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Cancer-associated unsuspected pulmonary embolism

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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 computed tomography (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'.

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Table 1
Incidence of unsuspected pulmonary embolism in cancer patients

Study	Study design	Cancer patients (N)	Cancer type	CT reassessment	CT scanner	Slice thickness	UPE
Gosselin *et al.* (1998) [23]	Prospective cohort	588	Mixed	Yes	4-row MDCT	5-8 mm	10 (1.7%)
Boswell *et al.* (2004) [48]	Prospective cohort	2,085	Mixed	NR	NR	2 mm	44 (2.1%)
Storto *et al.* (2005) [16]	Retrospective cohort	410	Mixed	Yes	4-row MDCT	5 mm	14 (3.4%)
Sebastian *et al.* (2006) [49]	Prospective cohort	385	Mixed	No	4-row MDCT	5-8 mm	10 (2.6%)
Gladish *et al.* (2006) [17]	Retrospective cohort	403	Mixed	Yes	4-row MDCT	3.75 mm	16 (4.0%)
Cronin *et al.* (2007) [50]	Retrospective cohort	397	Mixed	Yes	NR	8 mm	13 (3.3%)
Larici *et al.* (2007) [51]	Retrospective cohort	787	Mixed	Yes	16-row MDCT	2.5 mm	15 (1.9%)
Ritchie *et al.* (2007) [15]	Prospective cohort	343	Mixed	Yes	4-row or 16-row MDCT	1-3 mm	18 (5.2%)
Hui *et al.* (2008) [52]	Retrospective cohort	765	Mixed	Yes	16-row MDCT	2.5 mm	17 (2.2%)
Sun *et al.* (2010) [7]	Retrospective cohort	8,014	Lung cancer patients	No	NR	NR	180 (2.2%)
Farrell *et al.* (2010) [14]	Retrospective cohort	342	Mixed	Yes	4-row or 16-row MDCT	1-3 mm	6 (1.8%)
Di Nisio *et al.* (2010) [53]	Retrospective cohort	1,921	Solid tumors	Yes	NR	NR	24 (1.2%)
Browne *et al.* (2010) [11]	Prospective cohort	407	Mixed	Yes	64-row MDCT	1 mm and 5 mm	18 (4.4%)
Menapace *et al.* (2011) [54]	Retrospective cohort	135	Pancreatic cancer	No	NR	NR	4 (3.0%)
Shingare *et al.* (2011) [8]	Retrospective cohort	13,783	Mixed	No	4-row or 64-row MDCT	5-7 mm	395 (2.9%)
Bach *et al.* (2013) [31]	Retrospective cohort	3,270	Mixed	Yes	64-row MDCT	5 mm	129 (3.9%)

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 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 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 and bilateral lung involvement occurs in 23-46% of the cases (Table 2) [6–8,11,12,17,23,25–28]. 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