

Bronchoscopic assessment of bronchial anastomosis by visualizing local circulation status – index of hemoglobin (IHb) imaging

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Background: Healing of airway anastomosis is largely affected by local circulation. Index of hemoglobin (IHb) imaging is a color enhancement technique that clarifies local circulation in the gastrointestinal endoscopic field. In this study, we investigated the relationship between bronchoscopic assessment of bronchial anastomosis using IHb mode and occurrence of anastomosis-related complications.

Methods: IHb was calculated by logarithmic transformation for each pixel of the electronic endoscopic images and expressed by colors of red, green, and blue. The distribution of each color area was automatically calculated by the summation of pixels. A preliminary experiment spraying vasodilator on swine was performed to confirm the relationship between bronchial mucosal circulation and the IHb image. Forty consecutive patients who underwent bronchoplasty were divided into retrospective training and prospective validation cohorts, and anastomosis-related complications and IHb images were analyzed.

Results: The IHb images immediately and accurately reflected the mucosal changes in the animal experiment. Among 25 cases in the retrospective training cohort, 6 cases experienced complications, with significantly lower red and higher blue values in IHb observed ($P=0.03$ and $P=0.01$, respectively). A receiver operating characteristic (ROC) curve for IHb red and blue distributions revealed the thresholds to differentiate cases with complications as 89.2 and 109.0, respectively. An analysis of the prospective validation cohort revealed that IHb blue on POD 7 was a potentially reliable predictor of complications, with 60.0% sensitivity and 90.0% specificity.

Conclusions: IHb mode of bronchoscopy may be useful for assessing the local circulatory condition of bronchoplasty, which can predict anastomosis-related morbidity.

Keywords: Lung cancer; surgery; bronchoplasty; bronchial anastomosis

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Introduction

Bronchoplasty is a common method to preserve respiratory function, and exhibits a low postoperative mortality and equal radicality to pneumonectomy in lung cancer surgery (1-3). However, anastomotic complications are occasionally experienced, potentially due to local ischemia or hypoxia as well as technical problems (1-4). It is important to observe the anastomotic conditions, although a standard assessment method has yet to be established. We performed bronchoscopy after bronchoplasty to evaluate the anastomosis and detect signs of complications at anastomosis. Ludwig and Stoelben (5), Park *et al.* (6) developed classification schemes to assess anastomosis using bronchoplasty, however, evaluating ischemia or hypoxia of the anastomosis by the conventional white light (WL) mode of bronchoscopy remains difficult.

The index of the hemoglobin (IHb) is a mode of endoscopic observation that visualizes levels of mucosal circulation (7-9). In the field of gastrointestinal endoscopy, the IHb image was reported to be useful in the early detection of gastric cancer, colorectal cancer and *Helicobacter pylori* infection by differentiating the circulation condition of mucosa (10-13). We applied this technique to detect the mucosal circulation at bronchial anastomosis, and to investigate its clinical significance for prediction of anastomosis-related morbidity.

Methods

Patients

We retrospectively reviewed the medical records of 40 patients who consecutively underwent bronchoplasty at Chiba University Hospital between January 2006 and April 2015. The patients were divided into 2 cohorts, one of which was examined as a training cohort to determine the cut-off values of the IHb to discriminate cases with and without complications, another of which was examined as a validation cohort. In the training cohort, 25 patients underwent bronchoscopy to assess the condition of the anastomosis around 2 weeks after surgery, and the relationship between IHb parameters and occurrence of anastomosis-related complications was analyzed. In the validation cohort, 15 patients underwent bronchoscopy to assess the condition of the anastomosis on POD 1, 7, and 14, and were analyzed for the IHb parameters and occurrence of anastomosis-related complications using the cut-off values obtained by the training cohort. The study protocol was approved by

the Ethics Committee of Chiba University (No. 2158). The need for written informed consent was waived due to the retrospective nature of this chart review.

Technique of bronchoplasty

Standard interrupted sutures were utilized for each anastomosis using 4-0 polydioxanone suture (PDS II®, Ethicon, New Brunswick, Canada). Each suture was employed with a pitch of 2–3 mm and a bite of one cartilage depth. The first suture was placed at the deepest point from the surgeons, and in some cases knots of the first several sutures were made on the intraluminal side. As for the membranous portion, a continuous suture was also utilized. All of the cases except for lung transplantation underwent covered anastomosis using pedicle pericardial fat or intercostal muscle flap.

Bronchoscopy procedures

Flexible fiber optic bronchoscopy (BF-260, Olympus, Tokyo, Japan) and a high vision system (ELVIS LUCERA ELITE®, CV-290, Olympus, Tokyo, Japan) were used. The condition of anastomoses was assessed using both modes of WL and the IHb. Bronchoscopy was performed by thoracic surgeons under anesthesia with midazolam or short-acting benzodiazepine. All steps from the start of the pharyngeal anesthesia were completed within 30 minutes.

IHb mode

The IHb mode of bronchoscopy that is built in the high vision system can produce two-dimensional images of the mucosal blood flow by calculating the red views (Vr) and green views (Vg) (7). The IHb was calculated for each pixel of the electronic endoscopic images by logarithmic transformation of the Vr/Vg ratio using the following equation: $IHb = 32[\log_2 (Vr/Vg)]$ (8), where Vr indicates the signal brightness for red (wavelength near 650 nm, showing minimal absorption by Hb) and Vg indicates the signal brightness for green (wavelength near 560 nm, showing maximal absorption by Hb) (9). The IHb mode is easily activated by pushing a button of the high vision system during broncho fiber observation.

Evaluation of the anastomosis

For each case, we conducted a retrospective analysis of

Table 1 Clinical characteristics of patients in the training cohort

Assessment	Patients (n=25)
Age, median [range]	67 [55–79]
Male, n (%)	20 (80.0)
Histological type, n (%)	
Ad/SqCC	6 (24.0)/15 (60.0)
Pleo/Mucoepi/Carcinoid	1 (4.0)/1 (4.0) /1 (4.0)
Basic disease, n (%)	
COPD/IP	4 (16.0)/1 (4.0)
DM/HT	3 (12.0)/9 (36.0)
Induction therapy, n (%)	6 (24.0)
Pathological stage, n (%)	
0	1 (4.0)
IA/IB	3 (12.0)/2 (8.0)
IIA/IIB	4 (16.0)/4 (16.0)
IIIA/IIIB	10 (40.0)/ 1 (4.0)
Bronchoscopic complication, n (%)	6 (24.0)
Operative procedure, n (%)	
Rt wedge bronchoplastic upper lobectomy	1 (4.0)
Rt sleeve bronchoplastic lobectomy	
RUL/RML/RLL	5 (20.0)/1 (4.0)/2 (8.0)
RUML/RMLL	1 (4.0)/1 (4.0)
RUL + S6 segment/RUML + S6 segment	1 (4.0)/1 (4.0)
RUL + S5 WR + CWR/RLL + PPR	1 (4.0)/1 (4.0)
Lt sleeve bronchoplastic lobectomy	
LUL/LLL	5 (20.0)/2 (8.0)
LLL + S4,5 segment	3 (12.0)

Ad, adenoca.; SqCC, squamous cell ca.; Pleo, pleomorphic ca.; Mucoepi, mucoepidermoid ca.; COPD, chronic obstructive pulmonary disease; IP, interstitial pneumonia; DM, diabetes mellitus; HT, hypertension; RUL, right upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; RUML, right upper middle lobectomy; RMLL, right middle lower lobectomy; segment, segmentectomy; WR, wedge resection; CWR, chest wall resection; PPR, parietal pleura resection; LUL, left upper lobectomy; LLL, left lower lobectomy.

the conventional WL images and IHb color enhanced images using the electronic endoscopic image data. The WL images were classified according to Ludwig's (5) classification of tracheobronchial anastomosis. The analyzed IHb data were expressed by color images of red (R), green (G), and blue (B) (RGB) around the anastomosis view. The distribution area of the IHb color images were analyzed using the Image J software program (NIH, Bethesda, MD, USA) (14-16) (*Figure S1*).

Statistical analysis

Statistical analyses were performed using the StatMate® IV (GraphPad Software, Inc. La Jolla, CA, USA) and JMP® Pro version 12 software programs (SAS Institute Inc., Cary, NC, USA). In the training cohort, we compared several clinical factors using the Mann-Whitney U test. P values of <0.05 were considered to indicate statistical significance. We calculated receiver operating characteristic (ROC) curves for the distributions of IHb red and blue. The optimal cut-off value, with the highest Youden Index, would be the point nearest the top of the vertical axis in the ROC. In the validation cohort, we verified the accuracy of the IHb red and blue threshold values (89.2 and 109.0, respectively)—as determined in the training cohort—in the detection of anastomotic complications using the chi-squared test.

Results

Analysis of the training cohort

Bronchoplasty was performed on 25 patients, consisting of 19 men and 6 women. Fifteen cases were right-sided bronchoplasty, and 10 cases were left-sided (*Table 1*). The anastomosis-related complications were three cases of air leakage, two pneumonia, and one empyema with bronchopleural fistula (BFP) (*Table S1*). The IHb findings of the cases with anastomosis-related complications demonstrated narrower red distributions and wider blue distributions than those without complications. Some cases showed a discrepancy between the WL classification and IHb RGB distribution (*Figure 1*). We compared several clinical factors, WL classification (5), and IHb RGB distribution in *Table 2* between patients without



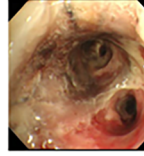
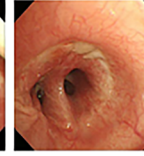
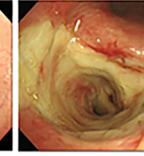
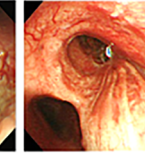
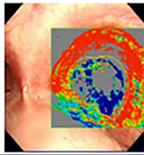
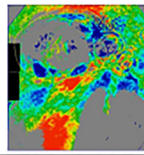
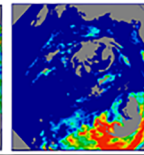
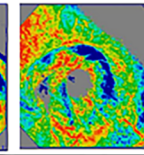
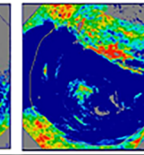
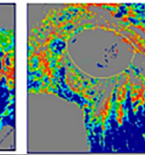
Case #	1	2	3	4	5	6
WL image						
POD	16	13	14	13	15	10
WL classification [¶]	3	2	3	1	3	1
IHb image						
IHb Red	89.2	86.5	73.0	81.9	7.0	127.0
IHb Blue	112.9	114.3	109.0	85.1	142.2	122.6

Figure 1 Bronchoscopic findings with anastomosis-related complications in the training cohort. [¶], This classification was defined by Ludwig *et al.* (5). WL, white light; POD, post-operative day; IHb, Index of hemoglobin.

Table 2 Patient characteristics with or without bronchial anastomotic complication in the training cohort

Factor	(-) (n=19)	(+) (n=6)	P value
Age (years), median [range]	67 [54-75]	68 [62-79]	0.35
Sex, male (%) / female	14 (73.6) / 5	6 (100.0) / 0	0.41
COPD, + (%) / -	2 (10.5) / 17	2 (33.3) / 4	0.49
IP, + (%) / -	1 (5.2) / 18	0 (0.0) / 6	0.53
DM, + (%) / -	3 (15.7) / 16	0 (0.0) / 6	0.75
HT, + (%) / -	7 (36.8) / 12	2 (33.3) / 4	0.74
Induction therapy, + (%) / -	5 (26.3) / 14	1 (16.6) / 5	0.94
Median (IQR)			
Alb	4.2 (3.9-4.4)	3.9 (3.4-4.0)	0.06
Hb	11.2 (10.2-11.8)	10.8 (9.7-11.1)	0.19
WL classification*	1.6 (1.0-2.0)	2.3 (1.7-3.0)	0.05
IHb RGB red	115.3 (92.1-144.1)	84.2 (56.5-98.6)	0.03
IHb RGB green	120.2 (108.1-138.0)	119.8 (84.3-134.7)	0.97
IHb RGB blue	91.4 (71.3-101.8)	113.6 (103.0-127.5)	0.01

*, this classification was defined by Ludwig *et al.* (4). P value <0.05 is significant. IQR, interquartile range; COPD, chronic obstructive pulmonary disease; IP, interstitial pneumonia; HT, hypertension; Alb, albumin; IHb, index of hemoglobin value; Hb, hemoglobin concentration of peripheral blood (g/dL).

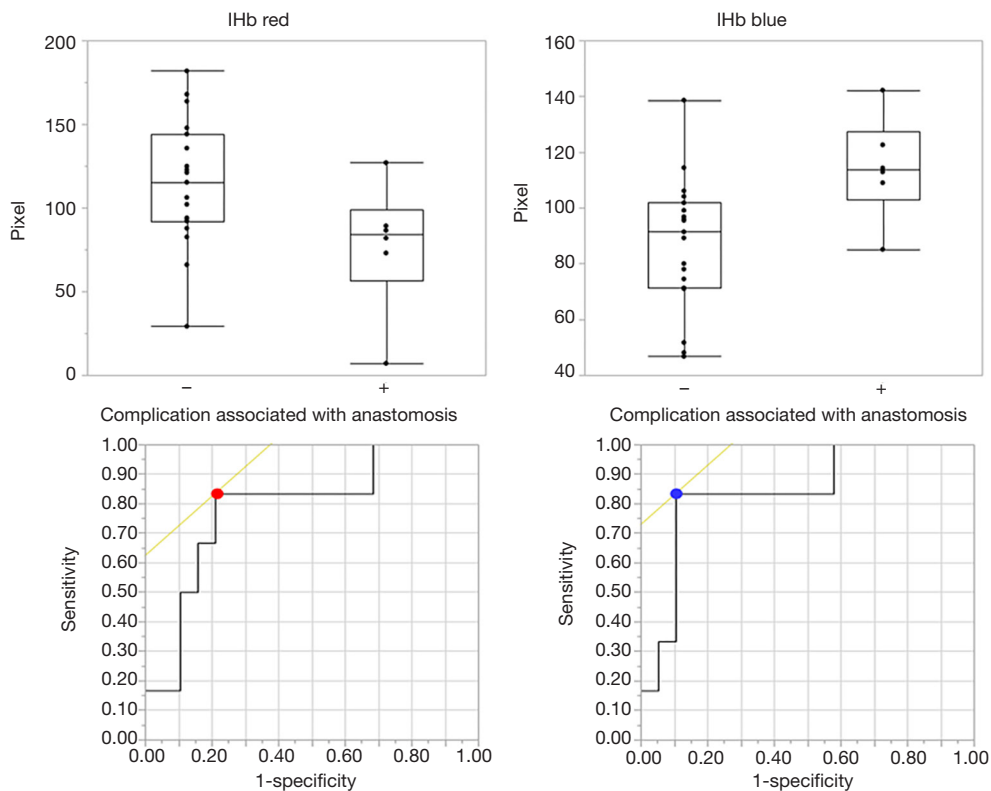


Figure 2 IHb red and IHb blue values related to the presence or absence of a complication at the bronchial anastomosis. IHb red 89.2 had a sensitivity of 0.833, specificity of 0.622 and AUC of 0.789. IHb blue 109.0 had a sensitivity of 0.833, specificity of 0.728 and AUC of 0.842. IHb, index of hemoglobin; AUC, area under curve.

complications (n=19) and with complications (n=6). There were no significant differences in age, sex, basic disease, induction therapy, or WL classification. However, there were significant differences in the IHb red and blue distributions ($P=0.03$, $P=0.01$, respectively) (Table 2). We analyzed the ROC curve of the IHb red and blue distributions (Figure 2). The IHb red threshold was 89.2 for whether a complication had occurred (sensitivity 83.3%, specificity 62.2%). The IHb blue threshold was 109.0 for whether a complication had occurred (sensitivity 83.3%, specificity 72.8%).

Analysis of the validation cohort

The operative procedures consisted of 15 bronchoplasty including 2 lung transplant recipients and 2 living lung donors. There were nine cases of right-sided bronchoplasty, seven left-sided, and one case of carinoplasty (Table 3). Six patients had complications (Table S2). The anastomosis-related complications were three cases of granulation, two

pneumonia with stenosis, and one anastomotic leakage. The mucosal ischemic changes were much clearer after the IHb color enhancement. Two representative cases are shown in Figure 3. Case 2 developed pneumonia with stenosis due to mucosal ischemic changes in the peripheral side from the anastomosis. On POD 1, neither the WL nor IHb images showed mucosal ischemia around the anastomosis. On POD 14, both WL and IHb images showed the presence of mucosal ischemic changes. Interestingly, On POD 7, the WL image failed to show the mucosal ischemia, but the IHb image revealed the spread of IHb blue distribution around the anastomosis compared to the image on POD 1. The IHb image was therefore able to detect mucosal ischemic changes earlier than the WL image.

The accuracy of the IHb red and blue threshold values (89.2 and 109.0, respectively) as determined in the training cohort to detect anastomotic complications was verified (Table 4). The IHb red distribution was able to detect the complication in only one case on POD 1 (16.7%), whereas the IHb blue was able to detect 2 cases with complications

Table 3 Clinical characteristics of patients in the validation cohort

Assessment	Patients (n=15)
Age, median [range]	62 [46–72]
Male, n (%)	11 (73.3)
Disease, n (%)	
Lung cancer	
Ad/SqCC	3 (20.0)/4 (26.7)
Large/combined SCLC	1 (6.7)/1 (6.7)
Sarcoma/meta LT	1 (6.7)/1 (6.7)
Lung transplantation	
Recipient/living donor	2 (13.3)/2 (13.3)
Basic disease, n (%)	
COPD/IP	5 (33.3)/5 (33.3)
DM/HT	2 (13.3)/1 (6.7)
Induction therapy, n (%)	2 (13.3)
Bronchoscopic complication, n (%)	6 (40.0)
Operative procedure, n (%)	
Rt wedge bronchoplastic upper lobectomy	2 (11.7)
Rt sleeve bronchoplastic lobectomy	
RUL	2 (11.7)
RUML/RMLL	1 (5.8)/1 (5.8)
RUL + S6 segment	1 (5.8)
RMLL + RLL-Tx./RPNT + RLL-Tx.	1 (5.8)/1 (5.8)
Lt sleeve bronchoplastic lobectomy	
LLL	1 (5.8)
LLL + S6 segment/LLL + S4,5 segment	1 (5.8)/3 (17.6)
LLL + RLL-Tx./LPNT + RLL-Tx.	1 (5.8)/1 (5.8)
Carinoplasty	1 (5.8)

Ad, adenoca.; SqCC, squamous cell ca.; Large, large cell ca.; SCLC, small cell lung ca.; COPD, chronic obstructive pulmonary disease; IP, interstitial pneumonia; DM, diabetes mellitus; HT, hypertension; RUL, right upper lobectomy; RUML, right upper middle lobectomy; RMLL, right middle lower lobectomy; segment, segmentectomy; RPNT, right pneumonectomy; RLL-Tx., right lower lobe transplantation; LPNT, left pneumonectomy; LLL, left lower lobectomy.

on POD 1 (33.3%). On POD 7, the IHb blue distribution was able to detect 3 cases with complications with a specificity of 90.0% and sensitivity of 60.0%. The IHb red and blue distributions on POD 14 had sensitivities of 60.0%

and specificities of 75.0%. These results indicate that the IHb blue distribution on POD 7 is potentially useful for prediction of complications associated with the anastomosis at the early healing phase.

Discussion

This retrospective study assessed the ability of IHb to detect anastomotic complications caused by ischemia in patients treated with bronchoplasty following radical surgery for lung cancer. The complications associated with anastomosis after bronchoplasty have been reported to occur in 4.0–22.4% of patients (1-4). The circulation and oxygenation at bronchial anastomosis is strongly related to occurrence of the complications. Concerning sleeve lobectomy, it has been accepted that the blood flow at anastomosis is supplied by the peripheral lung (17), while regarding lung transplantation, the blood supply at the bronchial anastomosis is dependent on the central bronchial artery and distal pulmonary artery (18,19).

In a preliminary experiment, we confirmed the IHb color change in relation to mucosal microcirculation using specific pathogen-free swine (SPF) 1 mL of isosorbide mononitrate (1 mg isosorbide mononitrate in 1 mL Nitorol®; Eisai, Tokyo, Japan) was sprayed on the bronchial mucosa through a bronchoscope (BF-260, Olympus, Tokyo, Japan), and observed periodically (20). The WL and IHb observations were subsequently compared. After spraying 1 mL of isosorbide mononitrate onto the right bronchial mucosa in SPF swine, the mucosa immediately changed to a reddish color in the WL images, and the red area spread in the IHb images (*Figure 4*). Forty-five minutes later, the mucosal redness faded. We were able to confirm that the changes that were visualized in the bronchial mucosal circulation were in line with those reported in the gastrointestinal mucosa (7-9).

In this study, the IHb was used as a surrogate of local circulation of the bronchial mucosa, and a preliminary animal study clearly demonstrated the theoretical function of the IHb. Then, the relationship between the IHb finding and anastomosis-related complications was investigated. Among the complications, prolonged air leakage and pneumonia were noted, which were not directly associated with the anastomotic condition. However, such pulmonary complications have an inherent indirect association with anastomosis, since ischemia or necrosis of the bronchial mucosa critically affects not only anastomotic healing but also peripheral condition. As a result, the distribution of

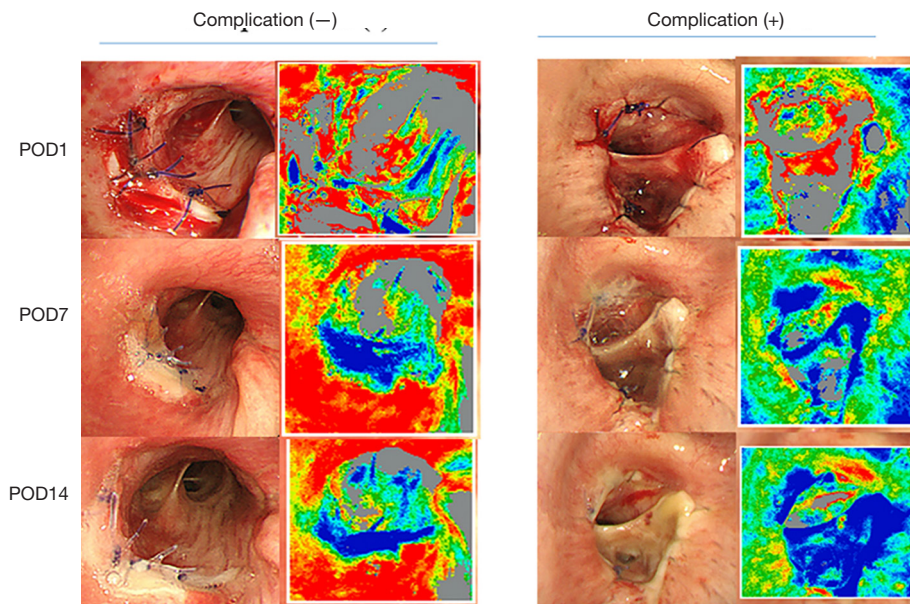


Figure 3 Bronchoscopic findings with or without anastomosis-related complications in the validation cohort. Bronchoscopy (in the WL and IHb images) was performed on POD 1, 7, 14. The left images show a case without anastomosis-related complications. The WL images revealed no mucosal ischemia in any phases, and the IHb blue distribution was fairly limited. The right images show a case with anastomosis-related pneumonia. On POD 1, both images revealed no ischemic changes around the bronchial anastomosis. On POD 14, both images revealed mucosal ischemia around the bronchial anastomosis. On POD 7, the WL images could not clearly show mucosal ischemia. However, the IHb images showed the spread of IHb blue and the reduction of IHb red. POD, postoperative day; WL, white light; IHb, index of hemoglobin.

Table 4 Sensitivity and specificity of the IHb red and blue distribution cut-off values in the validation cohort

IHb color	POD	Sensitivity	Specificity	PPV	NPV
IHb red	1	0.167	1.000	1.000	0.545
	7	0.200	1.000	1.000	0.714
	14	0.600	0.750	0.600	0.750
IHb blue	1	0.333	0.833	0.666	0.555
	7	0.600	0.900	0.750	0.818
	14	0.600	0.750	0.600	0.750

IHb, index of hemoglobin; POD, postoperative day; PPV, positive predictive value; NPV, negative predictive value.

IHb blue on POD 7 exhibited the closest association with the occurrence of the complications, and an IHb assessment on POD 7 could predict serious complications, such as BPF or stenosis.

Several modalities for assessing bronchial anastomosis have been reported in cases with lung transplantation (21). Bronchoscopic narrow-band imaging (NBI) mode and auto fluorescence imaging (AFI) have been used to assess airway

vascularity after lung transplantation (22,23). The NBI mode is an endoscopic technique that uses optical filters to narrow the bandwidth. However, the previous study did not report the anastomosis conditions and complications (22). AFI bronchoscopy visualized the intensity and spectral contrast of the auto fluorescence of the healthy bronchial mucosa and neoplastic or early cancerous lesions. Investigators produced airway ischemic damage in

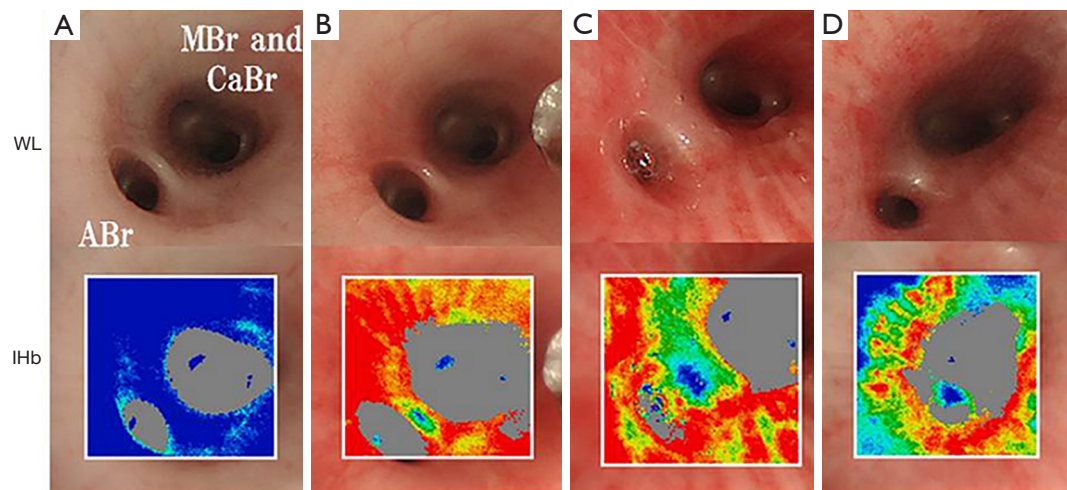


Figure 4 Imaging of swine bronchial mucosa. One mL of isosorbide mononitrate (Nitorol spray 1.25 mg, Eisai, Tokyo, Japan) was sprayed through the bronchoscope. Immediately, the bronchial mucosa turned red (A, before; B, immediately after). Three and 45 minutes later, the redness gradually disappeared (C, 3 minutes later; D, 45 minutes later). WL, white light; IHb, index of hemoglobin; MBr, middle lobe bronchus; CaBr, caudal lobe bronchus; AB, accessory lobe bronchus.

experimental swine models and compared the histological results and AFI findings (23). The bronchoscopic AFI mode can potentially detect the airway ischemic damage, however, the clinical patient examinations were not reported. Laser Doppler Flowmetry (LDF) was also reported to be useful for evaluating bronchial anastomosis of swine (20,24). LDF is a technique that involves a narrow beam of monochromatic light that hits moving blood cells and allows the blood flow to be detected. Clinical human cases, however, were not published.

To the best of our knowledge, we are the first to report the use of IHb images in assessing the anastomosis following bronchoplasty. The IHb mode is very simple to use and has the potential to assess the mucosal blood flow.

The most significant contribution of the study to the field of general thoracic surgery is to offer an objective and reproducible method to assess healing of tracheobronchial anastomosis. Tracheobronchial surgery comprises various modifications such as complete continuous sutures (25), the combination of interrupted and continuous sutures, telescopic anastomosis sutures (26), and figure-of-eight suture (27). The covering of anastomosis remains controversial in terms of its effectiveness or the types of utilized tissues, such as the pedicled pericardial fat pad (28), thymic tissue (29) and intercostal muscle flaps (30). IHb images can therefore be used to evaluate and compare the above procedures. However, The IHb assessment must

cover bronchial stump healing.

There are several limitations associated with our study. First, we defined the anastomosis-related complications in the training cohort as air leakage, pneumonia, and empyema with fistula. We were, however, unable to distinctly prove these complications or anastomotic mucosal conditions. Second, it was difficult to assess bronchial anastomosis just after the surgery due to mucosal edema or blood clots. Third, the number of patients in this study cohort was small. Thus, a larger cohort study is necessary to confirm our findings.

In conclusion, the present study showed that IHb images were useful for assessing the condition of the anastomosis after bronchoplasty. IHb images are simple to obtain and may be helpful in the diagnosis of mucosal ischemic damage of bronchial anastomosis after bronchoplasty.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the Ethics Committee of Chiba University (No. 2158). The

need for written informed consent was waived due to the retrospective nature of this chart review.

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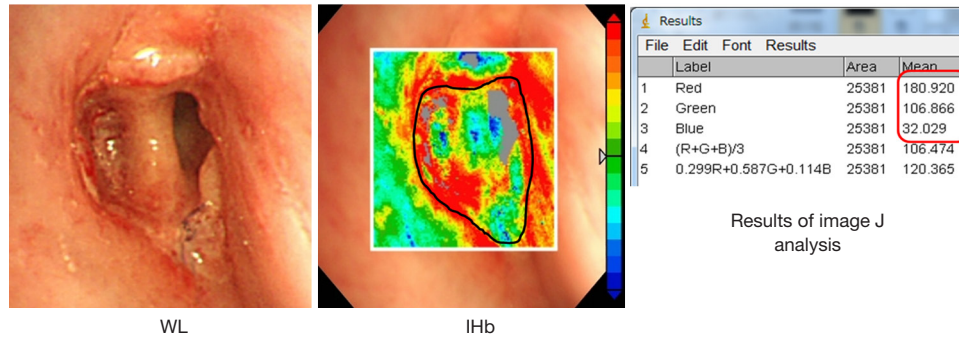


Figure S1 The method of calculating the IHB values. After fetching the IHB mode picture to Image J, we superimposed the bronchial anastomosis image against the WL mode picture (black circle) and calculated the RGB measure. We defined the mean scores of red, green and blue (red circle) as IHB red, IHB green, IHB blue, respectively. WL, white light; IHB, index of hemoglobin.

Table S1 Cases with anastomosis-related complications in the training cohort

No.	Sex	Age	Basic disease	Hist.	c-stage	Induction therapy	Procedure*	p-stage	Comp.	Therapy for comp.
1	M	63	HT, COPD, PTX(Rt)	Ad	T2aN1M0 IIA	–	RUML + S6 segment	T2aN1M0 IIA	Prolonged air leakage	Pleurodesis
2	M	68	–	SqCC	T1aN0M0 IA	–	RLL	T1sN0M0 0	Prolonged air leakage	Pleurodesis
3	M	73	COPD	SqCC	T1bN0M0 IA	–	RMLL	T3N1M0 IIIA	Pneumonia	antibiotics
4	M	68	–	SqCC	T2aN1M0 IIA	–	LLL + S4,5 segment	T2aN2M0 IIIA	BPF empyema	Thoracoplasty
5	M	79	HT ASO	SqCC	T2bN0M0 IIA	–	RLL + PPR	T3N0M0 IIB	Pneumonia	Antibiotic PG
6	M	62	–	SqCC	T2bN1M0 IIA	+ [§]	RUML	T1aN0M IA	Prolonged air leakage	Pleurodesis

*, Procedure with sleeve bronchoplastic lobectomy; [§], 2 courses of cisplatin + gemcitabine. Hist., Histology; c-stage, clinical stage; p-stage, pathological stage; Comp., bronchial anastomosis complications; HT, hypertension; COPD, chronic obstructive pulmonary disease; PTX, pneumothorax; Rt, right; ASO, arteriosclerosis obliterans; Ad, adenocarcinoma; SqCC, squamous cell carcinoma; RUML, right upper & middle lobectomy; segment, segmentectomy; RLL, right lower lobectomy; RMLL, right middle & lower lobectomy; LLL, left lower lobectomy; RLL, right lower lobectomy; PPR, parietal pleura resection; BPF, bronchopleural fistula; PG, administration of prostaglandin analog.

Table S2 Cases with bronchial anastomosis complications in the validation cohort

No.	Sex	Age	Basic disease	Hist.	c-stage	Induction therapy	Procedure*	p-stage	Comp.	Therapy for comp.
1	M	68	–	Ad	T4N2M0 IIIB	+ [§]	RLL	T0N0M0 0	Stenosis of anastomosis Pneumonia	Balloon dilation Antibiotics
2 [¶]	M	46	CADM -IP				Blt LL LTx		Prolonged air leakage	Antibiotics PG
3	F	54	COPD HT	Ad	T2aN1M0 IIA	–	LLL + S4,5 segment	T3N1M0 IIIA	Granulation of anastomosis	No treatment
4	M	68	–	SqCC	T2aN0M0 IB	–	LUL + S6 segment	T2aN0M0 IB	Granulation of anastomosis	No treatment
5	M	64	COPD	Ad	T2bN0M0 IIA	–	LLL + S4,5 segment	T3N0M0 IIB	Stenosis of anastomosis Pneumonia	Antibiotics
6	F	60	–	Sa.	T1aN1M0 IIA	–	Carina plasty	T2aN2M0 IIIA	Granulation of anastomosis	No treatment

*, Procedure with sleeve bronchoplastic lobectomy; [§], 2 courses of cisplatin + S-1 and concurrent radiotherapy (45 Gy); [¶], bilateral living-donor lobar lung transplantation sparing patient's bilateral upper lobes. Hist., Histology; c-stage, clinical stage; p-stage, pathological stage; Comp., bronchial anastomosis complications; CADM-IP, clinically Amyopathic dermatomyositis-associated interstitial pneumonia; HT, hypertension; COPD, chronic obstructive pulmonary disease; Ad, adenocarcinoma; SqCC, squamous cell carcinoma; Sa, sarcoma; RLL, right lower lobectomy; Blt LL LTx, bilateral lower lobe transplantation; LLL, left lower lobectomy; PG, administration of prostaglandin analog.