Does the anatomic distribution of acute pulmonary emboli at MDCT pulmonary angiography in oncology-population differ from that in non-oncology counterpart?

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Oncology population;
MDCT pulmonary angiography;
Cancer

Abstract  Objective: To compare the prevalence and the anatomic distribution of acute PE in oncology patients with those of non oncology patients using multidetector CT (MDCT) pulmonary angiography.

Material and methods: We prospectively reviewed 80 consecutive patients having pathologically proven neoplasms and clinically suspected to have acute PE. Similarly, the other group included 80 consecutive age-matched patients with the clinical suspicion of acute PE, nonetheless, with irrelevant oncologic history. All patients underwent MDCT pulmonary angiography. The PE involvement according to pulmonary arterial level was classified. Lobar location was also recorded using standard nomenclature.

Results: Twenty six patients (33%) of the 80 oncology patients compared to 19 patients (24%) of the 80 non oncology group had acute PE at pulmonary MDCT angiographic examinations. Among the oncology patients, acute PE was located in the main pulmonary artery in 7 (13%), the lobar pulmonary artery in 22 (40%), the segmental pulmonary artery in 17 (31%) and the subsegmental pulmonary artery in 9 (16%) patients. Whereas in the non oncology group, the level of involvement of PE was the main pulmonary artery in 4 (10%) patients, the lobar pulmonary artery in 17 (40%), the segmental pulmonary artery in 15 (36%) and the subsegmental pulmonary artery in 6 (14%). Alternatively, there was a lower lobar predominance in both groups.

Conclusion: The prevalence of acute PE is more common among oncology patients than previously reported and has a slight predilection to a central distribution.

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1. Introduction

Pulmonary embolism (PE) is a potentially life-threatening condition and is responsible for significant morbidity and mortality in adults (1,2). Cancer and its treatment are recognized risk factors for venous thromboembolism (VTE). It has been
demonstrated that there is a 6-fold increased risk of VTE in patients with cancer compared to those without (3). Moreover, the venous thromboembolic complication, pulmonary embolism (PE), is an important cause of death in cancer patients (4–6). Depending on the clinical presentation, the case fatality rate for acute pulmonary embolism ranges from about 60% to less than 1% (7). Trousseau in 1865 hypothesized that the procoagulant activity generated by tumor cells, macrophages, platelets and vascular endothelial cells contributed to a thrombophilic state in cancer patients (8). The use of newer and more aggressive chemotherapeutic agents has also been associated with an increased risk for thrombosis (7). PE is a difficult diagnosis to make on the basis of clinical and laboratory data alone. Thus, imaging studies play a critical role in establishing this diagnosis (9). During the past decade, CT pulmonary angiography has revolutionized the imaging of PE in adults and is now considered the reference standard for diagnosis (10,11).

With MDCT volumetric isotropic data on the entire thorax are acquired with thin collimation and few artifacts, therefore, images can be viewed in any plane (12–17). Multidetector row helical computed tomography (CT) is particularly helpful in the diagnosis of acute pulmonary embolism (PE) owing to its capacity to directly show emboli as intravascular filling defects (18). Moreover, with the advent of MDCT scanners, even the subsegmental pulmonary arteries can now be evaluated (19). MDCT pulmonary angiography has also been shown to have high specificity, sensitivity and negative predictive value for the diagnosis of acute PTE (20,21).

Thus, CT pulmonary angiography has become a commonly used non-invasive modality for the diagnosis of PE (22).

Likewise, MDCT pulmonary angiography is becoming the standard of care at many institutions for the evaluation of patients with suspected pulmonary embolism (23). The purpose of this study is to compare the prevalence and the anatomic distribution of acute PE in a cohort of consecutively selected oncology patients who are imaged with MDCT pulmonary angiography for the clinical suspicion of acute PE with those of consecutive age-matched patients clinically suspected to have acute PE, nonetheless, with irrelevant oncologic history.

2. Material and methods

2.1. Patients

Between April 2011 and November 2012, 80 consecutive oncology patients who had a pathologically confirmed diagnosis of cancer and were suspected of having acute PE, based on relevant clinical history, symptoms and vital signs were eligible for the study. They were included in the order they showed up and gave their informed written consents. They underwent MDCT pulmonary angiography. Demographic data including age and type of underlying neoplasm and disease stage were recorded. The presence of known metastasis, history of surgery, chemotherapy, radiation therapy or hormonal treatment was also recorded for each patient.

Likewise, 80 consecutive age-matched patients with the clinical suspicion of acute PE, however, with irrelevant oncologic history were enrolled in this study. The protocol of our study was approved by the Committee of Ethics.

We excluded patients with a history of previous PE, those with equivocal MDCT pulmonary angiographic examination and those with suboptimal quality of MDCT pulmonary angiographic images due to insufficient contrast opacification within the pulmonary arteries or the presence of artifacts limiting the evaluation of pulmonary arteries due to beam hardening or motion. In addition, patients with clinical symptoms of acute PE who had contraindications for a MDCT pulmonary angiography (renal failure and/or allergy to iodine contrast) were excluded and instead, they underwent ventilation/perfusion pulmonary scintigraphy.

3. Methods

3.1. CT Protocol and image evaluation

All patients underwent MDCT pulmonary angiography as follows:

An 18- or 20-gauge catheter was introduced into an upper extremity peripheral vein under complete aseptic condition. A volume of 120 mL bolus of non-ionic iodinated contrast material (iopromide 370 mg I/mL, Ultravist 370, Bayer HealthCare) was injected via a power injector (Stellant, Medrad, Indianola, PA) at a rate of 3–4 ml/sec followed by 20 mL of normal saline chasing. The start of image acquisition was determined by using an automatic detection of contrast (automatic triggering) by a bolus-tracking technique (CARE-Bolus, Siemens Medical Solutions, Erlangen, Germany) with contrast monitoring cursor placed in the main pulmonary artery. Contrast scanning was initiated when attenuation in the main pulmonary artery reaches 70 HU. Single breath hold scans were obtained.

Axial CT was performed with 16-section multidetector CT scanners (Somatom Sensation 16, Siemens Medical Solutions, Erlangen, Germany). Images were acquired from the lung bases to the apices using the following parameters: a peak voltage of 120 kVp, a tube current of 130 mAs, rotation time of 0.5 s, a detector collimation of 1.5 mm, a table movement of 15 mm per rotation with 2 mm slice thickness.

All images were sent to an offline workstation (Siemens Syngo). Image reconstruction from 2 cm below the diaphragm to the aortic arch was performed using 1.25 mm section thickness with 0.8 mm spacing. Images were reconstructed using multiplanar reformation (e.g., coronal and sagittal reforma-

MDCT pulmonary angiograms were interpreted separately by two independent experienced radiologists (having more than 10 years experience interpreting chest CT images) using the subsequently reported criteria for the diagnosis of pulmonary embolism. The two independent experienced radiologists were blinded to the type of the underlying neoplasm in the patients of the oncology group.

An angiogram was considered positive for acute PE if there was an intraluminal filling defect on more than one contiguous
axial section (on at least two consecutive transverse images), with expansion of the vessel and/or an abrupt termination of the opacified vessel peripherally. On the other hand, if neither of these findings was present, an angiogram was considered negative for acute PE. Equivocal angiograms were considered if there was a questionable filling defect on one or two images (24). However, the equivocal angiograms are not included in our study. We also evaluated the images using lung window settings for the presence of the ancillary finding of pulmonary infarct which is demonstrated as a peripheral wedge-shaped area of hyperattenuation along with linear bands (23). Diagnostic criteria for acute PE positive angiograms also included the visualization of a ‘polo mint’ or ‘railway track’ appearance where embolus is surrounded by contrast enhanced blood (25,26). A “polo mint” sign is seen when a partial filling defect surrounded by contrast material on images acquired perpendicular to the long axis of a vessel, while, the “railway track” sign is seen when a partial filling defect surrounded by contrast material on longitudinal images of the vessel (23).

For each lung, the main, lobar, segmental and subsegmental arteries were examined for pulmonary embolism. Embolus location was recorded according to the size of the affected pulmonary arterial vessels being classified as (main pulmonary artery, right pulmonary artery, left pulmonary artery, lobar (interlobar and lobar) or small vessel (segmental and subsegmental pulmonary artery) (24). Categorically, an embolus was assigned to the “central” group if there was radiologic evidence of a PE in the main stem, the right or the left pulmonary artery, the interlobar or lobar arteries alone with or without concomitant small vessel involvement. All the other patients with filling defects in one or more small vessels were assigned to the “peripheral” group.

Also, the distribution of the embolus between different lung lobes on both sides was recorded. A lobar location was also

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<td>Number of patients</td>
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<td>Bronchogenic carcinoma</td>
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<td>Lymphoma</td>
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<td>Breast cancer</td>
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<td>Type of patients included</td>
<td>MPA</td>
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<tr>
<td>Oncology group</td>
<td>7/55 (13%)</td>
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<tr>
<td>Non Oncology group</td>
<td>4/42 (10%)</td>
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MPA = main pulmonary artery, LPA = lobar pulmonary artery, SPA = segmental pulmonary artery, SSPA = subsegmental pulmonary artery.

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<th>Table 3</th>
<th>The lobar involvement of the pulmonary emboli detected on MDCT pulmonary angiography in both groups; oncology and non oncology.</th>
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<td>Type of patients included</td>
<td>RUL</td>
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<tr>
<td>Oncology group</td>
<td>8/56 (14%)</td>
</tr>
<tr>
<td>Non Oncology group</td>
<td>7/44 (16%)</td>
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RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe.
determined using standard nomenclature of Boyden (27) and Jackson and Huber (28): right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), lingula and left lower lobe (LLL). Location and level were determined on a per-embolus basis rather than a per-patient basis because several patients had more than one embolism. Furthermore, we measured the maximum minor axis of the right ventricle and the maximum minor axis of the left ventricle (LV) to assess for the right ventricular strain. The right ventricle (RV) was considered dilated if the RV cavity was wider than the LV cavity along the short axis (23). Similarly, the images were evaluated using the mediastinal window settings for evaluation of associated mediastinal adenopathies.

4. Results

The mean age of the oncology group was 61 years versus 63 years in the non oncology group. In addition, the oncology group consisted of 54% male patients and 46% female patients, whereas, the non oncology group consisted of 51% male patients and 49% female patients.

4.1. Types of cancer

In the oncology group, the patients included had diverse types of cancer; lymphoma in 13 patients (16%), breast cancer in 7

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**Fig. 3** A patient of pathologically proven colorectal carcinoma, consecutive axial (A and B) and coronal (C and D) MDCT pulmonary angiographic images show filling defects of pulmonary embolism (arrowed) in segmental and subsegmental arteries of the right middle lung lobe. Sagittal reformatted MDCT pulmonary angiographic image (E) displays detailed visualization of the course of obliquely oriented segmental and subsegmental branches containing the filling defects of the pulmonary emboli.
patients (9%), colorectal cancer diagnosed in 15 patients (19%), bronchogenic carcinoma in 9 patients (11%), hepatocellular carcinoma in 17 patients (21%), ovarian adenocarcinoma in 11 patients (14%) and gastric carcinoma in 8 patients (10%) (Table 1). The majority of patients had advanced disease stage; 43 patients (53.8%) had stage IV and 27 patients (33.8%) had stage III, whereas, only 3 patients (3.7%) had stage I and 7 patients (8.7%) had stage II. All patients were undergoing active treatment; 59 patients (74%) with chemotherapy, 21 patients (26%) with radiotherapy; none, however, were on hormonal therapy or had recently undergone surgery.

On the other hand, the oncology patients having positive angiograms for acute PE were diagnosed to have lymphoma in 7 patients (26.9%), bronchogenic carcinoma in 4 patients (15.4%), hepatocellular carcinoma in 4 patients (15.4%), ovarian adenocarcinoma in 6 patients (23.1%) and colorectal cancer in 5 patients (19.2%). No positive cases for acute PE were identified in any of the included patients with gastric carcinoma or breast cancer. All of them had advanced disease stage of stage IV. Regarding the treatment given, 22 of them (85%) (the patients who were diagnosed to have colorectal carcinoma, ovarian adenocarcinoma and lymphoma) had their PE while receiving their chemotherapeutic treatment while the other 4 cases (15%) of hepatocellular carcinoma were treated with palliative chemoembolization.

We did not find a significant association between the presence of acute PE and a specific type of neoplasm. However, this is explained by the few number of positive cases of acute PE for each type of cancer which limited our ability to make a definitive statement about such potential association.

4.2. CT pulmonary angiography results

In all included 160 patients, the two independent experienced radiologists verified the technical adequacy of the performed MDCT angiographic images. All MDCT pulmonary angiographic studies were technically successful in visualizing arteries to the level of subsegmental pulmonary arteries. Of the 160 patients included 45 (28%) had a CT angiogram that was positive and 115 patients (72%) had a CT angiogram that was negative for acute PE. Of the 45 patients who had acute PE detected at MDCT pulmonary angiography, 26 patients out of 45 patients (58%) belonged to the oncology patients and the other 19 patients out of the 45 patients (42%)
belonged to the non oncology group. Regarding the oncology patients, the acute PE positive MDCT pulmonary angiograms were 26 patients out of the 80 patients (33%) compared to 19 patients out of the 80 patients (24%) in the non oncology group of patients.

4.3. Distribution of PE

The anatomic location of PE is listed below in Tables 2 and 3, the distribution of pulmonary artery levels for the pulmonary emboli detected on MDCT pulmonary angiography (Table 2) was subsegmental in 9 patients (16%) of the oncology group versus 6 patients (14%) in the non oncology group, segmental in 17 patients (31%) in the oncology group versus 15 patients (36%) in the non oncology group, lobar in 22 patients (40%) in the oncology group versus 17 patients (40%) in the non oncology group and main pulmonary artery in 7 patients (13%) in the oncology group versus 4 patients (10%) in the non oncology group (Figs. 1 and 2). There was no case in which subsegmental PE was an isolated finding without evidence of additional PE at a more proximal level.

Consequently, assigning the detected emboli to central group or peripheral group, the oncology group showed 26 emboli in the peripheral group (Fig. 3) and 29 emboli in the central group (Fig. 4). On the other hand, the non oncology group showed equal number of emboli in the peripheral (Fig. 5) and central groups (Fig. 6), being 21 in each.

Regarding the lobar involvement of pulmonary emboli (Table 3), in the oncology group, the detected pulmonary emboli involved RUL in 8 patients (14%), RML in 5 patients (9%), RLL in 20 patients (36%), LUL in 4 patients (7%), lingula in 4 patients (7%) and LLL in 15 patients (27%) (Fig. 7). Acute PE was bilateral in 13 patients (50%), unilateral in the right lung in 9 patients (35%) and unilateral in the left lung in 4 patients (15%). A single lobar location was found in 12 patients (46%), two lobar locations in 6 patients (23%) and multiple lobar locations (>2 lobes) in 8 patients (31%).

As shown in Table 3, regarding the lobar affection of the detected pulmonary emboli in the non oncology group, they involved RUL in 7 patients (16%), RML in 5 patients (11%), RLL in 18 patients (41%), LUL in 2 patients (5%), lingula in 3 patients (7%) and LLL in 9 patients (20%) (Fig. 8). PE was bilateral in 11 patients (58%), unilateral in the right lung in 7 patients (37%) and unilateral in the left lung in 1 patient (5%). A single lobar location was found in 5 patients.

Fig. 6 Axial oblique MPR images of MDCT pulmonary angiography (A and B) assuming the sagittal orientation and showing intraluminal filling defects that occlude the right and the left interlobar arteries with further extension into posterior basal segmental and subsegmental arteries of both lower lung lobes.

Fig. 7 The lobar involvement in the patients of acute PE in the oncology group.

Fig. 8 The lobar involvement in the patients of acute PE in the non oncology group.
(26.3%), two lobar locations in 9 patients (47.4%) and multiple lobar locations (>2 lobes) in 5 patients (26.3%).

Note is made that not only the PE involving one lobe may also involve more than one pulmonary artery location but also the PE involving different lobes may be detected in same pulmonary artery location.

We also noted the diagnostic criteria for acute PE positive angiograms of "polo mint" sign (Figs. 9 and 12A) and "railway track" sign (Figs. 10 and 12C) in our study.

The ancillary finding of pulmonary infarct (Figs. 11 and 12A and B) was detected in 3 patients belonging to the non oncology group of patients.

Additionally, the right ventricle was dilated in 8 patients positive for acute PE belonging to the non oncology group (Figs. 12A and 13). There were enlarged mediastinal lymph nodes in the case of lymphoma implicating the pretracheal retrocaval region, prevascular aortic space, retrosternal space and subcarinal region (Fig. 14).

5. Discussion

In this study, we found a 33% prevalence of acute PE among a consecutive group of oncology patients referred for pulmonary CTA with clinical suspicion acute PE opposed to that of 24% among the non oncology group of patients. These results are compared to the 23.3% prevalence of PE reported in the recent adult PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis) trial (29). In addition, Hui and other colleagues (30) found that the prevalence of symptomatic PE on dedicated CT pulmonary angiography was 11.8%. On the other hand, Gladish et al (31) found that incidental pulmonary emboli were seen in 16 oncology patients (4%) but were initially reported in only four of them being explained by the small size of involved arteries which contributes to the failed detection at initial CT image interpretation.
We did not find a considerable association between the presence of acute PE in the oncology patients and a specific type of cancer. This concurs with Lee et al (32) who studied the MDCT of pulmonary emboli in pediatric oncology patients. However, Thodiyil et al (33) concluded from their study that the risk of VTE varies by cancer type and is especially high among patients with malignant brain tumors and adenocarcinoma of the ovary, pancreas, colon, stomach, lung and prostate. Other studies showed that a variety of tumors, including pancreatic, ovarian and brain tumors, are associated with an increased risk of pulmonary emboli and deep venous thrombosis (6,34). Alternatively, the study done by Gladish et al (31) revealed that patients with gynecologic malignancies and melanoma had a trend toward a higher prevalence of pulmonary emboli compared with the overall group.

On the other hand, Karippot and other colleagues (35) found that genitourinary cancer was most commonly associated with VTE followed by gastrointestinal, then lung cancer,
breast cancer, hematologic malignancies, melanoma and CNS tumors. Moreover, previous works in cancer patients with symptomatic VTE showed that the risk of VTE is lower in sites such as skin, breast and thyroid (36,37).

The advanced disease stage identified in all our patients was associated with higher risk of PE. This goes in agreement with Blom et al (38) who confirmed that though the risk of VTE varies with the stage of the disease, it is much higher with advanced stage than with early disease stage. Likewise, Chew and other colleagues (39) detected that the incidence of venous thromboembolism was highest among patients initially diagnosed with metastatic disease stage. In that study, they inferred that compared to patients with localized disease, the relative risk of developing symptomatic thromboembolism was more than 20-fold higher for metastatic melanoma, 9-fold higher for metastatic bladder cancer and 5- to 6-fold higher among patients with metastatic breast or uterine cancer. They also suggested that the biological aggressiveness of the cancer may be the principal risk factor associated with development of thromboembolism. As a result, they stated that the incidence of thromboembolism for some types of cancer was sufficiently high to warrant prospective clinical trials of primary thromboprophylaxis.

All patients in our study were undergoing active treatment; 59 patients (74%) with chemotherapy and 21 patients (26%) with radiotherapy. Karippot and other colleagues (35) established that pulmonary embolism is a common and potentially lethal disease in active cancer patients. In addition, Haddad and Greeno (40) deduced that the risk is also higher among cancer patients on active treatment with chemotherapy or radiotherapy. Whereas, Gladish et al (31) found that about one third of patients were currently undergoing chemotherapy or had completed their most recent course of chemotherapy within 1 month and few patients had recently undergone surgery or radiation therapy. Chew and other colleagues (39) also declared that major surgery, chemotherapy or radiation treatment contribute to the high incidence of thromboembolism in the months immediately following the diagnosis of cancer.

**Fig. 12** Axial MDCT pulmonary angiographic images in mediastinal window settings (A) and in lung window settings (B) at the level of the basal subsegmental pulmonary arteries revealing multifocal low-attenuation emboli producing the so-called “polo mint” sign (dashed arrow in A) in segmental and subsegmental arteries of the right lower lobe with a pleural-based and wedge-shaped area of hyperattenuation in the corresponding lung (white arrow in A and B). The latter represents the ancillary finding of pulmonary infarct. A note is also made on right ventricular strain caused by the acute pulmonary embolism denoted by wider short axis of the right ventricle (dashed line in A) in comparison to that of the left ventricle (solid line in A). Oblique MPR view of MDCT pulmonary angiography (C) showing the partial filling defects (arrowed) of the pulmonary emboli surrounded by contrast material on the longitudinal image of the vessel representing the so-called “railway track” sign.
Moreover, another study (41) has found many incidental PE in cancer patients, similar to symptomatic PE, with advanced disease stage and while undergoing active anti-cancer therapy. In that study, a significant percentage of patients had recurrent emboli pulmonary hypertension and sudden death.

The patients of the oncology group in our study comprised 26 peripheral and 29 central emboli. Our results are in agreement with Hasenberg et al (42) who reported higher incidence rate of central PEs in patients with malignant disease than patients without malignancies being about twofold in the earlier. Karippot and other colleagues (35) accomplished that active cancer patients appear to be at a higher risk for central PE reporting 63.4% incidence in the cancer group compared to 31.9% in the non-cancer group which they explained by the hypothesis of increased procoagulant activity in malignancy, in turn translating into extensive VTE.

As shown in Figs. 1 and 2, the pulmonary artery levels being involved in the acute PE in both groups whether oncology or non oncology patients were in order of frequency of affection: LPA, SPA, SSPA and MPA. The affection was lobar in 22 patients (40%), segmental in 17 patients (31%), subsegmental in 9 patients (16%) and main pulmonary artery in 7 patients (13%) in the oncology group, while, lobar in 17 patients (40%), segmental in 15 patients (36%), subsegmental in 6 patients (14%) and main pulmonary artery in 4 patients (10%) in.

Fig. 13  Axial images of MDCT pulmonary angiography (A and B) at the level of the basal subsegmental pulmonary arteries showing multifocal low-attenuation emboli involving the subsegmental arteries of both lower lung lobes (arrowed). Also the short axis of the right ventricle (dashed line) is wider than that of the left ventricle (solid line) representing right ventricular strain caused by the acute pulmonary embolism.
the non oncology group. This has a similar distribution to that in pediatric patients with clinically suspected PE (9).

Conversely, another study done by Lee et al (32) to detect unsuspected PE in routine thoracic MDCT examinations of pediatric oncology patients revealed that the pulmonary arterial locations of 17 emboli were nine (53%) segmental, five (29%) lobar, two (12%) central and one (6%) subsegmental.

With respect to the distribution of PE, the lower lobe predominance was evident in our study in both groups which corresponds with what was noted in other studies (2,31,43,44). Moreover, this is similar to that observed in particular pediatric population whether general pediatric population with PE (9) or oncology pediatric patients, in particular (32).

The few number of positive cases for acute PE for each type of cancer limits our ability to make an ultimate statement about the association between acute PE and specific type of cancer. A larger multicenter study would be helpful to more fully appraise this association.

To conclude, PE in oncology patients is more common than previously thought. This could be explained by the increased procoagulant activity in malignancy and the active anti-cancer therapy given. It tends to have a slight more central predilection. Additionally, it affects patients with advanced disease stage and those undergoing active anti-cancer therapy, thus, it may warrant primary thromboprophylaxis.

References


Fig. 14 Sequential axial (A–D) MDCT pulmonary angiography images displaying multiple enlarged mediastinal lymph nodes at the retrosternal space (arrows in A and B), pretracheal retrocaval region (solid arrow in C), prevascular aortic space (dashed arrow in C) and subcarinal region (arrowed in D).


