Is asymptomatic postoperative venous thromboembolism associated with long-term survival in patients undergoing lung resection for malignancy?

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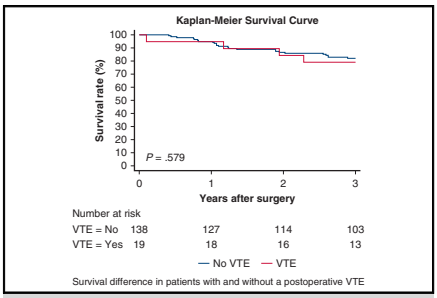

Survival difference in patients with and without a postoperative VTE.

CENTRAL MESSAGE

This study highlights that with regular venous thromboembolism (VTE) screening and subsequent treatment, postoperative thrombotic events may not impact the long-term survival of lung cancer patients.

See Commentaries on pages 246 and 248.

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality after lung resection.[1] Previous studies have found postoperative VTEs are associated with increased 30-day mortality.[2] Although the majority of patients with lung cancer receive in-hospital prophylaxis,[3] the American College of Surgeons National Surgical Quality Improvement Program reports that 44% of VTEs after lung resection occur after hospital discharge.[2] Although general surgical oncology and orthopedic surgery have developed recommendations for extended, postdischarge prophylaxis,[4] no such guidelines exist for lung cancer surgery. Furthermore, evidence suggests that VTE development after curative oncologic resections portends worse overall survival beyond the immediate postoperative period, potentially indicating a more aggressive malignancy.[5]

Our group previously conducted a prospective cohort study across 2 tertiary hospitals in the Canadian province of Ontario and found a 12% incidence of screening-detected postoperative VTEs, all diagnosed post-discharge.[1] In light of evidence suggesting VTEs are associated with poor oncologic outcomes, we conducted a follow-up analysis to examine the relationship between postoperative VTEs and long-term survival.

METHODS

The original study recruited patients undergoing lung cancer resection across 2 tertiary centers in Ontario.[1] Patients older than the age of 18 years undergoing lung resection were included. All patients received in-hospital pharmacologic and mechanical prophylaxis, including graduated compression stockings and chemical prophylaxis with daily subcutaneous low-molecular weight heparin, or twice-daily unfractionated heparin. All study patients underwent screening computed tomography pulmonary angiography and bilateral above-knee lower-limb venous Doppler ultrasonography at 30 days postoperatively. Screening of asymptomatic patients was conducted only for study patients and is not standard of care. Patients with previous thrombotic events or on therapeutic anticoagulation were excluded.[1]

For the present study, patients were examined with a median follow-up of 3.6 years after surgery. Patients with postoperative VTEs were compared with those without VTE. We used a proportional hazard Cox regression to compare survival between the groups. Age, sex, smoking status, and comorbidities were included in the univariate analysis. Variables that achieved significance were then included in the multivariable regression. Outcomes of interest were cancer recurrence and overall survival. Importantly, 22% of patients underwent pulmonary metastatectomy with a non-lung primary malignancy. Given the small number of total patients, all patients were included in the final survival curve. The patients provided informed consent for the publication of the study data.

RESULTS

The original analysis included 157 patients; 12% (n = 19) developed a postoperative VTE. One death from

TABLE 1. Baseline characteristics of the original cohort (N = 157)[1]

	No postoperative VTE (n = 138)*	Postoperative VTE (n = 19)	Total† (N = 157)	*P* value
Age, y	66.25 ± 8.88	69.05 ± 11.51	66.55 ± 9.24	.216
Sex (male)	62 (44.92)	10 (52.63)	72 (45.86)	.626
%Predicted FEV_1	72.34 (32.68)	82.50 (35.11)	73.51 (33.02)	.220
%Predicted DLCO	72.07 (19.88)	67.0 (14.13)	71.48 (19.33)	.326
Charlson Comorbidity Index	2.19 ± 2.07	2.42 ± 2.24	2.22 ± 2.08	.649
Length of stay, d	6 (3-24)	5 (1-5)	5 (1-24)	.185
Caprini score				
3-4	27 (19.56)	2 (10.52)	29 (18.47)	.441
5+	111 (80.43)	17 (89.47)	128 (81.52)	
Smoking status				
Never smoker	26 (83.9)	5 (16.1)	31 (19.7)	.441
Former smoker	79 (90.8)	8 (9.2)	87 (55.4)	
Current smoker	32 (84.2)	6 (15.8)	38 (24.2)	
Tumor pathology				
T1a	27 (81.8)	6 (18.2)	33 (26.0)	
T1b	18 (85.7)	3 (14.3)	21 (16.5)	
T2a	35 (83.3)	7 (16.7)	42 (33.1)	.513
T2b	11 (91.7)	1 (8.3)	12 (9.4)	
T3	16 (100)	0.0	16 (12.6)	
T4	3 (100)	0.0	3 (2.4)	
Lymph node pathology				
NX	4 (100)	0.0	4 (3.1)	
N0	79 (85.9)	13 (14.1)	92 (72.4)	.566
N1	21 (91.3)	2 (8.7)	23 (18.1)	
N2	6 (0.8)	2 (0.2)	8 (6.3)	
Pathologic stage (TMN)				
IA	37 (26.81)	7 (36.84)	44 (28.03)	
IB	31 (22.46)	6 (31.58)	37 (23.57)	
IIA	14 (10.14)	1 (5.26)	15 (9.55)	–‡
IIB	7 (5.07)	1 (5.26)	8 (5.10)	
IIIA	16 (11.59)	2 (10.53)	18 (11.46)	
IIIB	4 (2.90)	0 (0)	4 (2.55)	
Lung metastases	21 (15.22)	2 (10.53)	23 (14.65)	
Histology				
Squamous cell	29 (21.01)	4 (21.05)	33 (21.01)	.827
Adenocarcinoma	63 (45.65)	10 (52.63)	73 (46.50)	
Other	45 (32.61)	5 (26.32)	50 (31.85)	
Resection				
Pneumonectomy	6 (4.35)	0 (0)	6 (3.82)	
Bilobectomy	2 (1.45)	0 (0)	2 (1.27)	–‡
Lobectomy	87 (63.04)	15 (78.96)	102 (64.97)	
Sublobar	43 (31.16)	4 (21.05)	47 (29.93)	
Surgical approach				
VATS	76 (55.07)	9 (47.37)	85 (54.14)	
Thoracotomy	56 (40.58)	10 (52.63)	66 (42.04)	.452
Robotic	6 (4.35)	0 (0)	6 (3.82)	

Groups were compared using *t* tests and χ^2 tests as appropriate. *VTE*, Venous thromboembolism; *FEV_1*, forced expiratory volume in 1 s; *DLCO*, diffusion capacity of the lungs for carbon monoxide; *VATS*, video-assisted thoracoscopic surgery. *Values represent n (%), mean ± standard deviation, or median (range) unless otherwise specified. †Total for all variables may not add up to 157 due to missing data. ‡Due to small sample size, *P* value is not reliable.

TABLE 2. Survival rate (%) over time for patients with and without a postoperative screen–detected VTE

Time (years since surgery)	Number at risk	Survival rate (%)	95% confidence interval
No VTE			
0	138	100	NA
1	127	94.9	89.5-97.5
2	114	86.7	79.6-91.4
3	103	82.0	74.4-87.6
4	12	76.3	67.2-83.1
VTE			
0	19	100	NA
1	18	94.7	68.1-99.2
2	16	84.2	58.7-94.6
3	13	80.0	53.2-91.5
4	2	53.4	17.6-80.2

VTE, Venous thromboembolism; *NA*, not available.

massive PE resulted in a 5% 30-day mortality rate from VTE in the VTE group, whereas none of the non-VTE group died.[1] Only 4 patients (21.1%) were symptomatic.[1]

Univariate analysis showed no difference between patients with and without a VTE with regards to baseline characteristics (Table 1).[1]

TABLE 3. Proportional hazard Cox regression analysis of survival for all patients (VTE + no VTE)

	n	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Age, y	157	1.02 (0.98-1.06)	.239	–	–
Sex			.720	–	–
Female	72	Reference			
Male	85	1.12 (0.60-2.08)			
Smoking history			.832	–	–
No	127	Reference			
Yes	30	1.09 (0.50-2.36)			
Any VTE			.501	–	–
No	138	Reference			
Yes	19	1.34 (0.56-3.21)			
Pathologic stage	149	1.18 (1.05-1.32)	.004	1.17 (1.05-1.31)	.005
Histology			.336	–	–
Squamous cell	33	Reference	–		
Adenocarcinoma	73	0.92 (0.40-2.16)	.858		
Carcinoid	12	0.00	.974		
Metastatic	23	1.87 (0.74-4.76)	.184		
Mixed	15	1.90 (0.66-5.47)	.235		
Surgery			.742	–	–
Pneumonectomy	6	Reference	–		
Lobectomy	104	0.60 (0.14-2.56)	.495		
Segmentectomy	27	0.82 (0.17-3.80)	.798		
Wedge	20	0.50 (0.10-2.73)	.424		
FEV_1	149	0.99 (0.98-1.01)	.362	–	–
DLCO	146	0.98 (0.96-1.00)	.125	–	–
VATS			.036	NS	NS
No	71	Reference			
Yes	84	0.51 (0.27-0.95)			

(Continued)

TABLE 3. Continued

	n	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
CVA			.446	–	–
No	152	Reference			
Yes	5	1.74 (0.42-7.21)			
PVD			.076	NS	NS
No	148	Reference			
Yes	9	2.34 (0.91-5.98)			
CAD			.951	–	–
No	137	Reference			
Yes	20	0.97 (0.38-2.48)			
Diabetes			.066	NS	NS
No	134	Reference			
Yes	23	0.26 (0.06-1.09)			
Obesity			.724	–	–
No	137	Reference			
Yes	20	1.17 (0.49-2.80)			
CKD			.484	–	–
No	134	Reference			
Yes	22	1.34 (0.60-3.02)			

HR, Hazard ratio; *CI*, confidence interval; *VTE*, venous thromboembolism; FEV_1, forced expiratory volume in 1 s; *DLCO*, diffusion capacity of the lungs for carbon monoxide; *VATS*, video-assisted thoracoscopic surgery; *CVA*, cerebrovascular accident; *PVD*, peripheral vascular disease; *CAD*, coronary artery disease; *NS*, not significant; *CKD*, chronic kidney disease.

Long-term follow-up was complete for all patients and showed no difference in cancer recurrence between patients with and without a VTE (35% and 32%, respectively, $P = 1.000$; median follow-up 3.6 years). Results were unchanged when DVT and PE were analyzed separately. There was no difference in overall or disease-specific survival between the 2 groups (Tables 2 and 3, Figure 1). This effect persisted after stratification by disease stage and patient characteristics.

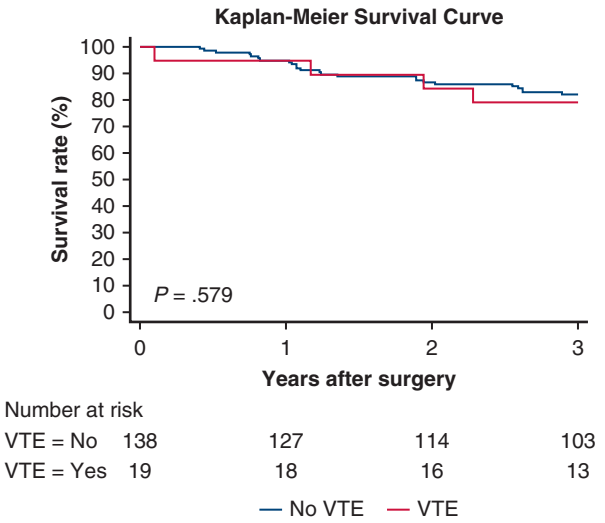

FIGURE 1. Overall long-term survival in patients undergoing lung cancer surgery with and without a postoperative screening–detected VTE. *Confidence intervals reported in Table 2. *VTE*, Venous thromboembolism.

DISCUSSION

This study found no difference in the long-term survival of patients with lung cancer based on postoperative VTE development. These results stand in contrast to previous evidence suggesting worse overall survival in patients with a postoperative VTE.[5] Notably, this study captured asymptomatic, screening-detected VTEs, prompting treatment of patients who may have not manifested clinical evidence of DVT/PE and remained untreated. It is possible that our findings are due to early identification and subsequent treatment of patients with subclinical VTEs, preventing long-term morbidity from undetected DVT/PEs.

The strengths of this study include long-term and granular follow-up of patients post-lung resection. The small sample size is the major limitation, as it increases the likelihood of type II errors. Furthermore, the inclusion of pulmonary metastases in the survival curve decreases the generalizability of results to patients with lung cancer. Finally, bleeding complications after the initiation of therapeutic anticoagulation in the VTE group were not tracked.

In conclusion, the present study found that with regular VTE screening and treatment when an event is detected, postoperative VTEs may not impact the long-term survival of patients undergoing lung resection for malignancy. Rather, the morbidity and mortality of postoperative VTEs seems to lie in the short-term postoperative period. To reduce the impact of VTEs on long-term survival, screening for high-risk patients may be warranted to promote early diagnosis and treatment, as treated events are unlikely to impact long-term outcomes. Similar to surgical

oncology, thoracic surgeons may consider extended postdischarge VTE prophylaxis for selected patient populations to prevent the development of thrombotic complications.

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