Combined CT Pulmonary Angiography & Indirect CT Venography in Evaluation of Clinically Suspected Cases of Pulmonary Embolism- Our Experience in an Oncologic Setup

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Abstract

The study was aimed at evaluating role of CT Pulmonary Angiography (CTPA) and Indirect CT venography (ICTV) in clinically suspected pulmonary embolism (PE) in oncology setup.17/31 (54.9%) patients were diagnosed with PE with or without deep vein thrombosis. DVT was diagnosed in 12(38.7%). 1 patient had DVT in absence of PE while 13/31 (41.9%) patients were diagnosed not to have PE or DVT. Clinical symptoms or pre-test probability determined by Well's criteria and other laboratory investigations were not found predictive of PE. CTPA diagnosed PE with greater ease, shorter time required with no dependence on clinical pretest probability unlike pulmonary scintigraphy. In cases with CTPA negative for PE, CT described additional findings possibly explaining patient's presenting symptoms unlike negative pulmonary scintigraphy. In cases where PE was excluded, CTV identified DVT (if present) in the same sitting, obviating separate venous Doppler. A single investigation with ability to deal with complete spectrum of DVT and PE makes CTPA & ICTV 'one stop shop' imaging modality for PE and DVT.

Keywords: CT Pulmonary angiography, CT venography, Deep vein thrombosis, pulmonary embolism, pulmonary scintigraphy.

Introduction

Pulmonary embolism (PE) is a complication of deep venous thrombosis (DVT) with considerable morbidity and mortality from which more than 100,000 people die annually.[1] The relationship between venous thromboembolism (VTE) and cancer was first highlighted by Trousseau A.[2] PE & VTE occurs more frequently and is the second commonest cause of death in patients with overt malignant disease. [3- 10]

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The diagnosis of VTE continues to be a challenge due to its non–specific clinical presentation.[11] Imaging has come a long way since the first radiographic description of PE on a chest radiograph.[12] For many years, angiography and ventilation-perfusion (V/Q) scintigraphy have been the mainstay for diagnosis, while venous doppler (VD) examinations are employed for diagnosis of associated DVT. More recently, computed tomography (CT) has been replacing invasive pulmonary angiography (PA) & V/Q scan for PE detection.[13-18]

In addition to diagnosis of PE, CT for evaluation of lower limb & pelvic veins came up in the form of direct[19] & indirect CT venography (ICTV).[20] ICTV immediately following CTPA allows simultaneous evaluation of DVT without administering additional contrast.

We undertook this study to evaluate the role of combined CT Pulmonary angiography (CTPA) with ICTV in diagnosis of PE & DVT among cancer patients.

Patients and methods

This prospective study was carried out in the Radiology department of a tertiary care centre for cancer patients. Among inpatients or those being treated on daycare/outpatient basis, total of 31 cases were referred to our department with clinical suspicion of PE during the duration of the study (one year). All these patients underwent CTPA & ICTV.

Patients with known hypersensitivity to iodinated intravenous contrast media, severe renal impairment or pregnancy were not included. Invasive PA was not performed in any case to confirm or exclude PE.

Study Protocol

A detailed clinical history and clinical findings were tabulated. All patients enrolled underwent a pretest clinical assessment of PE probability including Wells score (table 1).[21]

Table 1: Well's criteria for determining pretest clinical probability

Rules for predicting the probability of pulmonary embolism	
Variable	**No. of points**
Risk factors	
Clinical signs & symptoms of DVT	3.0
An alternative diagnosis deemed less likely than pulmonary embolism	3.0
Heart rate > 100ml/min	1.5
Immobilisation or surgery in the past 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Cancer (receiving treatment, treated in past 6 months or palliative care)	1.0
Clinical probability	
Low	<2.0
Intermediate	2.0-6.0
High	>6.0

CT Acquisition

CT examination was performed on a dual-slice configuration (Siemens Somatom Emotion Duo, Siemens Medical Solutions) CT scanner. Bolus tracking technique was utilized with the region of interest in pulmonary trunk. 80-100 ml of non ionic iodinated contrast agent - iohexol 300mg/ml was injected at 3-4ml/s through 18G i.v. cannula in antecubital vein. CTPA was triggered when threshold level of 120 HU

Table 2: Scanning parameters for CTPA & Indirect CT Venography

SCANNING PARAMETERS	
Scanner used	Siemens Emotion Duo (2 Slice spiral CT scanner)
Injector	Medrad Vistron
Contrast	Nonionic (Omnipaque 300mgI/ml)
IV cannula	18 to 20 G
Volume	100ml
Rate of injection	3-4ml/sec
Start delay	For pulmonary angiography- by bolus tracking (when threshold of 120 HU reached) For pelvic & lower limb angiography – 100s
Slice collimation	2.0 x 1.5mm (for pulmonary angiography) 8mm (for pelvic and lower limb venography)
Slice width Increment Reconstruction	2.0 mm (for pulmonary angiography) 8mm (for pelvic and lower limb venography)
Overlap	Nil
Direction	Craniocaudal
Scan range	Aortic arch to diaphragm (for pulmonary angiography) Iliac crest to popliteal fossa (for pelvic & lower limb venography)

was achieved in the pulmonary trunk. CTPA was performed in craniocaudal direction from aortic arch to dome of diaphragm with suspended inspiration or shallow breathing.CTV sections were acquired from iliac crest (lowermost part of IVC) to popliteal fossa with fixed post injection delay of 100s. Reconstruction was done at intervals of 2mm (for CTPA) and 8mm (for CTV). Scanning parameters for CTPA and lower limb ICTV are shown in table 2.

CT Interpretation

Images were viewed at mediastinum, lung and pulmonary embolism specific window settings (window width 700 HU; window level 100 HU) (Wittram et al, 2004)[22] on a workstation.

The diagnostic criterion for acute PE was a low attenuation area that completely or partially filled the lumen of opacified vessel. The criterion for DVT was presence of a filling defect in an opacified vein. In CTPA, pulmonary vasculature from level of pulmonary trunk upto subsegmental pulmonary artery level (5^{th} order) was evaluated.

Doppler Sonography

Patients were subject to VD examination whenever feasible from calf to the IVC using doppler sonography scanner (Logic 400, Wipro GE). Bilateral leg veins were examined using standard compression & doppler techniques. The criteria for DVT were presence of an intraluminal thrombus, incomplete compressibility of veins or both.

Pulmonary Scintigraphy

Whenever feasible, V/Q scanning (including ventilation scintigraphy, lung perfusion studies) & SPECT were performed and reported at the department of Nuclear

Risk factors	Total patients with risk factors (n=31)	Group A (n=17)	Group B (n=14)	p value
Immbolisation	31 (100%)	17 (100%)	14 (100%)	-
Recent surgery	11 (35.5%)	9 (52.9%)	2 (14.3%)	0.025
Previous DVT	15 (48.4%)	9 (52.9%)	6 (42.9%)	0.576
Anticancer chemotherapy	13 (41.9%)	5 (29.4%)	8(57.1%)	0.0119
Cardiovascular disease	2 (6.5%)	2 (11.8%)	0 (0%)	0.488
Respiratory disease	5 (16.1%)	3 (17.6%)	2 (14.3%)	0.99
Previous PE	0	0	0	-

Table 3: Distribution of risk factors in the two groups

Gastrointestinal & genitourinary malignancy	Group A	Group B	p value
No. of patients	13 (76.5%)	5 (35.7%)	0.022

Table 4: Gastrointestinal and genitourinary malignancies considered together showing predisposition for venous thromboembolism

Medicine just before or after the CT examination.

Results of CTPA and CTV (performed in all cases) were compared with other investigations (chest radiographs, D-dimer and fibrinogen degradation product (FDP), electrocardiogram (ECG), lower limb Doppler) wherever performed when requested by the referring physician.

Patient Follow-Up and Outcome

Patients with a diagnosis of PE were treated with anticoagulant therapy. Those with or without findings of PE on imaging were followed for 3-6 months using hospital records.

For purpose of comparison, patients enrolled were divided into two groups based on results of CTPA:

Group A: positive for PE on CTPA
Group B: negative for PE on CTPA

Statistical Analysis was performed to compare both groups of patients using pearson chi-square test, fisher's exact test and student's t-test with SPSS (Statistical package for social sciences) version 10.0.1 (released October 1999) (AIIMS, New Delhi). A p value < 0.05 was considered to be statistically significant.

Results

Based on results of CTPA, 17/31 (54.9%) and 14/31(45.1%) patients were in groups A and B respectively. PE and/or DVT were found in 18/31 (58%) cases on CTPA and ICTV considered together.

Mean age of patients included in the study was 51.5 years, 52.3 years in groups A & B respectively and 50.7 years overall. Most patients in group A were in the age range of 60-70 years. Of 31 patients, 14(45.1%) were males and 17(54.9%) were females. The relationship of occurrence of PE with mean age of patients in the two groups (p= 0.739) & patient's sex (p= 0.623) was not statistically significant.

All patients had history of prolonged immobilization while none had history of previous episode of PE. The difference between group A & B as regards to history of recent surgery was found to be statistically significant.(p=0.025). Distribution of risk factors in both groups is shown in table 3.

No statistically significant correlation between history of previous DVT, anticancer chemotherapy, pre-existing cardiovascular or respiratory disease and presence or absence of PE was seen.

The difference in distribution of various malignancies (considered separately) between the two groups was not found statistically significant.

On considering patients with gastrointestinal and genitourinary malignancies together, PE was diagnosed in 13/18 patients and found statistically significant for increased risk of PE (p=0.022). Table 4 shows the distribution of gastrointestinal & genitourinary malignancies in the two groups.

The presence of clinical symptoms (acute shortness of breath, chest pain, cough, expectoration, hemoptysis, fever and leg swelling) and presence of tachycardia, abnormal cardiovascular (CVS) &/or respiratory (RS) examination & pedal odema was not found to be predictive of presence of PE. Chest radiographs were performed prior to CTPA in 25 out of 31 patients. They were found to be abnormal in 21/25 cases (84%) overall, 11(73.3%) cases in group A and 10 cases (100%) cases in group B. Abnormal findings on chest radiographs, electrocardiogram and d-dimer/FDP assay was not found to be statistically significant.

In group A, pretest probability by Well's criteria[21] was found to be intermediate in 4(23.5%) and high in 13(76.5%) cases. In group B, pretest probability was intermediate in 8 (57.1%) and high in 6(42.9%) cases. Overall, the difference in pretest probability for PE between the two groups was not statistically significant. The distribution of pretest clinical probability in the two groups is shown in table 5.

Compression ultrasound and doppler examination of both upper and lower limbs was performed in 24/31 cases based on clinical suspicion of DVT. 19/24(79%) patients had evidence of DVT on ultrasound and Doppler. 11/19 patients with DVT had concomitant PE on CTPA.

Lung scintigraphy (both V/Q scan and SPECT) was done in 12/17 cases in group A and showed high probability of PE in all 12 (100%) cases. 9/14 cases in group B underwent lung scintigraphy which was normal in 6 and had low probability of PE in 3 cases.

Unlike abnormal doppler findings (p=0.630), lung scintigraphy findings between the two groups were statistically significant

Pretest probability	Group A	Group B	Total
Low	0	0	0
Intermediate	4 (23.5%)	8 (57.1%)	12 (38.7%)
High	13 (76.5%)	6 (42.9%)	19 (61.3%)
Total	17 (100%)	14 (100%)	31 (100%)

Table 5: Pre-Test probability (prior to performing CTPA)

Level	**1st order**	**2nd order**	**3rd order**	**4th order**	**5th order**	**Total**
Lobar Distribution	Pulmonary trunk	Main pulmonary a.	Lobar a.	Segmental a.	Sub segmental a.	
	1					1 (1.06%)
Right lung		8				8 (8.51%)
Upper lobe			7	3	2	12 (12.76%)
Middle lobe			2	4	2	8 (8.51%)
Lower lobe			7	13	6	26 (27.65%)
Left lung		8				8(8.51%)
Upper lobe			3	1	2	6(6.38%)
Lower lobe			8	12	5	25 (26.59%)
Total	**1 (1.6%)**	**16 (17%)**	**27 (28.7%)**	**33 (35.1%)**	**17 (18%)**	**94(100%)**

Table 6: Segmental distribution of pulmonary emboli on CTPA

	CT Venography		Total
	Negative for DVT	**Positive for DVT**	
Group A	6 (35.3%)	11(64.7%)	17 (100%)
Group B	13 (92.9%)	1 (7.1%)	14 (100%)
Total	19 (61.3%)	12 (38.7%)	31 (100%)

Table 7: Distribution of CT Venography findings in the two groups

(p=0.000) suggesting that lung scintigraphy findings can reliably diagnose pulmonary embolism.

In group A, CTPA quality was excellent in 16(94.1%) & good in 1(5.9%) cases based on attenuation measurements as suggested by Cham et al.[23] Motion artifacts (respiratory/cardiac) were seen in 3 cases. CTV quality in this group was good in all 17(100%) patients. Group B patients showed excellent CTPA quality in 14 (100%) cases with motion artifacts in 1 case. CTV quality was good in all 14 (100%) cases though blurring of images due to obesity was seen in 1 case.

So, overall both CTPA and CTV were found good to excellent in all studies performed.

Confident diagnosis was possible even in cases where artifacts were identified.

Segmental distribution of PE on CTPA is shown in table 6. Pulmonary emboli were found in 94 sites in the 17 patients found positive for PE. On an average, more than 5(5.52) emboli per patient were found within the pulmonary arterial system in patients diagnosed with PE.

Most emboli were located in central (segmental or larger) arteries (77 out of 94 i.e. 81.9%). Peripheral emboli (those in subsegmental branches) accounted for 17(18%) of all emboli. More emboli were found in the right than the left lung (54 and 39 respectively) – fig 1a & b.

Only one patient had an isolated embolus in the right lower lobe segmental (4^{th} order) artery (Fig.1c) Rest of the patients had multiple emboli at various locations.

Distribution of CTV findings is shown in table 7. CTV findings were positive for DVT in 11(64.7%) and 1(7.1%) cases from group A and B respectively and 12(38.7%) cases overall. One patient with DVT on ultrasound and doppler examination was ruled out to have DVT by CTV. The discordant findings were due to compression of left external iliac vein by lymph nodal mass detected on CTV. CTV depicted DVT in one case who had CTPA negative for PE (Fig. 2).

The difference in abnormal CTV findings between the two groups was found statistically significant. (p=0.001)

Among the ancillary findings (besides emboli) detected on CTPA (table 8), wedge shaped consolidation was found in 5 patients in group A with a statistically significant difference (p=0.048) in its occurrence between the two groups. Areas of consolidation, lung collapse, lung nodules, pleural effusion and other miscellaneous findings were seen to a variable extent in both groups without any reliable predictive value. CTPA revealed atleast one additional finding in 50% of patients in group B.

Among ancillary findings on CTV, enlarged lymphnodes, ascites, ventral hernias, lymphocele and mass involving the urinary bladder with sclerotic bone lesions were found in few cases of both groups of patients.

A clinical follow up and assessment of patient outcome was performed. In group A, 16/17(94.1%) patients received anticoagulant therapy as treatment for PE. 1 patient refused to take anticoagulant therapy as advised. Two group B patients were already on oral anticoagulants for pre-existing DVT. No other patient received anticoagulant therapy.

On 3 month follow up, 14/17(82.4%) and 6(42.9%) patients in group A & B respectively survived the initial episode. Overall, the two groups showed a statistically significant difference in survival (p=0.031).

No reactions to contrast media or any other complications were reported in the present study.

Discussion & Conclusion

DVT and consequently PTE needs to be realised as a major contributor to patient mortality and morbidity in the oncologic setup besides the malignant disease process

	Wedge shaped consolidation	Consolidation	Collapse	Lung nodules	Pleural effusion	Miscellaneous
Group A	5 (29.4%)	4 (23.5%)	1 (5.9%)	4 (23.5%)	7 (41.1%)	2 (11.8%)
Group B	0 (0%)	3 (21.4%)	5 (35.7%)	7 (50%)	7 (50%)	6 (42.8%)
p value	0.048	0.990	0.067	0.153	0.623	0.097

Table 8: Distribution of ancillary findings on CTPA in two groups

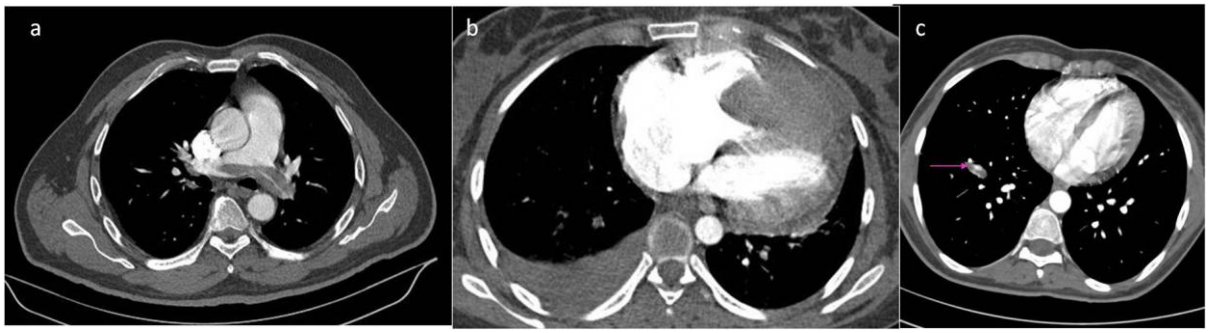

Fig 1: Spectrum of positive findings on CTPA- a) Saddle shaped thrombus, 1b) Thrombus in right ventricular cavity, c) Isolated right lower lobe segmental level pulmonary artery embolus

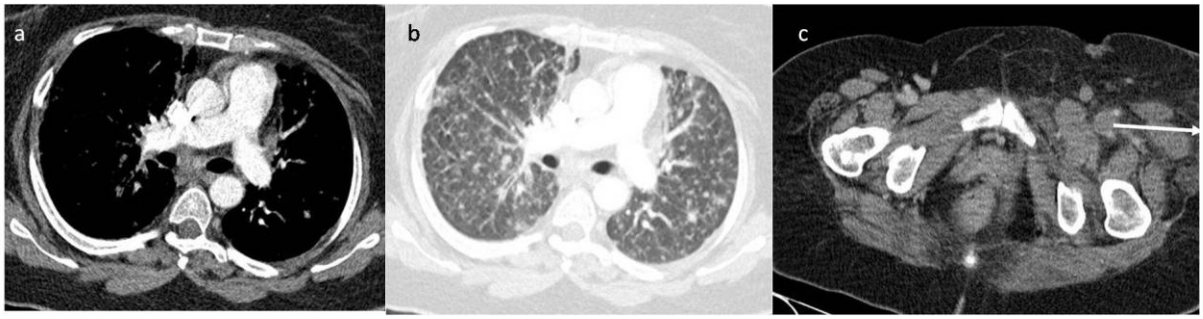

Fig 2: female with breathlessness and pedal odema, a) negative CTPA, b) bilateral lung nodules & parenchymal infiltrates, c) left CFV thrombus on ICTV

itself. Its timely diagnosis and institution of therapy can potentially prolong patient survival.

Sorensen et al[8] found that the 1-year survival rate for cancer patients with thrombosis was 12% compared with 36% in control patients (i.e., cancer patients without VTE) ($p< 0.001$). Patients with cancer have a higher risk of VTE as per Kakkar AK et al (2005)[5] and four- to eightfold higher risk of dying after an acute thrombotic event than patients without cancer as per Carson et al[9] and Prandoni P.[10] These studies highlight the relevance of effective pulmonary & venous thromboembolism diagnosis in this vulnerable group of patients.

History of recent surgery and presence of gastrointestinal or genitourinary primary malignancy were identified as risk factors for PTE in cancer patients in our study. Similar views were expressed in the studies by Martino MA et al (2006)[6] on cancer patients undergoing major abdominal surgery. Thus cancer patients in the post operative period

warrant a higher index of suspicion compared to the general population.
Immobilisation as a risk factor was universally present in both groups of patients included in the study.

Gastrointestinal and genitourinary malignancies were seen to be more frequently associated with the diagnosis of PE (76.5%) among the wide variety of malignancies encountered. Similar trend was observed in an autopsy series[24] which showed that among cases of PE in cancer patients, 75% occurred in patients with adenocarcinoma and 62% in those having tumors of the pancreas, breast, large bowel, prostate, lung, and ovary. One of every seven hospitalized cancer patients died not of cancer but of PE. 60% of all patients who died of massive PE had localized cancer or limited metastatic disease which would have allowed for reasonably long survival in absence of lethal PE.

Efforts for prompt and effective diagnosis of PTE are ridden with obstacles. Like the previous studies[25,26], none of the clinical symptoms or pre-test probability determined by Well's criteria were not found to be predictive of presence of PE in the present study. While such criteria for assessment of pre-test probability may appear to be useful in studies on the general population[21], the study by Pineda LA et al.[26] based on autopsy reports revealed that the current clinical syndromes used as markers for suspecting PE are not sufficient to detect patients who ultimately die of PE. Such criteria for pre-test probability appear to be less useful in high risk populations like cancer patients in the present study. Larger number of patients with intermediate & high pretest clinical probability require a more direct and reliable investigation like CTPA to diagnose or exclude PE. CTPA and ICTV proved to be a more decisive and direct approach than clinical findings and pretest clinical probability, chest radiography, ECG, d-Dimer and lower limb sonography for demonstrating and making the diagnosis of PTE and DVT in the present study.

The studies by Remy- Jardin et al[13,14] pioneered the role of spiral CT & CT angiography in the non invasive diagnosis of PE. They emphasized that spiral CT can reliably depict thromboemboli in second to fourth division pulmonary vessels and replace invasive pulmonary angiography for reliable diagnosis of PE.

A study by Gurney JW[15] further added that CT may be an ideal tool to diagnose suspected PE, obviating V/Q scanning entirely and markedly reducing the need for catheter based pulmonary angiography. Similar studies by Van Rossum et al[16] and Blachere et al[17] showed statistically significant differences in sensitivity, specificity, positive predictive value, and negative predictive value of CTPA and V/Q scan for PE. They suggested that helical CT angiography could replace V/Q scanning as the initial test for screening patients who are clinically suspected of having PE.

Among ancillary findings on CTPA in the present study, wedge shaped consolidation was found only among patients diagnosed with PE and is a known consequence of pulmonary infarction. Other parenchymal findings had no significant association with PE.

Also in cases where CTPA was negative for PE, CT findings still appeared useful in the

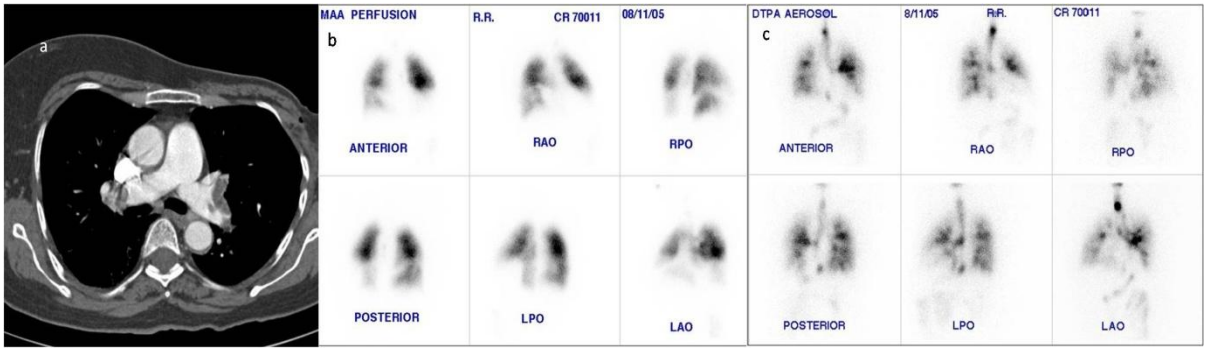

Fig 3a) CTPA showing bilateral pulmonary embolism correlating with mismatched perfusion defects on ventilation perfusion scan (b,c)

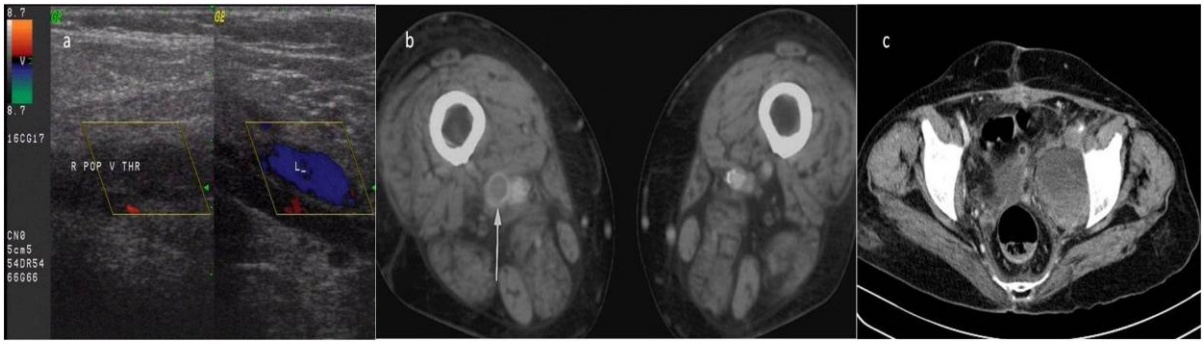

Fig 4 a) Venous doppler and CTV showing b) right popliteal v.thrombosis with c) left external iliac vein thrombosis & left iliac region lymphocele (additional finding)

clinical scenarios by describing additional findings (eg. parenchymal consolidation, lung collapse and pleural effusion) which possibly explain the patient's presenting symptoms and can modify the patient's management similar to the studies by Garg K et al.[18]

CTPA findings correlated well with lung scintigraphy findings (fig 3) wherever the later was performed. But the ease and shorter time required to perform CTPA, less dependence on clinical pretest probability and ability to offer alternative diagnosis in negative cases make CTPA a preferred investigation.

Loud et al[20] came up with the concept of combined CTPA & ICTV without administering any additional contrast to simultaneously evaluate for associated DVT. They showed that ICTV findings correlated well with VD and provided additional information about calf veins, deep femoral veins and areas poorly accessible to sonography including iliac veins and IVC (fig 4).

The studies by Garg K et al[27] and Loud et al[28] showed the combined approach (CTPA and ICTV) to be more efficacious than sonography or two separate examinations.

The use of combined CTPA & CTV is widely debated due to the additional radiation burden incurred by adding ICTV to CTPA protocol.[29] But there appears to be clear consensus among different workers that groups with higher risk of PE & DVT especially oncologic cases especially benefit from the combination. In a patient from this high risk group having a CTPA study

negative for PE, a negative CTV can prove reassuring that a possible source of thromboembolism for the near future has not been missed. The simultaneous detection of DVT in such patients still prompted initiation of anticoagulation therapy without need for additional imaging. Considering the higher possibility of DVT in oncologic setup, the ease of performing ICTV in the same sitting without additional contrast injection justifies the use of ICTV in this group of patients.

Rademaker et al analysed the additional radiation exposure incurred due to combination of CTPA and CTV.[30] Though CTV increases the gonadal dose by a significant factor, but the risk from incremental dose is low. The risk of radiation related death from leukemia is on the order of 1:8000 and a genetic risk of 1:15000 in patients of reproductive age group. The majority of patients in our study were beyond the reproductive age group (77.4%) patients were more than 40 years of age while 64.5% patients were more than 60 years of age). The benefit from diagnosis of VTE in these high risk patients outweighs radiation related risks. Still, the use of ICTV should preferably be avoided in younger patients.

In an attempt to lower the additional radiation dose from ICTV, we employed the protocol similar to Cham et al[23] by using 8mm wide sections for CTV with a pitch of 1:1. Using relatively thicker sections reduces the effective radiation dose while retaining diagnostic accuracy of CTV in diagnosis of DVT.[23]

Ability to deal with complete spectrum of DVT and PE using a single investigation makes CTPA & Indirect CT Venography 'one stop shop' imaging modality for VTE in the oncologic setup.

The significance of subsegmental emboli is a controversial, unsolved area of study.

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