually symptomatic at the time of diagnosis, but symptoms apparently do not
trigger the physician to order a dedicated CTPA for ruling out or ruling in PE. This could be explained by the poor specificity of many signs and symptoms of UPE (e.g. fatigue and dyspnea on exertion), that may erroneously be attributed to the cancer itself or its therapy (i.e. chemotherapy or radiotherapy), leading to a delayed or missed diagnosis of UPE.

**Prognosis of UPE**

VTE has been identified as a marker of worse survival in cancer patients irrespective of age, cancer stage or cancer histology (35). This poor prognosis is probably not a direct result of VTE, but more likely reflects an aggressive cancer biology. Few studies, none prospective, evaluated the clinical outcome of UPE in cancer patients (Table 7.3). To our knowledge, there are no reported cases of early UPE-related death in cancer patients, which is somewhat surprising given that a substantial proportion of UPE is located in central arteries (i.e. main or lobar arteries) (Table 7.2). However, it should be noted that all the available studies did not include patients with more severe cases of UPE associated with hemodynamic instability.

**Unsuspected vs. symptomatic pulmonary embolism**

Long-term mortality of 51 cancer patients with UPE versus 144 cancer patients with symptomatic PE was described by Den Exter et al. in a retrospective study (27). The clinical risk profile of both groups was similar and the vast majority of patients in both groups received long-term anticoagulant treatment (98% vs. 92%). No differences were observed between UPE and symptomatic PE patients in terms of the cumulative VTE recurrence risk (9.8% vs. 10.4%) or mortality rate (52.9% vs. 52.8%) after 12 months of follow-up. These results were later confirmed in a case-control study by Sahut d’Izarn et al. and in a retrospective cohort of lung cancer patients by Shinagare et al. (26,34). Both studies suggested similar mortality rates for cancer patients with symptomatic PE and UPE. In all of these studies, competing events such as death were not taken into account in the statistical analysis, possibly causing an overestimation of the absolute risk of VTE recurrence (36,37).

Sun et al. conducted a large retrospective cohort study including more than 8000 lung cancer patients. In total 180 patients developed PE (2.2%) of which 67 (37%) were symptomatic and 113 (63%) clinically unsuspected. Nearly half of the UPE patients were treated at the physician’s discretion and most received warfarin. Treated patients had a median survival of 30.9 months compared to 6.1 months of patients not receiving anticoagulation corresponding to a fourfold increase in survival (hazard ratio 4.1; 95% CI, 2.3–7.6). This survival difference was not explained by differences in
Table 7.3. Prognosis of cancer patients with unsuspected pulmonary embolism

<table>
<thead>
<tr>
<th>Study design</th>
<th>UPE (N)</th>
<th>Cancer type</th>
<th>Follow-up time</th>
<th>Patients treated (%)</th>
<th>Mortality (%)</th>
<th>Recurrent VTE (%)</th>
<th>Major bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al. (2010) (7)</td>
<td>Retrospective cohort</td>
<td>113</td>
<td>Lung</td>
<td>NR</td>
<td>51 (45.1%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>O’Connell et al. (2011) (25)</td>
<td>Case-control</td>
<td>70</td>
<td>Mixed</td>
<td>12 months</td>
<td>59 (84.3%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sahut d’Izarn et al. (2012) (26)</td>
<td>Case-control</td>
<td>66</td>
<td>Mixed</td>
<td>6 months</td>
<td>66 (100%)</td>
<td>11 (16.7%)</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>Den Exter et al. (2011) (27)</td>
<td>Retrospective cohort</td>
<td>51</td>
<td>Mixed</td>
<td>12 months</td>
<td>51 (100%)</td>
<td>27 (52.9%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Abdel-Razeq et al. (2011) (54)</td>
<td>Retrospective cohort</td>
<td>34</td>
<td>Mixed</td>
<td>NR</td>
<td>29 (85.3%)</td>
<td>9 (26.5%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Shinagare et al. (2011) (8)</td>
<td>Retrospective cohort</td>
<td>32</td>
<td>Lung</td>
<td>Median: 6.0 months</td>
<td>30 (93.8%)</td>
<td>28 (87.5%)</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Browne et al. (2010) (11)</td>
<td>Prospective cohort</td>
<td>18</td>
<td>Mixed</td>
<td>6 months</td>
<td>17 (94.4%)</td>
<td>NR</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Douma et al. (2010) (12)</td>
<td>Retrospective cohort</td>
<td>3</td>
<td>Mixed</td>
<td>3 months</td>
<td>2 (66.7%)</td>
<td>1 (33.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

UPE: unsuspected pulmonary embolism; NR: not reported.
performance status, cancer stage or tumor response status between the two groups. However, patients were not randomized to anticoagulant treatment and the influence of unmeasured confounders on the survival benefits cannot be ruled out. As current international guidelines recommend anticoagulant treatment for all cancer patients with UPE, it will be hard to gather prospectively data on the natural course of UPE in absence of anticoagulation.

Unsuspected pulmonary embolism vs. no pulmonary embolism
In a 2:1 case control study, Sahut d’Izarn et al. compared the clinical outcome of 66 cancer patients with UPE and 132 non-matched cancer patients without PE. All UPE patients were given anticoagulant treatment, mainly low-molecular-weight heparin (LMWH). After adjustment for performance status and tumor stage, no difference in the risk of death at 6 months was observed between UPE patients and patients without PE (26). In another case-control study, O’Connell et al. compared the mortality rates of 70 cancer patients with UPE with 137 control patients without PE matched for age, sex, cancer type and stage (25). Fifty-nine patients with UPE (84%) received some form of anticoagulant treatment. Patients with UPE had a significantly lower median survival (8 vs. 12 months; hazard ratio 1.51; 95% CI 1.01–2.27). No data were reported regarding the occurrence of recurrent PE or (major) bleeding.

Isolated sub-segmental pulmonary embolism
The clinical relevance of PE confined to one or more sub-segmental branches, i.e. isolated SSPE has been increasingly the subject of debate. Although improved CT scanning techniques over the past two decades have led to an increased detection rate of small clots in peripheral (sub-segmental) arteries, a recent systematic review showed no concurrent changes in mortality rates, suggesting that symptomatic SSPE might be of less clinical significance or even clinically unimportant (38). Support for this hypothesis was provided by several retrospective studies that showed no recurrent VTE or PE-related deaths during 3 months follow-up among patients with SSPE that were left untreated (39). By contrast, in a combined post-hoc analysis of two large prospective cohort studies, Den Exter et al. recently suggested that the prognosis for patients with SSPE may be comparable to patients with more proximally located PE studies (40). The rates of recurrent VTE, bleeding, and mortality were not significantly different between the two groups. The proportion of patients with active malignancy among the 116 patients with SSPE and 632 patients with proximal PE was 18.1% vs. 17.9% respectively.

Only limited data is available on the prognostic relevance of clinically unsuspected SSPE. O’Connell et al. included 17 cancer patients with unsuspected SSPE of whom 13 were treated with some form of anticoagulation (25). The median survival of these patients was significantly better compared to patients with more proximal PE (7 vs.
Chapter 7

12 months; hazard ratio 1.70; 95% CI 1.06–2.74) and did not differ from the survival of matched control patients without PE, suggesting that unsuspected SSPE in cancer patients is not associated with poor survival. These data suggest that withholding anticoagulant treatment may be a safe option in these patients.

Management

When PE or concurrent DVT is confirmed, international clinical guidelines suggest [41], or recommend [42], the same initial and long-term treatment for UPE as for patients with symptomatic PE (41,42). Based on these guidelines, cancer patients with UPE would receive LMWH for at least 3 months or until the disease is resolved, which in most cases would mean indefinite treatment. However, well-designed prospective studies on the treatment of UPE are lacking. This leaves doubts over the need for (indefinite) anticoagulation which appears associated with significant rates of major bleeding (Table 7.3). Insights into the natural course of UPE in the absence of anticoagulant treatment are mainly derived from retrospective series where data were retrieved from the subset of patients in whom UPE was left untreated. The small size and methodological quality of these studies hamper any generalization of these findings to the whole group of cancer patients with UPE. In the study of O’Connell et al. all four patients in whom SSPE was left untreated had complete resolution of the PE on the first follow-up CT scan, but one of them developed recurrent UPE on a subsequent scan (25). In another small case series, one patient with segmental UPE left untreated because of an increased risk of bleeding was diagnosed five weeks later with symptomatic bilateral PE (11). In a report by Storto et al. one out of four patients with UPE had progression of the PE on follow-up scans (16). Last, Gladish et al. reported no recurrent VTE in a series of eight cancer patients with UPE and no concurrent DVT (17). These small observational studies suggest that the risk of VTE recurrence in patients with UPE not receiving anticoagulant treatment is not negligible. Several treatment options including unfractionated heparin, (prophylactic to therapeutic dose) LMWH, vitamin K antagonists or vena cava filters have been reported for UPE, although none of these interventions was evaluated in properly conducted randomized clinical trials. While awaiting additional data on the management of UPE in cancer patients, it seems reasonable to provide the same anticoagulant treatment as for symptomatic PE in light of the apparent similar risk of recurrent VTE.

Patients with UPE may have a high risk of recurrent VTE despite anticoagulation, although the preliminary data are inconsistent. In the study of den Exter et al. the yearly VTE recurrence rates for both UPE and symptomatic PE were roughly 10% even though the majority of the patients were treated with LMWH (27). In an interim analysis of
cancer patients with UPE from the ongoing international RIETE registry study, Soler et al. observed no recurrences in 79 patients while receiving anticoagulation (33).

Selected subgroups of cancer patients with UPE such as those with unsuspected SSPE might benefit from a conservative ‘watchful waiting’ strategy instead of anticoagulation therapy (43,44). In a recent survey, a small proportion of physicians was reluctant to start anticoagulant treatment for unsuspected SSPE in a cancer patient (45). An ongoing randomized controlled trial is evaluating the safety of withholding anticoagulant treatment in symptomatic SSPE with no evidence of concomitant DVT (NCT01455818). However, patients with active malignancy are excluded from this study.

Future directions

Despite the growing attention in the literature for UPE in patients with cancer (Figure 7.1), a number of related issues remain unresolved. Future studies need to evaluate the actual incidence of UPE and assess risk factors for first and recurrent UPE. In cancer patients with symptomatic VTE, risk factors for recurrent VTE are female sex, lung cancer,
advanced disease stage, and a prior history of VTE (46). Whether these factors maintain their predictive value in cancer patients with UPE is unknown.

The type, dose and duration of anticoagulant therapy need to be established. One aspect specific to UPE is the uncertainty regarding the time of clot formation. UPE might have developed just before its detection on CT examination or rather be present for long time which raises the question whether all patients with UPE should be treated with therapeutic doses LMWH in the initial phase of anticoagulation. Future dedicated studies should assess the efficacy and safety of the novel oral anticoagulants in cancer patients with VTE compared to current standard treatment. These new agents may offer a significant improvement in quality of life for these patients that are exposed to a long-term treatment.

An ongoing international prospective study is recruiting cancer patients with UPE in over 30 centers worldwide. The aim of this study is to evaluate current treatment approaches and to prospectively assess the occurrence of major clinical outcomes such as mortality, recurrent VTE and bleeding (NCT01727427). The results are expected in 2015 and hopefully will provide more insight into the clinical course of this condition.

Acknowledgments

We would like to thank Harry Büller for his comments on the manuscript.
Cancer-associated unsuspected pulmonary embolism

References

Chapter 7


130
Cancer-associated unsuspected pulmonary embolism


