Clinical aspects of venous thromboembolism in special patient populations

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Unsuspected pulmonary embolism in cancer patients: interobserver agreement on the diagnosis and extent with a focus on distal clots

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Abstract

Background: The incidence of unsuspected pulmonary embolism (UPE) in cancer patients is increasing. There is scant information on the interobserver agreement among radiologists about the diagnosis of distal unsuspected clots and the actual radiologic extension of UPE.

Methods: A total of 88 contrast-enhanced computed tomography (CT) scans of cancer patients with UPE were reassessed blindly by two expert thoracic radiologists. First, 62 scans were reassessed and the interobserver agreement on most proximal extent of UPE was calculated between the two expert radiologists as well as between the initial and expert reading, using the Kappa statistic. The sample was enriched with 26 additional scans for a total of 30 segmental and 29 subsegmental UPE to determine the interobserver agreement on distal clots.

Results: The level of agreement regarding the most proximal extent of UPE between the expert radiologists was very good (kappa 0.84; 95% CI, 0.73–0.95) and poor between the original radiologist and expert radiologists (kappa 0.39; 95% CI, 0.22–0.56). In the patients with segmental or subsegmental UPE on initial reading, the expert radiologists agreed with the segmental location in 12 out of 30 patients (40%) and with the subsegmental location in 17 out of 29 patients (59%). The interobserver agreement between the expert radiologists was good (kappa 0.68; 95% CI, 0.46–0.90) and moderate (kappa 0.48; 95% CI, 0.25–0.71), respectively.

Conclusions: While the interobserver agreement between radiologists on the most proximal location of UPE in cancer patients appears to be fairly good, it decreases significantly for more distally located unsuspected clots.
Introduction

Cancer patients frequently undergo contrast-enhanced computed tomography (CECT) scanning for disease staging and for monitoring of the effects of treatment. Advancements in CT techniques over the past decades have drastically improved pulmonary arterial visualization (1,2). As a consequence, unsuspected pulmonary embolism (UPE) is increasingly detected in cancer patients, with a prevalence ranging from 1% to 5% (3,4). The true prevalence of UPE may even be higher, since the contrast enhancement of the pulmonary arteries on oncological CECT scans is suboptimal for PE detection, especially for clots in the more distally located segmental and subsegmental arteries (5). In addition, inattentional blindness of the observer may occur, since PE evaluation is not the primary goal of the scan (6). Several studies which reassessed routine CT scans of cancer patients for UPE have reported false-negative rates ranging from 30% to 75% (5,7–9). At the same time, a risk of false positive readings has been reported for distally located, symptomatic PE, and this may be worse for distally located UPE (10).

The clinical significance of UPE in cancer patients is not clear. Several retrospective studies suggest that the risk of recurrent venous thromboembolism (VTE) is similar in patients with UPE as compared to those with symptomatic PE (11–13). Subsegmental UPE seems associated with a better prognosis than more proximal UPE (14), although data have been conflicting (15,16). Current guidelines suggest that UPE should receive similar treatment as for symptomatic PE (17,18). Therefore, it is relevant to correctly ascertain the diagnosis in order to avoid unnecessary exposure to anticoagulant therapy.

Although interobserver agreement among radiologists for symptomatic PE has increased over the years due to the introduction of multi-detector CT scans, concordance still remains suboptimal for subsegmental symptomatic PE (2,19–25). Studies reporting on interobserver agreement for UPE in cancer patients are scarce, and no data exist on the interobserver agreement regarding the most proximal extent of UPE (5,26).

The objectives of the present study were to (1) evaluate the interobserver agreement on the most proximal extent of UPE between two expert thoracic radiologists, and subsequently between original and expert reading, and to provide a detailed description of the anatomical characteristics of UPE in cancer patients, and (2) evaluate the interobserver agreement on the diagnosis of segmental and subsegmental clots between expert radiologists and between original and expert radiologists.

Methods

A total of 88 CT scans from cancer patients with UPE were reassessed.
Chapter 9

Part 1
First, 62 consecutive CT scans from all patients included between April 2012 and November 2014 in three centers participating in an ongoing observational study on the management of UPE in cancer patients were reassessed (NCT01727427; Figure 9.1). In this international, prospective cohort, adult cancer patients with prospectively identified UPE are followed for 12 months for recurrent VTE, bleeding, and all-cause mortality. UPE is defined as one or more clots in the pulmonary artery tree detected on imaging performed for reasons other than a clinical suspicion of PE. For patients included in this registry, the local radiologist detailed the exact location of the UPE, and number of pulmonary arterial branches affected.

For the present study, baseline characteristics, including age, sex, and type of cancer, were collected. We recorded whether a computed tomography pulmonary angiogram (CTPA) was performed to confirm PE, and whether the presence of concomitant deep vein thrombosis (DVT) of the legs was verified by compression ultrasonography.

Two radiologists (LB and AR) with extensive experience in thoracic imaging, independently reassessed the thoracic images of all CT scans. Images were reviewed at least 6 months after

**Figure 9.1.** Flow diagram of part 1 and part 2 of the current study
* NCT01727427
** One academic and one non-academic center from the Netherlands, and one academic center from Italy
† According to the original reading
UPE: unsuspected pulmonary embolism
the test date to minimize recall bias. Reassessment was performed on a dedicated picture archiving and communication system (PACS) workstation (Impax 6.5, Agfa HealthCare NV, Mortsel, Belgium) using multiplanar reformats when needed. The window setting was left to the discretion of the reader. Readers were unaware of prior interpretation.

The radiologists assessed the following items: image quality (rated on a Likert scale from 1 to 5, corresponding to inadequate to excellent), contrast opacification of the subsegmental arteries (rated on a Likert scale from 1 to 5, corresponding to inadequate to excellent), confidence of the diagnosis of UPE (rated on a Likert scale from 1 to 5, corresponding to definitive no PE to definite PE), pulmonary arterial CT density in the pulmonary trunk in Hounsfield units (HU), the extent of PE (central, lobar, segmental, subsegmental, or no PE), and the number of thrombi (single or multiple). Central and lobar PE were collectively classified as “proximal PE” and segmental and subsegmental as “distal PE”.

The agreement between the two expert thoracic radiologists regarding the most proximal extension of the UPE, as well as the interobserver agreement between the original radiologist and the expert radiologists, were evaluated. A consensus reading between the radiologists was performed in case of disagreement. After the first consensus reading there was no remaining discordance; hence, the involvement of a third radiologist was not needed. The result of the consensus meeting was used as the reference to calculate the interobserver agreement between the expert radiologists and original radiologist.

**Part 2**

Interobserver agreement is expected to be lower for the diagnosis of distal UPE, similar to the setting of symptomatic PE (10). In order to evaluate the interobserver agreement between the expert thoracic radiologists and between the original and expert radiologists, in the second part of the study we enriched the sample with 26 additional scans from consecutive patients with segmental and subsegmental UPE according to the original reading (Figure 9.1). Both patients included in the prospective cohort study (n = 33) as well as patients who were excluded due to a life expectancy of less than three months or anticoagulant use in therapeutic doses at the time of the UPE diagnosis (n = 26), identified in the same hospitals as in part 1, were eligible for this part of the study. The radiologists independently reassessed the thoracic images of the additional CT scans for the extent of the PE and the number of thrombi. For patients already included in part 1, the first reading result was used.

**Statistical analysis**

Baseline characteristics were summarized using descriptive statistics. Cohen’s kappa coefficient was used to measure the interobserver agreement, and results were based
on the cut-off values proposed by Landis and Koch: a kappa value of < 0.20 representing poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good agreement (27). In addition, we assessed differences in image quality, contrast opacification of the subsegmental arteries, confidence of the UPE diagnosis and arterial contrast score between scans for which the original and expert radiologists agreed on the most proximal extent, and those for which no agreement was reached. Means were compared using the t-test for independent variables, and medians were compared using the Median Test for k samples. Analyses were performed using SPSS Statistics v 20.0 (IBM Corp., Armonk, NY, USA).

Results

Part 1
The baseline characteristics of the cancer patients included in the first part of the study are summarized in Table 9.1. The mean age was 65 years and 58% were men. The most prevalent types of cancer were gastro-intestinal (37%), lung (10%), gynecological (8%), and breast (8%) cancer.

The expert radiologists agreed with each other on the most proximal location of the UPE in 55 of 62 patients (89%) resulting in a very good interobserver agreement (kappa 0.84; 95% CI, 0.73 to 0.95). The interobserver agreement between the expert radiologists and original radiologist was poor (kappa 0.39; 95% CI, 0.22 to 0.56; Table 9.2). Fifteen of 33 scans (46%) classified as distal UPE by the initial radiologist were considered to be proximal (i.e. central or lobar) by the experts. According to the expert radiologists, the most proximal extent of the UPE was central in 16 patients (26%), lobar in 24 (39%), segmental in 17 (27%), and subsegmental in 5 (8%) of which 2 multiple and 3 single subsegmental.

Subsequent CTPA was performed in 3 patients (2%), 1 with central, 1 with lobar and 1 with multiple subsegmental UPE based on initial reading, and confirmed the presence of PE in all. Ultrasonography of the legs was performed in 11 patients (6%) of which 3 with central, 4 with lobar, 1 with segmental, 1 with multiple subsegmental and 2 with subsegmental UPE, and confirmed DVT in 7 (64%). The overall mean image quality of the CT scans was good (4.1 out of 5; standard deviation [SD] 0.8), as was the mean contrast opacification of the subsegmental arteries (3.9; SD 1.0). The mean confidence of diagnosis of UPE was excellent (4.8; SD 0.4), and the arterial contrast opacification reached a median HU of 169 (interquartile range 145–244).
Part 2

Table 9.3 details the baseline characteristics of the patients considered for the second part of the study. The mean age was 65 and 62 years in the patients with segmental and subsegmental UPE, respectively, and 60% and 52% of the patients were male, respectively.

In the 30 patients with segmental PE, the two expert radiologists agreed with each other on the most proximal clot location in 24 patients (80%), which resulted in good interobserver agreement (kappa 0.68; 95% CI, 0.46 to 0.90; Table 9.4A). In 3 of 6 cases of disagreement, the radiologists had used a different definition of the most proximal extent of UPE; during the consensus meeting, the most proximal location was based upon the biggest clot burden and number of involved vessels. Overall, the expert radiologist agreed with the original radiologists on the segmental location in 12 cases (40%), whereas the most proximal extent was judged to be central in 1 case (3%), lobar in 14 (47%), and single subsegmental in 3 (10%).
In the 29 patients with a subsegmental UPE according to the original radiologist, the two expert radiologists agreed with each other on most proximal extent in 17 patients (61%), resulting in to a moderate interobserver agreement (kappa 0.48; 95% CI, 0.25 to 0.71; Table 9.4B). In 8 of 11 cases of disagreement, the disagreement was the result of the use of different definition of the most proximal extent of UPE. After the consensus meeting, the expert radiologists concluded that UPE was subsegmental in 17 patients (59%), including multiple clots in 9 patients (31%) and a single clot in 8 patients (28%), whereas the most proximal extent was lobar in 2 cases (7%) and segmental in 9 (31%).

Table 9.2. Most proximal extent of unsuspected pulmonary embolism as adjudicated by the original and expert radiologists

<table>
<thead>
<tr>
<th>Result according to the original radiologist</th>
<th>Subsegmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>Lobar</td>
</tr>
<tr>
<td>Central</td>
<td>12</td>
</tr>
<tr>
<td>Lobar</td>
<td>2</td>
</tr>
<tr>
<td>Segmental</td>
<td>0</td>
</tr>
<tr>
<td>Subsegmental</td>
<td>Multiple</td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 9.3. Baseline characteristics of all patients with (sub)segmental unsuspected pulmonary embolism (Part 2)

<table>
<thead>
<tr>
<th>Segmental UPE*</th>
<th>Subsegmental UPE*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Result</strong></td>
<td><strong>N = 30</strong></td>
</tr>
<tr>
<td>Mean age, y, (SD)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Cancer type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lower GI tract</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Upper GI tract</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Lung</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Bladder</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>19 (63)</td>
</tr>
</tbody>
</table>

*Most proximal extent according to original radiologist
UPE: unsuspected pulmonary embolism, SD: standard deviation, GI: gastro-intestinal
In one patient (3%), judged by the original radiologist to have a subsegmental UPE, both expert radiologists concluded that no UPE was present.

In none of the segmental and in 5 (17%) of the subsegmental UPE cases, CTPA was performed to confirm the diagnosis. Ultrasonography of the legs was performed in one patient with segmental UPE (3%), which excluded concomitant DVT, and in 3 (10%) of the subsegmental UPE, confirming DVT in one case (33%).

**Impact of CT scan characteristics on interobserver agreement**

Table 9.5 details the CT scan characteristics for scans for which the original and expert radiologist agreed on the most proximal extent and scans for which no agreement was reached. The image quality and contrast opacification of the subsegmental arteries were better for the scans for which no agreement was reached. There was no difference in confidence of the UPE diagnosis and the arterial contrast score.
In the present analysis, the agreement between expert radiologists with regard to the most proximal location of UPE in cancer patients was very good, whereas it decreased to good or moderate for segmental and subsegmental clots. Overall, the agreement between original and expert reading was fair, although, once again, concordance decreased substantially for more distally located clots. Over 60% of all UPE in cancer patients that are detected, are proximally located.

For symptomatic PE, several studies have reported very good interobserver agreement regarding the presence of PE, although lower concordance has been observed in segmental and subsegmental PE (20–25, 28). In one study the overall agreement as assessed by the kappa statistic was 0.83 (range 0.68 to 0.91) for central and lobar, 0.61 (range 0.40 to 0.80) for segmental, and 0.38 (range 0.0 to 0.89) for subsegmental emboli (20). In another series of 70 cases with subsegmental symptomatic PE, the reviewing radiologist agreed with the subsegmental location in only 36 (51%), whereas a total of 26 cases (37%) were considered to involve more proximal arteries. Importantly, 8 cases (11%) were re-interpreted as without any evidence of PE (10). Our results suggest that, as for symptomatic distal PE, agreement on the diagnosis of subsegmental UPE is modest. Two studies have assessed the interobserver agreement regarding presence of UPE in cancer patients. In one retrospective study, 403 routine CT-scans of cancer patients were independently reassessed by two radiologists (5). In 14 patients, PE was identified by both readers. In another 12 subjects, PE was detected by only one reader. In only two of these patients, PE was detected by consensus (5). Another study found a

### Table 9.5. Characteristics of computed tomography scans for scans with agreement on most proximal unsuspected pulmonary embolism location and for scans with no agreement

<table>
<thead>
<tr>
<th></th>
<th>Agreement on most proximal UPE location between original and expert radiologists</th>
<th>No agreement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 46</td>
<td>N = 42</td>
<td></td>
</tr>
<tr>
<td>Image quality (scale 0–5), mean (SD)</td>
<td>3.9 (0.8)</td>
<td>4.2 (0.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Contrast opacification of subsegmental arteries (scale 0–5), mean (SD)</td>
<td>3.7 (0.8)</td>
<td>4.1 (0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Confidence of UPE diagnosis (scale 0–5), mean (SD)</td>
<td>4.7 (0.6)</td>
<td>4.8 (0.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Arterial contrast score in HU, median (IQR)</td>
<td>156 (141–181)</td>
<td>176 (147–746)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

UPE: unsuspected pulmonary embolism; SD: standard deviation; HU: Hounsfield units; IQR: interquartile range
high level of agreement between two expert readers on the presence of UPE, but this included only one patient (1.6%) with a subsegmental PE (26).

One potential reason for the significant discrepancy between radiologists regarding the most proximal extent of distal clots may be the use of different definitions. Clots located at the bifurcation from segmental to subsegmental may be classified as segmental (i.e. the most proximal location) or multiple subsegmental (based on the biggest clot burden and number of involved vessels). Indeed, in our study, most of the discrepancies at this level arose from the use of different definitions. In addition, limited visualization of segmental and subsegmental arteries in comparison to the visualization of the more proximal arteries on routine CT scans may play a role in the decreased interobserver agreement on most proximal UPE location. Interestingly, we found that the image quality and contrast opacification of the subsegmental arteries were better for scans for which no agreement was reached, compared to scans for which agreement was reached on the most proximal extent of UPE. We observed no difference in confidence of UPE diagnosis and the arterial contrast score. Although numbers are too small to draw robust conclusions, it seems that CT scan characteristics did not influence the interobserver agreement in our study.

While knowing the exact extent of a proximal PE has relatively limited clinical importance since anticoagulant therapy is indicated in all cases, the distinction between segmental and subsegmental PE may have therapeutic consequences. In a retrospective study, cancer patients with subsegmental UPE had a better survival compared to those with more proximal UPE, and those with isolated subsegmental UPE had a similar survival as matched control patients without UPE (14). Conflicting results were reported in another retrospective study (29). The clinical relevance of isolated subsegmental PE and the possibility to manage these PEs conservatively is currently under investigation in a prospective management cohort study that, unfortunately, excludes patients with cancer (ClinicalTrials.gov; NCT01455818).

A conservative management strategy for isolated subsegmental PE may have an even bigger impact in cancer patients in whom a diagnosis of PE usually implies lifelong exposure to anticoagulant therapy (17), with an associated risk of major bleeding up to 12% during 12 months of treatment, corresponding to 15.7 major bleeding events per 100 patient-years (30–33). In the present study, one patient diagnosed with a subsegmental UPE received therapeutic anticoagulation, but did not have PE according to central reading. Therefore, while a diagnosis of isolated subsegmental UPE may be relatively infrequent, it can have serious consequences as exemplified by this patient who was unnecessarily exposed to the potential harms of anticoagulation. Some authors have recently suggested that compression ultrasonography of the legs may be performed in cancer patients with isolated subsegmental UPE to guide therapeutic decisions (18). Our study suggests that this recommendation is not adopted frequently.
in clinical practice, since only in 10% of patient with subsegmental UPE, compression ultrasonography was performed. Similarly, although previous studies have suggested that CTPA may significantly increase the detection rate of UPE and improve the determination of clot extension (34), CTPA was rarely performed to confirm distal PE in the present study which may depend on the costs, technical difficulties, and concerns about contrast and radiation exposure (18).

What are the implications of the current study? The results indicate that for clinical outcome studies on UPE, central reading by an expert radiologist could be valuable to precisely define UPE extension and, therefore, have more reliable imaging for comparison in case of suspected recurrent PE. In clinical practice an extra dedicated reading in patients with UPE may be considered, especially for distal clots, as this may influence diagnostic decisions such as the performance of ultrasonography of the legs or CTPA.

Some limitations deserve to be acknowledged. First, the sample size of the study was relatively modest and the number of patients with subsegmental UPE still relatively small to reach firm conclusions. Second, the expert radiologists were blinded to the extension of the UPE while aware of its presence, which did not allow us to calculate false-positive or false-negative UPE reading rates.

In conclusion, the interobserver agreement between expert radiologists on the most proximal location of these UPE is good, but decreases for more distally located clots. Similarly, concordance between the initial and second reading is only modest for distal PE. Approximately 60% of all UPE in cancer patients involve the proximal pulmonary arteries.
Unsuspected pulmonary embolism in cancer patients

References


