



Cerebral infarction after left upper lung lobectomy with central vascular ligation

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Background: Thrombus of the pulmonary vein (PV) stump is reportedly more frequent after left upper lobectomy than after other lobectomies, risking postoperative cerebral infarction (PCI). We have performed central vascular ligation before vascular dissection to improve the safety of surgical stapling. The effects of central vascular ligation in terms of PV stump thrombus and PCI are uncertain.

Methods: This study retrospectively reviewed the records of patients who underwent left upper lobectomy at a single center (Hokkaido Cancer Center, Sapporo, Japan) between November 1, 2008 and July 31, 2018. Relationships between PCI, PV stump thrombus and background characteristics were investigated and analyzed.

Results: All 208 cases of left upper lobectomy underwent central vascular ligation of the PV during this study. PCI occurred in 8 of the 208 patients. PV stump thrombus was detected in 14 of the 132 patients. In comparison with no-PCI cases, PCI cases showed significantly higher rates of comorbidity with cardiovascular disease ($P=0.02$), double cancer within 5 years ($P=0.04$), intraoperative hyperthermic chemotherapy ($P=0.02$), postoperative intrapleural inflammation ($P=0.02$) and postoperative PV stump thrombus ($P=0.04$). Presence of both comorbid cardiovascular disease (odds ratio, 18.4) and intraoperative hyperthermic chemotherapy (odds ratio, 30.4) was associated with higher risk of PV stump thrombus than presence of none of these factors. Cerebral infarction within 30 days postoperatively was seen in only 2 of the 208 cases (1.0%).

Conclusions: Central ligation of the PV may prevent postoperative early cerebral infarction. Further study of the effectiveness of this method for preventing PV stump thrombus is needed.

Keywords: Left upper lobectomy; thrombus of pulmonary vein stump; postoperative cerebral infarction (PCI)

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Introduction

The frequency of thrombus at the pulmonary vein (PV) stump has recently been reported to be higher after left upper lobectomy than after other lobectomies. Thrombus of the PV stump has also been reported to cause postoperative cerebral infarction (PCI). Various causes of PV thrombus have been assumed, such as turbulence, abnormality of the

coagulation system and surgical staples (1). As a result, left upper lobectomy may carry a higher risk of PCI than other lobectomies (2). This is attributed to the longer PV stump with left upper lobectomy.

Generally, pulmonary vessels have been dissected using a linear stapler. We, however, have been performing central vascular ligation before vascular dissection since starting video-assisted thoracoscopic surgery in 1992 (*Figure 1*).

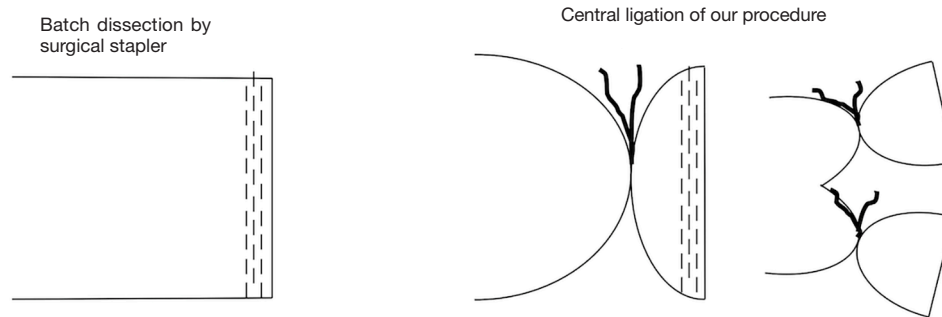


Figure 1 Schema of dissection for the pulmonary vein. Generally, the pulmonary vein is dissected directly by surgical linear stapler. Our procedure adds central ligation before stapler dissection to ensure safety.

Our rationale for this step was to ensure the safety of the procedure by including measures against dysfunction of surgical stapling. This central vascular ligation may reduce intravascular exposure of the staple and contribute to a short PV stump. However, the effect of this central vascular ligation in terms of preventing PV stump thrombus and PCI is uncertain. We therefore retrospectively investigated cases of left upper lobectomy we had performed.

Methods

This study retrospectively reviewed the records of patients who underwent left upper lobectomy at a single center, Hokkaido Cancer Center in Sapporo, Japan, between November 1, 2008 and July 31, 2018. The ethics approval for this study was granted by the ethics committee of Hokkaido Cancer Center (approval number: 30-101); the requirement to obtain informed consent directly was waived and Informed consent was obtained in the form of opt-out on the website. We investigated all patients who experienced cerebral infarction and in whom PV stump thrombus was detected on contrast-enhanced computed tomography (CT) during follow-up. Cerebral infarction was diagnosed and treated by a neurologist.

The procedure was performed in the lateral decubitus position under general anesthesia. The trachea was canalized with a double-lumen tube for selective ventilation of the lung. A 4-cm operator's port was made in front of the anterior line of the latissimus dorsi muscle on the posterolateral incision line (in the fourth or fifth intercostal space), and a 5-mm port for the thoracoscope was inserted at the mid-axillary line (in the fifth or sixth intercostal space, at a point that looks down the major fissure, sometimes more caudally). A 2-cm assistant working port was made at a posterior location on the same

line (in the sixth or seventh intercostal space). Thoracoscopic surgery was converted to open thoracotomy as necessary. Conversions were performed if lymph nodes were difficult to peel from vessels due to calcification or other factors. If adhesions and incomplete lobulation were not identified intraoperatively, the interlobar branches of the pulmonary artery were divided after central ligation. Subsequently, the pericardium was not opened and central ligation of the PV was performed and divided in all cases. The bronchus was divided with a linear stapler. Finally, lymphadenectomy was performed as necessary.

Pre- and peri-operative data were collected retrospectively from the hospital electronic medical record. Follow-up contrast-enhanced CT was performed within 6 months postoperatively, although non-contrast-enhanced CT was performed for patients with contraindications such as renal dysfunction, allergy, hyperthyroidism or lack of consent for administration of contrast agent. We divided patients into two subgroups according to the presence of PCI, then preoperative clinical variables and perioperative variables were compared between the two subgroups.

The background characteristics and long-term outcomes of patients were examined. Continuous variables are summarized as median (range). All statistical analyses were performed using the JMP[®] 13 (SAS Institute Inc., Cary, NC, USA). Pearson's chi-square test and Student's *t*-test were used for statistical analyses. For exploratory analyses, logistic regression models were performed to determine the association of clinical characteristics with PCI. Values of $P < 0.05$ were considered significant.

Results

All 208 cases of left upper lobectomy included in this study

underwent central vascular ligation of the PV (Table 1). Conversion to thoracotomy was seen in 28 of the 208 cases (conversion rate, 13.5%). Definitive diagnoses were: lung cancer, 200 patients; metastasis, 8 patients; and inflammatory mass, 1 patient. Contrast-enhanced CT was performed for 132 patients, with PV thrombus detected in 14 of these patients (10.6%). PCI occurred in 8 of the 208 patients (3.8%). In comparison with no-PCI cases, PCI cases showed significantly higher frequencies of comorbid cardiovascular disease ($P=0.02$), double cancer within 5 years ($P=0.04$), intraoperative hyperthermic chemotherapy ($P=0.02$), postoperative intrapleural inflammation ($P=0.02$) and postoperative PV stump thrombus ($P=0.04$). PCI within 30 days postoperatively was seen in only 2 of the 208 cases (1.0%). Of these two cases with early-onset PCI, one case showed postoperative nausea and vomiting and postoperative arrhythmia. The other case displayed recurrent nerve paralysis and aspiration pneumonia (Table 2). Two cases in which PCI developed after PV stump thrombus was detected had received intraoperative hyperthermic chemotherapy. In 6 of the 12 cases in which PV stump thrombus was detected, the thrombus disappeared spontaneously (Table 3). None of these 12 cases showed PCI or infarction of any other organ. In those cases, in which PV stump thrombus was detected after more than 1 year, cancer recurrence occurred and the cause of death was cancer (Figure 2). Patients with two factors of comorbid cardiovascular disease (odds ratio, 18.4; 95% confidence interval, 2.7–203.1) and intraoperative hyperthermic chemotherapy (odds ratio, 30.4; 95% confidence interval, 2.1–448.6) were considered to potentially be at higher risk of PV stump thrombus than those with none of these

factors, respectively (Figure 3).

Discussion

The rate of perioperative acute ischemic stroke has been reported as 0.6% for lobectomy/segmental lung resection (3). After left upper lobectomy, development of cerebral infarction reportedly occurs within 30 days postoperatively in 4.3% (4). In our study, the rate of cerebral infarction within 30 days postoperatively was 1.0%, lower than described in previous reports.

On the other hand, the rate of cases in which thrombus was identified at the PV stump on contrast-enhanced CT postoperatively was similar to previously reported values (2,3).

Schwalm *et al.* (5) first reported in 2004 that PV thrombus could cause cerebral infarction. Several reports have described PV thrombosis after left upper lobectomy (6–9). They reported that PV thrombosis can also cause renal infarction or thrombosis of the superior mesenteric artery. The rate of PV stump thrombus after left upper lobectomy has been reported as 6.4–17.9% (2,10,11). Ohtaka *et al.* reported finding PV thrombus on contrast-enhanced CT of three cases at 2, 6, and 18 months postoperatively, with 1 of the 3 cases showing cerebral infarction (12). Yamamoto *et al.* detected PV thrombus in 3 of the 117 patients who underwent left upper lobectomy (2.6%) within 30 days postoperatively (4). The frequency of PV stump thrombus is reportedly higher after left upper lobectomy than after lobectomy of other sites, and this finding has been detected in various periods. In our study, PV stump thrombus was detected in 14 of the 132 patients (10.6%) for whom contrast-enhanced CT was performed. This result is

Table 1 Univariate analysis of patient characteristics and postoperative cerebral infarction

Variable	Total (n=208)	Cerebral infarction (+) (n=8)	Cerebral infarction (–) (n=200)	P value
Sex				0.28
Male	117 (56.3)	6	111	
Female	91 (43.8)	2	89	
Age (years)	67±10	70±6	67±10	0.29
BMI (kg/m ²)	23.6±3.1	23.1±2.0	23.1±3.2	1.00
PS				0.82
0	187 (89.9)	7	180	
1	21 (10.1)	1	20	

Table 1 (continued)

Table 1 (continued)

Variable	Total (n=208)	Cerebral infarction (+) (n=8)	Cerebral infarction (-) (n=200)	P value
Brinkman index	680±679	1,512±1,149	647±636	0.07
Preoperative AF	2 (1.0)	0	2	0.78
Cardiovascular disease	30 (14.4)	4	26	0.02
Double cancer (within 5 years)	22 (10.6)	3	19	0.04
Cerebral infarction	11 (5.3)	2	9	0.06
Hypertension	94 (45.2)	3	91	0.66
Dyslipidemia	74 (35.6)	1	73	0.16
Diabetes mellitus	36 (17.3)	2	34	0.56
Renal dysfunction	32 (15.4)	2	30	0.44
Anticoagulant	11 (5.3)	0	11	0.50
Anti-platelet agent	32 (15.4)	2	30	0.44
Carotid artery stenosis by ultrasonography	19 (9.1)	0	19	0.36
Operative time (min)	223±60	226±63	223±60	0.91
Blood loss (mL)	75±138	69±63	75±140	0.80
Cases of blood transfusion	4 (1.9)	0	4	0.85
Operative procedure				0.14
VATS	151 (72.6)	4	147	
Thoracotomy	57 (27.4)	4	53	
Ligation point of PV				0.64
Root	39 (18.8)	1	38	
Branch	169 (81.3)	7	162	
Intraoperative hyperthermic chemotherapy	6 (2.9)	2	4	0.02
Diagnosis				0.33
Lung carcinoma	200 (96.2)	8	192	
Others	8 (3.8)	0	8 (metastasis: 7, granuloma: 1)	
TNM (7th edition) Stage ≥ II or metastasis	87 (41.8)	3	84	0.80
Postoperative AF	15 (7.2)	1	14	0.56
Prolonged air leak	16 (7.7)	1	15	0.60
Postoperative intrapleural inflammation	16 (7.7)	3	13	0.02
Contrast-enhanced CT	132 (63.5)	5	127	0.95
Postoperative thrombus of pulmonary vein stump	14 (6.7)	2	12	0.04
Follow-up period (days)	1,319±985	1,659±1,032	1,305±983	0.37

Values represent n (%) or mean ± SD. Postoperative intrapleural inflammation: pneumonia, pleuritis, or pleurodesis. BMI, body mass index; PS, performance status; AF, atrial fibrillation; VATS, video-assisted thoracoscopic surgery; PV, pulmonary vein; CT, computed tomography; SD, standard deviation.

Table 2 Characteristics of cases with postoperative cerebral infarction

Variable	Case							
	1	2	3	4	5	6	7	8
Age (years)	66	62	68	67	78	79	68	69
Sex	F	M	M	M	M	F	M	M
Contrast-enhanced CT	Yes	Yes	Yes	Yes	Yes	No	No	No
Thrombus at PV stump	Yes	Yes	No	No	No	No	No	No
Duration from surgery to first contrast-enhanced CT (days)	215	14	1,506	959	82	–	–	–
Number of CT from surgery to thrombus detection	1	1	–	–	–	–	–	–
Duration from surgery to thrombus detection (days)	215	14	–	–	–	–	–	–
Course of thrombus	Disappearance after cerebral infarction	Disappearance after cerebral infarction	–	–	–	–	–	–
Duration from surgery to onset of cerebral infarction (days)	310	158	444	842	39	1	11	1,231
History of preoperative cerebral infarction	No	No	Yes	No	No	No	No	Yes
Double cancer (<5 years)	No	No	Yes	No	No	Yes	Yes	No
Diabetes mellitus	No	No	Yes	No	No	No	No	Yes
Hypertension	No	No	Yes	No	Yes	No	Yes	No
Dyslipidemia	Unknown	Yes	No	Unknown	No	No	Unknown	No
Cardiovascular disease	No	No	Yes	Yes	Yes	No	Yes	No
Stenosis of carotid artery	No	No	No	No	No	No	No	No
Anticoagulants	No	No	No	No	No	No	No	No
Antiplatelet drugs	No	No	No	Yes	Yes	No	No	No
Intraoperative hyperthermic chemotherapy	Yes	Yes	No	No	No	No	No	No
Postoperative intrapleural inflammation	No	Yes	Yes	No	No	No	Yes	No
Postoperative AF	No	No	No	No	Yes	No	No	No

Table 2 (continued)

Table 2 (continued)

Variable	Case							
	1	2	3	4	5	6	7	8
Postoperative complication	–	Prolonged air leak, pleurodesis	Pneumonia	–	Atrial fibrillation	Postoperative nausea and vomiting, postoperative arrhythmia	Recurrent nerve paralysis, aspiration pneumonia	–
Characteristics	–	–	Anal canal carcinoma	During chemotherapy for recurrence of lung cancer	–	Leiomyosarcoma, colon cancer	Urothelial cancer, angina pectoris	dementia
Findings of cerebral infarction on MRI	Area of left middle cerebral artery	Area of right middle cerebral artery	Right temporal lobe and posterior lobe	Area of middle cerebral artery	Part of right parietal lobe	Left temporal lobe	Area of right middle cerebral artery	Left pons
Follow-up duration (days)	3,434	1,418	2,010	980	446	2,593	526	1,863
Death	No	Yes	Yes	Yes	No	No	Yes	Yes
Cause of death	–	Car accident	Cardiac failure	Cancer	–	–	Cancer	Pneumonia

Postoperative intrapleural inflammation: pneumonia, pleuritis, or pleurodesis. CT, computed tomography; PV, pulmonary vein; AF, atrial fibrillation; MRI, magnetic resonance imaging.

comparable to the findings of previous reports.

Cancer has been shown to be associated with cerebral infarction (13). Among patients who developed cerebral infarction, the most common cancer type was lung cancer (19.0%) (14). Lung cancer has been identified as a high-risk factor for cancer-associated venous thrombosis (15). Clearly, left upper lobectomy represents a potential cause of PCI. However, even lung cancer alone can be associated with a tendency to develop PCI. In addition, common risk factors such as hypertension, diabetes mellitus, hyperlipidemia, cardiac disease (e.g., cardiac fibrillation), smoking, and large vessel disease can be associated with cerebral infarction.

Thrombus formation is associated with Virchow's three signs: circulatory stasis; vascular wall injury; and a hypercoagulable state. Although we have performed central ligation of the pulmonary artery and PV before vascular dissection with the intention of providing a bulwark against stapler dysfunction, this central ligation could also be interpreted as providing benefit though separating the line of staples as foreign bodies from the blood stream and thus preventing vascular wall injury. Our frequency of detecting thrombus was comparable to those reported previously. Nevertheless, the factors contributing to our low rate of PCI remain unclear. Half of our cases of PV stump thrombus disappeared spontaneously. Presumably, even

once thrombus has formed because of turbulence and a postoperative hypercoagulable state, thrombus can dissolve over time. Namely, pulmonary stump thrombus arising from central ligation is presumably smaller or resolves more easily with the returning postoperative fibrinolysis compared to that from intravenous exposed stapling only. This may explain why the rate of cerebral infarction within 30 days postoperatively was lower in our study than that described in previous reports. Formation of thrombus at the PV stump even at a long period after surgery may be due to hypercoagulation from various causes. In both our cases in which PV thrombus was detected before PCI, high-risk factors had been present. Both patients had undergone pleurodesis or intrathoracic hyperthermic chemotherapy and intrapleural inflammation may have continued for a long time.

Neither of our two cases of early PCI showed any evidence of PV stump thrombus. However, both patients were at high risk of hypercoagulation. One had triple cancer, including lung cancer, while the other had experienced repeated aspiration due to recurrent laryngeal nerve paralysis. For such cases, it seems that postoperative anticoagulant should be considered. Including a case with atrial fibrillation, the other cases of late onset PCI also had risk factors for cerebral infarction, such as cardiac

Table 3 Characteristics of cases with PV stump thrombus

Variable	Case											
	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	73	70	61	68	64	66	73	76	76	58	69	63
Sex	M	F	M	F	F	F	M	F	F	M	M	F
Contrast-enhanced CT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of CT from surgery to thrombus detection	8	4	2	1	1	10	1	1	1	1	2	1
Duration from surgery to thrombus detection (days)	1,210	345	266	179	36	529	307	47	49	31	97	27
Course of thrombus	Spontaneous disappearance	Residual	Residual	Spontaneous disappearance	Spontaneous disappearance	Residual	Residual	Disappearance after anticoagulants	Spontaneous disappearance	Spontaneous disappearance	Spontaneous disappearance	Disappearance after anticoagulants
History of preoperative cerebral infarction	No	No	No	No	No	No	No	No	No	No	No	No
Double cancer (<5 years)	Yes	No	No	No	No	No	Yes	No	No	No	No	No
Diabetes mellitus	No	No	No	No	No	No	No	Yes	No	No	No	Yes
Hypertension	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Dyslipidemia	No	Yes	No	No	No	No	No	No	No	No	Yes	Yes
Cardiovascular disease	No	No	No	No	No	No	No	No	No	No	No	No
Stenosis of carotid artery	No	No	No	No	No	No	No	No	No	No	No	No
Anticoagulants	No	No	No	No	No	No	No	No	No	No	Yes	No
Antiplatelet drugs	Yes	No	No	No	No	No	No	No	No	No	No	No
Intraoperative hyperthermic chemotherapy	No	No	No	No	No	No	No	No	No	No	No	No
Postoperative intrapleural inflammation	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No
Postoperative AF	No	No	No	No	No	No	No	Yes	No	No	No	No
Postoperative complication			Pneumonia					Atrial fibrillation		Pneumonia	Liver dysfunction	Postoperative nausea and vomiting
Characteristics	Colon cancer	-	-	-	-	-	Colon cancer	-	-	-	-	-
Follow-up duration	2,040	859	467	2,947	2,971	2,073	1,727	570	2,445	2,565	702	252
Death	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No
Cause of death	Unknown	Cancer	Cancer	-	-	Cancer	-	Cancer	-	-	Cancer	-

Postoperative intrapleural inflammation: pneumonia, pleuritis, or pleurodesis. PV, pulmonary vein; CT, computed tomography; AF, atrial fibrillation.

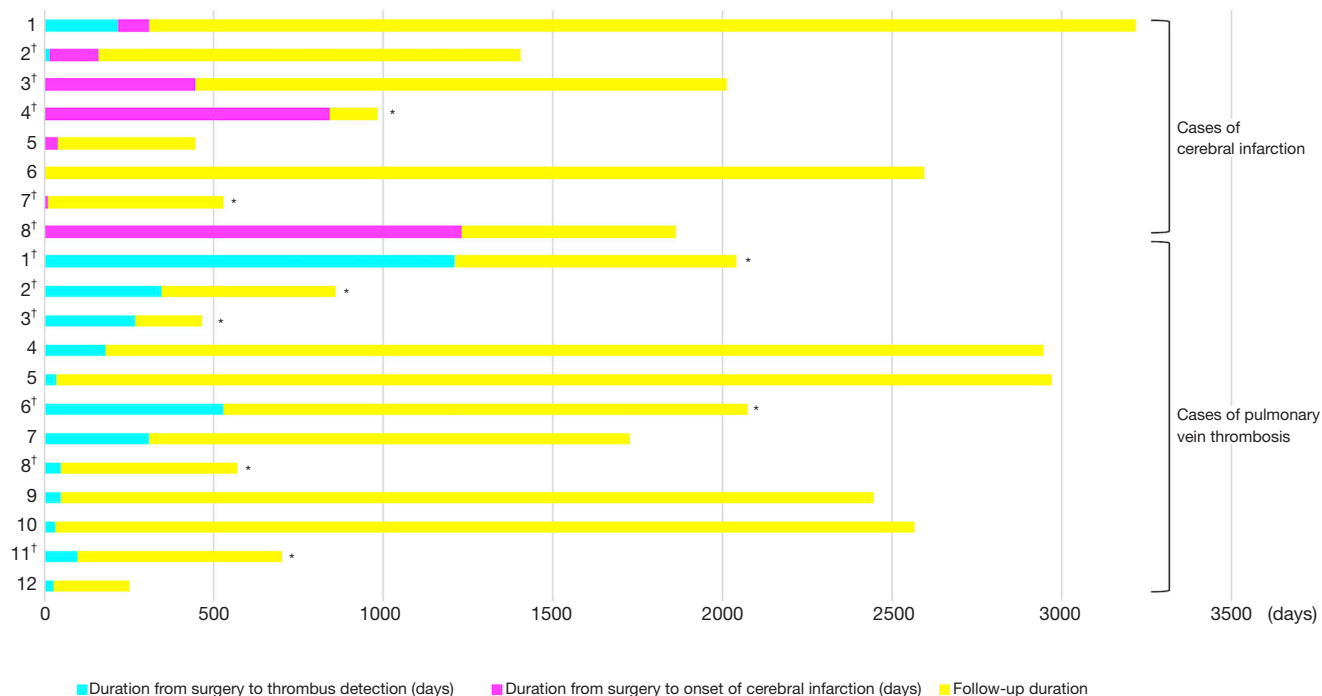


Figure 2 Period from surgery to onset of postoperative cerebral infarction or detection of pulmonary vein stump thrombus on contrast-enhanced computed tomography. The eight cases at the top of the graph developed postoperative cerebral infarction. Pulmonary vein stump thrombus was detected in the 12 cases at the bottom of the graph. †, cases of death by the end of follow-up; *, cases of cancer-specific death.

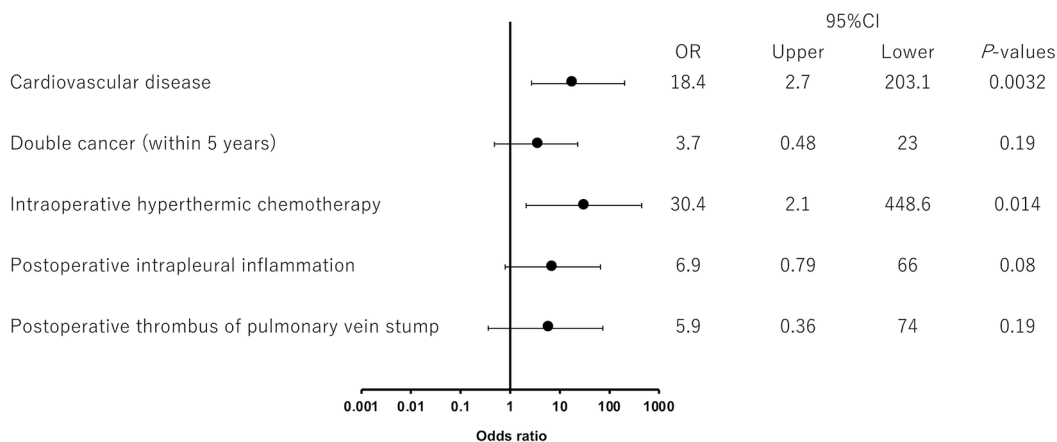


Figure 3 Exploratory logistic regression models. Forest plot of odds ratios for the five risk factors. Forest plot of the odds ratios, indicated by circles on the x-axis, for postoperative cerebral infarction. Horizontal lines show the 95% confidence interval. CI, confidence interval; OR, odds ratio.

failure, relapse of lung cancer and pneumonia associated with dementia. Although our logistic regression models were exploratory, history of cardiovascular disease and hyperthermic chemotherapy could be risk factors. Therefore, it is assumed that PCI is not necessarily associated with PV stump thrombus.

The present study has some limitations that need to be considered when interpreting the results. This investigation used a single-institution retrospective design, and a multicenter study is required to further evaluate the predictive and prognostic significance of preventing PCI by central ligation of the PV. Moreover, risk factors need to be evaluated.

In conclusion, central ligation of PV may prevent postoperative early cerebral infarction. The two factors of comorbid cardiovascular disease and intraoperative hyperthermic chemotherapy may carry a higher risk of PV stump thrombus than the absence of these factors. Further study of the effectiveness of this method in preventing thrombus of the PV stump should be conducted.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd.2020.04.02>). 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 ethics approval for this study was granted by the ethics committee of Hokkaido Cancer Center (approval number: 30-101). The requirement to obtain informed consent directly was waived and Informed consent was obtained in the form of opt-out on the website.

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