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Prediction of Pulmonary Artery-Adherent Lymph Nodes for Minimally Invasive Lung Resection

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ABSTRACT

BACKGROUND During minimally invasive surgery (MIS), pulmonary artery (PA)-adherent lymph nodes (LNs) may increase the risk of conversion to thoracotomy and/or PA injury. The aims of this study were to investigate (1) preoperative workups as predictors of PA-adherent LNs and (2) predictors of conversion/PA injury during MIS.

METHODS We investigated 1210 patients who underwent anatomical lung resection (MIS: 772, thoracotomy: 438) and determined the PA-adherent LN status by reviewing the operation video/record. The size and calcification of the hilar LNs on computed tomography, bilateral high metabolic activity on positron emission tomography, and mucosal dark pigmentation on bronchoscopy were evaluated as potential predictors for PA-adherent LNs.

RESULTS Among patients who underwent all 3 workups (n = 594), both bronchoscopy and computed tomography were independent predictors for PA-adherent LNs; the combination of dark pigmentation and LN size ≥8 mm stratified patients according to the risk of PA-adherent LNs (lowest to highest risk, 3%-65%). Among the patients who underwent MIS (n = 772), conversion and PA injuries were observed in 32 (4%) and 25 (3%) patients, respectively. Multivariate analysis revealed that the presence of PA-adherent LNs was an independent predictor of both conversion and PA injury (both $P < .001$). The effect of PA-adherent LNs on conversion risk was significantly modified by the resected lobe ($P = .008$).

CONCLUSIONS The presence of PA-adherent LNs is associated with a high risk of conversion/PA injury during MIS. Bronchial dark pigmentation, size of hilar LNs, and their combination are useful for predicting PA-adherent LNs; this finding may help in achieving safer MIS.

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The use of thoracic minimally invasive surgery (MIS), including video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS) has been increasing, with growing evidence of better postoperative pain control,[1] shorter hospitalization, and lower risk of postoperative complications[2] and noncancer-specific mortality[3] associated with these methods. During MIS, unexpected conversion to open thoracotomy is sometimes unavoidable, and is associated with an increased risk of postoperative complications and mortality.[4,5]

A pulmonary artery (PA)-adherent lymph node (LN),[6] which is an LN firmly adherent to the wall of the PA without a loose dissection plane due to hilar inflammation and/or anthracofibrosis, causes difficulty in hilar dissection and increases the risk of intraoperative catastrophes such as PA injury and/or conversion to thoracotomy.[6] We postulated that predicting the presence of PA-adherent LNs, the risk of intraoperative catastrophes, and the association between them using preoperative workups for lung cancer would help provide patients with safer MIS, including appropriate patient selection and operative preparation. Previous studies have reported that the

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Abbreviations and Acronyms

CT = computed tomography
LN = lymph node
MIS = minimally invasive surgery
PA = pulmonary artery
PET = positron emission tomography
RATS = robotic-assisted thoracic surgery
ROC = receiver operating curve
VATS = video-assisted thoracic surgery

presence of calcified hilar LNs detected on chest computed tomography (CT) is a predictor for PA-adherent LNs.[6,7] However, in our experience, a small number of patients who did not have calcification on preoperative CT were found to have PA-adherent LNs during surgery. Although several studies have suggested a possible association between PA-adherent LNs and size of hilar LNs on CT,[6] bilateral hilar fluorodeoxyglucose avidity on positron emission tomography (PET),[8] and/or bronchial mucosal dark pigmentation on bronchoscopy,[9] the predictive values of these findings and their relationship for preoperatively detecting PA-adherent LNs has not been elucidated.

To address the knowledge gap regarding preoperative prediction of PA-adherent LNs, PA injury during MIS, conversion to thoracotomy, and the association between the 2 factors to subsequently improve the safety of MIS for anatomical lung resection, we conducted this study with 2 objectives: (1) to evaluate preoperative workups as predictors of PA-adherent LNs, and (2) to investigate predictors of conversion and PA injury during MIS. To fulfill these objectives, we first reviewed operative videos and records to accurately evaluate the PA-adherent LNs, and subsequently analyzed the outcomes based on the presence of PA-adherent LNs.

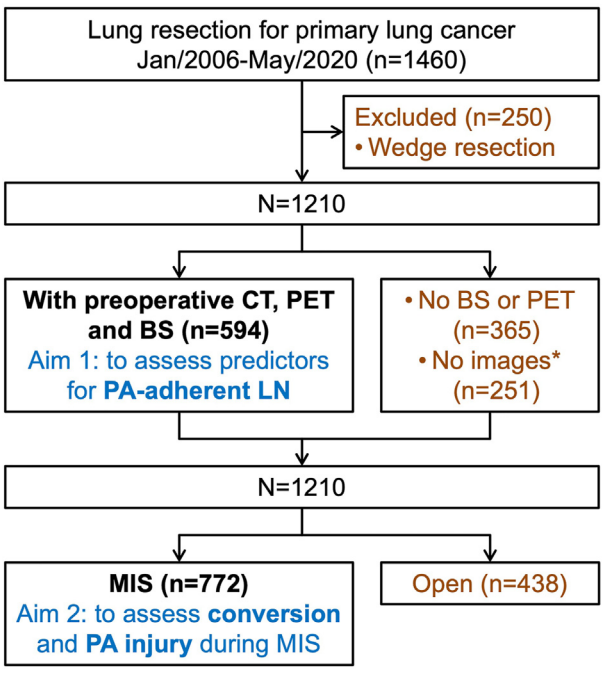

FIGURE 1 Schema for the study. *Patients with preoperative tests but without available images to evaluate mucosal dark pigmentation and/or bilateral metabolic activity. (BS, bronchoscopy; CT, computed tomography; LN, lymph node; MIS, minimally invasive surgery; PA, pulmonary artery; PET, positron emission tomography.)

PATIENTS AND METHODS

STUDY DESIGN. This was a single-institution study, and approval was obtained from the institutional review board of Shinshu University Hospital (project ID 4503). We utilized an opt-out approach instead of obtaining written informed consent from each patient. We investigated 1460 consecutive patients who underwent curative-intent lung resection for primary lung cancer via MIS or open thoracotomy performed by 18 operating surgeons between January 1, 2006, and May 31, 2020, in Shinshu University Hospital, Matsumoto, Japan. We excluded 250 patients who underwent wedge resection. We divided the remaining 1210 patients who underwent anatomical lung resection into 2 separate cohorts: (1) 594 patients who underwent CT, PET, and bronchoscopy as preoperative workups; these were studied to evaluate predictors for PA-adherent LNs; and (2) 772 patients who underwent MIS; these were analyzed to evaluate predictors for conversion to open thoracotomy and intraoperative PA injury (Figure 1). Four hundred patients were included in both the first and second cohorts. For the definition of MIS, we utilized the consensus definition of VATS, which was used in the Cancer and Leukemia Group B 39802 study.[10]

FINDINGS FOR PREDICTING PA-ADHERENT LNS. In this study, size (short diameter), calcification, metabolic activity, and bronchial infiltration of the hilar LNs (including hilar [#10] or interlobar [#11] LNs) were investigated as predictors for PA-adherent LNs. Size and calcification of the hilar LNs were evaluated using CT. Bronchial infiltration was evaluated using bronchoscopy with dark pigmentation in the bronchial mucosa. Representative findings for predicting PA-adherent LNs are shown in Figure 2. Detailed information on the findings of each workup for PA-adherent LNs can be found in the Supplemental Material.

OUTCOMES: PA-ADHERENT LNS, CONVERSION TO THORACOTOMY, AND PA INJURY DURING MIS. In this study, a PA-adherent LN was defined as a hilar LN that was adherent to the PA without loose dissection and

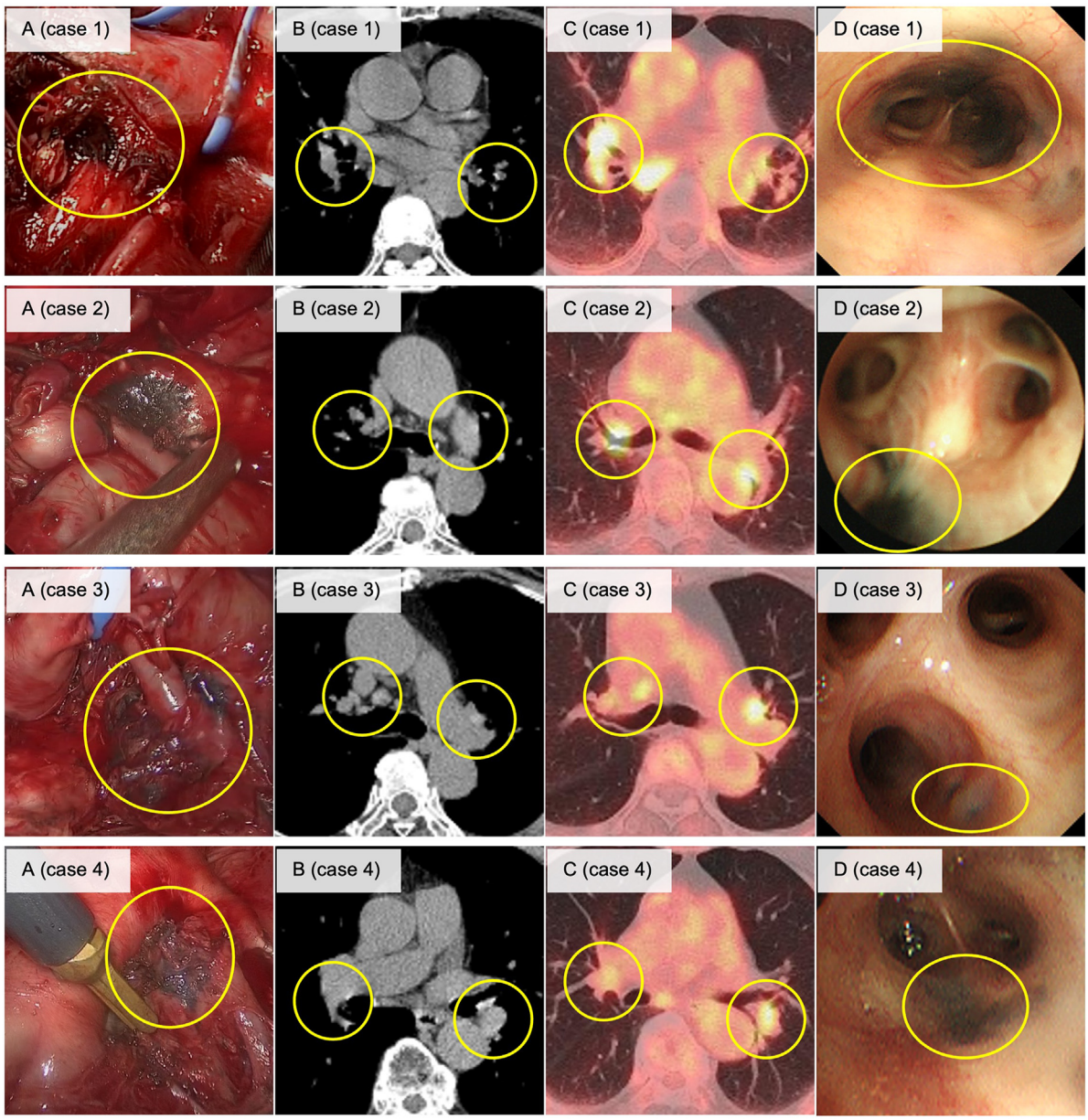

FIGURE 2 Representative images of pulmonary artery (PA)-adherent lymph nodes (LNs). (A) An intraoperative image of PA-adherent LN (*circle*). (B) Calcified hilar LNs (*circles*) on computed tomography without contrast. (C) High metabolic activity in the bilateral hilar LNs (*circles*) on positron emission tomography. (D) Bronchial mucosal dark pigmentation (*circle*) on bronchoscopy.

could not be dissected from the wall of the PA with sharp dissection using Metzenbaum scissors. The detailed information on the definitions of MIS, conversion to thoracotomy, and PA injury can be found in the Supplemental Material.

To determine the conversion status, PA injury, and PA-adherent LNs, the operation records and videos were reviewed by 2 thoracic surgeons (TT and SM).

STATISTICAL ANALYSIS. A receiver operating curve (ROC) analysis was conducted to evaluate the predicting ability of preoperative workups for PA-adherent LNs. The area under the curve values of individual workups and their combinations were assessed to identify clinically useful predictors for PA-adherent LNs. Between-group comparisons (presence vs absence of PA-adherent LNs, conversion, and PA injury) have been included in the Supplemental Material. All statistical analyses were

TABLE 1 Comparison Between Patients With and Without Pulmonary Artery-Adherent Lymph Nodes (Cohort 1)

Characteristic	Total N = 594	PA-Adherent LN (–) n = 542 [91%]	PA-Adherent LN (+) n = 52 [9%]	P
Patient background				
Age, y	70 (64-76)	70 (63-75)	76 (69-81)	**<.001**
Sex				
Male	316 (53)	285 (53)	31 (60)	.38
Female	278 (47)	257 (47)	21 (40)	
Smoking				
Never	261 (44)	232 (43)	29 (56)	.08
Former/current	333 (56)	310 (57)	23 (44)	
COPD	138 (23)	125 (23)	13 (25)	.73
Cardiovascular disease	56 (9)	50 (9)	6 (12)	.62
Anticoagulation drug use	66 (11)	59 (11)	7 (13)	.64
Induction chemotherapy	29 (5)	26 (5)	3 (6)	.73
%FEV1, %	96 (84-110)	95 (83-109)	102 (86-117)	.08
Tumor size on CT, mm	25 (19-35)	25 (19-35)	27 (23-36)	.16
SUV_{max} of tumor	3.8 (1.6-8.7)	3.8 (1.6-8.8)	3.1 (1.6-8.5)	.73
Clinical N stage				
N0	509 (86)	472 (87)	37 (71)	**.007**
N1	54 (9)	45 (8)	9 (17)	
N2	31 (5)	25 (5)	6 (12)	
Location of tumor				
RUL	185 (31)	168 (31)	17 (33)	.60
RML	43 (7)	38 (7)	5 (10)	
RLL	142 (24)	130 (24)	12 (23)	
LUL	137 (23)	123 (23)	14 (27)	
LLL	87 (15)	83 (15)	4 (8)	
Findings for predicting PA-adherent LN				
CT: LN size, mm	6 (5-8)	6 (5-7)	8 (5-10)	**<.001**
CT: calcified LN	66 (11)	50 (9)	16 (31)	**<.001**
PET: bilateral LN metabolic activity	208 (35)	176 (32)	32 (62)	**<.001**
Bronchoscopy: dark pigmentation	59 (10)	27 (5)	32 (62)	**<.001**

Data are shown as number (%) or median (25th-75th percentiles). Numbers in boldface indicate statistically significant *P* values. COPD, chronic obstructive pulmonary disease; CT, computed tomography; %FEV1, predicted forced expiratory volume in one second; LLL, left lower lobe; LN, lymph node, LUL, left upper lobe; MIS, minimally invasive surgery; PA, pulmonary artery; PET, positron emission tomography; pStage, pathologic stage; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUV_{max}, maximum standard uptake value.

conducted using IBM SPSS Statistics 27 (IBM, Armonk, NY). Statistical significance was set at $P < .05$.

RESULTS

PREDICTORS FOR PA-ADHERENT LNS. Table 1 summarizes the patient demographics and findings for predicting PA-adherent LNs in cohort 1, and presents comparisons between patients with and without PA-adherent LNs. Supplemental Table 1 shows the operative and pathological findings. In this cohort, PA-adherent LNs were observed in 52 patients (9%). Figure 2 shows a representative image of PA-adherent LNs.

The presence of PA-adherent LNs was significantly associated with increased age, higher clinical N-stage, larger size of the hilar LN on CT (CT-LN), presence of calcified CT-LN, bilateral LN metabolic activity on PET, and bronchoscopic dark pigmentation. In the multivariate analysis for predicting PA-adherent LNs, larger CT-LN size, calcified CT-LN, and bronchoscopic dark pigmentation were independent predictors of PA-adherent LNs (Table 2). The performance of preoperative workups for predicting PA-adherent LNs is shown in Table 3.

RISK STRATIFICATION FOR PA-ADHERENT LNS BY THE COMBINATION OF PREOPERATIVE WORKUPS. In the ROC analyses for predicting PA-adherent LNs, we found that the combination of CT-LN size ≥8 mm and dark pigmentation on bronchoscopy had the highest area under the curve (0.833) (Figure 3) among all the different combinations or individual tests (Supplemental Figure 1). Risk stratification for PA-

TABLE 2 Multivariate Binary Logistic Analysis for Predicting Pulmonary Artery-Adherent Lymph Nodes (Cohort 1)

Variables	OR	95% CI	*P*
Age (per 1 year increase)	1.04	0.99-1.09	.16
Smoking history (vs negative)	0.66	0.28-1.57	.35
%FEV1 (per 1% increase)	1.00	1.00-1.01	.64
Clinical N stage (ref cN0)			
cN0	1.00		.12
cN1	1.74	0.51-5.94	
cN2	3.86	1.04-14.37	
CT: LN size (per 1 mm increase)	1.22	1.05-1.42	**.009**
CT: calcified LN (vs negative)	2.88	1.10-7.54	**.03**
PET: bilateral LN metabolic activity (vs negative)	1.50	0.64-3.53	.35
Bronchoscopy: dark pigmentation (vs negative)	21.36	8.82-51.74	**<.001**

Numbers in boldface indicate statistically significant *P* values. CI, confidence interval; CT, computed tomography; %FEV1, predicted forced expiratory volume in one second; OR, odds ratio; PET, positron emission tomography.

adherent LNs and sensitivity/specificity to detect PA-adherent LNs based on the combination pattern of workups are also shown in Figure 3 and Supplemental Figure 1. In patients who had both CT-LN <8 mm and no dark bronchoscopic pigmentation, the risk of PA-adherent LNs was the lowest (3%); this risk was highest in patients with both CT-LN ≥8 mm and positive dark pigmentation (65%). The risk of PA-adherent LN significantly changed based on the combination pattern of tests (Figure 3).

CONVERSION TO OPEN THORACOTOMY. Thirty-two patients (4%) among 772 (cohort 2) underwent conversion to open thoracotomy. The reasons for the conversion were PA injury (n = 16, 50%, including 11 patients with PA-adherent LNs), PA-adherent LNs without PA injury (n = 6, 19%), bleeding without PA injury (n = 4, 13%), unexpected higher stage (n = 3, 9%), and other reasons (n = 3, 9%).

PA INJURY DURING MIS. Of the 772 patients in cohort 2, 3% had PA injuries during MIS. Among the 25 patients with PA injury, 16 underwent conversion to open thoracotomy (64%). Among the 12 patients with PA injury with PA-adherent LNs, 11 underwent conversion (92%); of the remaining 13 patients with PA injury without PA-adherent LNs, 5 underwent conversion (38%).

PREDICTORS FOR CONVERSION AND PA INJURY. Table 4 summarizes the patient demographics and operative findings in cohort 2 and presents the comparisons between patients with and without conversion, and with and without PA injury. The operative and pathologic findings are shown in Supplemental Table 2. Table 5 shows the multivariate analyses for predicting conversion and PA injuries. The use of anticoagulation/platelet drug(s), higher tumoral metabolic activity, the left upper lobe, and the presence of PA-adherent LNs were independent predictors for conversion to open thoracotomy. Induction chemotherapy, higher tumoral metabolic activity, and the presence of PA-adherent LNs were independent predictors of PA injury during MIS.

LOBE-SPECIFIC RISK OF CONVERSION/PA INJURY. Lobe-specific risk of conversion (Table 6) and PA injury (Supplemental Table 3) based on the status of the PA-adherent LNs are shown. In all patients, the risk of conversion was significantly different across the types of resected lobes ($P = .003$), with the highest risk associated with the left upper lobe, followed by the

TABLE 3 Performance of Preoperative Tests for Predicting Pulmonary Artery-Adherent Lymph Nodes

	PA-Adherent LNs		Predictive Performance				
Tests for Predicting PA-Adherent LNs	Positive	Negative	Accuracy	Sensitivity	Specificity	PPV	NPV
CT: LN size[a]							
≥8 mm	30	135	74%	58%	75%	18%	95%
<8 mm	22	407					
CT: calcified LNs							
Positive	16	50	86%	31%	91%	24%	93%
Negative	36	492					
PET: bilateral LN metabolic activity							
Positive	32	176	67%	62%	68%	15%	95%
Negative	20	366					
Bronchoscopy: dark pigmentation							
Positive	32	27	92%	62%	95%	54%	96%
Negative	20	515					

[a]Optimal cutoff was determined using a receiver operating characteristics curve analysis (available in the Supplemental Materials) Data are shown as number of patients or percentage. CT, computed tomography; LN, lymph node; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

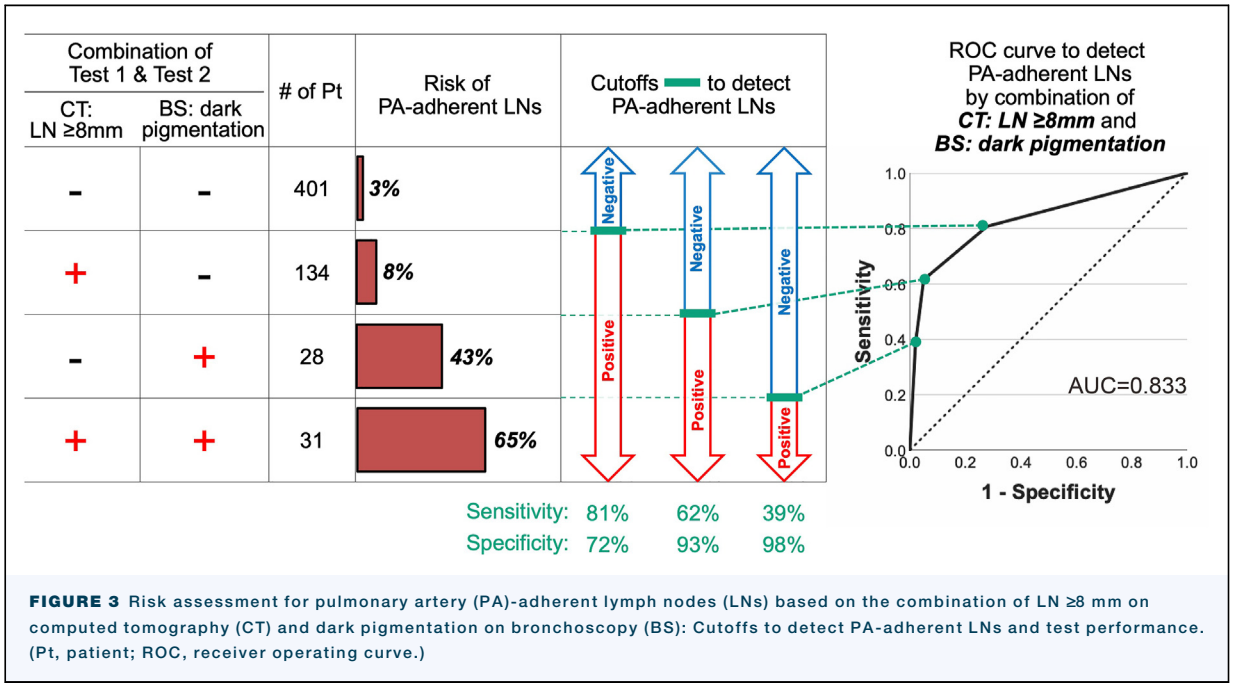

FIGURE 3 Risk assessment for pulmonary artery (PA)-adherent lymph nodes (LNs) based on the combination of LN ≥8 mm on computed tomography (CT) and dark pigmentation on bronchoscopy (BS): Cutoffs to detect PA-adherent LNs and test performance. (Pt, patient; ROC, receiver operating curve.)

right middle lobe, right upper lobe, and lower lobes. This effect was modified by the status of PA-adherent LNs; the difference was not significant in patients without PA-adherent LNs but was significant in patients with PA-adherent LNs ($P = .02$). There was no significant difference in the risk of PA injury across the types of resected lobes.

PROPOSAL OF ANATOMICAL COMPLEXITY OF THE LUNG. Based on the modified risk of conversion by the lobes and the presence of PA-adherent LNs, the potential differences in the anatomical complexity between the lobes can be determined based on two elements: (1) more than 1 PA branch in close proximity to each other and (2) a "perpendicular relationship" between the lobar bronchus and the main portion of the PA rather than a "parallel relationship" (details in the Supplemental Text and Supplemental Figure 2).

COMMENT

In this study, we demonstrated the usefulness of preoperative bronchoscopy and CT in predicting PA-adherent LNs, and the impact of PA-adherent LNs on intraoperative catastrophes (conversion/PA injury) during MIS. The novelty and strengths of this study are as follows: (1) we investigated predictors for PA-adherent LNs evaluating preoperative CT, PET, and bronchoscopy; (2) the combination of bronchoscopy and CT findings successfully stratified patients according to the risk of PA-adherent LNs, which will be useful in clinical practice; and (3) this is the first study to investigate lobe-specific analysis in predicting conversion, the results of which will provide thoracic surgeons with more specific and practical information.

We reviewed operation videos and records to accurately evaluate the presence/absence of PA-adherent LNs, which enabled us to analyze the association between PA-adherent LNs and intraoperative catastrophes in this study. To statistically assess the link between PA-adherent LNs, intraoperative catastrophes, and perioperative factors, the incidence of PA-adherent LNs in patients with and without intraoperative catastrophes must be investigated. However, in patients without intraoperative catastrophes, it is sometimes difficult to confirm the PA-adherent LN status, because the description of this status in the operative records depends on the surgeon. Therefore, we reviewed the operative videos for all patients. This enabled us to evaluate the potential influence of PA-adherent LNs on intraoperative catastrophes, investigate predictors for PA-adherent LNs, and conduct a detailed, lobe-specific analysis.

In general, a clinical test with high specificity is useful for the treatment decision-making process. Our risk-assessment model for PA-adherent LNs based on the ROC analyses revealed that dark pigmentation on bronchoscopy and its combination with other workups had high specificities (95%-98%) for predicting PA-adherent LNs. To demonstrate the clinical utility of the developed model, we developed a patient selection protocol for MIS based on the individual risk of PA-

TABLE 4 Demographics of Patients Who Underwent Minimally Invasive Surgery: Comparison of Conversion vs No Conversion and Pulmonary Artery Injury vs No Injury (Cohort 2)

		Conversion to thoracotomy			PA injury		
Variables	Total N = 772	(–) n = 740 [96%]	(+) n = 32 [4%]	P	(–) n = 747 [97%]	(+) n = 25 [3%]	P
PA-adherent lymph node							
Negative	722 (94)	707 (96)	15 (47)	**<.001**	709 (95)	13 (52)	**<.001**
Positive	50 (6)	33 (4)	17 (53)		38 (5)	12 (48)	
Patient background							
Age, y	70 (63-75)	70 (63-75)	75 (68-79)	**.006**	70 (63-75)	76 (69-79)	**.001**
Sex							
Male	392 (51)	376 (51)	16 (50)	>.99	378 (51)	14 (56)	.69
Female	380 (49)	364 (49)	16 (50)		369 (49)	11 (44)	
Smoking							
Never	375 (49)	357 (48)	18 (56)		364 (49)	11 (44)	.69
Former/current	397 (51)	383 (52)	14 (44)		383 (51)	14 (56)	
COPD	171 (22)	161 (22)	10 (31)	.20	159 (21)	12 (48)	**.005**
Cardiovascular disease	79 (10)	74 (10)	5 (16)	.36	75 (10)	4 (16)	.31
Anticoagulation drug use	72 (9)	63 (9)	9 (28)	**.002**	66 (9)	6 (24)	**.02**
Induction chemotherapy	24 (3)	22 (3)	2 (6)	.26	20 (3)	4 (16)	**.006**
%FEV1, %	97 (86-109)	97 (86-109)	100 (85-112)	.80	97 (86-109)	91 (79-106)	.27
Tumor size on CT, mm	22 (15-29)	22 (15-29)	26 (20-36)	**.002**	22 (15-29)	30 (21-38)	**.002**
SUV_{max}, tumor	2.4 (1.2-6.0)	2.3 (1.2-5.9)	2.9 (1.8-9.6)	**.04**	2.3 (1.2-5.8)	6.0 (1.9-11.2)	**.004**
Clinical N stage							
N0	714 (92)	688 (93)	26 (81)	**.03**	693 (93)	21 (84)	.26
N1	44 (6)	40 (5)	4 (13)		41 (5)	3 (12)	
N2	14 (2)	12 (2)	2 (6)		13 (2)	1 (4)	
Location of tumor							
RUL	247 (32)	238 (32)	9 (28)	**.003**	240 (32)	7 (28)	.15
RML	60 (8)	57 (8)	3 (9)		58 (8)	2 (8)	
RLL	169 (22)	166 (22)	3 (9)		166 (22)	3 (12)	
LUL	181 (23)	165 (22)	16 (50)		170 (23)	11 (44)	
LLL	115 (15)	114 (15)	1 (3)		113 (15)	2 (8)	

Data are shown as number (%) or median (25th-75th percentile). Numbers in boldface indicate statistically significant *P* values. CT, computed tomography; COPD, chronic obstructive pulmonary disease; %FEV1, predicted forced expiratory volume in one second; LLL, left lower lobe; LUL, left upper lobe; PA, pulmonary artery; pStage, pathologic stage; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUV_{max}, maximum standard uptake value.

adherent LNs (details in the Supplemental Text and Supplemental Figure 3). Importantly, the protocol addressed patients without preoperative bronchoscopy as well. In high-risk patients, we discuss the risk with the patients in the preoperative informed consent meeting and prepare for and prevent potential intraoperative complications by adopting measures such as avoiding assigning a trainee as the primary surgeon, preparing for blood transfusion, and administering epidural analgesia. After this protocol was implemented, between June 2020 and September 2021 we intended to perform 141, and performed 140 MIS anatomical lung resections; 11 patients (8%) had PA-adherent LNs, and in 9 (82%), we were able to predict the presence of PA-adherent LNs based on preoperative assessment. Among the 9 cases where we predicted PA-adherent LNs, 6 patients underwent planned MIS, 1 patient opted for open thoracotomy after preoperative informed consent meeting, and 2 patients (both undergoing left upper lobe procedures) required elective conversion, in whom preoperative epidural analgesia catheter placement was proactively conducted due to their high risk of conversion (we generally do not provide epidural analgesia for MIS[11]). There were no emergency conversions after the initiation of this protocol.

When we encounter PA-adherent LNs during MIS, intraoperative decision-making for conversion to thoracotomy may depend on whether the adhered PA can be treated safely using MIS. This may depend not only on the surgeons' experience/skill, but also on the anatomical complexity. Our lobe-specific analysis revealed that the impact of PA-adherent LNs on the conversion risk was higher in the right middle and the left upper lobes than the other lobes, suggesting high anatomical complexity in these 2 lobes (Supplemental Figure 2).

TABLE 5 Multivariate Binary Logistic Regression for Conversion and Pulmonary Artery Injury in Patients Who Underwent Minimally Invasive Surgery (Cohort 2)

	Conversion			PA Injury		
Variables	OR	95% CI	P	OR	95% CI	P
Age (per 1 year increase)	1.01	0.96-1.08	.63	1.06	0.99-1.14	.12
COPD (vs no COPD)				2.63	0.98-7.06	.06
Anticoagulation drug use (vs no use)	4.01	1.18-13.64	**.03**			
Induction chemotherapy (vs no induction)				6.53	1.63-26.08	**.008**
Tumor size on CT (per 1 mm increase)	1.02	0.98-1.06	.28	1.01	0.97-1.05	.63
Tumor SUVmax (per 1 SUV increase)	1.10	1.00-1.21	.05	1.11	1.02-1.20	**.02**
Clinical N stage (ref cN0)						
cN0	1.00		.17			
cN1	1.17	0.25-5.53				
cN2	7.33	0.91-59.34				
Location of tumor (ref RUL)						
RUL	1.00		**.008**			
RML	2.50	0.44-14.23				
RLL	0.17	0.02-1.60				
LUL	4.35	1.41-13.41				
LLL	0.59	0.06-5.46				
PA-adherent lymph node (vs negative)	21.99	7.28-66.36	**<.001**	11.90	3.83-37.02	**<.001**

Numbers in boldface indicate statistically significant *P* values. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; LLL, left lower lobe; LUL, left upper lobe; PA, pulmonary artery; OR, odds ratio; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUVmax, maximum standard uptake value.

This study has several limitations. First, we did not evaluate the surgeons' technical skills and preferences, which could have affected the outcomes (Supplemental Table 3 presents a comparison of the incidence of intraoperative catastrophes between surgeons). Second, more than half the patients were excluded due to unavailability of bronchoscopic images for bronchial pigmentation evaluation, which could have caused a potential selection bias and affected outcomes (Supplemental Table 4 presents the reasons for exclusion and a comparison of background demographics/incidence of PA-adherent LNs between excluded patients and included patients). Third, the number of events was relatively small, which might have affected the statistical accuracy, particularly in the lobe-specific analysis. Fourth, because this was a single-institution study and all the patients in our cohort were Japanese, we could not generalize our results to other populations. Fifth, the MIS cohort in this study included both patients who underwent VATS and RATS; however, a majority of the patients underwent VATS; fewer than 5% of the patients in the MIS cohort underwent RATS.

In conclusion, the presence of PA-adherent LNs is associated with a high risk of intraoperative catastrophes during MIS. Findings in preoperative workups such as bronchial dark pigmentation are useful for predicting PA-adherent LNs, which could assist in enabling safer surgery by adopting measures such as avoiding assigning a trainee as the primary surgeon, preparing for blood transfusion, and administering epidural analgesia.

TABLE 6 Lobe-Specific Risk of Conversion Based on the Presence/Absence of Pulmonary Artery-Adherent Lymph Nodes (Cohort 2)

		Resected Lobe					
Patients With or Without PA-Adherent LNs	Total N = 772	RUL n = 247	RML n = 60	RLL n = 169	LUL n = 181	LLL n = 115	*P*
All patients	4% (32/772)	4% (9/247)	5% (3/60)	2% (3/169)	9% (16/181)	1% (1/115)	**.003**
Patients without PA-adherent LNs	2% (15/722)	3% (6/232)	0% (0/56)	1% (2/159)	4% (6/163)	1% (1/112)	.30
Patients with PA-adherent LNs	34% (17/50)	20% (3/15)	75% (3/4)	10% (1/10)	56% (10/18)	0% (0/3)	**.02**

Data are shown as % (number of patients with conversion/number of all patients in each group). *P* values represent difference across the resected lobes. Numbers in boldface indicate statistically significant *P* values. LLL, left lower lobe; LNs, lymph nodes; LUL, left upper lobe; PA, pulmonary artery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

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SUPPLEMENTAL MATERIALS

Title: Prediction of pulmonary artery-adherent lymph nodes for minimally invasive lung resection

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<Clinicopathological data collection>

Patient demographic information was obtained from the prospectively maintained thoracic surgery database of the Division of Thoracic Surgery at Shinshu University Hospital. Data on clinicopathological variables were obtained by reviewing patient medical records specifically for this purpose. All preoperative variables were evaluated within three months of surgery.

<Findings for predicting PA-adherent LNs>

A size of hilar LN was defined as the short diameter of the largest hilar LN perpendicular to the maximum diameter of the node on the axial CT images. A calcified hilar LN was defined as a hilar LN with any calcification that was confirmed by a mediastinal window CT image without contrast. In cases with FDG avidity in the bilateral hilar LNs, the metabolic activity in these LNs was considered to be symmetrically increased as compared to the normal background mediastinal metabolic activity.

Dark pigmentation in the bronchial mucosa was considered a finding of potential perinodal infiltration of the hilar LNs. Dark pigmentation was defined as black pigmentation of the bronchial mucosa. Bronchoscopic color pictures were evaluated using our institutional PACS system. Any cases with preoperative bronchoscopy but with no available pictures on the PACS system were excluded from this study.

The radiological and bronchoscopic findings were evaluated by three thoracic surgeons (T.T., S.M., and T.E.) and the final status was determined after discussion in the consensus meeting as described below.

<Definitions: conversion to open thoracotomy and pulmonary artery (PA) injury during minimally invasive surgery (MIS) >

Conversion to open thoracotomy was defined as an unexpected intraoperative switch from MIS to open thoracotomy. For the definition of MIS, we utilized the consensus definition of VATS, which was used in the Cancer and Leukemia Group B 39802 study. Cases employing rib spreading or with an incision length > 8 cm were considered for open thoracotomy, regardless of the use of a thoracoscope. MIS included both VATS and RATS. Cases in which thoracoscopic procedures were utilized only for intraoperative staging purposes and converted to open thoracotomy from MIS were considered as an "expected conversion" and included in the open thoracotomy group.

A PA injury was defined as any injury to the main, lobar, or segmental PA that caused intraoperative bleeding requiring any type of hemostatic procedure, including simple compression, fibrin sealant patch placement, direct closure, and resection of the lungs.

<Consensus meeting to determine the final status of variables>

Any discrepancies in the evaluation of conversion, PA injury, PA-adherent lymph nodes (LNs), and findings of the preoperative workups for predicting PA-adherent LNs between surgeons were discussed in the consensus meeting with the three thoracic surgeons (T.T., S.M., and T.E.) to determine the final status.

<Statistical analysis>

The association between clinicopathological factors and outcomes (conversion, PA injury, PA-adherent LNs) was evaluated using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. A multivariate binary logistic regression analysis was conducted to determine the independent predictors for outcomes. Any preoperative factor with a P-value <0.1 in the univariate analyses was included in the multivariate analyses, in which the PA-adherent LNs status was included as a factor. A receiver operating curve (ROC) analysis was conducted to evaluate the predicting ability of preoperative workups for PA-adherent LNs. The area under the curve (AUC) values of individual workups and their combinations were assessed to identify clinically useful predictors for PA-adherent LNs.

<Predictors for conversion and PA injury >

In a comparison between patients with and without conversion, conversion was significantly associated with increased age, preoperative use of anti-coagulation/platelet drug(s), larger tumor size, higher metabolic activity in the tumor, type of resected lobe (more frequent with the left upper lobe), PA-adherent LNs, PA injury, greater blood loss, longer operation time, and higher stage.

In a comparison between patients with and without PA injury, PA injury was significantly associated with increased age, history of chronic obstructive pulmonary disease, induction chemotherapy, preoperative use of anti-coagulation/platelet drug(s), larger tumor size, higher metabolic activity in the tumor, PA-adherent LNs, conversion to open thoracotomy, greater blood loss, and longer operation time.

<Details of PA injury during MIS>

Among 25 patients with PA injury during MIS, the PA injury which was treated using the minimally invasive surgical method, without conversion, in 9 patients. In 5 patients with PA injury peripheral to the planned dividing level, hemostasis was obtained by mechanical compression and the PA was divided proximally to the injured site. In the 4 remaining patients, hemostasis was obtained by direct closure or using fibrin-sealant patch.

<Anatomical complexity>

We propose two potential elements to determine the "anatomical complexity"; 1) more than one PA branch in close proximity close to each other and 2) "perpendicular relationship" between the lobar bronchus and the central portion of the PA (the portion of the PA before or following the lobar branch but not the lobar branch itself), which can result in the lobar bronchus, which is the "center" of the pedicle of the lobe, to be surrounded by the central portion of the PA and more than one PA branch to the lobe (Supplemental Figure S1). In cases with high anatomical complexity, a hilar dissection would become challenging with PA-adherent LNs because those LNs are usually located surrounding the bronchus, resulting in multiple PA infiltrations, which will make safe dissection and encirclement of the lobar PA branch difficult using MIS and make thoracic surgeons elect to convert to thoracotomy.

A representative lobe with high anatomical complexity is the left upper lobe. On the left, the central portion of the PA goes around the left upper lobe bronchus (perpendicular relationship), usually sending four to five PA branches to the lobe. The right middle lobe is another representative lobe with high anatomical complexity. The middle lobe bronchus is perpendicularly surrounded by the central portion of the PA and its branches to the lobe. In contrast, the bilateral lower lobes have relatively low anatomical complexity; the direction of the lower lobe bronchus is similar (parallel relationship) to the PA (Supplemental Figure S1). Even if there are PA-adherent LNs in more than one PA branch to the lower lobes, their relatively parallel relationship may allow safe dissection, enabling them to be encircled using MIS.

<Patient selection protocol for MIS based on the risk assessment for PA-adherent LNs>

Based on the results of the risk assessment for PA-adherent LNs (Figure 3 and Supplemental Figure S1), and the fact that many patients do not undergo bronchoscopy before the date of surgery in clinical practice, we developed a patient selection protocol based on the potential presence of PA-adherent LNs (Supplemental Figure S3). If a patient has undergone preoperative bronchoscopy, since the presence of dark pigmentation is highly specific for the PA-adherent LN incidence, we consider any patients with dark pigmentation as having a high risk for PA-adherent LNs, and those without dark pigmentation as having a low risk for PA-adherent LNs (Supplemental Figure S1a). In high-risk patients, we explain the potential increased risk of PA-adherent LN incidence and the associated risk of conversion and PA injury in the preoperative informed consent meeting with the patient and his/her family members. We also determine the indication for MIS, particularly for high-risk lobe procedures, such as those involving the left upper and right middle lobes and/or cases with both dark bronchial pigmentation and increased LN size ≥8 mm. If the patient opts for and we elect to perform MIS, the risk of conversion and PA injury is

discussed with anesthesiologists, and we consider providing thoracic epidural analgesia to such patients due to the risk of conversion. In addition, we avoid involving a trainee as the primary operator in such cases and prepare for blood transfusion to address potential intraoperative bleeding.

The following patients who have not undergone preoperative bronchoscopy before the date of surgery are considered as having a moderately high risk for PA-adherent LNs, as test performance showed high specificity for PA-adherent LNs (specificity ≥90%): 1) patients with CT-calcified LNs (Supplemental Figure S1); and 2) patients with both PET-bilateral LN metabolic activity and CT-LN size ≥8 mm (Supplemental Figure S1h). In patients with a moderately high risk for PA-adherent LNs without preoperative bronchoscopy, we consider performing bronchoscopy before the date of surgery, particularly for high-risk lobe procedures, such as the left upper and right middle lobes. If we do not perform bronchoscopy before the date of surgery, we treat the patients as "potentially" having a high risk for PA-adherent LNs, and prepare for surgery as described above for high-risk patients with bronchoscopic dark pigmentation. For these patients, bronchoscopy is performed on the date of surgery after induction of general anesthesia.

Supplemental Table S1. Operative and pathologic findings - comparison between with and without pulmonary artery-adherent lymph nodes (cohort 1)

		Total		PA-adherent LN				
				(-)		(+)		
		N=594		N=542 [91%]		N=52 [9%]		P
Operative findings								
Procedure	Pneumonectomy	4	(1)	4	(1)	0	(0)	.57
	Bilobectomy	17	(3)	16	(3)	1	(2)	
	Lobectomy	541	(91)	491	(91)	50	(96)	
	Segmentectomy	32	(5)	31	(6)	1	(2)	
Approach	MIS*	400	(67)	367	(68)	33	(63)	.54
	Open	194	(33)	175	(32)	19	(37)	
Estimated blood loss (ml)		80	(50-150)	70	(40-150)	200	(60-350)	**<.001**
Operative time (min)		243	(200-317)	240	(197-307)	311	(262-391)	**<.001**
Pathologic findings								
Histologic type	Adenocarcinoma	456	(77)	414	(76)	42	(81)	.97
	Squamous cell	91	(15)	85	(16)	6	(12)	
	Others	47	(8)	43	(8)	4	(8)	
pStage	I	421	(71)	390	(72)	31	(60)	.19
	II	91	(15)	81	(15)	10	(19)	
	III	78	(13)	67	(12)	11	(21)	
	IV	4	(1)	4	(1)	0	(0)	

Data are shown as number (%) or median (25-75 percentiles). Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; %FEV1, predicted forced expiratory volume in one second; LLL, left lower lobe; LN, lymph node, LUL, left upper lobe; MIS, minimally invasive surgery; PA, pulmonary artery; PET, positron emission tomography; pStage, pathologic stage; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUVmax, maximum standard uptake value
*MIS includes conversion to thoracotomy.

Supplemental Table S2. Operative and pathologic findings in patients who underwent minimally invasive surgery - conversion vs. no conversion / pulmonary artery injury vs. no injury (cohort 2)

		Total		Conversion to thoracotomy				PA injury				
				(-)		(+)			(-)		(+)		
		N=772		N=740 [96%]		N=32 [4%]		*P*	N=747 [97%]		N=25 [3%]		*P*
Operative findings													
Procedure	Bilobectomy	11	(1)	11	(1)	0	(0)	.14	11	(1)	0	(0)	.26
	Lobectomy	651	(84)	620	(84)	31	(97)		627	(84)	24	(96)	
	Segmentectomy	110	(14)	109	(15)	1	(3)		109	(15)	1	(4)	
Conversion to thoracotomy	Negative	740	(96)	740	(100)	0	(0)		731	(98)	9	(36)	**<.001**
	Positive	32	(4)	0	(0)	32	(100)		16	(2)	16	(64)	
PA injury	Negative	747	(97)	731	(99)	16	(50)	**<.001**	747	(100)	0	(0)	
	Positive	25	(3)	9	(1)	16	(50)		0	(0)	25	(100)	
Blood loss (mL)		50	(20–150)	50	(20–108	640	(200–1473)	**<.001**	50	(20–120)	700	(360–3300)	**<.001**
Operative time (min)		242	(198–300)	238	(196–291)	369	(303–419)	**<.001**	240	(197–292)	364	(315–466)	**<.001**
Operator	Surgeon #1	83	(11)	77	(10)	6	(19)	.48	78	(10)	5	(20)	.48
	Surgeon #2	75	(10)	74	(10)	1	(3)		72	(10)	3	(12)	
	Surgeon #3	52	(7)	50	(7)	2	(6)		51	(7)	1	(4)	
	Surgeon #4	48	(6)	47	(6)	1	(3)		48	(6)	0	(0)	
	Surgeon #5	43	(6)	42	(6)	1	(3)		41	(5)	2	(8)	
	Others	471	(61)	450	(61)	21	(66)		457	(61)	14	(56)	
Operator-Assistant	Senior-Senior*	496	(64)	475	(64)	21	(66)	.79	478	(64)	18	(72)	.71
	Senior-Junior*	46	(6)	45	(6)	1	(3)		45	(6)	1	(4)	
	Junior-Senior*	230	(30)	229	(31)	10	(31)		224	(30)	6	(24)	
Pathologic findings													
Histologic type	Adenocarcinoma	641	(83)	616	(83)	25	(78)	.91	623	(83)	18	(72)	.16
	Squamous cell	77	(10)	72	(10)	5	(16)		72	(10)	5	(20)	
	Others	54	(7)	52	(7)	2	(6)		52	(7)	2	(8)	
pStage	I	638	(83)	618	(84)	20	(63)	**.03**	619	(83)	19	(76)	.86
	II	79	(10)	71	(10)	8	(25)		75	(10)	4	(16)	
	III	50	(6)	46	(6)	4	(13)		48	(6)	2	(8)	
	IV	5	(1)	5	(1)	0	(0)		5	(1)	0	(0)	

Data are shown as number (%) or median (25–75 percentile). Abbreviations: CT, computed tomography; COPD, chronic obstructive pulmonary disease; %FEV1, predicted forced expiratory volume in one second; LLL, left lower lobe; LUL, left upper lobe; PA, pulmonary artery; pStage, pathologic stage; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUV_{max}, maximum standard uptake value. *The senior surgeon was defined as a board-certified thoracic surgeon, and the junior surgeon was defined as a surgeon without board certification including surgical residents/fellows.

Supplemental Table S3. Lobe-specific risk of pulmonary artery injury based on the presence/absence of pulmonary artery-adherent lymph nodes (cohort 2)

Risk of PA injury	Total	Resected lobe					*P*
		RUL	RML	RLL	LUL	LLL	
	N=772	N=247	N=60	N=169	N=181	N=115	
All patients	3% (25/772)	3% (7/247)	3% (2/60)	2% (3/169)	6% (11/181)	2% (2/115)	.15
Patients without PA-adherent LNs	2% (13/722)	2% (5/232)	0% (0/56)	1% (1/159)	3% (5/163)	2% (2/112)	.42
Patients with PA-adherent LNs	24% (12/50)	13% (2/15)	50% (2/4)	20% (2/10)	33% (6/18)	0% (0/3)	.36

Data are shown as % (number of patients with PA injury/number of all patients in each group). P values represent difference across the resected lobes. Abbreviations: LLL, left lower lobe; LNs, lymph nodes; LUL, left upper lobe; PA, pulmonary artery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

Supplemental Table S4. Demographics of patients in the whole cohort and comparison between patients included into and excluded from the aim 1 analysis

		Total	Included vs excluded pts (the aim 1 analysis)					
			Included pts (cohort 1; #1)	All excluded (#2)	Excluded pts		P (#1 vs. #2)	P (#3 vs. #4)
					Without BS or PET (#3)	With BS and PET (#4)		
		N=1210	N=594 [49%]	N=616 [51%]	N=365 [30%]	N=251 [21%]		
Reason of exclusion								
Excluded because of no BS or PET		365 (30)	0 (0)	365 (59)	365 (100)	0 (0)	N/A	N/A
Neither BS nor PET		45 (4)	0 (0)	45 (7)	45 (12)	0 (0)		
Only PET (no BS)		250 (21)	0 (0)	250 (41)	250 (68)	0 (0)		
Only BS (no PET)		70 (6)	0 (0)	70 (11)	70 (19)	0 (0)		
Excluded because of unavailable images of tests*		251 (21)	0 (0)	251 (41)	0 (0)	251 (100)	N/A	N/A
Patient background								
Age		70 (63-76)	70 (64-76)	70 (63-75)	70 (63-75)	71 (63-77)	.64	**.02**
Sex	Male	663 (55)	316 (53)	347 (56)	191 (52)	156 (62)	.30	**.03**
	Female	547 (45)	278 (47)	269 (44)	174 (48)	95 (38)		
Smoking	Never	538 (44)	261 (44)	277 (45)	183 (50)	94 (37)	.73	**.002**
	Fomer/current	672 (56)	333 (56)	339 (55)	182 (50)	157 (63)		
COPD		275 (23)	138 (23)	137 (22)	73 (20)	64 (25)	.68	.11
Cardiovascular disease		104 (9)	56 (9)	48 (8)	32 (9)	16 (6)	.36	.28
Anticoagulation drug use		107 (9)	66 (11)	41 (7)	30 (8)	11 (4)	**.008**	**.06**
Induction chemotherapy		51 (4)	29 (5)	22 (4)	8 (2)	14 (6)	.32	**.03**
%FEV1 (%)		97 (85-110)	96 (84-110)	98 (87-110)	98 (87-109)	100 (68-113)	.07	.43
Tumor size on CT (mm)		24 (17-33)	25 (19-35)	21 (15-31)	17 (13-23)	30 (23-43)	**<.001**	**<.001**
SUVmax of tumor (115 patient data missing in #3)		3.4 (1.4-8.0)	3.8 (1.6-8.7)	2.6 (1.1-6.85)	1.4 (0.7-3.0)	4.9 (2.2-9.7)	**<.001**	**<.001**
Clinical N stage	N0	1070 (88)	509 (86)	561 (91)	357 (98)	204 (81)	**.009**	**<.001**
	N1	93 (8)	54 (9)	39 (6)	7 (2)	32 (13)		
	N2	47 (4)	31 (5)	16 (3)	1 (0)	15 (6)		
Location of the tumor	RUL	374 (31)	185 (31)	189 (31)	110 (30)	79 (31)	.85	.73
	RML	88 (7)	43 (7)	45 (7)	29 (8)	16 (6)		
	RLL	275 (23)	142 (24)	133 (22)	76 (21)	57 (23)		
	LUL	288 (24)	137 (23)	151 (25)	87 (24)	64 (25)		
	LLL	185 (15)	87 (15)	98 (16)	63 (17)	35 (14)		
Procedure	Pneumonectomy	12 (1)	4 (1)	8 (1)	2 (1)	6 (2)	**<.001**	**<.001**
	Bilobectomy	28 (2)	17 (3)	11 (2)	4 (1)	7 (3)		
	Lobectomy	1016 (84)	541 (91)	475 (77)	260 (71)	215 (86)		
	Segmentectomy	154 (13)	32 (5)	122 (20)	99 (27)	23 (9)		
PA-adherent lymph node	Negative	1120 (93)	542 (91)	578 (94)	346 (95)	232 (92)	.10	.23
	Positive	90 (7)	52 (9)	38 (6)	19 (5)	19 (8)		

Data are shown as number (%) or median (25-75 percentiles). Abbreviations: BS, bronchoscopy; CT, computed tomography; COPD, chronic obstructive pulmonary disease; %FEV1, predicted forced expiratory volume in one second; LLL, left lower lobe; LUL, left upper lobe; N/A, not applicable; PA, pulmonary artery; PET, positron emission tomography; pStage, pathologic stage; pts, patients; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SUVmax, maximum standard uptake value. *Patients who underwent both preoperative BS and PET but images of either test were not available for this study.

Supplemental Figure S1. Risk assessment and test performance for pulmonary artery-adherent lymph nodes based on preoperative workups and their combination

Abbreviations: AUC; area under the curve; BS, bronchoscopy; CT, computed tomography; LN, lymph node; PA, pulmonary artery; PET, positron emission tomography; Pt, patient; ROC, receiver operating characteristics.

Figure S1a. Bronchoscopic dark pigmentation

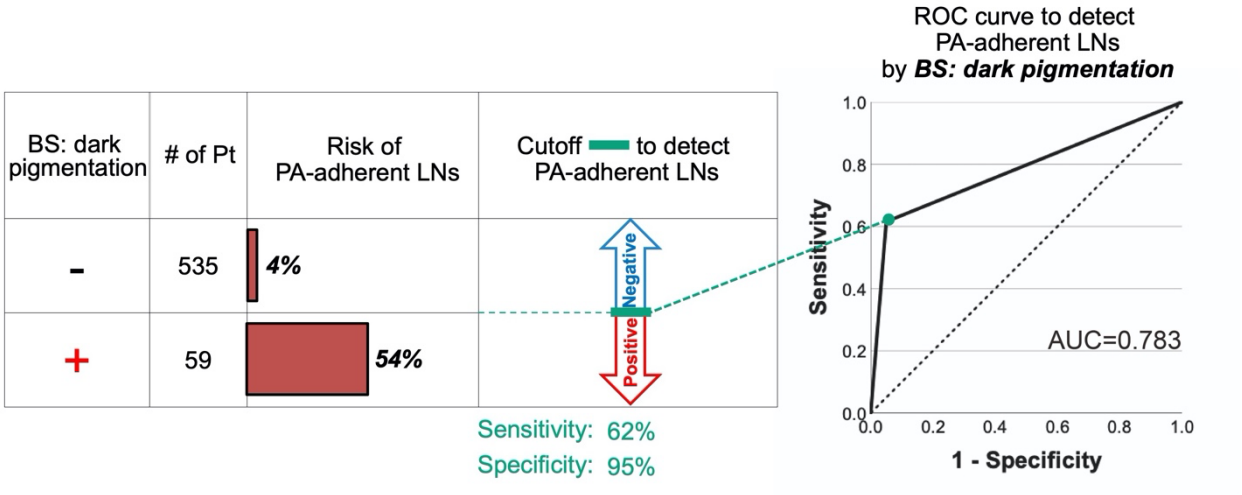


Figure S1b. Computed tomographic-hilar lymph nodal size

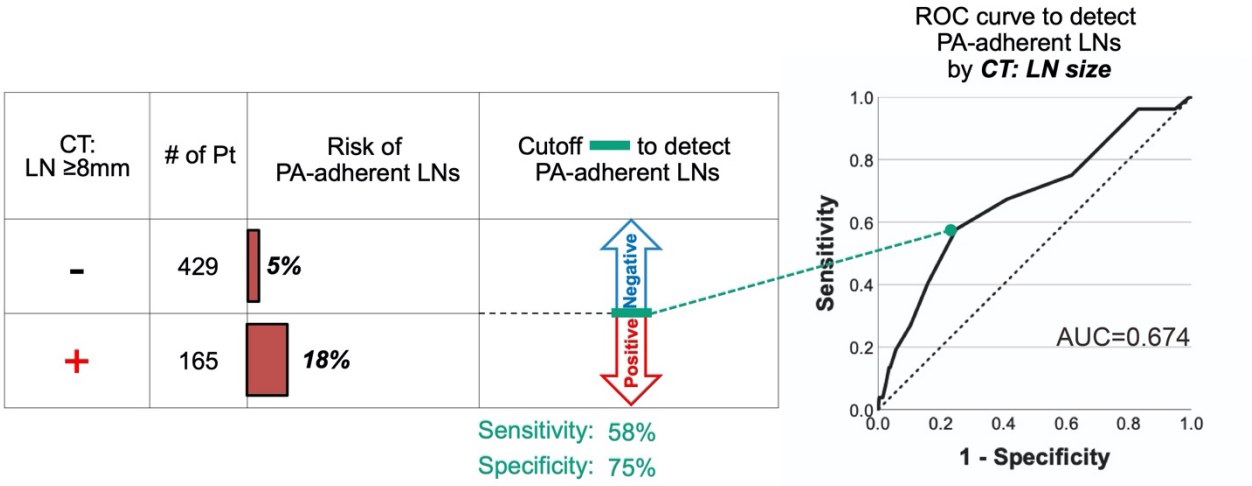


Figure S1c. Positron emission tomographic-bilateral hilar lymph nodal avidity

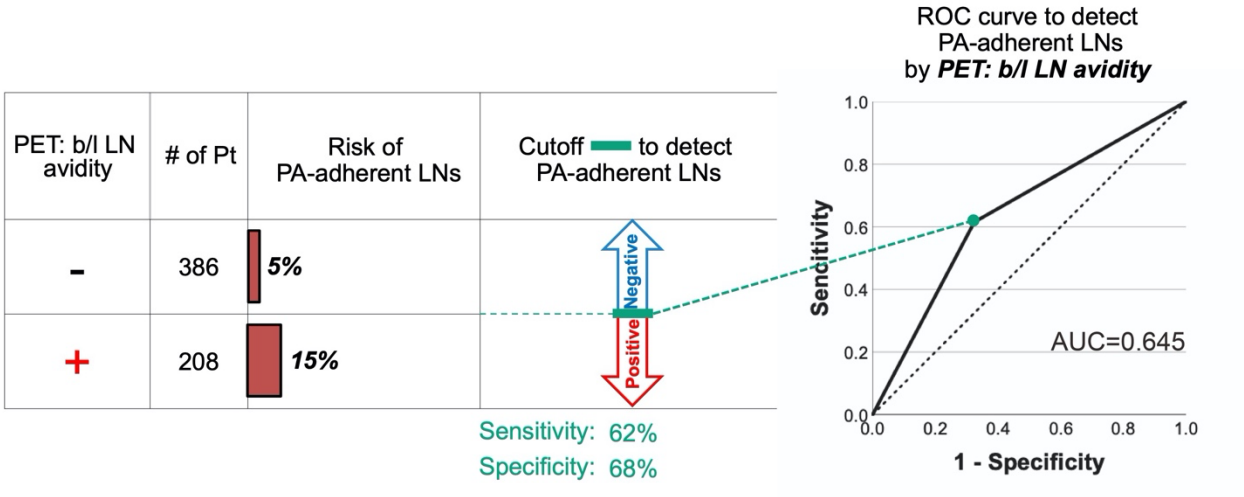


Figure S1d. Computed tomographic-hilar lymph nodal calcification

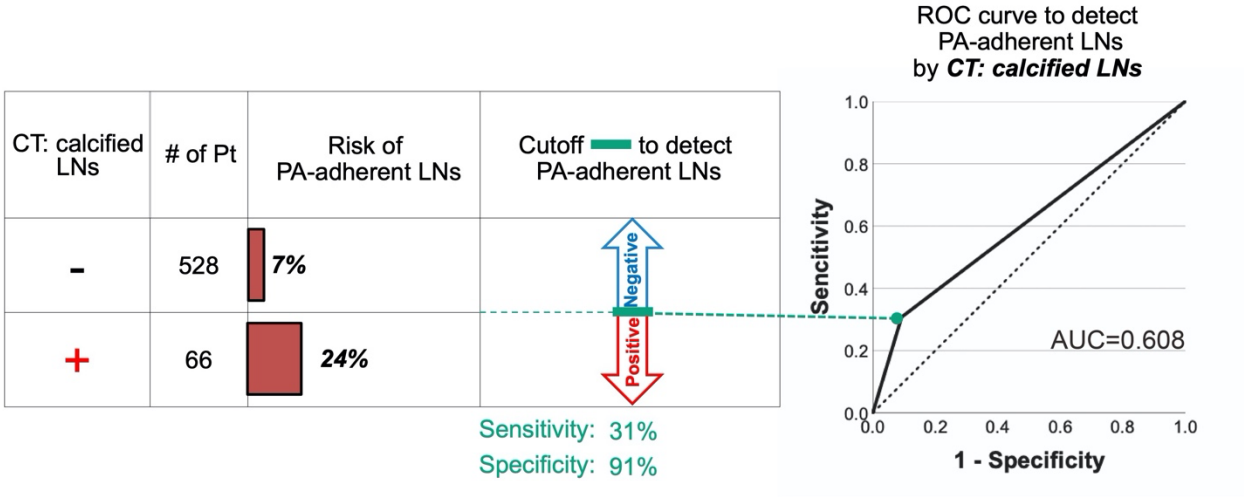


Figure S1e. Combination of computed tomographic-hilar lymph nodal calcification and bronchoscopic dark pigmentation

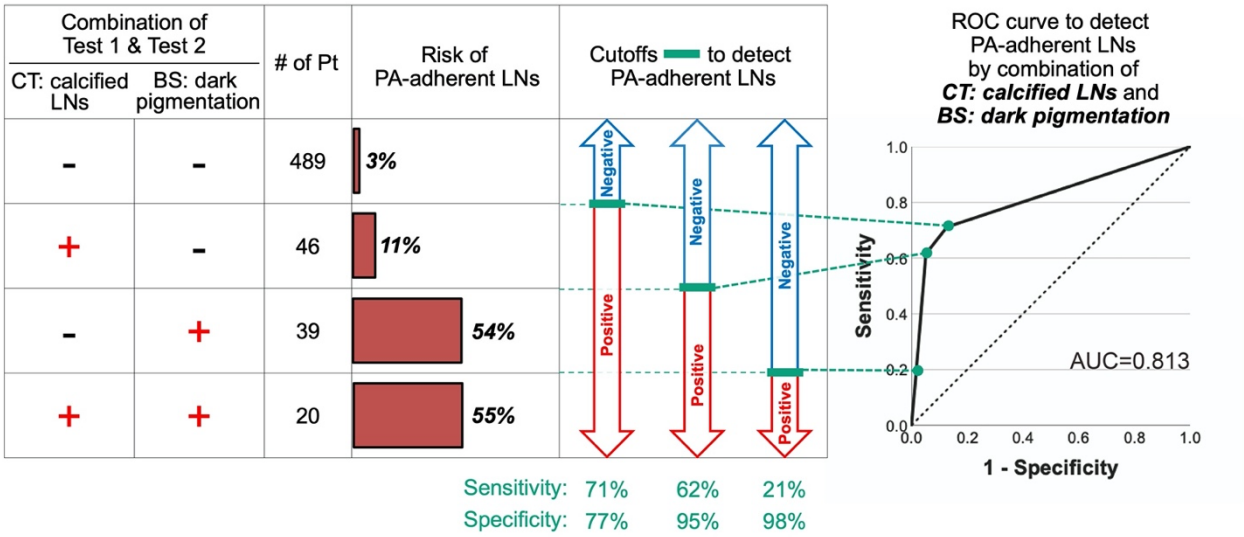


Figure S1f. Combination of positron emission tomographic-bilateral hilar lymph nodal avidity and bronchoscopic dark pigmentation

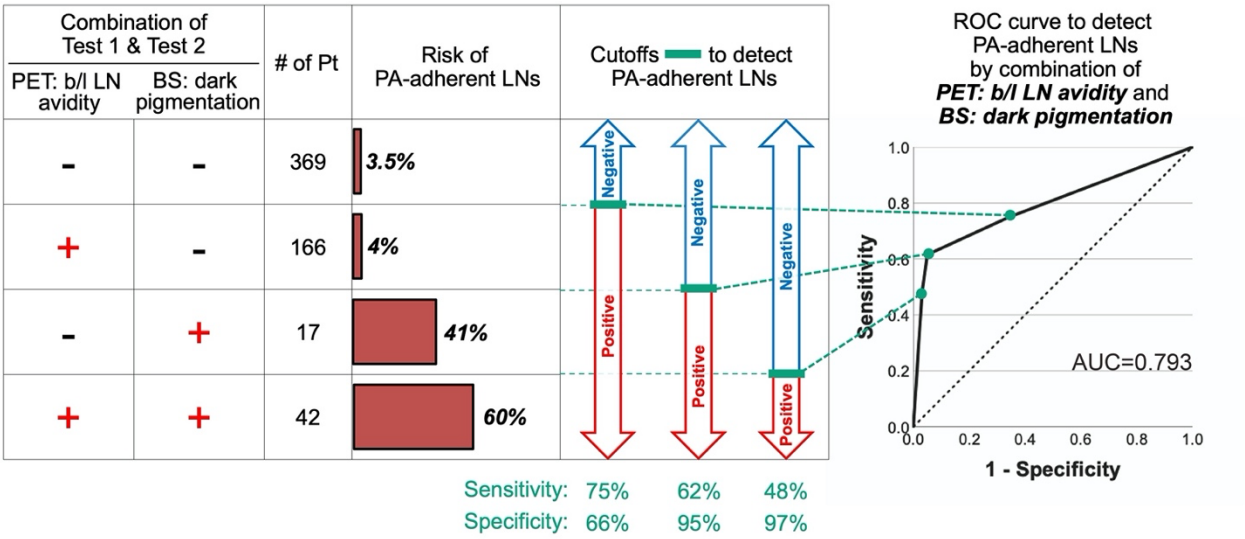


Figure S1g. Combination of computed tomographic-hilar lymph nodes ≥8mm and computed tomographic-hilar lymph nodal calcification

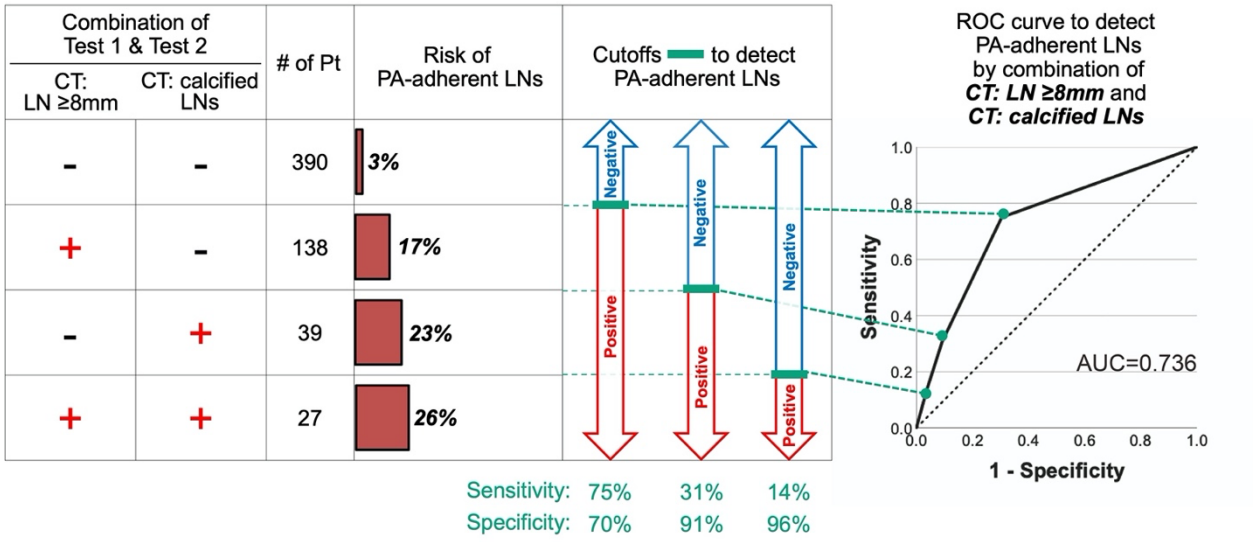


Figure S1h. Combination of positron emission tomographic-bilateral hilar lymph nodal avidity and computed tomographic-hilar lymph nodal size ≤8mm

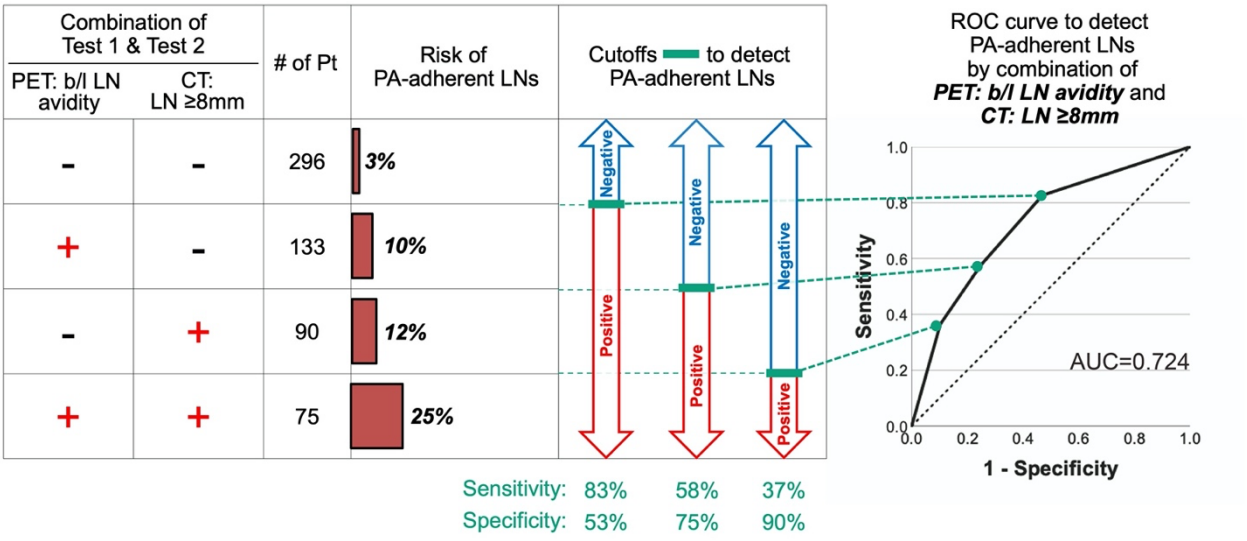
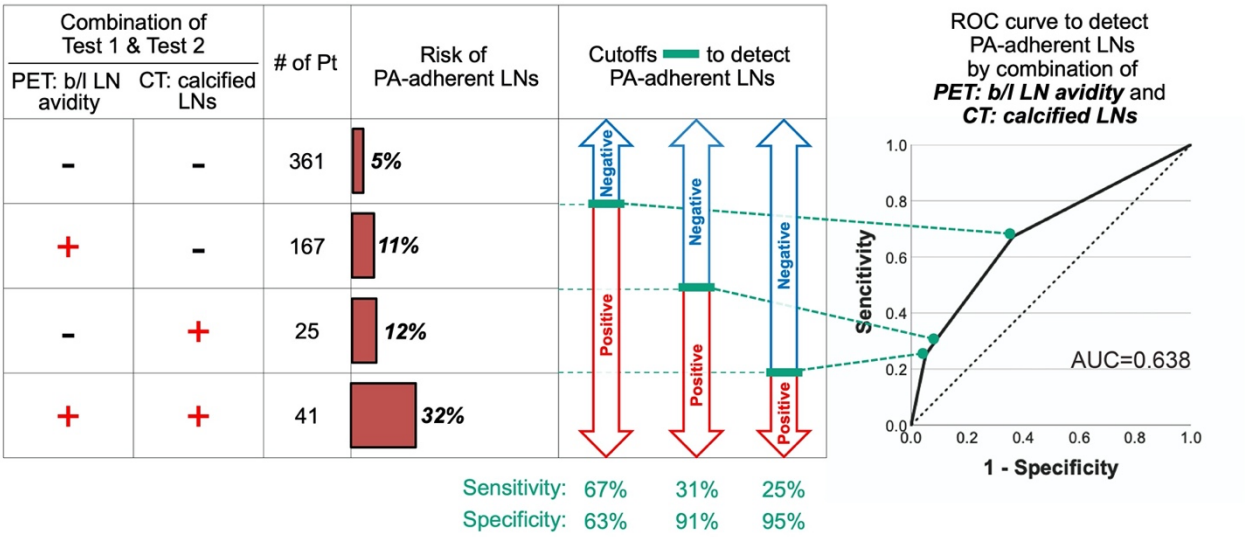
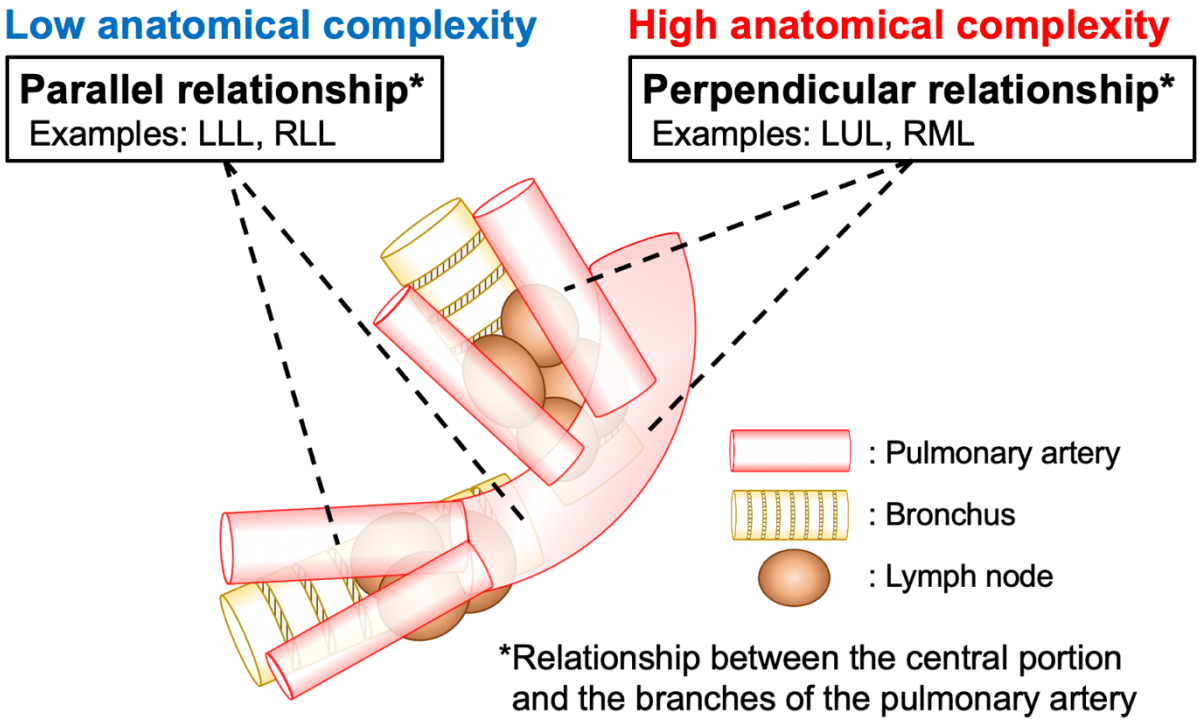


Figure S1i. Combination of positron emission tomographic-bilateral hilar lymph nodal avidity and computed tomographic-hilar lymph nodal calcification

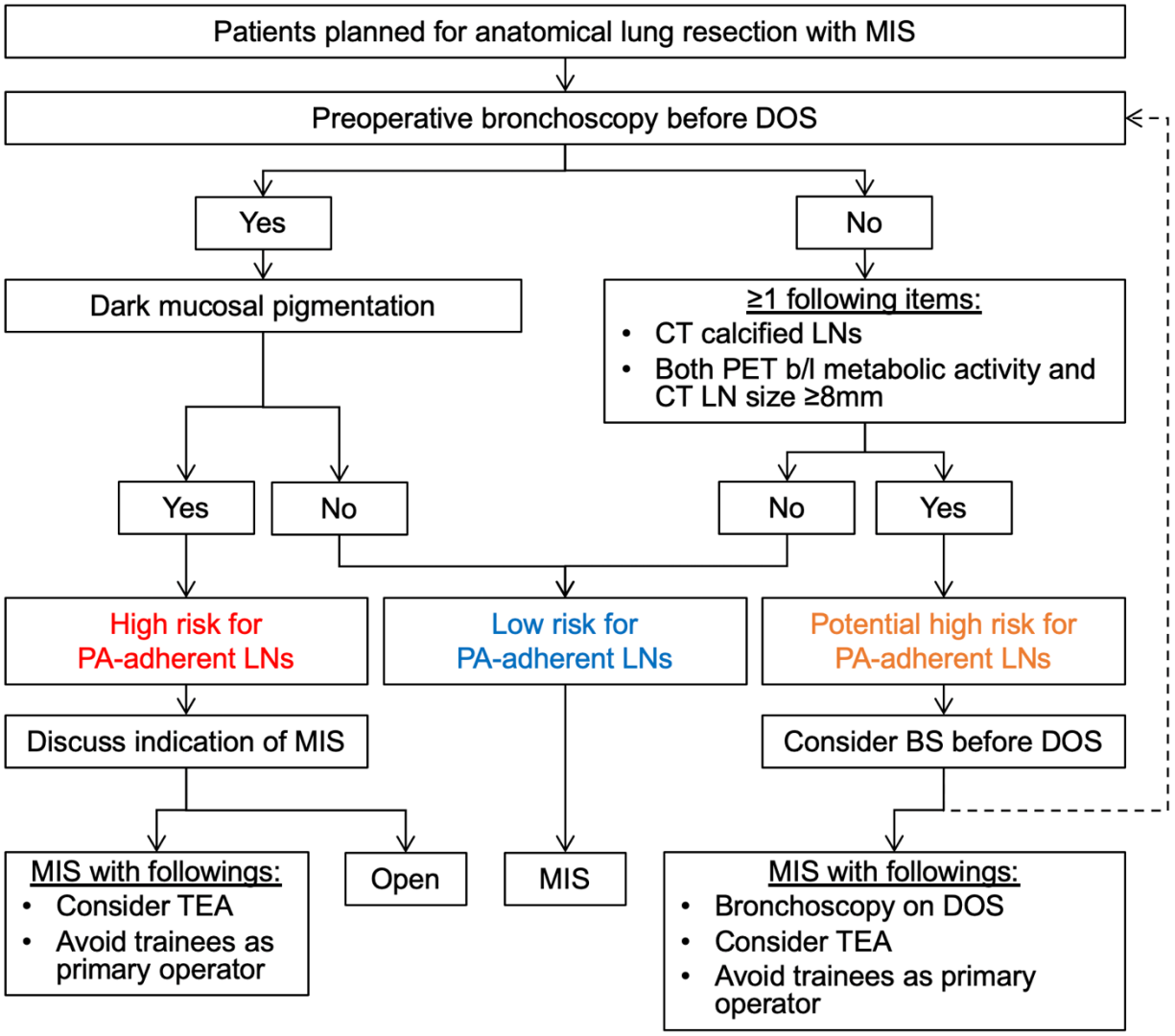


Supplemental Figure S2. Schema for the anatomical complexity of the hilar structures.



Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe.

Supplemental Figure S3. Patient selection protocol for minimally invasive surgery in Shinshu University



Abbreviations: b/l, bilateral; CT, computed tomography; DOS, date of surgery; LN, lymph node; MIS, minimally invasive surgery; PET, positron emission tomography; TEA, thoracic epidural analgesia.