Routine surveillance for diagnosis of venous thromboembolism after pleurectomy for malignant pleural mesothelioma

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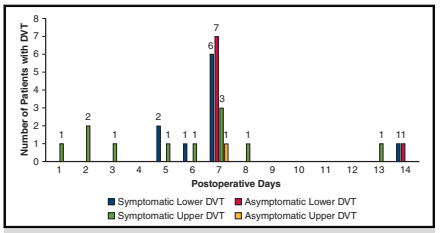
ABSTRACT

Objective: The purpose of this study was to determine the incidence of venous thromboembolism and utility of a routine surveillance program in patients undergoing surgery for mesothelioma.

Methods: Patients undergoing pleurectomy from May 2016 to August 2018 were included. A standardized surveillance program to look for venous thromboembolism in this group included noninvasive studies every 7 days postoperatively or earlier if symptomatic. All patients received external pneumatic compression sleeves in addition to prophylactic heparin. If deep vein thrombosis or pulmonary embolus was discovered, heparin drip was initiated until conversion to therapeutic anticoagulation.

Results: A total of 100 patients underwent pleurectomy for mesothelioma. Seven patients were found to have preoperative deep vein thrombosis, and as such only 93 patients were included for analysis. The median age of patients at surgery was 71 years (30-85 years). During the study, 30 patients (32%) developed evidence of thrombosis; 20 patients (22%) developed only deep vein thrombosis without embolism, 3 patients (3%) developed only pulmonary embolism, and 7 patients (7%) developed both deep vein thrombosis and pulmonary embolus. Of the 27 patients who developed deep vein thrombosis, 9 (33%) were asymptomatic at the time of diagnosis, and none of these developed a pulmonary embolus or other bleeding complications. There were 2 (2%) events of major postoperative bleeding related to therapeutic anticoagulation.

Conclusions: The incidence of venous thromboembolism is high (32%) among patients undergoing surveillance after pleurectomy for mesothelioma. Up to 33% of patients with deep vein thrombosis are asymptomatic at the time of diagnosis, and the incidence of complications related to anticoagulation is low. Routine surveillance may be useful to diagnose and treat deep vein thrombosis before it progresses to symptomatic or fatal pulmonary embolus. (J Thorac Cardiovasc Surg 2020;160:1064-73)



Routine surveillance with noninvasive studies can help diagnose DVT.

CENTRAL MESSAGE

Routine surveillance with upper- and lower-extremity noninvasive studies is effective and may help to diagnose and treat asymptomatic DVT before it progresses to symptomatic or fatal PE.

PERSPECTIVE

Patients undergoing P/D for mesothelioma are at increased risk of VTE. Up to 33% of patients with DVT are asymptomatic at the time of diagnosis. Routine surveillance can help to diagnose and treat symptomatic DVT before it progresses to symptomatic or fatal PE. This benefit should be weighed against the risk of bleeding complications.

See Commentaries on pages 1074, 1075, and 1076.

Both thrombotic disorders and postoperative bleeding are common events after surgical therapy for mesothelioma. The incidence of venous thromboembolism (VTE) is estimated to be 0.1% to 2% in the general population[1] and increases to 10% to 15% in patients with malignancy.[2] Postoperative VTE in patients with mesothelioma is estimated to be between 5% and 28%, varying by the nature of the surgical procedure.[3-5] In our previous reported experience with extrapleural pneumonectomies for patients with mesothelioma, we reported a 6.4% incidence

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Abbreviations and Acronyms

CT = computed tomography
DVT = deep vein thrombosis
IOHC = intraoperative heated chemotherapy
IVC = inferior vena cava
LENIS = lower-extremity noninvasive studies
PA = pulmonary angiography
P/D = pleurectomy and decortication
PE = pulmonary embolism
UENIS = upper-extremity noninvasive studies
VTE = venous thromboembolism

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of deep vein thrombosis (DVT) and a 1.5% incidence of pulmonary embolism (PE) in a nonscreened sample.[6]

The baseline risk of DVT is elevated in all patients presenting with pleural mesothelioma. Caprini scores have been widely validated to assess the risk of developing VTE in surgical patients. Patients with mesothelioma considering surgery have a baseline of 2 points given their diagnosis of malignancy. More than 75% of cases with mesothelioma are diagnosed in patients aged 65 years or more,[7] thus adding 2 more points to the equation. Those 2 factors place them at moderate risk (0.7%) of developing DVT. Surgery for mesothelioma is invasive and associated with extensive bleeding and coagulopathy[8,9]; this adds 2 more points to these patients. Thus, the immediate postoperative risk based on the Caprini score yields a minimum of 6 points, which is considered "high" risk or a quantitative 1.8% risk of VTE.

After our identification of elevated risk of thromboembolic events after extrapleural pneumonectomies in an unscreened population in 2004,[6] we developed a standardized surveillance protocol. The protocol is based on preoperative ultrasound to assess for asymptomatic preoperative thromboembolism, perioperative anticoagulation with heparin, and surveillance for asymptomatic DVT every 7 days postoperatively.

There is competing evidence regarding the risk–benefit of routine surveillance of asymptomatic patients.[10] More than 50% of patients who have "typical" symptoms do not have DVT, and as much as two thirds of all significant DVTs are not recognized or treated.[11] The literature has shown noninvasive vascular screening studies and prophylactic techniques have been a cost-effective method to prevent DVT and PE in certain high-risk patients.[6,12-14] Other studies suggest that increased medical testing and treatment of asymptomatic VTE (which may have never become clinically relevant otherwise) incur a higher risk of bleeding associated with anticoagulation treatment.[15-17]

The purpose of this study was to determine the incidence of VTE and describe the outcomes of a routine surveillance program of patients undergoing pleurectomy and decortication (P/D) for mesothelioma for which a standardized surveillance and antithrombotic prophylaxis protocol was established at a single large-volume center.

PATIENTS AND METHODS

All patients who underwent P/D for mesothelioma at Brigham and Women's Hospital between May 2016 and August 2018 were prospectively included. VTE included objectively confirmed evidence of new DVT using ultrasound, PE on computed tomography (CT) pulmonary angiography (PA), or ventilation/perfusion scan when there was a contraindication to angiography (chronic kidney disease, allergy to contrast). DVT was considered proximal or distal if it occurred in a vessel above or below the knee, respectively. Caprini scores were calculated using a web-based DVT Risk Assessment Tool.[18] Data were collected prospectively by the thoracic surgery team by daily visits to the hospital wards during the postoperative course. This study was approved by the Institutional Review Board at Brigham and Women's Hospital, and informed consent was waived.

Ultrasound Examinations

Lower- and upper-extremity noninvasive studies (LENIS and UENIS) were performed using venous duplex scanning, which included examination of the distal external iliac veins, common femoral veins, superficial femoral veins, popliteal veins, tibial veins, and the greater and lesser saphenous veins bilaterally. Examinations consisted of imaging and velocity measurements of all these vein segments. The presence of thrombus in the vein, the lack of compressibility, absence of flow, or abnormal flow diagnosed DVT.

Computed Tomography Pulmonary Angiograms

CT pulmonary angiograms were performed during the intravenous administration of 75 mL of contrast. Images were acquired at 1-mm thickness to evaluate the pulmonary vasculature and reconstructed at 3-mm thickness to evaluate the lung parenchyma and mediastinum. Three-dimensional angiographic postprocessing techniques were acquired in the form of axial maximum-intensity projection images.

Preoperative Course

Patients underwent preoperative LENIS ± UENIS within the week before surgery. Patients were excluded from the study if they were found to have a preoperative DVT. Chemical antithrombotic prophylaxis was provided with a single subcutaneous dose of 5000 units of unfractionated heparin within 2 hours of the beginning of each operation.

Postoperative Course

All patients received mechanical prophylaxis with external pneumatic compression sleeves (during and after the operation) in addition to chemical thromboprophylaxis with 5000 units of unfractionated heparin every 8 hours after surgery. All patients underwent LENIS ± UENIS on postoperative day 7 or earlier if patients developed signs and symptoms of VTE, such as pain, edema, or change of temperature in upper or lower extremities, chest pain, or increased work of breathing, or if they were deemed ready for discharge before postoperative day 7. If DVT or PE was discovered, a continuous heparin drip of 10 to 15 units per kg/h was initiated until patients were transitioned to a long-term therapeutic anticoagulation regimen with low-molecular-weight heparin, vitamin K

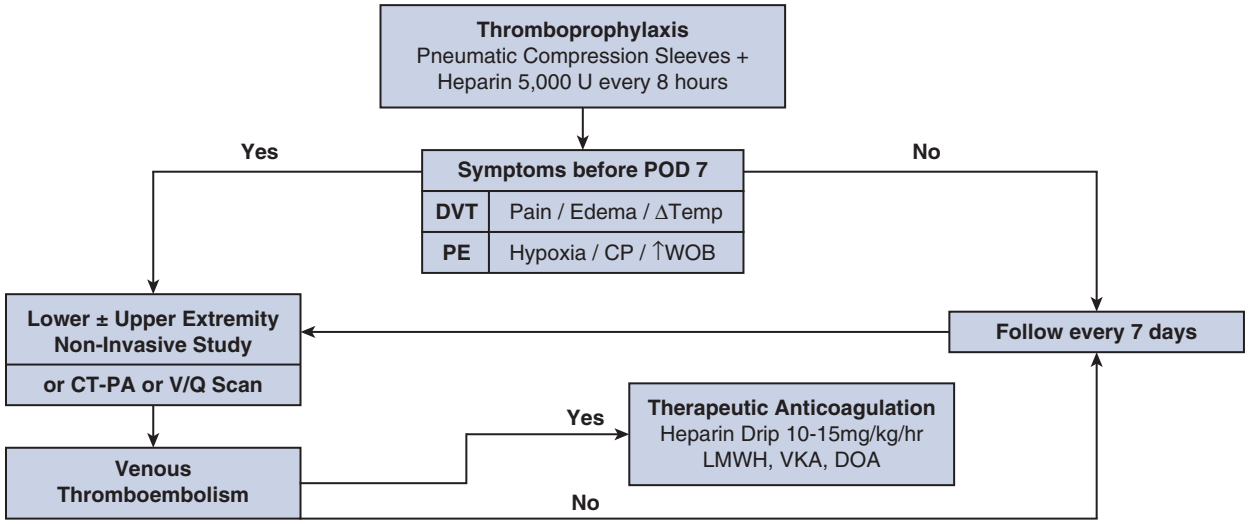

FIGURE 1. Postoperative protocol for surveillance and treatment of DVT. All patients received pneumatic compression sleeves intraoperatively and postoperatively, and chemical thromboprophylaxis every 8 hours after surgery. During follow-up, if patients developed symptoms of DVTs (pain, edema, or change in temperature in the extremities), they underwent LENIS ± UENIS. If they developed hypoxia, chest pain, or increased work of breathing, they underwent a CT-PA to rule out PE. If patients remained asymptomatic, they were followed every 7 days with repeated LENIS ± UENIS. If VTE was discovered, a continuous heparin drip was initiated until patients were transitioned to a long-term therapeutic anticoagulation regimen with low-molecular-weight heparin, vitamin K antagonists, or direct oral anticoagulants that were continued for the first 3 months postoperatively. *POD*, Postoperative day; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *CP*, chest pain; *WOB*, work of breathing; *CT-PA*, computed tomography pulmonary angiography; *V/Q scan*, ventilation perfusion scan; *LMWH*, low-molecular-weight heparin; *VKA*, vitamin K antagonist; *DOA*, direct oral anticoagulant.

antagonists, or direct oral anticoagulants for the first 3 months postoperatively (Figure 1). Major bleeding complications were defined as those in which the patient became symptomatic or required surgical, radiologic, or endoscopic intervention. Heparin-induced thrombocytopenia was defined as a Thrombocytopenia, Timing of platelet count fall, Thrombosis, other causes for Thrombocytopenia (4Ts) score 4 or greater[19] and a positive heparin-induced thrombocytopenia antibody.

Statistical Analysis

Descriptive statistics for categoric variables are expressed as frequency and percentages; continuous variables are expressed as mean and standard deviations or median and ranges, as appropriate. Two-tailed Fisher exact test or chi-square was used to compare categoric variables as appropriate. Mann–Whitney *U* and *t* test were used for continuous variables as appropriate. Statistical analyses were performed using SPSS 24 (IBM Corp, Armonk, NY).

RESULTS

A total of 100 patients underwent P/D for mesothelioma in a 27-month period. Seven patients were found to have preoperative DVT, and as such only 93 patients were included for analysis. The characteristics and outcomes of the 93 patients are shown in Table 1. Median age at surgery was 71 years (30-85 years). Seventy-four patients (80%) were male. All patients were at the highest risk category for VTE per the Caprini risk assessment model, with a mean score of 12 ± 1. Fifty-nine patients (63%) had intraoperative heated chemotherapy (IOHC) at the time of surgery. The histologic diagnosis was epithelioid in 60 patients, sarcomatoid in 4 patients, and biphasic in 29 patients. Median hospital length of stay was 15 days (4-85 days).

A comparison of the clinical characteristics and outcomes of patients in the study group of VTE and no VTE is shown in Table 1. There were no differences in the demographic variables between the 2 groups. The only statistically important difference was an unexpected slightly higher (12 + 1) average Caprini score in the no VTE group compared with the VTE (11+1) group. None of the Caprini score variables were significantly different between groups. The length of stay was slightly longer in the VTE group but did not achieve statistical significance.

Postoperative Venous Thromboembolism

During the study, 30 patients (32%) developed evidence of VTE; 20 patients (22%) developed only DVT without embolism, 3 patients (3%) developed only PE, and 7 patients (8%) developed both DVT and PE. Median time to any VTE was 7 days (1-14 days). The distribution of all VTEs for the cohort is shown in the lower half of Table 1. Patients underwent a median of 1 (1-4) noninvasive studies during their hospital course. There was no statistical difference in the rate of VTE based on IOHC or histologic type.

TABLE 1. Clinical characteristics and outcomes of patients undergoing pleurectomy for mesothelioma

	All patients (n = 93)	VTE (n = 30)	No VTE (n = 63)	*P* value	95% CI
Age, y, median (range)	71 (30-85)	70 (52-82)	72 (30-85)	.34	−2.3 to 5.2
Gender, male, n (%)	74 (80)	25 (83)	49 (78)	.59	−0.11 to 0.22
Caprini score, mean ± SD	12 ± 1	11 ± 1	12 ± 1	<.001*	1.0 to 1.9
IOHC, n (%)	59 (63)	21 (70)	38 (60)	.49	−0.11 to 0.30
Neoadjuvant chemotherapy, n (%)	15 (16)	4 (13)	11 (17)	.76	−0.20 to 0.11
Histology, n (%)					
Epithelioid	60 (65)	19 (63)	41 (65)		
Sarcomatoid	4 (4)	2 (67)	2 (3)	-	-
Biphasic	29 (31)	9 (30)	20 (32)		
Patients with complications, n (%)	72 (77)	25 (83)	47 (74)	.43	−0.08 to 0.26
Transfusion (n%)	30 (32)	12 (40)	18 (29)	.27	0.60 to 1.1
Epidural catheter (n%)	88 (95)	30 (100)	58 (92)	.33	0.67 to 0.82
Hematologic complications, n (%)	9 (10)	5 (17)	4 (6)	.14	−0.04 to 0.25
Postoperative LOS	15 (4-85)	17 (6-40)	14 (4-85)	.18	−6.0 to 1.0
Distribution of VTE					
VTE, n (%)		**30 (100)**			
DVT, n (%)†		27 (90)			
Asymptomatic		9 (33)			
Upper extremity		12 (44)			
Indwelling catheter		7 (58)			
Lower extremity‡		18 (67)			
Proximal		2 (11)			
Distal		17 (94)			
PE, n (%)		10 (33)			

Boldface emphasizes the denominator of 30. *VTE*, Venous thromboembolism; *CI*, confidence interval; *SD*, standard deviation; *IOHC*, intraoperative heated chemotherapy; *LOS*, length of stay; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism. *Statistically significant. †Three patients had both upper- and lower-extremity DVTs. ‡Four patients had both proximal and distal lower-extremity DVTs.

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Deep Vein Thrombosis

Twenty-seven patients (90%) developed DVT during the study (Table 1). Of these, 9 (33%) were asymptomatic at the time of diagnosis and did not develop a PE or other complication related to anticoagulation. Median time to diagnosis was 7 days (1-14 days) postoperatively. The timing of diagnosis for all DVTs is shown in Figure 2. All DVTs were diagnosed during the index hospitalization. Two DVTs in the lower extremity were proximal (11% of the lower extremity DVTs), occurring in the left femoral (n = 1) and left popliteal (n = 1) veins, none of which resulted in a PE.

All 12 patients with an upper-extremity DVT had the thrombus in a vein previously associated with a central line. Seven (58%) occurred while the central catheter was still in place. The rest of the patients developed thrombosis in a vessel where there had previously been a central line; however, this occurred after 2 days of catheter removal in 1 patient, 3 days in 2 patients, and 5 days in 2 patients. Four (33%) of the 12 patients with an upper-extremity DVT developed a PE.

Pulmonary Embolism

Ten patients (11%) developed PE during follow-up. The median time to event was 7 days (1-23). Pulmonary emboli demonstrated a contralateral predilection, with 8 (80%) occurring in the opposite lung to the one that underwent surgery. Emboli occurred in the right lung in 4 patients and in the left lung in 2 patients, and 4 patients had bilateral PE. The event occurred during the index hospitalization in 9 patients (90%) and in 1 patient during a readmission 2 days after discharge (postoperative day 16). Symptoms prompting evaluation were hypoxia in 7 patients, pulmonary hypertension in 2 patients, and tricuspid regurgitation in 1 patient. All patients were diagnosed with CT-PA, except 1 patient who had chronic kidney disease, and thus underwent a ventilation perfusion scan, which was diagnostic of bilateral PE. Six of the 10 patients had IOHC at the time of

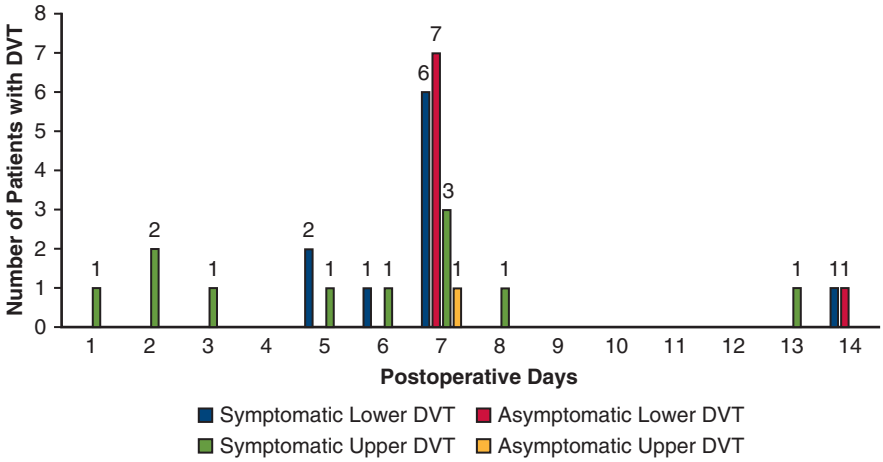

FIGURE 2. Time to postoperative diagnosis of symptomatic and asymptomatic upper- and lower-extremity DVTs. The majority of patients were diagnosed on postoperative day 7, ranging from 1 to 14 days. Nine of all DVTs (33%) occurred before day 7, which included half (6/12) of the upper-extremity DVTs. Only 3 patients with lower-extremity DVTs were symptomatic before day 7. There were 6 symptomatic patients who would have been screened on postoperative day 7 regardless of symptoms. Only 1 symptomatic patient, who would have been screened by the protocol, had a negative study on postoperative day 7. *DVT*, Deep vein thrombosis.

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surgery. Eight patients had evidence of multiple emboli, and 2 patients had only 1 PE. Most events were segmental or subsegmental; only 1 patient developed a central PE that extended into the right upper and lower segmental branches. Three patients with PE required placement of an inferior vena cava (IVC) filter after the event had occurred to prevent further events in anticipation of additional surgery.

Three patients (11% of all patients with a DVT) underwent placement of an IVC filter. Two of these patients had already developed PE but required additional surgical procedures. The third patient developed postoperative bleeding, so anticoagulation had to be stopped, and thus required an IVC filter to prevent PE.

Hematologic Complications

Nine patients experienced hematologic complications. Their characteristics are summarized in Table 2. There was no statistically significant difference in the rate of hematologic complications between those with and without VTE. There were 7 (8%) events of major postoperative bleeding within the cohort. Only 2 (2%) of them were related to the initiation of therapeutic anticoagulation. Median time to bleeding was 10 days (0-18). Three of these events occurred in patients with symptomatic VTE (patients 1-3 in Table 2). The first one developed a hemothorax before developing multiple symptomatic upper-extremity DVTs. The second occurred in a patient with right popliteal and left soleal DVT, who experienced increased bloody output from the chest tube 7 days after initiation of therapeutic enoxaparin. Anticoagulation was stopped, and the patient required placement of an IVC filter. The patient was discharged with 5 mg of apixaban twice per day. After 2.5 months of therapy, the patient experienced another episode of bleeding and anticoagulation was stopped. The third case was a patient with a left internal jugular vein DVT, who was discharged on enoxaparin 80 mg twice per day and readmitted 6 days after discharge with a hemothorax requiring return to the operating room. No asymptomatic patients with DVTs developed major bleeding or other hematologic complications.

Patients 4 to 7 shown in Table 2 did not have VTE and experienced bleeding complications. One patient appeared to develop disseminated intravascular coagulation with massive blood loss from small-vessel sources resulting in intraoperative death. Two of them developed a hemothorax requiring to go back to the operating room. The fourth patient developed hematuria and hemoptysis requiring an interventional bronchoscopy to address oozing from the right upper lobe.

Four patients developed HIT during follow-up (patients 6-9 in Table 2), 2 of whom had major bleeding complications (hematuria and hemoptysis, n = 1; hemothorax, n = 1). In all 4 cases, heparin was immediately discontinued and patients were transitioned to bivalirudin.

The 30-day mortality was 2%. Operative mortality was 5%. One of these was the patient who developed disseminated intravascular coagulation intraoperatively. One patient with a right internal jugular vein DVT and right upper and lower segmental and subsegmental PE developed pneumonia and acute respiratory distress syndrome, which ultimately caused the patient's death. Another patient with PE in the branches of the right upper and lower lobes

TABLE 2. Characteristics of patients who experienced major postoperative bleeding and other hematologic complications

Patient	Age, y	Gender	Histology	Caprini score	VTE	HIT	Event on index admission or readmission	Major bleeding event	Major bleeding days postoperatively	Bleeding related to AC	IVC filter	Long-term treatment
1	77	Male	Biphasic	9	RIJ, LIJ, axillary, subclavian DVTs right upper and lower lobe segmental, right middle lobe subsegmental PEs	No	Index admission	Yes, hemothorax	1	No	Yes, postoperative	Warfarin
2	67	Male	Biphasic	12	Yes, right popliteal, left soleal DVTs	No	Index admission	Yes, hemothorax	18	Yes, 7 d after AC	Yes, postoperative	Apixaban
3	62	Female	Biphasic	12	Yes, LIJ DVT	No	Readmission	Yes, Hemothorax	18	Yes, 13 d after AC	No	Enoxaparin
4	71	Male	Biphasic	12	No	No	Index admission	DIC	0	No	No	*
5	72	Female	Epithelioid	11	No	No	Index admission	Yes, hemothorax	16	No	No	-
6	73	Male	Biphasic	11	No	Yes	Index admission	Yes, hemothorax	1	No	No	-
7	78	Male	Epithelioid	12	No	Yes	Index admission	Yes, hemoptysis, hematuria	3	No	No	-
8	64	Female	Epithelioid	12	No	Yes	Index admission	No	-	No	No	-
9	68	Male	Epithelioid	10	Yes, LIJ, subclavian, axillary, soleal DVTs; right upper and lower lobe segmental and subsegmental PEs.	Yes	Index admission	No	-	No	No	*

VTE, Venous thromboembolism; *HIT*, heparin-induced thrombocytopenia; *AC*, anticoagulation; *IVC*, inferior vena cava; *RIJ*, right internal jugular; *LIJ*, left internal jugular; *DVT*, deep vein thrombosis; *PE*, pulmonary embolus; *DIC*, disseminated intravascular coagulation. *Perioperative mortality, not related to VTE.

developed pneumonitis and acute respiratory distress syndrome, which caused the patient's death. The other 2 patients did not have VTE events, and their causes of death were sudden cardiac arrest; both families denied autopsies.

Average Hospital Charges

Hospital charges for LENIS/UENIS averaged $2103. Total estimated hospital charges for all surveillance scans completed during this study period were $296,484. The median charge of surveillance per patient was $2103 ($2103-$10,115).

Hospital charges for CT-PA averaged $3392. Total estimated hospital charges for pulmonary angiographies completed during the study were $40,704.

DISCUSSION

VTE remains a major cause of postoperative morbidity and mortality after thoracic oncological surgery. Much of the variability on incidence and prevalence of VTE after

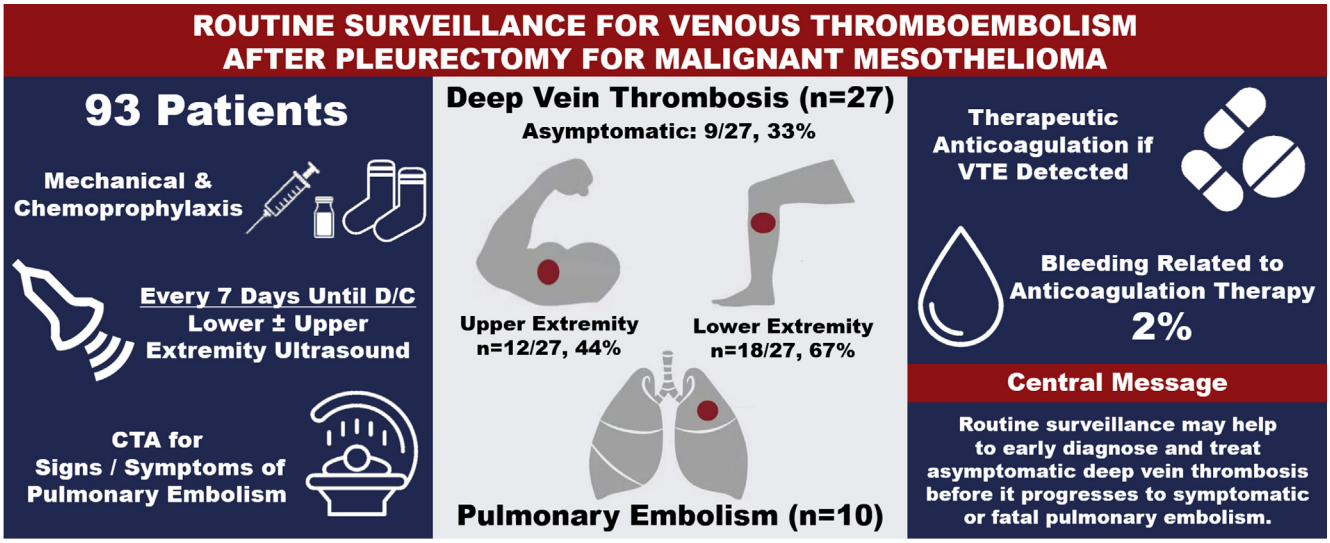

FIGURE 3. We implemented an aggressive surveillance protocol for VTE in 93 patients undergoing pleurectomy for mesothelioma. Patients received mechanical and chemoprophylaxis perioperatively and were followed every 7 days postoperatively, or earlier if symptomatic, with upper- ± lower-extremity ultrasounds. CT-PA was used to investigate patients who developed signs or symptoms suggestive of PE. Twenty-seven patients developed DVT, 9 of whom were asymptomatic; 10 patients developed PE. Therapeutic anticoagulation was initiated in these patients. There was only a 2% incidence of bleeding events related to therapeutic anticoagulation. *D/C*, Discharge; *CTA*, computed tomography angiogram; *VTE*, venous thromboembolism.

thoracic surgery is due to differences in definitions of symptoms as well as practices among surgeons related to surveillance for VTE in asymptomatic patients.[20]

It has been our approach to prevent and aggressively identify complications at an early stage, when they are easier to treat and their effect on patients remains minimal. We have adopted an aggressive surveillance protocol, obtaining noninvasive vascular studies on all patients undergoing surgery for mesothelioma, during the seventh postoperative day. We have a low threshold for using CT-PA in patients with moderate symptoms or minor oxygen desaturations, and thus have been diagnosing PE with a greater frequency. With the implementation of this aggressive surveillance protocol, this prospective study demonstrated a 32% incidence of postoperative VTE after P/D for mesothelioma, despite adherence to current thromboprophylaxis recommendations (Figure 3).

Current recommendations regarding anticoagulation prophylaxis of patients are based on risk factor analysis. The Caprini Scoring system is used to identify patients at increased postoperative risk of VTE.[21] Its scoring sheet recommends chemoprophylaxis in patients with a score of 4, which is considered "moderate risk," or greater.[22,23] Considering the average age of the patients in our cohort was 71 years, all have a diagnosis of malignancy, and all underwent major surgical intervention, it is not surprising that all the patients were found to be at the highest risk for development of VTE with an average score of 12 or a 10.7% risk of developing DVT. Therefore, prophylactic anticoagulation is justified according to the current American College of Chest Physicians guidelines.[24] It is our belief that if anticoagulation is indicated, so is surveillance to detect DVT early and any complications that may arise from it.

The screening and treatment of asymptomatic patients with VTE remain controversial because of the implication of treating a patient who otherwise would have never had clinical manifestations. In a study of 157 patients undergoing pulmonary oncologic resections, Agzarian and colleagues[20] found a VTE prevalence of 12.1% in the postdischarge period. Of these events, 15 (79%) were asymptomatic and only found after patients were screened. The rate of bleeding events in their cohort was 2.5%. Agzarian and colleagues[20] advocate for prophylactic screening before discharge after surgery for lung resection. Harris and colleagues[25] reported a 7.5% incidence of DVT after screening all patients in a surgical intensive care unit. On the basis of studies of the natural history of DVT and PE,[26] they calculated in their cohort a potential 2.25% incidence of PE and a 0.68% risk of death and concluded that screening for VTE was justified. Surveillance for DVT in the present study showed a 30% incidence of DVT, which is more than 4 times as much as what was found in their study. If we extrapolate the same figures of

the natural history of DVT presented in Harris and colleagues' study to our cohort, there is a potential 9% incidence of PE and a 3% potential mortality rate. Our data support that surveillance for patients undergoing surgery for mesothelioma is more justified.

Brasel and colleagues[14] found routine surveillance to be cost-effective in preventing PE. In the present study, we found that 3 LENIS/UENIS were necessary to detect 1 DVT overall, which generated estimated total hospital charges of $6309. This value is lower than the hospital charge of ICU care after development of a PE, which is averaged at approximately $9898 per day. Because all events were diagnosed by postoperative day 14, the value of surveillance beyond that point may be limited. Although 3 patients with no DVT developed a PE, we found no value for routine surveillance for PE using CT-PA. Further, CT-PA has associated risks of radiation, anaphylaxis, and kidney injury from contrast, which also discourage its routine use.

Our study found that all patients with upper-extremity DVT had a central line in place. Central lines are routinely placed in all patients undergoing P/D for hemodynamic monitoring. We do not routinely surveil patients for upper-extremity DVT, unless they become symptomatic, because historically the risk of PE from the upper extremity is low.[27] Because only 1 patient with upper-extremity DVT was asymptomatic and did not develop PE, we do not believe it is cost-effective to screen all patients for upper-extremity DVT. However, because one-third of these patients developed PE, we have been more actively looking for symptoms of DVT that would prompt further evaluation, specially within the first 7 days postoperatively because 80% of these patients developed DVTs in this period.

Finding the balance between postsurgical anticoagulation for prevention of DVT and reducing bleeding risk is an important and difficult factor to consider. The risk of hemorrhage from antithrombotic therapy is not insignificant.[17] We described an 8% incidence of major bleeding requiring intervention in our cohort, comparable to what has been reported previously for P/D for mesothelioma, with major bleeding ranging from 5% to 25%.[28-31] Further, P/D for mesothelioma itself is a complex operation that often involves significant blood loss and multiple blood products after surgery.[8] In a meta-analysis of the efficacy and safety of low-molecular-weight heparin in preventing VTE in postsurgical patients, Harris and colleagues[25] found that more patients experienced bleeding caused by low-molecular-weight heparin than avoided VTE: For every VTE prevented, 2 patients experienced major hemorrhage and 7 received a transfusion. In a 2017 meta-analysis of risks and benefits of VTE prophylaxis for surgical patients across all specialties stratified for VTE using the Caprini score, Pannucci and colleagues[32] report that only patients with Caprini scores greater than 7, which are high risk, had significant VTE risk reduction with chemoprophylaxis, without a significant increase in bleeding events. In line with these findings, the American College of Chest Physicians guidelines recommend that in patients undergoing thoracic surgery, patients at moderate and high risk for postoperative VTE, the benefit of VTE prevention through prophylaxis with heparin outweighs the risk for adverse bleeding events.[24] Further, the incidence of bleeding related to therapeutic anticoagulation in this cohort was 2%, suggesting that routine surveillance may not increase the rate of anticoagulation-related bleeding, despite an increased diagnosis and treatment of DVT.

Study Limitations

This study has several limitations. First, although this study demonstrates the effectiveness of perioperative surveillance to identify DVT, it cannot provide reliable data on the optimal type, timing, or duration of chemoprophylaxis. Second, although it is one of the largest cohorts of its kind, it is a single institutional experience, and as such, results may vary in other institutions. At the same time, this may be a strength of the present study because of a more uniform management strategy and follow-up compared with retrospective multi-institutional studies. Third, because the 2 patients with sudden cardiac death did not undergo autopsy, it is possible that the incidence of PE may be underestimated. It is possible that ultrasounds may have yielded false-negative results and that patients who had longer stays in the hospital underwent more surveillance studies, and thus those discharged earlier might have had an undiagnosed DVT, underestimating the incidence of DVT.

CONCLUSIONS

The implementation of an aggressive surveillance protocol for DVT in patients undergoing P/D for mesothelioma yielded a high (32%) incidence of VTE despite standardized antithrombotic prophylaxis. Up to 33% of patients with DVT are asymptomatic at the time of diagnosis, and the incidence of major bleeding and other complications related to anticoagulation is comparable to other studies for P/D. Further studies are needed to provide data on the benefits of prophylactic anticoagulation against the risk of bleeding, as well as the cost–benefit of surveillance in high-risk patients undergoing oncological thoracic surgery. Routine surveillance with lower- and upper-extremity noninvasive studies can be effectively implemented and may be helpful to diagnose and treat asymptomatic DVT before it progresses to symptomatic or fatal pulmonary embolus.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Sunday_May5/203BD/203BD/S62%20-%20Doing%20the%20right%20thing%20I/S62_4_webcast_044415994.mp4.

Conflict of Interest Statement

Dr Bueno has received grants from Roche, National Cancer Institute, Department of Defense, Epizyme, Genentech, Merck, Johnson & Johnson, Siemens, Gritstone, and Barr Foundation for the study of mesothelioma. Dr Bueno made possible philanthropic donations to our institution from individuals and Thornton Law Firm. All other authors have nothing to disclose with regard to commercial support.

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Key Words: mesothelioma, venous thromboembolism, pleurectomy, thoracic surgery, surveillance, morbidity, thromboprophylaxis, pulmonary embolism, postoperative care

Discussion

Dr Mark Onaitis *(La Jolla, Calif)*. Congratulations on this important article that highlights a high rate of VTE after P/D despite standard-of-care prophylaxis. This is important information, and I have 3 questions.

First, while acknowledging the bleeding risk, should we be doing more than the standard of care prophylaxis in terms of Lovenox (Sanofi-Aventis, Paris, France) or other things to prevent these DVTs?

Dr Michael T. Jaklitsch *(Boston, Mass)*. One alternative is to administer Lovenox at a more therapeutic rate. This particular protocol was developed about 10 to 12 years ago in the face of approximately a 4% fatal PE rate. The balance for malignant pleural mesothelioma in diseased pleurectomies leave an open, weeping, potentially bleeding source on the inside of the ribcage. That's why we have not gone to using Lovenox, but this is precisely the sort of data generation that would springboard us to then have a multispecialty discussion to see if there is a better way to do it.

Dr Onaitis. Second, do you use epidurals for these patients and did this affect the prophylaxis; you can't use Lovenox if you have an epidural in?

Dr Jaklitsch. Yes, that's true. We do use epidurals in the majority of these patients, and according to the recommendations by the anesthesiology professional societies, you can't have a dose of Lovenox and then get an epidural catheter.

Dr Onaitis. It seemed like a lot of the clots are due to the central line, and so have you changed management trying to avoid central lines in these patients?

Dr Jaklitsch. That was one of the more interesting aspects of the data that came out of this. I can't say that we have regimented against it, but obviously seeing that links of all the upper-extremity clots were from central lines, there are alternatives to central line placement.

Dr Benjamin D. Kozower *(St Louis, Mo)*. I think this is the third example I have seen where the more you screen the more you find. So your quality metrics don't look so good but yet you are delivering quality care. What are you going to do going forward?

Dr Jaklitsch. That's right. I think that we as a Society need to keep emphasizing to our public that screening for morbidity when it's grade 2 or grade 3 morbidity we believe prevents grade 4 and grade 5 morbidity. So the old method where the study was dinged by the morbidity rate, I think we have become more sophisticated to say lower-stage morbidity is worth searching for so you can prevent the grade 4s and grade 5s.

Unidentified Speaker. One clarification. I understand you found 30 VTEs, 33%, or 10 of them, were asymptomatic, and if I understand correctly, of those 10 that were asymptomatic, when you did anticoagulate them, none of them had a complication from the anticoagulation. Is that correct?

Dr Jaklitsch. That is correct.