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FULL PAPER

Incidental pulmonary embolism in CT scans of oncological patients with metastatic disease undergoing clinical trials: frequency and linkage with onset of disease progression (PE-PD association)

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Objectives: We aimed to analyze the association between the onsets of PE and of progressive disease (PD) in CT scans of oncological patients undergoing clinical trials.

Methods: We retrospectively searched our oncological clinical trials database (1/2012 - 6/2017). We retrieved patients who underwent protocol baseline and follow-up CT scans. RECIST 1.1 categories of response were calculated for each scan at interpretation. The entire dataset was searched for reports with incidental PE.

For patients with incidental PE, we collected all the scans conducted up to and including the scan with PE. For each scan, we retrieved the recorded RECIST 1.1 category. We excluded patients with PE at baseline.

The frequency of incidental PE in oncological clinical trial patients was calculated. For patients with incidental PE, we evaluated the association between PE and PD.

Results: During the study period, 1,070 patients underwent 3,818 CTs. The total number of follow-up months was 7,292 months. 18 patients developed incidental PE during follow-up. Thus, the frequency of incidental PE in oncological clinical trial patients was 3% per year of follow-up. Patients with incidental PE underwent 60 scans up to development of PE. Of 42 non-baseline scans, 6/6 (100%) PD showed PE, and 5/36 (13.9%) non-PD showed PE, making PE onset associated with PD onset ($p < 0.001$).

Conclusion: In oncological clinical trials, the frequency of incidental PE is 3% per year of follow-up. The onset of incidental PE is linked to the onset of PD.

Advances in knowledge: Incidental PE is associated with the onset of disease progression. Radiologists interpret oncological scans should be aware of the association between PE and PD.

INTRODUCTION

Incidental PE is defined as PE seen on CT ordered for indications other than suspected PE. Cancer patients frequently undergo CT for disease assessment.¹

Advancements in CT techniques over the past decades have improved pulmonary arterial visualization.² Incidental PE is increasingly detected, with a prevalence of 1–5%.^{3,4} Cancer is a recognized risk factor for PE, with some studies reporting a sixfold increased risk of PE.⁵ The occurrence of PE in oncology patients increases with advanced disease and is associated with a higher risk of mortality within 6 months.⁶

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) is a set of published rules that include definitions of the minimum size of measurable lesions, instructions about how many lesions to follow, and the use of uni-dimensional measures for evaluation of tumor burden.^{7,8} The RECIST criteria have gained widespread adoption and are widely used particularly in oncology clinical trials.⁹

Oncological clinical trials are an important part of medical practice. These studies entail many CT follow-ups. Yet, the frequency of incidental PE in this population has not been evaluated. Nor has the link between the onsets of disease

Figure 1. Flow chart of the patient cohort included in this study

progression (PD) and PE been studied. Shedding light on the possible linkage between the onsets of PE and PD may hint on the pathophysiology of PE.

We aimed to analyze the association between the onsets of PE and of PD in CT scans of oncological patients undergoing clinical trials.

METHODS AND MATERIALS

An institutional review board approval (IRB) was granted for this study. The IRB committee waived the need for informed consent.

We retrospectively searched our department's clinical trials database. We retrieved all patients who underwent chest-abdomen CT with i.v. contrast. The time frame of the search was January 2012 to June 2017. All the patients in the study were oncological patients with metastatic disease. All the patients were enrolled in oncological clinical trials. The patients underwent baseline and follow-ups CT as part of the trials' protocols.

All CTs were performed at our department on two machines (Philips Brilliance 256 or a GE Discovery 64). CTs were acquired with a slice thickness of 2.5 mm. Patients were scanned in the supine position from the cranial to the caudal direction at end inspiration. One hundred milliliters of Omnipaque (Iohexol 350 mg/ml up to 2 ml/kg, GE Healthcare) was injected with an automated injector at a rate of 2–3 ml s⁻¹. Axial images were reconstructed using standard algorithms.

RECIST 1.1 categories were calculated for each CT study at the time of interpretation. RECIST 1.1 definitions⁹:

Complete Response (CR): The disappearance of all target lesions. Any pathological lymph node (whether target or non-target) must have a reduction in short axis to <10 mm.

Table 1. Demographics and characteristics of patients with incidental PE (*n* = 18)

Characteristics	n (%)
Male	10 (55.6)
Female	8 (44.4)
Av. Age (range)	64.5 (45–89)
Cancer types	
Pancreas	4 (22.2)
Breast	3 (16.7)
Non-small-cell lung carcinoma	2 (11.1)
Ovary	2 (11.1)
Prostate	2 (11.1)
Renal cell	1 (5.6)
Endometrial	1 (5.6)
Colorectal	1 (5.6)
Transitional cell	1 (5.6)
Melanoma	1 (5.6)
Treatment type	
Chemotherapy	16 (88.9)
Radiotherapy	5 (27.8)
Surgery	9 (50)
Immunotherapy	1 (5.6)
Metastatic sites at presentation	
Bone	10 (55.6)
Liver	8 (44.4)
Lung	7 (38.9)
Peritoneum/omentum	4 (22.2)
Kidney	1 (5.6)
Ovary	1 (5.6)
Comorbidities	
Cardiovascular disease	12 (66.7)
Diabetes mellitus	4 (22.2)
Chronic renal disease	4 (22.2)
Chronic lung disease	5 (27.8)

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on

Table 2. The RECIST category and PE status for follow-up CT scans for each patient

Patient #	Age	Primary	The Response Evaluation Criteria in Solid Tumors (RECIST)										
			Scan 1	Scan 2	Scan 3	Scan 4	Scan 5	Scan 6	Scan 7	Scan 8	Scan 9	Scan 10	Scan 11
1	60	CRC	BL - PE										
2	75	Ovary	BL - PE										
3	52	NSCLC	BL - PE										
4	69	Melanoma	BL - PE										
5	86	Pancreas	BL - PE										
6	78	Pancreas	BL - PE										
7	45	Breast	BL - PE										
8	68	Endometrium	BL	PD - PE									
9	62	Prostate	BL	SD - PE									
10	63	NSCLC	BL	PD - PE									
11	73	Ovary	BL	PD - PE									
12	89	Prostate	BL	SD	SD - PE								
13	58	Breast	BL	SD	SD	PD - PE							
14	68	Pancreas	BL	SD	SD	SD - PE							
15	68	RCC	BL	SD	SD	SD	SD - PE						
16	70	Breast	BL	SD	SD	SD	SD	SD - PE					
17	65	Pancreas	BL	SD	SD	PR	PR	PR	PR	PR	PD - PE		
18	66	TCC	BL	PR	PR	PR	PR	PR	PR	PR	PR	PR	PD - PE

BL, Baseline; CRC, colorectal cancer; NSCLC, Non-small-cell lung carcinoma; PD, Progressive disease; PE, Pulmonary embolism; PR, Partial response; RCC, Renal cell carcinoma; SD, Stable disease.

study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The same board-certified radiologist SR, with more than 40 years of experience at reading CT, interpreted all scans and assigned the RECIST scores.

The retrieved reports were searched to identify scans with incidental PE. One-year follow-up frequency of incidental PE in oncological clinical trial patients was calculated.

For patients with incidental PE, we collected all the scans conducted up to and including the scan with PE. For each scan,

we retrieved the recorded RECIST 1.1 category of response. We excluded patients with PE at baseline.

For non-PD patients with incidental PE, we also evaluated the RECIST score in the following CT study. Similarly, the RECIST score of the following study was evaluated in patients with PE on the baseline study.

Statistical analysis

Descriptive statistics was used to summarize the study's characteristics. All analyses were conducted with Python (V.3.6.5). Statistical significance was established at a two-sided $p < .05$. The

association between the onsets of PE and of PD were determined using Fisher's exact test.

RESULTS

During the study period, 1,146 patients in the oncology clinical trials database were retrieved. Of them, 1,070 patients (ages 59.4 ± 13.0 , M:F 585:485) underwent 3,818 chest-abdomen CTs. The study inclusion flow chart is shown in Figure 1.

18 patients (ages 64.5 ± 6.3 , M:F 10:8) were diagnosed with incidental PE, giving an incidence of 1.7% per patient. The demographic characteristics of patients with incidental PE are summarized in Table 1. Cancer distribution and type of therapy are also included in Table 1.

The total number of months that enrolled patients were followed up, from baseline CT to last follow-up CT, was 7,292 months, with an average of 6.8 months of follow-up per patient. Thus, the period prevalence of incidental PE in oncological clinical trial patients was 3% per year of follow-up.

18 patients diagnosed with incidental PE underwent 60 CT scans up to development of PE. Table 2 presents the RECIST category and PE status of these scans. Seven patients had incidental PE at baseline scan and thus were excluded.

The final cohort included 11 patients with 42 scans. 36 scans (85.7%) were categorized as non-PD (SD = 19, PR = 17), and six scans (14.3%) were categorized as PD. All six PD scans (100.0%) showed incidental PE, while only five scans from the non-PD studies showed incidental PE (13.8%). Making the onset of incidental PE associated with the onset of PD category of response ($p < 0.001$).

For the five non-PD studies with incidental PE, 3/5 (60%) showed PD on the following CT study. Additionally, 2/7 (~30%) of the baseline studies with incidental PE progressed to PD on the following study. Figure 2 presents an example of a patient with metastatic transitional cell carcinoma who had incidental PE concurrent to the onset of PD

DISCUSSION

In oncological clinical trials, patients frequently undergo chest CT as part of protocols. The incidence of PE at our institution for patients enrolled in clinical trials was 1.7% per patient or 3% per year of follow-up. In a large meta-analysis of 12 studies, including over 10,000 patients, cancer patients had a weighted mean prevalence of incidental PE of 3.1%.¹⁰

The occurrence of PE in oncology patients increases with advanced disease.⁶ It has been shown that 77% of patients with incidental PE had stage IV disease, versus 23% with stages I to III.¹¹ Similarly, incidental PE prevalence was higher among patients with metastatic malignancy (7%) than in patients with localized disease (2%).¹²

In our study, all the patients had stage IV metastatic disease as a criterion for enrollment to the clinical trial. We have shown that in

Figure 2. Axial CT scans of a 67-year-old male diagnosed with transitional cell carcinoma of the bladder with liver metastasis (A,B) 6-month follow up images (C, D) show an increase in the size of the primary tumor and distant metastasis in the liver as well as pulmonary embolism (PE) (E).

these patients, the onset of incidental PE is linked to the onset of disease progression (PD), as defined by RECIST criteria. It should also be noted that of the five non-PD studies, 60% showed PD in the following study.

Our study has two implications. First, radiologists who interpret oncological scans should be aware of the PE-PD association. Second, the PE-PD link implies the underlying causative factors of hyper-coagulability associated with the onset of progression of stage IV cancer.

Our study has several limitations. This is a retrospective study with its inherent limitations. The number of patients with incidental PE is small although the association with PD is strong. It is therefore difficult to extrapolate to routine clinical practice. Additionally, standard chest CT protocol without thin-section dedicated CT pulmonary angiography technique was used to detect PE in patients with unsuspected PE. Therefore, the detection of PE in the smaller branches of the pulmonary artery may have been underestimated. Although the prevalence of incidental CT in our group of oncological patients is similar to a previous publication. Incidental PE can be missed on routine imaging, and by reviewing the reports alone the "true incidental PE" may not have been accurately assessed. Finally, some oncologists may routinely place some patients with certain malignancies on thromboembolic prophylaxis. However, these patients were not excluded from the present study and may have had decreased likelihood of developing PE.

CONCLUSION

In oncological clinical trials, the frequency of incidental PE is 3% per year of follow-up. The onset of incidental PE is linked to the onset of PD.

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