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ORIGINAL ARTICLE

Risk factor analysis of cerebral infarction and clinicopathological characteristics of left upper pulmonary vein stump thrombus after lobectomy

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Abstract

Objective We aimed to analyze the risk factors of postoperative cerebral infarction (CI) and thrombus formation in the left upper pulmonary vein (PV) stump after lobectomy.

Methods We retrospectively investigated 1670 patients who underwent lobectomy or more intervention, and analyzed the risk factors of postoperative CI. Furthermore, postoperative contrast-enhanced computed tomography (CE-CT) were reviewed in patients who underwent left upper lobectomy (LUL), and risk factors of the thrombus formation in the left upper PV stump were evaluated. Chi-square test or unpaired *t* test was used to compare the factors.

Results Cerebral infarction was observed in 10 (0.60%) patients, being more significant in patients with left side lesions (90%) who underwent LUL (50%). Eighty percent of the CI cases occurred by day 4 postoperative. CI was found in 1.47% after LUL. Among 339 patients who underwent LUL, CE-CT was performed in 137 (40%) postoperatively. Among them, left upper PV stump thrombus was found in 16 (11.7%), which was statistically significant in higher age and *p* stage II or more disease (=0.003, 0.040). In contrast, preoperative histories including anticoagulant administration, atrial fibrillation, diabetes mellitus, several surgical procedures or intraoperative factors were not associated statistically with thrombus formation.

Conclusion Postoperative CI occurred in the very early-phase after lobectomy, and the incidence was significantly higher in patients undergoing LUL. Because left upper PV stump thrombus was frequently found retrospectively, a prospective observation study would be required to investigate the real incidence of PV stump thrombus after lobectomy.

Keywords Cerebral infarction · Left upper lobectomy · Pulmonary vein stump thrombus · Risk factor

Introduction

Postoperative cerebral infarction (CI) is a relatively rare event with a reported incidence rate of approximately 0.5–1% after general thoracic surgery [1–5]. Recently, opportunities for lung cancer surgery in elderly patients or medically high-risk cases have been increasing, and meticulous perioperative management is needed to prevent several complications. Of these, postoperative CI is widely recognized as one of the lethal complications after pulmonary resection [6], and the cause or prevention of CI needs to be addressed aggressively in daily practice. Little is known about the critical cause of postoperative CI; however, a currently suggested hypothesis is that floating thrombus in the pulmonary vein (PV) stump after pulmonary lobectomy causes CI [7]. In particular, thrombus in the stump of the left superior PV after left upper lobectomy (LUL) has been introduced as a potential cause of several embolic morbidities to vital organs [5, 7–12]. However, the frequency, timing, operative procedures or other risk factors relating well with the formation of PV stump thrombus after pulmonary lobectomy remain controversial.

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Therefore, we retrospectively reviewed surgically resected patients who underwent lobectomy or more intervention to investigate the frequency and possible cause of the CI after general thoracic surgery. The primary aim of this study was to identify the risk factors of CI after lung resection. Furthermore, we aimed to elucidate the characteristics and risk factors of thrombus formation in the PV stump focusing particularly on patients who underwent LUL in our institute.

Materials and methods

Study population

We retrospectively evaluated 1670 surgically resected patients who underwent pulmonary lobectomy or more intervention between 2008 and 2015 (the lung cancer staging was based on the 7th edition of the TNM classification [13]). The database has been maintained prospectively, and so there was no missing data for the variables used in this study. The inclusion criteria were the completely resected cases, and preoperative chemo- and/or radiotherapy were excluded. Cerebral infarction after pulmonary lobectomy was diagnosed as both neurogenic symptoms and the magnetic resonance imaging findings under the consultations with neurologists at our institute. The medical record of each patient was reviewed retrospectively under a waiver of authorization approved by the institutional review board of Juntendo University School of Medicine, Tokyo, Japan. As shown in the study scheme in Fig. 1, the first aim of this study was to analyze the risk factors of CI after pulmonary lobectomy. The second aim was to elucidate the characteristics and risk factors of thrombus formation in the PV stump focusing on patients who underwent LUL.

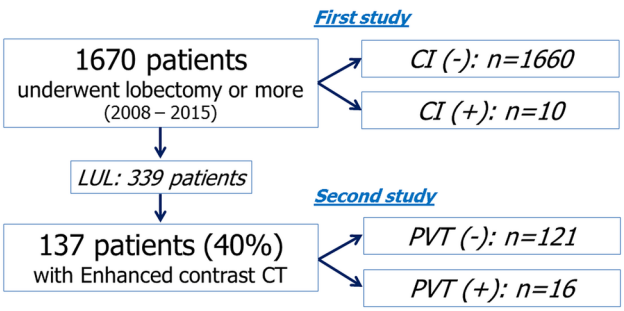

Fig. 1 Study scheme of this study. *LUL* left upper lobectomy, *CT* computed tomography, *CI* cerebral infarction, *PVT* pulmonary vein thrombus

Postoperative evaluations of left upper PV stump thrombus on computed tomography

In addition to the retrospective risk factor analysis for the postoperative CI, the findings of the postoperative contrast-enhanced thin-section CT (CE-CT) scan in patients who underwent LUL were reviewed in detail by the surgeons (A.H, Y.K, and K.T) and a radiologist (K.S) in this study to assess the presence of thrombus in the stump of left upper PV. In this study, thrombus examination was limited only to the LUL, because thrombus in the left upper PV stump after LUL was a possible cause of postoperative CI and the frequency of thrombus development was reported to be significantly high in the left upper PV stump compared with the other PV stump based on the previous study [7, 14]. Figure 2 presents the typical radiological findings of the thrombus in the stump of left upper PV. The postoperative follow-up was decided by each surgeon based on the pathological stage and pathological features of the tumors. The routine follow-up evaluation included physical examinations, chest

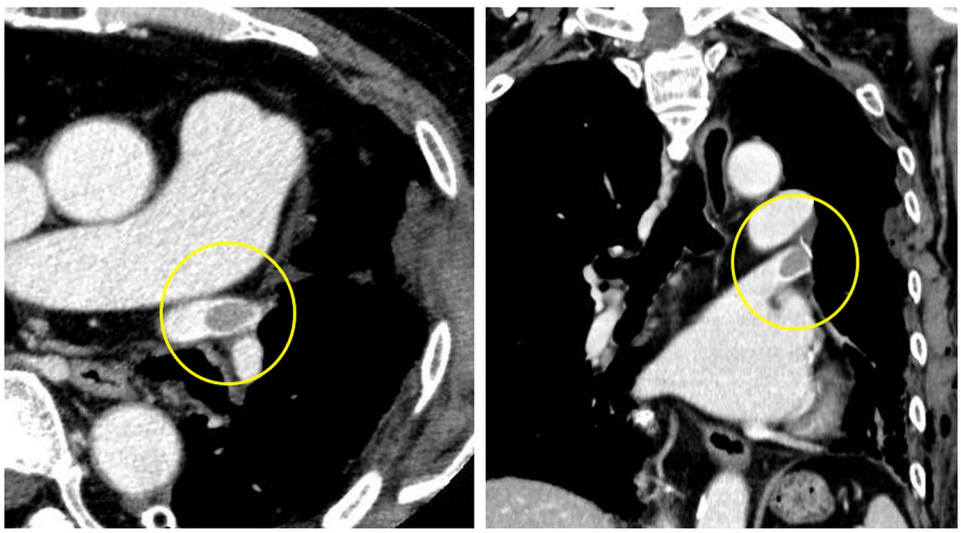

Fig. 2 Typical radiological image of thrombus in the stump of the left upper pulmonary vein

radiographs, and blood examinations (including measurements of tumor makers) every 6–12 months. Chest CT scans including CE-CT were also performed periodically after surgical resection. In the current study, the objectives for performing CE-CT after LUL in the postoperative examination were as follow: to investigate lung cancer recurrence in 95 (69%) patients, to assess the postoperative intrathoracic field after complicated or extended surgical procedures in 22 (16%) patients, and to subject 20 (15%) patients to the planned postoperative screening in some prospective clinical trials. The presence or absence of thrombus was evaluated by the same thin-section CT scan with 1–2 mm collimation in our institute, and the presence of a well-defined soft tissue density located within the stump without evidence of extravascular extension was recognized as a finding of favorable thrombus. The lung was scanned with a window level of − 500 to − 700 H and a window depth of 1000–2000 H as the "lung window", and a window level of 30 to 60 H and a window depth of 350–600 H as the "mediastinal window". Postoperative CE-CT scan was performed based on the standard protocol (GALACTIC: Guideline for ALI About CT exams: Imaging Concept) recommended from the Japanese Society of Radiological Technology.

Operation policy

With regard to the operative modes at our institution, a major lung dissection with systematic or lobe-specific lymph node dissection is warranted for resectable lung cancer. Extent of the lymph node dissection was defined using a criterion of the Japan Lung Cancer Society or International Association for the Study of Lung Cancer [15]. All of the releasing maneuvers in the intrathoracic field including pulmonary veins were essentially performed using an electric cautery. Dissection of a PV was performed in the extrapericardial space except for a few cases, where intrapericardial operation was needed. PV was generally dissected using several automated suture devices. Perioperative routine prophylaxis for the thrombus including a heparin was not administrated except an intraoperative sequential compression device for deep venous thrombus.

Statistics

Chi-square test was used to compare the factors. Unpaired *t* test was used if continuous variables were normally distributed and if not, Wilcoxon rank sum test was used. To assess the possible risk factors associated with thrombus development in the PV stump after LUL, univariable logistic regression analysis was performed. Because the event of thrombus development was relatively small, we did not perform multivariable analysis in this study. Statistics were performed using SPSS Statistics 21 (IBM Inc., USA). Continuous variables that were normally distributed were summarized as mean and standard deviation; those not normally distributed were summarized as median and interquartile range. A difference was considered statistically significant when p value was less than 0.05.

Results

In the overall, CI was observed in 10 (0.60%) cases after pulmonary lobectomy or more intervention that comprised of 4 (40%) men with an average age of 70 years (range 57–86 years). Clinicopathological and surgical characteristics of patients with postoperative CI are shown in Table 1. Postoperative CI after the surgery was significantly more in patients with a left side lesion ($n = 9$, 90%) and underwent LUL ($n = 5$, 50%). Furthermore, the frequency of CI was 1.47% among the 339 patients underwent LUL. Although the number of postoperative CI was small, the clinicopathological features including any surgical factors or pre and/or postoperative morbidities were almost similar between the two groups.

Table 2 shows the detailed characteristics of the patients suffering from postoperative CI. Most of the onset of CI was found in the very early-phase after pulmonary lobectomy or more intervention, i.e., 60% of the cases occurred within 2 postoperative days (POD), and 80% within 4 POD, respectively (range 1–60 postoperative day, median 2 POD). Unfortunately, one patient passed away at 2 POD due to sudden onset of the CI immediately after the operation. With regard to the possible cause of the CI among the 10 cases, 8 were examined by CE-CT and 2 by echo-cardiography after the onset of CI to determine whether residual thrombus was present in the PV stump or not. As a result, thrombus was found only in a patient who underwent LUL; however, the others were not detected in the post CI phase. One patient underwent brain MRI, and complete internal carotid artery stenosis was suspected as the cause of CI.

Furthermore, among 339 patients who underwent LUL, we reviewed postoperative CE-CT scan in 137 (40%) to explore the presence of thrombus in the resected left upper PV stump. Mean imaging time of the CE-CT after the operation was at 174 ± 135 POD (range 0–906 POD). Among them, PV stump thrombus was found in 16 (11.7%) patients. Table 3 presents clinicopathological characteristics of the thrombus development in the left upper PV stump after LUL. Furthermore, Table 4 shows the result of univariable analysis to assess the possible risk factors associated with thrombus development after LUL. As a result, higher age and advanced pathological stage (stage II or more) were significantly related with thrombus formation in the PV stump after LUL ($p = 0.003$, 0.040). However, preoperative patient

Table 1 Clinicopathological and surgical characteristics of patients with postoperative cerebral infarction

Factors	CI (+) ($n=10$)	CI (−) ($n=1660$)
Clinical factors		
Age (years)	70.3 ± 10.9 (57–86)	65.7 ± 11.6 (22–90)
Sex (Male)	4 (40)	1009 (61)
Side (Left)	9 (90)	617 (37)
Pack-years of smoking	41.7 ± 52.5 (0–180)	29.5 ± 34.8 (0–270)
COPD (GOLD I)	7 (70)	1164 (70)
Body mass index (kg/m^2)	1.59 ± 0.1 (1.43–1.71)	1.61 ± 0.2 (1.15–2.33)
CEA (ng/ml)	5.6 ± 3.5 (1.1–11.2)	8.0 ± 56.1 (0.2–2096)
Pathological factors		
Pathological stage (I)	4 (40)	807 (49)
Lung cancer (yes)	10 (100)	1395 (84)
Surgical factors		
Left upper lobectomy (yes)	5 (50)	334 (20)
Operative modes (lobectomy)	9 (90)	1559 (94)
Node dissection (mediastinal)	10 (100)	1190 (72)
Bronchial plasty (yes)	2 (20)	127 (8)
Pulmonary artery plasty (yes)	1 (10)	100 (6)
Pulmonary vein plasty (yes)	0 (0)	6 (0.3)
Adjacent organ resection (yes)	1 (10)	104 (6)
Operative time (min)	145 ± 39 (97–227)	163 ± 70 (45–642)
Bleeding amount (ml)	98 ± 203 (10–670)	118 ± 362 (0–6550)
Blood transfusion (yes)	1 (10)	89 (5)
Postoperative atrial fibrillation	1 (10)	200 (12)
Preoperative comorbidity		
Anti-thrombotic/coagulant drug	1 (10)	117 (7)
Chronic atrial fibrillation	0 (0)	72 (4)
Cardiovascular disease	4 (40)	438 (26)
Diabetes mellitus	1 (10)	114 (7)
Cerebral infarction	0 (0)	51 (3)

Categorical data are shown as numbers (%) and continuous data as mean ± SD if normally distributed, and median ± IQR if not normally distributed (range)

COPD chronic obstructive pulmonary disease, *CEA* carcinoembryonic antigen

Table 2 Characteristics of the patients with postoperative cerebral infarction

Case	Age	Sex	Side	Preoperative comorbidity	*p* stage	Operative mode	Interval[a] (day)	Cause of CI
1	81	F	Left	Hypertension	IIA	Sleeve left lingular and LLL	10	Unknown
2	74	F	Left	Hypertension	IA	LUL	60	PVT
3	58	F	Right	Cerebral artery aneurysm	IA	RUL	1	Unknown
4	71	F	Left	None	IIIA	LUL	0	Unknown
5	59	M	Left	ICA stenosis	IIIA	LLL	2	ICA stenosis
6	57	F	Left	None	IIIA	Left pneumonectomy	4	Unknown
7	63	M	Left	None	IIA	Double sleeve LUL	3	Unknown
8	84	F	Left	Diabetes mellitus	IA	LUL	2	Unknown
9	70	M	Left	MI, post PCI	IA	LUL	2	Unknown
10	86	M	Left	Hypertension, MI	IIA	LLL	1	Unknown

LUL left upper lobectomy, *LLL* left lower lobectomy, *RUL* right upper lobectomy, *ICA* internal carotid artery, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PVT* pulmonary vein thrombus

[a]Interval from operation to the occurrence of cerebral infarction

Table 3 Clinicopathological characteristics of the thrombus development in the left upper PV stump

Factors	Thrombus of the left upper PV stump		*p* value*
	Presence ($n=16$)	Absence ($n=121$)	
Clinical factors			
Age (years)	71.4 ± 6.0 (61–81)	64.3 ± 8.8 (41–84)	0.002
Sex (Male)	5 (69)	90 (74)	0.763
Pack-years of smoking	39.9 ± 60.6 (0–225)	30.5 ± 36.7 (0–180)	0.380
COPD (GOLD I)	10 (63)	86 (71)	0.563
Body mass index (kg/m^2)	1.62 ± 0.2 (1.33–1.94)	1.65 ± 0.2 (1.27–1.99)	0.511
CEA (ng/ml)	4.1 ± 2.3 (1.1–9.0)	7.5 ± 16.9 (0.7–145.9)	0.425
Interval[a] (day)	165 ± 195 (6–569)	175 ± 164 (0–906)	0.812
Pathological factors			
Pathological stage (I)	1 (6)	37 (31)	0.042
Lung cancer (yes)	13 (81)	109 (90)	0.216
Surgical factors			
Node dissection (mediastinal)	15 (94)	108 (89)	0.577
Bronchial plasty (yes)	4 (25)	23 (19)	0.571
Pulmonary artery plasty (yes)	5 (31)	34 (28)	0.793
Pulmonary vein plasty (yes)	0 (0)	0 (0)	–
Adjacent organ resection (yes)	2 (13)	109 (90)	0.216
Operative time (min)	206 ± 110 (71–482)	188 ± 79 (62–406)	0.413
Bleeding amount (ml)	280 ± 418 (10–1660)	153 ± 272 (3–1970)	0.103
Blood transfusion (yes)	3 (19)	8 (7)	0.120
Pre or postoperative comorbidity			
Anti-thrombotic/coagulant drug	1 (6)	13 (11)	0.577
Atrial fibrillation	2 (13)	6 (5)	0.236
Cardiovascular disease	4 (25)	30 (25)	0.986
Diabetes mellitus	2 (13)	38 (31)	0.150
Cerebral infarction	0 (0)	9 (7)	0.598
Postoperative atrial fibrillation	2 (13)	16 (13)	0.936
Postoperative anticoagulant drug	0 (0)	4 (3)	0.460

Categorical data are shown as numbers (%) and continuous data as mean ± SD if normally distributed, and median ± IQR if not normally distributed (range)

PV pulmonary vein, *COPD* chronic obstructive pulmonary disease, *CEA* carcinoembryonic antigen

*p value in Chi-square test, Student's t test or Wilcoxon rank sum test

[a]Time from operation to the enhanced computed tomography scan

comorbidities, postoperative complications, intraoperative factors, or the extent of surgical modes were not statistically associated.

Among the patients that developed the thrombus after LUL, anticoagulant agents were administrated to 5 patients and the thrombus was confirmed eliminated by CE-CT scan. Thrombus of another 7 patients was confirmed to have disappeared spontaneously without any anticoagulant agent in the course of observation using CE-CT scan, while the remaining patients were lost to follow-up due to lung cancer or other cancer deaths, without the onset of postoperative cerebral infarction.

Discussion

The primary aim of this study was to identify the risk factors of CI after pulmonary lobectomy. The results demonstrated that incidence of postoperative CI was relatively rare, but frequently occurs in the very early-phase after pulmonary lobectomy. Furthermore, CI was significantly observed in patients with a left side lesion, especially those who underwent LUL. According to the above analysis, the second study was conducted to elucidate the characteristics and risk factors of thrombus formation in the stump

Table 4 Univariable analysis to predict the thrombus development

Factors	Odds ratio (95% confidence interval)	*p* value*
Age (years)	1.123 (1.039–1.214)	0.003
Sex (male)	1.320 (0.425–4.098)	0.631
Pack-years of smoking	1.005 (0.994–1.017)	0.381
COPD (GOLD I)	0.678 (0.229–2.009)	0.483
Body mass index (kg/m^2)	0.342 (0.014–8.223)	0.508
CEA (ng/ml)	0.953 (0.846–1.074)	0.430
Pathological stage (II or more)	9.259 (1.102–76.92)	0.040
Node dissection (mediastinal)	1.801 (0.220–14.71)	0.582
More complicated procedures (yes)	0.969 (0.339–2.772)	0.953
Bronchial plasty (yes)	0.704 (0.208–2.383)	0.573
Pulmonary artery plasty (yes)	0.860 (0.278–2.659)	0.793
Adjacent organ resection (yes)	1.304 (0.274–6.208)	0.739
Operative time (min)	1.002 (0.997–1.008)	0.411
Bleeding amount (ml)	1.001 (1.000–1.002)	0.126
Anti-thorombotic/coagulant drug	1.806 (0.220–14.81)	0.582
Atrial fibrillation (yes)	0.365 (0.067–1.987)	0.244
Cardiovascular disease (yes)	0.771 (0.156–3.806)	0.749
Diabetes mellitus (yes)	3.205 (0.694–14.08)	0.136
Postoperative atrial fibrillation (yes)	1.067 (0.221–5.138)	0.936

COPD chronic obstructive pulmonary disease, *CEA* carcinoembryonic antigen

**p* value in logistic regression analysis

of PV focusing particularly on patients who underwent LUL in our institute. The findings indicated that the frequency of thrombus formation in the stump of resected PV after LUL may not be an uncommon event after pulmonary lobectomy, as the incidence was more than 10% in the current study. However, the correlation between the incidence of postoperative CI and floating thrombus in the PV stump remains unclear. Hence, we should pay close attention to the etiology of thrombus formation as a possible cause of postoperative CI after general thoracic surgery.

In this study, risk factors for thrombus formation after LUL were elderly age and advanced stage of lung cancer, which was similar to the previous study [14]. The former may correlate with fragileness of the endothelium, and the latter may contribute to the hyper-thrombotic state. In addition to the results of a multivariate analysis in this study, previous reports focused on the anatomical aspect of the resected PV, and elucidated that the length of the stump of the left upper PV was significantly longer than other PVs [16], which resulted in stasis of the blood flow and subsequent thrombus formation in the stump of the left upper PV [17, 18]. Peripheral PV dissection with multiple staplers or ligations would also result in longer PV stump. It can contribute the increase in thrombus formation. However, routine intrapericardial dissection of the left upper PV performed to shorten the stump would be challenging and provocative at this time. Furthermore, the mechanical factor owning to the use of automated suture devices may also relate to the formation of thrombus in the resected PV stump. The possibility that LUL is highly correlated with thrombus formation in the stump of resected PV is being recognized gradually [5, 7–12], and that may result in postoperative CI after general thoracic surgery. However, the actual frequency, time of onset, risk factors, surgical mode and other possible causes of thrombus formation remain unclear.

The fact that the period of the postoperative CE-CT scan after LUL was not uniformed in this study, which is a main limitation of the retrospective nature, indicates that the actual frequency of thrombus formation may likely be higher as some thrombi disappear spontaneously in the postoperative course. In the relatively low frequency of postoperative CI, the detected thrombus may not always relate with the onset despite the long stagnation in the resected PV stump. Hence, there is a discrepancy in the incidence between thrombus formation and the postoperative CI event. As just described, real incidence rate of the PV stump thrombus after lobectomy would not be clarified based on the retrospective study. Only a result of prospective observation study could answer this important clinical issue. Therefore, we did not compare the incidence rate of the PV stump thrombus after the LUL with the other lobectomy. Nonetheless, total cohort that investigated the postoperative CE-CT after LUL is larger than the previous report, so the present data regarding the incidence rate of PV stump thrombus after the LUL would be meaningful in our daily practice.

Therefore, if the etiology and risk factors of thrombus formation after pulmonary lobectomy are clearly identified at this time, we could effectively provide anticoagulant therapy to prevent the postoperative CI as much as possible. To resolve these issues and possibly prevent postoperative CI after general thoracic surgery, it is inevitable to evaluate the presence of thrombus in the PV stump by performing a uniformed postoperative EC-CT scan for the patients who undergo lobectomies. Furthermore, the survey should be performed in the very early-phase after lobectomy as the postoperative CI usually occurs immediately after the pulmonary resection. Early detection of the thrombus may contribute to the prevention of postoperative CI. Therefore, a multicenter clinical study is essential to elucidate the frequency, timing and conditions favoring the formation of PV stump thrombus using a postoperative CE-CT scan. Such a prospective observation study on this matter is presently ongoing in our institution. The results may raise a new question on perioperative management strategies after lobectomy.

In conclusion, postoperative CI, as a critical complication after pulmonary resection, may occur in the very early-phase after the pulmonary lobectomy, which is significantly

common in patients undergoing LUL. Furthermore, thrombus in the PV stump after LUL is relatively frequent based on the findings of the present study. To investigate the etiology of thrombus formation in resected PV and the need for anticoagulant therapy, a multicenter prospective observation study using postoperative periodical CE-CT scan would be timely.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to disclose.

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