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Incidental pulmonary embolism in pancreatic ductal adenocarcinoma: Impact of tumor and AJCC stages at initial staging CT

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ABSTRACT

Background/objectives: To determine the prevalence of incidental pulmonary embolism (PE) detected during initial staging CT among patients with newly diagnosed pancreatic ductal adenocarcinoma (PDAC) and assess their association with underlying tumor burden.
Materials and methods: This retrospective cohort study evaluated staging chest CT scans (2013–2017) to identify PE among patients with treatment naïve, biopsy-proven PDAC. Data included age, sex, T stage, AJCC stage, presence/absence of metastases and their location at diagnosis. The association of PE with tumor (T1-T4) and AJCC stage were assessed using Pearson Chi-square and Fischer's exact test. A threshold p-value of <0.05 indicated statistical significance.
Results: A total of 174 patients (90 female, mean age, 68 years; range: 34–93) were identified, of which 10 patients harbored incidental PE (prevalence, 5.7%). In the PE group, two patients presented with distant metastasis (liver, 20%), while eight patients had T4 tumors (80%). No statistical association was detected between PE and age, sex, and the presence/absence or location of distant metastasis ($p = 0.065$, $p = 0.59$, $p = 0.687$ and $p = 0.933$, respectively). Patients with T4 tumors and higher AJCC stages (stage III/IV) were significantly more likely to present with PE than those with lower T stage ($p = 0.045$) and AJCC stage (stage I/II; $p = 0.017$).
Conclusion: The prevalence of incidental PE among PDAC patients undergoing initial CT staging is 5.7%. Patients with T4 and AJCC stages III/IV are at higher risk of PE. Caution should be exercised during radiographic interpretation of initial staging chest CTs, as incidental PE may be lurking and require treatment.
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Introduction

Incidental PE is a filling defect of one or more pulmonary arteries on a contrast-enhanced CT scan performed for an indication other than PE, as defined by the International Society on Thrombosis and Hemostasis (ISTH) [1,2]. The incidence of incidental PE is 3.6% on routine computed tomography (CT) for oncologic assessment compared to 1.1% of non-oncologic CT scans [3].

The association of thromboembolic state and cancer is well known, leading to deep vein thrombosis and PE, and significantly

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increases morbidity and mortality. During post-mortem examination, the incidence of venous thromboembolism is as high as 50% of cancer patients [4,5]. Hence, a higher index of suspicion for PE is critical to multidisciplinary care of oncologic patients undergoing staging CT at initial diagnosis as well as on follow-up scans.

An investigation of the incidence of PE revealed that patients with pancreatic ductal adenocarcinoma (PDAC) have a significantly higher risk of developing PE. PE in PDAC patients has been reported to have an incidence of 5.81% during a follow up period of six years compared to an overall incidence of 2.87% in cancer patients in general [6]. However, the prevalence of incidental PE at initial staging CT at time of diagnosis of PDAC is unknown. Although staging CTs often have suboptimal contrast enhancement, an accurate diagnosis of PE is possible down to the subsegmental arteries [3]. Subsegmental PE (SSPE) are defined as peripheral PE limited to the fifth order of pulmonary arteries [7,8]. Despite the overall embolic burden being lower in incidental PE and, in SSPE in particular, studies have shown that patients with untreated incidental PE have a high 6-month risk of recurrent venous thromboembolism and mortality [9,10]. In one study, venous thromboembolism (VTE) within one year of cancer diagnosis was associated with advanced tumor stage, and lower one-year survival [11].

The aim of this study was to determine the prevalence of incidental PE detected during initial staging CT among patients with newly diagnosed PDAC and assess their association with underlying tumor burden.

Materials and Methods

Study design

This HIPAA compliant, retrospective cohort study aimed to quantify the presence or absence of incidental PE at initial staging CT of patients with newly diagnosed PDAC. The study was reviewed and approved by the IRB. The need for written informed consent was waived.

The primary outcome was the incidence of incidental PE discovered during routine staging CT of the chest. PE diagnosed during dedicated CT pulmonary angiography performed for indication other than staging were excluded.

The radiology reports of the study cohort were reviewed to record the positive diagnosis of PE detected on the initial staging CT and compared to the independent readout performed by a board-certified general radiologist with 11 years of experience in order to identify not reported cases of PE.

Screening procedures

A search of a prospectively updated database of a Pancreatic Cancer Multidisciplinary Clinic was performed. The database included cases from January 2013 to December 2017. 211 patients with treatment naïve, biopsy-proven PDAC were identified and underwent initial staging with contrast-enhanced chest CT at both our institution and outside facilities. Protocol-specific exclusions were applied to: inadequate contrast-enhancement of the pulmonary artery ($n = 18$), inadequate scan quality (motion artefacts, $n = 15$), patients with pre-existing cancer within five years ($n = 4$). The remaining 174 patients were considered eligible (Fig. 1).

The following parameters were recorded: age, sex, body mass index (BMI), T stage of the pancreatic cancer, AJCC staging at initial diagnosis, presence or absence of metastasis and, if present, the anatomical location of metastasis. Baseline biochemical parameters were also collected and included pre-treatment platelet count, haemoglobin level, pre-treatment leucocyte count, carbohydrate antigen (CA) 19–9 and carcinoembryonic antigen (CEA).

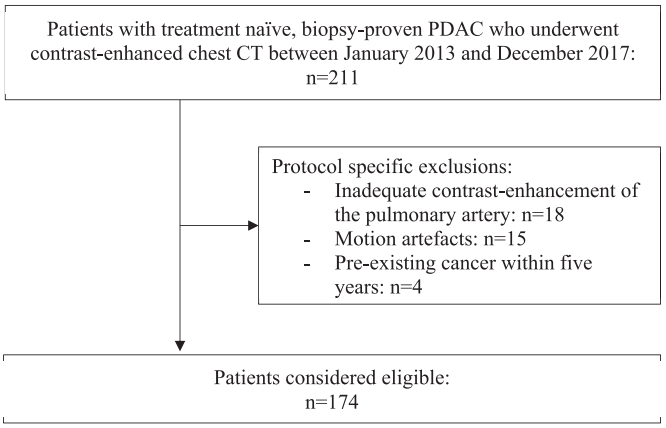

Fig. 1. Flow diagram of patient selection.

The Khorana score, a clinical risk stratification tool to identify patients with high risk of venous thromboembolism, was calculated for each patient [12]. Patients were classified as being of low risk (0 points), intermediate risk (1–2 points), and high risk for VTE (≧ 3 points), corresponding to a predicted 2.5 month risk of 0.3–0.8%, 1.8–2.0%, and 6.7–7.1%, respectively (Table 1) [12].

Imaging techniques

For initial staging CT, patients were scanned on multi-detector helical CT scanners at our institution and outside facilities (GE Lightspeed series, General Electric Healthcare; Aquilion series, Toshiba Medical Systems; SOMATOM series, Siemens Healthineers) at 120 kVp. The images were acquired in transverse plane at portal venous phase of imaging (1–5 mm slice thickness) and reconstructed at 5-mm section thickness in the sagittal and coronal planes using soft tissue (width: 400 HU, level: 40 HU) and lung algorithms (width: 1400 HU, level: -600HU) Patients received between 100 and 150 mL of intravenous nonionic iodinated contrast (Omnipaque 350, Mallinckrodt Pharmaceuticals) based on their BMI.

Image analysis

Staging chest CT images were reviewed using a commercially available Picture Archiving and Communications System (PACS—GE Healthcare/Milwaukee, USA).

One board-certified general radiologist (N.T.) with 11 years of experience evaluated the scans for the presence or absence of PE being unaware of the original report and Khorana score.

Both the pulmonary arterial level and lobar location of PE were evaluated. The level of pulmonary arterial involvement was classified as central (right and left main pulmonary arteries, and both

Table 1
Khorana score for risk stratification of PE.

	Criteria	Points
Body mass index	≧ 35 kg/m^2	1
Biochemical parameters		
Platelets count	≧350 × 10^9/L	1
Hemoglobin level	≦100 g/L	1
Leucocyte count	≧11 × 10^9/L	1
Site of cancer	Pancreas	2

Scoring system (risk of venous thromboembolism at 2.5 month): 0 points, low risk: 0.3–0.8%; 1–2 points, intermediate risk: 1.8–2.0%; ≧ 3 points, high risk: 6.7–7.1%.

interlobar pulmonary arteries); lobar; segmental; or subsegmental. PE involving main or lobar pulmonary arteries was considered to be proximal; PE involving segmental and subsegmental arteries was considered distal [6]. The lobar location of PE was assessed according to standard nomenclature, as follows: right upper lobe, middle lobe, right lower lobe, left upper lobe, lingula, and left lower lobe. In the event of multiple PE, the pulmonary arterial level and lobar locations of each PE were determined on a per-embolus (individual embolus, IE) basis. The total embolic burden was calculated per-patient. When PE involved multiple locations, only the most proximal location was recorded.

Statistical analysis

Statistical analyses were performed using SPSS (Version 22.0.0.0, IBM Corporation, Armonk, NY). The assessment of normality was performed with the Kolmogorov-Smirnov test. Normally distributed continuous variables were described by mean and standard deviation (SD). Not normally distributed continuous variables were described as median and interquartile range. Categorical variables were described as counts and percentages; difference between groups was evaluated using Fisher exact test. Mann-Whitney-U test was used for not normally distributed data. The association of PE with increasing T stage (T1-T4) and AJCC stage were assessed using Pearson Chi-square and Fischer's exact test. A p-value of <0.05 was considered statistically significant.

Results

Study population

A total of 174 consecutive treatment naïve patients (mean age, 68 ± 11 years; range, 34–93 years, 90 women, 51.7%) with histologically proven PDAC were eligible and underwent staging chest CT between 2013 and 2017 were included in this study.

Baseline clinical characteristics are shown in Table 2. No significant differences were discovered in age, sex, BMI and the presence/absence of distant metastasis, or location of distant metastasis based on the presence or absence of PE ($p = 0.065$, $p = 0.59$, $p = 0.529$, $p = 0.687$, and $p = 0.933$, respectively). No significant differences were found among any of the baseline biochemical parameters such as pre-treatment platelet count, hemoglobin level, pre-treatment leucocyte count, CA 19–9 or CEA (Table 3).

Furthermore, no baseline differences in Khorana score were identified upon initial staging CT between the non-PE and PE cohort ($p = 0.61$).

A total of 69 patients presented with T4 stage, 61 patients (88.4%) in the non-PE cohort and eight patients (11.6%) in the PE cohort.

Patients with incidental PE

Of the 174 patients in the study cohort, 10 (5.7%) had incidental PE at initial staging CT (Table 4). The PE group had a mean age of 74 ± 10 years (range, 60–89 years) and equal age distribution. Eight patients (80%) had T4 disease at initial presentation while two (20%) were early stage (T1 and T2 disease) (Fig. 3). Eight patients (80%) had AJCC stages III/IV and two patients (20%) with AJCC stages I/II. Distant metastasis was found in two patients (liver, 20%) while the other eight patients (80%) had no distant metastasis.

PE was significantly more common in patients with T4 and higher AJCC stages (stage III/IV) compared to patients with lower T stages ($p = 0.045$) and AJCC stage (stage I/II; $p = 0.017$) (Fig. 2).

In three patients (30%) the presence of PE was not reported at initial staging CT.

Pulmonary arterial level and lobar location of PE

In total, 27 IE were found in the subgroup with PE. The total emboli burden per-patient was 2.7 IE, range 1–6. Seven IE (26%) were proximal location (main right or left pulmonary artery, left or right interlobar or lobar arteries) and 20 IE (74%) in distal location (left or right segmental or subsegmental arteries), of which 16 (59%) were subsegmental. In four patients, the IE were isolated SSPE. 18 IE (66.6%) were located on the right of which 8 IE (29.6%) were found on the lower lobe, which showed the highest frequency of per lobe IE.

The most proximal location of the three unreported PE cases at initial staging were in the lobar right upper pulmonary artery, segmental right lower lobe, and subsegmental right and left lower lobe pulmonary artery, respectively (Fig. 4 and Fig. 5).

Table 2
Patients demographics of study cohort.

	Total (n = 174)	No PE (n = 164)	%	PE (n = 10)	%	p value
Age	67.8 ± 11	67.4 ± 11		74.0 ± 9.7		0.065
Sex						
Male	84	79	48.2	5	50	0.59
Female	90	85	51.8	5	50	
T stage						
T1	15	14	8.5	1	10	0.045
T2	57	56	34.1	1	10	
T3	33	33	20.1	0	0	
T4	69	61	37.2	8	80	
AJCC stage						
I/II	98	96	58.5	2	20	0.017
III/IV	76	68	41.5	8	80	
Presence of metastasis						
Yes	27	25	15.2	2	20	0.687
No	147	139	84.8	8	80	
Location of metastasis						
Live	19	17	10.4	2	20	0.933
Lung	4	4	2.4	0	0	
Omentum/Peritoneum	2	2	1.2	0	0	
Multiple sites	2	2	1.2	0	0	

Abbreviations: PE, pulmonary embolism; BMI, body mass index; T stage, Tumor stage; AJCC stage, American Joint Committee on Cancer stage.

Table 3
BMI, biochemical parameters and Khorana score at timepoint of initial staging CT.

	Total	n	No PE	n	PE	n	p value
Body mass index	26.8 ± 5.1	169	26.9 ± 5.0	160	25.8 ± 6.9	9	0.529
Biochemical parameters							
Platelet count*	223.5 [170–278.3]	166	223.5 [170–278.3]	157	266 [211.5–334]	9	0.338*
Hemoglobin level	12.4 ± 1.7	166	12.4 ± 1.7	157	12.5 ± 1.4	9	0.776
Leucocyte count	7.6 ± 2.6	166	7.5 ± 2.6	157	9.0 ± 2.9	9	0.102
CA 19–9*	203 [47.5–1318.3]	152	193 [46.5–1287.5]	145	87 [49–5833]	7	0.453*
CEA*	11.5 [3–30.8]	132	4 [2.4–7.2]	126	6.7 [3.1–35.6]	6	0.161*
Khorana score	2.26 ± 0.49	167	2.24 ± 0.47	158	2.56 ± 0.73	9	0.61

Abbreviations: PE, pulmonary embolism, CA 19–9, carbohydrate antigen 19–9, normal value, <37 U/ml; CEA, carcinoembryonic antigen, normal value, ≤ 3 ng/ml * not normally distributed data are expressed as median [interquartile range]. Data is otherwise displayed as mean ± standard deviation.

Table 4
Patients demographics of the patients' cohort with pulmonary embolism.

	Age	Sex	T stage	AJCC stage	Metastasis	Most proximal location of PE	PE not reported	Khorana score
1	77	F	T4	III	–	Subsegmental	–	4
2	78	M	T4	III	–	Subsegmental	Not reported	2
3	89	M	T2	I/II	–	Central	–	2
4	63	M	T4	III	–	Central	–	3
5	76	F	T4	III	–	Segmental	–	2
6	64	M	T4	IV	Liver	Segmental	Not reported	2
7	73	F	T4	III	–	Central	–	2
8	87	F	T1	I/II	–	Lobar	Not reported	3
9	60	F	T4	IV	Liver	Subsegmental	–	3
10	73	M	T4	III	–	Subsegmental	–	N/A

Abbreviations: T stage, Tumor stage; AJCC stage, American Joint Committee on Cancer stage; PE, pulmonary embolism; F, female; M, male; central, main pulmonary artery and interlobar artery.

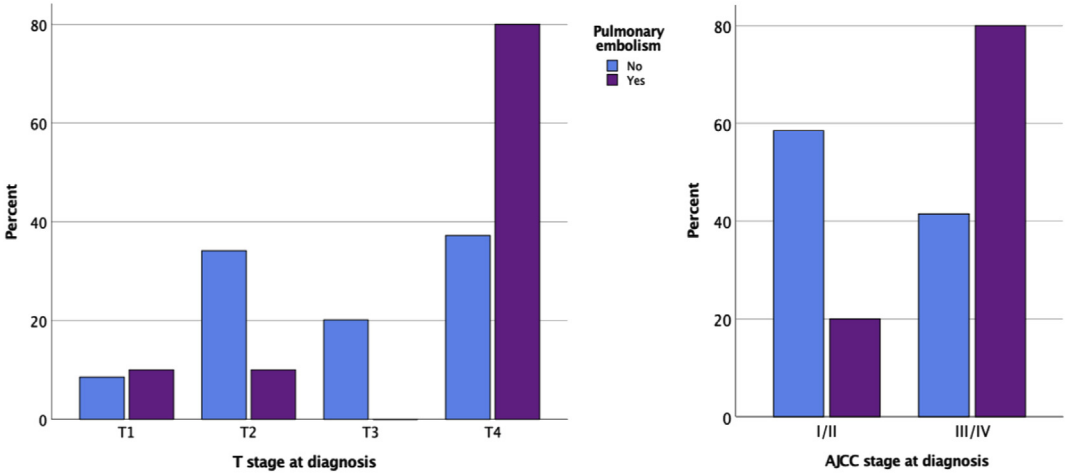

Fig. 2. Prevalence of pulmonary embolism at initial staging chest CT and association with T and AJCC stage at diagnosis.

Discussion

This retrospective cohort study investigated the prevalence of incidental PE at initial staging CT among patients with newly diagnosed treatment naive PDAC and assessed their association with underlying tumor burden. The prevalence of incidental PE was 5.7% in this patients' cohort. Patients with T4 disease and AJCC stages III/IV were at higher risk of PE.

A high index of suspicion for PE in the care of PDAC patients is required as it has been shown that among oncologic patients, which have a higher risk of developing PE, patients with PDAC are a population at even a significant higher risk. The incidence of PE in PDAC patients has been reported to be 5.81% [6]. However, the prevalence of incidental PE in PDAC patients is yet unknown. Because untreated incidental PE leads to a higher 6-month mortality rate [9,10] and a 2.2-fold increase in mortality as compared to matched cancer patients without PE [11], it is crucial not to miss treatment options in this patient population with this recalcitrant tumor and overall poor prognosis at initial presentation.

Patients demographics regarding age and sex as well as BMI and biochemical parameters at initial staging CT did not differ between the groups. Subsequently, the Khorana score, a scoring system designed to select patients in a high-risk group for thromboprophylaxis using these clinical parameters [13], did not differentiate

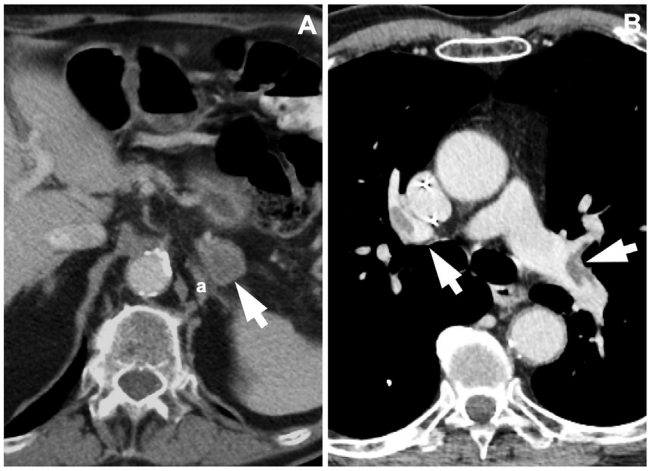

Fig. 3. A 89-year-old male with a hypoenhancing pancreatic ductal adenocarcinoma in the pancreatic tail (A: arrow) adjacent to the adrenal gland (a) with no evidence of distant metastasis (T stage 2, AJCC stage I/II). Extensive bilateral pulmonary emboli are seen in the main right and left pulmonary artery with extension into the interlobar arteries on both sides at initial staging chest CT (B: arrow).

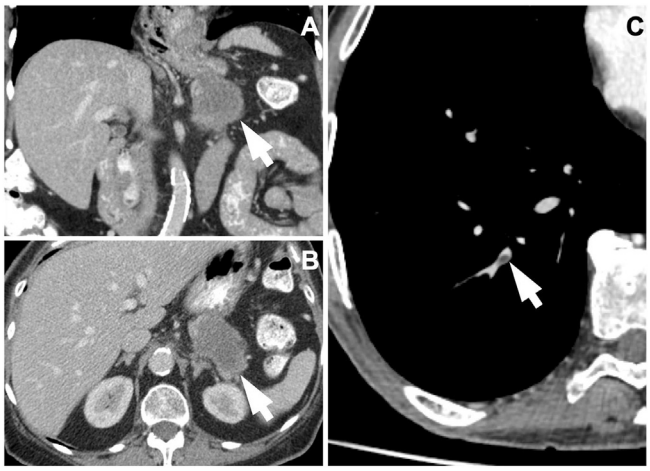

Fig. 4. A 78-year-old male patient with an hypoenhancing expansive pancreatic ductal adenocarcinoma in the pancreatic tail (A and B: arrow) with no evidence of distant metastasis. The tumor presents at an advanced local stage with direct infiltration of the stomach wall and left adrenal gland (T stage 4, AJCC stage III). The subsegmental pulmonary emboli of the right lower lobe was not mentioned in the report of the initial staging chest CT (C: arrow).

between the groups. As a consequence, a substantial amount of PDAC patients at high risk for recurrent thromboembolism are not identified with this clinical module of risk stratification.

It is important to define factors that help identifying PDAC patients at risk of incidental PE, as a study has shown that their incidence of incidental PE was significantly higher than that of suspected PE in PDAC (85% incidental PE) [6]. Our study shows that the risk of PE rises with advancing T status and AJCC stages in patients with PDAC. This is in line with previously published data that found that cancer diagnosed at the same time as or within one year of an episode of venous thromboembolism is associated with an advanced stage of cancer and a poor prognosis [11]. In this study cohort, eight out of 69 (11.5%) patients that presented with T4 stage at initial staging CT were positive for PE. Therefore, an advanced cancer stage in PDAC should raise awareness of a possible PE event and radiologists should actively search for incidental PE at initial staging CT.

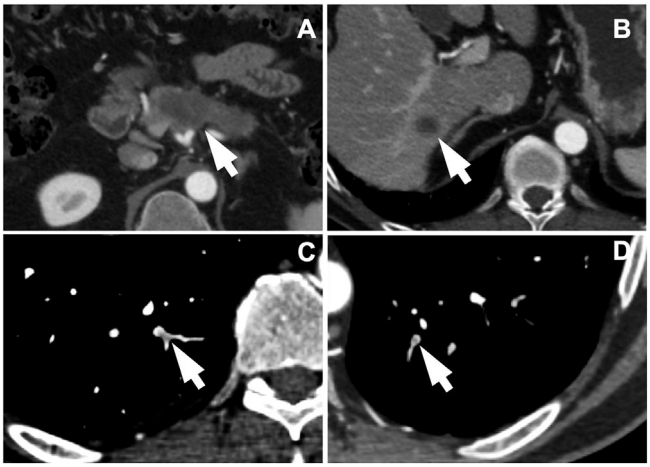

Fig. 5. A 64-year-old male presented with a pancreatic ductal adenocarcinoma in the pancreatic body (A: arrow) with invasion of the adjacent vessels (splenic artery and tumor thrombus into the superior mesenteric vein, T stage 4). The initial staging CT of the abdomen showed a hypoattenuating focal liver lesion in the hepatic segment V (B: arrow), consistent with liver metastasis (AJCC stage IV). The initial staging chest CT revealed subsegmental and segmental pulmonary emboli in the right (C: arrow) and left lower lobes (D: arrow) which were initially not mentioned in the radiological report.

A recently published study postulates an association of higher tumor marker levels (CA 19–9 and CEA) with an increased risk of VTE in pancreatic cancer [5], which is usually the case in patients with higher T and AJCC stages. In our population, however, we could not show a significant differences between level of serum tumor markers and presence of PE, most probably due to the fact that the CEA level was assessed in only six patient in the PE cohort and due to the overall high variability of CA 19–9 in both groups.

In 3/10 (30%) of patients with PE, the diagnosis was not reported at initial staging CT with the most proximal location of the not reported PEs being the lobar pulmonary artery followed by segmental and subsegmental arterial levels. The search for thoracic metastasis at initial staging chest CT in PDAC patients may distract from scrupulous assessment of the pulmonary arteries in this population. This observer error includes scanning error in this patients' population as the primary aim of radiologists in staging CTs is the search for metastasis and, in case of a positive finding, satisfaction of search error might occur [14]. In addition, technical aspects such as thick slices and motion artefacts can lead to missing of even proximally located PEs. Understanding the possible causes for unreported PE and knowing their actual prevalence and, therefore, their probability in PDAC patients at initial staging CT may possibly reduce this phenomenon.

The consensus in the current literature is that the management of incidental PE is identical to that of symptomatic PE [3]. A retrospective observational study showed that patients with incidental PE who did not receive anticoagulation therapy had poorer overall survival [10]. SSPE are of special interest. In this study, a total 27 IE were found and 16 IE (56%) of those were SSPE. In four patients, the IE where isolated SSPE. The clinical significance and management of isolated SSPE is debated in non-oncologic patients [15,16]. However, for patients with active cancer and higher risk of VTE recurrence, a recently published commentary in JAMA Internal Medicine suggests prophylactic dose anticoagulation [17]. Moreover, an experimental study investigated the role of the coagulation system and its linkage with tumor biology [18], and suggested that anticoagulation therapy may have other beneficial side effects in oncologic patients such as limitation of tumor dissemination and inhibition of metastasis formation. Also, a clinical study suggests

that the mechanism by which antithrombotic agents increase survival and decrease metastasis in cancer patients is through attenuation of platelet angiogenic potential [19].

This study has several limitations. First, staging CTs were used to identify patients with incidental PE without dedicated CT pulmonary angiography technique. To account for that, we excluded scans without sufficient contrast enhancement, that would preclude assessment of the pulmonary arteries. Despite the suboptimal contrast enhancement of staging CTs for the diagnosis of PE, accurate diagnosis of PE was feasible up to the subsegmental arteries. Second, we included CT scans from outside facilities, some without thin sections (max. slide thickness: 5 mm). Therefore, the prevalence of incidental PE in PDAC patients, especially those involving peripheral arterial branches, might be underestimated. Third, because of the retrospective nature of this cohort study, CT scanners and sequence parameters were variable. Although this is a limitation, it is also reflective of the clinical reality in a large radiological institution.

In conclusion, the prevalence of incidental PE among PDAC patients undergoing initial CT staging is 5.7%. Patients with T4 disease and AJCC stages III/IV are at higher risk of PE. Caution should be exercised during radiographical interpretation of initial staging chest CTs, as incidental PE may be lurking and require treatment. Therefore, radiologists must be diligent to detect incidental PE during initial staging CT scans for newly diagnosed PDAC patients.

Disclosures: A. James Moser, MD, has relationships with Abbvie, sigilon LCC

The other authors have no conflicts of interest to declare.

IRB statement

This HIPAA compliant, retrospective cohort study was approved by our institutional review board and patient's informed consent was waived.

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