Original Article

The early and long-term occurrence of symptomatic venous thromboembolism after lung cancer surgery without extended thromboprophylaxis—a single center experience with 435 patients

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Background: The incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), after lung cancer resections varies in the literature, and there is limited evidence regarding the optimal duration of thromboprophylaxis. This study aimed at determining the early and long-term occurrence of thromboembolic complications in patients who received in-hospital thromboprophylaxis and underwent resective surgery for lung cancer.

Methods: The study included all patients who underwent lung cancer surgery at Tampere University Hospital between 2004 and 2016. Postoperative thromboprophylaxis was administered for the duration of the hospitalization. Data on subsequent episodes of VTE and survival were obtained from national registries. The results were compared to a demographically matched reference population.

Results: The study comprised 435 patients and 4,338 individuals in the reference population. The overall occurrence of VTE in patients and the reference group was 0.3% *vs.* 0.2% at 90 days (P=0.56), 3.5% *vs.* 0.7% at 1 year (P<0.001), 9.2% *vs.* 2.2% at 3 years (P<0.001), and 18.7% and 3.9% at 5 years (P<0.001), respectively. The majority of cases represented PE. The overall mortality at 5 years was 44.4% *vs.* 11.6% (P<0.001). No associations between patient characteristics and the occurrence of VTE during follow-up were detected.

Conclusions: Patients undergoing lung cancer surgery and who receive in-hospital medical thromboprophylaxis do not seem to be in high risk for symptomatic VTE during the early postoperative period. However, during long-term follow-up the occurrence of symptomatic VTE was significant.

Keywords: Deep vein thrombosis (DVT); pulmonary embolism (PE); postoperative thrombosis; thoracic surgery; lung resection

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Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients, contributing to significant morbidity and mortality (1-4). Approximately 20% of all VTE cases may be attributed to cancer (5), and cancer patients experience more than three times higher mortality rates when compared to non-cancer controls (6). The management of VTE in cancer patients is challenging, often requiring long-term anticoagulation that increases the risk of bleeding. Additionally, recurrent VTE despite anticoagulant therapy is more frequent in patients with cancer (7).

In patients with lung cancer, the overall incidence of thromboembolic complications is high with an estimated rate of 39.2 per 1,000 person-years, surpassing the average incidence of thromboembolic complications in patients with cancer (8). Notably, VTE following lung cancer surgery is associated with an eight-fold increase in mortality rates which is higher than following other types of major cancer surgeries (9). However, the reported incidence of VTE in surgically treated lung cancer patients varies widely across the literature. A comprehensive systematic review encompassing 19 trials and 10,600 patients estimated the mean occurrence of VTE to be 2.0% during an average observation period of 16 months (10). Most studies have limited follow-up periods, predominantly focusing on immediate post-operative months, and studies with longer-term follow-up are scarce. Furthermore, variations in thromboembolic protocols and diagnostic methods for detecting thromboembolic events further complicate the interpretation and comparison of findings between studies.

Therefore, the aim of the study was to investigate both the early and long-term occurrence of VTEs in lung cancer patients undergoing curative-intent surgery. Additionally, the study aimed at identifying patient-specific risk factors associated with VTE. To facilitate comparisons with the expected rate of VTE in the general population, particularly during long-term follow-up, the rates were compared to those of a demographically matched reference population. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-308/rc).

Highlight box

Key findings

- The rate of symptomatic venous thromboembolism (VTE) after lung cancer surgery without extended prophylaxis was 0.3% at 3 months and reached 18.7% at 5 years.

What is known and what is new?

- The incidence of VTE, including deep vein thrombosis and pulmonary embolism, after lung cancer resections varies in the literature, and there is limited evidence regarding the optimal duration of thromboprophylaxis.
- The occurrence of VTE appears low early postoperatively, but the risk is significant during long-term follow-up. To the best of the authors' knowledge, the present study is the first to report the occurrence of VTE during extended follow-up in this patient group.

What is the implication, and what should change now?

- Based on this study the optimal duration of thromboprophylaxis after lung cancer surgery remains uncertain and there is no support for extended prophylaxis. However, this study reflects only the symptomatic cases as no routine screening was performed, possibly underestimating the true incidence of VTE.

Methods

Study patients and reference population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (No. R17575) and individual consent for this retrospective analysis was waived. The study population included all patients who underwent lung cancer surgery between February 2004 and December 2016 in the Tampere University Hospital, Tampere, Finland. The study hospital is a tertiary academic referral center and the second largest hospital in Finland with a catchment area exceeding 1 million residents. The patients were identified from the institutional database by retrieving all cases associated with the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedure codes for sublobar resections, lobectomies of one or more lung lobes, bronchial resections, as well as pneumonectomies. Each case was carefully reviewed and patients without histopathological confirmed lung cancer in the final analyses and those who did not undergo planned resections due to advanced disease stage observed during surgery were excluded. Relevant demographic information, medical history including possible data on neoadjuvant treatments, cancer stage and histopathology were collected from each patient. Data on surgical technique and extent of the surgery, recovery, including the length of hospitalization

and the occurrence and types of complications, were recorded. The demographically matched reference population was obtained by requesting a random sample of 10 individual controls for each patient that were matched for sex, age and the location of residence, from the Finnish Population Register Centre, a national registry that also provides large control materials for research purposes, from which survival data was also obtained for both the patients and the reference population. The follow-up period for individuals in the reference population commenced at the matching date to that of their corresponding patients' date of surgery. The follow-up included all deaths occurring until December 31st, 2018.

Thromboembolic complications

Over the study period the standard clinic practice for pharmacological thromboprophylaxis involved daily subcutaneous injections of low-molecular-weight heparin (enoxaparin 40 mg) during hospitalization. Deviations from this protocol (e.g., in cases with bleeding or in those with oral anticoagulants) were at the discretion of the treating clinician. Information regarding subsequent thromboembolic events, specifically DVT or PE, in both study cohorts were obtained from the National Institute for Health and Welfare database that contains complete data on all specialized medical care hospitalizations as well as emergency room and outpatient clinic visits in Finland. Treatment episodes associated with the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis codes "I80", "I82", or "I26", or any subclass of these diagnosis codes, following the date of the lung cancer surgery in patients and the corresponding index date in controls were identified from the database and classified as having DVT and/or PE for the purposes of the study. The follow-up lasted until the end of December 2016. The occurrence, type, and timing of VTE, and the number of related in-hospital days as well as patient-specific risk factors and overall long-term survival were ascertained using statistical methods. The occurrence of VTE and the survival rates were similarly compared to those of the reference population.

Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics version 28 statistical software for Windows (IBM Corp. Armonk, NY, USA). The cumulative occurrence and type of venous thromboembolism were compared between patient subgroups and between patients and the reference population at pre-determined time points. Any study participant, who did not complete the full follow-up period due to inadequate follow-up time or death were excluded from the relevant analyses at each time point, unless they had already experienced a venous thromboembolic event. Comparative analyses between the two groups were performed using Fisher's exact and χ^2 tests for categorical variables and Mann-Whitney *U* test for nonparametric continuous variables. Kaplan-Meier curves and the log rank test were used to illustrate and compare the occurrence of venous thromboembolic events in patients and the reference population. Statistical significance was set at $P<0.05$.

Results

The study included a total of 435 surgically treated lung cancer and 4,338 matched controls comprising the reference population. Nine patients were excluded from the analysis due to unavailable registry follow-up data due to, for example, expatriation or prohibitions regarding the individual's registry data use. For two patients there were fewer than 10 available controls, and the cases were included in the analysis. The median follow-up time for the patients and the reference population was 70 (range, 0–154) months. The cumulative total number of person-months followed-up was 30,478 for patients and 302,956 for the reference population. Altogether 150 patients and 2,101 controls completed the full 5-year follow-up. *Table 1* presents the demographic information of the study population, the histology, and the stage of lung cancer at the time of operation, patient comorbidities, types of surgeries performed, and clinical details regarding the postoperative course. Adenocarcinoma was the most common histology of lung cancer, accounting for 51.5% of all cases, and more than half of all cases (58.2%) were classified as stage I lung cancers. The majority of patients (73.1%) underwent open surgery, while the rest had video-assisted thoracic surgical procedures, and 12.6% required reoperations, primarily due to persistent air leak, infections, and bleeding. The median duration of postoperative hospitalization following lung cancer surgery was 5 (range, 1–53) days during the study period.

Table 2 and *Figure 1* present the main results of the study. The cumulative occurrence of VTE in patients who underwent lung cancer surgery was significant, reaching 18.7% at 5 years, compared to a rate of 3.9% in the

Table 1 The demographic information of the patients and the reference population, as well as the preoperative characteristics, cancer-related information, and details regarding the postoperative course of the patient group

Variable	Patients (n=435)	Reference population (n=4,338)
Age (years), median [range]	67 [17–87]	67 [17–87]
Gender, n (%)		
Male	257 (59.1)	2,558 (59.0)
Female	178 (40.9)	1,780 (41.0)
Comorbidities, n (%)		–
Diabetes	74 (17.0)	
Hypertension	204 (46.9)	
Coronary disease	68 (15.6)	
Congestive heart failure	18 (4.1)	
Dyslipidemia	107 (24.6)	
Chronic lung disease	144 (33.1)	
Previous malignancy	96 (22.1)	
Oral anticoagulation	54 (12.4)	
Histology, n (%)		–
Adenocarcinoma	224 (51.5)	
Squamous cell carcinoma	128 (29.4)	
Large cell carcinoma	18 (4.1)	
Small cell carcinoma	6 (1.4)	
Carcinoid tumor	42 (9.7)	
Other	17 (3.9)	
Non-small-cell carcinomas, n (%)	429 (98.6)	–
Small cell carcinomas, n (%)	6 (1.4)	–
Stage, n (%)		–
I	253 (58.2)	
II	110 (25.3)	
III	62 (14.3)	
IV	10 (2.3)	
Adjuvant therapy, n (%)	147 (33.8)	–
Smoking, n (%)		–
Yes	277 (63.7)	
No	93 (21.4)	
Ex-smoker	65 (14.9)	
Surgery type, n (%)		–
Open surgery	318 (73.1)	
VATS	117 (26.9)	
Surgical technique, n (%)		–
Wedge resection	30 (6.9)	
Segmentectomy	12 (2.8)	
Lobectomy	321 (73.8)	
Bilobectomy	27 (6.2)	
Sleeve resection	13 (3.0)	
Pneumonectomy	32 (7.4)	
Reoperation, n (%)	55 (12.6)	–
Bleeding	17 (3.9)	
Persistent air leak	41 (9.4)	
Infection	35 (8.0)	
Other	27 (6.2)	
Postoperative hospitalization (days), median [range]	5 [1–53]	–

Histology according to WHO 2015 Lung Cancer Classification. VATS, video-assisted thoracic surgery; WHO, World Health Organization.

reference population. Most VTEs were PE. The occurrence of VTEs appeared to gradually increase over the follow-up period, initially showing no statistically significant difference between patients and the reference population. No statistically significant associations were found between patient characteristics and the occurrence of VTEs during follow-up (*Table 3*). There were no associations with the surgical technique or the extent of surgery with later thromboembolic complications. Mortality rates for patients and the reference population are shown in *Table 4*, and the numbers of in-hospital days related to VTEs during follow-up are shown in *Table 5*.

Discussion

Patients with lung cancer are known to be at high risk for thromboembolic complications, and VTE has been associated with worse outcomes and early mortality in these patients (11-13). Surgery further increases the risk of

Table 2 The cumulative occurrence of treatment episodes for venous thromboembolism in patients surgically treated for lung cancer and in a demographically matched reference population during follow-up

Type of VTE	VTE (%)		P value	OR (95% CI)
	Patients	Reference population		
Any venous thromboembolism				
90 days	0.3	0.2	0.56	1.32 (0.16–10.55)
1 year	3.5	0.7	<0.001	5.28 (2.63–10.60)
3 years	9.2	2.2	<0.001	4.52 (2.65–7.74)
5 years	18.7	3.9	<0.001	5.72 (3.59–9.13)
Pulmonary embolism				
90 days	0.3	0.0	0.24	5.27 (0.48–58.27)
1 year	2.9	0.3	<0.001	9.42 (4.04–21.97)
3 years	6.8	1.1	<0.001	6.80 (3.53–13.08)
5 years	14.0	2.0	<0.001	7.98 (4.59–13.88)
Deep vein thrombosis				
90 days	0.0	0.1	>0.99	0.81 (0.05–14.36)
1 year	0.5	0.4	0.66	1.38 (0.32–6.02)
3 years	2.9	1.3	0.07	2.19 (0.91–5.24)
5 years	6.0	2.1	0.003	2.92 (1.40–6.09)

Statistical testing was performed by comparing the occurrence of thromboembolic events of the patient group to that of the reference population at each time point. All study subjects that did not complete the corresponding follow-up due to insufficient follow-up time or death during the follow-up were excluded from the corresponding analyses at each time point unless venous thrombo-embolic event had already occurred. VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval.

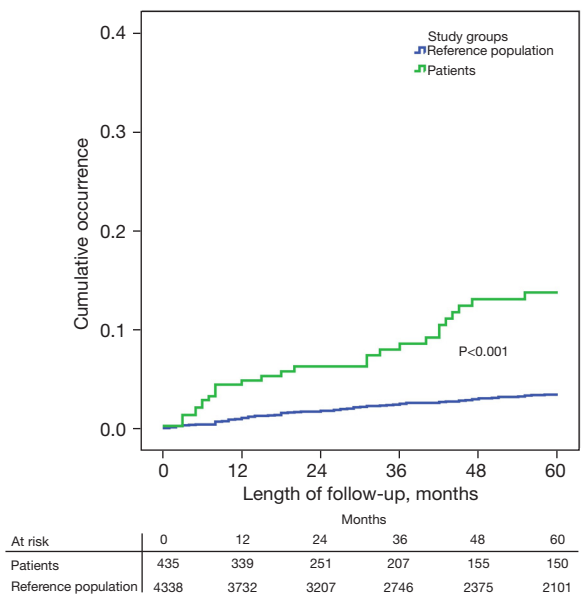

Figure 1 The cumulative occurrence of venous thromboembolic events in the patients and in the reference population.

thromboembolic events due to prolonged bed rest, reduced ambulation, and activation of platelets and the coagulation cascade (14,15). Furthermore, patients receiving surgery for malignant disease are in higher risk for developing thromboembolic complications than other surgically treated patients (9,16). In addition to a higher recurrence rate of VTE in cancer patients despite anticoagulation, these patients also seem to suffer from an increased risk of bleeding events during follow-up (7). A previous study from the COMMAND VTE registry showed that major bleeding events are common during anticoagulation therapy in cancer patients treated for VTE, and in their study population, 13% of lung cancer patients treated for VTE developed a major bleeding during follow-up (17). Consequently, in addition to analyzing the risks associated with VTE, morbidity due to bleeding events must also be regarded when considering the duration of postoperative anticoagulation. The present study demonstrates that the occurrence of symptomatic thromboembolic complications,

Table 3 The univariable associations of patient characteristics with the occurrence of venous thromboembolism during 90-day, 1-year and 5-year follow-up

Patient characteristics	90-day follow-up		One-year follow-up		Five-year follow-up	
	%	P value	%	P value	%	P value
All patients	0.3		3.5		18.7	
Gender						
Female	0.0	>0.99	3.4	0.89	19.7	0.79
Male	0.4	>0.99	3.3	0.89	18.0	0.79
Age ≥65 years	0.4	>0.99	3.8	0.77	21.1	0.45
Smoking	0.0	0.35	3.1	0.55	14.0	0.23
Comorbidities						
Diabetes	0.0	>0.99	4.7	0.66	23.5	0.53
Hypertension	0.0	>0.99	4.5	0.37	27.4	0.02
Coronary disease	0.0	>0.99	4.2	0.68	21.1	0.76
Congestive heart failure	0.0	>0.99	0.0	>0.99	0.0	>0.99
Dyslipidemia	0.0	>0.99	3.8	>0.99	25.0	0.39
Chronic lung disease	0.0	>0.99	1.8	0.35	18.2	0.92
Previous malignancy	0.0	>0.99	2.8	>0.99	24.0	0.45
Previous oral anticoagulation						
Yes	2.0	0.12	2.5	>0.99	14.3	>0.99
No	0.0	0.12	3.7	>0.99	15.2	>0.99
Stage						
I	0.4	>0.99	2.0	0.08	12.9	0.02
II	0.0	>0.99	6.9	0.049	23.1	0.41
III	0.0	>0.99	2.2	>0.99	31.3	0.17
IV	0.0	>0.99	20.0	0.17	100.0	0.03
Surgery type						
Open surgery	0.0	0.25	3.0	0.31	15.7	0.003
VATS	1.0	0.25	5.3	0.31	60.0	0.003
Reoperation						
Yes	0.0	>0.99	8.6	0.12	37.5	0.041
No	0.3	>0.99	3.0	0.12	16.4	0.041

Statistical comparisons were made between opposing groups, for example, between males and females. The study subjects that did not complete follow-up were excluded from the corresponding analyses. VATS, video-assisted thoracic surgery.

particularly PE, among patients undergoing lung cancer surgery is significant, especially during long-term follow-up. Furthermore, VTE and the related in-hospital treatment episodes in these patients appear to inflict a substantial burden and consequently costs for the health care system, as also shown in earlier literature (18).

Surprisingly, the occurrence of VTE was not significantly elevated during the early post-operative period. Instead,

Table 4 The mortality rates in patients operated for lung cancer and in the reference population during follow-up

Mortality	Patients % (n per number of patients)	Reference population % (n per number of the reference population)	P value
90 days	5.5 (24/435)	0.6 (24/4,338)	<0.001
1 year	14.0 (61/435)	2.3 (101/4,338)	<0.001
3 years	30.5 (117/383)	6.6 (253/3,818)	<0.001
5 years	44.4 (131/295)	11.6 (342/2,938)	<0.001

The study subjects with insufficient follow-up time were excluded from the corresponding analyses at each time point.

Table 5 The mean number of in-hospital days per study subject related to venous thromboembolism in patients treated for lung cancer and in a demographically matched reference population during the study period

Type of VTE	Mean number of in-hospital days		P value
	Patients	Reference population	
Any venous thromboembolism			
90 days	0.01	0.00	0.52
1 year	0.21	0.04	<0.001
3 years	0.58	0.13	<0.001
5 years	1.00	0.43	<0.001
Pulmonary embolism			
90 days	0.01	0.00	0.15
1 year	0.10	0.02	<0.001
3 years	0.44	0.08	<0.001
5 years	0.78	0.35	<0.001
Deep vein thrombosis			
90 days	0.00	0.00	0.58
1 year	0.11	0.02	0.50
3 years	0.14	0.05	0.13
5 years	0.22	0.09	0.01

The data includes all hospitalizations within the Finnish special medical care. Study subjects not completing the entire follow-up were excluded from the corresponding analysis at each time point. VTE, venous thromboembolism.

the episodes occurred gradually over the entire follow-up period, which differs somewhat from previous studies suggesting that the highest risk for thromboembolic complications is during the initial postoperative period (10,12,13,19-22). Consistent with our study, a recent retrospective analysis conducted by Akhtar-Danesh *et al.* (23) in a cohort of 12,626 patients, who underwent lung cancer surgery between 2005 and 2013, reported postoperative incidences of VTE at 90 days and one year to be 1.31% and 2.73%, respectively, in patients not subjected to routine VTE screening. In a study by Thomas *et al.* (12), comprising a large cohort of 14,308 patients treated between 2005 and 2015, the prevalence of VTE was 1.6% at 30 days and 44% of thromboembolic events occurred after hospital discharge. Another retrospective study by Hachey *et al.* (20) reported an overall 60-day incidence of VTE of 5.2% in a cohort of patients treated between 2005 and 2013 who received in-hospital thromboprophylaxis and were not routinely screened for VTE. To the best of the authors' knowledge, the present

study is the first to report the occurrence of VTE during extended follow-up in this patient group. The authors speculate that a major reason for the high occurrence of VTE during extended follow-up may be due to the significant risk for cancer recurrence in this patient group which unfortunately occurs relatively frequently (24,25) and is also reflected in the comparatively high mortality rates during follow-up.

Extended pharmacologic thromboprophylaxis has been proven to be effective in reducing postoperative VTE in major abdominal or pelvic oncological surgery (26). However, the optimal duration of thromboprophylaxis for lung cancer surgery remains uncertain. Current guidelines offer varying recommendations: the American College of Chest Physicians suggests in-hospital routine thromboprophylaxis for thoracic surgery patients (27), the European Society of Anesthesiology advocates for pharmacological prophylaxis alongside intermittent pneumatic compression without specifying the duration (28), and the American Society of Clinical Oncology and European Society for Medical Oncology recommend continuing thromboprophylaxis for 7–10 days post-surgery (29,30). Recently, evidence-based guidelines by The American Association for Thoracic Surgery and the European Society of Thoracic Surgery propose parenteral anticoagulation combined with mechanical methods for VTE prevention in patients undergoing surgery for lung cancer, during hospitalization in low-risk patients, and extended prophylaxis for 28–35 days for moderate or high-risk patients and for those undergoing pneumonectomies (31). However, an international survey involving members of various thoracic surgery associations reported that extended thromboprophylaxis is not routinely prescribed after lung cancer surgery (32).

Interestingly, in a recent single-center prospective study from China, in which no routine perioperative thromboprophylaxis after lung cancer surgery was utilized, the reported incidence rate for VTE reached 15% (33). In turn, Kho *et al.* recently studied the impact of extended thromboprophylaxis employed 28 days postoperatively in patients undergoing lung cancer surgery and the authors reported a significant reduction in PE, 4.0% *vs.* 0.4%, during a 6-month follow-up with active screening (34). A significant proportion of VTEs are asymptomatic or have symptoms that may be mistaken for those expected to occur postoperatively, and studies with active postoperative VTE screening have demonstrated an increased prevalence of VTE after lung cancer surgery, up to 12.1% (13,19).

This study did not find any patient or surgical technique-related risk factors, such as advanced age, cancer stage, neoadjuvant therapy or extensive surgery for VTE, likely due to the relatively small number of VTE events and limited statistical power. Other studies have identified several risk factors for thromboembolic complications including advanced age, obesity, advanced cancer stage, and pneumonectomy (12,22,23). The long-term mortality rates observed in the present study are similar to those described in the current literature, for example a report from the Danish Lung Cancer Registry showed 90-day and 1-year mortalities of 4.6% and 14.2%, respectively, and the 5-year survival rates were also comparable to the results published by others (35).

There are several limitations regarding the study. The material is complete but consists of patients treated at a single university hospital and may not accurately reflect the patient material at other institutions. Our results portray the rate of thromboembolic complications when only in-hospital thromboprophylaxis was used. Also, the retrospective setting of this study causes some limitations regarding the availability of some patient's medical history data limiting subgroup analyses. While information regarding the comorbidities of the reference population was not available, due to their large number, the reference population should accurately reflect the standard population with typical rates of comorbidities and similar age- and sex-distributions than those of the patient material. Furthermore, the proportion of patients that were prescribed on oral or other anticoagulation during follow-up is not known. The rate of thromboembolic complications observed in the present study probably reflects only the symptomatic cases as no routine screening was performed, possibly underestimating the true incidence of VTEs. Despite this, the odds of experiencing symptomatic VTE in patients were approximately five times higher when compared to the reference population over long term follow-up. Furthermore, the rate of DVT was relatively low in the patients, possibly because when concomitant DVT and PE were present only the diagnosis code of PE may have been used, and because DVTs may have been diagnosed and treated in primary health care. The exact methods by which venous thromboembolism was diagnosed and disease severity could not be controlled.

The proportion of patients undergoing video-assisted thoracic surgery (VATS) increased during the study period causing heterogeneity in the patient material. The strengths of the study include a large cohort of patients treated over

a time period of nearly two decades with extensive follow-up time, the robust and inclusive registry data available in Finland, as well as the presence of a reference population.

Conclusions

In conclusion, the authors report that patients undergoing lung cancer surgery, and who receive medical thromboprophylaxis during the hospitalization, do not seem to be in higher risk for thromboembolic complications during the initial postoperative period and short-term follow-up. However, during long-term follow-up the occurrence of symptomatic thromboembolic complications, particularly PE, was statistically significantly higher than in demographically matched controls. No clear patient-specific risk factors associated with the development of VTE were identified.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-308/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-308/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-308/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (No. R17575) and individual consent for this retrospective analysis was waived.

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