ANTICANCER RESEARCH *41*: 1523-1528 (2021)
doi:10.21873/anticanres.14911

Risk Factors for Venous Thromboembolism in Patients With Small Cell Lung Cancer

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Abstract. *Background/Aim: Small cell lung cancer (SCLC) accounts for 13% of all lung cancers. Venous thromboembolism (VTE) is a frequent complication. The purpose of this study was to investigate the incidence and risk factors for VTE in SCLC patients. Patients and methods: Retrospective analysis of patients with histologically confirmed SCLC treated between January 2015 and June 2018 at Sotiria General Hospital, Athens, Greece. Results: Two hundred and seventeen patients were included in the analysis. The incidence of VTE was 4.1%. Increased body mass index (BMI) was correlated with the development of VTE. Moreover, VTE appeared more frequently in patients with major vessel infiltration and with poor Eastern Cooperative Oncology Group Performance Status. Other factors, including gender, age, stage, presence of metastasis, treatment, immobilization, anticoagulation, comorbidities, and laboratory values did not correlate with the development of VTE. Conclusion: Factors associated with the development of VTE were BMI, major vessel infiltration and PS. Identifying factors that predispose to VTE could help physicians detect high-risk patients who would benefit from prophylactic anticoagulation therapy.*

Lung cancer is the second most frequent type of malignancy in both males and females in the United States and is projected to cause 131,880 deaths in the United States in 2021 (1). Small cell lung cancer (SCLC) accounts for approximately 13% of all new lung cancer cases (2, 3).
The annual incidence of venous thromboembolism (VTE) ranges from 1 to 2 per 1,000 individuals per year in the general population (4, 5). Malignancy constitutes a significant risk factor for VTE, with cancer patients facing 4 to 10 times higher risk of developing VTE compared with the general population; risk of developing VTE is 20 times higher in patients with lung cancer in particular (6-11). The incidence of VTE in SCLC patients ranges between 6.8% and 11.5% (12, 13). Risk factors for VTE can be classified as disease-, treatment- and patient-related. Extensive disease and infiltration of the superior vena cava have been shown to increase the risk of thromboembolism (14, 15). As far as treatment-related factors are concerned, chemotherapy and treatment with cisplatin in particular also appear to correlate with VTE (16, 17). Finally, smoking and coexisting disorders predispose patients for VTE.

VTE incidence has been associated with decreased survival, with a hazard ratio of 1.5 (7). Simultaneous detection of cancer and VTE further augments the risk of death in lung cancer patients (18). However, prophylactic anticoagulation therapy has been shown to improve one-year survival rates of SCLC patients with limited disease (19). Furthermore, anticoagulation treatment administered to SCLC patients in addition to chemotherapy or chemotherapy and radiotherapy, leads to improved median survival, along with better response to anticancer therapy (20, 21).

The purpose of this study was to determine the incidence and identify the risk factors associated with VTE in SCLC patients. This will enable the detection of patients at increased risk for VTE, who may benefit from early thromboprophylaxis.

Patients and Methods

Medical records of sequential, non-selected patients with lung cancer who were treated at the Oncology Unit, Sotiria General Hospital, Athens, Greece between January 2015 and June 2018 were reviewed. Patients with histologically confirmed SCLC were included. Basic demographic and anthropometric data (gender, age, body surface area (BSA), body mass index (BMI), performance

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Key Words: Small cell lung cancer, venous thromboembolism, risk factors.

status according to the Eastern Cooperative Oncology Group (ECOG PS), smoking status), data regarding the disease itself (stage, major vessel infiltration, presence of distant metastases), laboratory test results at baseline, assigned treatment regimen, Khorana Risk Score (KRS), Charlson Comorbidity Index (CCI), state of mobility or immobility, as well as administration of anticoagulation therapy prior to any thromboembolic incident) were recorded. The presence of VTE (either deep vein thrombosis or pulmonary embolism) was confirmed by computed tomography pulmonary angiography (CTPA), ventilation/perfusion lung scintigraphy, or venous duplex ultrasonography. In patients who developed VTE, the type of thromboembolic event, interval between malignancy diagnosis and VTE occurrence, as well as survival post the index event were also recorded.

Mean values, standard deviations (SD), median values and interquartile ranges were used to describe quantitative variables. Absolute (N) and relative (%) frequencies were used to describe qualitative variables. For ratio comparison, Fisher's exact test was applied. For quantitative variable comparison between two separate groups, Student's *t*-test or the nonparametric Mann-Whitney criterion was applied. For the identification of independent factors connected to the presence of venous thromboembolic disease, logistic regression analysis was carried out with a stepwise inclusion/exclusion method, and odds ratios (OR) with 95% confidence intervals (95%CI) were calculated. The level of statistical significance was two-tailed and set at 0.05 for all calculations. Analyses were carried out using the SPSS 22.0 software suite.

Results

Two hundred and seventeen patients were included in the analysis. Mean age of participants was 67.9 years. Table I summarizes patient characteristics. Most patients were men (81.1%). In addition, 72.3% were current smokers and 26.3% were former smokers; 39.3% of patients had normal weight, 36.6% were overweight and 24.1% were obese. ECOG PS was 0 in 26.9% of patients, 1 in 42.1%, 2 in 25.0%, 3 in 5.5% and 4 in 0.5%. As far as stage is concerned, 70.0% presented with extensive disease at baseline, major vessel infiltration was present in 11.5% of patients. While all patients received chemotherapy, only 69.1% received radiotherapy. Mean KRS was 1.6 (SD=0.7 points) and mean CCI was 8.4 (SD=2.5 points) (Table II). Thirty-two patients (14.7%) were receiving anticoagulants during treatment period.

Table I. *Patient characteristics*.

	N	%
Gender		
Male	176	81.1
Female	41	18.9
Age, mean (SD)	67.9 (8.6)	
BSA, mean (SD)	1.8 (0.2)	
BMI, mean (SD)	26.8 (4.5)	
BMI		
Normal (<25)	85	39.3
Overweight (25-30)	79	36.6
Obese (>30)	52	24.1
ECOG PS		
0	58	26.9
1	91	42.1
2	54	25.0
3	12	5.5
4	1	0.5
Smoking status		
Never	3	1.4
Current	157	72.3
Former	57	26.3
Stage		
Extensive	152	70.0
Limited	65	30.0
Major vessel infiltration		
No	192	88.5
Yes	25	11.5
Distant metastases		
No	65	30.0
Yes	152	70.0
Cancer treatment		
Chemotherapy	217	100.0
Radiotherapy	150	69.1
Immobilization		
No	205	94.5
Yes	12	5.5
Anticoagulation		
No	185	85.3
Yes	32	14.7

BSA: Body surface area; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; KRS: Khorana Risk Score; CCI: Charlson Comorbidity Index.

Thromboembolic complications were recorded in nine patients, representing 4.1% of the population, including six patients suffering from PE and three suffering from DVT (Table III). Mean time elapsed since diagnosis was 5.6 months. Mean survival post the index thromboembolic event was 2.3 months.

VTE rates did not differ significantly with respect to gender, age and BSA (Table IV). However, patients who suffered from VTE had significantly increased BMI in comparison with patients who did not (p=0.027). Importantly, rates of VTE were significantly higher in obese patients, as compared to both normal-weight (p=0.024) and overweight (p=0.011) patients included in the study. No significant difference in thromboembolic complications was detected with respect to smoking status, stage, presence of metastases, baseline laboratory test results, treatment, KRS, CCI, state of mobility or immobility and administration of anticoagulants during the treatment period. In addition, thromboembolic rates appeared somewhat elevated when a major vessel was infiltrated (8%) as well as with increasing ECOG PS values (7.5% for ECOG PS between 2 and 4).

Using stepwise multifactorial logistic regression, we set the presence of VTE as a dependent variable and the recorded data as independent variables and found that only

Table II. *Baseline laboratory values, Khorana Risk Score and Charlson Comorbidity Index for all study participants.*

	Mean value (SD)	Median (interq. range)
WBC	9.1 (3.6)	8.5 (6.7-10.8)
Hb	13 (1.8)	13.1 (11.9-14.3)
PLT	291.0 (113.2)	269 (212-346)
KRS	1.6 (0.7)	1 (1-2)
CCI	8.4 (2.5)	9 (7-10)

WBC: White blood cells; Hb: hemoglobin; PLT: platelets; KRS: Khorana Risk Score; CCI: Charlson Comorbidity Index.

Table III. *Index thromboembolic event characteristics.*

	N	%
Venous thromboembolism		
No	208	95.9
Yes	9	4.1
Type of event		
Pulmonary embolism	6	2.8
Deep vein thrombosis	3	1.4
Time elapsed since diagnosis in months, mean (SD)	5.6 (5.8)	
Survival post the index thromboembolic event in months, mean value (SD)	2.3 (1.2)	

BMI was significantly associated with the development of venous thromboembolic disease (p=0.032). More specifically, higher BMI values increased the odds for development of VTE (OR=1.18; 95%CI=1.01-1.36).

Discussion

In this study, we retrospectively assessed SCLC patients to find risk factors associated with the development of VTE. The incidence of VTE in our population was found to be 4.1%, which is lower than what has been reported in previous studies (6.8%-11.5%) (22). This could be explained by differences in trial design, inclusion and exclusion criteria, as well as the duration of follow-up. Out of the 217 patients, 176 (81.1%) were male and 41 (18.9%) were female. Current literature highlights a smaller difference in the incidence of SCLC between males and females. Given the fact that smoking is the main cause of SCLC, such differences may be directly attributed to the smoking habits of women in Greece. Mean patient age was 67.9 years, a finding compatible with data from current literature, which indicates that the disease in question mostly affects patients between 60 and 80 years of age. Two hundred and fourteen patients were active or former smokers; we recorded three women with SCLC that were never smokers, which is concordant with current literature indicating that a small percentage of non-smoking women may indeed develop SCLC (22, 23).

VTE occurred in 4% of men and 4.9% of women. According to the Centers for Disease Control and Prevention, 250,973 men and 296,623 women were diagnosed with VTE between 2007 and 2009 in the USA (24). Previous studies have reported that extensive disease, superior vena cava infiltration, administration of chemotherapy and treatment with cisplatin in particular, smoking and multiple comorbidities increase the risk of VTE in patients with SCLC (25, 26). However, occurrence of VTE has not been associated with disease recurrence in patients with advanced breast cancer (27). Even after controlling for multiple of the above factors, we found that increased BMI is the only factor significantly associated with increased risk for VTE in SCLC patients. On the contrary, age and gender have not been correlated with increased VTE risk. We also documented two additional factors that increase the risk of thromboembolic complications in patients with SCLC. The first one is infiltration of a major vessel, which occurred more often in patients who suffered a thromboembolic event in comparison with those who did not (8% *versus* 3.6%, respectively). This seems reasonable from a pathophysiological standpoint, since tumor cell infiltration destroys part of the vessel, and in some cases may even obstruct the blood flow. In a study by Lee *et al*., infiltration of the superior vena cava was investigated, and a relevant correlation was sought (17). The second factor was ECOG PS (p=0.257). Patients with thromboembolic events most often had PS scores of 2 to 4, which corresponded to a poorer functional status in general. Similarly, preoperative dehydration and poor nutritional status has been associated with increased risk for postoperative thromboembolic complications in patients subjected to pancreatic surgery, while treatment with enoxaparin reduced VTE risk post esophagectomy in patients with esophageal cancer (28, 29). No correlation was observed with disease stage and the presence of distant metastases. With some caution, we might surmise that the risk is increased when the aggravated condition is ascribed to the malignancy itself. The association of chemotherapy with thromboembolic complications could not be evaluated in the present study since all patients received chemotherapy and there was no control group. Smoking status could not be statistically correlated with VTE risk either, given that only 3 of our patients were never smokers. Laboratory test results and KRS also did not correlate with the VTE risk. Although KRS has been associated with thromboembolic risk prediction in cancer patients, no study has evaluated the predictive ability of KRS in SCLC in particular. Mansfield *et al*. assessed the predictive value of the KRS in a cohort of 719 lung cancer

Table IV. *Association of patient characteristics with VTE.*

	Venous thromboembolism				*p*-Value Fisher's exact test
	No		Yes		
	N	%	N	%	
Gender					
Men	169	96.0	7	4.0	0.679
Women	39	95.1	2	4.9	
Age, mean (SD)	67.8 (8.6)		68.6 (8.7)		0.809
BSA, mean (SD)	1.8 (0.2)		1.9 (0.1)		0.486+
BMI, mean (SD)	26.6 (4.4)		30 (5.9)		**0.027**
BMI					
Normal (<25)	83	97.6	2	2.4	**0.017**
Overweight (25-30)	78	98.7	1	1.3	
Obese (>30)	46	88.5	6	11.5	
ECOG PS					
0	57	98.3	1	1.7	0.257
1	88	96.7	3	3.3	
2-4	62	92.5	5	7.5	
Smoking status					
Never/Former	56	93.3	4	6.7	0.265
Active	152	96.8	5	3.2	
Stage					
Extensive	146	96.1	6	3.9	1.000
Limited	62	95.4	3	4.6	
Major vessel infiltration					
No	185	96.4	7	3.6	0.278
Yes	23	92.0	2	8.0	
Distant metastases					
No	62	95.4	3	4.6	1.000
Yes	146	96.1	6	3.9	
Immobilization					
No	196	95.6	9	4.4	1.000
Yes	12	100.0	0	0.0	
Anticoagulation					
No	178	96.2	7	3.8	0.624
Yes	30	93.7	2	6.3	
KRS, mean (SD)	1.6 (0.8)		1.4 (0.5)		0.880+
CCI, mean (SD)	8.4 (2.5)		8.3 (2.4)		0.780+

BSA: Body surface area; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; KRS: Khorana Risk Score; CCI: Charlson Comorbidity Index. +Student's *t*-test. Bold values indicate statistical significance.

patients, 93 of whom suffered from SCLC (30). In that study, KRS failed to predict the risk of VTE occurrence in patients with lung cancer, yet a separate subset analysis for SCLC patients was not performed. In the same study, a correlation between the risk of VTE and platelet count (>350,000/ml) was documented for all lung cancer patients; nonetheless, a separate analysis was not performed in the SCLC patient subgroup. In our study, platelet count was not correlated with increased VTE risk in patients with SCLC. Two more recent studies also found no correlation between KRS and VTE in patients with lung cancer in general and non-small cell lung cancer, adenocarcinoma (31, 32).

This study is subject to several limitations. First and foremost, it is a retrospective analysis, thus, prospective trials should be conducted in the future to validate its findings. Next, it is a single-institution study, therefore, the previously described associations should be assessed by multiple institutions in different countries. Future studies should address risk factors for VTE in patients with SCLC that are receiving the combination of chemotherapy and immune checkpoint inhibitors. Finally, the present study recorded nine VTE events and may be underpowered to investigate the association of major vessel infiltration and ECOG PS with VTE risk in SCLC patients.

Conclusion

In conclusion, we found that an increased BMI is significantly associated with increased VTE risk. In the era of personalized medicine, it is crucial to identify cancer type-specific thromboembolic risk factors and apply tailored VTE prevention that would alleviate the burden of thromboembolic complications and ultimately lead to better patient outcomes.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, ED, KL and IG; methodology, ED, IV, KL, IG, GG, EKa, EKo, KS; data collection and analysis, ED, IV, KL, IG, GG, EKa, EKo; supervision, ED, KS; writing—original draft preparation, ED, KL, IV, IG. All Authors read and approved the final version of the manuscript.

Acknowledgements

The Authors would like to thank Ioannis Botis for his assistance in translation.

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Received February 2, 2021
Revised February 11, 2021
Accepted February 12, 2021