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Early venous thromboembolic events are associated with worse prognosis in patients with lung cancer

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Abstract

Objectives—Venous thromboembolic events (VTE) are a leading cause of death in cancer patients. We hypothesized that early VTE (EVTE, within 3 months of diagnosis) in patients with lung cancer (LC) are associated with worse overall survival (OS).

Materials and methods—We identified 727 patients with LC between 1998 and 2011. Late VTE (LVTE) were defined as VTE occurring after 3 months from LC diagnosis. Advance disease (AD) was defined as patients with Stage IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer (SCLC), and non-advanced disease (non-AD) was defined as Stage III NSCLC or limited stage SCLC.

Results—Out of 727 patients included in our review, 617 patients had NSCLC (85%), 94 (13%) SCLC, and 16 (2%) low grade neuroendocrine tumors. Ninety five patients (13%) experienced VTE, 44 (6%) experienced an EVTE and 49 (7%) had a LVTE. Patients with an EVTE had worse OS when compared to all other patients (medians 4 vs. 17 months, $p < 0.0001$). EVTE were associated with worse OS in patients with non-AD (medians 12 vs. 42 months, $p = 0.01$) and AD (medians 4 vs. 6 months, $p = 0.02$). When considering patients with NSCLC only, in a multivariate model that included age, stage, performance status > 2 , administration of chemotherapy and Charlson comorbidity index, EVTE were an independent predictor of increased mortality (HR 2.4; 95% CI 1.6–3.3).

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Contributions

Conception and design: A.T. and A.M. Provision of study materials of patients: All authors. Collection and assembly of data: All authors. Data analysis and interpretation: T.K, E.W., A.M., A.T. Writing of manuscript: All authors. Final approval of manuscript: All authors.

Conflicts of interest

The authors have declared no conflicts of interest.

Conclusions—EVTE are associated with worse OS, irrespective of stage of the disease. Our findings underscore the need for an efficient preventive strategy for VTE among patients with lung cancer.

Keywords

Incidence; Lung neoplasms; Prognosis; Thrombosis; Venous thromboembolism

1. Introduction

Venous thromboembolic events (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), are a leading cause of morbidity and mortality among cancer patients [1,2]. As many as one in five patients with VTE also has a concurrent diagnosis of a malignancy [3]. Patients with lung cancer are at a particularly high risk for VTE when compared to other tumor types, and if one considers its high prevalence, lung cancer may be responsible for one of the highest incidence of thrombotic events associated with cancer [4].

VTE have been associated with worse prognosis among patients with solid malignancies [5,6], although it remains unclear whether VTE constitute an independent predictor of worse survival in this patient population or merely represent surrogates of more advanced malignancies overall. Primary prevention is effective in decreasing the incidence of cancer associated VTE [7]; however, the optimal timing and patient population that would most benefit from outpatient thromboprophylaxis is not well defined [8,9]. As a result, thromboprophylaxis is not routinely indicated in ambulatory patients with solid malignancies [10]. Furthermore, the majority of VTE events seem to occur within the first year after the diagnosis of cancer and there is evidence to suggest that early VTE might carry a worse prognosis in patients with newly diagnosed malignancies [11]. In an effort to clarify the impact of VTE on the prognosis of patients with lung cancer, we hypothesized that early VTE, occurring within 3 months of diagnosis, are associated with worse overall survival.

2. Methods

From a prospectively maintained lung cancer database, we retrospectively identified and reviewed 727 patients with lung cancer that were treated at the Mayo Clinic between January 1998 and December 2011. The Mayo Foundation Institutional Review Board approved the study, and all patients consented to have their medical records reviewed. The diagnosis of lung cancer was established after histological examination of biopsy specimens by a Mayo Clinic pathologist in all cases. Clinical and laboratory data as well as VTE occurrences were extracted after review of the electronic health records. The Charlson comorbidity index was calculated as previously described and comorbidities required to calculate the index were abstracted from the clinical charts [12]. ECOG performance status (PS) was considered as a dichotomous variable (> 2 or ≤ 2), since there was not always enough clinical information available in the charts to classify patients with a PS ≤ 2 further. Medication use thought to be associated with a higher risk of VTE was also abstracted and included: erythropoietin stimulating agents (ESA) [13], estrogen and progestin containing

medications [14], tamoxifen [15] and bevacizumab [16]. Overall survival follow-up was complete for all patients.

Diagnosis of DVT was confirmed in all cases by venogram, computed tomographic (CT) scan or magnetic resonance imaging scans. Diagnosis of PE was confirmed in all cases by pulmonary angiography, or CT angiography. Early VTE (EVTE) were defined as VTE occurring within 3 months from lung cancer diagnosis [11,17]. Late VTE (LVTE) were defined as VTE occurring after 3 months from lung cancer diagnosis and prior VTE (PVTE) as VTE occurring 3–12 months prior to their diagnosis of lung cancer. Patients who were already on anticoagulation prior to their lung cancer diagnosis were excluded, with the exception of patients with a PVTE on anticoagulation. Advanced disease was defined as patients with Stage IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer (SCLC), and non-advanced disease was defined as Stage III NSCLC or limited stage SCLC. For patients diagnosed after January of 2010, the 7th edition of the tumor node metastasis (TNM) staging system was used [18].

Survival was estimated by the Kaplan-Meier method. The Pearson chi-square test and the Kruskal-Wallis test were used to ascertain differences between nominal and continuous variables, respectively. A Cox proportional hazard regression model was used for multivariable analysis. *p* values less than 0.05 were considered significant. All statistics were done using JMP software (SAS, Carey, NC).

3. Results

Out of 727 patients, 617 patients had NSCLC (85%), 94 had SCLC (13%) and 16 had low grade neuroendocrine tumors (2%). Ninety five patients (13%) experienced VTE, of which 44 (6%) experienced an EVTE and 49 (7%) had a LVTE. Two patients had a PVTE 5 and 9 months prior to lung cancer diagnosis. The timing of VTE occurrence is shown in Fig. 1. Approximately two-thirds of VTE occurred within a year from diagnosis. The patients' clinical and laboratory features with and without EVTE are shown in Table 1. Patients with EVTE were more likely to have advanced disease (67% vs. 39%, $p < 0.001$), a higher Charlson comorbidity index (8 vs. 6, $p = 0.02$) and to have received chemotherapy within 60 days from lung cancer diagnosis (55% vs. 39%, $p = 0.04$). When considering the whole cohort, 13 VTE (14%), were discovered incidentally during imaging and were not associated with any symptoms. With a median follow-up of 15 months (range 0–191 months), overall survival of patients with incidental VTE was not significantly different from that of patients with symptomatic VTE (18 months vs. 11 months, $p = \text{NS}$). Thirty four VTE (36%) were PE, 35 (37%) DVT, 6 (6%) both PE and DVT, 15 (16%) upper extremity DVT and 5 (5%) were VTE of other venous systems. Seven (7%) patients had a major surgery within 4 weeks of their VTE and 8 (8%) patients had venous compression from masses (primary tumor or, more frequently, metastatic disease) resulting in venous stasis in the thrombosed venous system. Twenty-six (27%) patients had an acute infection within 2 weeks from VTE diagnosis and 6 patients with an upper extremity VTE had a central venous catheter at the time of VTE.

Patients with an EVTE had worse OS when compared to the rest of the group (medians 4 vs. 17 months, $p < 0.0001$) (Fig. 2a). EVTE were associated with worse OS in patients with non-advanced disease (medians 12 vs. 42 months, $p = 0.01$) and advanced disease (medians 4 vs. 6 months, $p = 0.02$) (Fig. 2b and c, respectively). Since Stage IIIB disease is frequently considered together with Stage IV in NSCLC as advanced disease, in a separate set of analyses, we found that EVTE were associated with worse OS in patients with Stage IV/IIIB/extensive SCLC as well as Stage I/II/limited SCLC disease (data not shown). When considering patients with non-advanced disease, 60% of patients with early VTE had died within a year of diagnosis as opposed to only 30% of patients without an early VTE. Patients with non-advanced disease and EVTE included mostly Stage III patients (5 Stage IIIB, 4 Stage IIIA) and 1 patient with limited stage SCLC. In patients with advanced disease a similar trend was noted, with 6 month mortality in the EVTE group of 48% as opposed to 30%. Although the exact cause of death for each case was not abstracted, none of the 40 deaths were clinically attributed to VTE and all were clinically attributed to progressive disease. No patients had autopsies performed and 6 patients died within a month of VTE. Out of 44 patients, 10 were on chemotherapy when EVTE were diagnosed; out of these only 2 had to interrupt chemotherapy because of reasons directly related to EVTE, 6 continued their treatment and 2 interrupted treatment for reasons unrelated to EVTE.

We then considered outcomes of patients with non-EVTE (LVTE/PVTE) separately. OS of patients with non-EVTE was not significantly different than that of patients with no VTE (25 months vs. 16 months, respectively, $p = 0.26$). This was also true for OS of patients with non-advanced disease (median OS for non-EVTE vs. no VTE, 41 vs. 43 months, respectively, $p = 0.76$). When considering patients with advanced disease, OS of patients with non-EVTE was better than that of patients with no VTE (20 vs. 5 months, $p = 0.002$). When considering the baseline clinical and laboratory characteristics shown in Table 1, patients with non-EVTE were younger; median age non-EVTE: 63 years vs. EVTE: 68 years and no-VTE 69 years respectively, $p = 0.002$. Patients with non-EVTE were more likely to have received chemotherapy within 60 days from lung cancer diagnosis; 64% for non-EVTE, 55% for EVTE, 37% for no VTE, $p = 0.0001$. No other baseline demographics were different between non-EVTE and patients with no VTE or EVTE (Table 2).

Since NSCLC is considered by some to be more thrombogenic [19], we then considered only patients with NSCLC for the remaining analyses. EVTE were associated with worse OS in patients with stages I–III disease (medians 12 vs. 46 months, $p < 0.001$) as well as patients with Stage IV disease (medians 3 vs. 5 months, $p < 0.01$). In order to elucidate interactions between EVTE and other prognostic variables, univariate and multivariate analyses were performed. On univariate analysis OS was associated with age, stage, ECOG PS > 2 , Charlson comorbidity index, chemotherapy administration at lung cancer diagnosis and EVTE ($p < 0.0001$ for all). Chemotherapy could be considered as a surrogate for advanced stage disease but given some evidence to suggest it might be an independent predictive factor for VTE [20] we included it in our multivariate analyses. In a multivariate model that included age, stage, administration of chemotherapy, performance status > 2 and Charlson comorbidity index, EVTE were an independent predictor of increased mortality (HR 2.3; 95% CI 1.6–3.3).

4. Discussion

In this study we demonstrate that EVTE are associated with worse OS independent of the stage of the disease. Additionally, in our series, we found that VTE occur in more than one in ten patients with lung cancer. Approximately half of them occur within 3 months from diagnosis of lung cancer, and the majority of them are symptomatic rather than incidentally discovered. Not unexpectedly, VTE are more common among patients with advanced disease.

The incidence of VTE in this study is similar to what has been reported in the literature [5,21]. Although this incidence is not as high as in other solid malignancies (e.g. pancreatic cancer [22]), lung cancer remains among the most prevalent malignancies and therefore maybe among the most common causes of cancer associated thrombosis [4]. It has been shown that VTE within the first year of diagnosis are more common in lung cancer [17,21] as well as other malignancies [23]. In some cases, VTE diagnosed immediately prior to the diagnosis of a solid malignancy confer a poor prognosis [6]. Although a higher incidence of VTE might serve as a surrogate of a less fit patient population (more comorbidities, worse performance status, more advanced stages of disease) or delayed diagnosis, our results suggest that EVTE is a powerful and independent predictor of worse survival outcomes. Notably, most deaths associated with EVTE occurred early in our cohort of patients. While this was not as striking for patients with metastatic disease, in patients with non-metastatic, potentially curable disease, 1 year mortality was twice as high in the EVTE group. Although the exact cause of death was not abstracted, none of these patients' deaths were attributed to EVTE. This suggests that EVTE may be an additional marker of aggressive disease biology and its early occurrence could help clinicians to refine the prognostication of this group and potentially alter management, e.g. recommend adjuvant chemotherapy in the non-advanced disease group or pursue early clinical trial participation in the advanced disease group. Furthermore, this observation is in line with the hypothesis that circulating tumor cells, in addition to facilitating metastatic spread, might also play a role in the hypercoagulable state seen in many malignancies [24]. Since an autopsy was not performed on any patient, it is conceivable that the six patients' deaths that were noted within 30 days of VTE might have been related to VTE.

The relative prognostic significance of EVTE is underlined but the fact that the outcomes of patients that experience a late VTE (> 3 months from lung cancer diagnosis) or a prior VTE (more than 3 months and up to a year before diagnosis of lung cancer) were not significantly different than those of patients who never had a VTE. In fact, patients with advanced disease and late VTE lived longer than those with an EVTE, which likely reflects the fact that these patients survived long enough to experience a late VTE.

Chemotherapy is also considered an additional risk factor for VTE in cancer patients [20,25,26] and higher incidence of VTE early after initiation of chemotherapy has been demonstrated in the past [17]. Here, we demonstrate that EVTE is predictive for worse outcomes irrespective of chemotherapy administration. Finally, patients with symptomatic VTE had similar outcomes compared to those with incidentally discovered, asymptomatic VTE, which is consistent with what has been reported so far [27].

Limitations of our study include its retrospective nature and the relatively smaller number of patients compared to similar studies that utilized medical claims registries. Furthermore, approximately half of our patients were diagnosed after 2006, when adjuvant chemotherapy was starting to become more widely adopted [28]. However, the proportion of patients diagnosed before and after 2006 was well balanced between patients with and without EVTE. We did not abstract specific causes of death and autopsies were not performed on patients. Furthermore, we did not abstract VTE treatment type and duration as well as lung cancer relapse data. In addition some of the patients in our cohort were staged using the 6th edition of the TNM staging system. The major changes in the 7th edition were the reclassification of malignant pleural effusions and separate tumor nodule(s) (previously called satellite nodules) as metastatic disease [18]. Finally, the patient population seen at the Mayo Clinic might not accurately represent what is seen in the community. For instance, more than a half of patients usually present with Stage IV disease (32% in our study) and approximately 1/5 present with Stage I disease (29% in our study) [29]. This probably is a reflection of the fact that many patients with limited disease present for consideration for surgical resection in centers of expertise (i.e. referral bias).

Strengths of our study include the fact that our cohort's characteristics, including stage, comorbidities, medication use, treatment and timing of VTE were complete and accurately defined.

In conclusion, we demonstrate for the first time that early VTE are associated with worse mortality independent of lung cancer stage. We also show that early VTE account for approximately half of VTE in this patient population. We propose that this group of patients needs to be identified for participation in thromboprophylaxis clinical trials to determine optimal prophylaxis strategies. This is becoming more and more relevant with the advent of new anticoagulants and possibility of different prophylactic strategies. Finally, since early VTE might be a surrogate for more aggressive disease biology, that has early metastatic potential, we believe with further validation it may warrant consideration as a separate risk factor in addition to stage for the purpose of clinical trial participation in lung cancer therapeutics. For instance, the incidence of early VTE should be reported separately and could be considered during randomization of patients to novel lung cancer treatment approaches.

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Abbreviations

DVT	deep venous thrombosis
ESA	erythropoietin stimulating agents
EVTE	early venous thromboembolic events

LVTE	late venous thromboembolic event
NSCLC	non-small cell lung cancer
OS	overall survival
PS	performance status
PVTE	prior venous thromboembolic event
SCLC	small cell lung cancer
VTE	venous thromboembolic event

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Fig. 1.
Timing of thrombosis from diagnosis of lung cancer.

Fig. 2.
Overall survival of patients with and without early venous thromboembolic events (VTE).

Table 1

Demographics and clinical characteristics of patients.

<i>N</i> = 727	No early VTE ^a (<i>N</i> = 683)	Early VTE (<i>N</i> = 44)	<i>p</i> value
Median (range)			
Male, <i>N</i> (%)	353 (52%)	23 (53%)	NS
Age, years	69 (30–95)	68 (40–91)	NS
Diagnosed after 2006, <i>N</i> (%)	298 (44%)	23 (53%)	NS
Stage I (<i>N</i> , %)	209 (31%)	3 (7%)	0.0001
Stage II (<i>N</i> , %)	38 (6%)	0	NS
Stage IIIA (<i>N</i> , %)	63 (9%)	5 (12%)	NS
Stage IIIB (<i>N</i> , %)	60 (9%)	4 (9%)	NS
Stage IV (<i>N</i> , %)	207 (30%)	24 (55%)	0.0003
Limited (<i>N</i> , % of ALL)	29 (4%)	1 (2%)	NS
Extensive (<i>N</i> , % of ALL)	58 (9%)	5 (12%)	NS
Stage IV/extensive	265 (39%)	29 (67%)	<0.001
Histology			
NSCLC	566 (83%)	36 (84%)	NS
SCLC	87 (13%)	6 (14%)	NS
Neuroendocrine	28 (4%)	1 (2%)	NS
OTHER	3 (0.4%)	0	NS
Charlson comorbidity index	6 (2–16)	8 (2–15)	0.02
ECOG performance status > 2	30 (5%)	2 (5%)	NS
BMI	25.5 (14.4–53)	26 (18–39)	NS
Chemotherapy within 60 days of lung cancer diagnosis	259 (39%)	24 (55%)	0.04
Use of high risk medications	44 (7%)	2 (5%)	NS
Concurrent active malignancy	23 (3%)	0	NS

VTE: venous thromboembolic events; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; BMI: body mass index; high risk medications: erythropoietin stimulating agents, estrogen and progestin containing medications, tamoxifen and bevacizumab.

^aIncludes patients with no VTE and patients with a late (> 3 months from diagnosis of lung cancer) or a prior VTE (3 months prior and up to 12 months before diagnosis of lung cancer).

Table 2

Univariate and multivariate survival analyses for patients with early venous thromboembolism (VTE).

Prognostic factor	Univariate analysis		Multivariate analysis	
	Risk ratio (95% CI)	<i>P</i>	Risk ratio (95% CI)	<i>P</i>
Age	2.9 (1.7–4.7)	<0.0001	1.7 (0.8–3.5)	NS
Stage	8.9 (6.9–11.4)	<0.0001	8.4 (6–11.8)	<0.0001
Chemotherapy within 60 days of lung cancer diagnosis	1.6 (1.3–1.9)	<0.0001	0.7 (0.6–0.85)	0.0009
ECOG performance status > 2	2.9 (2–4.1)	<0.0001	1.4 (0.89–2.17)	NS
Charlson comorbidity index	1.3 (1.26–1.35)	<0.0001	4.8 (2.1–11)	0.0002
Early VTE	2.3 (1.6–3.1)	<0.0001	2.4 (1.6–3.3)	<0.0001