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Advanced nodal stage predicts venous thromboembolism in patients with locally advanced non-small cell lung cancer

Richard Li[a,b], Gretchen Hermann[a], Elizabeth Baldini[a,b], Aileen Chen[a,b], David Jackman[b,c], David Kozono[a,b], Paul Nguyen[a,b], Anju Nohria[b,d], Graham Powell[a], Raymond Mak[a,b,*]

[a] Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, United States
[b] Harvard Medical School, Boston, MA, United States
[c] Lowe Center for Thoracic Oncology, Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States
[d] Department of Medicine, Cardio-Oncology Program Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, United States

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ABSTRACT

Objectives: Patients with non-small cell lung cancer (NSCLC) are known to be at high risk for venous thromboembolism (VTE), but previous studies have not specifically analyzed locally advanced disease. We performed a retrospective VTE risk analysis in a cohort of locally advanced NSCLC treated with definitive intent including radiation therapy.
Materials and methods: The cohort consisted of 629 patients with stage II–III NSCLC treated at a single institution from January 2003 to December 2012. All patients received treatment with curative intent, including radiation therapy. Fine and Gray's competing-risks regression model, accounting for death and distant metastasis as competing risks, was used to identify significant predictors of VTE risk, and cumulative incidence estimates were generated using the competing-risks model.
Results and conclusion: At a median follow-up of 31 months, 127 patients developed a VTE, with 80% of events occurring in the first year after treatment initiation. 1-year and 3-year overall cumulative incidence estimates were 13.5% and 15.4%, respectively. On univariate analysis, stage IIIB and N3 nodal disease were associated with increased VTE risk. In the final multivariable model, N3 nodal disease was associated with increased VTE risk (Hazard ratio 1.64; 95% CI 1.06–2.54; p = 0.027). In conclusion, patients with locally advanced NSCLC are at high risk for VTE, especially in the first year after treatment initiation, with a 1-year cumulative incidence of 13.5%. N3 nodal staging was associated with significantly higher VTE risk compared to N0-N2 staging.

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1. Introduction

Patients with an underlying malignancy have a markedly elevated incidence of venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE), with previous studies estimating up to a 7-fold increase in risk compared to healthy controls [1,2]. Development of VTE in cancer patients has been linked to significant morbidity and worse overall prognosis [3,4].

The risk of VTE with malignancy varies according to the primary site of the cancer, with lung cancer being among the highest risk [5–8]. Early analyses of large inpatient registries estimated VTE incidence rates in lung cancer patients to be between 1.4% and 7.0% [7,9–11]. More recent studies have found an even higher incidence of VTE in the outpatient setting, with estimates ranging from 7% to 13% [12–18]. A number of clinical predictors for increased VTE risk have been identified—including race [9], receipt of surgery and chemotherapy [17,19], receipt of VEGF inhibitors [20], and advanced stage [16,17]. Histologic subtype appears to be an independent risk factor for VTE as well, with NSCLC, particularly adenocarcinoma, conferring a higher risk than small cell lung cancer (SCLC) [9,21].

Previously published studies have analyzed highly heterogeneous populations of lung cancer patients, including both SCLC and NSCLC patients or including patients with all stages (I–IV) of NSCLC. Our study focuses on a cohort of locally advanced (stage II–III) NSCLC patients treated with radiation therapy (RT). These patients represent a substantial proportion of those with lung

* Corresponding author at: Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, 75 Francis St Boston, MA 02115, United States.
E-mail address: rmak@partners.org (R. Mak).

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Table 1
Summary statistics of overall patient cohort.

Characteristic	No. of patients (N = 629)	%
Age, years		
Median	64	
Range	28–88	
Sex		
Male	304	48.3
Female	325	51.7
Smoking status		
Current	251	37
Former (quit >1 year ago)	355	53
Never	65	10
Performance status		
0	214	34.0
1	357	56.7
2+	58	9.3
Overall stage		
IIA	37	5.9
IIB	32	5.1
IIIA	353	56.1
IIIB	207	32.9
Nodal stage		
N0	60	9.5
N1	89	14.1
N2	328	52.1
N3	152	24.2
Tumor stage		
T0	47	7.4
T1	123	19.6
T2	188	29.9
T3	134	21.3
T4	137	21.8
Initial tumor status		
New primary	554	88
Treated for recurrence	75	12
Tumor grade		
Well-differentiated	9	1.4
Moderately differentiated	147	23.4
Poorly differentiated	312	49.6
Not available	160	25.4
Histology		
NSCLC NOS	123	19.6
Squamous cell carcinoma	181	28.8
Adenocarcinoma	325	51.6
Received surgery		
No surgery	324	51.5
Surgery upfront	136	21.6
Surgery after neoadjuvant RT	169	26.9
Chemotherapy sequencing		
Concurrent chemoradiation	539	85.7
Sequential chemoradiation	59	9.4
No chemotherapy	31	4.9
Overall treatment regimen		
RT alone	17	2.7
RT with surgery	14	2.2
Chemoradiation alone	307	48.8
Chemoradiation with surgery	291	46.2

cancer and have a poor prognosis despite treatment with aggressive multimodality therapy, with 5-year overall survival of 9–36% depending on stage [22]. Patients with locally advanced NSCLC may be at increased risk for VTE, as standard of care therapy typically includes both chemotherapy and radiation therapy (RT) [23].

To the best of our knowledge, no published studies have been performed assessing the VTE risk specifically in patients with locally advanced NSCLC. Thus, we performed a large retrospective analysis of 629 patients with stage II–III NSCLC treated with RT. Our aim was to estimate the risk of VTE and to identify clinical predictors of the risk of VTE development in the locally advanced NSCLC population.

2. Materials and methods

2.1. Patients

An IRB-approved retrospective medical record analysis was conducted on all stage II–III NSCLC patients who presented to our institution with diagnosis dates between January 2003 to December 2012 and treatment with definitive intent including radiation therapy (>45 Gy) (n = 673). Patients who initiated but did not complete radiation therapy due to death, disease progression, or toxicity were excluded. Patients receiving anti-platelet agents were included in the analysis. Patients who were on anticoagulation at the time of diagnosis (n = 44) were excluded, leaving 629 patients for analysis.

2.2. Covariates and endpoints

Clinical covariates were recorded based on medical record and encompassed patient characteristics, treatment characteristics, and disease characteristics. Patient characteristics included age, gender, smoking status, and performance status. Disease characteristics included histology (classified as squamous cell carcinoma, adenocarcinoma, or non-small cell lung carcinoma not otherwise specified) and TNM stage per the American Joint Committee on Cancer (AJCC) 7th edition [24]. Patients were staged surgically if treated with initial surgery followed by adjuvant radiation therapy with or without chemotherapy, and staged clinically otherwise. Treatment characteristics included surgery (upfront or after neoadjuvant therapy) and type of chemotherapy.

The primary endpoint was defined as the development of pulmonary embolus or deep vein thrombosis. Patients were included if they developed a VTE after their diagnosis date, or within a 3-month period prior to diagnosis, as previous analyses have shown a significantly elevated risk of malignancy-associated VTE during this time period [25]. VTE risk was analyzed as a time-dependent variable, calculated from the first day of treatment (receipt of surgery, chemotherapy, or radiation therapy). For patients who did develop a VTE, the date of diagnosis of the VTE was used as the end time. Patients who did not develop a VTE were censored at last known follow-up.

For patients who did develop a VTE, a number of descriptive characteristics were recorded. We noted whether the VTE was associated with the development of atrial fibrillation, whether the VTE was provoked (by immobilization, recent surgery, or indwelling catheter), the method of diagnosis, and the treatment. The severity of the VTE was classified as asymptomatic, symptomatic, or requiring an emergency department (ED) visit or inpatient admission.

2.3. Competing-risks regression for VTE risk

Both death and distant relapse modify the risk of VTE occurrence. Death of a patient prevents future occurrences of VTE leading to over-estimation of risk with Kaplan-Meier estimates [26]; metastatic disease has been consistently associated with a markedly elevated risk for VTE in previous studies [16,17]. Thus, we utilized Fine and Gray's competing-risks regression model [27] for the purposes of survival analysis and included death and distant relapses as competing risks.

The endpoint used for survival analysis was time to VTE, censored at last known follow-up. The following predictor variables were included in the regression, all of which were treated as categorical variables: age (<65 vs ≥65), gender (male vs female), stage at diagnosis (IIIB vs IIA–IIIA), T staging (T3/T4 disease vs T1/T2 disease), N staging (N3 disease vs N0-N2 disease), histology (squamous vs non-squamous), surgery (performed for this diagnosis or not), chemotherapy sequencing (concurrent vs sequential or none) and

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