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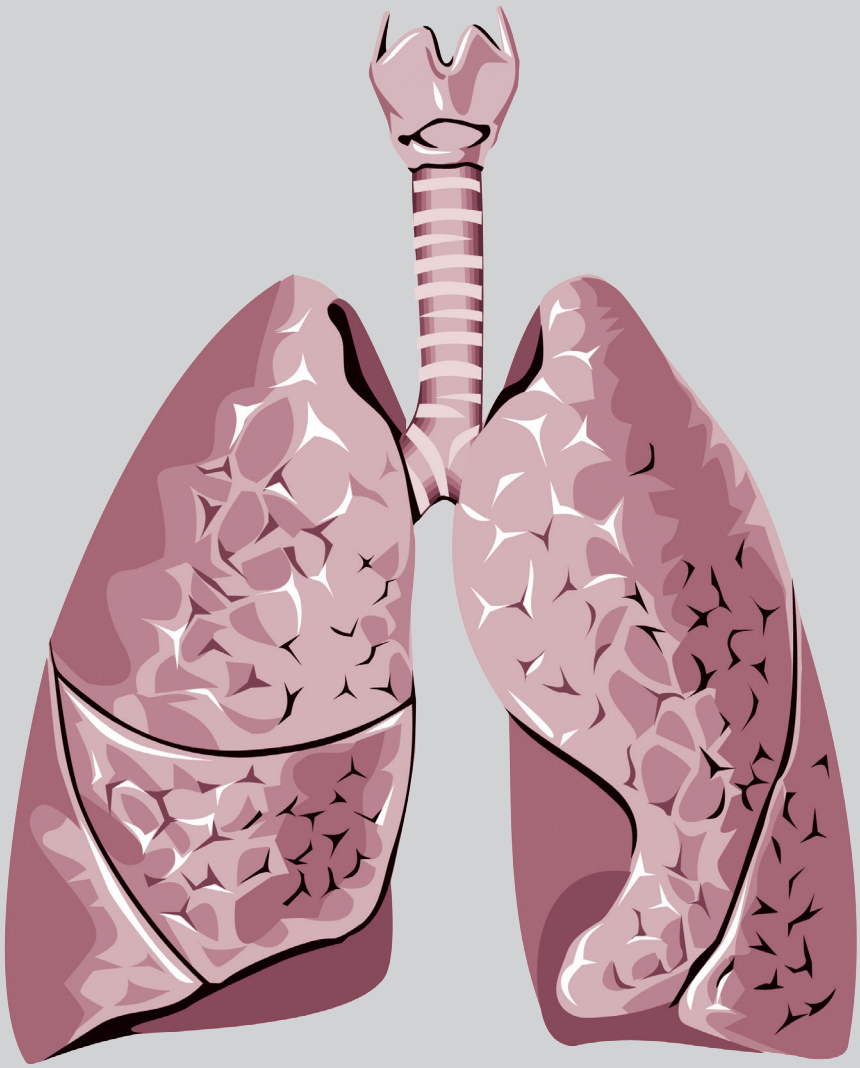

The Official Journal of

Taiwan Society of Pulmonary and Critical Care Medicine

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Determinants for Concurrent Use of a Long-Acting β-2 Agonist and a Long-Acting Muscarinic Antagonist in COPD Management: A Retrospective Cross-Sectional Study

Yu-Cheng Wu[1], Ming-Feng Wu[1,2], Jeng-Yuan Hsu[1], Hui-Chen Chen[1], Wei-Chang Huang[1,3,4,5]

Introduction: Although co-administration of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is more effective in managing stable chronic obstructive pulmonary disease (COPD) than either LABA or LAMA alone, it is costlier and only provides a small increase in the number of responders with clinically important improvements. This study aimed to investigate determinants for concurrent use of a LABA and a LAMA, as considered by physicians actively involved in COPD management.

Methods: This was a retrospective cross-sectional study. The data, collected from electronic medical records, were managed and analyzed.

Results: Of 757 participants, 29.8%, 27.2%, 31.4%, and 31.5%, in groups A, B, C, and D, respectively, were co-administered LABA and LAMA with and without inhaled corticosteroids as the maintenance pharmacological treatment (LABA/LAMA combination users). Moreover, the low-risk group, high-risk group, fewer-symptoms group, and more-symptoms group comprised 28.9%, 31.4%, 30.5%, and 30.0%, respectively, of LABA/LAMA combination users. The logistic regression model found that a positive bronchodilator test (BT), post-BT forced expiratory volume in 1 second/forced vital capacity ≦60, and having any hospitalization for a COPD exacerbation within the last year were significant determinants associated with the prescription of a LABA/LAMA combination therapy.

Conclusion: Our findings provide useful information for future cost-effectiveness analysis of using a LABA and a LAMA concurrently when managing stable COPD patients. ***(Thorac Med 2020; 35: 152-164)***

Key words: bronchodilator combination therapy, COPD, long-acting β2-agonist, long-acting muscarinic antagonist

[1]Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, 407, Taiwan
[2]Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, 406, Taiwan
[3]Department of Life Sciences, National Chung-Hsing University, Taichung, 402, Taiwan
[4]Department of Medical Technology, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, 350, Taiwan
[5]Department of Industrial Engineering and Enterprise Information, Tunghai University, Taichung, 407, Taiwan
Address reprint requests to: Dr. Wei-Chang Huang, Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung, Taiwan 40705

Introduction

The Global initiative for Chronic Obstructive Lung Disease (GOLD) committee in 2017 provided a 2-dimensional assessment of the complexities of chronic obstructive pulmonary disease (COPD) that takes into account both exacerbation risk and symptom assessment [1].

The exacerbation risk of COPD is determined by exacerbation history in the previous year, and symptoms are measured by either the COPD assessment test (CAT) or the modified Medical Research Council dyspnea scale (mMRC). This combination of assessments classifies COPD patients into 1 of 4 categories: A, B, C or D. The management strategy is thereby determined according to this categorization.

The use of long-acting bronchodilators, including the long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA), is the mainstay of COPD management. Increasing evidence shows that co-administration of a LABA and a LAMA can produce greater improvements in lung function and health status without an increase in adverse effects, compared to using either a LABA or LAMA alone [2-4]. For this reason, the GOLD committee recommends combining long-acting bronchodilators with different mechanisms of action if the control of COPD is insufficient with a single agent [1]. However, clinical practice and published evidence show that treatment with the combination of a LABA and a LAMA is costlier and only provides a small increase in the number of responders with a clinically important improvement, compared to either a LABA or LAMA used alone [5].

In such situations, it is reasonable to hypothesize that, with regard to long-acting bronchodilators, there should be determinants associated with the prescription of a LABA/LAMA combination therapy that are considered by physicians actively involved in COPD management. Therefore, the aim of this study was to clarify, with regard to long-acting bronchodilators, the determinants associated with concurrent use of a LABA and a LAMA in COPD management.

Materials and Methods

Study design and population

In this retrospective cross-sectional study, the participating physicians, who were qualified pulmonologists and actively involved in COPD management, screened outpatients for study entry at Taichung Veterans General Hospital between January 2012 and December 2016. Patients aged 40 and older, with a confirmed diagnosis of COPD based on the GOLD 2017 recommendation and a spirometry within the year before enrollment were invited to participate [1]. Patients were excluded if they participated in interventional clinical trials in the previous year or had a history of asthma. The Institutional Review Board and Ethics Committees of Taichung Veterans General Hospital approved this study (approval number: CE13164) and waived the need for informed consent from the participants because the study was based on a retrospective electronic medical chart review.

Data collection

Participating physicians completed a detailed patient record form, which included demographic information, smoking history, the presence or absence of wheezing on presentation to outpatient clinics in the previous year, spirometry, CAT scores, mMRC scales,

exacerbation history in the previous year, comorbidities of interest including cardiovascular diseases (e.g., ischemic heart disease, congestive heart failure, hypertension and arrhythmia), chronic lung diseases (e.g., previous pulmonary tuberculosis, bronchiectasis and pneumoconiosis) and lung cancer. The COPD groups were categorized according to the GOLD 2017 recommendation using CAT scores as the proxy to assess symptoms for the undetermined COPD grouping of patients with discordant COPD group categorization between CAT and mMRC [1]. Maintenance pharmacological treatments for each participant were based on electronic medical records from a single study visit. A positive bronchodilator test (BT) was defined as FEV1 or forced vital capacity (FVC) improvement from the pre-dose value ≧12% and ≧200 ml, according to the American Thoracic Society Statement [6]. An acute exacerbation was defined as a worsening of symptoms that required antibiotics or systemic steroids, emergency room visits, or hospitalizations. Maintenance pharmacological treatments were defined as those continuously prescribed in the previous 3 months. "LABA/LAMA combination users" referred to COPD patients with co-administration of a LABA and a LAMA with and without inhaled corticosteroids as the maintenance pharmacological treatments. Otherwise, the COPD patients were non-LABA/LAMA combination users. After that, the patient record forms were collected for further data management and analysis. Moreover, patient information was anonymized and de-identified prior to analysis.

Statistical Analysis

All data are expressed as mean and standard deviation (SD) for continuous variables or number (percentage) for categorical variables. Comparisons were conducted using the independent t-test for continuous variables and chi-square test for categorical variables. The logistic regression model was used to analyze potential determinants associated with concurrent use of a LABA and a LAMA, if there was significance in univariate analysis. Statistical significance was set at $p<0.05$. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 757 subjects fulfilled the inclusion criteria and were included in the analysis. More than half of the participants were aged over 70 years and the majority were male. Cigarette smoking was the leading cause of COPD in 92.1% (697/757) of the participants. We found that approximately 30% of the participants in each COPD group had a positive BT (Table 1).

Table 1. Baseline Characteristics of the Analyzed Participants

Group	A (n=228)	B (n=125)	C (n=172)	D (n=232)	Total (n=757)
Age	72.6 ± 9.4	72.8 ± 9.8	70.1 ± 8.9	73.0 ± 9.3	72.2 ± 9.4
<60	18 (7.9%)	15 (12.0%)	19 (11.0%)	15 (6.5%)	67 (8.9%)
60-69	66 (28.9%)	29 (23.2%)	56 (32.6%)	65 (28.0%)	216 (28.5%)
70-79	85 (37.3%)	42 (33.6%)	72 (41.9%)	89 (38.4%)	288 (38.0%)
≧80	59 (25.9%)	39 (31.2%)	25 (14.5%)	63 (27.2%)	186 (24.6%)

Gender					
Male	218 (95.6%)	121 (96.8%)	168 (97.7%)	221 (95.3%)	728 (96.2%)
Female	10 (4.4%)	4 (3.2%)	4 (2.3%)	11 (4.7%)	29 (3.8%)
Smoking					
Never	16 (7.0%)	9 (7.2%)	11 (6.4%)	24 (10.3%)	60 (7.9%)
Ex- smoker	129 (56.6%)	68 (54.4%)	113 (65.7%)	133 (57.3%)	443 (58.5%)
Current smoker	83 (36.4%)	48 (38.4%)	48 (27.9%)	75 (32.3%)	254 (33.6%)
Wheezing					
Presence	66 (28.9%)	58 (46.4%)	72 (41.9%)	143 (61.6%)	339 (44.8%)
Absence	162 (71.1%)	67 (53.6%)	100 (58.1%)	89 (38.4%)	418 (55.2%)
Spirometry (Post-BT)					
FEV_1/FVC (%)	60.4 ± 6.5	59.9 ± 7.9	52.0 ± 8.9	49.1 ± 9.6	54.9 ± 9.7
FEV_1 (L)	1.6 ± 0.5	1.6 ± 0.4	1.1 ± 0.4	1.0 ± 0.3	1.3 ± 0.5
FVC (L)	2.7 ± 0.7	2.7 ± 0.6	2.1 ± 0.6	2.0 ± 0.6	2.3 ± 0.7
FEV_1 % predicted	72.1 ± 15.4	70.4 ± 15.7	43.1 ± 15.6	39.1 ± 14.5	55.1 ± 21.6
BT					
Positive	68 (29.8%)	41 (32.8%)	56 (32.6%)	70 (30.2%)	235 (31.0%)
Negative	160 (70.2%)	84 (67.2%)	116 (67.4%)	162 (69.8%)	522 (69.0%)
GOLD spirometric classification					
I	59 (25.9%)	32 (25.6%)	6 (3.5%)	4 (1.7%)	101 (13.3%)
II	169 (74.1%)	93 (74.4%)	20 (11.6%)	28 (12.1%)	310 (41.0%)
III	0 (0.0%)	0 (0.0%)	124 (72.1%)	146 (62.9%)	270 (35.7%)
IV	0 (0.0%)	0 (0.0%)	22 (12.8%)	54 (23.3%)	76 (10.0%)
CAT scores	5.0 ± 2.3	15.1 ± 5.2	5.4 ± 2.5	17.4 ± 6.2	10.6 ± 7.2
<10	228 (100%)	0 (0.0%)	172 (100%)	0 (0.0%)	400 (52.8%)
≧10	0 (0.0%)	125 (100%)	0 (0.0%)	232 (100%)	357 (47.2%)
mMRC	1.4 ± 0.7	1.9 ± 0.8	1.6 ± 0.9	2.4 ± 0.9	1.9± 0.9
0-1	122 (53.5%)	41 (32.8%)	78 (45.3%)	39 (16.8%)	280 (37.0%)
2-4	106 (46.5%)	84 (67.2%)	94 (54.7%)	193 (83.2%)	477 (63.0%)
Exacerbation numbers for the previous year	0.1± 0.3	0.1 ± 0.4	0.9 ± 1.4	1.1 ± 1.4	0.6 ± 1.1
0-1	228 (100%)	125 (100%)	137 (79.7%)	164 (70.7%)	654 (86.4%)
≧2	0 (0.0%)	0 (0.0%)	35 (20.3%)	68 (29.3%)	103 (13.6%)
Hospitalization for a COPD exacerbation within the last year					
Yes	0 (0.0%)	0 (0.0%)	34 (19.8%)	63 (27.2%)	97 (12.8%)
No	228 (100%)	125 (100%)	138 (80.2%)	169 (72.8%)	660 (87.2%)
ICS users	102 (44.7%)	67 (53.6%)	106 (61.6%)	130 (56.0%)	405 (53.5%)
Usage of methylxanthines	168 (73.7%)	96 (76.8%)	127 (73.8%)	172 (74.1%)	563 (74.4%)
Co-morbidities					
Cardiovascular disease[1]	54 (23.7%)	29 (23.2%)	51 (29.7%)	57 (24.6%)	191 (25.2%)
Chronic lung disease[2]	22(9.6%)	5 (4.0%)	19 (11.0%)	19 (8.2%)	65 (8.6%)
Lung cancer	2 (0.9%)	3 (2.4%)	3 (1.7%)	6 (2.6%)	14 (1.8%)

*Acronyms: BT, bronchodilator test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; mMRC, modified Medical Research Council dyspnea scale; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.

[+]Cardiovascular disease included ischemic heart disease, heart failure, atrial fibrillation and hypertension.

[+]Chronic lung disease included previous pulmonary tuberculosis, bronchiectasis and pneumoconiosis.

Using univariate analysis, we found that 30.3% of the study population were LABA/LAMA combination users. Positive BT and post-BTFEV_1/FVC ≦60 were associated with concurrent use of a LABA and a LAMA for all participants (p=0.034 and p=0.018, respectively) (Table 2). Furthermore, univariate analysis of demographic characteristics and clinical

Table 2. Univariate Analysis of Demographic Characteristics and COPD-Related Clinical Data for the Analyzed Population

	Non-LABA/LAMA combination users	LABA/LAMA combination users	*p*-value
Patient number	528 (69.7%)	229 (30.3%)	
Gender			0.261
Male	511 (96.8%)	217 (94.8%)	
Smoking			0.571
Never	39 (7.4%)	21 (9.2%)	
Ex- smoker	307 (58.1%)	136 (59.4%)	
Current smoker	182 (34.5%)	72 (31.4%)	
Wheezing			0.530
Yes	232 (43.9%)	107 (46.7%)	
No	296 (56.1%)	122 (53.3%)	
Post-BT FEV_1/FVC (%)			0.018*
>60	201 (38.1%)	66 (28.8%)	
≦60	327 (61.9%)	163 (71.2%)	
Post-BT FEV_1 % predicted			0.543
≧50	291 (55.1%)	120 (52.4%)	
<50	237 (44.9%)	109 (47.6%)	
BT			0.034*
Positive	151 (28.6%)	84 (36.7%)	
Negative	377 (71.4%)	145 (63.3%)	
CAT scores			0.560
≧15	132 (25.0%)	52 (22.7%)	
<15	396 (75.0%)	177 (77.3%)	
mMRC			0.190
0-2	410 (77.7%)	167 (72.9%)	
3-4	118 (22.3%)	62 (27.1%)	
Exacerbation numbers in the previous year			0.897
0-1	455 (86.2%)	199 (86.9%)	
≧2	73 (13.8%)	30 (13.1%)	
Hospitalization for a COPD exacerbation within the last year			0.325
Yes	63 (11.9%)	34 (14.8%)	
No	465 (88.1%)	195 (85.2%)	
Any co-morbidity			0.524
Yes	168 (31.8%)	79 (34.5%)	
No	360 (68.2%)	150 (65.5%)	

*Acronyms: LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; also see Table 1.

+: p<0.05.

data for individual groups revealed that 29.8%, 27.2%, 31.4%, and 31.5% of LABA/LAMA combination users were in groups A, B, C, and D, respectively. Positive BT was associated with co-administration of a LABA and a LAMA in group A (p=0.049). Post-BT FEV_1 % predicted <50 and ≧50 were associated with concurrent use of a LABA and a LAMA in group C (p=0.009) and group D (p=0.026), respectively (Table 3).

With regard to risk and symptoms, 28.9%, 31.4%, 30.5%, and 30.0% of LABA/LAMA combination users were in the low-risk group, high-risk group, fewer-symptoms group, and more-symptoms group, respectively. Positive BT was associated with the prescription of a LABA/LAMA combination therapy in the low-risk and fewer-symptoms groups (p=0.042 and p=0.006, respectively). Post-BT FEV_1/FVC ≦60 was associated with co-administration of a LABA and a LAMA in the high-risk group (p=0.014). Moreover, having any hospitalization for a COPD exacerbation within the last year was associated with concurrent use of a LABA and a LAMA in the more-symptoms group (p=0.045) (Table 4).

Logistic regression modeling incorporating all significant factors in the univariate analyses in Tables 2, 3 and 4, including positive BT, post-BT FEV1/FVC ≦60 and having any hospitalization for a COPD exacerbation within the last year, revealed the following: Post-BT FEV_1 % predicted was not considered to be a significant parameter due to the paradoxical results in Table 3. Positive BT was still a significant factor associated with the prescription of a LABA/LAMA combination therapy for all participants (p=0.028), groups A (p=0.035), A+B (low-risk, p=0.032), and A+C (fewer-symptoms, p=0.009), post-BT FEV_1/FVC ≦60 in all participants (p=0.015), groups C (p=0.047) and C+D (high-risk, p=0.011), and in those with any hospitalization for a COPD exacerbation within the last year in group B+D (more-symptoms, p=0.033), respectively (Table 5).

Discussion

Main findings

This study found that, with regard to long-acting bronchodilators, the prevalence of the concurrent use of a LABA and a LAMA as maintenance pharmacological treatment was 29.8%, 27.2%, 31.4%, and 31.5% in groups A, B, C, and D, respectively. Moreover, the low-risk group, high-risk group, fewer-symptoms group, and more-symptoms group had 28.9%, 31.4%, 30.5%, and 30.0% of LABA/LAMA combination users, respectively. Positive BT, post-BT FEV_1/FVC ≦60, and having any hospitalization for a COPD exacerbation within the last year were significant determinants to be taken into account for concurrent use of a LABA and a LAMA in COPD management.

Interpretation of findings relative to previously published work and implications for future research, policy and practice

In the present study, we found as many as 31.0% (235/757) of the participants had positive BT. Compared to those with negative BT, COPD patients with positive BT were more challenging to treat because COPD patients with bronchodilator responsiveness have an increased airway wall thickness, presumably caused by a greater degree of airway smooth muscle mass, as well as a greater degree of bronchoconstriction [7]. Moreover, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study

Table 3. Univariate Analysis of Demographic Characteristics and COPD-Related Clinical Data for the Individual COPD Groups

	Group A			Group B			Group C			Group D		
	Non-LABA/LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/LAMA combination users	LABA/LAMA combination users	*p*-value
Patient number	160 (70.2%)	68 (29.8%)	0.000*	91 (72.8%)	34 (27.2%)	0.000*	118 (68.6%)	54 (31.4%)	0.000*	159 (68.5%)	73 (31.5%)	0.000*
Gender			0.490			1.000			0.092			0.745
Male	154 (96.3%)	64 (94.1%)		88 (96.7%)	33 (97.1%)		117 (99.2%)	51 (94.4%)		152 (95.6%)	69 (94.5%)	
Smoking			0.709			0.820			0.224			0.970
Never	11 (6.9%)	5 (7.4%)		7 (7.7%)	2 (5.9%)		5 (4.2%)	6 (11.1%)		16 (10.1%)	8 (11.0%)	
Ex-smoker	88 (55.0%)	41 (60.3%)		48 (52.7%)	20 (58.8%)		80 (67.8%)	33 (61.1%)		91 (57.2%)	42 (57.5%)	
Current smoker	61 (38.1%)	22 (32.4%)		36 (39.6%)	12 (35.3%)		33 (28.0%)	15 (27.8%)		52 (32.7%)	23 (31.5%)	
Wheezing			0.795			0.911			0.972			0.308
Yes	45 (28.1%)	21 (30.9%)		43 (47.3%)	15 (44.1%)		50 (42.4%)	22 (40.7%)		94 (59.1%)	49 (67.1%)	
No	115 (71.9%)	47 (69.1%)		48 (52.7%)	19 (55.9%)		68 (57.6%)	32 (59.3%)		65 (40.9%)	24 (32.9%)	
Post-BT FEV1/FVC (%)			0.625			0.659			0.067			0.143
>60	92 (57.5%)	36 (52.9%)		54 (59.3%)	18(52.9%)		29 (24.6%)	6 (11.1%)		26 (16.4%)	6 (8.2%)	
≦60	68 (42.5%)	32 (47.1%)		37 (40.7%)	16 (47.1%)		89 (75.4%)	48 (88.9%)		133 (83.6%)	67 (91.8%)	
Post-BT FEV1 % predicted			NA			NA			0.009*			0.026*
≧50	160 (100%)	68 (100%)		91 (100%)	34 (100%)		24 (20.3%)	2 (3.7%)		16 (10.1%)	16 (21.9%)	
<50	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		94 (79.7%)	52 (96.3%)		143 (89.9%)	57 (78.1%)	
BT			0.049*			0.564			0.169			1.000
Positive	41 (25.6%)	27 (39.7%)		28 (30.8%)	13 (38.2%)		34 (28.8%)	22 (40.7%)		48 (30.2%)	22 (30.1%)	
Negative	119 (74.4%)	41 (60.3%)		63(69.2%)	21 (61.8%)		84 (71.2%)	32 (59.3%)		111 (69.8%)	51 (69.9%)	
CAT scores			NA			0.506			NA			0.126
≧15	0 (0.0%)	0 (0.0%)		35 (38.5%)	16 (47.1%)		0 (0.0%)	0 (0.0%)		97 (61.0%)	36 (49.3%)	
<15	160 (100%)	68 (100%)		56 (61.5%)	18 (52.9%)		118 (100%)	54 (100%)		62 (39.0%)	37 (50.7%)	
mMRC			0.759			0.336			1.000			0.228
0-2	150 (93.8%)	65 (95.6%)		71 (78.0%)	23 (67.6%)		102 (86.4%)	46 (85.2%)		87 (54.7%)	33 (45.2%)	
3-4	10 (6.3%)	3 (4.4%)		20 (22.0%)	11 (32.4%)		16 (13.6%)	8 (14.8%)		72 (45.3%)	40 (54.8%)	
Exacerbation numbers in the previous year (For groups A and B)			0.629			1.000						
0	144 (90.0%)	59 (86.8%)		78 (85.7%)	29 (85.3%)							
1	16 (10.0%)	9 (13.2%)		13 (14.3%)	5 (14.7%)							

Exacerbation numbers in the previous year (For groups C and D)						0.544				1.000
0-1					92 (78.0%)	45 (83.3%)		112 (70.4%)	52 (71.2%)	
≧2					26 (22.0%)	9 (16.7%)		47 (29.6%)	21 (28.8%)	
Hospitalization for a COPD exacerbation within the last year			NA				NA		0.370	0.071
Yes	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	26 (22.0%)	8 (14.8%)		37 (23.3%)	26 (35.6%)
No	160 (100%)	68 (100%)		91 (100%)	34 (100%)	92 (78.0%)	46 (85.2%)		122 (76.7%)	47 (64.4%)
Any co-morbidity			0.666			1.000			0.202	0.860
Yes	51 (31.9%)	19 (27.9%)		25 (27.5%)	10 (29.4%)	41 (34.7%)	25 (46.3%)		51 (32.1%)	25 (34.2%)
No	109 (68.1%)	49 (72.1%)		66 (72.5%)	24 (70.6%)	77 (65.3%)	29 (53.7%)		108 (67.9%)	48 (65.8%)

*Acronyms: NA, not applicable; also see Tables 1 and 2.

+: $p<0.05$.

Table 4. Univariate Analysis of Demographic Characteristics and COPD-Related Clinical Data for the Combined COPD Groups

	Low-risk group (group A+B)			High-risk group (group C+D)			Fewer-symptoms group (group A+C)			More-symptom groups (group B + D)		
	Non-LABA/ LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/ LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/ LAMA combination users	LABA/LAMA combination users	*p*-value	Non-LABA/ LAMA combination users	LABA/LAMA combination users	*p*-value
Patient number	251 (71.1%)	102 (28.9%)	0.000*	277 (68.6%)	127 (31.4%)	0.000*	278 (69.5%)	122 (30.5%)	0.000*	250 (70.0%)	107 (30.0%)	0.000*
Gender			0.557			0.256			0.138			0.777
Male	242 (96.4%)	97 (95.1%)		269 (97.1%)	120 (94.5%)		271 (97.5%)	115 (94.3%)		240 (96.0%)	102 (95.3%)	
Smoking			0.615			0.519			0.438			0.900
Never	18 (7.2%)	7 (6.9%)		21 (7.6%)	14 (11.0%)		16 (5.8%)	11 (9.0%)		23 (9.2%)	10 (9.3%)	
Ex-smoker	136 (54.2%)	61 (59.8%)		171 (61.7%)	75 (59.1%)		168 (60.4%)	74 (60.7%)		139 (55.6%)	62 (57.9%)	
Current smoker	97 (38.6%)	34 (33.3%)		85 (30.7%)	38 (29.9%)		94 (33.8%)	37 (30.3%)		88 (35.2%)	35 (32.7%)	
Wheezing			1.000			0.532			0.925			0.448
Yes	88 (35.1%)	36 (35.3%)		144 (52.0%)	71 (55.9%)		95 (34.2%)	43 (35.2%)		137 (54.8%)	64 (59.8%)	
No	163 (64.9%)	66 (64.7%)		133 (48.0%)	56 (44.1%)		183 (65.8%)	79 (64.8%)		113 (45.2%)	43 (40.2%)	

Post-BT FEV_1/FVC (%)			0.436			0.014*			0.111			0.090
>60	146 (58.2%)	54 (52.9%)		55 (19.9%)	12 (9.4%)		121 (43.5%)	42 (34.4%)		80 (32.0%)	24 (22.4%)	
≦60	105 (41.8%)	48 (47.1%)		222 (80.1%)	115 (90.6%)		157 (56.5%)	80 (65.6%)		170 (68.0%)	83 (77.6%)	
Post-BT FEV_1 % predicted			NA			1.000			0.116			0.569
≧50	251 (100%)	102 (100%)		40 (14.4%)	18 (14.2%)		184 (66.2%)	70 (57.4%)		107 (42.8%)	50 (46.7%)	
<50	0 (0.0%)	0 (0.0%)		237 (85.6%)	109 (85.8%)		94 (33.8%)	52 (42.6%)		143 (57.2%)	57 (53.3%)	
BT			0.042*			0.368			0.006*			0.894
Positive	69 (27.5%)	40 (39.2%)		82 (29.6%)	44 (34.6%)		72 (25.9%)	49 (40.2%)		76 (30.4%)	34 (31.8%)	
Negative	182 (72.5%)	62 (60.8%)		195 (70.4%)	83 (65.4%)		206 (74.1%)	73 (59.8%)		174 (69.6%)	73 (68.2%)	
CAT scores			0.799			0.226			NA			0.540
≧15	35 (13.9%)	16 (15.7%)		97 (35.0%)	36 (28.3%)		0 (0.0%)	0 (0.0%)		132 (52.8%)	52 (48.6%)	
<15	216 (86.1%)	86 (84.3%)		180 (65.0%)	91 (71.7%)		278 (100%)	122 (100%)		118 (47.2%)	55 (51.4%)	
mMRC			0.780			0.282			1.000			0.072
0-2	221 (88.0%)	88 (86.3%)		189 (68.2%)	79 (62.2%)		252 (90.6%)	111 (91.0%)		158 (63.2%)	56 (52.3%)	
3-4	30 (12.0%)	14 (13.7%)		88 (31.8%)	48 (37.8%)		26 (9.4%)	11 (9.0%)		92 (36.8%)	51 (47.7%)	
Exacerbation numbers in the previous year (For the low-risk group)			0.700									
0	222 (88.4%)	88 (86.3%)										
1	29 (11.6%)	14 (13.7%)										
Exacerbation numbers in the previous year (Except for the low-risk group)						0.644			0.652			0.972
0-1				204 (73.6%)	97 (76.4%)		252 (90.6%)	113 (92.6%)		203 (81.2%)	86 (80.4%)	
≧2				73 (26.4%)	30 (23.6%)		26 (9.4%)	9 (7.4%)		47 (18.8%)	21 (19.6%)	
Hospitalization for a COPD exacerbation within the last year			NA			0.451			0.466			0.045*
Yes	0 (0.0%)	0 (0.0%)		63 (22.7%)	34 (26.8%)		26 (9.4%)	8 (6.6%)		37 (14.8%)	26 (24.3%)	
No	251 (100%)	102 (100%)		214 (77.3%)	93 (73.2%)		252 (90.6%)	114 (93.4%)		213 (85.2%)	81 (75.7%)	
Any co-morbidity			0.829			0.275			0.643			0.759
Yes	76 (30.3%)	29 (28.4%)		92 (33.2%)	50 (39.4%)		92 (33.1%)	44 (36.1%)		76 (30.4%)	35 (32.7%)	
No	175 (69.7%)	73 (71.6%)		185 (66.8%)	77 (60.6%)		186 (66.9%)	78 (63.9%)		174 (69.6%)	72 (67.3%)	

*Acronyms: see Tables 1-3.

$^{+}$: $p<0.05$.

Table 5. Logistic Regression Analysis of Significant Factors in Univariate Analysis for All Participants and Individual and Combined COPD Groups

Characteristics	Parameter estimate	Standard error	Odds ratio (95% CI)	*P*-value
All				
Bronchodilator test: positive versus negative	0.369	0.168	1.45 (1.04, 2.01)	0.028*
Post-BT FEV1/FVC: ≦60 versus >60	0.417	0.171	1.52 (1.09, 2.12)	0.015*
Hospitalization for a COPD exacerbation within the last year: yes versus no	0.252	0.229	1.29 (0.82, 2.02)	0.271
Group A				
Bronchodilator test: positive versus negative	0.648	0.307	1.91 (1.05, 3.49)	0.035*
Post-BT FEV1/FVC: ≦60 versus >60	0.184	0.291	1.20 (0.68, 2.13)	0.526
Group B				
Bronchodilator test: positive versus negative	0.331	0.420	1.39 (0.61, 3.17)	0.430
Post-BT FEV1/FVC: ≦60 versus >60	0.260	0.404	1.30 (0.59, 2.87)	0.520
Group C				
Bronchodilator test: positive versus negative	0.530	0.344	1.70 (0.87, 3.33)	0.123
Post-BT FEV1/FVC: ≦60 versus >60	0.958	0.483	2.61 (1.01, 6.72)	0.047*
Hospitalization for a COPD exacerbation within the last year: yes versus no	-0.486	0.443	0.62 (0.26, 1.47)	0.273
Group D				
Bronchodilator test: positive versus negative	-0.002	0.308	1.00(0.55, 1.83)	0.994
Post-BT FEV1/FVC: ≦60 versus >60	0.781	0.477	2.18 (0.86, 5.56)	0.102
Hospitalization for a COPD exacerbation within the last year: yes versus no	0.601	0.308	1.82 (1.00, 3.34)	0.051
Low-risk group (Group A+B)				
Bronchodilator test: positive versus negative	0.532	0.247	1.70 (1.05, 2.76)	0.032*
Post-BT FEV1/FVC: ≦60 versus >60	0.212	0.236	1.24 (0.78, 1.96)	0.369
High-risk group (Group C+D)				
Bronchodilator test: positive versus negative	0.232	0.228	1.26 (0.81, 1.97)	0.310
Post-BT FEV1/FVC: ≦60 versus >60	0.865	0.339	2.37 (1.22, 4.61)	0.011*
Hospitalization for a COPD exacerbation within the last year: yes versus no	0.217	0.246	1.24 (0.77, 2.01)	0.379
Fewer-symptoms group (Group A+C)				
Bronchodilator test: positive versus negative	0.597	0.229	1.82 (1.16, 2.85)	0.009*
Post-BT FEV1/FVC: ≦60 versus >60	0.384	0.226	1.47 (0.94, 2.29)	0.089
Hospitalization for a COPD exacerbation within the last year: yes versus no	-0.385	0.420	0.68 (0.30, 1.55)	0.359
More-symptoms group (Group B+D)				
Bronchodilator test: positive versus negative	0.107	0.248	1.11 (0.69, 1.81)	0.666
Post-BT FEV1/FVC: ≦60 versus >60	0.487	0.269	1.63 (0.96, 2.76)	0.070
Hospitalization for a COPD exacerbation within the last year: yes versus no	0.614	0.287	1.85 (1.05, 3.25)	0.033*

*Acronyms: CI, confidence interval; also see Table 1.

+: $p<0.05$.

found that COPD patients with positive BT had a 17±4 ml per year greater rate of decline in FEV_1 compared to those with negative BT [8]. Therefore, it is possible that the concurrent use of a LABA and a LAMA would be able to overcome the greater degree of bronchoconstriction, followed by decelerating the rapid rate of decline in FEV_1 for COPD patients with positive BT. These findings indicate that positive BT should be considered as the determinant for co-administration of a LABA and a LAMA in COPD management, as we found in our study.

Exacerbations of COPD, particularly if they require hospitalization, negatively impact the patient's quality of life and mortality [9-11]. This suggests that exacerbations in COPD patients should be prevented, as much as possible. The ECLIPSE study found a positive relationship between the severity of airflow limitation and the rate of exacerbation with and without requiring hospitalization [12]. Therefore, improving lung function as much as possible is the cornerstone to preventing exacerbation in COPD patients, especially in those with a high risk of exacerbation, as defined by having frequent exacerbations (≧2 per year) or any exacerbation requiring hospitalization in the previous year based on GOLD recommendations [1].

With regard to long-acting bronchodilators, previous studies have shown that co-administration of a LABA and a LAMA can provide the greatest improvement in lung function for COPD patients [2-4]. This suggests that more severe airflow limitation and having frequent exacerbations or any hospitalization for a COPD exacerbation within the last year should be taken into account as the determinant for the prescription of LABA/LAMA combination therapy in COPD management. These findings, with the exception of frequent exacerbations, are consistent with the results of our study.

Of interest, rather than post-BT FEV_1 % predicted <50, which represents more severe airflow limitation as recommended by GOLD, post-BT FEV_1/FVC ≦60, which indicates a more severe airflow limitation than post-BT FEV_1/FVC >60, was the determinant to be taken into consideration for combining a LABA and a LAMA in COPD management in our study. In clinical practice, the majority of COPD patients have concurrent restrictive lung diseases and co-morbidities, and this may lead to an overestimation of the severity of airway obstruction in the spirometry using FEV_1 % predicted values. In contrast, grading the severity of airway obstruction on the basis of the FEV_1/FVC ratio of spirometry can avoid the problem of overestimating the degree of airway obstruction [13]. This indicates that, compared to post-BT FEV_1 % predicted <50, post-BT FEV_1/FVC ≦60 may be a better determinant for the prescription of a LABA/LAMA combination therapy in COPD management.

Several previous studies found that, compared to either LABA or LAMA monotherapy, the use of combined LABA/LAMA therapy provided significantly greater improvements in health status and dyspnea severity for COPD patients [2-4]. Therefore, it was reasonable to presume that both the more impaired health status defined as CAT ≧15 and the more serious breathlessness defined as mMRC 3-4 were associated with the concurrent use of a LABA and a LAMA for COPD patients. However, both CAT ≧15 and mMRC 3-4 were not the determinants that were considered when prescribing a LABA/LAMA combination therapy for COPD patients in the final analysis. This surprising finding may be related to the study limitation mentioned below, that COPD patients

with a worst health status and respiratory capacity (e.g., CAT score ≧30 and mMRC scale =4) were more unwilling to participate in the study; therefore, underestimations of the association between the prescription of a LABA/LAMA combination therapy and symptom assessment may exist.

Co-administration of a LAMA and a LABA is more effective in managing stable COPD than either drug class alone, given that studies have indicated greater improvements in lung function, symptoms, and health status with the former [2-4]. However, compared to either LABA or LAMA alone, the higher cost of this combination therapy is a major concern in COPD management. As a result, further cost-effectiveness analysis is required to determine whether or not to recommend treating COPD patients with positive BT, post-BT FEV_1/FVC ≦60, and having any hospitalization for a COPD exacerbation within the last year with concurrent use of a LABA and a LAMA.

Strengths and limitations of this study

Based on the GOLD recommendation, several previous studies found that group assignment of COPD patients based on CAT was not consistent with that using mMRC [14-16]. This inconsistency, however, may influence the results of studies on COPD. In the present study, we used CAT to assess the symptoms of COPD patients with discordant group assignment between CAT and mMRC. This methodological standardization renders our results easier to compare in future studies. However, there were still a number of limitations in our study. First, instead of recording all COPD-related co-morbidities, we kept a record of co-morbidities of interest only, including cardiovascular diseases, chronic lung diseases and lung cancer. As a result, the association between COPD-related co-morbidities and the prescription of LABA/LAMA combination therapy could not be evaluated comprehensively. Second, the participants were not sampled randomly. COPD patients with a worst health status and respiratory capacity (e.g., CAT score ≧30 and mMRC scale =4) were more unwilling to participate in the study. Hence, underestimations of the association between health status as determined by CAT and prescription of a LABA/LAMA combination therapy, as well as between breathlessness severity as determined by mMRC and prescription of a LABA/LAMA combination therapy, may exist. Third, bronchodilator reversibility status varies between visits in certain patients with COPD [17-18]. This made positive BT a significant determinant to be taken into account for concurrent use of a LABA and a LAMA in COPD management in our study, and may not be generalizable to patients with a variable responder status.

Conclusions

With regard to long-acting bronchodilators, our study found that positive BT, post-BT FEV_1/FVC ≦60, and having any hospitalization for a COPD exacerbation within the last year were significant determinants to be taken into account for concurrent use of a LABA and a LAMA in COPD management. Our findings should be useful for future cost-effectiveness analysis of using a LABA and a LAMA concurrently when managing stable COPD patients.

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Low-Dose Computed Tomography for Lung Cancer Screening in the General Population: Experience at a Local Hospital in Taitung, Taiwan

Chiu-Fan Chen[1,2], Wei-Lun Huang[3], Chih-Hsun Lin[2], Chia-Hao Chan[4]

Introduction: Lung cancer screening with low-dose computed tomography (LDCT) has been shown to effectively reduce lung cancer mortality in heavy smokers. However, evidence on the benefits of using LDCT to survey a general population, including non-smokers, in Taiwan is limited.

Methods: We enrolled patients receiving LDCT during the year 2016 at a local hospital in Taitung City. Our aim was to analyze the features of pulmonary nodules found by LDCT in a general population, and to evaluate the follow-up results.

Results: A total of 371 patients were collected. The mean age was 59.2±11.9 years. Ninety patients (24.3%) were smokers. A total of 252 patients (67.9%) had pulmonary nodules ≧2 mm on LDCT. Smoking status was not significantly different between patients with and without pulmonary nodules. Of the nodules <6 mm with LDCT follow-up, 73.6% showed a stable size for 1~2 years, 17.2% showed regression, and only 1.1% had nodule progression (5 mm ground-glass nodule progression to 6 mm with density increase at 24 months); 8% had follow-up of <1 year. The overall lung cancer detection rate was 1.3%.

Conclusion: This study found that pulmonary nodules <6 mm are very common in the general population of Taitung undergoing LDCT. Up to 1/4 of patients were found to have pulmonary nodules ≧6 mm on LDCT. The cancer detection rate in this study was similar to that of LDCT screening for heavy smokers in the United States. LDCT may be an effective tool for lung cancer screening in the general population in Taiwan. ***(Thorac Med 2020; 35: 165-177)***

Key words: low-dose computed tomography, lung cancer screening, pulmonary nodule

Introduction

Lung cancer is the most deadly cancer worldwide. According to global cancer statistics for 2018, lung cancer is the most common cause of cancer death [1]. Lung cancer in Taiwan also has been the leading cause of cancer death for the last 20 years, and the incidence and death rate of lung cancer are still increasing [2-3]. In Taiwan, most lung cancers were diagnosed at

[1]Division of Chest Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [2]Division of Chest Medicine, [3]Division of Family Medicine, [4]Division of Radiology, Taipei Veterans General Hospital, Taitung Branch, Taitung, Taiwan.

Address reprint requests to: Dr. Chih-Hsun Lin, Division of Chest Medicine, Department of Internal Medicine, Taipei Veterans General Hospital, Taitung Branch, Taitung, Taiwan. No. 1000, Gengsheng Rd., Taitung City, Taitung 95050, Taiwan.

a late stage, and less than 1/3 of patients could receive surgical resection [4]. Most early lung cancers are asymptomatic. Even with the recent advances in lung cancer therapy (chemotherapy, targeted therapy, immunotherapy) and significant survival prolongation, the lung cancer mortality rate remains high. These therapies are very expensive, and still are unable to cure late-stage lung cancer. Similar to most cancers, the only way to gain some success in treating lung cancer is through early-stage diagnosis, which improves the opportunity for curative surgical resection, and lung cancer screening is the best way to achieve early diagnosis of lung cancer.

However, there has been no effective lung cancer screening tool for a long time. Although chest X-ray is inexpensive, fast and convenient, the low sensitivity (78%) and high false negative rate is not suitable for lung cancer screening [5]. As early as the 1970s, several large-scale randomized controlled trials (RCT) showed that chest X-ray screening plus sputum cytology failed to improve the lung cancer mortality rate [6-7]. In the PLCO study, the most recent large-scale RCT comparing annual chest X-ray screening and usual care, the chest X-ray group showed some increase in early-stage lung cancer diagnosis, but the lung cancer mortality rate still did not improve [8]. As for chest computed tomography (CT), despite the advantages of excellent accuracy in evaluating lung lesions and nearly no blind spots on image interpretation, its radiation dose is too high. In general, the effective dose of a chest CT (4 mSv) is about 100-fold that of a chest X-ray (0.04 mSv). Therefore, the high radiation dose of chest CT makes this tool unsuitable for widespread and frequent examinations, and limits its use in lung cancer screening.

Later, between 1990 and 2000, the development of low-dose CT (LDCT) successfully reduced the radiation dose to around 1/3 that of traditional CT, and preserved the image quality of the lung parenchyma, although the image quality of the mediastinum and soft tissue decreased [9-10]. The radiation absorption dose of LDCT is usually set at 3 mGy, equivalent to an effective dose of ~1.5 mSv. This radiation dose of LDCT is around 30- to 40-fold that of chest X-ray, and is similar to the annual natural background radiation dose [10-11]. Therefore, LDCT has become a potential tool for lung cancer screening.

In recent years, the most important landmark lung cancer screening studies have been the 2 largest RCTs: the National Lung Cancer Screening Trial (NLST) of the United States, and the NELSON study of the Netherlands and Belgium [12-13]. These 2 studies arranged LDCT lung cancer screening for heavy smokers--the population with the highest risk of lung cancer--and showed that LDCT not only detects more early-stage lung cancers, but also significantly reduced the lung cancer mortality rate by 20~24% [12-13]. Now, the National Comprehensive Cancer Network (NCCN), the American College of Chest Physicians (ACCP), and the American Society of Clinical Oncology (ASCO) already recommend LDCT lung cancer screening for heavy smokers (>30 pack-years, current smokers or those who have quit smoking for <15 years) [10].

Most lung cancer patients in the United States and Europe were smokers (75~90%). In contrast, the percentage of lung cancer patients in East-Asia who were smokers is lower, and around 1/3 of lung cancer patients were never-smokers [14]. In Taiwan, the never-smoker percentage among lung cancer patients is even as high as 53% [15]. Therefore, the American and

European LDCT recommendations focusing on heavy smoker lung cancer screening will miss half of lung cancer patients in Taiwan. Obviously their recommendations are not completely suitable for the lung cancer population of Taiwan and require further modification. Although there is still no evidence for LDCT lung cancer screening of never-smokers, a large-scale lung cancer screening study on never-smokers in Taiwan is already ongoing [16].

Furthermore, air pollution is already a well-known lung cancer risk factor. It is gaining more and more public attention, and the numbers of patients receiving a health exam LDCT are also increasing. However, the air quality in Taitung remains some of the best in Taiwan. The annual average particulate matter 2.5 (PM2.5) level in Taitung was 8.6 μg/m^3 in 2018 [17-18]. Therefore, this study aimed to analyze the screening results of a general population receiving LDCT in Taitung, and to determine if the good air quality in Taitung was associated with different LDCT results.

Methods

Subjects

This retrospective cohort study was conducted in a local hospital in Taitung, Taiwan. Patients aged ≥18 years receiving LDCT lung cancer screening from January 1, 2016 to December 31, 2016 were enrolled in the study. The patients received either self-paid LDCT in the health exam department or National Health Insurance-paid LDCT in chest medicine outpatient department.

LDCT interpretation and follow-up

LDCT was performed using GE Optima CT660 (128 slices), from the lung apex to the lung base, without contrast enhancement. The radiation absorption dose ranged from 3~3.12 mGy, and the effective dose ranged from 1.3~1.9 mSv. The image was displayed with 5 mm thickness. The lung window was set at a window width of 1,500 HU and a window center of -700HU, and the mediastinal window was set at a window width of 330HU and a window center of 35HU. The nodule size was measured at the lung window, and was defined as an average of the longest and shortest diameter. A nodule ≧2 mm was defined as a positive pulmonary nodule. Solid nodule was defined as a nodule density equal to or greater than that of the pulmonary vessel. A ground-glass nodule was defined as a nodule density less than that of the pulmonary vessel and with preservation of bronchial and pulmonary vessel margins. A part-solid nodule was a nodule with both solid and ground glass components [19]. Nodule growth was defined as an increase in size of >1.5 mm [20]. All LDCT images were interpreted by a radiologist (CH Chan).

The management decision based on the LDCT result (LDCT follow-up or referral for lung biopsy) was determined by each patient's attending physician. The LDCT follow-up time interval was also determined by the attending physician, based on their clinical experience. Image reports and medical records were retrospectively collected, and the LDCT follow-up reports were collected up to Oct 31, 2019.

Data collection

The following data were collected: age, sex, smoking history, comorbidity, residence, nodule size, nodule number, nodule nature (solid, part-solid, ground-glass, calcified, undetermined), other imaging findings, Lung-RADS category [20], follow-up result, and follow-up

time. Follow-up results included: no follow-up, follow-up <1 year, stable for ≧1 year but <2 years, stable for ≧2 years, regression, progression, and referral at first. Since a patient may have multiple lung nodules, we chose the largest nodule as the index nodule for statistical analysis and for follow-up results evaluation. A new nodule larger than the index nodule was recorded as an additional result for the patient.

Statistical analysis

Continuous variables are presented as mean ±standard deviation (SD), and were compared using an independent t-test or 1-way ANOVA. Categorical variables are presented as number (percentage), and were compared using Pearson's chi-square tests. A 2-tailed *p* value <0.05 was considered as statistically significant.

Results

During the 1-year period of 2016, a total of 371 patients received LDCT lung cancer screening at our hospital. The mean age was 59.2 ±11.9 years, and 195 (52.6%) patients were male. The age distribution of these patients is shown in Figure 1. Ninety patients (24.3%) were current smokers or ex-smokers. Medical records of 1 or more comorbidities were found for 133 patients (35.8%). In all, 334 patients (90%) lived in Taitung, and 217 (58.5%) received a self-paid LDCT from the health exam department. There were no significant difference in age, sex, smoking status, residence and self-paid LDCT between patients with and without lung nodules. However, the comorbidity percentage was significantly higher in patients with lung nodules than in those without lung nodules (39.3% vs 28.6%, p =0.045) (Table 1).

A total of 252 patients had an LDCT showing lung nodules ≧2mm in size: 69 (18.6%) of the nodules were 2-3mm, 96 (25.9%) were 4-5mm, 35 (9.4%) were 6-7mm, 39 (10.5%) were 8-14mm, and 13 (3.5%) were ≧15mm. Among the 252 patients with lung nodules, the median nodule number was 2, with an interquartile range (IQR) = 1-3, and the average nodule size was 5.9 ±4.5mm (median size 4.5 mm, IQR=3-6). The most common appearance of the nodules was ground-glass (n=114,

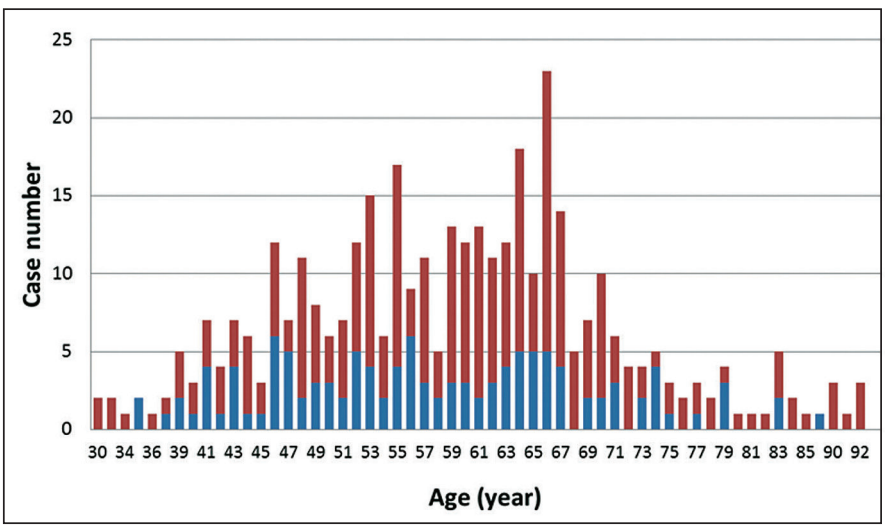

Fig. 1. Age distribution of patients receiving low-dose CT.
Red bar: nodule ≧2 mm, blue bar: no nodule.

Table 1. Baseline Demographic Features, n=371

	All (n=371)	No nodule N(n=119)	≧2 mm (n=252)	*p* value
Age	59.2 ±11.9	57.6 ±11.5	59.9 ±12	0.08
Sex				0.321
male	195 (52.6)	67 (56.3)	128 (50.8)	
Smoking				0.761
Current	52	18	34	
Ex-smoker	51	18	33	
Nil	268	83	185	
Comorbidity				0.045*
Any	133 (35.8)	34 (28.6)	99 (39.3)	
Residence				0.961
Taitung	334 (90)	107 (89.9)	227 (90.1)	
Health exam	217 (58.5)	70 (58.8)	147 (58.3)	0.929
Nodule number	0 (0-2)	0	2 (1-3)	
Nodule size+		0	5.9 ±4.5	
Lung-RADS				
1	123 (33.2)	119	4	
2	188 (50.7)	0	188	
3	28 (7.5)	0	28	
4	32 (8.6)	0	32	

Mean ± SD or n (%). *$p < 0.05$, +The size of the largest nodule in a patient

45.2%), followed by solid (n=61, 24.2%), part-solid (n=25, 9.9%), calcified (n=8, 3.2%), and undetermined (n=44, 17.5%). The relationship between nodule size and appearance is shown in Figure 2. Lung-RADS classification showed 123 (33.2%) patients as Lung-RADS 1, 188

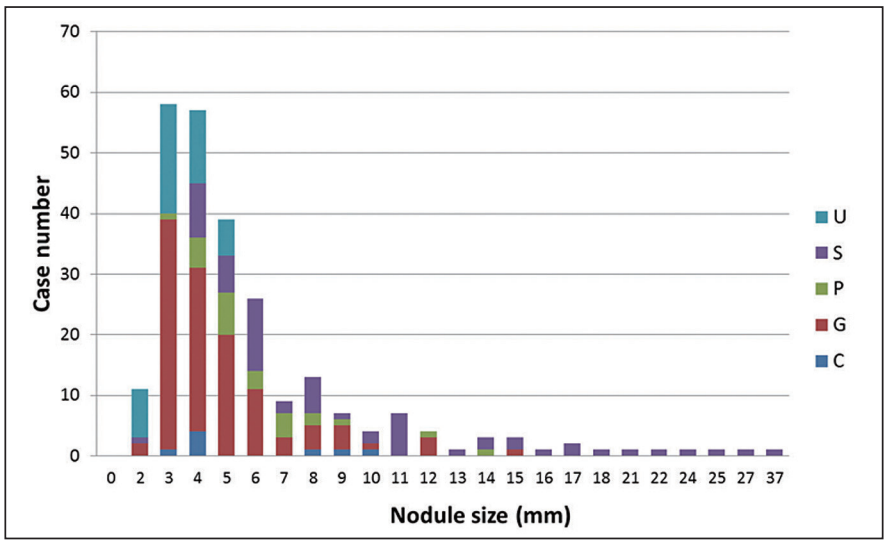

Fig. 2. Relationship between nodule size and nature, n=252.
C = calcified; G = ground-glass; P = part-solid; S = solid; U = undetermined.

(50.7%) as Lung-RADS 2, 28 (7.5%) as Lung-RADS 3, and 32 (8.6%) as Lung-RADS 4. Among the Lung-RADS 4 patients, 14 (3.8%) were 4A, 10 (2.7%) 4B, and 8 (2.2%) 4X.

Among the 252 patients with LDCT images showing nodules ≧2 mm, 144 (57.1%) had follow-up results (at least 1 LDCT follow-up or referral). Of these 144 patients with follow-up results, 61 (42.4%) had ≧2 years of stable nodules, 26 (18.1%) had 1~2 years of stable nodules, 11 (7.6%) had a follow-up of <1 year, 32 (22.2%) had nodule regression, 6 (4.2%) had nodule progression, and 8 (5.6%) were transferred at first. The average follow-up time was 24.8±13.1 months (median 25 months, IQR = 15.25-33). Analysis of nodule change timing showed that the mean time to nodule regression was 11.9±11.3 months (median 8 months, IQR = 5.25-12.75), and the time to nodule progression was 14.5±8.4 months (median 13 months, IQR = 8.75-24). Furthermore, 8 patients (5.6%) had new lung nodules larger than the index nodules, and none of the new nodules required transfer for further management. There were significant follow-up result differences among the nodule size subgroups (p <0.001) (Table 2).

A total of 14 patients were transferred for further lung nodule management. Five were confirmed to have lung cancer by pathology (4 by surgical biopsy, 1 by sputum cytology), and 3 were considered to have benign nodules (2 by pathology confirmed, 1 was suggested to be old TB-related and was stable for 25 months by chest X-ray follow-up); the remaining 6 patients had uncertain results (3 were transferred at first, and 3 were transferred after nodule progression). The lung cancer detection rate was 1.3% (5/371) in this study, and the 5 patients who were confirmed to have lung cancer had an initial detected nodule size of 8, 12, 14, 14, and 27 mm, respectively.

There were significant differences in follow-up results between patients with nodules <6 mm and those with nodules ≧6 mm (p < 0.001). In patients with nodules <6 mm, 48.3% had stable nodules for ≧2 years, and 24.1% had stable nodules for 1~2 years; 8% were followed for <1 year, 18.4% had nodule regression, 1.1% had nodule progression (5 mm progressed to 6 mm, with a density increase at 24 months of follow-up), 0% were transferred at first, and no patients were confirmed to have lung cancer. As for pa-

Table 2. Comparison of Lung Nodule Follow-up Results in 4 Nodule Size Groups

Nodule size	Total	2-3 mm	4-5 mm	6-7 mm	≧8 mm	p value
Total case	252	69	96	35	52	
with f/u result	144	33	54	23	34	
f/u <1 yr	11 (7.6)	1 (3)	6 (11.1)	2 (8.7)	2 (5.9)	<0.001*
1-2 yr stable	26 (18.1)	8 (24.2)	13 (24.1)	2 (8.7)	3 (8.8)	
≥2 yr stable	61 (42.4)	17 (51.5)	25 (46.3)	11 (47.8)	8 (23.5)	
Regression	32 (22.2)	7 (21.2)	9 (16.7)	6 (26.1)	10 (29.4)	
Progression	6 (4.2)	0 (0)	1 (1.9)	2 (8.7)	3 (8.8)	
Refer at first	8 (5.6)	0 (0)	0 (0)	0	8 (23.5)	
New nodules^{+}	8 (5.6)	4 (12.1)	0	0	0	
F/u time (mo)	24.8±13.1	27.3±10.7	25.6±12.3	27.3±11.6	19.2±15.9	0.036*

Mean ±SD or n (%). *p < 0.05, $^{+}$New nodule larger than the index nodule, this is an extra result in addition to the follow-up result. f/u = follow-up, mo = month, yr = year

tients with nodules ≧6 mm, 33.3% had stable nodules for ≧2 years, and 8.8% had stable nodules for 1~2 years; 7% were followed <1 year, 28.1% had nodule regression, 8.8% had nodule progression, and 14% were transferred at first. In all, 5 patients (5.7%, 5/87) were confirmed to have lung cancer in this group (Table 3).

In summary, almost all patients with a nodule <6 mm had a benign outcome, more than 90.8% had stable nodules for ≧1~2 years or nodule regression, and only 1.1% (1 patient) had nodule progression. In contrast, patients with a nodule ≧6 mm had a higher malignancy risk, and 22.8% of them required further management (14% were transferred at first for investigation and treatment, and 8.8% had nodule progression during follow-up). However, stable nodules for ≧1~2 years or nodule regression was still common (70.2%) in this group.

The follow-up results for the Lung-RADS 2 nodules were similar to those of the <6 mm nodules. Among patients with Lung-RADS 2 nodules, 91.2% had stable nodules for ≧1~2 years or nodule regression, 1.9% had nodule progression, and none were transferred at first (Table 4).

Table 3. Comparison of Follow-up Results between Nodules <6 mm and ≧6 mm

Nodule size	2-5 mm	≧6 mm	p value
Total case	165	87	
With f/u result:	87	57	
f/u <1 yr	7 (8)	4 (7)	<0.001*
1-2 yr stable	21 (24.1)	5 (8.8)	
≥2 yr stable	42 (48.3)	19 (33.3)	
Regression	16 (18.4)	16 (28.1)	
Progression	1 (1.1)	5 (8.8)	
Referred at first	0 (0)	8 (14)	
New nodules+	4 (4.6)	0 (0)	
F/u time (mo)	26.3±11.7	22.5±14.8	0.104
Confirmed lung cancer***	0 (0)	5 (5.7)	<0.001*

Mean ±SD or n (%). *$p < 0.05$, +New nodule larger than the index nodule, this is an extra result in addition to the follow-up result, ***Percentage of confirmed lung cancer was calculated as cancer case/total case.

f/u = follow-up, mo = month, yr = year.

Table 4. Comparison of Follow-up Results between Lung-RADS Classifications

Lung-RADS	1	2	3	4A	4B	4X
Total case	123	188	28	14	10	8
With f/u result:	11	103	17	8	7	7
f/u <1 yr	1	7 (6.8)	1	1	1	0
1-2 yr stable	1	23 (22.3)	0	0	2	0
≥2 yr stable	0	52 (50.5)	6	2	1	0
Progression	0	2 (1.9)	3	0	0	1
Referred at first		0	1	1	1	5
Regression	0	19 (18.4)	6	4	2	1
New nodules*	2	7 (6.8)	0	1	0	0
F/u other finding	7	0	0	0	0	0
F/u time (mo)	12.5±3.5	26.4±11.9	29.1±12.9	24±16.4	15±11.1	4.1±7
Confirmed lung cancer	0	0	2	0	0	3

Mean ±SD or n (%). *New nodule larger than the index nodule, this is an extra result in addition to the follow-up result. f/u = follow-up, mo = month, yr = year

In addition to the thoracic region, the chest LDCT exam also included part of the cervical and upper abdominal region. The common abnormalities other than lung nodules were segmental or subsegmental atelectasis, bronchiectasis, emphysema, tiny nodules (centrilobular nodule, tree-in-bud), hepatic cyst, fatty liver, and gallbladder stone (Table 5).

Discussion

LDCT screening in this study revealed that pulmonary nodules ≧2 mm are very common (67.9%) in the general population of Taitung. Of the nodules detected by screening, 2/3 were <6 mm, and LDCT follow-up results showed that >90% of these nodules were stable for more than 1~2 years or spontaneously regressed.

Table 5. Summary of Other Image Findings

Region and findings, n					
Lung		Chest wall		Gallbladder stone	16
Segmental atelectasis	12	Rib fracture	3	CBD dilate	2
Subsegmental atelectasis	29	Bone island	3	Stomach calcification	1
Tiny nodules		Pectus excavatum	3	Hiatal hernia	1
Centrilobular nodules	13	Rib sclerosis	1	Spleen	
Tree-in-bud	13	Chest wall tumor	1	Accessary spleen	4
Cluster nodules	4	Mediastinum		Spleen nodule	5
Emphysema	18	Pulmonary trunk dilate	5	Splenorenal varices	1
Bronchiectasis	18	Mediastinal nodule/mass	8	Splenomegaly	2
Fibrosis		Aortic dilatation	2	Pancreas nodule/mass	2
Focal fibrotic change	9	Cardiomegaly	2	Spine compression fracture	1
Reticulation	4	Thyroid enlargement	5	Kyphosis	1
Honeycomb	2	Thyroid nodule	8	Breast	
Traction bronchiectasis	2	Liver		Mastectomy	1
Opacity		Fatty liver	26	Breast nodule	2
Ground-glass opacity	9	Hepatic cyst	36	Mammoplasty	2
Consolidation	3	Cirrhosis	1	Gynecomastia	3
Air trapping	1	Hepatic tumor	3		
Lung cyst	5	Kidney			
Bleb	6	Hydronephrosis	1		
Bullae	2	Renal nodule/mass	6		
Pleural plaque	9	Kidney atrophy/resection	3		
Pleural thickening	2	Renal cyst	7		
Plate-like lesion	2	Renal stone	4		
Old TB	5	Adrenal nodule/mass	5		

CBD = common bile duct; TB = tuberculosis

Only 1% (1 patient) had nodule progression at the 2-year follow-up and required further management. Therefore, this study confirmed that a 1-year follow-up interval for nodules <6 mm is reasonable. This follow-up strategy could reduce exposure to unnecessary CT exams and radiation. However, pulmonary nodules ≧6 mm were not uncommon (accounting for 1/3 of the nodules detected by screening), and had a higher probability of nodule progression and a higher malignancy risk.

The 2 largest RCTs of LDCT lung cancer screening, the NLST of the United States and the NELSON study of the Netherlands-Belgium, showed that LDCT screening can significantly reduce lung cancer mortality by 20-24% in heavy smokers [12-13]. In the NLST, 100% of the screening population were smokers (>30 pack-years and quit smoking <15 years), and in the NELSON study, as well (≧15 cigarettes a day for 25 years or ≧10 cigarettes a day for 30 years, current or ex-smokers). The NLST also showed that LDCT screening is most effective for reducing adenocarcinoma mortality, but showed no significant improvement for squamous cell carcinoma and small cell lung cancer mortality [21]. In the NLST, LDCT had higher sensitivity (93.8%) and lower specificity (73.4%) for detecting pulmonary nodules than chest X-ray (sensitivity 73.5% and specificity 91.3%) [22]. The ideal screening tool must have high sensitivity to reduce the number of false negative results. Therefore, LDCT is more effective for lung cancer screening than chest X-ray.

In the NLST of the United States, LDCT screening revealed that 24.2% of patients had pulmonary nodules ≧4 mm. However, the prevalence of pulmonary nodules in our study, as determined by LDCT, was higher (nodules ≧4 mm were found in up to 49.3% of patients). As for the lung cancer detection rate, the result in our study was comparable to that of the NLST (1.3% vs. 1.03%) [12]. The result in another LDCT screening study of the general population in Taichung City in Taiwan was similar to that of our study, in which LDCT showed nodules of ≧4 mm in 38.3% of patients, and the lung cancer detection rate was 1.02% (around 90% were early-stage adenocarcinoma) [23].

Although the air quality in Taitung is some of the best in Taiwan, LDCT screening detected a great many pulmonary nodules. Since most of the LDCT-detected nodules were benign, the prevalence of nodules may not be associated with lung cancer risk factors such as air pollution. However, the similar lung cancer detection rates between the studies in Taiwan and in the United States suggest that LDCT lung cancer screening for the general population in Taiwan should be beneficial, especially for early diagnosis of adenocarcinoma.

In fact, lung cancer in Taiwan is significantly different from that found in the United States and in Europe. In the United States, more than 90% of lung cancer patients are smokers, and the male and female smoking population is similar. In European countries, smokers account for 75% of lung cancer patients. Therefore, smokers in these countries are the major high-risk group for lung cancer. An LDCT lung cancer screening focus on this patient group is reasonable. However, a higher percentage (around 30%) of lung cancer patients in East Asia are never-smokers, and among female lung cancer patients, the never-smoker percentage is even higher (72~95%) [14]. In Taiwan, the never-smoker percentage among lung cancer patients is especially high (up to 53%). Female lung cancer patients have a much higher never-smoker percentage (92.1-93.6%) than male pa-

tients (22.9~25.5%) in Taiwan [14-15].

Although smoking has been considered as the strongest lung cancer risk factor, the literature has shown many other lung cancer risk factors, including environmental tobacco smoke, air pollution, menopausal hormone replacement therapy, cooking oil fumes, a history of tuberculosis, and low socioeconomic status [24]. In Taiwan, the association among air pollution, PM2.5, and the risk of lung adenocarcinoma is gaining more and more attention, and is worthy of further investigation.

The current American and European recommendation on LDCT lung cancer screening focuses only on the population of 55~74-year-old heavy smokers (>30 pack-years, current smoking or quit smoking <15 years) [25]. The Taiwan LDCT lung cancer screening consensus was released in 2015 by the Taiwan Lung Cancer Society [26]. It follows the guideline recommendation of Western countries, and the screening mainly of heavy smokers. As for patients with other lung cancer risk factors (lung cancer family history, occupational exposure, and radon exposure), the consensus suggests LDCT screening may be considered, but its effectiveness is unproven.

However, lung cancer patients in Taiwan are different -- half of them in a recent study were never-smokers, and most of them were female with adenocarcinoma [15]. The current recommendation will miss half of the lung cancer patients in Taiwan, and therefore, additional screening criteria are required. With the increasing incidence of adenocarcinoma [15], never-smokers may be a potential population requiring LDCT lung cancer screening, although there is not enough evidence for this yet. A multi-center study, the Taiwan Lung Cancer Screening study, is ongoing to evaluate LDCT screening in never-smokers, and to evaluate lung cancer risk factors including cooking, lung cancer family history, second-hand smoke, and chronic lung diseases [16]. A total of 10,397 never-smokers have been enrolled in the study, and the results will be reported in the near future.

Small pulmonary nodules are quite commonly detected by LDCT, and the strategy of nodule follow-up is an important issue. A shorter follow-up interval may result in increased medical costs and radiation exposure. However, a longer follow-up interval may increase the risk of delay in the diagnosis and treatment of lung cancer. How to choose an ideal LDCT follow-up interval to balance the benefit and adverse effects is a clinical dilemma. In this study we showed that in patients with small pulmonary nodules <6 mm, >90% had stable nodules for ≧1~2 years or regression, and only 1% of patients had nodule progression (progression occurred at 2 years). The NELSON study in Europe also showed similar follow-up results: as much as 98.1% of LDCT-screened patients with nodules had nodule volume doubling time (VDT) of >600 days, 0.6% had VDT of 400~600 days, and only 1.3% had VDT of <400 days [29]. Therefore, most of the LDCT-detected small nodules had a benign pattern (stable or regressed), and for nodules <6 mm, a 1-year follow-up time interval should be reasonable.

The NCCN 2020 guideline [27] and the American College of Radiology Lung-RADS 2019 [20] have similar LDCT follow-up recommendations for small pulmonary nodules in heavy smokers, and are summarized below. For solid nodules <6 mm: a 12-month LDCT follow-up; for solid nodules of 6~7 mm: a 6-month follow-up. As for part-solid nodules <6 mm, a 12-month follow-up; for part-solid nodules ≧6 mm and solid components <6 mm, a

6-month follow-up. And, for ground-glass nodules <20~30 mm, a 12-month follow-up. On the other hand, for the never-smoker population, the Radiology 2017 guideline suggests that for pulmonary nodules <6 mm (no matter whether solid, part-solid or ground-glass) and with low-to-medium lung cancer risk, there is no need for LDCT follow-up [28]. However, unlike Western countries, in which most lung cancer patients were smokers, half of the lung cancer patients in Taiwan were never-smokers. Therefore, the Radiology 2017 guideline suggestion of no follow-up of small pulmonary nodules in never-smokers should not be applied directly to LDCT-screened patients in Taiwan.

How long a stable pulmonary nodule should be followed is also an important issue. The NCCN 2020 guideline suggests heavy smokers should maintain annual LDCT follow-up for stable nodules, until the patient can no longer tolerate curative surgery (early diagnosis of lung cancer is meaningless because the patient is unable to undergo surgery) [27]. Even for heavy smokers without a nodule on LDCT, the NCCN 2020 and Lung-RADS 2019 still recommend annual LDCT screening, because these patients are at high risk of developing new lung cancer in the following years [20,27]. As for never-smokers, the Radiology 2017 guideline suggests that stable solid nodules should be followed up for 2 years, and that since part-solid and ground-glass nodules have a slower growth rate, they should be followed up for at least 5 years, and the follow-up interval can gradually be lengthened to 2 years [28].

LDCT detects more early-stage lung cancers and reduces cancer mortality, but it cannot prevent lung cancer. The lack of evidence of a pulmonary nodule does not guarantee there will be no lung cancer development in the future. Eliminating lung cancer risk factors by quitting smoking, for example, should be combined with LDCT screening. Although the prevalence of LDCT-detected pulmonary nodules is high, the lung cancer diagnosis rate is only around 1%. Therefore, the false positive rate of LDCT screening is very high (>96%) [12]. Many patients with screening-detected nodules do not require tissue biopsy, but long-term LDCT follow-up is required, and this also increases the patient's emotional stress and anxiety. A careful and clear explanation by the physician is important to avoid unnecessary exams and invasive procedures.

This study has several limitations. First, this was a retrospective study at a single local hospital, and the LDCT features presented in this study may not represent those of the whole population of Taiwan. Second, the LDCT follow-up rate of patients with LDCT-detected pulmonary nodules ≧2 mm was only 57%, and this may have influenced the study results. Third, the lung cancer detection rate in this study was 1.3%, but there were 6 cases with an unknown transferal result. Therefore, the exact lung cancer detection rate may be higher. Fourth, we did not have mortality data. Fifth, the information on lung cancer staging was unknown; however, based on the nodule size at transferal, these LDCT-detected lung cancers should be in the early stage).

In conclusion, this LDCT study showed that pulmonary nodules were very common, and were detected in 2/3 of the general population screened in Taitung. Among these nodules, 2/3 were <6 mm, and LDCT follow-up showed that >90% of the nodules were either stable for ≧1~2 years or spontaneously regressed. However, nodules ≧6 mm were also common, and were detected in nearly 1/4 of the population.

This study also showed that a 1-year follow-up interval for nodules <6 mm is a reasonable strategy, and can reduce both the number of LDCT exams and radiation exposure. Even in a region with the best air quality in Taiwan, LDCT may still be an effective lung cancer screening tool for the general population.

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Change in End-Expiratory Lung Volume in Response to PEEP Adjustment and Extubation Outcome among Mechanically Ventilated Patients

Shih-Yu Chen[1], Hui-Chuan Chen[2], Sheng-Yuan Ruan[1], Chun-Ta Huang[1]
Jung-Yien Chien[1], Ping-Hung Kuo[1], Huey-Dong Wu[1]

Introduction: End-expiratory lung volume (EELV) is measured at the average end-expiratory level in patients on mechanical ventilation. EELV may substantially change after altering positive end-expiratory pressure (PEEP) levels. The change in EELV between different PEEP levels before extubation may serve as a predictor for extubation outcome.

Methods: This prospective observational study enrolled 75 intubated patients ready for extubation. EELV was measured at different PEEP levels before extubation using the nitrogen breath washout method. Areas under the receiver operating curve (AUROC) were used to evaluate the discriminative capacity of EELV for extubation outcome.

Results: The median age of the study cohort was 71 [IQR, 58-81] years, and pneumonia (60%) was the leading cause of respiratory failure. After extubation, 12 patients (16%) required reintubation within 48 hours. The EELV measured at a PEEP of 5 cm H_2O was significantly higher than that measured at zero-PEEP (25.5 mL/Kg versus 23.3 mL/Kg, *p<0.001*). The successfully extubated patients had a greater change in EELV than those with extubation failure (2.8 mL/Kg versus 0.9 mL/Kg, *p=0.09*). The discriminative capacity for the change in EELV was only acceptable in the total cohort (AUROC, 0.65, 95% CI, 0.49-0.82). Subgroup analysis was performed for different etiologies of respiratory failure.

Conclusion: The change in EELV in response to PEEP adjustment was not a good predictor for extubation outcome in an unselected population, although the change in EELV appeared greater in successfully extubated patients than in patients with extubation failure. ***(Thorac Med 2020; 35: 178-185)***

Key words: mechanical ventilation, end-expiratory lung volume (EELV), functional residual capacity (FRC), weaning parameters

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan, [2]Division of Respiratory Therapy, Department of Integrated Diagnostic and Therapeutics, National Taiwan University Hospital, Taipei, Taiwan,
Shih-Yu Chen and Hui-Chuan Chen contributed equally to this work.
Address reprint requests to: Dr. Sheng-Yuan Ruan, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan.

Introduction

Invasive mechanical ventilation is increasingly used worldwide [1-2]. More than 70% of mechanically ventilated patients were able to survive the critical illness and start weaning trials [3]. After planned extubation, 10-20% of patients would require reintubation, and reintubation was subsequently linked to a poor outcome [4]. Previous studies have proposed various predictors to identify those patients at high risk for extubation failure [5]. These parameters were derived from patients' clinical conditions such as age, vital signs, and nutrition status, respiratory parameters such as respiratory compliance, laboratory data such as PaO_2/FiO_2, and comorbidities [5-6]. Among these factors, respiratory parameters are of great interest because they are a direct measure of respiratory system functioning in mechanically ventilated patients.

End-expiratory lung volume (EELV) is a measure of aerated lung volume at the average end-expiratory level [7-8]. Our previous work showed that pre-extubation EELV was associated with weaning outcome, and reduced EELV was linked to an increased risk of extubation failure [9]. Another pilot study by Heinze and colleagues showed that EELV decreased in parallel with PaO_2/FiO_2 ratios during the weaning process with positive end expiratory pressure (PEEP) down titration [10]. The data from these pilot studies suggest that EELV may be a useful parameter for predicting weaning outcome [9-10]. In this study, we aimed to evaluate the association between the change in EELV in response to PEEP adjustment and extubation outcome. We hypothesized that the change in EELV between a PEEP of 5 cm H_2O and zero-PEEP would be parallel to distensibility of the lung, and higher distensibility might indicate better recovery from the airspace occupying diseases causing the index respiratory failure.

Materials and Methods

Study design and data collection

This prospective cohort study was conducted in medical intensive care units in National Taiwan University Hospital, Taipei, Taiwan, from November 2016 to December 2017. We enrolled adult mechanically ventilated patients who were considered ready to be liberated from mechanical ventilation. EELV was measured before the planned extubation using a standardized protocol provided in the following section. The study design and flow are illustrated in Figure 1. The inclusion criteria were adults older than 18 years old, intubation due to hypoxemic

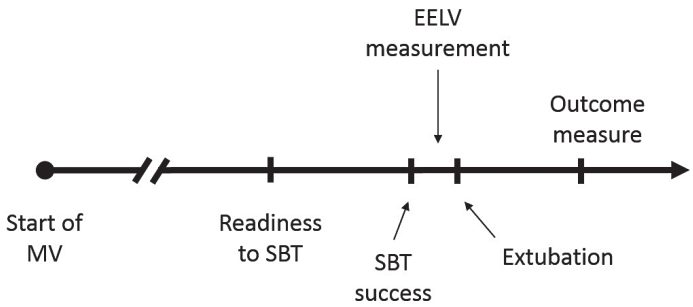

Fig. 1. Study process and timing for EELV measurement.

respiratory failure, having received mechanical ventilation for more than 48 hours, passing a spontaneous breathing test and being considered ready for extubation by primary care physicians. The exclusion criteria were intubation for hypercapnic respiratory failure, requiring an artificial airway for medical reasons, having a do-not-resuscitation order and refusal to reintubate after extubation. The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital (No. 201606049RINB). Written informed consent was obtained from each participant or their next of kin.

Weaning protocol

All patients were supported by Engstrom ventilators (GE Healthcare, Chicago, USA) throughout the study period. They received daily screening for weaning readiness and the spontaneous breathing trial (SBT) was initiated once patients met the following criteria: (1) hemodynamic stability without vasopressors, (2) able to follow simple commands with adequate cough and inspiratory effort, (3) FiO_2 ≤40%, (4) PEEP ≤8 cmH_2O, (5) PaO_2 ≥75mmHg, (6) pH >7.25, (7) no worsening of non-pulmonary organ systems and (8) approval by the primary care physician. An SBT was determined to be either a success or a failure based on the weaning guideline of Boles *et al*. [11]. A cuff-leak test was performed during the weaning period. The decision to extubate was made by the primary care physicians. There was no routine use of prophylactic noninvasive positive pressure ventilation or a high-flow nasal cannula after extubation in the study hospital.

Measurement of end-expiratory lung volume (EELV)

EELV was measured using the FRC INview^{TM} tool (GE Healthcare, Chicago, USA), based on the nitrogen multiple breath washout technique. EELV was determined by the change in lung nitrogen volume after a change of at least 10% in the inspired oxygen fraction. We used a standardized procedure to measure EELV [9]. Before the measurement of EELV, the patients were put in a semi-recumbent position at 45^{o} and ventilated with pressure support of 5 cm H_2O. The cuff pressure of the endotracheal tube was checked to prevent air leakage, and endotracheal suction was performed to remove possible airway secretions. The humidifier was temporarily off during the measurement. The measured value of EELV was read through the FRC INviewTM tool after a steady state had been maintained for 10 minutes. EELV was checked twice, and the whole process would be repeated once the variation in those 2 values exceeded 25%. The procedure was repeated after another steady state for at least 10 minutes. The mean of the 2 measured values was recorded as the patients' EELV value. After the measurement, PEEP was switched to 0 cm H_2O. Then, the same measurement process was repeated to obtain the EELV at zero-PEEP. EELV5 and EELV0 were defined as EELV measured at a PEEP of 5 and 0 cm H_2O, respectively. Parts of the EELV5 data were published in our previous work [9].

Because there are no established reference values of EELV, we reported both the absolute values of EELV and the ratio of EELV to predicted body weight (EELV/pBW). Predicted body weight was estimated using the formula suggested by the Taiwan Health Promotion Administration for adult Taiwanese, as follows: (height [cm]–80)* 70% for men and (height [cm]–70)* 60% for women.

The change in EELV between a PEEP of 5 and 0 cm H_2O was calculated as EELV5 – EELV0, in which EELV5 and EELV0 denote EELVs measured at a PEEP of 5 cm H_2O and zero-PEEP, respectively. EELV delta (%) was defined as (EELV5 – EELV0)/[(EELV5 + EELV0)/2].

Data collection and outcome measure

Patient demographics, etiology of respiratory failure, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, hemogram and arterial blood gas data on extubation day, the date of intubation, extubation ICU admission and ICU discharge, weaning parameters, extubation outcome and vital status at hospital discharge were recorded. The primary outcome was extubation success, defined as remaining ventilator-free and alive 48 hours after extubation [12].

Statistical analysis

Demographic data were expressed as mean with standard deviation (SD), medians with interquartile range (IQR) or number with proportion, as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test or Wilcoxon signed-rank test. Categorical data were compared using the Chi-square test or Fisher's test. The logistic regression model was used to evaluate the association between EELV and extubation outcome. Discriminative capacity of EELV for extubation outcome was determined by the area under the receiver operating characteristic curve (AUROC). Point estimates and corresponding 95% confidence intervals (95% CI) were reported. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 15 software (StataCorp, LLC, TX).

Results

Characteristics of the study cohort

A total of 75 patients were enrolled. The median age was 71 (IQR, 58-81) years and 59% were male. The etiologies of hypoxemic respiratory failure were pneumonia (60%), lung edema (10.7%) and lung cancer (8%). Median duration of mechanical ventilation before extubation was 7 days (IQR, 4-11). After extubation, 12 (16%) of the 75 patients required reintubation within 48 hours (Table 1).

EELV5, EELV0 and Change in EELV (delta-EELV)

The median EELV5/pBW and EELV0/pBW were 25.5 ml/kg (IQR, 17.6-33.6 ml/kg) and 23.3ml/kg (IQR, 16.6-29.9 ml/kg), respectively ($p<0.001$). Figure 2 shows the EELV0, EELV5 and delta-EELV values in patients with extubation failure and success. EELV0 and EELV5 were both greater in the group with extubation success (24.7 mL/Kg [IQR, 17.6-30.9] and 27.2 mL/Kg [IQR, 19.4-34.8]) than in the group with extubation failure (15.2 mL/Kg [IQR, 11.2-21.8] and 16.7 mL/Kg [IQR, 11.2-20.6]). There was a trend showing that successfully extubated patients had greater delta-EELV than those with extubation failure (2.8 mL/Kg [IQR, 0.1-6.6] versus 0.9 mL/Kg [IQR, -2.5-2.6], $p=0.09$). Logistic regression models revealed that delta-EELV was likely associated with extubation outcome (odds ratio, 1.13, 95% CI, 0.98-1.30).

Figure 3 shows the probabilities of extubation success under conditions stratified by baseline EELV5 and delta-EELV. Patients with a higher EELV5 (defined as greater than median) and delta-EELV >20% had the best extubation outcome in this study cohort. In contrast, patients with a lower LLEV5 and less EELV

Table 1. Characteristics of the Study Cohort

	Extubation Success (n=63)	Extubation failure (n=12)	*P* value
Age, yr, median (IQR)	70 (57-78)	74.5 (65-83)	0.33
Male gender, n (%)	38 (60.3)	6 (50)	0.51
BMI, mean (SD)	22 (3.7)	23.9 (6.1)	0.44
Apache II score, mean (SD)	22.2 (5.8)	24.7 (5.8)	0.16
Duration of mechanical ventilation, days (IQR)	7 (4-10)	9 (3.5-17)	0.34
Frequency of SBT before extubation, median (IQR)	2 (1-3)	2 (1-3)	0.69
Causes of hypoxemic respiratory failure, n (%)			
Pneumonia	39 (61.9)	6 (50)	0.92
Lung edema	6 (9.5)	2 (16.7)	
Lung cancer	5 (7.9)	1 (8.3)	
Cardiac arrest	3 (4.8)	1 (8.3)	
Others	10 (15.9%)	2 (16.7%)	
Respiratory parameters before extubation			
RSBI, median (IQR)	63(42-88)	81(65-105.5)	0.03
Minute ventilation, L/min (IQR)	8.2 (6-10.6)	6.7 (4.5-12.3)	0.40
Maximal inspiratory pressure, cm H_2O, mean (SD)	37.4 (9.7)	37.5 (6.9)	0.45
Maximal expiratory pressure, cm H_2O, mean (SD)	36.6 (10.8)	37.3 (9.1)	0.78
PaO_2/FiO_2 ratio, mean (SD)	360.7 (95.4)	298.8 (77.6)	0.04
PaO_2, mmHg, mean (SD)	108.6 (25.8)	94.4 (20.4)	0.07
PCO_2, mmHg, mean (SD)	34.4 (6.2)	34.8 (9.9)	0.78

APACHE, Acute Physiologic And Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; IQR, interquartile range; RSBI, rapid shallow breathing index; SD, standard deviation; SBT, spontaneous breathing trial.

change had the worst outcome.

Discriminative capacity of EELV5, EELV0 and delta-EELV

Figure 4A shows the ROC curves of EELV5/pBW, EELV0/pBW and delta-EELV/pBW for the total cohort. The AUROCs were 0.66 (95% CI, 0.49-0.82) for delta-EELV, 0.76 (95% CI, 0.59-0.92) for EELV0, and 0.77 (95% CI, 0.61-0.93) for EELV5, but their differences did not reach statistical significance (*p=0.20*). In the subgroup of patients intubated for diseases sensitive to PEEP (11 fluid overload and 4 cardiogenic collapse), delta-EELV revealed greater discriminative capacity than EELV5 and EELV0 (Figure 4B).

Discussion

This prospective study evaluated the role of EELV and change in EELV in response to PEEP adjustment in predicting extubation outcome.

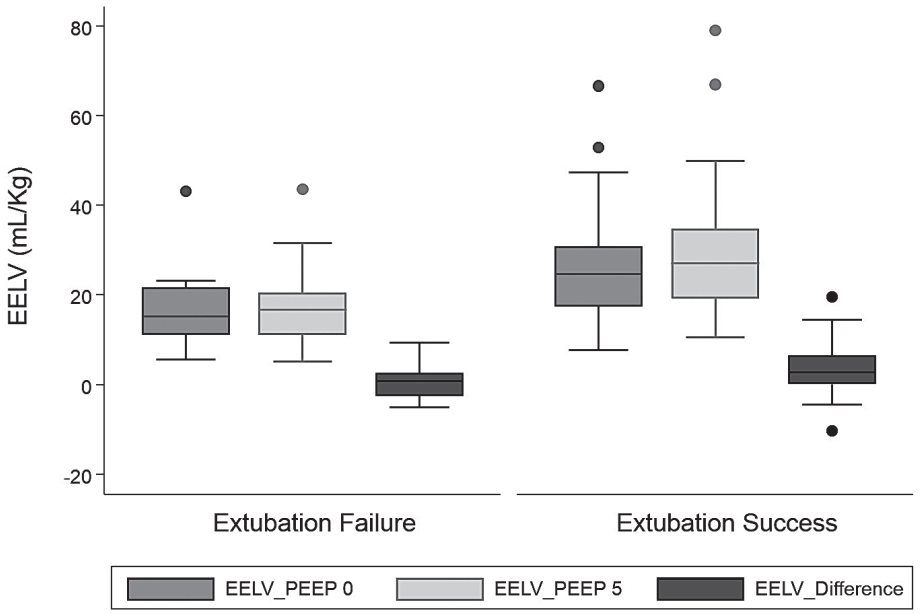

Fig. 2. Box plots of EELV/pBW measured at a PEEP of 5 and 0 cm H_2O, and the difference in EELV between a PEEP of 5 and 0 cm H_2O in patients with extubation failure and success.

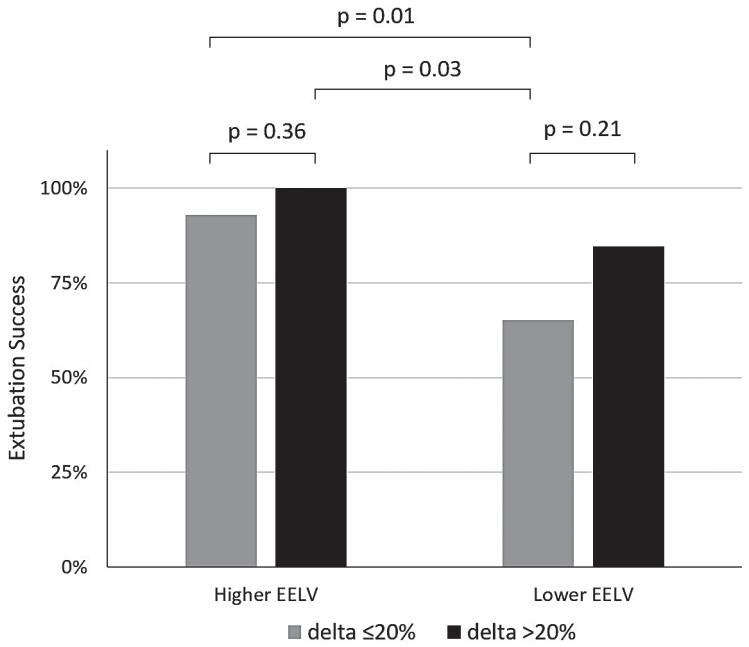

Fig. 3. Probabilities of extubation success in patient subgroups stratified by EELV5 and change in EELV.

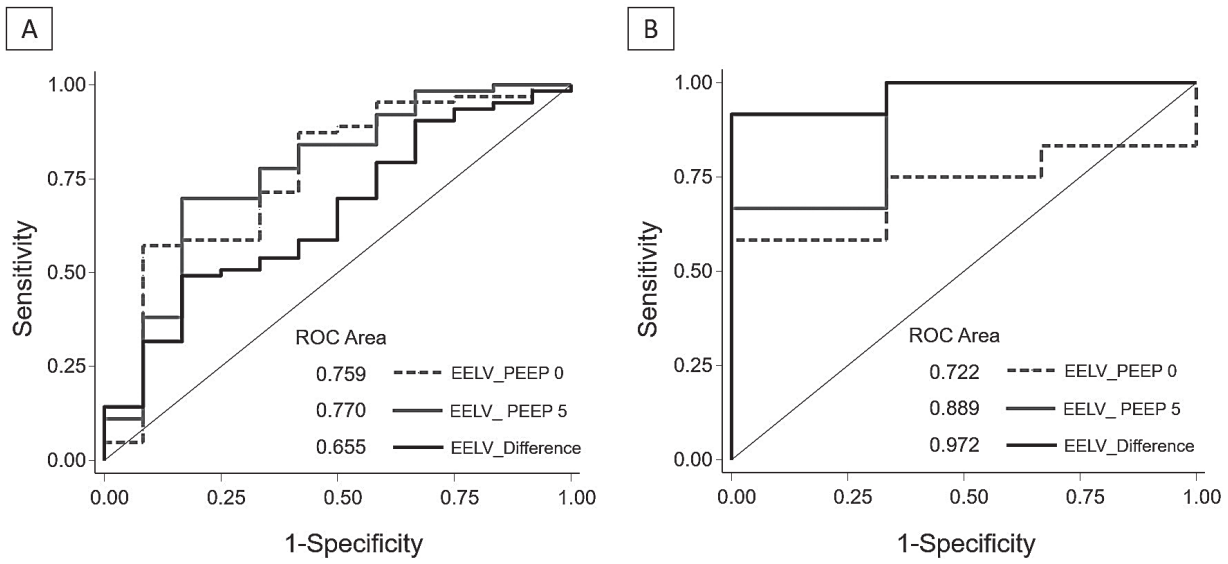

Fig. 4. (A) Area under receiver operating characteristic curves (AUROCs) for discrimination capacity for extubation success in the total cohort. (B) AUROCs for discrimination capacity for extubation success in subgroups of patients with diseases sensitive to PEEP.

The study findings suggested that a change in EELV between a PEEP of 5 and 0 cm H_2O was not a good predictor for extubation outcome in an unselected patient population, because the discriminative capacity was less than 0.7. However, its discriminative capacity was excellent in selected patients with diseases sensitive to PEEP. Nevertheless, these findings require further validation since our study was underpowered to test statistical significance in the subgroup analysis.

EELV represents the aerated lung volumes at the average end-expiratory level in mechanically ventilated patients [13]. Reduced EELV is usually encountered in hypoxemic situations such as alveolar collapse, pulmonary edema and reduced thoracic compliance [14-15]. Our previous work found that pre-extubation EELV is well correlated to extubation outcome. In this study, we assumed that the change in EELV at different PEEP levels was a better predictor of extubation outcome than a single measure of EELV. However, we did not find that delta-EELV outperformed EELV in predicting extubation outcome. The result remained the same even when EELV change was further divided into groups of significant change (>20%) and no change (≤ 20%). However, patients who had significant change in EELV appeared to have more successful extubation rates (100% vs 92.9% in the higher EELV group and 84.6% vs 65.2% in the lower EELV group). In a study conducted by Lindner and colleagues, patients under continuous positive airway pressure (CPAP) needed end-expiratory pressure of 12 cm H_2O for better lung recruitment. Heinze *et al*. found that decreased FRC correlated with a decreased P/F ratio by titrating PEEP from 10 mbar to 7 mbar under both biphasic positive airway pressure and CPAP support. It is noteworthy that the participants in both studies were surgical patients with normal lungs [10,16]. In our study, all included patients had diseased lung, and the 5 cm H_2O difference in the PEEP

level might be too small to make a substantial change in EELV.

There are limitations to this study. (1) The measurement of EELV is easily affected by patient and environmental factors, such as body position, intraabdominal pressure, and the ventilator circuit. Even using a standardized measurement protocol, intra-operator variability may be significant. (2) Because of the limitation of sample size, this study was underpowered to test statistical significance in the subgroup analysis.

Conclusion

EELV could be easily measured at bedside using the nitrogen breath washout method. Although pre-extubation EELV has been shown to be a good predictor of weaning outcome, the change in EELV to PEEP did not show a good discrimination capacity for extubation outcome in this study. However, its discrimination capacity improved in selected patients with diseases sensitive to PEEP.

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Management for Recurrent Primary Spontaneous Pneumothorax after Repeated Surgery

Chen-Hao Hsiao[1,2], Jin-Shing Chen[3]

Introduction: Conservative treatment is advised mainly for the first episode of primary spontaneous pneumothorax. Surgery is reserved for recurrence, or in some instances, for the first episode of primary spontaneous pneumothorax. Repeated surgery is also suitable for treating recurrent pneumothorax after the initial surgery. Nevertheless, some patients still experience subsequent recurrence even after having undergone repeated surgery. Our aim in this study was to investigate the proper treatment for these patients.

Methods: Primary spontaneous pneumothorax patients were retrospectively reviewed from January 2005 to December 2009. Patients who developed subsequent recurrence after repeated surgery for pneumothorax were included. Patients then received conservative treatment or underwent surgery. All patients were followed up for 5 years or until there was a subsequent recurrence. Recurrence-free survival was analyzed.

Results: A total of 38 patients were included in our study. Twenty patients underwent surgery, and 18 received conservative treatment. Twelve patients developed subsequent recurrence. The median body mass index was significantly lower in patients with recurrence than in those without (p value=0.026). Thirty percent of patients who underwent surgery developed subsequent recurrence, and 33.3% of those who received conservative treatment developed subsequent recurrence. The 5-year recurrence-free survival rate was not significantly different between the surgery and conservative treatment groups (p value=0.707).

Conclusion: Patients rarely develop recurrence after repeated surgery for pneumothorax. The patient's body mass index might be associated with subsequent recurrence. Conservative treatment might be an alternative that is not inferior to surgery in preventing subsequent recurrence in these patients. ***(Thorac Med 2020; 35: 186-195)***

Key words: pleural disease, pneumothorax

[1]Genome and Systems Biology Degree Program, National Taiwan University and Academia Sinica, Taipei, Taiwan, [2]Department of Surgery, Cheng Hsin General Hospital, Taipei, Taiwan, [3]Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.
Address reprint requests to: Dr. Jin-Shing Chen, Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan.

Introduction

Kjærgaard first described pneumothorax occurring in heathy people in 1932, and primary spontaneous pneumothorax (PSP) is still common in young individuals worldwide, with a male predominance [1-5]. The age-adjusted incidence of PSP is 7.4/100,000 per year for men and 1.2/100,000 per year for women [3]. The male-to-female ratio is 2.7:1 to 6.2:1 [3-5]. Simple aspiration and chest drainage are advised as first-line management strategies for the first episode of PSP [6-8]. However, the recurrence rate is approximately 30% (range, 20-60%), and it increases with each subsequent episode [4-10]. The association between body mass index (BMI) and PSP recurrence is controversial, but recurrence is more common in tall men and women [3, 9, 11-14].

Surgery is reserved for recurrent pneumothorax, synchronous bilateral spontaneous pneumothorax, and other conditions [6-8]. Some retrospective studies and review articles have reported that video-assisted thoracoscopic surgery (VATS) is better than conservative treatment for managing the first episode of PSP [10, 15-19]. A recent clinical trial has suggested that surgery may have the benefit of preventing recurrence after the first episode of PSP [20]. Chemical pleurodesis is also recommended for nonresolving pneumothorax or ongoing air leakage during the second occurrence if patients are unwilling or unable to undergo surgery [6-8]. Ipsilateral recurrent PSP occasionally occurs after VATS, and repeated VATS is thought to be a feasible treatment in these cases [21-22], but some patients experience ipsilateral recurrent PSP after repeated VATS. There is no clear suggested treatment for this kind of patient. Therefore, we investigated the effects of surgery versus conservative treatment on this kind of PSP patient.

Methods

The study was a retrospective observational study of PSP patients. The Institutional Review Board of National Taiwan University Hospital approved the study. The requirement for informed consent was waived because of the retrospective nature of the study. Patients who presented with their first episode of PSP from January 2005 to December 2009 were retrospectively identified. These patients underwent VATS when the first and second PSP occurred, and then underwent VATS or received conservative treatment for the third PSP. After the third PSP, patients were followed up annually for 5 years until a PSP recurred.

Eligibility Criteria

Patients were recognized as eligible for inclusion based on the following criteria: aged between 15 and 50 years old, having undergone VATS twice for ipsilateral pneumothorax, and having had full lung expansion on a chest roentgenogram before discharge. Exclusion criteria were as follows: having an underlying lung disease, congenital disorder, previous ipsilateral thoracic surgery not for PSP, or familial spontaneous pneumothorax, refused or did not receive treatment, and lost to follow-up.

Treatment

Patients received conservative treatment or underwent surgery for the third PSP. Conservative treatments included a small-bore pigtail catheter for drainage with intrapleural minocycline pleurodesis (IMP) or simple aspiration [23]. The surgical methods were VATS partial

resection for blebs or bullae with pleural abrasion or pleurectomy.

Assessment

Recurrence-free survival (RFS) was assessed from the date of discharge after the previous PSP to the date of a subsequent recurrent PSP or after 5 years of follow-up. The patients were evaluated every week after discharge for 1 month and annually thereafter for 5 years. Follow-up evaluations included history-taking, physical examination, and chest roentgenogram.

Results

A total of 1,175 patients presented with their first PSP from January 2005 to December 2009. In all, 141 of the 1175 patients received repeated surgeries for PSP; 38 developed subsequently recurrent PSP and were included in our study. After undergoing surgery or receiving conservative treatment for their third PSP, the patients were followed up annually for 5 years. The last patient completed the 5-year follow-up in 2018. The first and second PSPs in these patients occurred on the same side. VATS was performed for the first and second PSPs. The third PSP occurred later. There were 35 men and 3 women, with a male-to-female ratio of 11.7:1. The median age was 20 years (range, 15 to 44 years); median height was 1.77 meters (range, 1.58 to 1.88 meters); median weight was 57.5 kilograms (range, 41 to 74 kilograms); and median BMI was 17.8 (range, 15.32 to 22.84). Three patients had a history of smoking. In total, 22 patients presented with left-side pneumothorax, and 16 presented with right-side pneumothorax. The symptom was chest pain in all patients. The median follow-up time was 60 months (range, 0.63 to 60 months).

The demographic characteristics, treatments, and outcomes of these 38 patients are shown in Table 1. There were 20 patients in the surgery group and 18 in the conservative treatment group. The sex, age, height, weight, BMI, smoking history, side involvement, symptoms, and percentage of pneumothorax did not differ between the groups. The patients had no systemic disease. The changes in atmospheric pressure during the 72 hours before the diagnosis date were not statistically significant between the 2 groups. Seventeen patients received pigtail drainage with IMP in the conservative treatment group. In the surgery group, most patients underwent VATS partial resection with pleural abrasion. The median duration of operation was 105.5 minutes (range, 80 to 138 minutes). However, 8 patients (40%) had postoperative persistent air leak, with a median duration of 4 days (range, 1 to 5 days). The surgery group had significantly more days of hospitalization than the conservative treatment group. Twelve patients developed recurrent PSP, and all recurrences were ipsilateral. Three of the 12 patients received further surgery, and 9 patients received conservative treatment. There were no mortalities in either group. The differences between the 2 groups in terms of recurrences were not significant.

For the second PSP of these 38 patients, the resected lesions were blebs in 5 patients and bullae in 33. For the third PSP, 6 patients in the surgery group later developed recurrent PSP. The resected lesions for the second and third PSPs in these 6 patients were bullae. As for the third PSP lesions, all 6 patients had pleural fibrosis, and 4 of the 6 patients also had mesothelial cells proliferation. In the conservative treatment group, the pathology of the third PSP lesions was unavailable. The patients

Table 1. PSP Patients' Characteristics, Treatments, and Outcomes

	Surgery Group (n=20)	Conservative Treatment Group (n=18)	*p* value
Gender			
Male	18	17	
Female	2	1	0.6119
Age (years)			
Median	21	19.5	
Range	15-40	15-44	0.8066
Height (meters)			
Median	1.76	1.775	
Range	1.60-1.88	1.58-1.87	1.0000
Weight (kilograms)			
Median	57	58	
Range	45-68	41-74	0.6325
Body mass index			
Median	17.86	17.52	
Range	15.87-22.20	15.32-22.84	0.3909
Smoking	1	2	0.5946
Involved side			
Left	11	11	
Right	9	7	0.9586
Symptom			
Chest pain	20	18	
Dyspnea	0	0	1.0000
Atmospheric pressure change (hPa*)			
Median	5.2	5.0	
Range	2.3-16.7	2.5-9.5	0.4534
Percentage of pneumothorax (%)$			
Median	47.5	45.5	
Range	37-62	33-58	0.2634
VATS+		N/A	N/A
Partial resection and pleural abrasion	16		
Partial resection and pleurectomy	4		
Conservative treatment	N/A		N/A
Pigtail drainage with IMP#		17	
Simple aspiration		1	
Hospital stay (days)			
Median	5	4	
Range	3-9	2-6	0.0123
Subsequent ipsilateral recurrence	6	6	1.0000
Mortality	0	0	1.0000

* Hectopascal = hPa. The data on local atmospheric pressure was obtained from the Taiwan Central Weather Bureau.

$ Percentage of pneumothorax was estimated using Light's formula.

+ VATS: video-assisted thoracoscopic surgery

IMP: intrapleural minocycline pleurodesis

whose resected second PSP lesions were bullae subsequently developed PSP after conservative treatment. Univariate analyses showed that smoking, the involved site, treatment, age, and height had no significant effect on the risk of recurrence (Table 2). Men and patients with bullae predominantly developed recurrences, but the effects were not significant. Weight also affected the risk of recurrence. Of the 38 patients, BMI was significantly lower in patients with recurrence than in those without. Multivariate logistic regression showed that sex and PSP lesion had no significant effect on recurrence. However, BMI had a significant effect on the risk of recurrence (Table 3).

The mean RFS and standard deviations in

Table 2. Univariate Analyses for Recurrences

Risks	Recurrences n (%)		*p* value
Gender			
Male	10 (28.6)		
Female	2 (66.7)		0.2295
Smoking			
Yes	0 (0)		
No	12 (34.3)		0.5377
Involved side			
Left	6 (27.3)		
Right	6 (37.5)		0.7249
Second PSP lesions			
Blebs	0 (0)		
Bullae	12 (36.4)		0.1583
Third PSP lesions*			
Blebs	0 (0)		
Bullae	6 (35.3)		0.5211
Treatment			
Conservative	6 (33.3)		
Surgery	6 (30.0)		1.0000
	Yes (median)	No	
Age	21	20.5	0.5784
Height (meters)	1.80	1.765	0.7735
Weight (kilograms)	56.0	57.5	0.1140
BMI	17.29	18.21	0.026

* Third PSP lesions were available in the surgery group only.

Table 3. Multivariate Logistic Regression Analyses for Recurrences

Variables	Regression coefficient (B)	Significance	Odds ratio exp (B)
Gender	2.550	0.161	12.807
Second PSP lesion	-20.467	0.999	0.000
BMI	-0.871	0.041	0.419
Constant	26.841	0.999	

the conservative treatment group and surgery group were 43.21 ± 5.85 months and 47.62 ± 4.38 months, respectively. In the conservative treatment group, the 1-year and 5-year RFS rates were 72.2% and 66.7%, respectively. In the surgery group, the 1-year and 5-year RFS rates were 95% and 70.0%, respectively. The RFS rate was not significantly better in the surgery group than in the conservative treatment group after a 5-year follow-up.

Discussion

Patients traditionally receive observational treatment for the first episode of PSP [6-8]. Sometimes, surgery may be considered for the first episode of PSP to prevent recurrence [10, 15-20]. Repeated surgery is also thought to be effective management for patients with a second episode of PSP [21-22]. However, some patients develop a third episode of PSP, even if they previously underwent surgery twice. These patients may question the efficiency of further surgery, and this is a challenge for surgeons to address. Also, repeated surgeries after adequate pleurodesis would result in difficulty performing another operation. In our study, patients that underwent surgery for the third PSP had a prolonged hospital stay, and some of the patients developed postoperative persistent air leak. There are some issues that should be discussed regarding this type of patient. First, are there risk factors associated with the subsequent recurrence? Second, does conservative treatment have a higher recurrence rate than surgery? Third, should patients undergo a third surgery for recurrent PSP? The American College of Chest Physicians and the British Thoracic Society have published recommendations for the management of spontaneous pneumothorax [6-7]. However, there are no specific guidelines on how to deal with these patients because of the low postsurgical recurrence rates.

In our study, 38 patients presented with recurrent PSP after receiving 2 surgeries. Twelve patients (31.6%) developed subsequent recurrence after surgery or conservative treatment. Men predominantly had PSP, but their recurrence rate was lower than that of women. This bias may be due to the small number of included female patients. The main finding of our study was that BMI was a risk factor associated with subsequent recurrence. Patients who developed subsequent recurrence had lower BMIs than those without subsequent recurrence. Previous studies have reported a relationship between BMI and PSP recurrence [13-14]. The reason may be the increasing negative pleural pressure because of body height, or it may be related to bullae formation [14,24]. However, height and the presence of bullae did not have significant effects on recurrence in our study.

A possible reason for our finding is an α1-antitrypsin deficiency caused by poor nutrition or energy. A deficiency in α1-antitrypsin may lead to emphysematous changes responsible for subsequent recurrence [9,25]. Although some authors have suggested that changes in atmospheric pressure may cause the onset of PSP, there was no significant difference in the changes in atmospheric pressure between the 2 groups (Table 1) [26-28]. The changes in atmospheric pressure were also smaller than those in a previous study [28].

There are many factors that may affect PSP recurrence. Different treatment methods may lead to different recurrence rates [10-13,15-20]. In our study, nearly half of the patients (47.4%) received conservative treatment instead of undergoing surgery. Patients that have undergone surgery might hesitate to undergo surgery again. Although surgery is recommended for recurrent PSPs, the recurrence rates were not significantly different between the 2 groups (Table 2). Also, RFS was not significantly different between the 2 groups (Figure 1). Surgery has shown an ef-

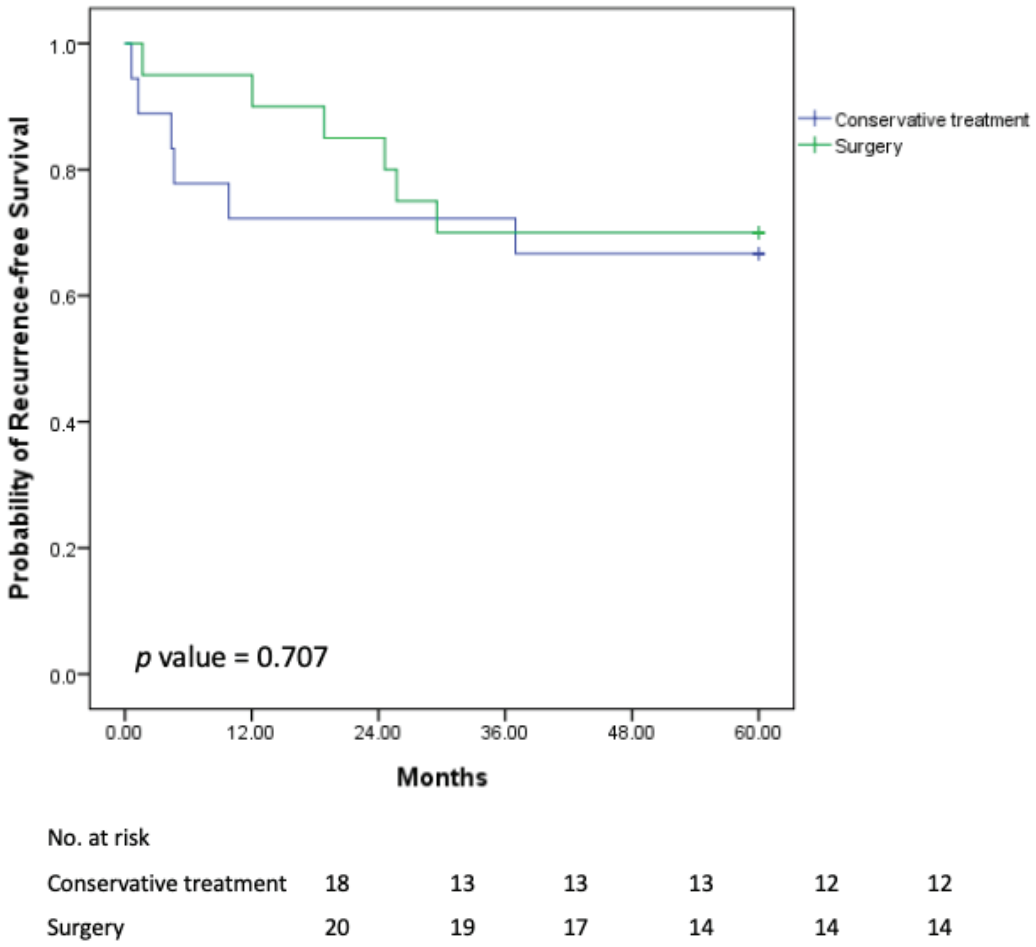

Fig. 1. Kaplan-Meier curves for recurrence-free survival in the conservative treatment and surgery groups.

fect on preventing subsequent recurrence [6-8], but the effect was not significant in our study. A possible explanation for this is that these patients might have had underlying characteristics that made them prone to developing PSP. Although the patients underwent surgery to resect bullae, new lesions developed later. Therefore, the surgical effects might not have been sufficient to prevent subsequent recurrence in these patients.

Of the 18 patients in the conservative treatment group, 17 (94.4%) received pigtail drainage with IMP. We previously reported this method as an effective treatment for PSP [23]. Since all patients underwent 2 surgeries, including mechanical pleurodesis or pleurectomy for the first and second PSP, the integrity of the pleura was most likely defective, which might have led to a strong reaction of pleural adhesion when chemical pleurodesis was performed for the third PSP. This hypothesis could possibly explain why conservative treatment was not significantly inferior to surgery in our study. Pleurodesis, whether chemical or mechanical, might play a role in preventing subsequent recurrence, regardless of whether the patient received conservative treatment or underwent surgery. The recurrence rate has been recognized to increase with subsequent episodes [4-10]. These patients' conditions might have been different from the conditions of patients with their first PSP or first recurrent PSP. Chemical pleurodesis might have a role in preventing subsequent recurrence. A recent study reported that mesothelial cells may play a critical role in effective chemical pleurodesis [29]. However, resected lesions for the third PSP in our study revealed mesothelial cells proliferation. Further mechanisms should be investigated and studied.

Limitations

There are some limitations in our study, so selection biases may have occurred. First, few patients developed a third PSP after 2 surgeries, so we were able to include only 38 patients in our study. Second, we considered patients who failed conservative treatment and then underwent a surgery during the same clinical course as the part of the surgery group. This may underestimate the recurrence rate of PSP after conservative treatment. Third, we excluded patients who were discharged after the chest roentgenogram revealed full lung expansion without pneumothorax and who experienced ipsilateral PSP again within 3 days after a previous discharge due to PSP. This exclusion could lead to overestimation of ipsilateral recurrence due to slowly prolonged and ongoing air leakage [30]. However, some patients who received conservative treatment again within 3 days without recurrence were also excluded, which could possibly lead to an underestimation of how much conservative treatment prevented ipsilateral recurrence of PSP. Fourth, other factors such as genetic risks and environmental risks that would influence PSP were not considered in detail in our study [26-28,31]. The ipsilateral recurrence of PSP may act as a model of systems biology, but ours was a retrospective study. Further prospective, randomized, controlled, and comprehensive studies are required in the future.

Conclusion

In conclusion, patients who develop recurrent ipsilateral PSP after repeated surgery are rare. Our study indicates that BMI might be associated with subsequent recurrence. We recognize that this study is retrospective in design

with a small number of patients. Nevertheless, our study provides an alternative way in which conservative treatment, pigtail with IMP, might be effective and not inferior to surgery for these patients in preventing subsequent recurrence and hospitalization. We also suggest that pleurodesis might play a role in conservative treatment or surgery to prevent subsequent recurrence in these patients. Although physicians may deal with PSP patients who are unwilling to undergo surgery, thoracic surgeons should still be consulted to evaluate recurrent PSP patients.

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Endobronchial Leiomyoma -- A Rare Endobronchial Tumor with Recurrent Hemoptysis

Meng-Cheng Ko, Chen-Yiu Hung, Shu-Min Lin, MD

A 69-year-old female with underlying diabetes mellitus, dyslipidemia, and hypertension, presented with recurrent mild hemoptysis for 1 week. Bronchoscopy exam revealed an endobronchial tumor at the proximal edge of RB8 that did not show in the chest X-ray or on high-resolution computed tomography. The nodular lesion presented a magenta color with loss of normal green autofluorescence under autofluorescence imaging bronchoscopy. The final diagnosis was confirmed by pathology, which showed a benign spindle cell tumor – an endobronchial leiomyoma. ***(Thorac Med 2020; 35: 196-199)***

Key words: benign endobronchial tumor, leiomyoma, hemoptysis

Introduction

Benign lung tumors are uncommon, comprising just 2-5% of all lung tumors. Pulmonary leiomyomas, accounting for only 2% of benign lung tumors, are extremely rare. Furthermore, only one-third of pulmonary leiomyomas are endobronchial leiomyomas [1]. Here, we present the case of a rare endobronchial leiomyoma with recurrent hemoptysis.

Case Report

A 69-year-old female with underlying diabetes mellitus, dyslipidemia, and hypertension presented with a recurrent small amount of hemoptysis for 1 week. She denied purulent phlegm, fever, chills, night sweating, body weight loss, skin rashes, or joint pain. She also denied gynecological diseases. Physical examination revealed course breathing sounds at the right anterior chest wall. Chest plain film showed neither a lung parenchymal lesion nor vascular deformity (Figure 1). High-resolution computed tomography (CT) (Figure 2) for an unknown cause of hemoptysis was arranged, and revealed mild bronchiectasis in the right middle and left lower bronchus, with absence of a visible endobronchial lesion. In order to find the cause and bleeder, we arranged autofluorescence imaging bronchoscopy (AFI).

We found a small well-defined nodule with

Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan.
Address reprint requests to: Dr. Shu-Min Lin, Department of Thoracic Medicine, Chang Gung Memorial Hospital, 199 Tun-Hwa N. Rd., Taipei, Taiwan.

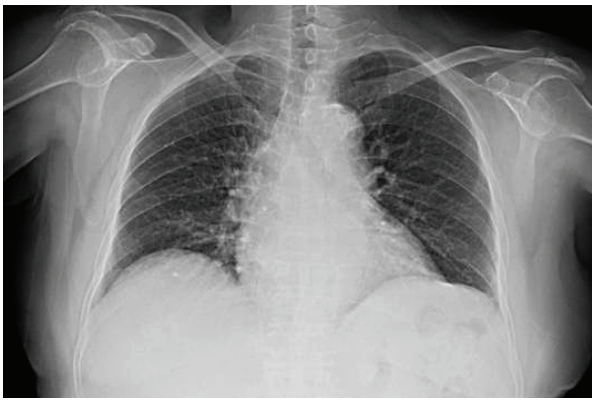

Fig. 1. Initial chest X-ray did not show an endobronchial lesion.

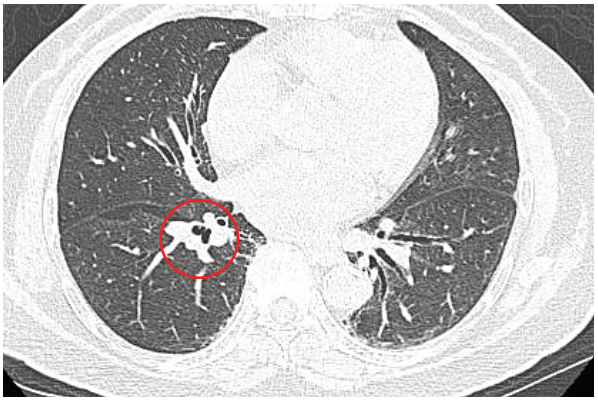

Fig. 2. High-resolution computed tomography did not show an endobronchial lesion, eithe.

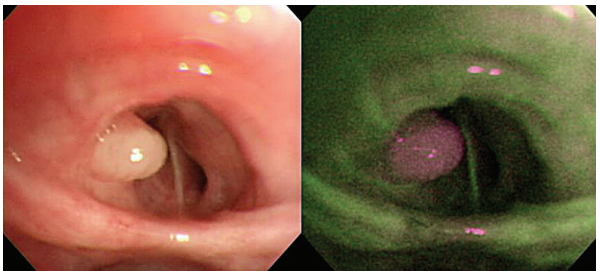

Fig. 3. White light bronchoscopy revealed the endobronchial nodule at RB8. Autofluorescence imaging of the nodule showed a magenta color without normal green autofluorescence.

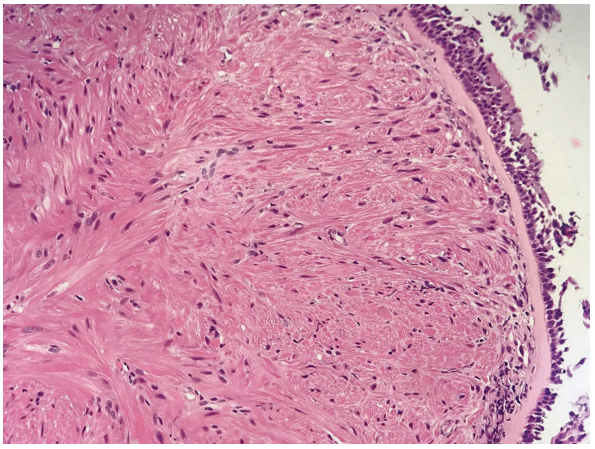

Fig. 4. Pathology of the submucosal tumor consisted of cells arranged in a spiral and bundle, including simple cells with elongated nuclei.

a smooth surface at the proximal edge of RB8 (Figure 3). There was no obvious obstruction at the lesion site. The nodular lesion presented a magenta color with loss of normal green autofluorescence under AFI. Endobronchial mucosa revealed normal architecture and normal green light (Figure 3). Pathology of the submucosal tumors revealed cells arranged in a spiral and bundle, with simple cells with elongated nuclei. No necrotic or mitotic activity was observed. Histopathology was consistent with benign spindle cell tumors, which was suggestive of leiomyoma (Figure 4).

We discussed with the patient and her family the indications and risks of procedures to remove tumors, including cryotherapy. The patient did not consider resection, even after notifying her of the possibility of malignant transformation. After a series of AFI and biopsies, we found that the nodule did not enlarge, block the bronchi or continue to bleed. We will continue to track the patient's clinical symptoms and nodular status.

Discussion

Leiomyoma rarely presents in the respiratory tract. We described a 69-year-old woman who had repeated hemoptysis and an endobronchial leiomyoma. The endobronchial leiomyoma was not revealed by chest X-ray or high-resolution CT. It was of a magenta color without normal green autofluorescence. Pathology of the endobronchial leiomyoma showed cells arranged in a spiral and bundle, with simple cells with elongated nuclei.

Leiomyomas account for less than 2% of all benign lung tumors [1]. In a review article, leiomyomas of the respiratory tract developed mostly in the fourth decade and were female-predominant. The clinical symptoms of the leiomyomas differed based on the site and size of the tumor [2]. Parenchymal lesions, which constituted 51% of lung leiomyomas, were usually asymptomatic [3-4]. Tracheal leiomyomas, which were the least common presentation, caused intermittent or persistent wheezing and dyspnea. Bronchial leiomyomas produced significant symptoms and signs, such as repeated fever, cough, chest pain, and wheezing, after bronchial obstruction [2]. Atelectasis and bronchiectasis developed after complete or partial obstruction. Hemoptysis is relatively common in endobronchial leiomyomas, and may be caused by bronchiectasis or tumor surface ulceration [2].

Chest imaging findings from a series of case reports found that airway leiomyomas appeared normal in chest plain films of cases with a small tumor nodule. In the other cases, airway leiomyoma was an identifiable endobronchial nodule with obstructive pneumonia or atelectasis (most commonly), an endotracheal nodule, or an intratracheal and extratracheal or intrabronchial and bronchial mass [5]. CT image features including an airway intraluminal nodule, iceberg tumor, lobulated contour, round contour, obstructive pneumonia, atelectasis, mucus plugging, heterogeneous enhancement, homogenous enhancement, and calcifications have been reported [5-6]. Loss of normal green autofluorescence or a magenta color on AFI images can be caused by an increase in the thickness of the epithelial layer and an accumulation of cancerous substances in the local tissue of the surface, which is characteristic of early lung cancer and precancerous lesions [7]. A magenta-colored area of the endobronchial mucosa indicates the location of the endobronchial leiomyoma.

Although image studies can accurately show the location and characteristics of the tumor, the definite diagnosis is reached by pathology. Endobronchial smooth muscle tumors including leiomyoma and leiomyosarcoma were believed to arise from the peri-bronchiolar/interstitial smooth muscle, or more rarely from smooth muscle of the arteriolar walls [4]. The malignant transformation of pulmonary benign metastasizing leiomyoma has been described in only 2 case reports [8]. Due to this scarcity of cases, the proportion of leiomyosarcoma transformation remains unclear. Bronchoscopy interventions such as electrocautery, argon plasma coagulation, cryotherapy, and Nd:YAG laser have a good effect on the resection of endobronchial leiomyomas [3]. Although bronchoscopy is effective and safe, cases of recurrence have been reported [3]. Our patient did not undergo intervention due to her personal wish and the subsided symptoms.

We still have many limitations in the diagnosis and treatment of bronchial leiomyoma. First, there is currently no AFI image for endo-

bronchial leiomyoma that can be used for comparison. Second, the ratio of leiomyosarcoma transformation is still unclear. Third, there is no conclusion as to whether patients who have no symptoms or mild symptoms of bronchial leiomyoma require intervention.

Conclusion

Leiomyoma is a rare endobronchial tumor. We reported the case of a 69-year-old woman with endobronchial leiomyoma and recurrent hemoptysis. Her imaging examination did not reveal an endobronchial tumor, but the bronchoscop examination located a nodule at RB8. Past literature does not indicate the ratio of malignant transformation, so continuous bronchoscopy follow-up is reasonable.

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Blurred Vision as the Initial Presentation of Choroidal Metastasis of Lung Cancer in a 40-Year-Old Man– A Case Report

Po-Chuan Shen[1], Chih-Yen Tu[1], Te-Chun Hsia[1], Ning-Yi Hsia[2]

Choroidal metastasis (CM) from primary lung cancer is uncommon and has a poor prognosis. It can be treated with an external beam of radiation or by laser photocoagulation. However, visual defects and blindness are possible complications after radiotherapy. Systemic chemotherapy for such a condition would be a better choice, if no targeted therapy or immunotherapy could be used. We reported a 40-year-old patient who had CM with the initial presentation of blurred vision. Fundoscopy, fluorescence angiography and optic coherence tomography indicated CM of the right eye. He was then referred to the chest outpatient department where an endobronchial ultrasound biopsy for a right middle lobe nodule was performed. The pathology showed adenocarcinoma without epidermal growth factor receptor mutation, and PD-L1 expression was weakly positive (20%). We prescribed 6 cycles of systemic chemotherapy with carboplatin, pemetrexed and bevacizumab. A follow-up examination revealed complete remission of the CM. He then underwent a lobectomy for the primary site. Due to disease progression with bone metastases in October 2018, he received chemotherapy and immunotherapy with Taxotere and pembrolizumab combined with denosumab. Herein, we report this case of CM of lung cancer in a 40-year-old man with the initial presentation of blurred vision. ***(Thorac Med 2020; 35: 200-204)***

Key words: choroidal metastasis, lung adenocarcinoma, pembrolizumab

Introduction

Lung cancer is the most common cause of cancer-related mortality in Taiwan. It may spread to many organs, such as the brain, bones, adrenal glands and liver. Choroidal metastases (CM), however, has seldom been reported, but has a poor prognosis [1]. Even now, treatment for advanced non-small cell lung cancer (NSCLC) has its limitations, and thus, further investigation is needed. It seems chemotherapy alone is the last choice of treatment for advanced NSCLC if no targeted therapy can be used. Herein, we report a 40-year-old man who suffered from CM. He received systemic chemotherapy with carboplatin, pemetrexed and

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, [2]Department of Ophthalmology, China Medical University Hospital, Taichung, Taiwan
Address reprint requests to: Dr. Po-Chuan Shen, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, No. 2, Yude Road, North District, Taichung City, Taiwan

bevacizumab with complete regression of the CM and partial response at the primary site. Surgical resection of the primary site was performed in August 2018. However, due to bone metastasis, he was then given chemotherapy with Taxotere, and immunotherapy with pembrolizumab and denosumab [12].

Case Report

This 40-year-old male was diagnosed as having lung adenocarcinoma in March 2018. He had been well prior to this, and had no cancer-related family history. He was an engineer, a non-smoker, and denied having any chemical exposure. He initially visited National Taiwan University Hospital due to blurred vision, and ophthalmoscopic examinations revealed a choroidal tumor of the right eye (Figure 1). Chest film showed a nodule at the right lower lung field (Figure 2). A chest CT showed a nodule at the right middle lobe (RML) of the lung (Figure 3). The patient then came to China Medicine University Hospital for a second opinion. We performed an endobronchial ultrasound biopsy of the RML nodule. The pathological and immunohistochemical study revealed adenocarcinoma, positive for TTF-1, negative for ALK, ROS-1 and p40, and weakly positive for PD-L1 expression (tumor proportion score: 20%).

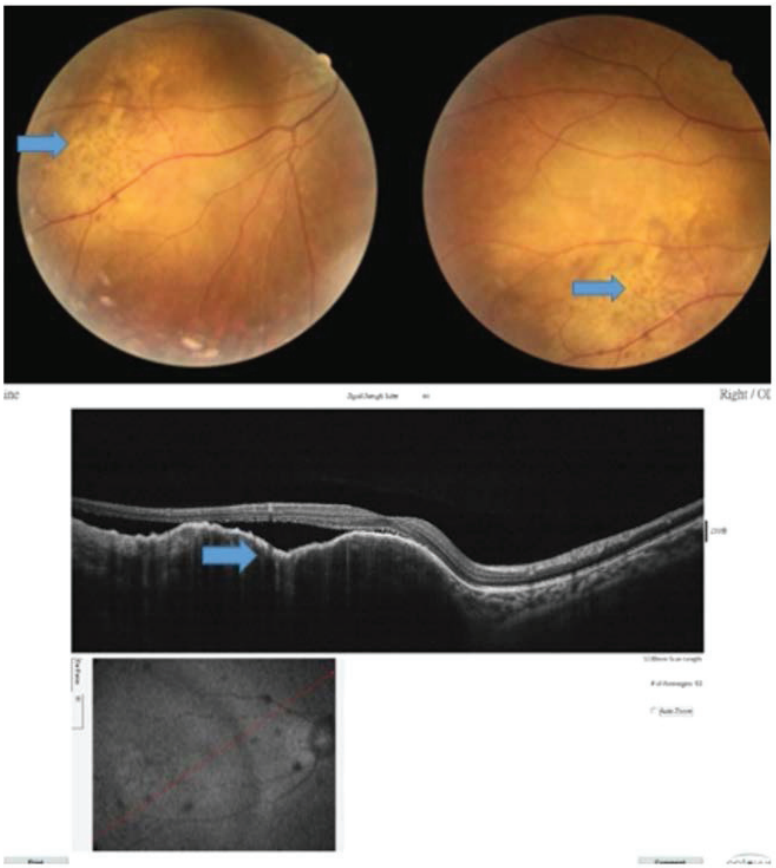

Fig. 1. A. Ophthalmoscopic findings revealed multiple lesions in the choroid of the right eye (blue arrows). B. Optical coherence tomography showed a choroidal tumor in the right eye (blue arrowhead).

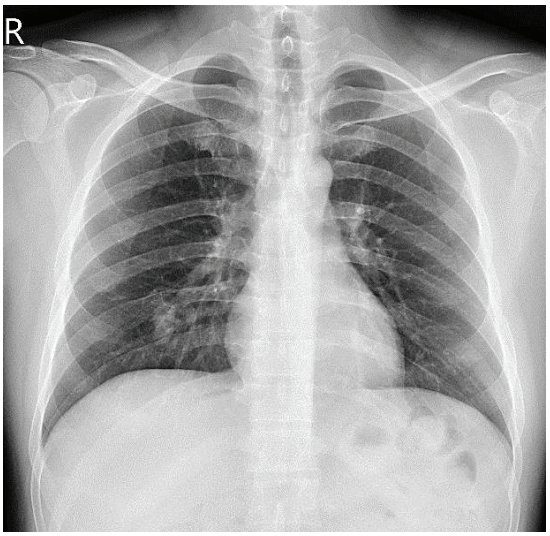

Fig. 2. Chest X-ray showed a nodule in the right lower lung field.

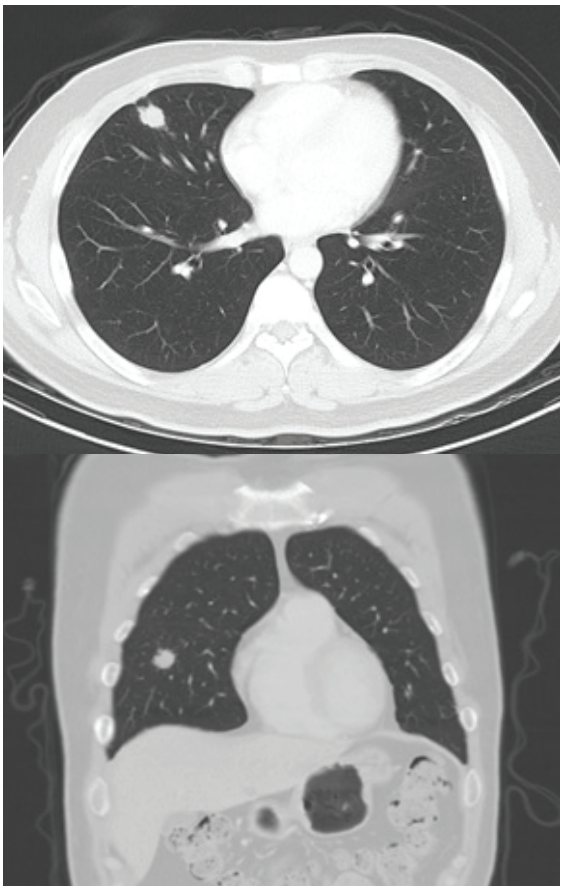

Fig. 3. Chest CT showed a right middle lobe nodule.

In April 2018, he received chemotherapy with 6 cycles of carboplatin, pemetrexed and bevacizumab. Complete regression of the CM and partial response at the primary site were found in July 2018. He underwent a RML lobectomy in August, 2018, followed by 2 cycles of adjuvant chemotherapy with carboplatin, pemetrexed and bevacizumab. However, bone metastasis was noted in October 2018. The chemotherapy regimen was then changed to Taxotere, pembrolizumab and denosumab. He is still alive as of this writing, and is receiving monthly chemotherapy plus immunotherapy, with a good performance status.

Discussion

The choroid is located between the retina and the sclera, and is a vascular, pigmented tissue layer. The choroid provides the vascular supply to the outer part of the retina [2]. Metastatic tumors are the most common intraocular malignancy and the choroid is the most common site. The uveal tract is the most commonly involved site in the metastasis of primary non-ocular tumors. Intraocular metastasis is generally located in the posterior uvea because of the abundant supply of posterior ciliary arteries to the choroid. Recent clinical and autopsy studies have reported that 9.3-10% of patients who died of cancer had ocular metastasis, and that most metastases were localized in the choroid. The route of metastasis to the choroid is hematogenous [2]. Nevertheless, CM is rare and often asymptomatic. The first CM case was described by Perl *et al* in 1872 [3]. Breast cancers are the most common primary tumors to have CM, followed by lung cancer [2,4-6]. CM can also be detected in other primary cancers, such as hepatocellular carcinoma, and esophageal,

ovarian, colon [6], prostate, and pancreatic cancer [7]. CM from primary tumors is representative of a poor outcome [2], and most patients die within months of diagnosis. Mean survival is approximately 10 months, and the 5-year overall survival rate is 24% [8-9]. Kreusel *et al*. [10] reported a retrospective review of 22 consecutive patients with symptomatic CM that resulted from lung cancer; 36% of patients with lung cancer had been diagnosed before the occurrence of CM. CM was often unilateral, solitary and located close to or at the posterior pole in the majority of patients. In 20% to 40% of cases, the lesions were bilateral.

Patients with CM detected in a screen study [1] would have only a short median survival period of 2 months. Though only a minority of patients have symptomatic CM, they would have a median survival of 13 months [10], for they may still be healthy enough to be aware of the symptoms of CM and look for ophthalmic care. The clinical presentations of CM include blurred vision, decreased visual acuity, tenderness, flashes, floaters, metamorphopsia and scotomas [2,4]. Blurred vision and decreased visual acuity are the most common among these symptoms [2,4]. CM can cause visual dysfunction due to the accumulation of subretinal fluid and/or the tumoral involvement of the macular region. However, some patients with CM are asymptomatic [4]. The differential diagnosis of a choroidal mass includes choroidal neovascularization, primary choroidal malignant melanoma, CM, inflammatory granulomas and hemangioma. The related diagnostic procedures include slit-lamp biomicroscopy, ophthalmoscopy, ultrasonography, fluorescent angiography, CT and magnetic resonance imaging [2]. Typical ophthalmoscopic features include 1 or multiple creamy yellow choroidal lesions associated in some advanced cases with secondary retinal detachment [4,11]. With fluorescein angiography, these lesions are usually fluorescent in the early phases of the study and become progressively hyperfluorescent in the late phases. B-scan ultrasound shows an echogenic sub-retinal mass with diffuse, ill-defined borders.

In conclusion, CM from primary lung cancer as an initial presentation is rare and a poor outcome indicator. Systemic chemotherapy could be a relatively safe method to treat symptomatic CM, compared to radiotherapy. When a patient with lung cancer complains of a visual defect, we should include CM as a differential diagnosis.

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Metastatic Adenocarcinoma of the Lung with Small Bowel Perforation Complicated with Sepsis - A Case Report

Chen-Yu Kao, Mei-Yin Chen, Ching-Min Tseng, Chi-Wei Tao

Lung cancer is the most common cause of cancer-related death, according to the statistics of the by Ministry of Health and Welfare in Taiwan. The incidence of gastrointestinal metastases from lung cancer is low; however, when it occurs, it is usually asymptomatic and fatal. We present the case of a 62-year-old patient with ileal perforation and intestinal metastases of adenocarcinoma of the lung. Tracing his medical history, he had unresectable adenocarcinoma of the right upper lobe of the lung, with right middle lobe and bilateral adrenal metastases that was proven about 1 month prior to this admission. He developed generalized abdominal pain 3 days after chemotherapy. Abdominal computed tomography scan revealed bowel perforation. Emergency exploratory laparotomy revealed diffuse purulent peritonitis and a perforated ileal tumor; a segmental small bowel resection with end-to-end anastomosis of the perforated bowel was then performed. Histological and immunohistochemical findings were consistent with metastatic adenocarcinoma of the lung. Despite adjuvant treatment, the patient died of progressive disease 1 month after surgery. ***(Thorac Med 2020; 35: 205-208)***

Key words: intestinal metastasis, intestinal perforation, lung adenocarcinoma

Introduction

In lung cancer patients, distant metastases to the brain, bone, kidney, adrenal gland, and other organs are common, but gastrointestinal tract metastases are fairly rare [1]. Small bowel metastases were present in 46 of 431 patients with primary lung cancer who underwent autopsy during an 11-year period [2]. The incidence of gastrointestinal metastases from lung cancer was about 2-14% of cases in autopsy studies [3]. However, clinically significant metastases are rare. We present the case of a patient with ileal perforation and intestinal metastases of adenocarcinoma of the lung.

Section of Respiratory Therapy, Department of Internal Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan
Address reprint requests to: Dr. Chi-Wei Tao, Section of Respiratory Therapy, Department of Internal Medicine, Cheng-Hsin General Hospital, No. 45, Zhenxing St., Beitou Dist., Taipei City 112, Taiwan (R.O.C.).

Case Report

This 62-year-old male patient, a heavy-smoker, was diagnosed with right upper lung adenocarcinoma with mediastinal invasion, causing encasement of the right subclavian artery and superior vena cava, invasion of the recurrent laryngeal nerve, and metastatic subcarinal lymphadenopathy, with right middle lobe and bilateral adrenal metastases, T4N2M1b, stage IV, at another hospital about 1 month prior to this admission. Test results for epidermal growth factor receptor or anaplastic lymphoma kinase mutation were negative. The patient underwent radiotherapy (2,500cGy/10 fractions) due to the development of superior vena cava syndrome beginning on 14 August 2017.

Upon admission, the patient was afebrile and in mild respiratory distress. His chest radiograph showed a right middle lung metastatic mass lesion and chest computed tomography (CT) revealed a right middle lobe mass lesion with central cavitation with pleura traction (Figure 1A & 1B). Due to productive cough with yellowish-white sticky sputum, empiric antibiotics with ampicillin/sulbactam were used. He was given 1 course of chemotherapy with cisplatin (60mg/m^2), alimta (500mg/m^2) and avastin (7.5mg/kg) on 11 September 2017. However, he developed generalized abdominal pain 3 days after beginning chemotherapy, and leukopenia was also found. Physical exam showed diffuse tenderness and equivocal rebounding pain. Antibiotics were then shifted to empiric piperacillin/tazobactam. KUB revealed diffuse bowel distention (Figure 2). Abdominal CT scan revealed bowel perforation (Figure 3), so emergency exploratory laparotomy was performed and revealed diffuse purulent peritonitis with moderate turbid ascites and a perforated

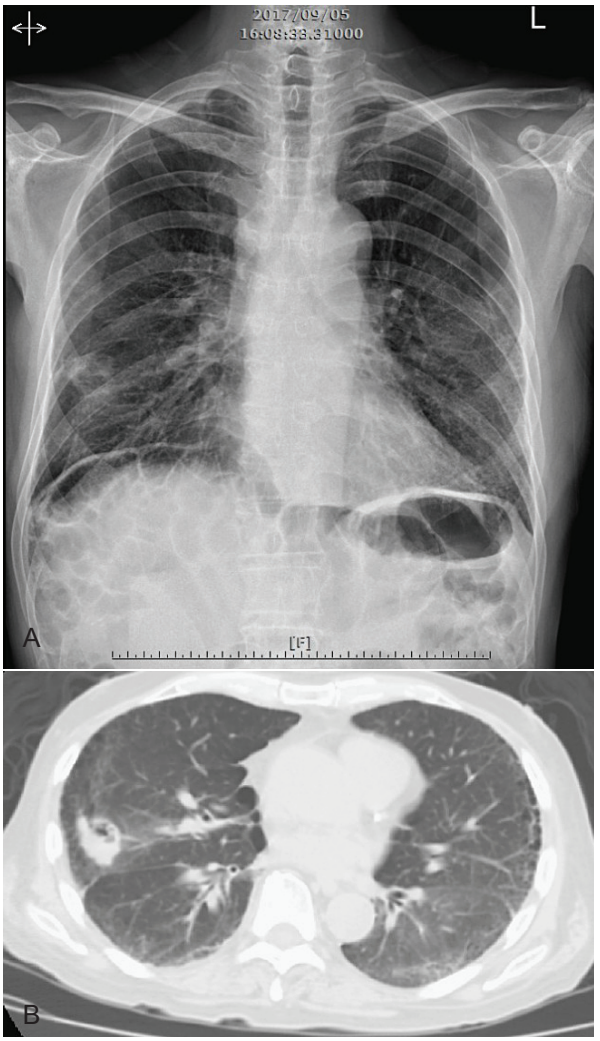

Fig. 1. A. Chest radiography: right middle lung metastatic mass lesion. B. Chest computed tomography: right middle lobe mass lesion with central cavitation with pleura traction.

ileal tumor, about 1.0 cm in size; the antimesenteric side of the proximal ileum was covered by the omentum. Multiple tumor masses in the distal ileum and peritoneum were also noted. Abscess drainage and a segmental small bowel resection with end-to-end anastomosis of the perforated bowel were performed (Figure 4). He received empiric antibiotic treatment with doripenem, teicoplanin and anidulafungin, and the pus culture result revealed *Klebsiella pneumoniae*. Histological and immunohistochemical

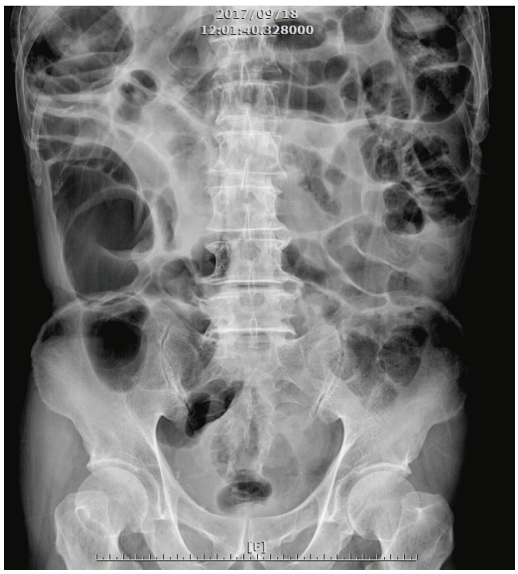

Fig. 2. KUB: diffuse bowel distention.

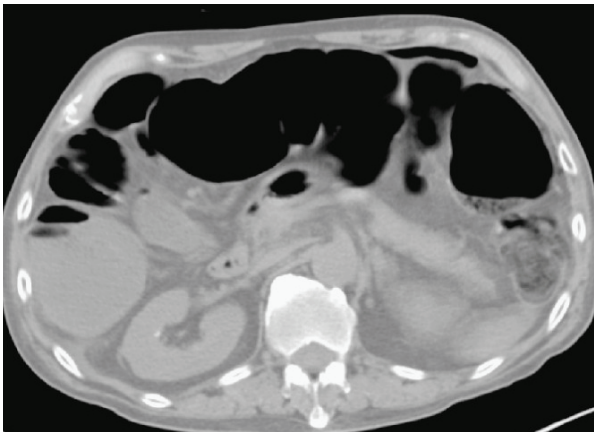

Fig. 3. Abdominal computed tomography scan: bowel perforation.

findings were consistent with metastatic adenocarcinoma of the lung. The patient was kept on temporary fasting, and given total parenteral nutrition support. However, despite adjuvant treatment and intensive care, the patient died of progressive disease 1 month after surgery.

Discussion

In lung cancer patients, gastrointestinal tract metastases are fairly rare [1]. The incidence of small bowel metastases was found to be about 10% in deceased primary lung cancer patients who underwent autopsy during an 11-year period [2]. Only a few (1.77%) patients with primary lung cancer had symptomatic gastrointestinal metastasis, but almost one-third of symptomatic patients had fatal small bowel perforation [4]. Although small bowel perforation secondary to lung cancer metastasis remains relatively rare, it has a significant impact on mortality. The possibility of small bowel metastases should be kept in mind in patients with lung cancer presenting with an acute abdomen [3]. The diagnosis relies on a high degree of clinical suspicion. According to a literature review, the most common site of small bowel perforations was the jejunum(53%), followed by the ileum(28%) [5]. Jejunum and ileum lesions accounted for 6%

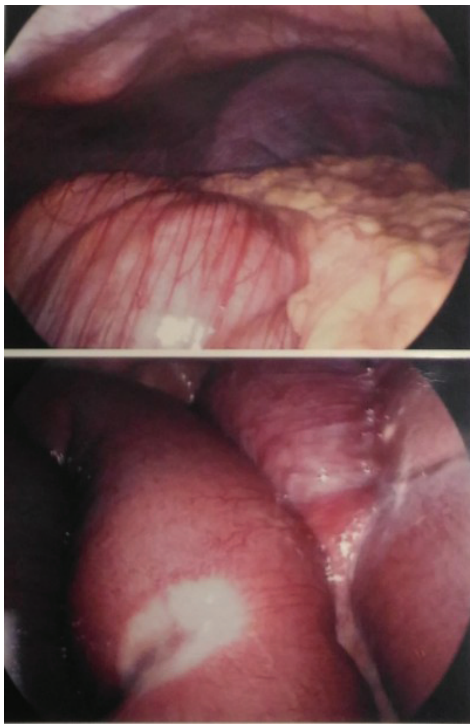

Fig. 4. Metastatic lesion on the ileum with perforation.

of the perforations [5-6]. Leidich *et al* showed that there was no predilection for any particular histological cell type to perforate [7]. Nevertheless, the prognosis is considered to be very poor. Perioperative mortality previously reported varies from 60% to 100% [2,8], and mean survival was 66 days with 50% of patients not surviving past 90 days.

In conclusion, lung cancer with symptomatic gastrointestinal metastasis is unusual and rare. Metastasis to the gastrointestinal tract is a dismal prognostic sign. Although surgery for these patients might be associated with high morbidity and mortality, early detection and aggressive interventions are still recommended for most patients.

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Acute Ischemic Stroke and Myocardial Infarction during Bronchoscopy

Wei-Wei Ng[1], Diana Yu-Wung Yeh[1,2], Chen-Chun Lin[1,2]

Acute ischemic stroke coinciding with myocardial infarction has rarely been reported. We report a 74-year-old gentleman who lost consciousness in the middle of a bronchoscopy examination. Subsequent work-up revealed both an acute ischemic stroke and myocardial infarction. The patient recovered fully with minimal neurological sequelae after thrombolytic therapy. Vasovagal response during the invasive procedure may have induced cardiac arrhythmia, leading to both myocardial infarction and stroke. ***(Thorac Med 2020; 35: 209-212)***

Key words: acute ischemic stroke, myocardial infarction, bronchoscopy

Introduction

Concurrent acute ischemic stroke and acute myocardial infarction (AMI) have rarely been reported in the medical literature. Some reports have described multiple vessel obstructions in patients with multiple risk factors. Here, we report a case of acute ischemic stroke and AMI occurring during bronchoscopy. The patient was discharged with minimal neurological sequelae after treatment.

Case Report

A 74-year-old gentleman with newly diagnosed gastric adenocarcinoma presented to our clinic with a right lower lung tumor noted on the pre-operative routine chest X-ray. Lung computed tomography (CT) confirmed a right lower lung tumor 3 x 2 cm in size. Bronchoscopic biopsy was arranged. In the middle of the procedure, the patient suddenly became unresponsive, diaphoretic, and cyanotic. Oxygen desaturation was also noted. The electrocardiogram (ECG) revealed wide-QRS bradycardia, and the patient's blood pressure was unmeasurable. Cardiopulmonary cerebral resuscitation (CPCR) was initiated immediately and endotracheal intubation performed. Intravenous epinephrine 1 mg and atropine 12 mg were administered in total. After 1 minute of CPCR, he regained spontaneous circulation. Twelve-lead ECG revealed sinus tachycardia and ST-segment elevations in leads II, III, and AVF (Figure

[1]Division of Pulmonary Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.
[2]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan.
Address reprint requests to: Dr. Chen-Chun Lin, Division of Pulmonary Medicine, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, No. 95, Wen Chang Road, Shih Lin District, Taipei City, Taiwan.

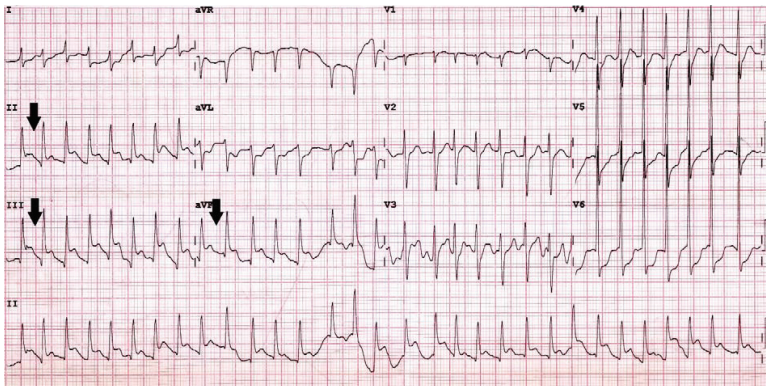

Fig. 1. Initial 12-lead ECG showing sinus tachycardia with a ventricular rate of 196 beats per minute and QTc interval of 497 ms. ST elevations are seen in leads II, III, and AVF, >10 mV in lead III, consistent with acute infarction in the right coronary artery territory. (black arrow).

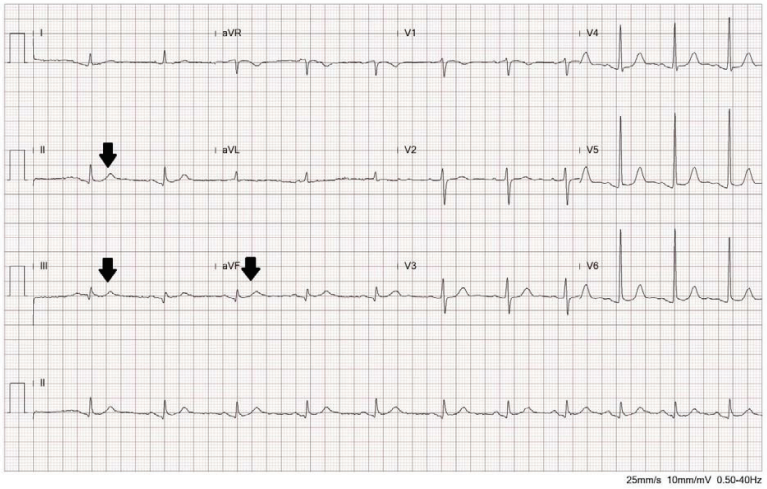

Fig. 2. 12-lead ECG obtained 2 hours after the event, showing sinus arrhythmia with a ventricular rate of 69 beats per minute and QTc of 447 ms. There are mild ST elevations in leads II, III, and AVF. (black arrow) This showed overall improvement compared to Figure 1.

1). At this time, eye deviation to the right with left hemiparesis was found on physical examination. A whole-body CT was arranged, and showed no evidence of intracranial hemorrhage or aortic dissection. Cardiac enzymes, including creatine phosphokinase (CK), CK-MB and troponin-I, were within normal limits initially, but became elevated 5 hours after onset of symptoms. Other biochemistry data were unremarkable (white blood cell count: 6,200/uL, hemoglobin: 10.8g/dL, platelet count: 288/uL, PT: 12.4 second, INR: 1.08 ratio, GOT: 20/uL, CPK: 52/uL, BUN: 14mg/dL, creatinine: 1.04 mg/dL, eGFR: 69.81, Na: 138 mmol./L, K: 2.9 mmol/L, troponin-I: 0.012ng/ml [highest: 2.863 ng/mL, 8 hours later], myoglobin: 32.4ng/mL). Neurology and cardiology services were both consulted and acute right middle cerebral artery territory infarction, as well as acute inferior wall myocardial infarction, were diagnosed (Figure 2).

After a multidisciplinary discussion, intra-

venous tissue-plasminogen activator (t-PA) (IV loading: 6.4 mg, 58.4 mg IV drip) was administered to treat both acute ischemic stroke and AMI. Thrombolytic therapy was initiated within 2 hours after onset of symptoms.

Brain angiography was arranged 1 hour after t-PA for planned endovascular thrombectomy; however, no embolus was found. The patient was successfully extubated on day 4 after the initial event. Subsequent brain magnetic resonance imaging (MRI) showed reperfusion edema of the right middle cerebral artery territory (Figure 3). Holter ECG recorded no paroxysmal atrial fibrillation. Cardiac sonography revealed fair left ventricular (LV) contractility with an ejection fraction of 65%. Neither LV hypokinesis nor intracardiac thrombus was observed. The patient recovered fully and was discharged home on the 17th day of admission with the very minimal neurological sequela of a mildly unsteady gait.

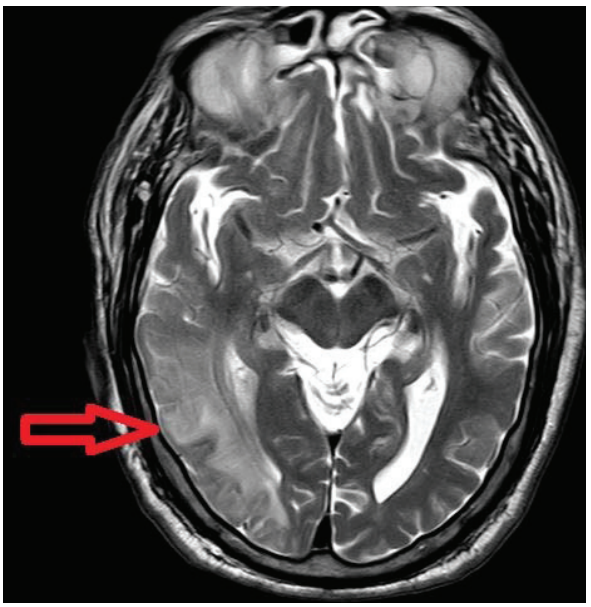

Fig. 3. Brain magnetic resonance imaging on day 4 post-t-PA therapy, showing hyperintense white matter signal changes in the right middle cerebral artery territory with reperfusion edema. (red arrow).

Discussion

Acute ischemic stroke and acute coronary syndrome both share the same risk factors, including diabetes, hypertension, and atrial fibrillation. There are several case reports on the simultaneous occurrence of both acute ischemic stroke and acute coronary syndrome; most of them are related to paroxysmal atrial fibrillation [1-3]. One case report described an air embolism-related acute ischemic stroke and non-ST elevation myocardial infarction (NSTEMI) resulting from percutaneous transthoracic lung biopsy [4].

In our case, the patient had neither a history of atrial fibrillation, nor a record of paroxysmal atrial fibrillation on Holter ECG. An invasive procedure-related vasovagal response leading to cardiac arrhythmia was highly suspected in this case. During the vasovagal response, increased vagal activity and decreased sympathetic output result in bradycardia and vasodilatation, which causes hypotension and a significant decline in cardiac output. Most of the time, this may lead to transient syncope and decreased end-organ perfusion; the heart will contract vigorously to maintain cardiac output--which will stimulate receptors in the heart wall--and increased ventricular stretch will cause vasodilatation and profound bradycardia [5]. A pre-existing vascular disease, however, may induce an ischemic event or, rarely, involve more than 1 organ simultaneously, such as the brain and the heart, resulting in acute ischemic stroke and AMI. This could explain why the rhythm first seen on the monitor in this case was widening QRS bradycardia.

To our knowledge, there is no published

case report to date on a vasovagal response concurrently inducing both acute coronary syndrome and acute ischemic stroke. There is a case study on the use of atropine in the prevention of all types of vasovagal response induced by cryoballoon ablation in patients with atrial fibrillation [6]; however, the evidence is still too limited for its routine application.

As our patient had a history of gastric cancer, malignancy-related thrombosis cannot be excluded. One case report in the literature described the development of an ischemic stroke in a patient with metastatic gastric cancer after treatment with ramucirumab, a vascular endothelial growth factor receptor-2 inhibitor [7]. Our patient had not yet received treatment for gastric cancer at the time of the event.

Determining the optimal treatment sequence for our patient was a dilemma, as well--which should have priority, acute ischemic stroke or AMI? Coronary artery intervention was suggested initially by the cardiologist after the patient's hemodynamics were stabilized. However, considering the "golden time" of thrombolytic therapy for acute ischemic stroke is shorter than that for cardiac catheterization for AMI, we decided to administer intravenous t-PA, which can treat both acute ischemic stroke and AMI. Although there are recommendations for distinct dosing, timing, duration, and method of administration of t-PA in acute ischemic cerebrovascular stroke, STEMI and pulmonary embolism individually [8-9], there is no written guideline for simultaneously occurring events.

In conclusion, even in patients with no identifiable risk factor, vasovagal response-induced cardiac arrhythmia should be considered a possible cause leading to simultaneous acute ischemic stroke and AMI.

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