Influence of caliber mismatch on patients' clinical course after sleeve lobectomy

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Original article**Influence of Caliber Mismatch on Patients' Clinical Course after Sleeve Lobectomy**

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Keywords

Primary lung cancer • Bronchoplasty • Caliber mismatch • Respiratory complication •

Bronchopleural fistula

Abstract

Objective Respiratory complications are critical events after sleeve lobectomy. A caliber mismatch is an important factor in wound healing at the anastomotic site. This study aimed to determine the influence of caliber mismatches on patients' clinical courses after sleeve lobectomy.

Methods We investigated the clinical courses of 56 patients with primary lung cancer who underwent pulmonary resection with end-to-end bronchoplasty. Anastomoses between the main bronchus and the segmental, right upper or middle bronchus, and between the trunks intermedius and the segmental or middle bronchus are categorized as an "anastomosis with caliber mismatch".

Results Among the 56 patients, 22 underwent bronchoplasty with caliber mismatch. There were no in-hospital deaths, and the mortality rates at the 30- and 90-day evaluations were zero. Respiratory complications ($n = 10$, 52%, $p = 0.005$), such as pneumonia ($n = 7$, 32%, $p = 0.029$), retention of pleural effusion ($n = 6$, 27%, $p = 0.026$) and bronchopleural fistula ($n = 3$, 14%, $p = 0.027$), were significantly increased after bronchoplasty with caliber mismatch. Lower body mass index (BMI) is a significant risk factor for respiratory complications after sleeve

lobectomy with caliber mismatch (median value; 23.2 vs 21.2, $p = 0.036$).

Conclusions Significant respiratory complications are apparent after bronchoplasty with caliber mismatch, especially patients with low BMI have a high risk of respiratory complications.

Appropriate patient selection and cautious perioperative management are mandatory for this type of lung-preserving surgery.

Introduction

A caliber mismatch between the distal and proximal stumps at the airway anastomotic site is an important factor in wound healing. High-caliber mismatch is commonly encountered during extended sleeve lobectomy, which requires airway reconstruction between the main and segmental bronchi (1). Tapering the proximal stump using adjustment stitches in the membranous portion (2, 3) or telescopic anastomosis (3, 4) were suggested to avoid airway complications after bronchoplasty with high caliber mismatch. To adjust the caliber mismatch, the distal stump could be enlarged using a bronchial cuff or flap (5, 6).

Overcoming a caliber mismatch between the main and lobar bronchi during bronchoplasty can be problematic. A right main-to-upper bronchus anastomosis is required after right middle and lower sleeve bilobectomy. Because the right upper bronchus consists of only three segmental bronchi, there is a high rate of caliber mismatch at the anastomotic site. We therefore sometimes undertake airway reconstruction between the intermedius trunk and the right middle bronchus after right lower sleeve lobectomy. The intermedius trunk is an extra-pulmonary bronchus with a cartilaginous ring. Because the right middle bronchus consists of only two segmental bronchi, a high caliber mismatch is commonly observed during bronchoplasty

following right lower sleeve lobectomy.

We investigated the influence of caliber mismatch at the anastomotic site on patients' clinical courses after sleeve lobectomy in patients with primary lung cancer.

Methods

Altogether, 58 patients with primary lung cancer underwent sleeve lobectomy at our institution from January 2010 to December 2019. Among them, two patients who underwent double-barreled airway reconstruction after right lower sleeve lobectomy were excluded. We thus investigated the clinical courses of 56 patients who underwent end-to-end airway reconstruction after sleeve lobectomy. We divided these cases into two groups, the caliber mismatch group and the non-mismatch group. Anastomoses between the main bronchus and the segmental, right upper or middle bronchus, and between the trunks intermedius and the segmental or middle bronchus are categorized as an “anastomosis with caliber mismatch”. Anastomoses between the right main bronchus and the trunks intermedius or the lower bronchus, and between the left main bronchus and the upper or lower bronchus are categorized as “anastomosis without caliber mismatch”. Furthermore, we divided the caliber mismatch group

into two categories according to the degree of the discrepancy. One is a large group; anastomoses between the main bronchus and the segmental, right upper or middle bronchus. Another is a small group; anastomoses between the trunks intermedius and the middle or basal bronchus, and anastomoses between the left main bronchus and the basal bronchus.

All patients provided informed consent for the use of their examination outcomes and clinical data. The local institutional ethics committee approved the study (approval no. 4403; approval date October 3, 2019). We selected patients from the 2010–2019 period because most of the surgical instruments that might have affected outcomes remained unchanged during those years.

We used the eighth edition of the tumor, node, metastasis classification of malignant tumors to determine the clinical and pathological stage. Mediastinal lymph nodes with a short axis (>10 mm) on enhanced computed tomography (CT) were diagnosed as clinically positive for metastasis. In all, 54 of the 56 patients underwent positron emission tomography (PET)/CT, which was used to exclude those with distant metastasis.

Our inclusion criteria for surgical resection were the absence of distant metastasis, no cancer cell-positive pleural or pericardial effusion, no N2 disease at two or more mediastinal levels, no

bulky N2 disease, no N3 disease, and a predicted postoperative percent of vital capacity of >40%.

When nodal extension was within the N0 or N1 category, these patients were deemed to have surgically removable T4 lung cancer. Induction chemoradiotherapy with platinum-based doublet and concurrent radiotherapy (40Gy) was planned for patients with enlarged, but completely removable, N2 lymph node metastasis. Induction therapy was not mandatory for all patients with N2 lymph node metastasis. Patients with pathological stage II and III disease were given adjuvant chemotherapy with a platinum-based doublet. Those with pathological stage I disease were given adjuvant chemotherapy with oral uracil–tegafur. Induction and adjuvant chemotherapy regimens were administered based on empirical decisions made by the physician in charge of each patient.

Bronchoplasty was performed using interrupted or continuous 4-0 absorbable monofilament sutures. All through the bronchoplasty, we sewed the large caliber bronchial stump with wide pitches and the small caliber bronchial stump with narrow pitches to correct the caliber mismatch. We sometimes used big bites to avoid suturing fragile bronchial walls. Layer-to-layer bronchial anastomosis is a standard, but not strictly so, technique. Because of caliber mismatch,

a distal stump often enters a proximal stump, as in a telescopic anastomosis. Each anastomosis site was covered with a pedunculated pericardial fat pad or thymus. Because an intrapulmonary bronchus does not have a cartilaginous ring, the distal stump is expanded to fit the proximal stump. Therefore, strict measurements of the proximal stump are not considered essential during an anastomosis with caliber mismatch.

A standard bronchoscopic examination was performed 1 week postoperatively. When wound healing at the anastomosis site seemed protracted, the bronchoscopic examination was repeated until healing occurred. When chest radiography revealed an abnormality, the patient underwent a CT examination. Adverse events within 3 months after the operation were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0). Adverse events of grade ≥ 3 were recorded. Respiratory complications included pneumonia, pleural effusion, empyema, prolonged air leakage and broncho-pleural fistula.

Differences in clinicopathological factors according to the presence of caliber mismatch were assessed using the Mann–Whitney U test and the χ^2 test. A value of $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using JMP 10 statistical software (SAS Institute, Cary, NC, USA).

Results

Surgical details for the patients are shown in Table 1. Right upper sleeve lobectomy was the most commonly used approach in this study.

Patients' characteristics according to the presence of a caliber mismatch are shown in Table

2. There is not significant difference in patients' characteristics according to the presence of a caliber mismatch.

Table 3 shows details of the surgical procedures and postoperative clinical courses. The median postoperative follow-up period was 21 months, during which time the 30- and 90-day mortality rates were zero; there were also no hospital deaths during this time. Respiratory complications, however, were significantly increased after bronchoplasty with caliber mismatch ($n = 10$, 52%, $p = 0.005$).

Table 4 shows risk factors for respiratory complications after bronshoplasty with caliber mismatch. Lower body mass index (median value; 23.2 vs 21.2, $p = 0.036$), large caliber mismatch ($n = 7$, 70%, $p = 0.035$) and tumor size (median value; 40mm vs 60mm, $p = 0.025$) are significant risk factors for respiratory complications in these patients.

Table 5 shows the characteristics and clinical courses of patients with broncho-pleural fistula (BPF). Patient 1 underwent a fenestration. In a short time, a completion pneumonectomy was required, because the fistula was too larger for him to maintain a normal respiratory condition. He developed a liver metastasis after completion pneumonectomy. Despite systemic chemotherapy, the patient died of the cancer recurrence. Because patient 2 had BPF after right lower sleeve lobectomy, he underwent a completion middle lobectomy. However, he had another BPF at a stump of the trunks intermedius, therefore, a fenestration was required. Patient 3 underwent induction chemotherapy consisting of weekly carboplatin plus paclitaxel with concurrent radiotherapy (40 Gy in 20 fractions). The radiological response was partial. The patient developed BPF 28 days after left lingular division and lower sleeve lobectomy. An ischemic change was observed at proximal side of anastomotic site. The ischemic findings and fistula persisted, therefore the residual lung changed to destroyed lung. A completion pneumonectomy was selected to avoid a change from bad to worse.

Discussion

Pulmonary resection with bronchoplasty at a peripheral bronchus aims to complete the

tumor resection and preserve pulmonary volume. Significant respiratory complications have been observed after this type of surgery. Especially, a large caliber mismatch is a significant risk factor for respiratory complications. Because of a complex healing process at the anastomotic site, patients frequently develop pneumonia owing to sputum retention. In most cases, the preserved lung tissues are not massive enough to occupy the residual thoracic cavity. Hence, it is difficult to avoid retention of pleural effusion. The prolonged postoperative recovery period may prevent the use of adjuvant chemotherapy after this type of lung-preserving surgery. Low BMI was a risk factor of respiratory complications after bronchoplasty with caliber mismatch. Preoperative BMI may be one of important factors for patient selection. Although three patients developed a BPF, there were no treatment-related deaths in this study. We suggest it is difficult for covering the anastomotic site with a pedunculated fat flap to prevent BPF. However, the intervening pedunculated fat flap might have prevented broncho-vascular fistulas, which comprise the most critical adverse event after bronchoplasty.

Low BMI before surgery have a negative effect on surgical outcomes for patients with non-small-cell lung cancer (7). BMI is one of important indicators of a nutritional condition. In critical clinical courses after invasive surgery, such as bronchoplasty with caliber mismatch, a

nutritional condition may correlate with incidence of respiratory complications. Because sleeve lobectomy is commonly indicated for advanced lung cancer patients, they do not have time to improve their nutritional status before surgery. Preoperative BMI may become one of criteria for patient selection. Patients with extremely poor nutritional condition should avoid invasive surgery. However, because no patients had treatment related death in this study, we suggest that bronchoplasty with caliber mismatch may be acceptable for patients with poor nutritional condition under cautious perioperative management. Establishing surgical indications and appropriate measures for patients with poor nutritional condition is an important problem that remains to be solved.

Induction chemoradiotherapy followed by surgery is one of the reliable methods for treating locally advanced lung cancer (8, 9). In this study, one patient who underwent induction chemoradiotherapy followed by extended sleeve lobectomy developed a BPF. Toyooka and colleagues (10) reported details of nine patients who underwent extended sleeve lobectomy after induction chemoradiotherapy. One of the nine had a BPF, and another had a bronchovascular fistula. Careful attention should be paid to the possibility of a postoperative BPF after induction chemoradiotherapy (11). Neoadjuvant “programmed death-1 blockade” was reported to be

beneficial in a patient with resectable lung cancer (12). Bott and colleagues (13), however, reported a severe inflammatory response and fibrosis after induction therapy using this regimen. Although programmed death-1 blockade may become an accepted beneficial induction method, its use followed by lung-preserving surgery with bronchoplasty should be used only after its effects on bronchial healing are established.

This study included eight patients undergoing right lower sleeve lobectomy. One developed a BPF, which might have been caused by the caliber mismatch. Right lower sleeve lobectomy aims to preserve the right middle lobe. This is different from other lobar sleeve resections, which aims to avoid pneumonectomy. Kocaturk and colleagues (14) investigated patients' clinical courses following right middle-lower bilobectomy and lower sleeve lobectomy. They showed that filling the thoracic cavity with the preserved middle lobe could reduce prolonged air leakage and other complications. An anastomosis between the right middle bronchus and intermedius trunk requires highly advanced surgical technique and careful perioperative management. Kocaturk and colleagues (14) concluded that this method should be applied only to appropriate patients at experienced centers.

One of our patients who underwent right upper and lower sleeve bilobectomy developed a

BPF. In this case, there was not only a caliber mismatch but severe tension at the anastomosis site between the right main and middle bronchi. Moriyama and colleagues (15) reported a case of right upper and lower sleeve bilobectomy. They anastomosed the right main and middle bronchi without addressing the proximal stump. A latissimus dorsi flap was used to separate the thoracic cavity into upper and lower portions, and the preserved middle lobe was fixed in the upper portion to prevent torsion. Despite its success, it is not considered a reliable method because of several associated risks, including the high-caliber mismatch, severe tension at the anastomotic site, and torsion of the preserved lung.

This study had some limitations. First, because it was a retrospective trial and included only a small number of patients, some items (e.g., details of their adverse events) were likely not evaluated accurately. A prospective, observational study with centrally located lung cancer patients is now ongoing at our institution. It will allow us to select patients at high risk for postoperative adverse events. Second, there are various factors in the development of airway complications after bronchoplasty. A tension at the anastomotic site is also an important factor for bronchial healing. Because it was difficult to measure the tension at the anastomotic site, we could not investigate the tension in this article. This is a problem to be solved in next study. The

risk of airway complications may not be reduced unless we pinpoint the probable causes of BPF development (other than a caliber mismatch). Finally, because of an inadequate follow-up period, we did not investigate the postoperative prognosis. After an adequate follow-up, we will be able to determine the treatment efficacy of this type of lung-preserving surgery.

Conclusion

Significant respiratory complications are apparent after bronchoplasty with caliber mismatch, especially patients with low BMI or the largest discrepancy have a high risk of respiratory complications. The preservation of the right middle lobe may not be recommended, because of several associated risks. Other types of lung-preserving surgery are suggested to be acceptable after appropriate patient selection and under cautious perioperative management. Several factors were involved in the development of post-bronchoplasty airway complications. We must continue to investigate the causes of BPF to reduce the incidence of this critical complication.

Conflict of interest

All authors have no conflicts of interest.

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Table 1 Details of surgical procedure

Resected lung	Right	upper	18
		lower	8
		middle and lower	4
		upper and middle	1
		upper and lower	1
		middle and segment 6	1
	Left	upper	8
		lower	7
		lower and lingular segment	5
		upper and segment 6	3

Table 2 Patient characteristics

	Total (n=56)	Caliber mismatch		P value
		No (n=34)	Yes (n=22)	
Age (years)	71 (42 - 84)	72 (42 - 82)	71 (48 - 84)	0.372
Gender (Male/female)	45/11	27/4	14/5	0.231
Performance status (0/1/2)	27/27/2	16/14/1	9/9/1	0.915
BMI (kg/m ²)	22.5 (15.8 - 34.4)	23.2 (15.8 - 34.4)	21.7 (16.2 - 27.5)	0.212
Comorbidities*	30 (54%)	16 (47%)	14 (64%)	0.222
Cardiovascular disease	24 (43%)	12 (35%)	12 (54%)	0.155
Other organ malignant tumor**	9 (16%)	3 (9%)	6 (27%)	0.069
Diabetes melitus	9 (16%)	4 (12%)	5 (23%)	0.281
Liver disease	5 (9%)	3 (9%)	2 (9%)	0.973
Cerebrovascular disease	5 (9%)	4 (12%)	1 (5%)	0.334
%VC (%)	102 (73 - 144)	103 (73 - 126)	103 (75 - 144)	0.546
FEV1.0% (%)	68 (40 - 88)	71 (48 - 88)	62 (40 - 80)	0.070
%DLCO (%)	91 (50 - 149)	92 (52 - 149)	87 (50 - 135)	0.343
Clinical T factors (1/2/3/4)	18/17/14/7	10/10/8/6	8/7/6/1	0.545
Clinical nodal status (0/1/2)	13/32/11	7/22/5	6/10/6	0.333
Clinical stage (I/II/III)	8/22/26	5/12/17	3/10/9	0.741
Induction chemoradiotherapy	4 (7%)	3 (9%)	1 (5%)	0.577
Pathological T factors (1/2/3/4)	17/19/13/7	9/11/10/4	8/8/3/3	0.580
Pathological nodal status (0/1/2)	12/31/13	8/19/7	4/12/6	0.803
Pathological stage (I/II/III)	6/26/24	3/15/16	3/11/8	0.689
Histologic subtype (Sq/Ad/Others)	42/8/6	24/7/3	18/1/2	0.232

Values are median (range). BMI, body mass index; %VC, percent of vital capacity; FEV1.0%, forced expiratory volume in 1 second as a percent of forced vital capacity; %DLCO, percent of diffusing capacity of lung for carbon monoxide; Sq, squamous cell carcinoma; Ad, adenocarcinoma. *: Some patients have more than one comorbidities. **: malignant tumor within five years.

Table 3 Sugical procedures and postoperative clinical courses

	Total (n=56)	Caliber mismatch		P value
		No (n=34)	Yes (n=22)	
Operation time (minutes)	342 (226 - 659)	338 (226 - 659)	344 (229 - 526)	0.440
Total blood loss (ml)	245 (20 - 1480)	280 (30 - 1330)	165 (50 - 460)	0.030
Additional procedures*	30 (54%)	17 (50%)	13 (59%)	0.505
Pulmonary angioplasty	24 (43%)	14 (41%)	13 (59%)	0.813
Pericardium resection	5 (9%)	2 (6%)	3 (14%)	0.320
Chest wall resection	3 (5%)	2 (6%)	1 (5%)	0.828
Esophageal muscular wall resection	2 (4%)	1 (3%)	1 (5%)	0.755
Vagus nerve resection	2 (4%)	0 (0%)	2 (9%)	0.050
Phrenic nerve resction	2 (4%)	2 (6%)	0 (0%)	0.247
Superior vena cava resection	2 (4%)	2 (6%)	0 (0%)	0.247
Left atrium resection	1 (2%)	1 (3%)	0 (0%)	0.417
Complications**	19 (34%)	8 (24%)	10 (52%)	0.088
Respiratory complications***	14 (25%)	4 (12%)	10 (52%)	0.005
Pneumonia	10 (18%)	3 (9%)	7 (32%)	0.029
Pleural effusion	8 (14%)	2 (6%)	6 (27%)	0.026
Empyema	5 (9%)	2 (6%)	3 (14%)	0.320
Prolonged air leakage	4 (7%)	1 (3%)	3 (14%)	0.129
Broncho-pleural fistula	3 (5%)	0 (0%)	3 (14%)	0.027
Brain infarction	2 (4%)	2 (6%)	0 (0%)	0.247
Arrythmis	1 (2%)	1 (3%)	0 (0%)	0.417
Recurent nerve palsy	1 (2%)	1 (3%)	0 (0%)	0.417
Paralytic ileus	1 (2%)	0 (0%)	1 (5%)	0.210
Postoperative bleeding	1 (2%)	1 (3%)	0 (0%)	0.417
Surgical site infection	1 (2%)	1 (3%)	0 (0%)	0.417
Drainage period (days)	4 (2- 12)	4 (2 - 12)	4 (2 - 12)	0.877
Postoperative hospital stay (days)	15 (7 - 95)	14 (7 - 43)	17 (8 - 95)	0.096
Adjuvant chemotherapy****	24 (44%)	18 (55%)	6 (29%)	0.058

Values are median (range). *: Some patients have more than one additional procedures. **: Some patients have more than one complications. ***: respiratory complications included pneumonia, pleural effusion, empyema, prolonged air leakage and broncho-pleural fistula. ****: Two patients with pStage1A disease were excluded.

Table 4 Risk factors for respiratory complications after bronchoplasty with caliber mismatch

	Respiratory complications	
	No (n = 12)	Yes (n = 10)
Age	71 (48 - 83)	71 (60 - 84)
BMI	23.2 (18.5 - 27.5)	21.2 (16.2 - 22.5)
Comorbidities	8 (67%)	6 (60%)
% VC (%)	105 (88 - 134)	111 (75 - 144)
FEV1.0% (%)	56 (40 - 80)	65 (46 - 77)
DLCO (%)	89 (56 - 135)	87 (50 - 103)
White blood cells (ul)	6700 (4100 - 12800)	7950 (5000 - 16000)
Serum CRP level (mg/dl)	0.32 (0.04 - 3.68)	1.12 (0.03 - 6.05)
Serum albumin level (g/dl)	4.1 (3.1 - 4.4)	3.9 (3.4 - 4.5)
<u>Degree of caliber mismatch</u>		
<u>Large</u>	<u>3</u>	<u>7</u>
<u>Small</u>	<u>9</u>	<u>3</u>
Operation time (minutes)	280 (229 - 526)	372 (246 - 526)
Total blood loss (ml)	150 (10 - 350)	295 (50 - 460)
Tumor size (mm)	40 (10 - 50)	60 (25 - 76)

Values are median (range). BMI, body mass index; %VC, percent of vital capacity; FEV1, first expiratory volume in 1 second as a percent of forced vital capacity; %DLCO, percent of diffusing capacity of lung for carbon monoxide; CRP, C-reactive protein.

atch

P value

0.597

0.036

0.746

0.198

0.741

0.339

0.323

0.277

0.446

0.035

0.156

0.105

0.025

1.0%, forced
diffusing

Table 5 Details of patients with broncho pleural fistula

	Gender	Age	Histology	Comorbidities	BMI	Surgical procedure	TMN	Stage	Induction chemoradiotherapy	Date of occurrence (days after the operation)	Treatments for BPF
1	M	64	SQ	Liver disease, other organ malignant tumor	22.2	RULL	T1cN1M0	IIB	No	9	Fenestration →Completion pneumonectomy
2	M	84	SQ	Hypertension	19.8	RLL	T3N0M0	IIB	No	14	Completion middle lobectomy →Fenestration
3	M	74	SQ	Diabetes melitus, hypertension,cerebral infarction	22.5	LLDLL	T1bN1M0	IIB	Yes	28	Fenestration →Completion pneumonectomy

M, male; SQ, squamous cell carcinoma; BMI, body mass index; RULL, right upper and lower bilobectomy; RLL, right lower lobectomy; RUL, right upper lobectomy; LLDLL, left lingural division and lower lobectomy; BPF, broncho pleural fistula; POD, postoperative day.