Venous thromboembolism in patients receiving multimodality therapy for thoracic malignancies

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Objective: The rate of venous thromboembolism in patients undergoing multimodality therapy for lung malignancy and the impact of preoperative venous thromboembolism on postoperative outcome have not been analyzed systematically.

Methods: We performed a retrospective review of all patients undergoing induction therapy before lung resection for non-small cell lung cancer and malignant pleural mesothelioma at the University Health Network between January 1996 and December 2007.

Results: Venous thromboembolism developed in 23 (12.3%) of 186 patients undergoing induction therapy. The venous thromboembolism was diagnosed during induction therapy in 11 patients. The proportion of pulmonary embolism was higher during induction therapy (9/11 patients), whereas deep venous thromboses were observed predominantly postoperatively (7/12 patients) ($P = .02$). The risk of postoperative complications or death was not increased in patients undergoing surgery despite a preoperative diagnosis of venous thromboembolism. However, the risk of postoperative pulmonary embolism was higher in patients undergoing surgery without insertion of an inferior vena cava filter (1/2 patients vs 0/7 after insertion of an inferior vena cava filter, $P = .047$). The overall survival was similar between patients with or without venous thromboembolism complications.

Conclusion: This study demonstrates that venous thromboembolism events in patients undergoing multimodality therapy for lung malignancies is high and deserves careful consideration. Patients with a venous thromboembolism diagnosis during induction therapy may potentially benefit from a temporary inferior vena cava filter before surgery to limit the risk of recurrent pulmonary embolism. A preoperative diagnosis of venous thromboembolism, however, does not affect early and late outcomes after surgery and should not be viewed as a negative prognostic marker.

Venous thromboembolism (VTE) is a common complication that has been studied extensively in postsurgical patients because of its impact on morbidity and mortality.¹ The rate of postoperative VTE has decreased dramatically since a large multicenter trial demonstrated that low-dose heparin (5000 units) administered 2 hours before incision and then every 8 hours postoperatively significantly reduced the incidence of VTE.² However, the impact of induction therapy on the incidence of preoperative and postoperative VTE in patients undergoing lung resection for malignancy has not been reported. This question is of importance considering that an increasing number of patients with lung cancer are treated with induction chemotherapy or chemoradiation therapy for locally advanced disease.^{3,4} Preoperative VTE may increase the risk of surgery because of a reduction in

the pulmonary vascular bed in patients with other potential comorbidities and be associated with a higher risk of postoperative thrombotic and bleeding events.

The aim of this study is to review the rate of preoperative and postoperative VTE in patients treated with induction therapy and to analyze the impact of preoperative VTE on postoperative outcome. On the basis of our experience and that of the literature, recommendations for management of patients presenting with preoperative VTE are presented.

MATERIALS AND METHODS

We performed a retrospective chart review of 186 consecutive patients undergoing induction therapy for non-small cell lung cancer (NSCLC) and malignant pleural mesothelioma (MPM) at the University Health Network between January 1996 and December 2007. The study was approved by the Research Ethics Board of the University Health Network.

All patients with NSCLC presenting with superior sulcus tumors, spinal involvement, or stage IIIA (N2) disease underwent induction chemoradiation therapy with cisplatin-etoposide concurrently with 45 Gy of radiation, and all patients with MPM underwent induction chemotherapy with cisplatin-vinorelbine ($n = 26$), cisplatin-pemetrexed ($n = 24$), cisplatin-raltrexed ($n = 6$), cisplatin-gemcitabine ($n = 4$), or cisplatin-doxorubicin ($n = 3$) followed by extrapleural pneumonectomy (Table 1). Surgery was usually performed 3 to 6 weeks after completion of induction therapy.

Prophylaxis for VTE during the study period was unfractionated subcutaneous heparin 5000 units twice daily starting the day of surgery until hospital discharge. Pneumatic stockings have been used systematically during

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Abbreviations and Acronyms

IVC	= inferior vena cava
MPM	= malignant pleural mesothelioma
NSCLC	= non-small cell lung cancer
PE	= pulmonary embolism
VTE	= venous thromboembolism

the perioperative period since 2003. No VTE prophylaxis was used during induction therapy. No systematic screening for VTE was performed before or after surgery. The decision to investigate for deep vein thrombosis or pulmonary embolism (PE) was decided on the basis of clinical suspicion.

PE had to be documented by computed tomography scan or V/Q scan, and deep vein thrombosis had to be documented by Doppler ultrasonography. Patients presenting with sudden death from a suspected PE were also included in this study. Patients diagnosed with VTE during induction therapy were switched to unfractionated intravenous heparin at the time of surgery, and therapeutic dose of heparin was resumed within 24 to 96 hours postoperatively. The decision to insert an inferior vena cava (IVC) filter or not was made by the surgical team on a case-by-case basis. Data were collected from electronic patient records and paper charts. Age, gender, type of malignancy, type of surgery, timing of VTE, management of VTE, and postoperative complications were recorded for each patient.

Postoperative deaths included all patients who died within 30 days of surgery or during the same hospitalization. Postoperative complications were defined as complications within 30 days of surgery or during the same hospital stay. Major cardiac and pulmonary complications were defined as grade 3, 4, or 5 complications according to the National Cancer Institute Common Terminology Criteria for Adverse Events 3.0 guidelines.

Results are presented in absolute number and percentage, or median and range. Categorical variables were compared by chi-square analysis, and numeric variables were compared by Student *t* test. Cumulative proportion of VTE from the start of induction therapy was obtained by using the Kaplan–Meier method. Multivariate analysis was assessed by logistic regression analysis to determine independent predictors of major cardiopul-

monary complications and postoperative death. Overall survival was estimated using the Kaplan–Meier method. Differences in survival were tested for significance by the log-rank test. Because the characteristics of patients with VTE complications were different (Table 1), a propensity score was developed to reduce selection bias in comparing outcomes.^{5,6} The propensity score for each patient who underwent surgery was calculated on the basis of gender, age (continuous variable), type of cancer (NSCLC vs MPM), and induction treatment (chemotherapy alone vs chemoradiotherapy). Cox regression modeling was then performed with the calculated propensity scores and the event of VTE (either pre- or postoperative vs non-VTE) as variables to determine if VTE was an independent predictor of outcome. Statview V (Abacus Concept, Berkeley, CA) and STATA 10 (StataCorp LP, College Station, TX) were used for all analyses.

RESULTS

VTE developed in 23 (12.3%) of 186 patients undergoing induction therapy during the 11-year study period. The cumulative proportion of VTE from the start of induction therapy is presented in Figure 1. VTE was diagnosed during induction therapy in 11 patients and postoperatively in 12 patients. The proportion of PE was higher during induction therapy (9/11 patients), whereas deep vein thromboses were observed predominantly postoperatively (7/12 patients) ($P = .02$). Among patients with NSCLC, VTE was seen in 8 of 57 patients (14%) with adenocarcinoma compared with 11 of 66 patients (17%) with other histologic subtypes of NSCLC ($P = .7$).

Among the 12 patients with VTE postoperatively, 8 were diagnosed while in hospital (after admission to the intensive care unit in 4 patients) and 4 were diagnosed after being discharged from hospital. Postoperative VTE did not develop in any patient during consolidation chemotherapy. The introduction of pneumatic stockings in 2003 did not reduce the risk of postoperative VTE (4 postoperative VTEs in 77

TABLE 1. Patient characteristics

	All patients (n = 186)	Patients with VTE complications (n = 23)	Patients without VTE complications (n = 163)	P value
Age, y				.6
Median	60	63	60	
Range	21–80	21–75	32–80	
Gender				.9
Male	122	15	107	
Female	64	8	56	
Indications for induction therapy				.07
MPM	63	4	59	
NSCLC	123	19	104	
Induction therapy				.2
Chemoradiation therapy	119	17	102	
Chemotherapy alone	67	6	61	
Type of surgery				.4
Extrapleural pneumonectomy	48	3	45	
Pneumonectomy	20	4	16	
Lobectomy	90	13	77	
Wedge resection	2	1	1	
No surgery	26	2	24	

VTE, Venous thromboembolism; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer.

FIGURE 1. Cumulative proportion of VTE complications after initiation of induction therapy. *Dashed lines* represent the 95% confidence interval. VTE, Venous thromboembolism.

patients undergoing surgery between 1996 and 2002 and 5 postoperative VTEs in 83 patients between 2003 and 2007 (5.2% vs 6.0%, $P = .8$).

Among the 11 patients diagnosed with VTE during induction therapy, 9 proceeded to surgery: Five patients underwent a lobectomy, 2 patients underwent a pneumonectomy, and 2 patients underwent an extrapleural pneumonectomy. The period of time between the diagnosis of VTE and surgery ranged from 17 to 107 days (median 28 days). In 2 patients, the treatment plan was changed after the diagnosis of VTE. In 1 patient with large bilateral PE, the radiation

TABLE 2. Major postoperative cardiopulmonary complications*

Complications	No. of patients (%)
Major cardiopulmonary complications	42 (26%)
Pulmonary complications	
Respiratory failure/Pneumonia	21
Empyema	6
Bronchopleural fistula	3
Pulmonary emboli	3
Cardiac complications	
Atrial fibrillation	19
Myocardial infarction	1
Cardiac herniation	1

*Some patients had > 1 complication.

dose was boosted from 45 to 60 Gy in the event that surgery was not going to be feasible. In the second patient, a left pneumonectomy was planned and surgery was delayed by 8 weeks to allow resolution of a large right-sided PE. In the remaining 7 patients, the protocol of induction therapy and surgery was completed as anticipated with no delay in surgery despite the VTE. Seven patients underwent insertion of an IVC filter immediately before surgery.

Among 160 patients undergoing surgery, major cardiopulmonary complications developed in 42 (26%) and 10 (6.3%) died postoperatively (Table 2). The risk of major cardiopulmonary complications was significantly higher in men and in patients aged more than 60 years (Table 3). Patients undergoing pneumonectomy were also at greater risk of major cardiopulmonary complications and death than patients

TABLE 3. Risk factors for major cardiopulmonary complications

Factors	All patients undergoing surgery (n = 160)	Complications		P value	
		Yes (n = 42)	No (n = 118)	Univariate analysis	Multivariate analysis
Type of resection				.06	.06
Pneumonectomy or EPP	68	23	45		
Lobectomy or wedge	92	19	73		
Side of surgery				.6	.6
Right	89	22	67		
Left	71	20	51		
VTE during induction therapy				.2	.2
Yes	9	4	5		
No	151	38	113		
Age > 60 y				.04	.04
Yes	74	25	49		
No	86	17	69		
Gender				.04	.04
Male	101	32	69		
Female	59	10	49		
Indication for induction therapy				.6	.3
MPM	48	14	34		
NSCLC	112	28	84		
Type of induction therapy				.3	.6
Chemoradiation therapy	108	27	81		
Chemotherapy	52	15	37		

EPP, Extrapleural pneumonectomy; VTE, venous thromboembolism; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer.

TABLE 4. Risk factors for postoperative deaths

Factors	All patients undergoing surgery (n = 160)	Postoperative death		P value	
		Yes (n = 10)	No (n = 150)	Univariate analysis	Multivariate analysis
Type of resection				.01	.03
Pneumonectomy or EPP	68	8	60		
Lobectomy or wedge	92	2	90		
Side of surgery				.3	.4
Right	89	7	82		
Left	71	3	68		
VTE during induction therapy				.4	.9
Yes	9	0	9		
No	151	10	141		
Age > 60 y				.8	.8
Yes	74	5	69		
No	86	5	81		
Gender				.6	.6
Male	101	7	94		
Female	59	3	56		
Indication for induction therapy				.5	.8
MPM	48	4	44		
NSCLC	112	6	106		
Type of induction therapy				.2	.2
Chemoradiation therapy	108	5	103		
Chemotherapy	52	5	47		

EPP, Extrapleural pneumonectomy; VTE, venous thromboembolism; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer.

undergoing lobectomy (Tables 3 and 4). A preoperative diagnosis of VTE, however, did not increase the risk of postoperative cardiopulmonary complications or death (Tables 3 and 4). Major positive complications developed in 3 of the 9 patients (33%) with a preoperative diagnosis of VTE: recurrent PE (n = 1), hemothorax (n = 1), and pneumonia (n = 1). Among patients with a diagnosis of VTE made during induction therapy, the risk of postoperative PE was higher in those undergoing surgery without insertion of an IVC filter (PE developed in 1/2 patients without IVC filter vs 0/7 patients with an IVC filter, $P = .047$).

After a median follow-up of 1.5 years after surgery, 11 of 21 patients (52%) with a history of VTE and 80 of 139 patients (58%) without VTE have died ($P = .7$). The overall survival was similar between patients with or without VTE complications (Figure 2). After adjustment for the propensity score, the hazard ratio of VTE was 1.004 (95% confidence interval, 0.53–1.89; $P = .99$), confirming that preoperative or postoperative VTE did not affect patients' survival after surgery. Among patients with a preoperative diagnosis of VTE, 5 are alive without recurrence 2.5 to 8.5 years after surgery (median 2.1 years), and the 5-year survival reached 54% in patients with NSCLC (Figure 3).

DISCUSSION

This study demonstrates that the rate of VTE in patients undergoing induction therapy for lung malignancy is high,

ranging between 6.3% in patients undergoing induction chemotherapy for MPM and 15.4% in patients undergoing induction chemoradiation therapy for NSCLC. The number of VTE events was higher than in other series of lung resection for malignancy and relates to the fact that approximately half of the VTE complications occurred during induction therapy before surgery.⁷⁻⁹

The rate of postoperative VTE in our series ranged between 7% and 8%. The majority of postoperative VTE occurred in patients admitted to the intensive care unit for major postoperative complications or in patients already

FIGURE 2. Overall survival of patients with or without VTE complications. VTE, Venous thromboembolism.

FIGURE 3. Survival of patients with NSCLC with a VTE diagnosis during induction therapy compared with patients with NSCLC without preoperative or postoperative VTE complications. VTE, Venous thromboembolism.

discharged from the hospital. This experience is similar to that reported by other groups and suggests that particular attention should be given to these 2 groups of patients.⁷

During the past decade, early hospital discharge has been associated with an increasing incidence of VTE in the outpatient setting, and some studies suggest that continued prophylaxis after hospital discharge may be beneficial in patients at high risk of VTE.^{10,11} In our experience, VTE developed in 4 patients after being discharged from the hospital and 2 of them died suddenly at home from a presumed PE. Thus, patients undergoing induction therapy seem to be a high-risk group and should potentially be kept on prophylactic anticoagulation after hospital discharge for up to 4 weeks after surgery. The guidelines recently published by the American College of Chest Physicians and American Society of Clinical Oncology also suggest that some selected patients at high risk of VTE may benefit from continuing thromboprophylaxis after hospital discharge with low molecular weight heparin for up to 28 postoperative days.^{12,13}

VTE developed in 11 of 186 patients during induction therapy. This translates into an incidence of VTE of approximately 59 per 1000 patient-years in our experience. This incidence is similar to other studies looking specifically at the association between VTE and lung cancer with an incidence ranging between 44 and 100 per 1000 person-years.^{14,15} A diagnosis of VTE during induction therapy did not increase the risk of not proceeding to surgery. It did, however, lead to a change in the treatment plan in 2 of the 9 patients scheduled for surgery. The radiation dose was boosted from 45 to 60 Gy in 1 patient, and surgery was delayed to allow resolution of the PE in 1 patient.

Although a preoperative diagnosis of VTE did not have a significant impact on the overall risk of postoperative complications or deaths, complications developed in 2 patients that were directly related to their VTE postoperatively. Recurrent PE developed in 1 patient on the second postopera-

tive day, and a tension hemothorax in the pneumonectomy cavity developed in 1 patient. The only patient in whom recurrent PE developed did not have an IVC filter inserted before surgery. The role of an IVC filter in a patient with acute PE remains controversial, and firm recommendations cannot be drawn from this small series of patients. However, we think that the specific subgroup of patients presenting with clinically significant VTE during their induction therapy may potentially benefit from a temporary IVC filter because the anticoagulation has to be stopped perioperatively. Temporary IVC filters can be removed after the patient has recovered from the surgery and completed all postoperative therapy, thereby avoiding long-term complications associated with their use.¹⁶

The resolution of acute PE is maximal during the first 6 weeks after the initiation of therapeutic anticoagulation.^{17,18} Thereafter, improvement may still be observed but at a lower rate. Thus, a period of 6 weeks between the diagnosis of PE and surgery may be optimal, particularly for patients presenting with large PE. The diagnostic workup before surgery should include a V/Q scan and an echocardiogram to ensure that there is complete resolution of the PE and no residual pulmonary hypertension.¹⁹ The V/Q scan remains a better test than multislice computed tomographic angiogram to rule out chronic thromboembolic disease and will also identify differential perfusion between the right and left lung that may be useful for planning surgery, particularly if a pneumonectomy is anticipated.²⁰

Some series suggest that patients with malignancy who develop VTE have a substantially worse survival than patients without VTE.^{7,21} However, it remains unclear whether VTE in surgical patients is a direct cause of poor outcome or a marker of more aggressive malignancy. In our experience, the overall outcome was not significantly different whether patients were diagnosed with VTE or not. By looking more specifically at the group of patients with NSCLC, survival was identical between patients with a VTE diagnosis before surgery and patients without VTE complications before or after surgery. This is similar to the results recently reported from the National Cancer Institute of Canada Clinical Trial Group pooled analysis.²² VTE developed in 3% of the patients treated with adjuvant chemotherapy for stage IB and II NSCLC in the JBR.10 trial, but VTE was not associated with poorer survival in this group of patients with early-stage NSCLC.^{22,23} Thus, we believe that a preoperative diagnosis of VTE should not necessarily be viewed as a negative prognostic marker in early-stage disease and that a diagnosis of VTE should not be a reason to select a nonsurgical approach to potentially curative surgery.

This study has several limitations related to the retrospective nature of the data collection and the mixed patient population. The true prevalence of patients with VTE is likely underestimated because we did not prospectively perform imaging studies to detect patients with asymptomatic VTE.

The type of induction therapy is also variable between institutions, and, although unlikely, induction therapy with platinum and taxane may have a different impact on the risk of VTE than we observed in our series.

CONCLUSIONS

This large study of patients undergoing induction therapy for lung malignancy demonstrates that the rate of VTE during induction therapy is high and deserves careful consideration. Patients with a VTE diagnosis during induction therapy may require a change in their treatment plan and are at risk of recurrent VTE and bleeding postoperatively. The insertion of a temporary IVC filter at the time of surgery in patients with a preoperative diagnosis of VTE remains controversial but may be beneficial in this subgroup of patients. The immediate postoperative outcome and long-term survival of patients with a preoperative diagnosis of VTE are similar to those of other patients without any VTE complications. Thus, we believe that a preoperative diagnosis of VTE should not be viewed as a negative prognostic marker and should not be a reason to select a nonsurgical approach to potentially curative surgery.

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