

Examination of the effectiveness of perioperative venous thromboembolism prevention according to in-house guidelines in lung cancer surgery

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Abstract

Purpose: In-hospital venous thromboembolism (VTE) prevention guidelines were established in February 2019 at Kindai University Hospital. This study examined the effectiveness of postoperative pulmonary embolism prevention in cases in which perioperative management was performed in accordance with this guideline. **Methods:** A total of 740 patients were enrolled in this study. The patients underwent lung cancer surgery based on the new guidelines between July 2019 and August 2023. The control subjects were 944 patients who underwent lung cancer surgery between January 2013 and December 2018. **Results:** In this study, the prevalence of reduced resections, such as wedge resection and segmentectomy and of thoracoscopic surgery was higher compared to that in the control group. Thirty-three patients (4.5%) were diagnosed with deep venous thrombosis preoperatively,

and this was lower than in the control group. Perioperative VTE risk assessment according to the hospital guidelines included four patients of moderate risk, 681 patients of high risk, and 55 patients of highest risk. Of the 55 highest risk patients, 13 patients received perioperative anticoagulant therapy. In the control group, one patient with pulmonary embolism was observed, but no postoperative pulmonary embolism was observed in the study group. **Conclusion:** No postoperative pulmonary embolism occurred in patients with lung cancer who underwent perioperative VTE prophylaxis in accordance with our hospital guidelines. VTE prophylaxis in accordance with the guidelines was considered appropriate.

Key words: Venous thromboembolism, deep venous thrombosis, lung cancer

Introduction

Pulmonary thromboembolism (PTE) is one of the life-threatening complications in patients with lung cancer who undergo pulmonary resection. In cancer surgery, the guidelines for venous thromboembolism (VTE) recommend perioperative prevention in high-risk patients¹⁻³. According to the Japanese guidelines, patients with a history of VTE are classified as exhibiting the highest risk. For these patients, it is recommended that anticoagulants be administered in addition to mechanical prevention using elastic stocking or intermittent pneumatic compression devices². Of 944 patients that underwent lung cancer surgery from

June 2013 to December 2018 in Kindai University Hospital, ninety one patients (9.6%) were diagnosed with preoperative deep vein thrombosis (DVT) with postoperative symptomatic PTE occurring in one patient (0.11%)⁴. In this report, VTE prophylaxis was performed for patients with preoperative DVT, through perioperative anticoagulant therapy while taking into consideration the risk of postoperative bleeding. However, of the patients diagnosed with DVT preoperatively, 74 (81.3%) were diagnosed with distal DVT, and the necessity of perioperative anticoagulant therapy was unclear. Studies have reported that observation is a viable option, as many distal DVTs will spontaneously resolve, although the exact

percentage is unclear⁵. The efficacy and safety of anticoagulant treatment is not established for patients with distal DVT⁶. Studies have suggested that anticoagulant treatment was not superior to placebo for reducing the risk of proximal extension or venous thromboembolic events in low-risk outpatients with symptomatic distal DVT, but it did increase the risk of bleeding⁷. Conversely, the VTE prevention guidelines recommend stratifying risk factors before surgery and taking preventive measures according to the risk. However, the Japanese guidelines do not provide recommended rules for risk stratification, and in practice, each institution sets its own guidelines for VTE risk stratification. In February 2019, Kindai University Hospital established VTE prevention guidelines that made it possible to select VTE prevention methods by stratifying VTE risk. Perioperative management in accordance with this guideline was performed for our study cohort. This study examined the effectiveness of postoperative pulmonary embolism prevention in cases where perioperative management was performed in accordance with this guideline.

Methods

Patient Selection

In-hospital VTE prevention guidelines in our hospital were established in February 2019. A total of 740 patients who underwent lung cancer surgery based on the new guidelines between July 2019 and August 2023 were enrolled in this study. The control subjects were 944 patients who underwent lung cancer surgery between January 2013 and December 2018, as previously reported. This study was approved

by the research ethics committee (31-068). Clinicopathological data for the patients were retrieved by a retrospective review of patient medical records.

Preoperative screening for VTE

As a prescreening for DVT, the outpatient physician assessed the VTE risks and measured the D-dimer levels (Nanopia® D-dimer, Sekisui Medical, Tokyo, Japan) at preoperative consultation⁴. If the patient was deemed high risk for preoperative thrombosis, they underwent venous ultrasonography of the lower extremities. D-dimer levels at or above 1.0 µg/ml were considered a high-risk indicator for VTE. If DVT was confirmed on ultrasonography, the patient was then screened for PTE using contrast-enhanced computed tomography (CT). If no preoperative thrombotic risk factor was present or if ultrasonography findings were normal, the patient was classified as “without preoperative DVT”.

VTE risk stratification

The criteria for VTE risk assessment of Kindai University were established by an in-hospital working group including cardiologists. VTE risk assessment was performed for all hospitalized patients according to the criteria. VTE risk was classified into five levels—no risk, low risk, intermediate risk, high risk, and highest risk—based on the total score in category A (Table 1A). Depending on the type of surgery, in the case of major surgery the risk assessment was increased by one level (Table 1B). Major surgery was defined as “all abdominal surgeries or surgeries that take more than 45 minutes.”

Table 1 VTE Prevention Guidelines in Kindai University hospital

Table1A Category A

Clinicopathological factor	Score
Age, 40-59 years old	1
≥ 60 years old	3
Obesity, BMI ≥25	1
Decreased activity [#]	2
Active cancer	2
History of VTE	2
History or Predisposition of thrombophilia	1
Lower limb paralysis	1
Emergency hospitalization	1
Hormone therapy	1

[#] More than 4 days of bed rest before hospitalization, ^{\$} Congenital and acquired diseases, taking oral contraceptives, female hormones, or steroids

Table1B Category B

Type of surgery	Classification of risk
Non-major surgery	No change
Major surgery ^{##}	Increase risk by 1 grade

^{##} Major surgery was defined as “all abdominal surgeries or surgeries that take more than 45 minutes.”

Table1C VTE prevention according to the classification of VTE

Score of category A	Classification of risk	VTE Prevention
0	no risk	none
1-2	Low risk	Early ambulation and active exercise
3-6	Intermediate risk	Elastic stockings or IPC
7-8	High risk	IPC or anticoagulation therapy
≥ 9	Highest risk	(Anticoagulation therapy plus IPC) or (Anticoagulation therapy plus Elastic stockings)

VTE: venous thromboembolisms, BMI: body mass index, IPC: intermittent pneumatic compression

VTE prevention method

At the time of hospitalization, the attending physician prescribed a preventive method according to the VTE risk assessment (Table 1C). For perioperative anticoagulant therapy, we consulted a cardiologist to determine whether administration was warranted. Under the direction of a cardiologist, oral anticoagulants were prescribed before surgery, and unfractionated heparin was administered intravenously or subcutaneously after surgery. All postoperative anticoagulation therapies started on day 1 or 2 postoperation, after confirming that the risk of postoperative bleeding decreased, and were continued until the patient became to walk sufficiently. During the administration of heparin or warfarin, the dose of drugs was controlled by measuring the blood coagulation times. If clinical findings suggestive of VTE—such as oxygen desaturation, dyspnea, chest pain, or swelling in the lower extremities—were observed postoperatively, contrast-enhanced CT or venous ultrasonography of the lower extremities was performed.

Statistical analysis

Statistical analysis was conducted using JMP version 17.0 for Windows (SAS Institute, Cary, NC, USA). The chi-square test was used to evaluate differences between categorical parameters when appropriate. Continuous variables were compared using Student's t-test. A p-value <0.05 was considered statistically significant.

Results

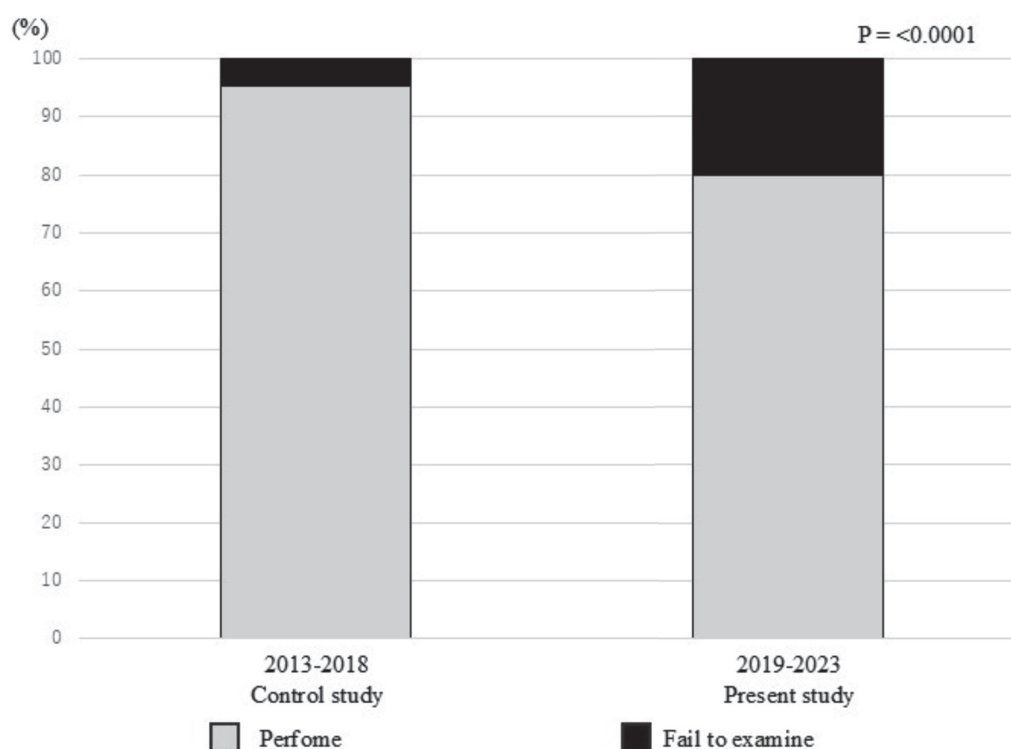
The enrolled patients' characteristics are listed in

Table 2. The median age of the patients was 73 years, which is older than that of the control group. Regarding surgical factors, there was an increase in the reduced resections, such as wedge resection and segmentectomy and in thoracoscopic surgery; however, the operation time was prolonged. In this study, thirty-three patients (4.5%) were diagnosed with DVT preoperatively, and this was lower than that in the control group. Although fewer patients had DVT in this study group, there was no difference in preoperative D-dimer values. Additionally, many patients with elevated D-dimer did not undergo preoperative venous ultrasonography (Figure 1). Conversely, the incidence of proximal DVT tended to be lower in this study group than in the control group (Figure 2). Perioperative VTE risk assessment, performed according to the hospital guidelines, identified four patients at moderate risk, 681 at high risk, and 55 at highest risk (Table 3). Among the 55 highest-risk patients, those with distal DVT or old DVT were not anticoagulated perioperatively at the discretion of the cardiologist, resulting in 13 patients receiving anticoagulation therapy perioperatively. In particular, anticoagulant therapy was performed in two of the three patients with proximal DVT. The remaining patient did not receive anticoagulant therapy due to a bleeding tendency after surgery. Among the 13 patients receiving anticoagulation therapy, no postoperative bleeding was observed. In the control group, pulmonary embolism occurred in one patient (from 2013 to 2018), whereas no postoperative pulmonary embolism was observed in this study group.

Table 2 Difference in the patients' characteristics between 2013-2018 and 2019-2023

Clinicopathological factor	2013-2018 Control study n = 944	2019-2023 Present study n = 740	<i>P</i> -value
Age, years	72 (67-76)	73 (68-78)	0.0012
Gender, female	381 (40.4)	267 (36.1)	0.07
BMI, kg/m ²	22.1 (20.1-24.5)	22.5 (20.0-24.7)	0.06
Chronic obstructive pulmonary disease, yes	327 (34.6)	228 (30.8)	0.097
Carcinoembryonic antigen, ≥ 5 ng/mL	268 (28.39)	215 (29.05)	0.76
D-dimer, $\mu\text{g/ml}$	0.8 (0.6-1.1)	0.7 (0.6-1.0)	0.2
DVT, yes	91 (9.6)	33 (4.5)	<0.0001
Operative method			<0.0001
Wedge resection or Segmentectomy	182 (19.3)	270 (36.5)	
Lobectomy or Pneumonectomy	762 (80.7)	470 (63.5)	
Thoracotomy or VATS			<0.0001
Thoracotomy	408 (43.2)	129 (17.4)	
VATS	536 (56.8)	611 (82.6)	
Operative time, minutes	180.5 (141.8-216)	203 (160-253.8)	<0.0001
Blood loss, ml	25 (0-75)	40 (0-100)	0.44
Histology			0.37
Adenocarcinoma	658 (69.7)	492 (66.4)	
Squamous cell carcinoma	184 (19.5)	161 (21.8)	
Others	102 (10.8)	87 (11.8)	
pStage			0.08
I	664 (70.3)	549 (74.2)	
$\geq$ II	280 (29.7)	191 (25.8)	

BMI: body mass index, DVT: deep venous thrombosis, VATS: Video-assisted thoracic surgery, Data are expressed as the median (interquartile range) or n (%).

**Figure 1.** Venous ultrasonography of the lower extremities performed in patients with elevated preoperative D-dimer

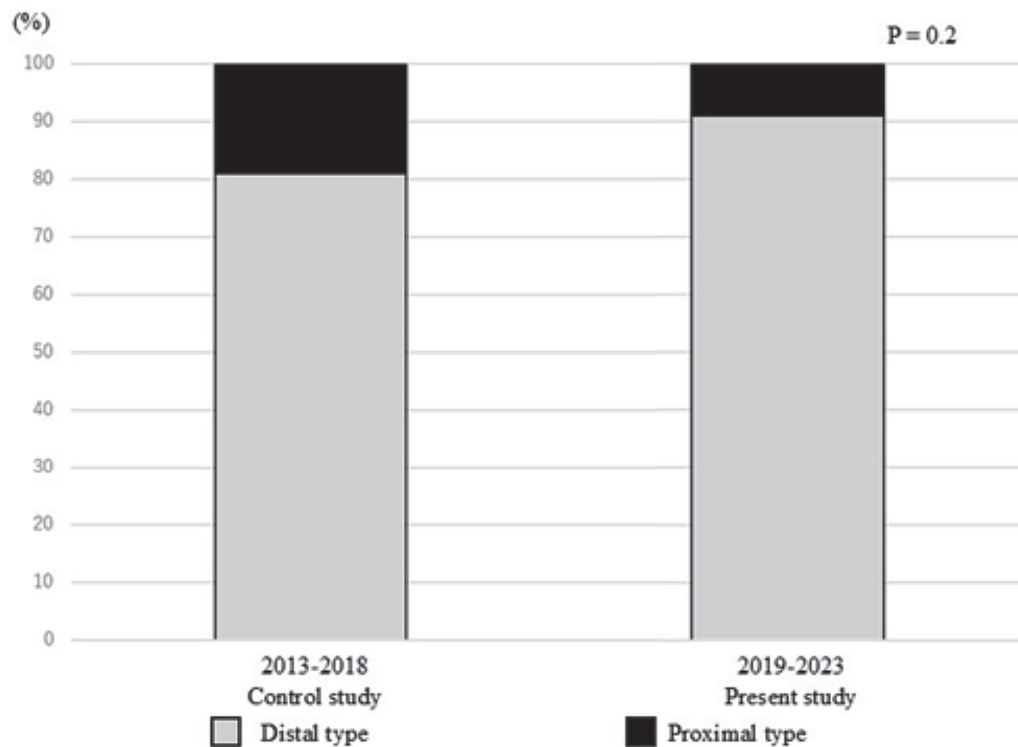


Figure 2. Anatomic distribution of DVT
DVT: deep venous thrombosis

Table 3 Classification of risk of venous thromboembolisms in patients performed surgery between 2019 and 2023

Classification	2019-2023 n = 740
Intermediate risk	4
High risk	681
Highest risk	55

Discussion

For VTE prevention, it is recommended to perform a VTE risk assessment and implement preventive measures according to that assessment². At Kindai University Hospital, the VTE prevention risk assessment score was developed by cardiologists who evaluated multiple existing methods. The guidelines recommend—but do not require—D-dimer measurement; in cases of elevated D-dimer levels, venous ultrasonography is recommended as needed. Additionally, the presence or absence of preoperative DVT is considered in risk stratification, but the decision to use perioperative anticoagulant therapy is made in consultation with a cardiologist following a comprehensive evaluation of bleeding and thrombosis

risk after surgery. In this study, among 55 patients deemed at highest risk, 13 received perioperative anticoagulant therapy, which is not a large proportion. However, most of these patients had preoperative DVT, which was primarily distal. In such cases, the decision was made to prioritize reducing the risk of postoperative bleeding over administering anticoagulant therapy for distal DVT. Conversely, two of the three patients with proximal DVT underwent anticoagulant therapy.

The optimal prevention method for VTE is early mobilization. In recent years, minimally invasive procedures have become the standard in lung cancer surgery, a major advantage for promoting early mobilization. In this study group, segmentectomy for lung cancer increased compared to the control group.

Segmentectomy has been shown to have outcomes

comparable to lobectomy for early-stage lung cancer (<2 cm)⁸. Consequently, in 2021, our department adopted segmentectomy as the standard surgical procedure for lung cancer <2 cm. Segmentectomy helps preserve postoperative respiratory function, which facilitates early mobilization. Additionally, our department introduced Uniportal Video-Assisted Thoracic Surgery (VATS) for lung cancer in 2018 and robot-assisted thoracic surgery (RATS) in 2019. Such minimally invasive surgeries are expected to further improve postoperative early mobilization. Particularly, Uniportal VATS has been reported to cause less acute postoperative pain than does multiportal VATS or RATS^{9,10}. In a situation where lung cancer surgery is becoming more minimally invasive, comprehensive risk stratification according to our hospital's guidelines appears to have been effective.

In this study, the preoperative venous ultrasonography implementation rate was lower compared to the control group. Patients had failed to examine venous ultrasonography had D-dimer values of 1–2 µg/ml and no clinical findings suspected to be DVT preoperatively. However, to rule out DVT, acute DVT can be ruled out if clinical findings are poorly suspected of DVT and D-dimer levels are normal². This is due to the negative predictive value of D-dimer in DVT diagnosis being 99.1%¹¹. It seems necessary to perform venous ultrasonography when D-dimer is elevated to reliably exclude DVT preoperatively. In this study, the reason for the decrease is the following two points to be considered. First, the medical system has changed significantly due to staff changes. Second, postoperative PTE is very rare, and the awareness of the danger may have weakened.

Our study has certain limitations. First, it was a single-center study design, which may limit its generalizability. Due to the retrospective nature of the study, data collection was limited to information recorded in patient medical charts. Second, in this study group, fewer patients underwent preoperative venous ultrasonography compared to the control group, potentially underestimating the actual rate of preoperative DVT. Third, because anticoagulant therapy decisions were made in consultation with a cardiologist, treatment options may vary depending on the physician consulted. It would be desirable to revise the guidelines to include more specific indications for anticoagulant therapy.

In conclusion, no postoperative pulmonary embolism occurred among patients with lung cancer who underwent perioperative VTE prophylaxis according to our hospital guidelines. VTE prophylaxis following these guidelines was considered appropriate.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical standards

All procedures were in accordance with the ethical standards of the responsibility committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or an approved substitute was obtained from all patients included in the study.

References

1. Gould MK, et al. (2012) *Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. Chest, 141(2 Suppl): p. e227S–e277S
2. Group J.J.W (2011) *Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009)*. Circ J, 75(5): p. 1258–1281
3. Khorana AA (2007) *The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients*. Oncologist, 12(11): p. 1361–70
4. Takemoto T, et al. (2021) *The prevalence and risk factors associated with preoperative deep venous thrombosis in lung cancer surgery*. Surg Today, 51(9): p. 1480–1487
5. Schellong SM (2007) *Distal DVT: worth diagnosing? Yes*. J Thromb Haemost, 5 Suppl 1: p. 51–4
6. Robert-Ebadi H, Righini M (2017) *Management of distal deep vein thrombosis*. Thromb Res, 149: p. 48–55
7. Righini M, et al. (2016) *Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial*. Lancet Haematol, 3(12): p. e556–e562
8. Saji H, et al. (2022) *Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial*. Lancet, 399(10335): p. 1607–1617
9. Homma T, Shimada Y, Tanabe K (2022) *Decreased postoperative complications, neuropathic pain and epidural anesthesia-free effect of uniportal video-assisted thoracoscopic anatomical lung resection: a single-center initial experience of 100 cases*. J Thorac Dis, 14(9): p. 3154–3166
10. Zhang K, et al. (2024) *Comparison of early postoperative patient-reported outcomes after multiportal robotic-assisted thoracoscopic surgery and uniportal video-assisted thoracoscopic surgery for non-small cell lung cancer*. Eur J Surg Oncol, 50(9): p. 108481
11. Wells PS, et al. (2003) *Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis*. N Engl J Med, 349(13): p. 1227–1235