Incidence Of Pulmonary Embolism And Mortality Of Upper-Extremity Deep Venous Thrombosis As Compared To Lower-Extremity Deep Venous Thrombosis In Cancer Patients

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Citation

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Abstract

BACKGROUND: The prevalence of upper-extremity deep venous thrombosis (UEDVT) and its associated factors in cancer patients with suspected pulmonary embolism (PE) remain unknown. The prevalence and mortality of UEDVT-related PE compared to that of lower-extremity deep venous thrombosis (LEDVT) are yet to be established. This study was conducted to investigate the period prevalence of UEDVT in cancer patients with suspected PE, to determine its associated factors, and differences with LEDVT, and to compare outcomes.

METHODS: A retrospective, cross-sectional study was performed at a tertiary-level cancer center by reviewing 132 patients with confirmed UEDVT, LEDVT, or both upper and lower DVT (BDVT) out of 291 patients with suspected PE whose charts, and pertinent imaging studies were reviewed.

RESULTS: Of the 132 patients with DVT, 74.2% had UEDVT, 16.7% had LEDVT, and 2.3% had BDVT. UEDVT was related to central venous catheters (CVC) in 36% of cases. Chemotherapy was frequently associated with UEDVT (P<0.001). PE was more frequently associated with LEDVT (p<0.001). Mortality associated with UEDVT-related PE (33%) was significantly higher (p=0.024) than that of UEDVT without PE (19%) and LEDVT with (17%) PE (p=0.014). There was no significant difference in mortality between UEDVT and LEDVT in patients without PE (p=0.85).

CONCLUSIONS: The UEDVT in cancer patients with suspected PE is highly prevalent. CVC and chemotherapy have a predominant role in the development of UEDVT. PE was more frequently associated with LEDVT; however, a significantly higher mortality rate was associated with UEDVT-related PE.

BDVT	Both upper and lower DVT
CVC	Central venous catheters
DVT	Deep venous thrombosis
LEDVT	Lower-extremities deep venous thrombosis
PE	Pulmonary embolism
PVC	Polyvinyle chloride catheters
UEDVT	Upper-extremities deep venous thrombosis
V/Q Scan	Ventilation-perfusion lung scanning

VTE Venous thromboembolism

INTRODUCTION

It is now accepted that pulmonary embolism (PE) and deep vein thrombosis (DVT) are two clinical presentations of the same disease: Venous thromboembolism (VTE) (1). Deep venous thrombosis (DVT) of the lower limbs is widely recognized as a leading cause of PE. Using sensitive methods to detect PE, approximately 50% of the patients with proved DVT of the lower extremity (LEDVT) have been found to have PE (2-6). By contrast, upper-extremity venous thrombosis (UEDVT) is much less common (7), and earlier clinical observations suggested that PE occurred rarely before invasive venous cannulation was widely used (8,9). Aggressive cancer treatment, blood products and antibiotics administration, and parenteral nutrition required externally or totally implanted central venous catheters (10,11). Thus, the relative incidence of UEDVT has increased in recent years (12,13).

Many cancers induce hematologic abnormalities that increase the risk of a hypercoagulable state and thromboembolic disease. The overall frequency of thrombosis in cancer patients has been estimated to be 5% to 15% (14,15). Tumors may directly or indirectly activate blood coagulation, cause extrinsic compression and venous stasis (16,17).

Few significant, retrospective clinical studies have evaluated the prognostic impact of UEDVT in the general population (18 -20). However, factors involved in the development of DVT and PE as well as significance of UEDVT in cancer population remains to be established.

The aim of this study was to investigate the period prevalence of UEDVT in cancer patients with suspected PE, to determine the associated factors, coexistence, and differences with LEDVT, and to compare their outcome based on the development of PE.

MATERIALS AND METHODS

We retrospectively reviewed the charts of 291 patients who underwent ventilation/perfusion lung scanning (V/Q Scan) for suspected diagnosis of PE seen as inpatients or outpatients at The University of Texas M.D. Anderson Cancer Center between January 1, 1994 and June 30, 1995. The diagnosis of DVT was done clinically by one or more of the following tests: Doppler ultrasound, contrast and/or nuclear venogram. All patients had undergone careful physical examination and recording of symptoms and signs suggestive of DVT (pain, swelling, redness) and PE (dyspnea, chest pain, hemoptysis). We obtained 132 cases that were clinically suspected to have DVT. After ruling out 9 cases, 123 had DVT either UEDVT (subclavian, axillary, or bilateral veins), LEDVT (common femoral, external iliac, superficial femoral, or popliteal veins) or both upper and lower DVT (BDVT). Data collected included: personal data, clinical characteristics, etiologies (catheter related, hypercoagulable state in malignant patients, and tumor compression either as superior vena cava syndrome or cervical or axillary compression), laboratory results, electrocardiogram, arterial blood gases, chest x-ray findings, V/Q Scan results, outcome, and autopsy results.

Statistical analysis: It was conducted to establish frequency distribution of site for DVT and associated etiology by PE development and mortality within three months of the diagnosis of each site for DVT, and type of therapy and underlying malignancy by site for DVT, respectively; besides the analysis was performed to prove statistical association using Chi square test between type of treatment and site for DVT an differences in mortality rates between sites for DVT or associated etiologies by development or not of PE. A p value of less than 0.05 was considered statistically significant using Fischer exact test or Yates correction when appropriate. All computations were processed by SPSS 8.0 (SPSS Inc., Chicago, IL) and EpiInfo 6.04 (WHO, Geneve, Switzerland).

Lung scan: Ventilation scans were performed with 15-30 mCi of Xe-133. Perfusion scans were obtained with 4 mCi of technetium-99m macroaggregated albumin. Methods of performance of ventilation and perfusion scans have been described in detail, as have been the criteria for interpretation (21).

This study was approved by the Surveillance Committee (Institutional Review Board) of The University of Texas M.D. Anderson Cancer Center. Because the study was retrospective, the Committee deemed not necessary to obtain informed consent.

RESULTS

The number of patients with confirmed diagnosis of DVT was 123 among 132 cases with clinical suspicion for

DVT, and consisted of 67 females (54.5%) and 56 males (45.5%), their ages (standard deviation) ranged from 18 to 82 years old (51.95 14.49). Edema of the extremity was the most common presenting complaint followed by pain. Physical examination usually revealed increased circumference of the limb, tenderness, prominent superficial veins, erythema and a palpable cord.

Table 1 shows frequency distribution of sites for DVT by etiology and pulmonary embolism development.

Table 1

Frequency distribution of sites for DVT by etiology and development of pulmonary embolism

Site for DVT	Catheter	Tumor	Hypercoagulability	Total		PE	
				N	%	N	%
UEDVT	35	10	53	98	74.2	3	3
LEDVT	0	2	20	22	16.7	12	54
BDVT	0	1	2	3	2.3	2	66
No DVT	0	0	9	9	6.8	1	11
Total	35	13	84	132	100	18	13.6

These data proves that PE was more frequently associated with LEDVT than UEDVT or BDVT (p< 0.001).

UEDVT was more frequently associated with the left (52.8%) than the right side (27.6%). A bilateral involvement of the upper limbs was seen in 20.3% of the UEDVTs. Catheters were preferred in the left side due to the less anatomical variation.

Table 2 shows the frequency distribution of type of malignancy by site for DVT.

Table 2

Frequency distribution of type of malignancy by site for DVT

Type of Malignancy	UEDVT N = 98	LEDVT N = 22	BDVT N = 3
Lymphoma	19.4	13.6	0
Breast Cancer	20.4	4.5	33.3
Pulmonary Cancer	10.2	22.2	0
Leukemia	17.3	4.5	0
Gastrointestinal Cancer	9.2	23.2	33.3
Genitourinary Cancer	9.2	23.2	33.3
Sarcomas	8.2	9.2	0
Other Cancers	10.2	18.4	33.3

*All frequencies are expressed in percentages

Table 3 reveals the frequency distribution of type of therapy by sites for DVT that patients received within the last three months.

Table 3

Frequency distribution of type of therapy by site for DVT

Type of Therapy	UEDVT N = 98	LEDVT N = 22	BDVT N = 3	Total N = 123
Chemotherapy	71.4	40.9	0	64
Radiotherapy	4.1	13.6	0	5.7
Surgery	7.2	40.9	66.7	14.7
No therapy associated	17.3	4.6	33.3	15.6

*All frequencies are expressed in percentages

These data proves that UEDVT was more frequently associated with chemotherapy than with LEDVT (p< 0.001).

Table 4 shows Outcome of PE by site for DVT.

Table 4

Outcome of PE by site for DVT

	PE Present			PE Absent			Comparative
Site for DVT	Survivors	Dead	Mortality	Survivors Mortality	Dead		p value
UEDVT	2	1	33%	77	18	19%	0.024
LEDVT	10	2	17%	8	2	20%	0.580
BDVT	0	1	100%	1	1	50%	< 0.01
No DVT	1	0	0%	6	2	25%	

*Only Mortality Rate is expressed as percentage. Mortality rates are compared by site for DVT according to development of PE and by using Chi Square test (p value).

These data illustrates that patients with BDVT had significantly higher mortality rates than the other groups eithejr with PE (p< 0.001) or without PE (p=0.046). The mortality rate in UEDVT patients with significantly higher (p < 0.001) as they progressively developed PE or BDVT (19%, 33%, 50%, and 100%, respectively). This difference was not significant for disease progression in LEDVT cases (p = ????). In patients with PE, UEDVT cases had significantly higher mortality rates than LEDVT ones (p=0.014). Conversely, in patients without PE, UEDVT cases had a similar mortality rate to that of LEDVT ones (p = 0.85).

Table 5 displays the outcome of development of PE in UEDVT by etiology.

Table 5

Outcome of Development of PE in UEDVT by Etiology

	PE Present			PE Absent		
Etiology	Survivors	Dead	Mortality	Survivors	Dead	Mortality
Catheter	1	1	50%	27	6	18%
Tumor	0	0	0%	7	3	30%
Hypercoagulability	1	0	0%	43	9	17.3%
Total	2	1	33%	77	18	19%

*Only Mortality Rate is expressed as percentage

These data reveals that mortality associated with PE secondary to catheter-related UEDVT was significantly higher ($p<0.001$) than other causes of UEDVT. However, tumor related mortality was significantly higher ($p = 0.046$) than other etiologies when PE was absent.

DISCUSSION

In the present study, the period prevalence of UEDVT in cancer patients with suspected PE was 74.2%. The factors associated with UEDVT were hypercoagulable states followed by central venous catheter (CVC) placement as opposed to hypercoagulation and tumor compression in LEDVT cases. Breast cancer, lymphoma, and leukemia were more frequent among UEDVT patients as opposed to lung and genitourinary cancer in LEDVT ones. The main complication of DVT, PE, was more frequently associated with LEDVT. However, except for the highest BDVT related mortality, a significantly higher mortality rate was seen among UEDVT patients with PE than in those without PE or with LEDVT. Conversely, mortality among patients without PE was similar between UEDVT and LEDVT.

In UEDVT, catheter-related cases had a significantly higher mortality when PE developed. Conversely, tumor compression had the worst outcome when mortality was not associated with PE.

In relation to therapy, chemotherapy was more frequently associated with UEDVT. However, surgery and chemotherapy were the most frequent treatment modalities among LEDVT patients.

The high prevalence of UEDVT in suspected cases of PE, first reported in our study to the best of our knowledge, is related to the nature of our cancer population in whom exists, among other factors such as the use of polyvinyle chloride (PVC) catheters, a well-documented prothrombotic condition and frequent use of drug delivery systems such as CVC (16,22). The common use of chemotherapy and radiotherapy such the one required in the frequently observed cases of breast cancer, lymphoma, and leukemia explains the higher prevalence of UEDVT. Veno-occlusive disease and late thrombosis have been described after the use of radiation (23,24).

Although in the retrospective design of our study we have observed the prothrombotic state as a more frequent cause of thrombosis than CVC (usually asymptomatic and frequently reinserted), we sustain that the former condition may be an expression of the subclinical vascular damage, partial thrombosis secondary to CVC placement or radiation that may evolve into late thrombosis with clinical manifestations (23-26). Thus, future prospective studies to understand this phenomenon are still needed.

One of the differences between UEDVT and LEDVT is their second most frequent cause: CVC and tumor obstruction, respectively. The less infectious complications and easier utilization has made upper-limb catheters the most preferred. This explains the more prevalent catheter related thrombosis in upper extremities as reported previously as well (7,18,26,27). The Virchow's triad of altered blood flow, blood constituents, and vessel wall may be a consequence of CVC insertion (13,28). Moreover, the higher prevalence of PE in LEDVT than in the arm has been hypothesized to be due to the larger amount of blood, the presence of a calf pump that may easily dislodge thrombi, and its lower fibrinolytic activity (18). Conversely, the fewer and smaller venous valves, less cessation of limb motion, and smaller size of the veins in upper extremities favor its decreased predisposition to thrombosis (28-31). Yet, fatalities are more significant among UEDVT-related PE patients, predominantly among those with CVC as seen in our population. We believe that this critical difference is related to the severity of the underlying illness, which may have been able to overcome the stability of the arm vein thrombi causing it to embolize. Our findings of highest mortality in BDVT patients with PE and lowest mortality in UEDVT without PE, correlate clinically with a continuum of disease progression and severity.

In terms of treatment modalities, chemotherapy had a significant association with UEDVT, most likely secondary to its immediate contact with the upper venous system. Chemotherapeutic agents may release procoagulants and cytokines from targeted tumor cells, damage vascular endothelium, and decrease anticoagulants partially due to hepatotoxicity (17). Besides, drugs used in marrow

transplant (such as for breast cancer, lymphoma, or leukemia) are reported to cause veno-occlusive disease (17). Conversely, the more frequent genitourinary cancer seen in LEDVT cases may explain the association between surgery and LEDVT. Surgery is a precipitating factor for thromboembolic disease postoperatively (17).

Previous reports have acknowledged the use of CVC as the most common cause of UEDVT (18,26,32). However, a reference bias exists in our study population that is reflected in the hypercoagulable state of cancer as the most common cause of UEDVT. We have observed that 37% of UEDVT cases are catheter related in cancer patients. This finding is similar to that reported by other authors in cancer and non-cancer patients (18,32,33).

As seen in our study, PE has repeatedly been reported as more frequent between LEDVT than UEDVT patients (18,34). Prospective studies have reported a higher prevalence of PE in UEDVT than retrospective ones probably due to under-reporting in the latter designs (18,22). Similarly, mortality rates have been reported as higher in patients with PE related to UEDVT than LEDVT with or without concomitant malignancy, although being even higher among patients with neoplasms as previously reported within six months of the diagnosis of UEDVT or LEDVT (20). The fact that mortality in UEDVT-related PE is lower than that associated with coexistent upper and lower extremity DVT has led Hingorani et al to propose a mechanism of severity of underlying illness to explain the worse prognosis reported in UEDVT-related PE patients (19). Few objective data on this matter has been reported previously (20,35,36). Our results, although from a different perspective, help clarify that UEDVT patients have a much higher mortality as they start worsening in their clinical condition and proportionally impairing the anti-thrombogenic state of upper limb veins, which is expressed in our study analysis as significantly higher mortality with superimposed PE or LEDVT. Furthermore, in UEDVT patients without PE, the main cause of mortality was due to tumor obstruction, which implies the presence of advanced disease as well.

We first report comparatively treatment modalities in relation to development of DVT. In our study, chemotherapy and surgery have been seen more frequently in UEDVT and LEDVT cases respectively. Other authors have pointed out the development of UEDVT in the use of radiation and chemotherapy (23,24,27,37).

Additionally, catheter materials and properties are important to consider in thrombogenesis and mechanical complications predisposing to UEDVT. Various authors reported a significantly higher frequency of PE in patients with PVC catheters than with polyurethane or siliconized catheters (25,31).

In view of all these data, we suggest that bigger efforts should be made to improve catheter biocompatibility and establish consensus guidelines in the management of CVC in an attempt to reduce the important mortality rates, especially among cancer population, related to UEDVT as the clinical benefit has been indicated previously by the prophylactic use of low-dose warfarin or low-molecular weight heparin (26,39-41).

The limitations encountered in our study were diagnosis bias of DVT due to its retrospective design and lack of specificity of venogram and ultrasound studies. The lack of activated markers of clotting and fibrinolysis impeded our findings to clearly prove the relationship between hemostasis impairment and disease severity.

CONCLUSION

The high prevalence of UEDVT in cancer patients with suspected PE is mainly due to secondary thrombosis (hypercoagulable state followed by CVC use in frequency). PE was more frequently associated with LEDVT; however a significantly higher mortality rate was associated with catheter-related UEDVT and worsening medical illness in UEDVT patients. In UEDVT cases, CVC use was the only factor associated with mortality among those with PE as opposed to being second to neoplastic obstruction as factor associated with mortality in those without PE. CVC and chemotherapy have a predominant role in the development of UEDVT.

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